NATIONAL COLLEGE
OF
CHEST PHYSICIANS (INDIA)

Lung Bulletin

NEWSLETTER OF NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

THIRD ISSUE JANUARY – JUNE 2021

ALL ABOUT OXYGEN THERAPY

HIGHLIGHTS


NATIONAL COLLEGE OF CHEST PHYSICIANS
NCCP
INDIA
Wishes All
Members ,
Fellows ,
and
Their Families
HAPPY
Diwali
FESTIVAL OF LIGHTS

NATIONAL COLLEGE OF CHEST PHYSICIANS
NCCP
INDIA

Celebrate the Festival of Lights with Sweets

Dr. B. O. Tayade
President

Dr. S. N. Gaur
Secretary

NCCP(I) LUNG BULLETIN INDEX

NCCP(I) LUNG BULLETIN INDEX

ACADEMIC CALENDAR
KINDLY BLOCK YOUR DATES !

Sr. No.	DATES	CONFERENCE	VENUE	WEBSITE
1.	January 27 - 31	**NAPCON 2020** 22nd National Conference on Pulmonary Diseases - Joint National Conference of National College of Chest Physicians (India) and Indian Chest Society	VIRTUAL	https://www.virtualnapcon2020.com
2.	March 13 - 14 20 - 21	AIIMS - INTERNATIONAL WORKSHOP ON MECHANICAL VENTILATION AIIMS PULMOCRIT 2021	Virtual	https://www.aiimspulmocrit2021.com/
3.	April 20 - 21	6th Annual Inhalation and Respiratory Drug Delivery Congress 2021	London	https://www.oxfordglobal.co.uk/formulation-delivery-series-uk/
4.	May 14 - 19	American Thoracic Society (ATS) International Conference 2021	San Diego (Virtual)	https://conference.thoracic.org
5.	June 24 - 27	20th International Congress on Pediatric Pulmonology (CIPP XX)	Virtual	https://www.cipp-meeting.org/en/
6.	June 25 - 26	Pneumo Update Europe 2021	Vienna	https://pneumo-update-europe.eu/
7.	September 5 - 8	European Respiratory Society (ERS) Congress	Barcelona (Virtual)	https://live.ersnet.org/
8.	October 15 - 17	APAAACI 2021 Joint TAACI - International Conference of the Asia-Pacific Association of Allergy, Asthma and Clinical Immunology	Kaohsiung (Taiwan)	https://apaaaci2021.org/
9.	October 17 - 20	American College of Chest Physicians (ACCP) CHEST Annual Meeting (CHEST 2021)	Orlando (Virtual)	https://chestmeeting.chestnet.org/
10.	October 29 - 31	53rd and 54th Annual Convention of the Indian College of Allergy, Asthma and Clinical Immunology ICAAICON 2020 & 2021	Virtual	http://icaai.net/
11.	October 30 - 31	22nd Annual National Conference of Academy of Pulmonary and Critical Care Medicine - PULMOCON 2021	Thrissur (Hybrid)	https://aptcr.org/pulmocon-2021/
12.	November 20 - 21	25th Congress of the Asian Pacific Society of Respirology (APSR)	Kyoto (Hybrid)	https://apsr2021.jp/
13.	February 1 - 4 **2022**	**NAPCON 2021** 23rd National Conference on Pulmonary Diseases - Joint National Conference of Indian Chest Society and National College of Chest Physicians (India)	VARANASI	https://www.napcon2021varanasi.com/

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)
GOVERNING COUNCIL 2021 – 2022 (W.E.F. 01-04-2021)

Dr. B. O. Tayade
President (2021-22)

Dr. S. N. Gaur
Secretary (2019-22)

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Dr. J. C. Suri
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Editor, IJCDAS
Director, VPCI
(Special Invitee)

Dr. J. K. Samaria
Organising Chairman
NAPCON 2021 Varanasi
(Special Invitee)

Dr. S. K. Katiyar
Chairman
Academic Forum
& Scientific Committee

Dr. K. B. Gupta
Member
Academic Forum

Dr. Rajesh Solanki
Member
Academic Forum

Dr. Rajesh Chawla
Member
Academic Forum

From the Desk of President, NCCP(I)

Prof. Dr. B. O. Tayade
President, NCCP(I) (2021-2022)
Senior Professor and Head, Department of Respiratory Medicine,
N. K. P. Salve Institute of Medical Sciences and Research Centre
and Lata Mangeshkar Hospital, Nagpur, Maharashtra
Formerly Professor and Head, Department of Respiratory Medicine,
Government Medical College and Hospital, Nagpur, Maharashtra
Organising Secretary, NAPCON 2006

E-mail : botayade123@gmail.com

Dear Members and Fellows of NCCP(I),

I am humbled by the opportunity to serve as the President of National College of Chest Physicians (India) [NCCP(I)], one of the largest, most vibrant and also one of the oldest societies. We are blessed with many dedicated members and volunteers who care deeply about our discipline, its' standing and contributions in a fast-changing environment. They also care about serving our members and fellows, and the contributions and efforts of all, from our fast energetic young junior members to the most-experienced senior veterans for the academic activities of the College, betterment and advancement of their careers, as well as their services to society are highly appreciated.

The E-Newsletter of our College, the NCCP(I) Lung Bulletin is well into the launch of its third issue, on the topic *' Oxygen therapy '*, compiled and edited by Dr. Nikhil Sarangdhar. I am positive and have great hope that it will prove to be useful and helpful for everyone, especially during this pandemic era of COVID-19.

Looking forward to a successful tenure as the President of NCCP India, with the earnest goodwill, help and support of all our esteemed fellows and members. Together, we are sure to take NCCP(I) to greater heights.

From the Desk of Immediate Past President, NCCP(I)

Prof. Dr. P. D. Motiani
Immediate Past President, NCCP(I) (2020-2021)
Retd. Senior Professor and Head (Pulmonary Medicine),
Dr. S. N. Medical College, Jodhpur, Rajasthan
Organising Chairman, NAPCON 2010
Recipient of NCCP(I) - German Remedies Chest Oration and
NCCP(I) Rajasthan Chapter - Prof. S. N. Gaur Oration

E-mail : drpdmotiani@gmail.com

Dear Colleagues,

During my tenure as President, National College of Chest Physicians (India) [NCCP (I)] from 1st April 2020 to 31st March 2021, the pandemic of COVID-19 started and the whole world, including our country India has witnessed lockdown, limited outdoor activity to prevent and minimize the spread of infection from person to person from aerosol droplets. The concept of wearing masks, social distancing, frequent hand washing and use of sanitizers, though curtailed the spread, and many of the people developed lower respiratory tract infections – viral pneumonitis, leading to hypoxia, with varied mortality.

Vaccination against COVID-19 in the world is the only effective measure to raise immunity against the SARS-CoV-2 virus and prevent the spread of infection and severity of disease and decrease mortality due to COVID-19. The upcoming news and reports about vaccination against COVID-19 will definitely improve our understanding about immunity and protection against COVID - 19 disease and various aspects of different COVID-19 vaccines.

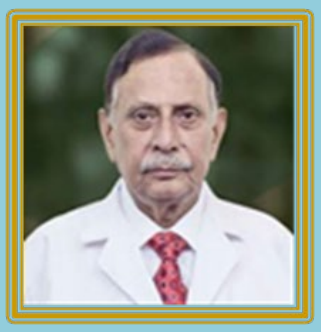
During this period, we took the initiative to host NAPCON 2020, the 22nd joint national conference of National College of Chest Physicians (India) and Indian Chest Society, for the very first time on a virtual platform from 27th to 31st January 2021. Though the time left to organise was short, the conference was a gargantuan success as the response to NAPCON 2020 from the pulmonary fraternity and post-graduates was unexpected and overwhelming. NAPCON 2020 broke the record of previous physical conferences, with 4321 delegates registering and 1002 abstracts submitted for presentation for the conference. The highlight of the conference was the state-of-the-art scientific programme for NAPCON 2020 drafted meticulously under the leadership of Dr. S. K. Katiyar, Chairman, Scientific Committee, with inputs from the scientific committee members and which experienced participation of more than 550 faculty members, with more than 100 overseas faculty. Apart from workshops, lectures, debates, panel discussions, symposia and other sessions, there were also free oral paper and E-poster presentations. The NCCP(I) Post-Graduate Quiz in Respiratory Diseases witnessed record participation by 526 post-graduates across the country at State level and the Final National Quiz was hosted at NAPCON 2020. I congratulate Prof. Dr. S. N. Gaur, Organising Chairman and Dr. Nikhil Sarangdhar, Organising Secretary along with other members of the Organising Committee of NAPCON 2020 for their hard work and efforts to organise a highly successful conference and creating a milestone for NAPCON in the future. I also thank our colleagues of the Indian Chest Society and international chest associations for their goodwill and active participation which helped to ensure that NAPCON 2020 was a grand success.

NCCP(I) also took the initiative to revive its Newsletter, introduced initially as *' Pulmonary Communications '* by Dr. Rajesh Chawla in 2016, and later on taken up by Dr. Nikhil Sarangdhar as *' NCCP(I) Lung Bulletin '* during 2020. NCCP(I) News Letter has met with unparalled enthusiasm and success and currently has a wide circulation of more than 3500 readers.

I extend my best wishes to Dr. Nikhil Sarangdhar, for his efforts in bringing out the third issue of NCCP(I) Newsletter, Lung Bulletin dedicated to the theme *' Oxygen therapy '*. This issue of the Newsletter of NCCP (I) will be informative to all of us, contributed by eminent pulmonologists in our country and from overseas on different aspects of Oxygen therapy.

I would like to take this opportunity to express my sincere gratitude and thanks to all my Colleagues of the National College of Chest Physicians (India), all its Governing Council Members as well as Members and Fellows of the College, for their cooperation and support during my tenure as President, to take NCCP(I) to greater heights .

From the Desk of Secretary, NCCP(I)



Prof. Dr. S. N. Gaur
Secretary, NCCP(I), President, ICAAI, Organising Chairman, NAPCON 2020 Virtual
Professor and Head, Department of Respiratory Medicine,
School of Medical Sciences and Research, Sharda University, Greater Noida, U. P.
Former Director (Acting), Vallabhbhai Patel Chest Institute, University of Delhi
Recipient of 15 national awards and other academic honours including Commonwealth Fellowship and Fellowship of National Academy of Medical Sciences
Chairman, Allergen Standardization Committee, Government of India

E-mail : sngaur9@gmail.com

Dear Colleagues,

The National College of Chest Physicians (India) [NCCP(I)] is a registered body functioning to promote the cause of Chest Diseases and Allied Sciences in India and to take this specialty forward in the field of Medicine. It was formed originally with 58 founder members as the Indian Association of Chest Diseases (IACD) in 1959 at the Indian Science Congress. The IACD in its meeting held on November 15, 1979 subsequently ratified by the General Body meeting held on November 6, 1979, unanimously decided to change the name of IACD to National College of Chest Physicians (India) and to make consequential changes/amendments in the memorandum of the Association, and its rules and regulations by a sub-committee, duly constituted for this purpose and the recommendations were confirmed and approved by the prescribed authority and confirmed at a subsequent special meeting of the General Body held on August 14, 1980. The National College of Chest Physicians (India) thus came into being in January, 1981. Since then, it has grown from strength to strength and currently has on its roll 1589 Members and 259 Fellows, making it one of the largest national registered professional medical associations, contributing to the development of the specialty of Pulmonary Medicine since its inception. The mission of NCCP(I) is to promote academic growth, partnership and collaboration for education in a rapidly developing world and develop strategies for better clinical practice in Pulmonary Medicine.

The NCCP(I) official website is www.nccpindia.org. The Indian Journal of Chest Diseases and Allied Sciences, indexed in Index Medicus is the official publication of NCCP(I) and is published jointly with Vallabhbhai Patel Chest Institute, Delhi and has been widely acclaimed at both national and international levels. In addition, the NCCP (I) publishes a Directory of Chest Physicians, which is updated every 5 years. Under the convenorship of Dr. Rajesh Chawla, Past President of NCCP(I), the College has launched two E-courses - Comprehensive Pulmonary Medicine E-course (CPMeC) in 2017 and Interventional Pulmonology E-course (IPeC) in 2019 for the benefit of post-graduates and clinicians practising in the specialty. CPMeC was the first online course in Pulmonary Medicine in India accredited by the National Board of Examinations, New Delhi and met with resounding success, having nationwide enrolment of more than 1800 doctors. NCCP(I) in collaboration with ICS has developed guidelines for Pneumonia, Vaccination, ILD, COPD, Bronchoscopy and Spirometry, and the development of guidelines for Pleural Diseases and Medical Thoracoscopy and revised guidelines for COPD is in progress. NCCP(I) has also developed National guidelines on Nebulization therapy. NCCP(I) also encourages original research by young scientists and consultants by providing travel grants to all members and fellows for upgrading their knowledge by attending national and international conferences.

Ever since its inception, the College held 33 conferences with the Association of Physicians of India and since the 28thconference, it has organized its annual conferences (NACCON) independently. These conferences were highly successful and were chaired by the President of NCCP(I). From 1999, the NCCP(I) with ICS is having Joint National Conference on Pulmonary Diseases – NAPCON. I am happy to inform you that all the twenty-two NAPCONs were a grand success, appreciated by the delegates and faculty. 22nd NAPCON 2020 Virtual (January 27-31, 2021) surpassed all records of previous conferences with the largest number of registered delegates, attendees, international participation and abstracts submitted for presentation, setting a benchmark for other virtual conferences to follow and creating a milestone for medical conferences in the near future. As the Organising Chairman, I am grateful to all delegates, faculty members and our colleagues for their goodwill and participation at the conference, which helped greatly towards making the first-ever Virtual NAPCON a grand success. I am sure that the same spirit will continue and we will have more and more participation as well as better conferences in future. This year, NAPCON 2021 is being organized as a physical event at Varanasi, and; as in the past, we expect a good number of delegates and faculties to participate from India and neighboring countries. I have full confidence that NAPCON 2021 will be organized with efforts in a manner to make it a most memorable event. I extend my best wishes to Prof. Dr. J. K. Samaria, Organising Chairman of NAPCON 2021 Varanasi and to the Organising Committee for a successful conference.

NCCP(I) also started a Newsletter titled *'Pulmonary Communications'* in 2016 under the leadership of its' then President Dr. Rajesh Chawla, which was continued as *'NCCP(I) Lung Bulletin'* in 2020 with Dr. Nikhil Sarangdhar as the Editor, NCCP(I) Newsletter, published twice-yearly with each issue dedicated to a different topic. The first and second issues of NCCP(I) Lung Bulletin, dedicated to Pulmonary Hypertension and Pulmonary Function Tests respectively were very successful and appreciated by all members and fellows of the college and other consulting pulmonologists and post-graduate trainees. On behalf of the NCCP(I) as well as on my personal behalf, I congratulate Dr. Nikhil Sarangdhar, who is the Editor, NCCP(I) Lung Bulletin for his hard work in bringing out this third issue dedicated to the topic *'Oxygen Therapy'* which I am confident will be appreciated by all our colleagues in the field. I wish this issue all success.

From the Desk of Chairman, Scientific Committee and Academic Forum, NCCP(I)

Prof. Dr. S. K. Katiyar
Chairman, Scientific Committee and Academic Forum, NCCP(I)
Zonal Chairman (Central Zone), NCCP(I), Lifetime Achievement Awardee, NCCP(I)
Gold Medal Awardee, Tuberculosis Association of India and U.P. TB Association
Formerly
Principal and Dean, Professor and Head, Department of Tuberculosis and Respiratory Diseases, G.S.V.M. Medical College and C.S.J.M. University, Kanpur, U.P.
President, NCCP(I) (2003-2004); TB Association of India (2007-2008); ICS (2009-2010)
Chairman, Scientific Committee, NAPCON 2014, 2016, 2018 and 2020
Organizing Secretary, NAPCON 2000
E-mail : skkatiyar_in@yahoo.com

Dear Colleagues,

I congratulate Dr. Nikhil Sarangdhar and his entire editorial team for successfully launching the third issue of the Newsletter of National College of Chest Physicians (India), ' *NCCP(I) Lung Bulletin* '. It indeed requires a great and sincere effort to bring out a thematic issue, this time based on ' *Oxygen Therapy* '. What they have tried to create is a practice-specific newsletter providing a better alternative to just a general type newsletter which is much more effective and useful and has the flexibility to be tailored to member's needs and demands.

A newsletter must have the quality to capture the readers' attention quickly to maintain their interest, which it does quite successfully. If you lose the readers in their first few lines or 30 seconds of reading the newsletter, you have lost them for the duration and this is not so with the ' *NCCP(I) Lung Bulletin* '. It is using plenty of high-quality graphics, pictures, and charts to capture the reader's interest and make it more informative and interesting.

Besides the scientific information the NCCP(I) Newsletter also carries several articles of general information about the members, the College, the events and conferences, and the pulmonary speciality and fraternity as a whole.

I strongly feel that our NCCP(I) Newsletter has been quite effective for the purpose that it has been created for, and its usefulness is much worth beyond the time and effort that it takes to write and create.

Congratulations to NCCP(I) for the great effort and best wishes for launch of the third issue. Keep the torch of knowledge burning !

Please Take Care, Stay Safe and Healthy during this COVID-19 crisis !

From the Desk of Editor, NCCP(I) Lung Bulletin

Dr. Nikhil Sarangdhar
Editor, NCCP(I) Lung Bulletin
Organising Secretary, NAPCON 2020 and 2016
Former Assistant Professor, Department of Tuberculosis and Chest Diseases,
K. J. Somaiya Medical College and Research Centre, Mumbai, Maharashtra
Young Scientist Awardee of the Indian College of Allergy, Asthma and Immunology (2011, 2014, 2015), Association of Physicians of India (2015), Indian Chest Society (2015), National College of Chest Physicians - India (2017)
E-mail : ncsarangdhar@rocketmail.com

Dear Colleagues,

It is with great pleasure that National College of Chest Physicians (India) [NCCP(I)] launches the third issue of its News Letter, the NCCP(I) Lung Bulletin. It is now being published regularly on a biennial basis with the aim to make it a highly sought-after publication. The News Letter provides a common academic platform to post-graduate trainees as well as practising pulmonologists to learn from interaction with each other by exchanging their ideas, knowledge and experiences. The objective of Lung Bulletin is to keep up scientific temper with focus on chest physicians of the future, by keeping us acquainted with current events of interest in Pulmonary Medicine through articles written by senior colleagues and young budding pulmonologists from north to south and east to west of our country, to reflect a truly national outlook, as well as a few articles written by pulmonologists from neighbouring countries in which technical information about basic sciences is supplemented by interesting real-life case reports to ensure a unique amalgamation of theoretical knowledge, clinical experience and practical skill. Each issue of Lung Bulletin is bifurcated into two sections, a general section that provides information about NCCP(I), its activities, publications and academic activities as well as upcoming events and other developments in our field, followed by an academic section exclusively dedicated to a specific disease or topic of interest in Pulmonary Medicine. Lung Bulletin is meticulously compiled to ensure that every issue is unique, with the ultimate goal to provide a comprehensive all-in-one review and up-to-date source of information on the subject to the reader.

The inaugural issue (January – June 2020) of NCCP(I) Lung Bulletin, dedicated to the theme *"Pulmonary Hypertension"* was received with unparalleled excitement and enthusiasm by all members and fellows of our college. Thereafter, we were privileged to launch the second issue (July – December 2020), dedicated to the theme *"Pulmonary Function Tests"* during the inaugural function of NAPCON 2020 (Virtual). This issue (January – June 2021), the third of the series, is dedicated to the theme *"All about Oxygen Therapy"*, a burning topic that attracted global attention during the COVID-19 pandemic.

Four new exciting features have been added to this issue. Firstly, the Members' corner has been spruced up in an attempt to make it more inclusive, and to give a voice to Women's empowerment, it begins with a spotlight on our female members. We have added a sub-section dedicated to NAPCON, the joint national conference of National College of Chest Physicians (India) and Indian Chest Society, followed by flyers of other conferences. Another unique attractive feature is a sub-section to congratulate our outstanding fellows and members by acknowledging their achievements. Last, but not the least, for the very first time, the academic section contains four articles written by international pulmonologists, in acknowledgement of the growing popularity and appeal of Lung Bulletin beyond our shores.

I take this opportunity to express my gratitude to NCCP(I) for entrusting me with the responsibility of compiling and publishing NCCP(I) Lung Bulletin. I am personally grateful for the unconditional support and encouragement extended by the Governing Council of NCCP(I), particularly Prof. Dr. B. O. Tayade (President), Prof. Dr. S. N. Gaur (Secretary), Prof. Dr. S. K. Katiyar (Chairman, Scientific Committee and Academic Forum) and Prof. Dr. P. D. Motiani (Immediate Past-President). I thank our authors for their efforts and also for being accessible, cooperative and supportive like a family throughout this endeavour. Lastly, I place on record the personal feedback and appreciation given by everyone in support of our endeavour which made it possible for us to publish Lung Bulletin in the most scientific and professional manner and steer it to greater heights to propel the ever-expanding future of Pulmonary Medicine in our vast country.

The enormous task of organising NAPCON 2020, the 22nd joint national conference on Pulmonary Diseases of the National College of Chest Physicians (India) and Indian Chest Society, for the very first time on a Virtual Platform due to the COVID-19 pandemic, from 27th to 31st January 2021, was entrusted to our team. In the limited time of five months available we worked round-the-clock to put together a state-of-the-art Scientific Programme, rich in academic content, exceptional in diversity and expertise of faculty in the wide arena of Pulmonary Medicine and Allied Sciences designed to change the perspective of our day-to-day clinical practice. The theme of NAPCON 2020, *"Preparing Together for a Better Future",* reflected not only contemporary health dynamics but also the need to remain vigilant continuously. The Workshops and Scientific Programme witnessed the participation of 119 international faculty, deputed from 21 different international Chest associations, apart from 460 national faculty. The keen interest and enthusiasm to participate in NAPCON 2020 were palpable, as evidenced by the overwhelming figures of 4321 delegate registrations, 1002 abstracts for oral or E-poster presentation, and more than 11000 logins on the very first day of the scientific programme, an unprecedented record in the history of NAPCON. As the Organising Secretary, I personally thank NCCP(I), ICS and all of You for making NAPCON 2020 a grand success.

I have always cherished the importance of the "personal touch", be it while editing NCCP(I) Lung Bulletin, organising NAPCON 2020 and 2016, coordinating NCCP(I) PG quiz and other academic activities and I welcome inputs from all of You, whether you happen to be post-graduates, teachers or practising consultants in the field of Pulmonary Medicine to take Lung Bulletin to greater heights. Please feel free to write to me at **ncsarangdhar@rocketmail.com. Wish You All Pleasant Reading !**

MEMBERS' CORNER (NATIONAL)

Thank you for giving me the opportunity to write a message in our NCCP(I) News Letter. I feel proud to be a member of the NCCP India community and I am equally happy to write for the Third issue of our News Letter, which is about Oxygen Therapy. The first issue had covered Pulmonary Hypertension while the second issue covered Pulmonary function tests. I congratulate Dr. Nikhil Sarangdhar and the entire editorial team of the News Letter for this initiative and for creating a milestone in the history of NCCP(I). We are receiving national guidelines and other updates that greatly help us for managing patients through different sources including journals and news letters that reflect the hard work of the NCCP(I). It provides us a feast of knowledge and awareness. There are many components of this News Letter. It not only publishes information about a national directory, but also upcoming events, details of academic courses, scholarships, publications like guidelines and books. Apart from these, the scientific section of the News Letter includes in-depth knowledge of the particular topics. NCCP(I) has helped during the lockdown period by facilitating e-learning. It provides various grants. The association also organizes conferences and conducts quizzes for postgraduates. Creating awareness is a step towards success. I wish the NCCP(I) News Letter all success !

Dr. Arti Shah, DNB, DTCD
Professor and Head, Deptt. of Respiratory Medicine,
In-charge, COVID care and medical education, SBKS Medical College and Research centre,
Sumandeep Vidyapeeth, Vadodara, Gujarat

It is heartening to know that the third issue of NCCP(I) News Letter, themed on 'Oxygen therapy' has been launched. This is a laudable initiative, as I am confident that the articles written in this News Letter by eminent authors will update our knowledge and clear certain myths too, regarding the principle and practice of Oxygen therapy in various respiratory conditions. I congratulate and thank the NCCP(I) leadership, Dr. Nikhil Sarangdhar and his editorial team for initiation and continuation of this News Letter, the NCCP(I) Lung Bulletin. I am sure this News Letter will enlighten us and give way to provide service to humanity.

Dr. Shubhra Jain, MD, IDCCM
Associate Professor, Deptt. of Pulmonary Medicine,
SMS Medical College, Jaipur, Rajasthan

I feel honoured to write a message for the NCCP(I) News Letter Lung Bulletin. I am thankful to Prof. Dr. S. N. Gaur and Dr. Nikhil Sarangdhar for giving me this opportunity. This issue of the News Letter is the third issue, the previous two issues had great response and were very well received. This time, the theme of the News Letter is 'Oxygen therapy', which will be very useful to all practitioners in our field and will also be very helpful for the young trainees. I congratulate the NCCP(I) leadership, Dr. Nikhil Sarangdhar and editorial board for the great success of the previous two issues and wish them success for all forthcoming issues of the NCCP(I) News Letter.

Dr. Savita Jindal, MD, FNCCP
Associate Professor, Deptt. of Respiratory Medicine,
AMC MET Medical College, Ahmedabad, Gujarat

I am extremely happy to learn that the third issue of National College of Chest Physicians (India) News Letter themed on 'Oxygen therapy' is being released. This is an applaudable initiative by NCCP(I). The first two issues, on Pulmonary Hypertension and Pulmonary function tests, were very popular amongst both experienced pulmonologists and students, with contributions from the stalwarts in the field. I am sure that under the able leadership of Dr. Nikhil Sarangdhar and the editorial board, this issue of the NCCP(I) News Letter Lung Bulletin would be a very useful tool as a comprehensive source of information for all pulmonologists and a grand success !

Dr. Poulomi Chatterjee, MD, DNB, FISDA, EDARM
Assistant Professor, Deptt. of Pulmonary Medicine,
Government Medical College, Nalhar, Haryana

It gives me immense pleasure to write this message for the third issue of NCCP(I) News Letter. We, the Pulmonary and Critical care specialists have served as frontline warriors at the forefront of health care during the COVID-19 pandemic, as our patients and society as a whole relied on our efforts. Amid this crisis, there is renewed appreciation for the work that all of us do. This issue dedicated to 'Oxygen therapy' will be very much appreciated by all doctors and post-graduate trainees. I congratulate the National College of Chest Physicians (India) for taking the lead to ensure that our fraternity of Chest physicians gets recognition and emerges stronger.

Dr. Naveed Shah, MD, FERS, FAGE, FAPSR
Professor and Head, Deptt. of Pulmonary Medicine,
Government Medical College, Srinagar, Kashmir

NCCP(I) under its dynamic leadership is always in the lead to produce high quality evidence based learning material and the NCCP(I) News Letter Lung Bulletin devoted each time to a specific theme is a 'knowledge basket'. I thank Dr. Nikhil Sarangdhar, Editor of NCCP(I) Lung Bulletin for having given me an opportunity to share my message, coinciding with the launch of this third issue of the News Letter which is dedicated to the theme 'Oxygen therapy'. I am sure this topic which is especially relevant in the current scenario of COVID-19 will equally satisfy both the resident trainee and the seasoned clinician. I wish the NCCP(I) editorial team all success for the launch of this issue and eagerly await future issues.

Dr. Kiran Vishnu Narayan, MD, DNB, DM, MRCP SCE (Resp), EDARM, EDIC, DAA
Associate Professor, Deptt. of Pulmonary Medicine,
Government Medical College, Thiruvananthapuram, Kerala

Change is a must for any organization to survive and excel. National College of Chest Physicians (India) has shown phenomenal growth and the efforts of mentors and seniors in promoting research and academic activities is indeed creditworthy and laudable. The extraordinary achievement of launching this issue of the NCCP(I) News Letter is inspiring for all fellows and members. Let us all be proud to be a part of the NCCP (I) family and let us take it to greater heights. My heartfelt congratulations and best wishes for this issue of the NCCP(I) News Letter.

Dr. Saurabh Karmakar, MD, FCCP, FNCCP, FAPSR, FIMSA
Associate Professor, Deptt. of Pulmonary Medicine,
All India Institute of Medical Sciences (AIIMS), Patna, Bihar

National College of Chest Physicians (India), has always been the pioneer in training residents and updating physicians by organising workshops and conferences and publishing Journals and News Letters. The third issue of NCCP(I) News Letter Lung Bulletin is yet another milestone in this direction. Oxygen Therapy, the theme for this News Letter is a burning topic. Various experts from all over the country have made valuable contributions to this News Letter. I congratulate the team for their successful endeavour in publishing the current issue of NCCP(I) News Letter. I am confident that in the times to come, the NCCP(I) leadership and the editorial team with Dr. Nikhil Sarangdhar at the helm will steer this News Letter to great heights.

Dr. Rohit Kumar, MD, DNB, DM, MNAMS, MRCP (UK), MRCP SCE, EDRM, FCCP, FSM, FIACM
Assistant Professor, Deptt. of Pulmonary Medicine, Critical Care Medicine & Sleep Disorders,
Vardhman Mahavir Medical College and Safdarjung Hospital (VMMC & SJH), New Delhi

MEMBERS' CORNER (INTERNATIONAL)

As a member of the National College of Chest Physicians (India), I feel elated to know about the launch of the third issue of its News Letter Lung Bulletin, dedicated to the theme 'Oxygen therapy'. It is an honor for me to write this message for its' launch.

NCCP(I) has the reputation of being a highly respected association of Pulmonologists in India as well as worldwide. I remember the high academic benchmark set by the state of the art scientific programme of Virtual NAPCON 2020. I am confident this News Letter will be successful in dispersing knowledge about the practice of Oxygen therapy, a modality used worldwide for the management of acute as well as chronic respiratory conditions to healthcare professionals worldwide.

On the occasion of Diwali, the festival of lights, I send my Best Wishes and Greetings to all members and fellows of NCCP(I) on the occasion of publication of this News Letter, which is a long-awaited event. I extend my heartfelt congratulations to all members of the Editorial Board and wish this project all success !

Dr. Ashutosh Sachdeva, MBBS, FCCP
Chief, Section of Interventional Pulmonology, Division of Pulmonary and Critical Care,
University of Maryland School of Medicine, Baltimore, USA

National College of Chest Physicians (India) is an Institution exceptional in its diversity and expertise of professionals in the wide arena of Pulmonary Medicine. The launch of each issue of the NCCP(I) News Letter, every time dedicated to a different topic is looked forward to with eagerness by all, as it provides a comprehensive platform to share knowledge and provide updates in the field of Pulmonary Medicine among all our colleagues.

I have gone through both previous issues of the NCCP (I) News Letter and find them to be extremely informative and interesting. It rightfully reflects the hard work and creativity of the Editorial Team. The scientific contents are very up to date and state of the art. I appreciate the commendable efforts of NCCP (I) towards this endeavour.

I am glad to know that the current issue of NCCP (I) Lung Bulletin is dedicated to Oxygen therapy. I feel greatly privileged and honoured to have had an opportunity to write a short message for this special issue. The use of oxygen in clinical practice is common for centuries and it is considered as one of the most effective and safe medicines. I am sure that the exciting new articles and information related to 'Oxygen Therapy' in this special issue will enlighten us with many known and unknown aspects of clinical use of oxygen in health and diseases. In the spirit of theme of this special issue, as a fellow of NCCP (I), I would like to extend my congratulations to the Editorial Team for bringing out this issue, and send my warm wishes for celebrations of their past achievements and my best wishes for their future endeavours !

Dr. Narendra Bhatta, MD, MSc, FNCCP, FCCP, FAPSR
Professor and Head, Deptt. of Pulmonary, Critical Care and Sleep Medicine,
B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal

As a Fellow of our College, I feel elated to know that NCCP(I) is going to launch third edition of its News Letter, the NCCP(I) Lung Bulletin. NCCP(I) is one of the oldest established associations of Chest Physicians with an outstanding reputation nationally as well as internationally and has played a key role in fostering the growth of many budding Pulmonologists during their professional careers in India and abroad.

The objectives of this News Letter are many, for one, it will acquaint our colleagues with the academic endeavours and activities of NCCP(I), keep them updated about current events in the field of Respiratory Medicine and allied sciences as well as bring us all together on a single platform to exchange views, ideas and achievements for professional growth like a fraternity.

I congratulate NCCP(I) and the Editor, NCCP(I) Lung Bulletin Dr. Nikhil Sarangdhar for their efforts in bringing out this issue, dedicated to the theme 'Oxygen therapy' which I am sure will prove to be a highly useful publication that will benefit all our colleagues and post-graduate students alike. My best wishes for the grand success of this novel venture !

Dr. Vikram Sarbhai, MD, DNB, FCCP (USA), FACP (USA), FNCCP (India), FISDA (India)
Specialist in Pulmonology, R.A.K. Hospital, United Arab Emirates, and Senior Consultant,
Pulmonology, Critical Care and Sleep Medicine, National Heart Institute, New Delhi

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

A PROFESSIONAL SOCIETY
for Continuing Education and Research in
RESPIRATORY DISEASE & ALLIED SCIENCES

NCCP(I) MEMBERSHIP DRIVE - BECOME A MEMBER TODAY !

President : Dr. B. O. Tayade
Convenor, Membership drive : Dr. S. K. Katiyar

Secretary : Dr. S. N. Gaur
Co-Convenor, Membership drive : Dr. Nikhil Sarangdhar

COMMUNICATE WITH US

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www.nccpindia.org

Dr. S. N. Gaur, Gaur Clinic, 130 - A, Patparganj Village, Delhi – 110091

sngaur9@gmail.com , ncsarangdhar@rocketmail.com

(+91) 9811271916 , (+91) 9029429015

MEMBERSHIP BENEFITS

1. Discounted Registration for NCCP(I) Members and Fellows at NAPCON.
2. Discounted Course fee for NCCP(I) Comprehensive Pulmonary Medicine E-Course (CPMeC) and NCCP(I) Interventional Pulmonology E-Course (IPeC) [Course Website : https://chestcourses.org].
3. Opportunity to participate and present your original research work at national conference (NAPCON) with travel grant for NCCP(I) - Prof. Dr. S. N. Gaur young scientist award.
4. Travel Grant for International Conferences (Rs. 80,000/- for U.S. & Canada & Rs. 60,000/- for other countries) and National Conferences (Rs. 20,000/-) each year.
5. Lifelong subscription to quarterly issues of Indian Journal of Chest Diseases and Allied Sciences, one of the top rated and cited indexed journals of Respiratory Medicine.
6. Lifelong subscription to biennial issues of NCCP(I) Newsletter Lung Bulletin.
7. Lifelong subscription to Directory of Chest Physicians (updated every 5 years).
8. Opportunity to avail of the Prestigious NCCP(I) Fellowship.
9. Opportunity to participate in Research Activities conducted under aegis of NCCP(I).
10. Upgradation of Knowledge and Technical Skills by attending accredited Conferences, Workshops and CME programmes organised under the aegis of NCCP(I).
11. Opportunity to Associate, Collaborate and have One-to-One interaction with the top level practising Clinicians and Researchers in Pulmonary Medicine in India .
12. Vote during Elections and Introduce New Members at Annual General Body Meeting during NAPCON.

TAKE A TOUR OF OUR WEBSITE : www.nccpindia.org

National College of Chest Physicians (India)

(Formerly Indian Association for Chest Diseases)

V. P. Chest Institute, University of Delhi, Delhi - 110007

NCCP(I) MEMBERSHIP ENROLMENT FORM

Regd. No. : S/1421 (1981)

Send both **Membership Form and the Directory Entry Form (see overleaf),** completed and signed along with supporting documents (Degree & Medical Council Registration Certificate), photograph and payment by DD / Cheque for Rs. 7080/- in favour of **" National College of Chest Physicians (India) "** by post to :

Dr. S. N. Gaur , Gaur Clinic , 130 – A , Patparganj Village , Delhi – 110091.

Instructions :

1. Entries in Boxes should be in Capital letters Only.
2. Information in Cols 1 to 5 and Cols 15, 16 are Mandatory and should be in Capital Letters only.
3. DD/Cheque should be drawn in favour of "National College of Chest Physicians (India)" payable at Delhi.
4. All correspondence and the IJCDAS (Journal) will be dispatched at your Mailing address.
5. Filled applications to be sent to **Prof. S. N. Gaur, GAUR Clinic, 130 - A, Patparganj Village, Delhi – 110091.**

To ,

The Secretary,
National College of Chest Physicians (India)

Dear Sir,

I request that I may be enrolled as a Member of National College of Chest Physicians (India). The Annual Subscription of Rs. 7080/- [Life Membership fee Rs.5000/- and Enrolment fee of Rs. 1000/- + GST 18% (Rs.1080/-) (Total Rs.7080/-)] is enclosed herewith by Cash / Cheque / Demand Draft.

DD/Cheque No: ……. Date: …….. Amount Rs.7080/- Drawn on ……..…….…….....
…….....……
…….....Name of the Bank and address)

1.

Applicant's Surname	
First Name	
Middle Name	

2.

Marital Status	

3.

Date of Birth	**Place of Birth**	

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4.

Permanent Address:			
		City	
State		**PIN**	

5.

Mailing Address*:			
		City	
State		**PIN**	

6. Telephone / Fax (with Area Code)

Residence:		**Office:**	
Fax:		**Mobile:**	

7.

E-mail Address:																																

8. Medical Education : (ENCLOSE COPIES OF DEGREE / DIPLOMA)

Degree/ Diploma	**Name of the College /University**	**Qualifying Year**

9. Experiences in Chest Speciality :

10. Any Other Experience :

11. Affiliation to other Scientific Bodies :

12. Present Appointment and Office Address :

13. Research Activities & Publications : (ENCLOSE LIST)

14. Any other Relevant Information :

15. Proposed and Seconded by :

Name	**NCCP(I) Fellowship/ Membership No.**	**Address**	**Signature**
Proposer :			
Seconder :			

16. Signature of Candidate (Applicant) :

Remarks of Credential Committee :

President NCCP(I) …… **Secretary NCCP(I)** ……

For any difficulties encountered while filling up Membership form, write to ncsarangdhar@rocketmail.com

National College of Chest Physicians (India)

(Formerly Indian Association for Chest Diseases)

V. P. Chest Institute, University of Delhi, Delhi - 110007

Ref No: NCCP (I) Secy./Directory/ Dated : ……..

Regd. No. : S/1421 (1981)

NCCP(I) DIRECTORY ENTRY FORM

Instructions :

1. Please use Capital Letters or Type.
2. Please mention your Membership / Fellowship number for all future correspondence with College.
3. All correspondence and the IJCDAS (Journal) will be dispatched at your Mailing address.
4. Filled applications to be sent to **Prof. S. N. Gaur, GAUR Clinic, 130 - A, Patparganj Village, Delhi – 110091.**

Membership/ Fellowship No.								**MembershipYear**					**FellowshipYear**				

(Leave blank if submitted along with application for new membership)

Surname																																					
First Name																																				
Middle Name																																				

Date of Birth:								
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Present Designation & Organisation:																																				

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Telephone (with Area Code)

Residence:														**Office:**												
Fax:														**Mobile:**												

E-mail Address:																																				

Degrees:	

Affiliation to other Scientific Bodies:		

Specialties:	**1**		**2**	
	3		**4**	

Interest Section:																																				

Spouse Name:																																				
Spouse Profession:																																				

* Please let us know about any other information / suggestion or out of date information printed in the last Directory.

** Enclose any other information to be added in the Directory on a separate sheet.

COMPREHENSIVE Pulmonary Medicine eCourse

Dr. Rajesh Chawla
NCCP(I) E-Course Director

CPMeC HIGHLIGHTS

- CPMeC has been meticulously prepared by National College of Chest Physicians (India) with the help of Eminent National and International Pulmonology Experts
- CPMeC is useful for Students as well as Practising Pulmonologists for updating themselves with latest recommendations and standards of care for the management of various respiratory diseases
- CPMeC consists of 50 online modules to cover all aspects of Pulmonary Medicine over a span of 150 days
- Each module contains Master Class, Take Home Points, Suggested Reading and Feedback
- More than 1400 Doctors have successfully enrolled in CPMeC accredited by National Board of Examinations, New Delhi (II-A)
- NCCP (I) E-Courses will issue online certificate after successful completion of the course

Website - https://chestcourses.org **Support - https://support.chestcourses.org , +91 - 8454094444**

Course Fee : NCCP(I) Members - 4000 INR ; Non-NCCP(I) Members - 6000 INR ; Foreign Nationals - 149 USD

Interventional Pulmonology E-course

Dr. Rajesh Chawla
NCCP(I) E-Course Director

IPeC HIGHLIGHTS

- Nowadays, Interventional Pulmonology has progressed from simple Bronchoscopy to highly advanced diagnostic and therapeutic Bronchoscopy and Thoracoscopic procedures
- IPeC has been meticulously prepared by National College of Chest Physicians (India) with the help of Eminent National and International Experts in International Pulmonology
- IPeC is useful for Students as well as Practising Pulmonologists for to acquaint and update themselves with the skills required to perform a variety of diagnostic and therapeutic procedures including Bronchoscopy, Endobronchial Ultrasound (EBUS), Medical Thoracoscopy, Cryobiopsy, Airway Stenting , Management of Air Leaks and Hemoptysis and Percutaneous Tracheostomy
- IPeC consists of 30 online modules to cover all aspects of Interventional Pulmonology over a span of 180 days
- Each module contains Master Class, Take Home Points, Suggested Reading and Feedback
- NCCP (I) E-Courses will issue online certificate after successful completion of the course

Website - https://chestcourses.org **Support - https://support.chestcourses.org , +91 - 8454094444**

Course Fee : NCCP(I) Members - 4100 INR ; Non-NCCP(I) Members - 6100 INR ; Foreign Nationals - 137 USD

INDIAN GUIDELINES ON NEBULIZATION THERAPY
an educational initiative of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Dr. Rajesh Solanki
President, NCCP(I) [2018-19]

Dr. S. N. Gaur
Secretary, NCCP(I)

Dr. S. K. Katiyar
Chairman and Convenor

Dr. Nikhil Sarangdhar
Coordinator

Dear Colleagues,

You will be happy to know that we are soon going to publish *' Indian Guidelines on Nebulization Therapy '* under the aegis of the National College of Chest Physicians (India). These guidelines are the first of their kind in our country and their compilation a pioneering achievement by our College in the field of Medical Education.

To formulate, compile and publish the Indian Guidelines on Nebulization Therapy under the aegis of the National College of Chest Physicians (India) was the brainchild of Prof. Dr. S. K. Katiyar. The Meeting of Experts for the Indian Guidelines on Nebulization Therapy was convened at Delhi on 3rd and 4th November 2018. A total of 67 Experts in Pulmonary Medicine across India, including members from states like Jammu & Kashmir and Assam were invited to ensure unique pan-Indian representation of ideas, expertise and opinion. Dr. S. K. Katiyar planned and convened the meeting, which was chaired by Dr. Rajesh Solanki [President, NCCP(I), in chair] and Dr. S. N. Gaur [Secretary, NCCP(I), in chair] and coordinated by Dr. Nikhil Sarangdhar.

The expert members were allocated into five groups consisting of a Group Convenor, Chairpersons, Advisor and Expert Members to cover different aspects of Nebulization therapy as follows :

1. Group A - Introduction, basic principles and technical aspects of nebulizers, types of equipment, their choice and maintenance.
2. Group B - Nebulization therapy in obstructive airway diseases
3. Group C - Nebulization therapy in the intensive care unit
4. Group D - Use of various drugs (other than bronchodilators and inhaled corticosteroids) by nebulized route and miscellaneous uses of nebulization therapy
5. Group E - Domiciliary nebulization therapy, public and healthcare workers education and future research
   Five groups were constituted originally, but looking at the present global crisis created due to the pandemic of COVID-19 and consequently the apprehensions and concerns raised by spread of infection through nebulization it was thought to include a sixth group in the expert panel to provide guidance to caregivers while nebulizing patients, as follows :
6. Group F - Nebulization Therapy during COVID-19 pandemic and in patients of other contagious viral respiratory infections

Each group discussed the review of scientific evidence by members with intra-group discussions. Evidence and recommendations were presented by individual groups in the final meeting, for deliberations on the recommendations and arrival of consensus. After the meeting concluded, the guidelines were compiled subsequently groupwise and sent to the Convenor for editing . The edited and refined versions of each group draft was circulated to group members for their final comments prior to publication.

The final document of the Indian Guidelines on Nebulization Therapy under the aegis of NCCP(I) consists of six group drafts compiled after systematic review of evidence in order to cover each and every aspect of Nebulization therapy. The guideline document is meticulously compiled and edited with text, level of evidence and grade of recommendation, abbreviations and references.

It gives us immense pleasure to announce to this effect that the compilation of the Indian Guidelines on Nebulization Therapy under the aegis of NCCP(I) is complete and its publication is under progress. We are sure it will be immensely useful as a source of academic knowledge as well as a reference guide for practitioners, teachers, post-graduate medical students, researchers and healthcare workers in the field of Respiratory Medicine, Internal Medicine and other allied sciences which everyone would like to keep ready on their desk.

INDIAN GUIDELINES ON NEBULIZATION THERAPY
an educational initiative of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

ORGANIZERS

President : Dr. Rajesh Solanki (2018-19) | **Secretary : Dr. S. N. Gaur**
Chairman and Convenor : Dr. S. K. Katiyar | **Coordinator : Dr. Nikhil Sarangdhar**

PARTICIPANTS

Group Convenors					
Dr. J. C. Suri	Dr. Raj Kumar	Dr. G. C. Khilnani	Dr. Dhruva Chaudhry	Dr. Rupak Singla	Dr. Parvaiz Koul
Group Advisors					
Dr. Dhiman Ganguly		Dr. V. K. Vijayan		Dr. Randeep Guleria	Dr. V. K. Arora
Dr. H. Paramesh			Dr. S. K. Jindal		Dr. P. S. Shankar
Group Chairpersons					
Dr. S. N. Gaur	Dr. D. Behera	Dr. Rajesh Chawla	Dr. Deepak Talwar	Dr. A. G. Ghoshal	Dr. P. D. Motiani
Dr. D. J. Christopher	Dr. S. K. Luhadia	Dr. Mohan Kumar T	Dr. K. B. Gupta	Dr. Rajesh Solanki	Dr. A. Mahashur
Group Members					
Dr. C. Ravindran	Dr. Narayan Mishra	Dr. R. Narasimhan	Dr. Rajendra Prasad	Dr. J. K. Samaria	
Dr. D. Bhattacharya	Dr. Virendra Singh	Dr. N. T. Awad	Dr. Jogesh Sarma	Dr. Surya Kant	
Dr. S. Chakravarti	Dr. George D'Souza	Dr. R. Vijai Kumar	Dr. P. R. Mohapatra	Dr. Rajesh Swarnakar	
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GROUP PHOTOGRAPHS OF NCCP(I) – INDIAN GUIDELINES ON NEBULIZATION THERAPY

NCCP(I) TEXTBOOK OF RESPIRATORY MEDICINE
a publication of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Dr. D. Behera
Editor-in-Chief

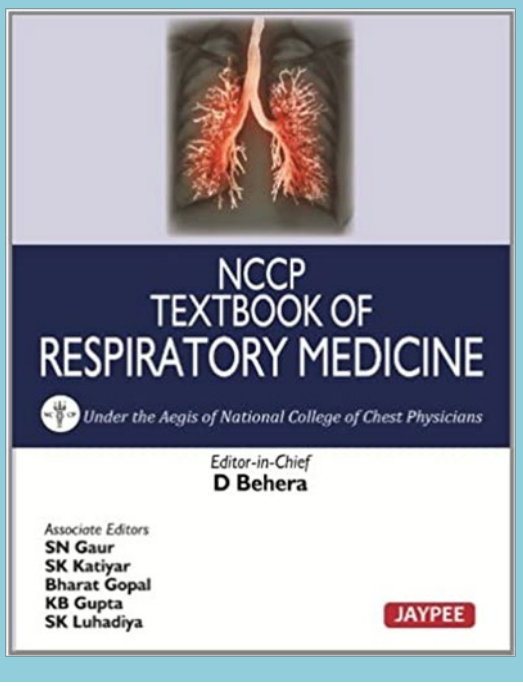
Dr. S. N. Gaur
Associate Editor

Dr. S. K. Katiyar
Associate Editor

Dr. S. K. Luhadia
Associate Editor

Dr. K. B. Gupta
Associate Editor

Dr. Bharat Gopal
Associate Editor



National College of Chest Physicians (India) published the NCCP(I) Textbook of Respiratory Medicine as part of its continuing educational activities. NCCP(I) Textbook of Respiratory Medicine has been edited by Prof. Dr. D. Behera who has been assisted by five associate editors Prof. Dr. S. N. Gaur, Prof. Dr. S. K. Katiyar, Prof. Dr. S. K. Luhadia, Prof. Dr. K. B. Gupta and Dr. Bharat Gopal. This multi-authored textbook contains 41 chapters contributed by senior and experienced authors, both from India and abroad which have been compiled in a single volume so as to provide comprehensive yet concise information on the ever expanding field of respiratory medicine, with special emphasis on the respiratory disorders prevalent in our country. The objective of this book is to address the needs of a diverse audience and become a par- excellent source of information and references for the post-graduate as well as undergraduate medical students as well as serve as a guide to busy practitioners for management of common respiratory illnesses.

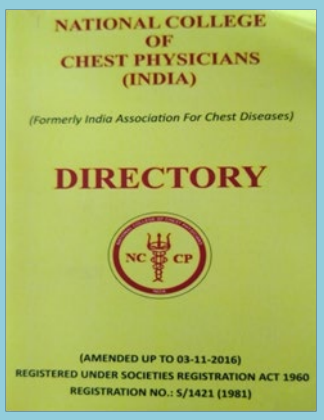
NCCP(I) Textbook of Respiratory Medicine begins with an overall review of the respiratory system, including clinical examination, respiratory symptomatology and physiology, followed by a wide array of chapters on diverse topics, taking care to cover all respiratory diseases common to our country. The text is well referenced and lucid in style for better language flow and adequately supplemented by tables, figures and diagrams. Respiratory disorders have been covered according to their prevalence in our country and relevance in clinical practice. Chapters have been well compiled and edited in order to provide updated and relevant information, keeping in mind that the textbook is meant for a diverse readership comprising of post-graduate, undergraduate and post-doctoral medical students of Respiratory and Internal Medicine as well as practicing Chest Physicians. Overall the textbook is well illustrated and informative, a much sought-after valuable addition to the libraries of medical colleges and teaching institutions and has evolved into a highly popular publication as it highlights the current status and updates on various respiratory diseases and their diagnosis and management.

TEXTBOOK CHAPTERS

1. Physical Examination of Respiratory System
2. Common Clinical Symptoms
3. Growth, Development and Morphology of the Respiratory System
4. Normal Respiratory Physiology
5. Defense Mechanisms of the Respiratory System
6. Diagnostic Methods in Respiratory System
7. Interventional Pulmonology & Electromagnetic Navigation
8. Antimicrobials in Respiratory Medicine
9. Pneumonias
10. Anaerobic Pleuro-pulmonary Infections
11. Parasitic Lung Diseases
12. Tropical Pulmonary Eosinophilia
13. Lung Abscess
14. Bronchiectasis
15. Tuberculosis
16. Non-tubercular Mycobacterial Diseases
17. Bronchial Asthma
18 A. Chronic Obstructive Pulmonary Disease
18 B. Rehabilitation in Chronic Obstructive Pulmonary Disease
19. Aerosol Therapy
20. Respiratory Failure
21. Cor Pulmonale
22. Oxygen Therapy
23. Pulmonary Embolism
24. Acute Respiratory Distress Syndrome
25. Lung Cancer
26. Pulmonary Neoplasms other than Bronchogenic Carcinoma
27. Smoking and Lung Diseases
28. Air Pollution and Respiratory Diseases
29. Essentials of Polysomnography and Recommendations in Adults
30. Sarcoidosis
31. Lungs in Collagen Vascular Diseases and other Systemic Diseases
32. Vasculitis and the Lungs
33. Interstitial Lung Diseases
34. Occupational Lung Diseases
35. Hypersensitivity Pneumonitis
36. Disorders of the Diaphragm and Chest Wall
37. Congenital Anomalies of the Respiratory System
38. HIV and Respiratory Diseases
39. Lung Transplantation
40. Non-invasive Ventilation in Acute Respiratory Failure
41. Pleural Diseases

NATIONAL DIRECTORY OF CHEST PHYSICIANS
a publication of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Dr. S. N. Gaur
Secretary, NCCP(I), President, ICAAI
Organising Chairman, NAPCON 2020 Virtual
Professor and Head, Department of Respiratory Medicine, School of Medical Sciences and Research, Sharda University, Greater Noida, U. P.
Former Director (Acting), V. P. Chest Institute, University of Delhi
Recipient of 15 national awards and other academic honours including Commonwealth Fellowship and
Fellowship of National Academy of Medical Sciences
Chairman, Allergen Standardization Committee, Govt. of India
E-mail : sngaur9@gmail.com



Dear Colleagues,

You are very well aware that National College of Chest Physicians (India) publishes a National Directory of Chest Physicians in India every five years, with the objective of providing contact details of all Chest Physicians across the country. The last NCCP(I) Directory was published in 2016. We thank all members and fellows of NCCP(I) and request You to inform us in case of any change of residential, official or postal address, mobile number and E-mail ID in order for us to prepare the forthcoming Directory, for which You can fill up the Directory Entry Form in this Newsletter and send by post to the NCCP(I) secretariat address below (or download from our website **www.nccpindia.org** and send by E-mail to **sngaur9@gmail.com**).

We also welcome all to submit their plans for events and activities for the forthcoming year. In addition, we would like to ensure You are aware of all your NCCP(I) membership benefits , which include :

- Electronic Voting for Yearly Elections to NCCP(I) Governing Council through E-voting form sent to Your E-mail ID
- Subscription to Indian Journal of Chest Diseases and Allied Sciences (Quarterly issues)
- NCCP(I) National Directory of Chest Physicians (Every 5 years)
- Discounts in Registration for NCCP(I) E-Courses (CPMeC & IPeC)
- Discounts in Registration for participating at National Conferences (including NAPCON), International Conferences (Gulf-Thoracic and others), State Conferences and Workshops and other educational activities under the aegis of NCCP(I)
- Travel Grants for National & International Conferences
- Communications through E-mail and Invitation to attend NCCP(I) Annual General Body Meeting
- Access to NCCP(I) Newsletter – Lung Bulletin (Biennial issues starting from this year)

Should You need any assistance or have any queries regarding Your NCCP(I) Membership or Benefits, please feel free to contact us, our support is always available to help You.

COMMUNICATE WITH US

www.nccpindia.org

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(+91) 9811271916 , (+91) 9029429015

CLINICAL PEARLS IN RESPIRATORY MEDICINE
a publication of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

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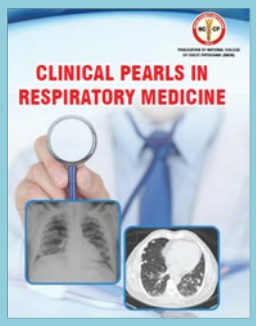

Dear Colleagues,

My observations and experience since last two decades as postgraduate teacher has led to writing a book. Primary aim of the book is to make the beginners in respiratory medicine to understand the basic concepts in a simple way. The book has three sections – interactive case discussions, discussion on chest images and multiple choice questions. One can easily understand the topics as I have tried to present the discussion in interesting way with clinical touch. One can self-assess using the discussions and MCQs.

I express my sincere gratitude to Professor Dr. S. N. Gaur, Honorary Secretary, NCCP(I) for suggesting me to write this book and constantly encouraging me in the process. My sincere gratitude to Professor Dr. P. D. Motiani, President, NCCP(I), for his guidance. I express my sincere gratitude to Dr. Nikhil Sarangdhar, Organizing Secretary, NAPCON 2020 for his help in bringing out this book. I am indebted to NCCP(I) for releasing the book during NAPCON 2020 from January 27-31, 2021. My sincere gratitude to my teacher Prof. Dr. V. K. Arora who has been a guide in my academic career.

I also express my gratitude to all who have contributed and helped me in compiling this book. My sincere thanks to all the Past and present post-graduates in our department who helped me in compiling this book, especially in collecting the images and patient details.

TEXTBOOK OF EMERGENCIES IN RESPIRATORY MEDICINE
an upcoming publication of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

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Former Professor and Head, Deptt. of Pulmonary Medicine, MKCG Medical College, Berhampur, Odisha
Past President, National College of Chest Physicians (India) (2015-16) & Indian Chest Society (2011-12)
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Dear Colleagues,

You will be happy to know that we are going to bring out soon a textbook on 'Emergencies in Respiratory Medicine' under the aegis of the National College of Chest Physicians (India) which will be published by Jaypee Brothers. This book is the first of its kind and an excellent step taken by the College in the field of Medical Education. It contains several chapters written by pioneering experts in the field of Respiratory Medicine of our vast country. An attempt has been made to cover each and every aspect of Respiratory Emergencies. Each chapter is meticulously written and edited with abstract, key words, introduction and description of the topic including information on diseases and conditions along with references. It's our immense pleasure to announce to this effect the work of compilation is under progress. We are sure it will be immensely useful as a source of academic and clinical knowledge for practitioners, teachers, post-graduate medical students and researchers in the field of Respiratory Medicine and other allied sciences which everyone would like to keep ready and have with them.

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)
NCCP(I) - TRAVEL GRANT FOR CONFERENCES

- The American Thoracic Society (ATS) and American College of Chest Physicians (ACCP) have agreed to the nomination of 2 delegates as representatives of the National College of Chest Physicians (India) to attend and participate in their annual conferences. These NCCP(I) nominees (Fellows only) will be provided complimentary registration and local accommodation by the Organizers. Travel has to be arranged by the nominees themselves.
- In addition, NCCP(I) is providing travel grant worth a fixed amount to its Members and Fellows for participation in national* and international conferences* as follows :
  - Rs. 20,000/- for national conferences in India*
  - Rs. 80,000/- for international conferences in U.S. & Canada
  - Rs. 60,000/- for international conferences in other countries
- Those NCCP(I) Fellows or Members interested, can apply to Hon. Secretary, NCCP(I), preferably before March each year (as ATS conference is usually held in May and ACCP annual meeting in October of the calendar year) for consideration providing details on a request letter as follows :

NCCP(I) TRAVEL GRANT CHECK-LIST

1.	Name, Dates and Venue of conference	☒
2.	Details of Participation in the concerned conference (Delegate/Faculty)	☒
3.	Letter of Abstract Acceptance or Invitation at the concerned conference	☒
4.	Applicant Particulars (Full name, age in years, gender, Postal address, E-mail ID & Mobile number for communication)	☒
5.	Present designation/affiliation	☒
6.	NCCP(I) Life Fellowship (LF) or Life Membership (LM) number	☒
7.	Number of NAPCONs attended in last 5 years	☒
8.	Number of total conferences (national + international) attended in last 5 years	☒
9.	Number of publications in last 5 years (attach list)	☒
10.	Forwarding letter preferably signed by Head of Department or Institution or a Fellow of NCCP(I)	☒
11.	Hard copies of receipts for reimbursement (Registration, Travel, Stay) with breakup of expenses	☒
12.	Disclaimer or statement whether availing travel grant/other monetary assistance from any other source for the same	☒

- The grant applications should be sent by post addressed to Hon. Secretary, NCCP(I) at the following address :
  Dr. S. N. Gaur, Gaur Clinic, 130-A, Patparganj Village, Delhi – 110091.
  Phone : +91- 9811271916 E-mail : sngaur9@gmail.com
- All applicant requests will be scrutinized by a Credential committee at NCCP(I) Governing Council meeting, for those selected, expenses as per norms will be reimbursed by postal cheque in the name of the applicant only.

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)
NCCP(I) - PROF. Dr. S. N. GAUR's YOUNG SCIENTIST AWARD

- The applicant should not be more than 35 years of age and should be the first author of the abstract submitted for Oral presentation at NAPCON mentioning selection for NCCP(I) – Prof. S. N. Gaur Young Scientist award.
- All abstracts forwarded by the NAPCON for NCCP(I) – Prof. S. N. Gaur Young Scientist Award will be scrutinized by an Academic Committee specially constituted by NCCP(I) for this purpose. A maximum of 9-10 abstracts will be selected for presentation in this award session and the presenters informed accordingly prior to the conference.
- All selected presenters will receive Rs. 5000/- as travel grant by cheque and a certificate of presentation, in addition to certificates and award adjudged for the First, Second and Third prizes.

**** For NAPCON, NCCP(I) - Prof. Dr. S. N. Gaur's Young Scientist Award is available for Young Scientists Only.***
NAPCON Registration is Discounted for All Life Members and Fellows of NCCP(I) and ICS.

POST-GRADUATE QUIZ IN RESPIRATORY DISEASES 2020 (VIRTUAL)
an academic initiative of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

For all medical students, continuing medical education (CME) programmes, seminars, updates, workshops and conferences form an integral part of their training apart from the bedside clinical teaching, ward rounds and lectures imparted at medical colleges or teaching institutions. Quiz competition comes as a refreshing change from all these academic activities to enhance and fine-tune their learning and it is something they look forward to with excitement and enthusiasm. To encourage and recognize the budding potential in our Chest Physicians of tomorrow, National College of Chest Physicians (India) undertook the initiative to conduct Post-graduate Quiz Competition in Respiratory diseases with the objective to promote scientific temper in PG students of Pulmonary medicine in India, state-wise as well as nationally.

Due to the situation caused by COVID-19 pandemic, with restrictions on travel and gathering, the NCCP(I) State PG Quiz in Respiratory diseases for 2020 was organised for the very first time, on a Virtual Quiz platform. To keep up the academic enthusiasm in times with the challenging scenario, it was decided to organise the PG Quiz virtually. A unique virtual platform for the quiz was designed and tested and after several trial runs, was finalised in December 2020.

The NCCP(I) State level post-graduate quiz was organised in 22 states (up from 15 states in 2019) virtually, keeping nationally renowned faculty in Pulmonary medicine as state PG quiz anchors. Before each state quiz, a trial run and mock demonstration with the Participants and Quiz Anchors was conducted, to ensure smooth and glitch-free conduction. The first two winners in order of merit in each state were awarded NCCP(I) prize certificate and prize money of Rs. 5000/- and Rs. 2500/- respectively, with a certificate of participation distributed to all participants. The NCCP(I) State PG quiz programme was a grand success, with record participation of 526 post-graduates from different states across the country, up from 290 post-graduates in the previous year.

To give an impetus to the scientific temper and encourage the qualifying participants at state level, National College of Chest Physicians (India) organised the All-India PG quiz competition in Respiratory diseases on a virtual platform at NAPCON 2020, the 22nd Joint National Conference of Pulmonary Diseases of the National College of Chest Physicians (India) and Indian Chest Society. Two winners in order of merit from each state quiz were invited to participate in the NCCP(I) All-India PG quiz at NAPCON 2020. Dr. Vishnu Sharma, Professor and Head, Department of Respiratory Medicine, A J Institute of Medical Sciences, Mangalore was invited to be the National Quiz Master along with Dr. Rajesh Venkitakrishnan, Professor and Head, Department of Pulmonary Medicine, Rajagiri Institute of Medical Sciences, Kochi as the Co-Quiz Master. A trial run was organised with the Quiz Masters and participants on 24th January 2020 to avoid technical glitches and ensure smooth and hassle-free conduction of the All-India PG Quiz programme.

The NCCP(I) All-India PG Quiz was convened virtually on Saturday, 30th January 2021 during NAPCON 2020 in Hall F from 3:00 p.m. to 5:00 p.m by Dr. Nikhil Sarangdhar. The quiz was inaugurated by Dr. P. D. Motiani (President), Dr. S. N. Gaur (Secretary) and Dr. S. K. Katiyar (Chairman, Academic Forum) from NCCP(I). After wishing all success to the participants, the quiz programme was outlined by the Quiz Masters, and coordination and functioning of audio-visuals and virtual platform were cross-checked and verified prior to commencement. As the quiz was entirely virtual, keeping in mind the technical issues involved, the qualifying post-graduates were encouraged to participate individually this time, rather than as a team. 64 single-best response type multiple choice questions, divided equally between both Quiz Masters were flashed on-screen in turn to all participants. After participant response, the answers were discussed at the end of each question, with the participant who provided the first correct answer being awarded the most points.

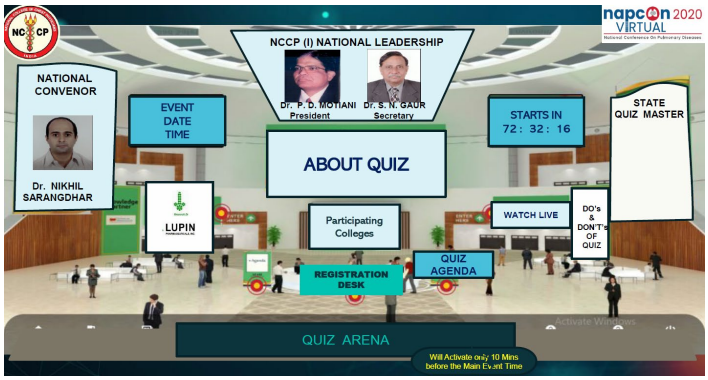
The first prize carried NCCP(I) prize certificate, award of Rs. 25000/- and plaque of *"D.B. Gupta budding talent award"* and was awarded to Dr. Suyash Singh Rathore from AIIMS Rishikesh, Uttarakhand who scored 13 points. The second prize carried NCCP(I) prize certificate and award of Rs. 15000/- and was awarded to Dr. Archit Krishna Manohar from Madurai medical college, Madurai, Tamil Nadu who scored 11 points. The third prize carried NCCP(I) prize certificate and award of Rs. 10000/- and was awarded to Dr. Amruta Peter from Netaji Subhas Chandra Bose medical college, Jabalpur, Madhya Pradesh who scored 7 points. All winners and participants were congratulated.

As a token of appreciation, a certificate of participation from NCCP(I) was awarded to all 40 PG students, with congratulations for their efforts and best wishes for their future. A special certificate of appreciation on behalf of NCCP(I) was awarded to Dr. Vishnu Sharma and Dr. Rajesh Venkitakrishnan in recognition of their efforts towards conducting the NCCP(I) All-India PG Quiz 2020 in a professional and transparent manner.

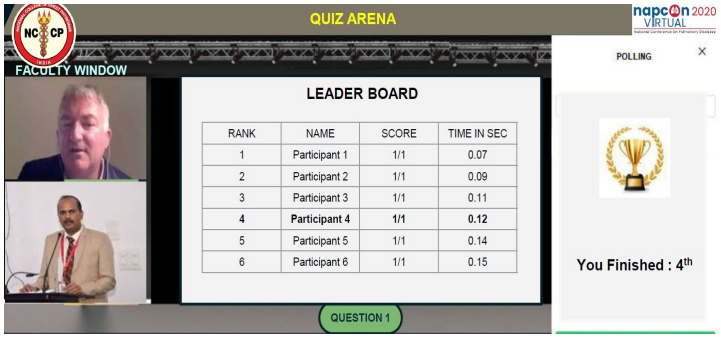
State(s)	PG Quiz Anchor(s)	Winners	
		Name	Institute
Andhra Pradesh and Telangana	Dr. Alladi Mohan	Dr. Kunal Waghray Dr. Allampati B Sree Sowmya	SVS medical college, Mahabubnagar Kurnool medical college, Kurnool
Bihar and Jharkhand	Dr. Saurabh Karmakar	Dr. Priya Sharma Dr. Sanket Joshi	AIIMS, Patna Himalayan institute of medical sciences, Patna
Delhi	Dr. Vivek Nangia	Dr. Vatsal Bhushan Gupta Dr. Rishi Kumar Mangal	Vallabhbhai Patel Chest institute, Delhi Sir Ganga Ram hospital, Delhi
Gujarat	Dr. Savita Jindal Dr. Amit Dedun Dr. Vishakha Kapadia	Dr. Khusboo Chahwala Dr. Richa Udhwani	GMERS medical college & hospital, Vadodara GMERS medical college & hospital, Vadodara
Haryana	Dr. Dhruva Chaudhry	Dr. Vishal Raj Dr. Ayush Pandey	PGIMS, Rohtak SGT medical college & hospital, Gurugram
Himachal Pradesh	Dr. Malay Sarkar	Dr. Aseem Sirkeck Dr. Anurag Tripathi	Indira Gandhi medical college, Shimla Indira Gandhi medical college, Shimla
Kashmir	Dr. Naveed Shah	Dr. Mir Shahnawaz Dr. Saurabh Ojha	Government medical college, Srinagar Government medical college, Srinagar
Karnataka	Dr. Shashi Bhushan	Dr. Ningappa Dr. Megha Leo	Sapthagiri institute of medical sciences, Bengaluru A.J. institute of medical sciences, Mangalore
Kerala	Dr. P. S. Shahjahan	Dr. Anand Vijay Dr. Aswathy G.	Rajagiri medical college & hospital, Kochi Cosmopolitan hospital, Thiruvananthapuram
Madhya Pradesh	Dr. Trinath Dash	Dr. Amruta Peter Dr. Pournami	NSCB medical college, Jabalpur NSCB medical college, Jabalpur
Chhatisgarh	Dr. Trinath Dash	Dr. Karthik Tipparapu Dr. Riju Sanjay Desai	J.L.N. hospital and research centre, Bhilai J.L.N. hospital and research centre, Bhilai
Maharashtra	Dr. Sushant Meshram	Dr. Sanket Agarwal Dr. Robin Choudhary	Government medical college, Nagpur Cardio-thoracic centre, AFMC Pune
Odisha	Dr. Narayan Mishra	Dr. Kinshuk Sarbhai Dr. Jeeshita Mariam Reddy	KIIMS Bhubaneshwar KIIMS Bhubaneshwar
Puducherry	Dr. S. Yuvarajan	Dr. Vinayak Nandhanan Dr. K. Prathaban	SMV medical college & hospital, Puducherry SMV medical college & hospital, Puducherry
Punjab	Dr. Vishal Chopra	Dr. Karan Sharma Dr. Amritpal Kaur	Government medical college, Patiala SGRD institute of medical sciences, Amritsar
Rajasthan	Dr. Rajendra Takhar	Dr. Sumit Kumar Jain Dr. Sethuraman M	SMS medical college, Jaipur RNT medical college, Udaipur
Tamil Nadu	Dr. V. Vinod Kumar	Dr. Archit Krishna Manohar Dr. Mathew Varghese	Madurai medical college, Madurai Christian medical college, Vellore
Uttar Pradesh	Dr. Surya Kant	Dr. Anil Maurya Dr. Shubham Jain	Dr. SPM civil hospital, Lucknow Rohilkhand medical college, Bareilly
Uttarakhand	Dr. Girish Sindhwani	Dr. Prateek Gupta Dr. Suyash Singh Rathore	Shri Mahant Indiresh hospital, Dehradun AIIMS, Dehradun
West Bengal	Dr. Shelley Shamim	Dr. Riksoam Chatterjee Dr. Soumyadeep Ghosh	IPGMER & SSKM medical college, Kolkata Medical college, Kolkata

PHOTO GALLERY OF NCCP(I) STATE AND ALL – INDIA PG QUIZ 2020

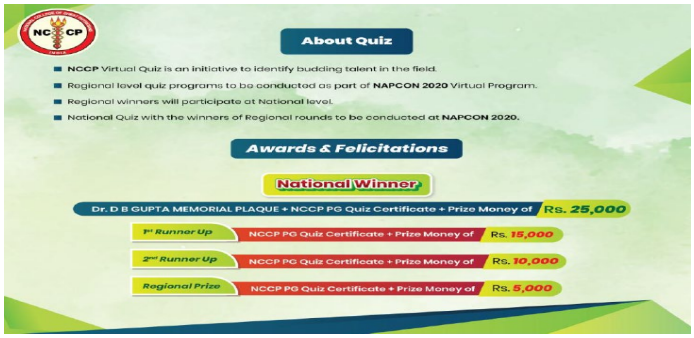
NCCP(I) Virtual PG Quiz Platform – Outer Fascia



NCCP(I) Virtual PG Quiz Platform – Lobby



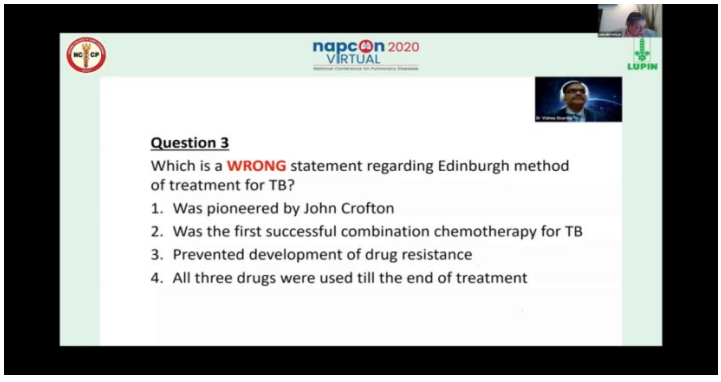
NCCP(I) Virtual PG Quiz Platform – Score and Ranking



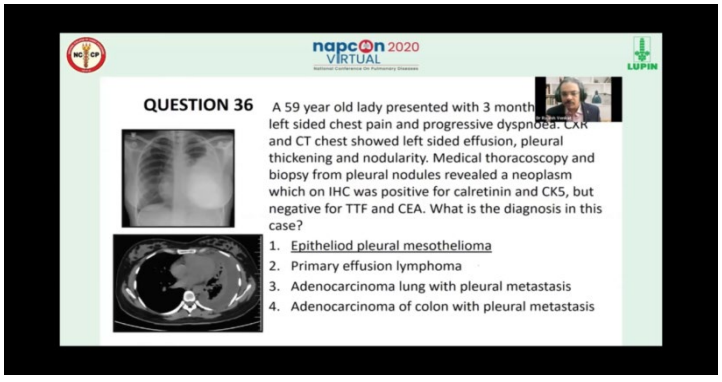
NCCP(I) Virtual PG Quiz Platform – Prize Notification

NCCP(I) All-India PG Quiz – Inauguration and Welcome

NCCP(I) All-India PG Quiz – Concluding Remarks



NCCP(I) All-India PG Quiz – Question



NCCP(I) All-India PG Quiz – Question

NCCP(I) All-India PG Quiz – Announcement of Prize Winners

How to Be a Good Quiz Master

Dr. Vishnu Sharma M.
Quiz Master, NCCP(I) All-India PG Quiz 2019 and 2020
Professor and Head, Department of Respiratory Medicine,
A. J. Institute of Medical Sciences and Research Centre, Kuntikana, Mangalore, Karnataka

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There is nothing as satisfying as preparing for and conducting a Quiz. People genuinely enjoy Good Quiz Masters. There are no definite guidelines on how to be a good quiz master. I have tried to compile a few points based on my experience as quiz master for more than a decade.

Who can be a Quiz Master ?

1. Quiz master should have enough experience. He/she should have participated in at least 5 to 10 quiz events before becoming a quiz master.
2. Quiz master should be an avid learner who can gather information from all sources.

What are the Basic Steps before conducting a Quiz ?

1. Get to know the quiz participants and audience because the questions framed should be relevant to them. Quiz master's students/close associates who are familiar with his/her questions should better be avoided as participants.
2. Get to know the time allotted and plan accordingly.
3. Come up with a topic and title.
4. Framing the questions in a quiz is the key. Questions with proper fundamentals where the participants can actually work out the answers are ideal rather than questions where answers can be given only by rote learning facts.
5. Incorporate each level of intelligence within the questions in the quiz so as to reach each and every type of learner to access knowledge, abilities, or skills.
6. Audio and video rounds enhance the creativity level and standard. Hence include these rounds whenever possible.
7. Keep an audience question after every round, to keep the audience also involved in the quiz.
8. Be sure about the rules and regulations for the quiz, the marking pattern, time allotted for each question/round and all the small details of each and every round before staring the quiz.
9. Try to distribute the difficulty of the questions evenly. All the easy questions and/or all difficult questions should not be placed together. Include a mix of easy questions and difficult questions in the content so the competitors can still be challenged and have fun. Having a variety of questions can also keep the competition interesting and engaging for any spectators in the room.
10. Always keep extra information about the answers; you never know when you might be contradicted.
11. Check beforehand whether the host / venue has the capacity for functioning audio-visual equipment, proper functioning buzzers etc or not before you include the audio-visual and buzzer rounds in your Quiz.
12. Explain the rules to the participants and make sure all participants understand the rules and regulations of the quiz.

Do's and Dont's during the Quiz :

1. Encourage all the participants and demonstrate the opportunity for growth
2. Encourage reflection and discussion from the audience
3. Have fun with explanations
4. Wear a smile and handle everything patiently
5. Never make others feel you are partial to some team

My Thoughts about Quiz :

Quiz is basically a form of mind sport, in which the players (as individuals or in teams) attempt to answer questions correctly. The word "Quiz" may have originated in student slang and it means to "test knowledge". Quiz is used in education to test knowledge, abilities or skills of individuals. Quiz during a conference with provision of scholarship to meritorious students always generates a lot of excitement, with all participating enthusiastically. A properly conducted quiz with academic focus helps to enhance post-graduate learning. It was a great honour for me to be invited by the National College of Chest Physicians (India) as the Quiz Master to conduct their All-India level quiz for PG students of respiratory medicine. The NCCP(I) All-India PG quiz programme since the last two years has been an academic success in achieving its objective of identifying young talent among the post-graduates, who are one day going to be the future of Pulmonary Medicine in our country.

My Experience of NCCP(I) PG Quiz 2020

Dr. Rajesh Venkitakrishnan
Co-Quiz Master, NCCP(I) All-India PG Quiz 2020
Senior Consultant and Head,
Department of Pulmonary Medicine, Rajagiri Hospital, Kochi, Kerala

E-mail : rajeshdhanya@rediffmail.com

It gives me immense pleasure to share my experiences of being the All-India (National level) Co-Quiz Master in the Post-Graduate Quiz in Respiratory Diseases organised by the National College of Chest Physicians (India) [NCCP(I)], the final round of which was conducted along with the spectacularly organised Virtual NAPCON 2020 on 30th January 2021.

NCCP(I) is the first and oldest professional organisation of pulmonologists of our country and being invited to be an anchor of their prestigious national level quiz competition is an honour and recognition. In this regard, I would like to express my sincere gratitude to the senior teachers and office bearers of NCCP(I), Prof. Dr. S. N. Gaur Sir and Prof. Dr. S. K. Katiyar Sir for placing trust in me and alloting me the responsibility. Dr Nikhil Sarangdhar has been the live wire behind Virtual NAPCON 2020 and the Post-graduate Quiz, and has been my guide and leading lamp into the smooth conduct of the quiz. The initial state level quiz competitions were conducted by reputed teachers attached to medical colleges or teaching institutes in their respective states and the top two performers, in order of merit were invited to participate in the national level PG Quiz competition.

I had the good fortune of having Prof. Dr. Vishnu Sharma as the Chief Quiz Master, a seasoned campaigner and one of the most popular figures in national level pulmonology post- graduate competitions. He was prompt to advise me on the topic distribution of question setting and the standard of questions to be followed. I could turn to him at any point if any doubt or challenge rose, and he would ensure that the issue is solved in a matter of minutes. Together, we have striven to ensure that all relevant aspects and subjects of pulmonology are covered and given due representation. We attempted to set questions of varying standards from relatively easy puzzles to the hard-to-crack ones, which will bring out the best in the budding scholars. We sincerely hope that the All-India Quiz competition was thoroughly enjoyed by the participants and Virtual NAPCON delegates alike.

I understand that the Quiz program was made possible by academic support from Lupin Respira, who provided the technical platform and ensured periodic communication with the post graduate students. The platform, barring a few initial challenges, ensured a smooth conduct of the quiz at the end and the efforts of the Lupin team are also to be applauded.

I sincerely congratulate all the post graduate residents who made it to the final round and performed brilliantly, with additional claps for the winners. In a competition of this nature, it may not be possible for everyone to occupy the top spot and the judges are forced to select the best performers of the day. If we have disappointed anyone we would like to clarify that it was purely unintentional. As the saying goes, it is more important to take part than to win.

Before concluding, I would once again like to congratulate the efforts of Dr. Nikhil Sarangdhar, the mastermind behind the NCCP(I) PG quiz who has ensured smooth conduct from grass root level to the final moment. He has been a perfectionist over the years and we all owe a lot to him for the success of the post-graduate quiz event. From a personal perspective, it has been extremely gratifying for me to be associated with NCCP(I) Post-graduate Quiz in Respiratory Diseases 2020 and I look forward to participating in academic events organised in the coming years too.

NAPCON
NATIONAL CONFERENCE OF PULMONARY DISEASES
Joint National Conference of
NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)
and
INDIAN CHEST SOCIETY

The National College of Chest Physicians (India) organized several conferences since it was formed. The first conference of NCCP(I) (then IACD) was hosted in 1960 at New Delhi jointly with the Association of Physicians of India and other specialist organisations. Subsequent annual conferences were also held jointly with the Association of Physicians of India till 1963, in which year the Association sponsored the 8th International Congress on Chest Diseases in New Delhi. The following year, the Association held its fourth annual conference independently at New Delhi to which the President of the Royal College of Physicians of Edinburgh was a special invitee and guest of honour. In 1974, it held its annual conference jointly with the Tuberculosis Association of India.

Since 1989, NCCP(I) organised its annual conferences, called NACCON (National Chest Conference). These conferences were very successful and popular and were chaired by the then Presidents of NCCP(I). The Indian Chest Society (ICS) was also hosting its annual national conference, called NCRD (National Congress on Respiratory Diseases), also very successful and popular which were chaired by the President of ICS. Keeping in mind the greater interest of the Pulmonology fraternity of our country, the need to have a joint national conference of both NCCP(I) and ICS, the two largest national associations of Pulmonary Medicine was felt. After several positive negotiations and meetings spread over almost 8 years, the President, Secretary and Governing Bodies of both NCCP (I) and ICS, evolved a consensus to conduct their joint national conference together. From 1999, the NCCP(I) with ICS is having Joint National Conference on Pulmonary Diseases, called NAPCON. The guidelines for organising NAPCON were finalized to assist the organizers and also to have uniformity in organization and maintain a high academic standard of the scientific programme of NAPCON. NCCP(I) and ICS alternatingly select the venue and organisers of NAPCON each year and a similar sequence is followed for selection of Chairperson of the Scientific Committee, which consists of equal number of members from both associations and the organising committee. To promote national integration, each year NAPCON is hosted at a different city and has been organised in turn in the north, south, east and western regions of our country, truly reflecting a pan-Indian character. The NAPCON logo shows two hands representing both NCCP(I) and ICS working together in harmony.

NAPCON as a joint academic venture of NCCP (I) and ICS has been a grand success right from the beginning, providing opportunity to every person in the specialty of Pulmonary Medicine to come together under one roof to achieve the maximum scientific benefit. NAPCON has been attended by eminent faculty from the American Thoracic Society (ATS), American College of Chest Physicians (ACCP), European Respiratory Society (ERS), Asia Pacific Society of Respirology (APSR) and other Chest Specialists from abroad and from neighbouring Asian countries. The scientific programmes of NAPCONs are also state-of-the-art and widely acclaimed internationally. Not only Chest Physicians but also Physicians, Critical care specialists, Radiologists, Infectious disease specialists, Microbiologists and Pathologists, Cardiologists and Thoracic Surgeons and learned faculties from other allied specialties are invited to deliver guest lectures or participate in debates, panel discussions, and other symposia to enrich the diversity and academic content of the scientific programme.

The scientific programme covers a plethora of topics on different aspects of respiratory diseases and other allied sciences including critical care, pneumonia, tuberculosis, viral and other respiratory infections, diffuse lung diseases, asthma, COPD, interstitial lung diseases, sleep disorders, cardio-thoracic surgery, lung cancer, bronchoscopy, thoracoscopy and other thoracic interventions, pleural diseases, pulmonary vascular disorders, pediatric pulmonology, respiratory allergy and immunology, environmental and occupational problems, pulmonary imaging, sports medicine and rehabilitation apart from several other topics to constitute a unique academic feast.
Apart from the much-awaited scientific programme, delegates are also given the opportunity to participate in several workshops on a wide variety of topics like pulmonary function tests, imaging, research methods and scientific paper writing, critical care, mechanical ventilation, bronchoscopy and interventional pulmonology, allergy, sleep disorders, interstitial lung diseases, tuberculosis and others to refine their technical knowledge and skills. Satellite symposia and free paper oral and poster presentations add to the academic flavour. The Young budding Chest Physicians and Post-graduates eagerly look forward to the opportunity to present their original research work and more than 700 different abstracts are presented at NAPCON year after year. NAPCON is truly a complete scientific and cultural feast, providing opportunity for many pulmonologists and doctors of other specialties of all ages to meet, interact and have discussion with each other to share their knowledge and experiences to evolve strategies for better management of respiratory diseases.

Right since its inception, NAPCON has grown from strength to strength each year to become one of the largest conferences of Pulmonary diseases in Asia and globally with attendance of nearly 3000 delegates annually. NAPCON is a unique success story in itself, a testimony of unity, strength and cooperation between NCCP(I) and ICS and has evolved into a much sought-after "Brand name" and "Status symbol" popular amongst the Chest Physicians and Post-Graduates in India and abroad.

All NAPCONs till date were a grand success, appreciated by members and fellows of both NCCP(I) and ICS, faculty, delegates and post-graduate students, as well as the foreign faculty and delegates. Credit for this success goes to team work from NCCP(I) and ICS, the Organising Committee and the Scientific Committee for working hard in tandem to ensure fabulous conferences of high repute which are appreciated and acclaimed internationally. We are confident the same spirit will continue, year after year, as we look forward to greater participation as well as better conferences in the future.

NAPCONs FROM 1999 ONWARDS

Sr. No.	YEAR	VENUE	ORGANISING CHAIRMAN	ORGANISING SECRETARY
1.	1999	Delhi		Dr. J. C. Suri
2.	2000	Kanpur		Dr. S. K. Katiyar
3.	2001	Mumbai	Dr. J. C. Kothari	Dr. Rohini Chowgule
4.	2002	Jaipur	Dr. T. N. Sharma	Dr. N. K. Jain
5.	2003	Coimbatore	Dr. T. K. Moinudeen	Dr. T. Mohan Kumar
6.	2004	Ahmedabad	Dr. Gautam Bhagat	Dr. Rajesh Solanki
7.	2005	Kolkata	Dr. A. K. Ghosh	Dr. A. G. Ghoshal
8.	2006	Nagpur		Dr. B. O. Tayade
9.	2007	Chandigarh	Dr. S. K. Jindal	Dr. Dheeraj Gupta
10.	2008	Lucknow		Dr. Rajendra Prasad
11.	2009	Calicut		Dr. C. Ravindran
12.	2010	Jodhpur	Dr. P. D. Motiani	Dr. K. C. Agarwal
13.	2011	Delhi	Dr. V. K. Vijayan	Dr. Raj Kumar
14.	2012	Bhubaneshwar	Dr. N. K. Gacchayat	Dr. Narayan Mishra
15.	2013	Chennai	Dr. Vijayalakshmi Thanasekaraan	Dr. B. Rajagopalan
16.	2014	Agra	Dr. A. S. Sachan	Dr. Rakesh Bhargava Dr. Santosh Kumar
17.	2015	Jaipur	Dr. N. K. Jain	Dr. Virendra Singh
18.	2016	Mumbai	Dr. K. C. Mohanty	Dr. Agam Vora Dr. Nikhil Sarangdhar
19.	2017	Kolkata	Dr. A. G. Ghoshal	Dr. Dhrubajyoti Roy Dr. Raja Dhar
20.	2018	Ahmedabad	Dr. Rajesh Solanki	Dr. Raj Bhagat Dr. Tushar Patel
21.	2019	Kochi	Dr. C. Ravindran	Dr. Rajesh Venkat
22.	2020	Virtual	Dr. S. N. Gaur	Dr. Nikhil Sarangdhar
23.	2021	Varanasi	Dr. J. K. Samaria	Dr. Kumar Utsav Dr. Mohit Bhatia
24.	2022	Udaipur	Dr. S. K. Luhadia	Dr. Mahendra Kumar Dr. Atul Luhadia

napcon 2020 VIRTUAL
National Conference on Pulmonary Diseases

27th – 31st January, 2021

PREPARING TOGETHER FOR A BETTER FUTURE

CONFERENCE REPORT OF VIRTUAL NAPCON 2020

Dear Colleagues,

22nd NAPCON 2020, the 22nd Joint National Conference of Pulmonary Diseases of the National College of Chest Physicians (India) and Indian Chest Society, was organized for the very first time as a virtual conference due to the prevailing situation caused by COVID-19. The virtual conclave was planned as a five-day event from 27th to 31st January 2021 under the leadership of Dr. S. N. Gaur as Organising Chairman and Dr. Nikhil Sarangdhar as Organising Secretary. Dr. S. K. Katiyar was nominated as the Chairman, Scientific Committee and entrusted with the task of drafting a state-of-the-art scientific programme for the virtual conclave.

Though time was short, having less than 5 months to go, the Organising Committee with the support and goodwill of the national leadership of NCCP(I) and ICS began preparations in right earnest. The theme " *Preparing Together for a Better Future* " was selected for virtual NAPCON 2020, with the objective to design a spectacular scientific and workshop programme, rich in academic content, exceptional in diversity and expertise of faculty and designed to change the perspective of day-to-day-clinical practice in the field of Pulmonary Medicine in this era of COVID-19. The first announcement brochure was released on 8th October and the website with online registration became operational on 10th October 2020. NAPCON 2020 website became highly popular within a short span of time, recording more than 10000 visits within two months and subsequently social media presence with pages on Facebook and Linked In also became operational. A sponsor brochure for industry participation was released on 29th October and a final brochure with complete scientific and workshop programmes was released on 28th December 2020.

Though organised differently, for the very first time as an entirely virtual conference, the response to NAPCON 2020 from the pulmonary fraternity and post-graduates was unexpected and overwhelming. A total of 4321 delegates registered for the conference. 1002 abstracts were submitted for presentation at NAPCON 2020, out of which 9 were selected for Oral presentation in the NCCP(I) - Prof. Dr. S. N. Gaur Young Scientist Award, 8 for ICS - Dr. J. C. Kothari Young Scientist Award and 350 for twelve different categories of NAPCON 2020 Award (Oral Paper) sessions, and the remaining 635 on display as E-Posters for NAPCON 2020 Award (Poster) in the Virtual E-Poster Gallery. Competitions like the NCCP(I) Post-Graduate Quiz and Talent Hunt were organised under the banner of NAPCON 2020 for delegates and post-graduates to encourage participation in academic as well as extra-curricular activities.

A unique 3-D virtual platform was designed under supervision of Organising Committee for virtual NAPCON 2020 after four months of preparation and demonstration which went online just prior to conference commencement. The platform had several new features such as a virtual convention centre entry and red-carpet walkthrough, separate lobby for conference

and workshop, 7 halls for the scientific programme and free papers, E-Poster gallery with separate displays for posters categorized into twelve different categories of respiratory diseases, Virtual Delegate E-Kit, entertainment zone, networking lounge, and exhibition. The attractive design, layout and novel features of the virtual platform were highly appreciated by all national and overseas delegates, faculty and post-graduates alike. The Virtual Delegate E-Kit incorporated the NAPCON E-Souvenir as a digital flipbook with sound, NCCP(I) text book on Clinical Pearls in Respiratory Medicine for the post-graduates, membership benefits and enrolment forms of both NCCP(I) and ICS, NCCP(I) Newsletter Lung Bulletin based on Pulmonary function tests, ICS Newsletter Respire and other publications of academic value. An entertainment zone with more than 370 online games provided opportunity for relaxation and refreshment from time to time. A delegate-cum-snack kit was dispatched personally by courier on a first-come-first-served basis to the address of registered delegates .

A total of nine pre-conference virtual workshops under the leadership of workshop Directors on different topics like Allergy and Immunotherapy (by Dr. Raj Kumar), Thoracic Imaging (by Dr. Bhavin Jankharia), Pulmonary function tests (by Dr. Mohan Kumar Thekkinkattil), Respiratory failure and assisted ventilation (by Dr. Dhruva Chaudhry), Bronchoscopy (by Dr. Rajesh Chawla), Thoracoscopy (by Dr. Rakesh Chawla), Advanced Sleep medicine (by Dr. Vikram Sarbhai), Interstitial lung diseases and Lung transplantation (by Dr. Deepak Talwar and Dr. Apar Jindal respectively) and a new workshop on Objective structured clinical examination (by Dr. Mansi Gupta and Dr. Pranav Ish) were systematically planned by the Organising committee, with support from the Scientific and Workshop committees. Dr. Nasser Yusuf in his capacity as Convenor, Workshop committee ensured smooth coordination between workshop directors and faculty for glitch-free conduction of the entire workshop programme.

NAPCON 2020 began with an auspicious start on Wednesday, 27th January 2021 with the nine pre-conference workshops well attended by a total of 860 delegates. The conclave was virtually inaugurated on Wednesday, 27th January 2021 at the hands of our Chief Guest Hon'ble Dr. Harsh Vardhan Ji , Union Minister for Health and Family Welfare, Science and Technology and Earth Sciences, Government of India and our Guest of Honor Hon'ble Dr. Jitendra Singh Ji, Minister of State for North-East region, Prime Minister's Office, Ministry of Personnel, Public Grievances and Pensions , Department of Atomic Energy and Space, Government of India, who also released the NAPCON 2020 E - Souvenir and other conference publications in the presence of Dr. S. N. Gaur, Organising Chairman, NAPCON 2020 and Secretary, NCCP(I), Dr. Nikhil Sarangdhar, Organising Secretary, NAPCON 2020, Dr. P. D. Motiani, President, NCCP(I), Dr. D. J. Christopher, President, ICS, Dr. Rajesh Swarnakar, Secretary, ICS and Dr. S. K. Katiyar, Chairman, Scientific Committee, NAPCON 2020. The lifetime achievement awardees Dr. Rajendra Prasad of NCCP(I) and Dr. V. K. Arora, Dr. Mohammed Sabir and Dr. Surender Kashyap of ICS and the oration awardees Dr. Surender Kashyap, Dr. Manoj Goel, Dr. Nikhil Sarangdhar and Dr. Hari Mohan Kansal of NCCP(I) and Dr. Sudhir Chaudhri, Dr. Raj Kumar, Dr. Balamugesh Thanmugam and Dr. Salil Bhargava of ICS were also felicitated during the inaugural ceremony which was virtually attended by 642 delegates.

An extensive state-of-the-art scientific programme for NAPCON 2020 was drafted under the dynamic leadership of Dr. S. K. Katiyar, Chairman, Scientific Committee, with inputs from other members of the scientific committee and included participation of 460 national and 119 international faculty. For the very first time, 19 international Chest associations were invited to design symposia on specific topics of interest and depute their senior faculty members to participate in the scientific deliberations. The Asian-Pacific Society of Respirology designed a symposium on COVID-19 in the Asia-Pacific and deputed faculty members from 9 societies including the Japan Respiratory Society, Thoracic Society of Australia and New Zealand, Taiwan Society of Pulmonary and Critical Care Medicine, Indonesian Society of Respirology, Malaysian Thoracic Society, Singapore Thoracic Society, Hong Kong Thoracic Society, Mongolian Respiratory Society and the Sri Lanka College of Pulmonologists. Symposia were also designed by the American Thoracic Society, American College of Chest Physicians, European Respiratory Society, Cleveland Clinic, International Union against Tuberculosis and Lung Diseases (The Union), Turkish Thoracic Society, Japan Anti-TB Association, Bangladesh Primary Care Respiratory Society and Nepalese Respiratory Society and approved by the Scientific Committee. The scientific programme of NAPCON 2020 commenced on Thursday, 28th January till Sunday, 31st January 2021 from 9 a.m. to 6:30 p.m. on all days and witnessed record attendance of 3548 delegates (11071 logins) on 28th January, 2658 delegates (9320 logins) on 29th January, 2588 delegates (7752 logins) on 30th January and 1961 delegates (5833 logins) on 31st January 2021. The NCCP (I) and ICS orations also witnessed record attendance of 469 and 426 attendees respectively. The best attended session in the scientific programme was the APSR symposium on COVID-19 on 28th January 2021 with 468 attendees.

An All-India PG Quiz in Respiratory Diseases for post-graduates, an academic initiative of NCCP(I), was convened virtually by Dr. Nikhil Sarangdhar on 30th January 2021, along with Dr. Vishnu Sharma as the Quiz Master and Dr. Rajesh Venkitakrishnan as the Co-Quiz Master. 526 post-graduates had participated in the state-level NCCP(I) PG Quiz, organised in 22 different states of the country, and from these, 40 post-graduates were shortlisted in order of merit to participate in the All-India NCCP(I) PG Quiz at NAPCON 2020, which was inaugurated by Dr. S. N. Gaur, Dr. P. D. Motiani and Dr. S. K. Katiyar from NCCP(I). First, second and third prizes, each with a certificate and cash award were awarded to the first three post-graduates in order of merit, along with a certificate of appreciation to all participants.

Virtual Cultural programmes were broadcast on 28th and 30th January 2021 during the evening. One of the cultural programmes, compiled by the Academy of Pulmonary and Critical Care medicine under the leadership of Dr. Jayaprakash B. had participation from medical college chest faculty and was very much appreciated by the delegates. As per tradition, NAPCON 2020 also hosted the virtual Governing Council and Annual General Body meetings of National College of Chest Physicians (India) and Indian Chest Society. The highly successful and much-appreciated scientific deliberations of the conference concluded with the valedictory function on Sunday, 31st January 2021.

22nd NAPCON 2020 surpassed all records of previous conferences with the largest number of registered delegates, attendees, international participation and abstracts submitted for presentation at NAPCON, setting a benchmark for other virtual conferences to follow and creating a milestone for medical conferences in the near future. We humbly thank and acknowledge all delegates, faculty members and our colleagues for their goodwill and participation at the conference, which helped greatly towards making the first-ever Virtual NAPCON a grand success.

The theme of NAPCON 2020, " *Preparing Together for a Better Future* ", reflects not only our response to keep up with contemporary health dynamics but also the need to remain vigilant continuously and stay safe always. We acknowledge the crucial roles, that we, as pulmonologists, have to play in the dissemination of knowledge for better standards of healthcare, as well as the advocacy of COVID-19, pneumococcal and influenza vaccination. The scientific deliberations of NAPCON 2020 will continue to guide us to overcome the COVID-19 pandemic through education, research, scientific enlightenment, technical skills, advocacy, and social mobilization.

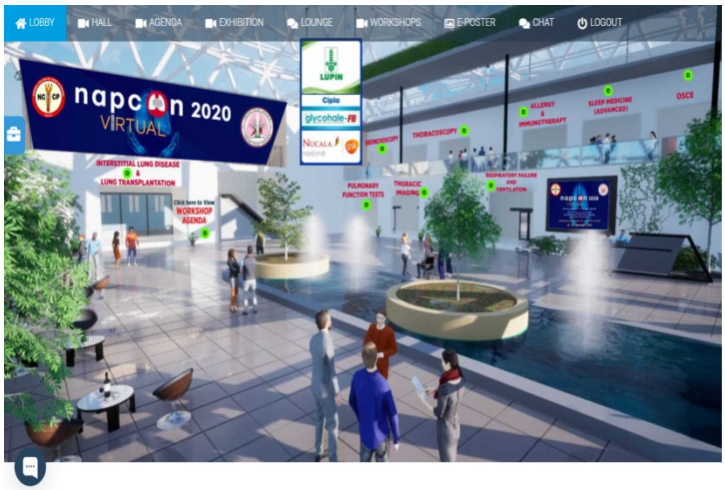
Prof. Dr. S. N. Gaur
Organising Chairman, NAPCON 2020

Dr. Nikhil Sarangdhar
Organising Secretary, NAPCON 2020

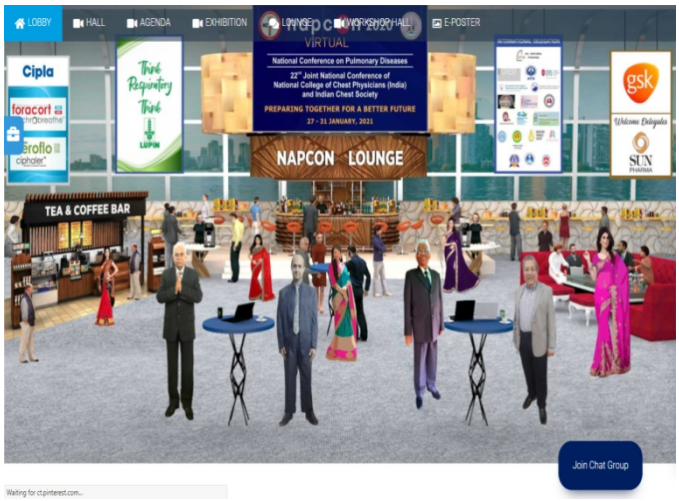
GLIMPSES OF VIRTUAL NAPCON 2020

VIRTUAL CONVENTION CENTRE ENTRY AND RED-CARPET WALKTHROUGH

CONFERENCE LOBBY



WORKSHOP LOBBY



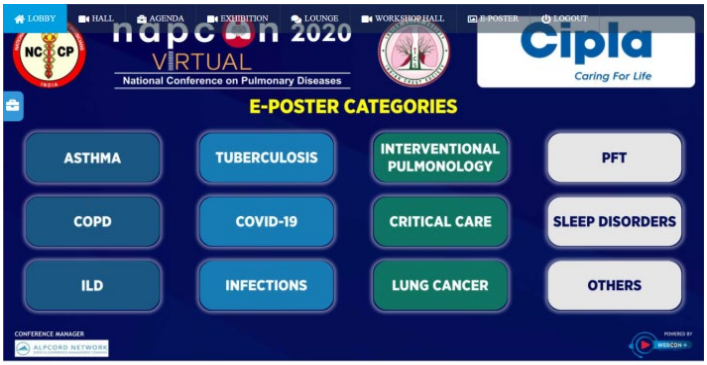
LOUNGE





INAUGURAL CEREMONY

Dignitaries from Left to Right : Dr. S. N. Gaur (Organising Chairman, NAPCON 2020 & Secretary, NCCP[I]), Dr. Nikhil Sarangdhar (Organising Secretary, NAPCON 2020), Dr. P. D. Motiani (President, NCCP[I]), Dr. D. J. Christopher (President, ICS), Dr. Rajesh Swarnakar (Secretary, ICS), Dr. S. K. Katiyar (Chairman, Scientific Committee, NAPCON 2020), Dr. Jitendra Singh (Guest of Honor, Hon'ble Union Minister of State for North-East region, Prime Minister's Office, Ministry of Personnel, Public Grievances and Pensions , Department of Atomic Energy and Space, Government of India)



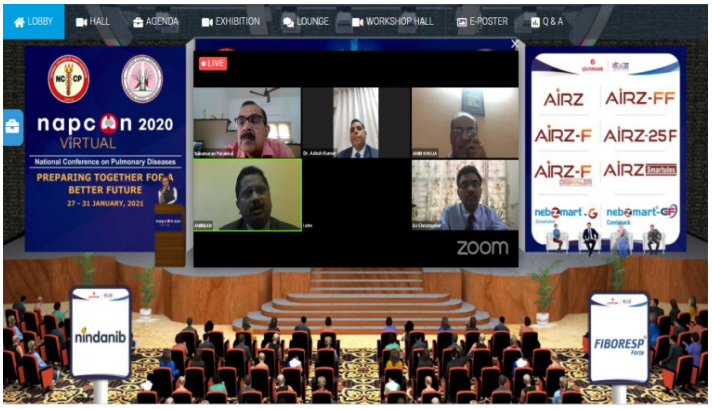
E – POSTER GALLERY

EXHIBITION

NCCP(I) – PROF. Dr. S. N. GAUR YOUNG SCIENTIST AWARD

ICS – Dr. J. C. KOTHARI YOUNG SCIENTIST AWARD

APSR INTERNATIONAL SYMPOSIUM ON COVID-19



NATIONAL SYMPOSIUM

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates All Awardees

Dr. Rajendra Prasad
awarded
NCCP(I) – Prof. M. M. Singh Lifetime Achievement Award

Dr. V. K. Arora
awarded
ICS – Lifetime Achievement Award

Dr. Surender Kashyap
awarded
ICS – Lifetime Achievement Award

Dr. M. Sabir
awarded
ICS – Lifetime Achievement Award

Dr. Surender Kashyap
awarded
NCCP(I) – Prof. Dr. Raman Vishwanathan Memorial Chest Oration

Dr. Manoj Goel
awarded
NCCP(I) – Prof. Dr. A. S. Paintal - Prof. Dr. R. C. Jain Memorial Chest Oration

Dr. Nikhil Sarangdhar
awarded
NCCP(I) – Prof. Dr. P. S. Shankar - Prof. Dr. K. C. Mohanty Chest Oration

Dr. Hari Mohan Kansal
awarded
NCCP(I) – Prof. Dr. S. K. Jain - Prof. Dr. S. K. Katiyar Chest Oration

Dr. Sudhir Chaudhri
awarded
ICS – Dr. S. N. Tripathy Presidential Oration Award

Dr. Balamugesh T
awarded
ICS – Dr. K. J. R. Murthy Oration Award

Dr. Raj Kumar
awarded
ICS – Dr. C. V. Ramakrishnan Oration Award

Dr. Salil Bhargava
awarded
ICS – Dr. O. A. Sarma Oration Award

NAPCON 2020
RESULTS OF ORAL AND E–POSTER PRESENTATIONS

Congratulations to All Awardees

NCCP(I) – PROF. Dr. S. N. GAUR's YOUNG SCIENTIST AWARD

THURSDAY 28-01-2021 11:15 – 13:00

RESULTS	
1ST	SHONA ARLIN CHRISTOPHER
2ND	SHARAD BAGRI
3RD	AHMED SAFWAN

ICS – Dr. J. C. KOTHARI YOUNG SCIENTIST AWARD

FRIDAY 29-01-2021 11:30 – 13:15

RESULTS	
1ST	TARANG KULKARNI
2ND	SHONA ARLIN CHRISTOPHER
3RD	ANAND VIJAY

NAPCON 2020 AWARD ORAL

WEDNESDAY 27-01-2021			
TIME	**SESSION**	**RESULTS**	
9:30 - 11:30	ASTHMA (RESEARCH PAPERS)	1ST	PRASHAMSA CHELIMALLA
		2ND	LUBAIBA K
		3RD	MIDHUN MOHAN K
11:00 - 12:30	COPD (RESEARCH PAPERS) - I	1ST	ALEKYA KALLA
		2ND	ANIKET MONDAL
		3RD	DEESHA GHORPADE
12:30 - 13:45	MISCELLANEOUS (RESEARCH PAPERS) - I	1ST	AKHIL BABU C
		2ND	AJIT KUMAR J SOUNDARIYAN
		3RD	MONICA BANSAL DEEP KOTHARI
13:45 - 15:45	LUNG CANCER (CASE REPORTS) - I	1ST	JITENDRA SINGH
		2ND	ASHA U
		3RD	BENJAMIN WILLIAMS
15:45 - 18:00	TUBERCULOSIS (MOLECULAR DIAGNOSTICS - BEST PAPER)	1ST	VIPUL KUMAR
		2ND	PAULAMI PALCHOWDHURY
		3RD	PIYALI SARKAR RAJAT AGARWAL
THURSDAY 28-01-2021			
TIME	**SESSION**	**RESULTS**	
9:00 - 10:15	INFECTIONS (CASE REPORTS)	1ST	ANEESHA KONDURU
		2ND	SINDHU RAVALI
		3RD	ANAND V
10:15 - 11:30	INTERVENTIONAL PULMONOLOGY (RESEARCH PAPERS) - I	1ST	MATHEW VARGHESE
		2ND	PAPIA MONDAL ASHA NAIR
		3RD	M BRIGHTON KRUTESH TRIPATHI
11:30 - 13:15	TUBERCULOSIS (RESEARCH PAPERS) - I	1ST	ANANTHU JOSEPH
		2ND	ANISH
		3RD	M RAJEEV NAIK
13:15 - 15:15	COVID-19 (RESEARCH PAPERS) - I	1ST	JYOTHI GEETHA MOHANKUMAR
		2ND	ANERI PAREKH
		3RD	JAYAVIGNESH J
15:15 - 17:15	CRITICAL CARE (RESEARCH PAPERS)	1ST	LOVELEEN SHARMA
		2ND	VAIBHAV PADASHETTI
		3RD	RISHNA RAVINDRAN SHONA ARLIN CHRISTOPHER
17:15 - 18:15	ILD (RESEARCH PAPERS)	1ST	ANCY ELSA THOMAS
		2ND	ASHISH PRAKASH SUTHIRTH VAIDYA
		3RD	BELINDA ANET PREETI VIDYASAGAR

FRIDAY 29-01-2021

TIME	SESSION	RESULTS	
9:00 - 10:15	OTHERS (RESEARCH PAPERS) - I	1ST	S CHANDRASHEKHAR
		2ND	SEJAL RADIA
		3RD	ANAS S
10:15 - 11:30	INTERVENTIONAL PULMONOLOGY (RESEARCH PAPERS) - II	1ST	UMANG SHAH
		2ND	SAPAN KUMAR
		3RD	SUVARNA KALLI
11:30 - 13:30	COVID-19 (RESEARCH PAPERS) - II	1ST	MADHURI KALYANI K
		2ND	R ANAND MYTHIRI G
		3RD	POOJITHA BAI MERIN THOMAS
13:30 - 15:30	LUNG CANCER (CASE REPORTS) - II	1ST	PRONOY SEN
		2ND	N BHANUTHEJA
		3RD	RAMYA PRIYA SANGAVI R
15:30 - 16:30	OTHERS (CASE REPORTS) - I	1ST	ARCHIT KRISHNA MANOHAR
		2ND	ASHA U
		3RD	ABIRAMI DHARMALINGAM
16:30 - 17:30	OTHERS (CASE REPORTS) - II	1ST	UJWAL JAIN
		2ND	S PUGAZHENDI
		3RD	MOHAMMED ABDUL BASITH
17:30 - 18:15	MISCELLANEOUS (CASE REPORTS)	1ST	RITA GOJIYA
		2ND	SHRADDHA TEWARI
		3RD	ANVESHA TUMMALA

SATURDAY 30-01-2021

TIME	SESSION	RESULTS	
9:00 - 10:15	OTHERS - KARTAGENER'S SYNDROME (BEST CASE REPORTS)	1ST	INDRANIL BANERJEE
		2ND	D SHIVA KUMAR NAYAK
		3RD	ORUGANTI SINDHUJA
10:15 - 11:45	COVID-19 (RESEARCH PAPERS) - III	1ST	TEJAS SURI
		2ND	SAGAR PANCHAL
		3RD	SHAMA SHARMA SHILPA K V
11:45 - 13:15	INFECTIONS (RESEARCH PAPERS)	1ST	RISHAB RAMPRADEEP
		2ND	SAYANI BOSE
		3RD	G LOHITHA SRI GAURI
13:15 - 14:30	PFT (RESEARCH PAPERS)	1ST	VISHAL MORE
		2ND	MANU SIVA
		3RD	NAYEEM KADIR VARDHELLY RAMESH
17:15 - 18:15	LUNG CANCER (RESEARCH PAPERS)	1ST	PRIYA N
		2ND	SUTHIRTH VAIDYA
		3RD	APARNA SURESH
18:15 - 19:30	CONSULTANTS (BEST PAPERS)	1ST	RAJA DHAR
		2ND	DEEPAK TALWAR
		3RD	RAJANI BHAT

SUNDAY 31-01-2021

TIME	SESSION	RESULTS	
9:00 - 10:15	SLEEP DISORDERS (RESEARCH PAPERS)	1ST	ANSHUL JAIN
		2ND	ASHA U JUVA KISHAN SRIKANTH
		3RD	RAHUL GHOSH
10:15 - 11:45	OTHERS - DEVELOPMENTAL ANOMALIES (BEST CASE REPORTS)	1ST	TEJAWAT KUSHAL KUMAR
		2ND	PRAKHAR SHARMA
		3RD	PRASHANTHI R KRUNAL THUMAR
11:45 - 13:00	INTERVENTIONAL PULMONOLOGY (CASE REPORTS)	1ST	AMUTHA PRIYA S M
		2ND	SHARON ARUNA CATHY C
		3RD	AVINASH DAL N A ARUN
13:00 - 14:15	COPD (RESEARCH PAPERS) - II	1ST	PRABHURAM J
		2ND	PRIYANKA SINGH
		3RD	PRATEEK GUPTA
14:15 - 16:15	TUBERCULOSIS (RESEARCH PAPERS) - II	1ST	SHILPA K V
		2ND	SHARAN KUMAR
		3RD	RICHU BOB KURIEN
16:15 - 18:15	TUBERCULOSIS (CASE REPORTS)	1ST	SIVASANKARI R
		2ND	APARNA SURESH
		3RD	RISHAB RAMPRADEEP
18:15 - 19:15	YOUNG CONSULTANTS (BEST PAPERS)	1ST	UMANG SHAH
		2ND	ARJUN KHANNA
		3RD	PRANAV ISH SAMEER ARBAT

EXTRA SESSION

(ORGANISED ON SPECIAL REQUEST BY THOSE WHO COULD NOT LOG IN ONLINE TO PRESENT THEIR ORAL PAPERS DURING THEIR SCHEDULED SESSIONS AT THE TIME OF THE VIRTUAL CONFERENCE)

SESSION	RESULTS	
MISCELLANEOUS (RESEARCH PAPERS) - II	1ST	CAROL HANNAH BABU
	2ND	KANDAVEL
	3RD	MONISHA ANANDHAN YADVENDRA SINGH

NAPCON 2020 AWARD
E–POSTER

SESSION	RESULTS	
ASTHMA (RESEARCH PAPERS)	1ST	RASHMI RANJAN DAS
	2ND	SAI RAMYA G
	3RD	VAISHALI NAIK
ASTHMA (CASE REPORTS)	1ST	AJEESH K P
	2ND	MUDRA KHARE
	3RD	ANKUR GUPTA
COPD (RESEARCH PAPERS) - I	1ST	LAVANYA S V
	2ND	NEETHU K
	3RD	EVELIN ROY HAADI NIZAR AHAMMED OMKAR PRASAD RATH
COPD (RESEARCH PAPERS) - II (21-34)	1ST	SONALI JADHAV
	2ND	RUCHIRA ROY
	3RD	SANDIP DAS
COPD (CASE REPORTS)	1ST	HEMALATHA DARSI
	2ND	ATHUL THULASI
	3RD	SREERAG VARRIOR
ILD (RESEARCH PAPERS)	1ST	KAUMUDI DEVI
	2ND	MONICA BANSAL MUNIZA BAI
	3RD	CHAITANYA KIRAN GARA SAMIKSHA KAMBLE
ILD (CASE REPORTS) - I (1-16)	1ST	BHUMIN PATEL
	2ND	MOHAMMED AFAQUE
	3RD	ATHUL THULASI
ILD (CASE REPORTS) - II (17-32)	1ST	RAMEES NAJEEB
	2ND	RIKSOAM CHATTERJEE
	3RD	SONAL GOYAL
TUBERCULOSIS (RESEARCH PAPERS)	1ST	JAGRUTI AHIR
	2ND	SRIKEERTHI S
	3RD	ACHAL SINGH SHABNA A
TUBERCULOSIS (CASE REPORTS) - I (1-17)	1ST	AMIT GOYAL
	2ND	ARULMURUGAN D
	3RD	AVANI RAJPUT
TUBERCULOSIS (CASE REPORTS) - II (18-34)	1ST	JITENDRA KUMAR CHOUDHARY
	2ND	KOVURI VENKATESH
	3RD	IJAS V I
TUBERCULOSIS (CASE REPORTS) - III (35-51)	1ST	UMA SHARMA
	2ND	SHRUTI NARAYAN GUDHANE
	3RD	S MADHAN
COVID-19 (RESEARCH PAPERS) - I (1-14)	1ST	JAYALAKSHMI T K
	2ND	CAROL HANNAH BABU
	3RD	JANNELA BHAVNARAYANA
COVID-19 (RESEARCH PAPERS) - II (15-28)	1ST	SAGAR PANCHAL
	2ND	MERIN THOMAS
	3RD	SAGAR BHAGAT

COVID-19 (RESEARCH PAPERS) - III (29-42)	1ST	SUTHIRTH VAIDYA
	2ND	SINDHU RAVALI
	3RD	VIJAY BABU R
COVID-19 (CASE REPORTS) - I (1-13)	1ST	ASHISH PRAKASH
	2ND	ABHIJEET LONSANE
	3RD	DINAKARAN UMASHANKAR
COVID-19 (CASE REPORTS) - II (14-26)	1ST	MIHIR GANGAKHEDKAR
	2ND	REVANTH KUMAR NAKKA
	3RD	RAMEES NAJEEB
INFECTIONS (RESEARCH PAPERS)	1ST	A J MAHENDRAN NISNA MEDAPPIL
	2ND	ARITRA GANGULY K SHYAMALA PRAGNYA
	3RD	ANIRBAN MONDAL P TANUJA SHIVAM PRIYADARSHI
INFECTIONS (CASE REPORTS) - I (1-16)	1ST	KARTHIKA PRASAD
	2ND	FEBI ANN ROY
	3RD	E RAJU
INFECTIONS (CASE REPORTS) - II (17-32)	1ST	VATSAL GUPTA
	2ND	SYED MUFTHAH
	3RD	SATHISH CHANDAR REDDY
INTERVENTIONAL PULMONOLOGY (RESEARCH PAPERS)	1ST	SHAFIN BABU
	2ND	UMANG SHAH
	3RD	KOVVADA ASWINI
INTERVENTIONAL PULMONOLOGY (CASE REPORTS)	1ST	BHUMIKA MADHAV
	2ND	MUTHULAKSHMI S
	3RD	ANAND RAJA
CRITICAL CARE (RESEARCH PAPERS)	1ST	ASHWINI NAIK
	2ND	SHIVAM PRIYADARSHI
	3RD	RICHIE GEORGE
CRITICAL CARE (CASE REPORTS)	1ST	KARTHIK K RAMYA PRIYA
	2ND	RUCHA SANE WANBOR SUNGOH
	3RD	ATHUL C ANGAJ KIRAN ASHOK BALANI S GOWTHAM
LUNG CANCER (RESEARCH PAPERS)	1ST	AJIT KUMAR SHRAVANI D
	2ND	B RAMYA KRISHNA JITENDRA KUMAR BAIRWA
	3RD	KAPIL TOMAR KARAN RAJ SINGHAL NAMAN AJWANI
LUNG CANCER (CASE REPORTS) - I (1-15)	1ST	ASHISH KAUSHIK
	2ND	ASHA U B SNEHA
	3RD	ANU KUMARI
LUNG CANCER (CASE REPORTS) - II (16-30)	1ST	GAUTHAMRAM KARTHIK
	2ND	JUVA KISHAN SRIKANTH
	3RD	HARITHA SREE C H
LUNG CANCER (CASE REPORTS) - III (31-45)	1ST	MEGHANA SUBHASH
	2ND	ORUGANTI SINDHUJA
	3RD	PREETAM PARIDA

LUNG CANCER (CASE REPORTS) - IV (46-62)	1ST	S MATHIVADANI
	2ND	SAMEENA URS
	3RD	RUPAL NAIR
PFT (RESEARCH PAPERS)	1ST	APARNA NIRMAL
	2ND	PRAJJWAL SARKAR
	3RD	SHAFNA P
SLEEP DISORDERS (RESEARCH PAPERS)	1ST	NIDHI SUDHAKAR SAROJ MEENA
	2ND	DIPANSHU JAIN PRASHANT YADAV
	3RD	AMRUTHA MOHAN V NITHIN KUMAR REDDY PRATEEK AGARWAL RAHUL
OTHERS (RESEARCH PAPERS)	1ST	GEORGE ROSHAN PRASHANTH D
	2ND	ROSHAN KUMAR M
	3RD	ATIT SHAH DHARAMENDRA KUMAR GUPTA PAYYAVULA VENKAIAH
OTHERS (CASE REPORTS) - I (1-15)	1ST	ANURAG TRIPATHI
	2ND	AKILAN M ANURAG SHARMA
	3RD	AJEET SINGH THAKUR
OTHERS (CASE REPORTS) - II (16-30)	1ST	GOWTHAM KUMAR V
	2ND	B RAMYA KRISHNA HARSHAVARDHINI P
	3RD	BASEERAHMMAD WALIKAR DARSHAN NIMAVAT FASIL N HIMAJA REDDY INEX ANN JOSEPH JEEVA BABU
OTHERS (CASE REPORTS) - III (31-44)	1ST	MUNIZA BAI
	2ND	K PREMCHAND
	3RD	MEGHNA RAI PRASAD OMKAR KONJETI
OTHERS (CASE REPORTS) - IV (45-60)	1ST	ROBIN VARGHESE JOHN SEJAL RADIA
	2ND	K LOGESWARI MONICA Y
	3RD	POOJA BAJAJ RITAMVARA OLI VENKATESWARAN

EXTRA SESSIONS

(ORGANISED ON SPECIAL REQUEST FOR THOSE POST-GRADUATES ON COVID-19 DUTIES COULD NOT SUBMIT THEIR E-POSTERS ON TIME FOR UPLOADING TO THE VIRTUAL E-POSTER GALLERY BY 25th JANUARY 2021)

SESSION	RESULTS	
MISCELLANEOUS (RESEARCH PAPERS)	1ST	ALEENA MATHEW
	2ND	GAURI GADGE
	3RD	AASTHA GUPTA
MISCELLANEOUS (CASE REPORTS)	1ST	PRANZAL GARG
	2ND	K SHYAMALA PRAGNYA
	3RD	KRISHNAPRIYA S KUMAR

23RD JOINT NATIONAL CONFERENCE ON PULMONARY DISEASES ORGANIZED BY
INDIAN CHEST SOCIETY(ICS) AND NATIONAL COLLEGE OF CHEST PHYSICIANS(NCCP) (INDIA)
COMMEMORATING RESPIRATORY CARE: RESILIENCE, STRENGTH, SKILL, INNOVATION AND HOPE
01-04 February 2022 | Trade Facilitation Center & Craft Museum, Varanasi

Invitation and Message from the Chairman, Organizing Committee, NAPCON 2021 at Varanasi

Prof. Dr. J. K. Samaria
Chairman, Organizing Committee
NAPCON 2021 at Varanasi

Dear Members,

Our country and especially our fraternity in the specialty of respiratory medicine has seen really hard times in the last one and a half years. However now it is the time to move on and look forward. After a difficult first wave of COVID-19 last year and a devastating second wave early this year and now a massive vaccination drive undertaken by the Government of India, it seems that gradually the COVID disease may come under complete control in our country. Based on this hope and positivity, we plan to organize the annual conference NAPCON in conventional physical form, from 1st to 4th February 2022 at Varanasi.

This is high time for the colleagues from the specialty of respiratory medicine and associates meet and interact physically with their colleagues, seniors and juniors and try to move forward.

For this purpose there could not have been a better place for NAPCON-2021 other than Varanasi or Kashi as we call it, the oldest living city of the world.

Varanasi is one of the most ancient cities of the world and is considered as the spiritual and cultural capital of India. For centuries, Varanasi is famous for spiritualism, mysticism, Indian philosophy and Hinduism. The microcosm of Varanasi has fascinated the world for ages and people from across the world come to Varanasi to understand the spiritual tradition of Varanasi. I am assured that along with the best scientific content the participants of this conference will be exposed to the spiritual and cultural heritage of Varanasi. A visit to places like Sarnath where Lord Budhha gave his first sermon, Famous Hindu Temples, Ghats of River Ganges, and many other places shall be a life time experience for all the participants. Events like Ganga Arti, Subah-e-Banaras and many more are an experience worth taking.

Along with its spiritual and ethnic texture, Varanasi is also equipped with all the modern amenities for its Visitors. World class Airport, Number of five star hotel brands, great connectivity by rail and road are just to name a few. For last few years especially after it has become the constituency of our Hon. Prime Minister, Varanasi has become a model of development for the rest of the country.

To conclude, I very proudly and enthusiastically invite you all to Varanasi for NAPCON-2021 and assure you for a scientific extravaganza along with the memory of a lifetime.

Thanks and Welcome to NAPCON 2021 at Varanasi !

Prof. Dr. J. K. Samaria
Chairman, Organizing Committee
NAPCON 2021 at Varanasi

23RD JOINT NATIONAL CONFERENCE ON PULMONARY DISEASES ORGANIZED BY INDIAN CHEST SOCIETY(ICS) AND NATIONAL COLLEGE OF CHEST PHYSICIANS(NCCP) (INDIA)

COMMEMORATING RESPIRATORY CARE: RESILIENCE, STRENGTH, SKILL, INNOVATION AND HOPE

01-04 February 2022 | Trade Facilitation Center & Craft Museum, Varanasi

REGISTRATION FORM (PLEASE FILL IN UPPER CASE)

Title: Prof. ☐ Dr. ☐ Mr. ☐ Ms. ☐ Mrs. ☐ Gender: Male ☐ Female ☐ Age_____

First Name*: _____ Last Name: _____

Institute/ Hospital: _____ Designation: _____

Postal Address: _____

_____ City: _____

State: _____ Pin: _____ Country: _____

Member ICS ☐ NCCP ☐ Membership No.: _____ MCI Registration: _____

Mobile*: _____

E-mail*: _____ Food Preference:* Veg. ☐ Non Veg. ☐

* Mandatory for Registration

REGISTRATION FEE DETAILS

	Category	Early Bird upto 30th Nov 2021		Late Risers upto 15th Jan 2022		On Spot after 15th Jan 2022	
☐	ICS/NCCP Members	₹ 12000	☐	₹ 14000	☐	₹ 17000	☐
☐	Non Members	₹ 13000	☐	₹ 15000	☐	₹ 18000	☐
☐	Accompanying Person	₹ 11000	☐	₹ 12000	☐	₹ 15000	☐
☐	PGs/ Residents	₹ 10000	☐	₹ 12000	☐	₹ 13000	☐
☐	Corporate Delegates	₹ 15000	☐	₹ 18000	☐	₹ 20000	☐
☐	Delegates of SAARC Countries	$ 300	☐	$ 350	☐	$ 400	☐
☐	Delegates of Non SAARC Countries	$ 300	☐	$ 350	☐	$ 400	☐
☐	Foreign Accompanying Person	$ 300	☐	$ 350	☐	$ 400	☐

**Registration fee includes of GST 18%*

FULL DAY WORKSHOPS (Please choose anyone)

☐	Workshop (Full Day)	₹ 3500	☐	₹ 4500	☐	₹ 5000	☐

1. How to set up a Severe Asthma Clinic? ◯
2. Interstitial Lung Disease - Including CT Imaging and Cryobiopsy ◯
3. CHEST IMAGING - Thoracic Ultrasound and CT ◯
4. Want to start a sleep Clinic? We got you covered. ◯
5. Management of Acute & Chronic Ventilatory Failure (IVM, NIV, HFNO, LTOT) ◯
6. Basic Bronchoscopy including the use of a rigid bronchoscope ◯
7. Pulmonary Interventions (EBUS, Cryo, and others) ◯
8. Advanced PFTs (DLCO, FENO, IOS, 6MWT) ◯
9. Allergy & Immunotherapy ◯
10. Medical Thoracoscopy (Including use of Rigid and Semirigid Thoracoscope) ◯
11. ICS ERS WORKSHOP ◯
12. ICS-ACCP (CHEST) WORKSHOP ◯
13. Setting up a post covid care clinic & Lung Transplantation ◯
14. OSCE (Objective Structured Clinical Examination) & Mock PG Practical ◯
15. Beginner's guide on doing drug trials and writing Scientific in Journals ◯
16. How to set up a Pulmonary Rehabilitation Unit? ◯

**Workshop is subject to availability.*
**Conference registration is mandatory for workshop registration.*
** One candidate can register one full day workshop.*
** No Spot registration for workshops*

ACCOMPANYING PERSON

Title: Prof.☐ Dr.☐ Mr.☐ Ms.☐ Mrs.☐	Age	Male	Female	Veg.	Non Veg.
1. Name: _____	___	☐	☐	☐	☐
2. Name: _____	___	☐	☐	☐	☐
3. Name: _____	___	☐	☐	☐	☐
4. Name: _____	___	☐	☐	☐	☐

I am enclosing herewith a Cheque/ Demand Draft no. _____ dated _____/ _____/ _____

of Rs._____ (in words: _____) only

drawn on bank _____ in favour of

***"NAPCON 2021 U/O India Chest Society"** payable at Varanasi.*

.....

Signature

Bank Details of NAPCON 2021:

Bank Name: **Kotak Bank**	A/C No: **0015028402**
A/C Name: **NAPCON 2021 U/O India Chest Society**	IFSC: **KKBK0005323**
Swift Code: **KKBKINBBCPC**	MICR: **221485007**
Branch: **Kotak Mahindra Bank Ltd; Plot No. 6A, UGF, 27/92, Jawahar Nagar Colony, Near Chetmani Crossing, Bhelupur, Varanasi - 221010**	

REGISTRATION GUIDELINES

- Membership number is mandatory for registration in membership category.
- Online charges will be applicable at 2.5% of the total amount.
- Registration for children below 5 years is complimentary. however it is mandatory to mention their details above for security purpose
- Registration fees include admission to the scientific halls, trade exhibition, inaugural function, lunch and delegate kit.
- Provide us your updated email id & mobile number. As it will be used for the registration receipt and other conference communication.
- Organizing committee shall not be liable in any form in case of changes in date / venue due to unforeseen reasons.
- Conference organizers are not responsible for postal delays / failure of delivery by post or failure of electronic communication.
- It is mandatory for all delegates to carry there photo id (government approved) for smooth registration procedure.
- *It is mandatory to submit HOD Letter/ PG certificate to avail the registration in PG category.
- Conference registration will be mandatory for attending and registering for the workshop.

CANCELLATION & REFUND

- Requests for cancellation for refunds must be made in writing or through e-mail.
- Request must be sent to conference secretariat.
  E-mail: **napcon2021@gmail.com**
- No refund of registration fee will be provided for cancellation request received after 31st December 2021.
- 10% of the registration would be deducted as processing charges and rest will be refunded one month after conference completion.

Please send duly filled Registration form along with Cheque or DD in favour of "NAPCON 2021 U/O India Chest Society" payable at Varanasi.

COVID GUIDELINES:
In order to ensure safety and well being of all attending delegates, faculty, accompanying persons and trade partner sorganising committee has taken a decision to allow only fully vaccinated delegates, faculty, accompanying persons and trade delegates to attend the event.

- **Covid 2nd vaccine certificate e-copy mandatory for delegates.**
- **Covid appropriate behaviours shall be followed at all times.**

Everyone is kindly requested to cooperate for their own safety.

For office use only: Receipt No.: _____ Registration No.: _____

Conference Secretariat:
Dr. JK Samaria *(Org. Chairman)*
Centre for Research and Treatment of Allergy,
Asthma & Bronchitis
Chest Clinic Varanasi
36-A, Kabir Nagar Colony, In front of Raj Sweet House,
Durgakund, Varanasi, Uttar Pradesh-221005
Mob.: +91 8115945399
Mail: napcon2021@gmail.com, Web.: www.napcon2021varanasi.com

ICS GLOBAL
INSTANT CONFERENCE SOLUTIONS
PROFESSIONAL CONFERENCE ORGANIZER
A UNIT OF ITS GLOBAL
706, 7th Floor, Precious Mall,
M.D. Road, Jaipur, Rajasthan - 302004
Mob.: +91 98112 65527

NAPCON 2022

24th Joint National Conference on Pulmonary Diseases of National College of Chest Physicians (India) and Indian Chest Society

Dear Delegates,

It is a matter of great pride and privilege that NAPCON 2022, the 24th Joint National Conference on Pulmonary Diseases of the National College of Chest Physicians (India) and Indian Chest Society is going to be held at Udaipur (Rajasthan, India) under the aegis of NCCP(I) and ICS. The conference and pre-conference workshops will be organized jointly by the Departments of Tuberculosis and Respiratory Medicine of Geetanjali Medical College and Rabindra Nath Tagore Medical College at Udaipur, Rajasthan.

It gives us immense pleasure to invite and welcome you to NAPCON 2022. Udaipur is a worldwide popular tourist destination and a smart city. Besides this, it is also an academic city, having six medical colleges, IIM and many other teaching institutions with a rich heritage.

It is a historical place and beautiful natural city surrounded by hills, having many lakes in and around, and is famous globally as "The city of lakes". Udaipur is also famous for its ancient culture based on the concept of

"Athithi Devo Bhav " (Guest is like GOD).

The Scientific Programme will be prepared by the Scientific Committee under the Chairmanship of Prof. Dr. S. K. Katiyar, who is a well known pulmonologist and great academician. We will also organize many workshops on basic and advanced aspects of Pulmonary Medicine. The dates will be finalized shortly.

Looking Forward to Welcome You and Family at Udaipur !

Prof. Dr. S. K. Luhadia
Organising Chairman
9414165733

Dr. Mahendra Kumar
Organising Secretary
8769163850

Dr. Atul Luhadia
Organising Secretary
9982260458

Conference Secretariat : Luhadia's Chest & Allergy Clinic, 165-A Block Chitrakoot Nagar, Udaipur - 313001
Email ID : napcon22udr@gmail.com
Website : In Process

Venue of NAPCON 2022

Geetanjali Medical College and Hospital, Udaipur

Places to visit in and around UDAIPUR

Pratap Smarak : Located on the top of Moti Margi or Pearl Hill, which was built in the 18th century. One of the most thrilling features of the Memorial is a life-sized bronze statue of Maharana Pratap sitting on his faithful horse, Chetak. The figure is 11 feet high and weighs about 70 tonnes. The museum built on the premises of the Memorial has an enormous collection of paintings. These paintings depict the rich history of Kumbhalgarh and Chittorgarh along with the few instances from the battle of Haldighati.

City Palace : The city palace towers over Lake Pichola. The balconies, cupolas and towers of the palace give a wonderful view of the lake and the surrounding city. This complex actually consists of four major and several minor palaces that collectively form the magnificent City Palace. The main part of the palace is now preserved as a museum displaying artifacts.

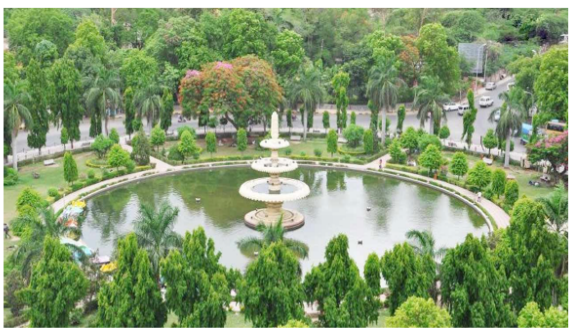
Monsoon Palace : Situated just outside Udaipur, this 19th century palace is built on top of Bansdara hills. Used as a monsoon palace and hunting lodge, built by Maharana Sajjan Singh. It is an awe-inspiring sight on Udaipur skyline and offer spectacular views of city and area around.

Lake Palace : Now a globally famous hotel but was originally called Jagniwas and served as a summer palace, Built between 1743 and 1746 on the island near Jagmandir in Lake Pichola. The palace faces east and is a wondrous sight to behold.

Fateh Sagar Lake : This delightful lake, bordered by hills and woodlands, lies to the north of Lake Pichola. The lake houses the beautiful Nehru Island as well as an Island on which stands the Udaipur solar observatory. Boating in the lake gives an immense pleasure and relaxation. The largest fish aquarium in India, UNDER THE SUN is situated close to the Lake Fatehsagar Paal.

Jaisamand Lake : Jaisamand Lake is known for being the second largest man-made sweet water lake in Asia. It is popular among the local as a weekend picnic destination. Locals say that the lake was constructed to halt the water of Ruparel river. This lake boasts of a largest island, which is home to various species of birds, at its centre. It is situated around 60 km from Udaipur.

Saheliyon ki Bari : Built by Maharana Sangram Singh II as a garden for women, Saheliyon ki bari or the Garden of Maidens is a popular tourist destination. Along with a small museum, it has several attractions such as marble elephants, fountains, kiosks and a lotus pool.



Sukhadia Circle: Sukhadia circle lies to north of Udaipur. It comprises a small pond that also houses a 21 foot tall, three-tiered marble fountain. Decorated with beautifully carved motifs, the fountain looks spectacular at night when it lit up. The fountain is surrounded by gardens, creating a perfect oasis in a city bustling with tourists.

Wax Museum : The Hollywood Wax Museum is an exciting interactive visitor attraction located on Sajjangarh road. The Museum has been designed to deliver an interactive experience taking you on a journey through wax effigy. The exceptional life-like wax work characters you can expect at the celebrity wax museum. The wax museum also offers 9-D Action cinemas, Gaming Zone, Mirror Image and Horror Show.

Vintage Car collection : The collection within the grounds of the Garden Hotel comprises a variety of vintage and classic vehicles like Cadillac, Chevrolet, Morris, etc. owned by the Maharajas of Udaipur. They used these automobiles as their luxurious modes of transport.

Shrinath Ji temple at Nathdwara : Shrinath Ji is basically a small version of Krishna that was brought to the temple of Nathdwara centuries ago. This temple has been ever since attracted tourists in large numbers annually this temple is basically an illustration of the time Krishnaji picked up the Gowardhan hill. The aartis here are a complete delight to attend and the architecture of the temple you should definitely not miss. It is around 45 km far from Udaipur.

Ranakpur Jain temple: The temple in Ranakpur is a breath-taking place to see, but also a peaceful sanctuary that encourages this sort of quiet reflection. Built entirely of white marble, this Jain temple was constructed in the 15th century by a local businessman, Dharma Shah, who had a divine vision. He started the temple with funding from the Rajput monarch Rana Kumbha and it took over 50 years to complete. It is around 95 km from Udaipur.

Kumbhalgarh fort : It is a World Heritage situated on Hill of Rajasthan. It was built during the course of the 15th century by Rana Kumbha. This fort has perimeter walls that extend 36 km, making it the second longest wall in the world, the frontal walls are fifteen feet thick. There are over 360 temples within the fort, 300 ancient Jain and the rest Hindu. It is around 80 km from Udaipur.

APSR2021

The 25th Congress of the Asian Pacific Society of Respirology

OUR FUTURE

Register online at
https://apsr2021.jp

Hybrid Congress

In-person and Virtual

November 20-21, 2021

at/from Kyoto International Conference Center

Hosted by The Japanese Respiratory Society and Asian Pacific Society of Respirology

APSR 2021 Secretariat: 4F Hongo UC Building, 3-35-3 Hongo, Bunkyo-ku, Tokyo 113-0033 Japan, c/o Convention Academia Inc. TEL. +81-3-5805-5261 FAX. +81-3-3815-2028 E-MAIL: info-apsr2021@coac.co.jp


UDAIPUR
पधारो म्हारे देस
NATIONAL COLLEGE OF CHEST PHYSICIANS
NCCP
INDIA
INDIAN CHEST SOCIETY
ICS
INDIAN CHEST SOCIETY
RAJPULMOCON
UNDER THE AUSPICES OF RAJASTHAN STATE CHAPTER OF NCCP(I) & ICS
Organized by Dept. of Pulmonary Medicine, R N T Medical College and
in association with United Academy of Pulmonary Medicine INDIA
& a Workshop on
INTERVENTIONAL PULMONOLOGY
mainly (EBUS Linear, RADIAL &
Navigational Bronchoscopy,
Cryotechnique, ELectrocautry,
APC and Medical Thoracoscopy)
: 7th January 2021
January 7-9, 2022
RNT MEDICAL COLLEGE, UDAIPUR
ORGANISING CHAIRMAN
Dr Mahendra Kumar Bainara
Senior Professor & HOD
Dept of Pulmonary Medicine
R.N.T. Medical College, Udaipur &
Superintendent
TB & CHEST HOSPITAL, UDAIPUR RAJASTHAN

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. D. Behera

Former President, NCCP(I) [2010 – 2011]
and President, ICS [2021 – 2022]

for being

1. **Awarded the**
Padma Award [2020]
and conferred with the prestigious title of
‘ Padma Shri ’
by the Government of India

2. **Elected as**
President – Elect [2024 – 2027]
of the
National Academy of Medical Sciences

3. **Awarded the**
ICAAI – Dr. D. N. Shivpuri Oration [2020]
at ICAAICON 2020 – 2021 by the
Indian College of Allergy, Asthma and Clinical Immunology

His Excellency The President of India

Hon'ble Rashtrapati

Shri Ram Nath Kovind Ji

presents the

Padma Award Scroll

to

Dr. D. Behera

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. S. N. Gaur

Secretary, NCCP(I)

for being

Elected as

President

of the

Indian College of Allergy, Asthma and Clinical Immunology

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. S. K. Katiyar

Former President of
NCCP(I) [2003 – 2004]
and ICS [2009 – 2010]

for being

Honoured and felicitated by

Chhatrapati Shahu Ji Maharaj University, Kanpur

for

Outstanding contribution in the field of education

on the occasion of

‘ Teachers Day ’

on 5th September 2021 at Kanpur

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Nasser Yusuf

Fellow of NCCP(I)

for being

1. Elected as

President

of the

Rotary Club of Calicut

2. Recognised for

Service as an Eminent Thoracic Surgeon

by publication in the

‘ Indian Express ’

Kochi on 13th August 2021

(see next page)

THE NEW INDIAN EXPRESS

WAR ON CORONA

02 KOCHI | FRIDAY 13.08.2021 | newindianexpress.com

VACCINATION SO FAR 2,28,46,384 | 1st dose 1,63,32,678 | 2nd dose 65,13,706

VACCINATED ON THURSDAY 4,04,465 | STOCK LEFT NA (Data not updated)

	NEW CASES	RECOVERIES	DEATHS	TESTS
AUG 12	21,445	20,723	160	1,45,582
AUG 11	23,500	19,411	116	1,62,130

TEST POSITIVITY RATE: August 12 — 14.73% | August 11 — 14.49%

POSITIVE CASES SO FAR	PEOPLE UNDER TREATMENT	TOTAL RECOVERIES	TOTAL DEATHS
36,31,638	1,76,518	34,36,318	18,280

DISTRICT-WISE FIGURES
Kerala has been witnessing a surge in the number of positive cases. Here's a look at the district-wise figures

CONFIRMED CASES | PATIENTS UNDER TREATMENT | POSITIVE CASES ON THURSDAY | CONFIRMED DEATHS

T'Puram	3,44,023	9,790	930	3,391	P'thitta	1,37,403	6,976	630	558	Kottayam	2,33,183	8,510	1,188	769
Kollam	2,85,603	4,588	1,339	1,402	Alappuzha	2,38,371	9,962	1,238	1,157	Idukki	97,161	5,149	589	238
Ernakulam	4,32,821	24,156	2,425	1,844	Palakkad	2,71,216	15,819	2,268	1,679	Kozhikode	3,90,107	26,145	2,534	1,878
Thrissur	3,57,474	12,206	2,465	1,983	Malappuram	4,44,034	30,401	3,300	1,533	Wayanad	84,389	7,180	720	301
Kannur	2,00,574	8,539	1,338	1,164	Kasaragod	1,15,276	7,097	578	382					

If 5 or more test +ve, it's a micro-containment zone

As per revised guidelines, curbs to be imposed on flat complexes, malls, residential areas or even big houses depending on cases

EXPRESS NEWS SERVICE @T'Puram

THE high number of positive cases could qualify an apartment complex, a residential area or even a big house to be declared a micro-containment zone (MCZ) with stringent triple lockdown restrictions in force, as per the guidelines announced by the Kerala State Disaster Management Authority (KSDMA) on Thursday.

An MCZ has the potential for high spread due to the presence of more than five people with infection on a given day. This could be a shopping mall, street, market, workshop, harbour, fishing village, fish landing centre, office, IT company, etc.

Clustering potential may be evaluated at the district level on a daily basis and the notification may be restricted to 100 metres such that the restrictions are limited to the most affected stretch, said the guidelines. Any micro-containment zone should remain so for seven days from the date of such notification and it will not be a micro-containment zone if no further notification comes on the eight day. The micro-containment zones will be monitored by sectoral magistrates to ensure Covid-appropriate behaviour. The guidelines also suggest more testing, contact tracing activities and support through ASHA workers.

The state government has introduced its Covid containment strategy based on the density of new positive cases in a week in a particular location. It will be managed by imposing restrictions at the ward level and through MCZs. As many as 634 local body wards with a Weekly Infection Population Ratio (WIPR) of eight have been put under control from Thursday. These included 87 local self-government bodies, including 20 grama panchayats. Last week, 266 wards in 52 local bodies, including seven grama panchayats, with a WIPR of above 10 were put under control.

The revision was made after the Covid spread in the state did not come down despite the control measures. WIPR is calculated based on the density of infection (number of positive cases per 1,000 people) in a region in a week.

18-year-old girl dies of haemorrhage in P'thitta, relatives blame Covishield

EXPRESS NEWS SERVICE @Pathanamthitta

AN 18-year-old girl, a native of Cherukole, died of intracerebral haemorrhage at a private hospital here on Thursday. Pathanamthitta District Medical Officer (DMO) A L Sheeja said she has sought an inquiry report after the relatives of the girl raised a suspicion that her health worsened after she received the first dose of Covishield on July 28.

The DMO said Reproductive and Child Health Care Officer R Santhosh will submit the report. "We will conduct an inquiry if anybody died here within 28 days after receiving the vaccine. We have also directed to conduct an autopsy of the body," said Dr Sheeja.

Santhosh said he is awaiting the autopsy report. "The girl died due to intracerebral haemorrhage. So far, we haven't confirmed whether she died due to the after-effect of vaccination. She received vaccination from a private hospital in Kochi on July 28. But her relatives suspect that she died because of the after-effect of vaccination," he said.

"After getting the autopsy report and medical records from the hospital where she underwent treatment, we will submit a report," he said.

SURGERY AN OPTION FOR PATIENTS WITH POST-COVID LUNG AILMENT

ANUJA SUSAN VARGHESE
@Kochi

MUCH like a tsunami battering the best coastal defences, a Covid infection can wreak havoc on the human body. Persistent breathlessness, cough, chest pain, fever, and recurrent infections, including pneumonia, even after the infection is overcome, can leave one's respiratory system crippled. While a majority of such cases can be cured through medications, there are certain patients who would benefit greatly from surgical intervention, say experts. So far, more than 36 lakh people have been infected with Covid in Kerala, and more than 18,000 deaths recorded officially.

According to experts, many lung complications can be triggered during the post-Covid phase, including lung fibrosis, bronchiectasis, empyema, bullae, pulmonary infarction, and cavities.

"For up to weeks and sometimes even months after testing negative, people are left with persistent symptoms. Those patients with post-Covid lung complications, seen as specifically localised infections in CT scans, can undergo early surgery and recover. Currently, there is no data available on patients who require surgery. Scientists, researchers, and the medical world is still learning about the novel coronavirus and its treatment. Not many are aware of the possibility of surgery. However, some cases that we have attended to and found fit for surgery, underwent surgeries successfully," said Dr Nasser Yusuf, cardiothoracic surgeon in Kochi.

In one such case, a 52-year-old native of Beypore in Kozhikode with empyema (a condition in which pus gathers in the area between the lungs and the inner surface of the chest wall) recovered after surgery.

According to doctors, months of reliance on antibiotics, discomfort, and risk of further deterioration due to the underlying issues, as well as money spent on medications, can be saved through surgery. "Medical intervention, identifying the infection and complications at the right time, and knowing what to do about them are the key factors in saving a patient. Even a common man should be able to understand his options, rather than giving up at an early stage," said Dr Nasser.

It is not only patients admitted for Covid treatment at hospitals who are at risk. Even those who underwent treatment at homes due to mild symptoms can develop lung complications. "The symptoms will be the same for all lung complications. Lung fibrosis leading to breathlessness is one of the common symptoms. Subsequent to the viral infection, bacterial infections pose a large threat. Earlier, when respiratory complications such as cavities, bullae, and empyema were observed, surgeries were performed. Why not do the same when such cases are triggered by Covid?" asked Dr Nasser.

"For the surgery, preferably, the patient must have tested negative at least two weeks prior. The patient should be fairly stable. Also, the surgery can be conducted only after consulting a surgeon. Video-assisted thoracoscopic surgey an be perfomed, with minimal pain, leading to quick recovery," he added.

When do you need surgery

When medication fails to help, surgery can be a means for lasting relief. A rundown of some symptoms to look out for...

Symptoms
Persisting symptoms like cough, breathlessness, coughing out blood, fever, chest pain, and recurrent pneumonia may indicate that the lungs are damaged despite medications. These leave one's respiratory system crippled.

Localised pneumonia/Infection
If pneumonia sets in, one or more specific parts of the lungs become irreversibly damaged. Removal of the diseased segment through surgery can bring relief. Once the affected part is taken out, then there is space for the rest of the lung to expand. However, if the infection spreads to the whole lung, surgery is not an option. If both the lungs are affected gravely, lung transplant is the only option.

Empyema
Empyema is a condition in which pus gets formed and collected in the space between the lung and the inner chest wall. Although the pus can be cleared with medication & aspiration, sometimes when the pus remains beyond two weeks it hardens and medication will not help. This causes compression of the lungs. Once this is removed, the lungs start to function healthily.

Cavity
Lung cavities can cause bleeding and when the cavities are large, the rest of the lungs get compressed. Sometimes, fungus starts to grow in these cavities. Surgery is an option here as this can otherwise lead to fatal bleeding.

Bullae
Due to Covid, sometimes the surface membrane of the lung becomes weak and balloon-like structures are formed. In certain situations, these bullae rupture & lead to a life-threatening condition that causes collapse of the lungs and pressure on the heart.

> Post-Covid bacterial infections also pose a large threat. Surgeries are the usual resort when it comes to respiratory issues. Why not do the same when such cases are triggered by Covid?
>
> Dr Nasser Yusuf

Bronchiectasis
In some, after recovery from infection, a portion of the lung is permanently destroyed by bronchiectasis (multiple small cavities that appear like a honeycomb). If it is confined to one area, this can be treated successfully only by surgery.

Pulmonary Infarction
Due to the formation of blood clots in the lungs, there will be no blood supply to a particular portion and as a result, the lung function is lost and permanently damaged. These clots can be removed through surgery.

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. G. C. Khilnani

Former President of

NCCP(I) [2011 – 2012, 2012 – 2013]

for being

Elected as

Vice – President

of the

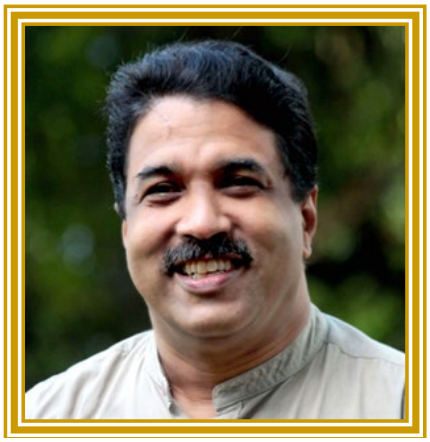
Indian Chest Society

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. P. S. Shajahan

Fellow of NCCP(I)



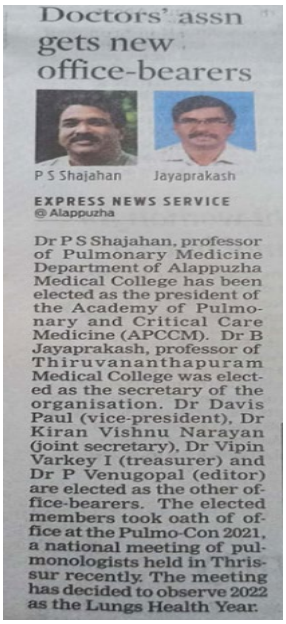
for being

Elected as

President

of the

Academy of Pulmonary and Critical Care Medicine



Doctors' assn gets new office-bearers

P S Shajahan

Jayaprakash

EXPRESS NEWS SERVICE
@ Alappuzha

Dr P S Shajahan, professor of Pulmonary Medicine Department of Alappuzha Medical College has been elected as the president of the Academy of Pulmonary and Critical Care Medicine (APCCM). Dr B Jayaprakash, professor of Thiruvananthapuram Medical College was elected as the secretary of the organisation. Dr Davis Paul (vice-president), Dr Kiran Vishnu Narayan (joint secretary), Dr Vipin Varkey I (treasurer) and Dr P Venugopal (editor) are elected as the other office-bearers. The elected members took oath of office at the Pulmo-Con 2021, a national meeting of pulmonologists held in Thrissur recently. The meeting has decided to observe 2022 as the Lungs Health Year.

The New Indian Express, Alapuzzha, 1st November 2021

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Jayaprakash B.

Fellow of NCCP(I)

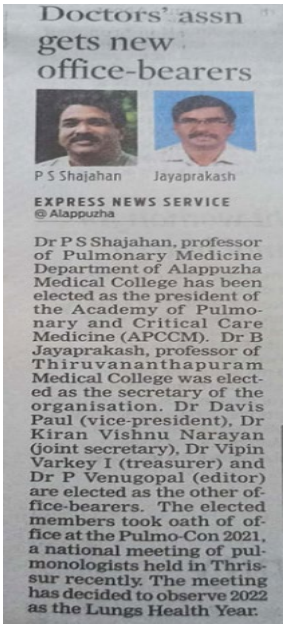
for being

Elected as

Secretary

of the

Academy of Pulmonary and Critical Care Medicine



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The New Indian Express, Alapuzzha, 1st November 2021

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. V. K. Jain

Former President of

NCCP(I) [2004 – 2005]

and ICS [2005 – 2006]

for being

Elected as

Fellow

of the

National Academy of Medical Sciences

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Surya Kant

Former President of
NCCP(I) [2019 – 2020]
and ICS [2017 – 2018]

for being Awarded

1. LMA COVID-19 Leadership Award
on 30th April 2021 by
Lucknow Management Association (LMA)

2. COVID Saviour Award
on 8th August 2021 * at Haryana Respicon, Gurugram by
Indian Chest Society (Haryana State Chapter)

3. Dr. Nand Lal Bordia Oration
on 8th August 2021 * at M. P. Pulmocon, Indore by
Organising Committee, M.P. Pulmocon 2021

4. Honorary Professorship of IMA-CGP
on 5th September 2021 (IMA Medical Teachers' Day) by
Indian Medical Association - College of General Practitioners

**** Dates Verified and Confirmed***

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. H. Paramesh

Member of NCCP(I)

for being

Selected as

Spokesperson

for

WHO – NGO Climate and Health

at the

2021 United Nations Climate Change Conference

Conference of Parties (COP-26) at Glasgow

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Prasanta R. Mohapatra

Fellow of NCCP(I)

for being

Elected as

Fellow

of the

Infectious Disease Society of America

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Kiran Vishnu Narayan

Member of NCCP(I)

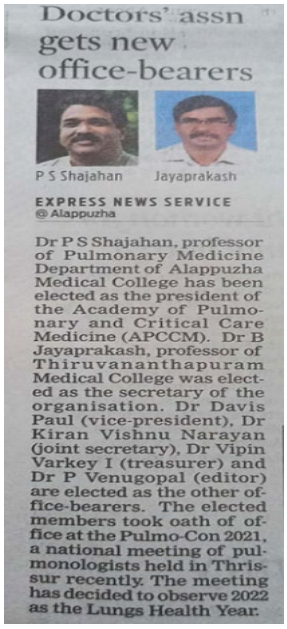
for being

Elected as

Joint - Secretary

of the

Academy of Pulmonary and Critical Care Medicine



Doctors' assn gets new office-bearers

P S Shajahan Jayaprakash

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@ Alappuzha

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The New Indian Express, Alapuzzha, 1st November 2021

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Rajesh Venkitakrishnan [1]

Member of NCCP(I)

and Department Colleagues

Dr. Jolsana Augustine [2]

Dr. Divya Ramachandran [3]

Dr. Melcy Cleetus [4]

Dr. Anand Vijay [5]

Dr. Aparna Nirmal [6]

for their publication

ARTWORK

(Acceptance and Results of Therapy With Omalizumab in Realworld Kerala Settings)

in the

Journal of Asthma

A study on the real world experiences of omalizumab therapy in severe asthmatics in India. This is perhaps the first Indian work of this nature, describing patient perspectives and efficacy of Omalizumab after therapy discontinuation.

Link to access the article : https://doi.org/10.1080/02770903.2021.1968425

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[2], [3], [4]. Consultant Pulmonologists, Department of Pulmonary Medicine, Rajagiri Hospital, Kochi
[5], [6]. Senior Residents, Department of Pulmonary Medicine, Rajagiri Hospital, Kochi

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Shital Vishnu Patil

Member of NCCP(I)

for being Awarded

1. ‘ ERS Best Abstract Grant ’ in ARDS

by

European Respiratory Society (ERS)

at

ERS Congress 2021

2. ‘ Rising Star ’ Award for Lung Health

at

9th International Workshop on Lung Health (IWLH) 2022

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Dr. Sharad Bagri

Member of NCCP(I)

for being Awarded

Vice-Chancellor's Gold Medal

for securing

FIRST position in M.D. (Respiratory Medicine)

at

Sharda University

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Chaitashree Chordia

Granddaughter of

Dr. Ravindra Chordia

Daughter of

Dr. Rohit Chordia

Members of NCCP(I)

for scoring

98.83%

in

Higher Secondary (12th) Board Examination

NATIONAL COLLEGE OF CHEST PHYSICIANS (INDIA)

Congratulates

Nupoor Shah

Daughter of

Dr. Arti Shah

Member of NCCP(I)

for

Getting Admission

in

Bachelor of Architecture (B. Arch)

at

Institute of Architecture and Planning, Nirma University

COVID-19 Vaccination and the Common Man

Dr. P. D. Motiani
Immediate Past President, NCCP(I) (2020-2021)
Retd. Senior Professor and Head (Pulmonary Medicine),
Dr. S. N. Medical College, Jodhpur, Rajasthan
Organising Chairman, NAPCON 2010
Recipient of NCCP(I) - German Remedies Chest Oration and
NCCP(I) Rajasthan Chapter - Prof. S. N. Gaur Oration
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Introduction :

The COVID-19 pandemic in India began in March 2020, during which time measures to fight against pandemic were very much limited. Step-by-step, gradually, measures were implemented for development of procurement and supply chain for masks, PPE kits, ventilators, medicines and the development of vaccine against COVID-19 as a self-dependent model. Vaccination is one of the measures to increase immunity to a protective level against an infection, to reduce the severity of infection, prevent its' spread of infection and the complications resulting from severe infection or disease. From 16th January 2021 onwards, a mega nation-wide COVID-19 vaccination program was launched in India, using two approved vaccines, the Oxford - AstraZeneca COVISHIELD, manufactured by Serum Institute of India and COVAXIN, manufactured by Bharat Biotech. Certain queries still exist in the minds of many. Let us discuss the following :

1. Should We Delay the Second Dose of the COVID-19 Vaccine ?

It is debatable to manage the demand of the COVID-19 vaccine and existing shortage, countries are coming up with different strategies such as vaccinating complete populations only with the first dose and later administering the second dose.The clinical efficacy of any such modification in the vaccination protocol is unknown. Due to the pandemic situation, it is not practical to put the vaccine through established clinical trial protocols and evaluate the safety and efficacy, which is a time-consuming process. Researchers from the University of Western Ontario, London, University of Quebec, Canada, and Lakehead university Canada used the mathematical method to solve this most debatable question, i.e. is it advisable to delay the second dose of the COVID-19 vaccine ?

The efficacy-based optimal strategy for the first and second dose was suggested in this article, the theoretical findings show that optimal scheduling of the second dose depends on the efficacy of the first and second dose. Most of the pharmaceutical vaccine manufacturers have announced that the first dose of the vaccine is at least 50% or more efficient. This mathematical method can help countries to calculate the time that can be considered to delay the second dose.

2. Is Covishield Effective against the U.K. Variant ?

Researchers from the COVID-19 Genomics United Kingdom Consortium, the AMPHEUS Project, and the Oxford COVID-19 Vaccine Trial Group published the results of their exploratory analysis of a randomized controlled trial of the ChAdOx1 nCoV-19 (AZD1222) vaccine against the SARS-CoV-2 variant of concern 202012/01 or the B.1.1.7 variant in the Lancet. The researchers found that the adenoviral vector vaccine, ChAdOx1 nCoV-19 (AZD1222), exhibited reduced neutralization activity against the SARS-CoV-2 U.K. variant, which may affect the current vaccination efforts of multiple countries.

However, the vaccine helped protect against symptomatic disease caused by the novel variant. To arrive at these findings, the researchers enrolled volunteers who are more than 18 years old. The participants were enrolled in phase 2/3 vaccine efficacy studies in the U.K. and were randomly assigned to receive the vaccine. The team collected upper airway swabs weekly, and if the subjects developed COVID-19 symptoms, including fever, cough, shortness of breath, and loss of smell or taste. The swabs underwent testing using a nucleic acid amplification test (NAAT) for SARS-CoV-2, and positive samples were sequenced using the COVID-19 Genomics U.K. consortium. A live-virus microneutralization assay against the U.K. variant was performed to measure the participants' neutralizing antibody responses. The efficacy analysis included symptomatic COVID-19 in seronegative individuals with a NAAT positive

swab more than 14 days after a second vaccine dose. The team analyzed the study participants according to the vaccine received. The study findings showed that of the 8,534 participants in the primary efficacy group, 520 developed COVID-19. About 1,466 NAAT-positive nose and throat swabs were collected from the participants. Of these, 401 swabs were sequenced, finding that the laboratory virus neutralization activity was lower against the U.K. variant. Furthermore, the team found that the clinical efficacy against symptomatic NAAT positive infection was 70.4 % for B.1.1.7 and 81.5 % for non-B.1.1.7 lineages. Though there is reduced neutralization activity, the vaccine protected against symptomatic disease caused by the B.1.1.7 lineage, hence, vaccination with the Oxford-AstraZeneca vaccine resulted in a reduction in the duration of shedding and viral load, which may reduce viral transmission.

3. What are the Common Side-effects of COVID-19 Vaccines ?

Side effects develop because the immune system is reacting to the vaccine. People may start to develop fever, fatigue, headache and soreness around the injection area 12 to 24 hours after vaccination. Because side effects can be a sign of a robust immune system training to detect and destroy the virus, younger people may be more likely to experience stronger side effects than the elderly. With vaccines that require two shots, side effects may also be worse after the second shot than the first one, because T-cells remember the previous encounter with the spike protein. Without hesitation, the body quickly unleashes a strong immune response to destroy the antigen, including upregulation of cytokines, which is mainly responsible for the side effects. Consistently, the second shot is showing more side effects but a better immune response . People who previously recovered from COVID-19 are also more likely to experience strong side effects, even after the first shot, this is because their immune systems have already been primed to react to the virus. Individual differences, such as stress levels and diet, can also influence side effects. In very rare instances, people may develop anaphylaxis - a life-threatening but easily treatable allergic reaction, to COVID-19 vaccines. This reaction occurs within 15 minutes of vaccine administration, meaning that it is very easy for health care providers to identify and treat it promptly .

4. How Long does it take to Develop Immunity after getting the COVID-19 Vaccine ?

It typically takes about two weeks after vaccination for the body to start developing immunity against SARS-CoV-2, with complete immunity after four weeks. Hence, it is quite possible for a person to get infected with COVID-19 before or just after vaccination because the vaccine did not have enough time to confer protection. People are considered to be fully vaccinated 2 weeks after their second dose of the Pfizer-BioNTech or Moderna COVID-19 vaccines, or 2 weeks after the single-dose Johnson & Johnson's Janssen COVID-19 vaccine. For double-dose vaccines, effective protective immunity against COVID-19 reaches its maximum level a few weeks after the second dose and for single-dose vaccines, a few weeks after getting vaccinated.

5. Should Individuals who have already Recovered from COVID-19 also be Vaccinated ? (Yes)

Though past coronavirus infection does offer some protection, vaccination can still help people who have already recovered from COVID-19 by boosting their immune system against future infections. Vaccination against COVID-19 will also help patients from becoming seriously ill even if they do get infected later on. Vaccination showed higher efficacy against severe–critical COVID-19 (76.7% for onset at 14 days and 85.4% for onset at 28 days). The U.S. Centers for Disease Control and Prevention (CDC) recommends that people get vaccinated regardless of whether they've already suffered from COVID-19 or not. This is because it is still unclear for how long the protective immunity conferred by natural infection will last. Studies have shown that antibodies linger in the blood for at least 8 months after natural infection, though some recovered patients did get re-infected. Research reveals that COVID-19 jabs give the immune systems of people who were previously infected an extra boost to fight the coronavirus, including some immunity against new and more transmissible variants. Since the delta variant, first identified in India, can also spread among vaccinated people, that extra layer of protection for recovered patients is probably helpful.

Lab-based studies also suggest that a single dose of COVID-19 vaccine might alone suffice to protect people who have already recovered from the infection. In a study published in JAMA, researchers reported that one shot for those who recovered from a prior infection boosted virus-attacking antibodies to levels similar to those of vaccinated people who got two doses of an mRNA vaccine, whereas a second shot did not further increase antibody levels for previously infected people. Apart from antibodies, the activity of memory T-cells, which coordinate and ramp up the immune response when a person is exposed to the virus again, is also increased after the first dose of COVID-19 vaccination . This suggests that people who had COVID-19 and then were vaccinated with a single dose could be nearly as protected as fully vaccinated people with both doses who were never sick.

6. What is Vaccine Hesitancy ? How can it be Resolved ?

Vaccine hesitancy refers to is a delay in acceptance, or refusal of vaccines by the target population despite the availability of vaccination services. It could seriously threaten efforts to combat the pandemic. Vaccine hesitancy on the controversy, misinformation, a lack of confidence surrounding vaccine trial data, anxiety about vaccine safety, and historical mistrust of the medical establishment due to current or past negative treatment. There exist important differences between people who are vaccine-hesitant versus people who are anti-vaccine, who deliberately spread misinformation. Health experts should communicate vaccine information with more empathy and address all vaccine questions or concerns without any prejudice or bias.

Practical tips for addressing parental vaccine hesitancy in primary care include starting vaccination programs early, presenting vaccination as the default approach, building trust, being honest and open about side effects, providing reassurance on a robust vaccine safety system. Also provided are statements that providers could use in vaccination-related conversations; answers to commonly asked questions on benefits, safety, and immunologic aspects of vaccines; and links to a number of online resources for physicians and patients. Healthcare professionals and family physicians also play a key role in driving vaccine acceptance.

7. Are COVID-19 Vaccines Safe for Patients on Blood Thinners ? (Yes : ICMR)

Both the COVID-19 vaccines approved for emergency use in India - Covaxin and Covishield are safe for people on blood thinners, says the Indian Council of Medical Research (ICMR). Blood thinners are of two categories - anti-platelets and anti-coagulants. For those on anti-platelets like aspirin, the vaccine causes no problem but for those on anti-coagulants, the tendency to bleed is much higher. This is also a relative contra-indication and the anti-coagulant can be stopped a day or two before administering the vaccine.

Caution with Blood Thinners : The Food and Drug Administration (FDA) recommends the patient should inform the vaccine provider if he /she is on blood thinners when they go to receive their COVID-19 shots. Blood thinners prevent clotting, so even a small injury such as a needle piercing the skin can cause more bleeding or bruising than usual. Neither the FDA nor the Centers for Disease Control and Prevention (CDC) recommend that patients should avoid coronavirus vaccination just because they are on blood thinners.

8. Are COVID-19 Vaccines Safe and Effective in Pregnancy ? (Yes)

Preliminary research shows that the Moderna and Pfizer COVID-19 vaccines trigger strong immune responses in pregnant and breastfeeding women, equivalent to that of other women of reproductive age. The data also suggests that the vaccines are equally safe in all women of reproductive age and that they are also likely to offer at least some protection to the fetus through the placenta, and to newborns through breast milk. One study included a relatively small group of participants; a total of 131 vaccinated women participated in the study, including 84 pregnant, 31 breastfeeding, and 16 non-pregnant women. For comparison, the study authors also analyzed banked blood samples from 37 women infected with COVID-19 during pregnancy. This is preliminary evidence but from the results that were presented, COVID-19 vaccines work well in pregnant and lactating women, similar to non-pregnant women, and better than natural immunity. Scientists suspected that COVID-19 vaccines would be safe and effective in pregnant and breastfeeding women, but they lacked herd data because these demographics were excluded from vaccine trials.

9. Do COVID-19 Vaccines Interfere with the Actions of Commonly Prescribed Medications ?

Medical experts say the vast majority of prescribed drugs will work just as well on patients after COVID-19 vaccination, and they won't affect the effectiveness of the shot. The fact is that most of the maintenance medications (Anti-diabetic drugs, anti-hypertensive drugs, anti-hyperlipidemic drugs, etc.) that are commonly prescribed do not have any action on the immune system where the COVID-19 vaccines act. Albuterol (Salbutamol), Acetaminophen (Paracetamol), Atorvastatin, Amlodipine, Gabapentin , Hydrocodone, Lisinopril, Losartan, Levothyroxine, Metformin are all safe with COVID-19 vaccination.

Some medications may, however decrease the efficacy of the vaccine and dampen vaccine effectiveness, namely :

- Drugs prescribed for patients who underwent organ transplant (immunosuppressant drugs)
- Drugs to treat an autoimmune disease (immunosuppressant drugs)
- Drugs for Cancer chemotherapies
- Drugs to treat HIV that act on the immune system

However, patients on these medications are still advised to take the vaccine, though the protective efficacy may not be as much as in the general population, still, some degree of protection is conferred, which is better than nothing .

10. Is Covishield 100% Effective in Preventing Severe Disease ?

AstraZeneca's vaccine Covishield was co-developed by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

The AstraZeneca US Phase III trial of AZD 1222 (Covishield in India) demonstrated a statistically significant vaccine efficacy of 79% at preventing symptomatic COVID-19 and 100% at preventing severe disease and hospitalization. In this double-blinded, placebo-controlled multicenter trial, safety and efficacy were analyzed. The trial included 32,449 participants accruing 141 symptomatic cases of COVID-19. The trial had a 2:1 randomization of vaccine to placebo. In this trial, 20% of participants were aged 65 years and above and approximately 60% had co-morbidities that increase the risk of having severe COVID-19. The participants received two doses administered at a four-week interval.

Trials have shown that an extended interval of up to 12 weeks demonstrated greater efficacy, which was also supported by immunogenicity data. This evidence suggested that administration of the second dose after an interval longer than four weeks could further increase vaccine efficacy. This would also increase the number of available doses enabling widespread vaccine coverage. There was no increased risk of thrombosis or events characterized by thrombosis. Trial results also revealed that there was comparable efficacy of the vaccine across different ethnicity and age groups, with 80% efficacy in participants aged 65 years.

11. What is the Current Status of Additional Booster Shots of COVID-19 Vaccine ?

Three new studies published by the US CDC reveal that the immunity conferred by the Pfizer and Moderna vaccines waned over time, prompting a debate among experts about the need for additional booster shots. Even so, these studies also found that these vaccines were largely effective against hospitalisations. These studies were released just about a week after the FDA authorised booster shots for transplant recipients and people with weakened immune systems, with the objective to offer them better protection against infection with COVID-19 variants. The FDA said those who had received either the Moderna or Pfizer-BioNTech vaccines could take a third dose. There is no information on beneficiaries of the Johnson and Johnson single-dose vaccine yet, but recipients of this vaccine are also to likely require booster shots. Countries such as France, Israel and Germany have already laid out plans to roll out the administration of booster shots. Meanwhile, the WHO has placed a moratorium on additional shots of COVID-19 vaccines, largely due to the disparity in vaccination coverage in low and high-income countries. The Director-General of the World Health Organization (WHO), Dr. Tedros Adhanom Ghebreyesus, emphasised previously that countries which have already consumed a major chunk of the global vaccine supply cannot go on using more of it.

12. Can we try to Mix and Match COVID-19 Vaccines ?

Currently, guidelines in the United States and in the U.K. recommend that COVID-19 vaccines should not be used interchangeably unless the same type of vaccine isn't available for a person's second dose or if it's unknown what vaccine the person got as a first dose.

The Oxford-AstraZeneca and the Pfizer vaccines were developed using two different approaches; to spur the immune system, the former uses a weakened adenovirus to deliver the genes of the spike protein and the latter uses messenger RNA enveloped in a nanoparticle. It is not yet clear if giving two different vaccines would confer any benefit. The closest data we have on this is on Russia's Sputnik-V vaccine, which was 91% effective in preventing COVID-19 and uses two slightly different versions of its vaccine for its two separate doses. Still, both versions were developed using the same adenovirus-based technology.

Researchers at the University of Oxford in the U.K. will begin to test what happens when they give people a mix of different COVID-19 vaccines. Amid a shortage of vaccine supplies and the threat of emerging coronavirus variants, such an approach might provide an answer for both, according to a statement. This study, which will include more

than 800 volunteers across England who are 50 years of age or older, is the first to analyze a mix-and-match approach to COVID-19 vaccination. Some participants will be given a first dose of the Oxford-AstraZeneca vaccine followed by a second dose of the same vaccine or the Pfizer vaccine, and some will be given the Pfizer vaccine followed by a second dose of the same vaccine or the Oxford-AstraZeneca vaccine. Some participants will be given the two doses four weeks apart and others will be given the vaccines 12 weeks apart (which is in line with the U.K.'s policy to vaccinate as many people as possible and delay the second dose by 12 weeks). All participants will periodically give blood samples and the researchers will test the impact of the mixing and matching on their immune responses and will also test for any adverse reactions. If the study does indeed show that a mix-and-match approach confers a great benefit, it will still be formally reviewed for safety and efficacy by the Medicines and Healthcare products Regulatory Agency (MHRA) before such an approach is taken to vaccinate the rest of the public.

13. What about COVID-19 Vaccination for Infants and Young Children ?

Moderna has begun testing its COVID-19 vaccine in children as young as 6 months old and up to 11 years old. The clinical trial includes healthy children in the U.S. and Canada and will be conducted in two parts according to the company's statement. In the first stage, the company will test how the participants respond to different dose levels of the vaccine. Children older than two years may receive 50 or 100 micrograms of vaccine per dose, while those younger than two years may receive 25, 50, or 100 mcg. All children will receive two doses in total, each dose given 28 days apart, the same spacing as adult shots. The first children in each group will receive the lowest dose of the vaccine in order to watch for side effects before giving higher doses to other children. An interim analysis will be performed after the first stage to determine which dose level is appropriate for each age group.

Burning Questions that only the Future can Answer :

- ***Will existing or newer vaccines be able to control the COVID-19 pandemic and bring about its end ?***
- ***Will vaccines protect the most vulnerable sections of society ?***
- ***Will it be possible to overcome economic and political problems to allow universal equitable access to COVID-19 vaccines for all ?***

Figure 1. COVID-19 Vaccines

Summary :

- For a novel and evolving disease like COVID-19, it is difficult to predict which subset of the immune response and therefore which vaccine will be more effective.

- There are currently over 150 official vaccine projects, about 50 of which have already progressed to the stage of human clinical trials.

- Different vaccines will induce different types, levels and duration of immunity against COVID-19.

- It is hoped that vaccines will contribute significantly to the control and elimination of the deadliest pandemic of the 21st century.

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PREFACE TO THE ACADEMIC SECTION

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Dear Colleagues,

As the Editor of our NCCP(I) Newsletter - Lung Bulletin, it is my privilege to welcome You to the academic section of the Newsletter. For this issue, the theme is *" All About Oxygen Therapy "*. You would, no doubt, wonder about the selection of this topic. Well, Oxygen is compatible with life, as evidenced by the very first breath of a newborn child. While Oxygen has been prevalent in our atmosphere for eons, it may interest You to know that it wasn't originally a part of the Earth's environment when our planet was first formed. As time progressed, Oxygen was slowly added to our atmosphere by cyanobacteria, one of the earliest unicellular life forms on Earth till it happened to reach significant proportions, which represented a "turning point" in the evolution of life, as the new oxygen-rich atmosphere led to gradual depletion of the anaerobic life forms, and their replacement with aerobic life forms, which constitute the dominant species on Earth today.

In spite of its ancient origins, Oxygen wasn't recognised as an essential component of air that was compatible with life until much later. Alchemists were the first to recognize that a portion of air was necessary for combustion. The seventeenth and eighteenth centuries witnessed a spurt in scientific experiments and research, and as alchemy gave way to scientific chemistry, more and more scientists became interested in isolating this combustible fraction of air. The identification of oxygen as a gas compatible with life and its isolation in pure form from air came only during the later half of the eighteenth century. Physicians were quick to express interest in oxygen therapy for the treatment of both acute and chronic illnesses soon after its discovery; and; while it initially did take off with a good start, unfortunately followed a trajectory of disrepute and scepticism, due to rampant unscientific and irrational practices, akin to quackery, fuelled by commercial interests, and was largely abandoned, except for occasional experiments and case reports where it was found to be useful.

The beginning of the twentieth century, coinciding with the dawn of the era of modern medicine, witnessed a revival of interest in oxygen therapy by practitioners; and; this time; aided by leaps and bounds in technological advances, as well as circumstances created by the two World Wars and pandemics of infectious diseases like influenza and polio, led to its resurgence, this time with strong physiological rationale, robustly supported by clinical evidence in animal and human studies, as well as advances in research and basic sciences. Pandemics are like teachers who teach us all a lesson, and the current global pandemic of COVID-19 is no exception to this rule, as many of the shortcomings in oxygen storage, supply, transport and delivery identified during the first World war and the influenza and polio pandemics of the twentieth century are known to remain largely uncorrected even today.

In today's era of modern medicine, the practice of Oxygen therapy is indispensable, indeed, reviving a critically ill patient of respiratory failure without supplemental oxygen is unheard of. Oxygen therapy is inextricably linked to assisted ventilation, both invasive as well as non-invasive, and has, over the years, gained acceptance as a modality for the management of acute exacerbations with hypoxia as well as several chronic respiratory and non-respiratory conditions. One cannot imagine a hospital, nursing home, operation theatre, intensive care unit, casualty or emergency room without facilities for oxygen therapy. The advent of oxygen concentrators and pulse oximeters has rendered possible the administration and monitoring of oxygen therapy in the convenience of the patients' home environment. While these advances are applaudable, it is astonishing to realise that Oxygen therapy in modern medicine is barely seven decades old, and its widespread acceptance by the medical fraternity came much later. To commemorate the contributions of all whose efforts led to oxygen therapy and assisted ventilation achieving their current status in modern medicine, I have compiled a photo gallery in the very first chapter on historical and current and future perspectives '*Past, present and future of Oxygen therapy*', which I admit is by no means complete, and I welcome suggestions for improvement.

This academic section of this issue of NCCP(I) Lung Bulletin is true to its name i.e. ' *All about Oxygen Therapy* '. Not only are the historical perspectives of the discovery of oxygen and the evolution of oxygen therapy in medicine from the past to the present discussed, but also the physiological basis of gas exchange, respiratory failure, the scientific basis, indications, modalities and devices for administration and monitoring of oxygen therapy for different medical conditions, acute and chronic, and its administration, either alone or along with assisted ventilation and pulmonary interventions, for both the adult and the pediatric patient population have been covered, as well as sources, supply, storage, transport, toxicity, conservatory strategies of oxygen, oxygen audits, practice points useful to manage oxygen crisis during pandemics as well as valuable lessons for the future. It must not be forgotten that Oxygen, like any other medication, is considered as a drug and, as such, has to be administered accordingly just like any other drug, keeping in mind its benefits versus risk and fine-tuning the dose, delivery and duration of oxygen therapy to every patient.

India is as diverse as it is vast, and we at NCCP(I) are committed to upholding this diversity, by giving recognition to seniority and experience as well as providing an opportunity for young talent across the country to share their expertise in clinical as well as evidence-based medicine. As You read further, You would realise that we have carefully selected from a pool of authors belonging to different age groups and from regions spanning the very length and breadth of our vast country, as well as from neighbouring and western countries in Asia and Europe, some of them from premier medical institutions, to share their knowledge and experience regarding the principles and practice of Oxygen therapy with You, reflecting the importance we attach to cultural and regional diversity, as well as national and global representation.

Clinical medicine was the old, and evidence-based medicine the new norm in healthcare, while precision medicine is the upcoming frontier in research. Once the spark of scientific temper is ignited, the mind, ever hungry for knowledge, is gripped with a thirst that can only be quenched from a large pool of information about natural history as well as current perspectives and progress in new vistas of medicine. We, at NCCP(I) acknowledge and give due recognition to both the old and the new. Each issue of NCCP(I) Lung Bulletin is concocted with a novel recipe to satisfy the voracious appetite of information in our hungry young readers. The buffet of knowledge begins with an appetizer of historical perspectives, accompanied by a salad of physiology and other basic sciences, topped with a dressing of clinical application relevant to the real world. This is followed by the first, second and main courses of clinical presentation, diagnosis and management. Finally, the service ends with dessert, comprising of case reports abundant in clinical experience and discussion. This academic cocktail ensures a unique amalgamation of knowledge, experience and skill in a dynamic attempt to balance and cherish the clinical approach in today's era of precision and evidence-based medicine.

While compiling Lung Bulletin, we have made a sincere attempt to cater to the needs, aspirations and expectations of all our readers, the young, senior as well as middle-aged Chest Physicians, as well as the post-graduate trainees, keeping true to the vision of NCCP(I). All articles have been written and edited to follow a standard pattern. Each article includes an introduction and summary or key points, with references for those who wish to read further. Some case reports that reflect commonly encountered clinical scenarios are also discussed in depth for the reader to develop a better grasp of the subject. To break the monotony of reading subjective articles and make it more lively and interesting for the reader, some articles have been written in a question-answer format. We have attempted to provide a concise, yet comprehensive review of the historical and current perspectives, theory, practice and clinical applications of Oxygen therapy in a nutshell and I hope both teachers and post-graduate students of Pulmonary Medicine as well as young Chest Physicians who have just commenced practice will appreciate our endeavour. While I confess there exists some overlap in the content of different articles, I would like to clarify that this is with the intent to ensure each article remains complete in itself, mainly for the convenience of the reader.

I acknowledge and appreciate the efforts and hard work of all our distinguished authors, as all articles were meticulously written. I personally express my gratitude to all of them for being prompt in the submission of their articles, especially when the devastating second wave of COVID-19 wreaked havoc in the world around us. I would like to place on record that most of our authors were active and busy with official COVID-19 duties in their respective institutions, or were personally afflicted with infection themselves or to their near and dear ones, and were stressed for time and availability, yet all remained accessible, responsive and supportive, almost like a family throughout this endeavour. Refining each article to meet standards of excellence was an uphill task rendered possible only by their cooperation, and I am particularly grateful for their patience, especially while accomodating my attempts to edit and fine-tune their submissions. Our goal for this Newsletter is to provide valuable insight and promote good clinical practice ensuring a standard of care for the administration of oxygen therapy. I hope the popularity and appeal of NCCP(I) Lung Bulletin grows across India as well as extends beyond our borders and that everyone finds this issue useful as a single all-in-one source of information about oxygen therapy, as well as a reliable guide for resolution of dilemmas regarding its application in their day-to-day clinical practice, and it acquires status as a reference source and handy guide which everyone would like to keep ready on their desks.

Wish You All Pleasant and Informative Reading of NCCP(I) Lung Bulletin !
We hope it Enriches Your Understanding and Quenches Your Thirst for Knowledge !

Past, Present and Future of Oxygen Therapy

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Introduction :

The first breath of a newborn child begins with a "cry" and brings joy to all. Breathing air or "vayu" is considered to be the first sign compatible with life. Life today depends heavily on oxygen. This is because 20.95% of the atmospheric air we breathe consists of oxygen, which all aerobic organisms require for survival by generating energy via ATP production from energy-rich substrates such as glucose in the mitochondria, a process we know as aerobic respiration. In addition, several essential organic molecules in living organisms such as nucleic acids, proteins, carbohydrates and fats contain oxygen, as do inorganic compounds found in teeth, bone and animal shells. Most of the mass of living organisms is composed of oxygen bound to hydrogen as water. Oxygen is the third most abundant element in the universe. However, it is believed than when the Earth was formed, it possessed a "weakly reducing" atmosphere composed mainly of volcanic gases like nitrogen, hydrogen, carbon dioxide and methane which was practically devoid of oxygen. Oxygen, in those times, was either bonded to minerals like iron in the earth's crust or to hydrogen in water, and did not exist abundantly in the free form. Cyanobacteria, unicellular blue-green algae that were the precursors of modern plants originated about 3.5 billion years ago in the ocean and are believed to be responsible for producing oxygen in the free form for the very first time on Earth in marine environments. For a while, this free oxygen produced by cyanobacteria would react with iron and other minerals and a balance was established as the oxygen absorbed by the environment could keep up with its production. However, as cyanobacteria flourished, the minerals and other sinks became saturated and could no longer absorb the free oxygen being produced, which accumulated in the water bodies, and from there, began to leak into the weakly reducing atmosphere, slowly converting it into a more oxidizing one. This event, designated as the "Great Oxidation Event" is believed to have occurred about 2.5 billion years ago and is described as a "Turning Point", as the new oxygen-rich atmosphere led to gradual extinction of the predominantly anaerobic life forms on earth such as bacteria and other anaerobic organisms that were unable to adapt to the presence of oxygen, and their replacement by aerobic life forms, which constitute the dominant living species today [1,2,3].

Discovery of Oxygen :

Philo of Byzantium, Greece, in the 2nd century B.C. in his work *'Pneumatica'*, described what is possibly the first known experiment which demonstrated that a portion of air is made up by a combustible gas, by inverting a glass vessel over a burning candle and surrounding the vessel's neck with water which resulted in water rising into the neck, but he incorrectly surmised that a portion of the air in the vessel was converted into fire [4]. Centuries later, the Italian genius Leonardo da Vinci built on Philo's work during the Renaissance period by observing that a portion of air is consumed during combustion and respiration [5]. A substance in air, released by the thermal decomposition of potassium nitrate, was first isolated by the Polish alchemist and physician Michael Sendivogius who referred to it as "Cibus Vitae" (food of life) in the compilation of his experiments between 1598 and 1604 titled '*De Lapide Philosophorum Tractatus duodecim e naturae fonte et manuali experientia depromti*', also known as '*Novum Lumen Chymicum'* (New Chemical Light) [6]. During the 17th century, the Anglo-Irish physicist Robert Boyle proved that air is necessary for combustion and metals gained weight when heated [7]. Experiments conducted by the English chemist John Mayow supported the observations of Boyle by showing that fire requires only a portion of air, called "Spiritus Nitroaereus" by him. In one such experiment, Mayow found that placing either a mouse or a lit candle inside a closed container over water caused the water to rise and displace one-fourteenth of the volume of air before extinguishing the subjects, from which, he concluded that "nitroaereus" was consumed during both respiration and combustion. In addition, Mayow observed that antimony increased in weight when heated, he inferred that the "nitroaereus" portion of air must have combined with it. Mayow was the first to surmise that the lungs separate this "nitroaereus" portion from inspired air and pass it onto the bloodstream and that animal heat and muscle movements result from the reaction of "nitroaereus" with certain substances in the body, accounts of these and other experiments and ideas were published in 1668 in his work *'Tractatus Duo'* in the tract *'De Respiratione'* [8,9,10]. The phlogiston theory (derived from the ancient Greek word "phlogiston" which means "burning up"), the concept of which was proposed in 1667 by the German alchemist Johann Joachim Becher, and formally established later by his student

Georg Ernst Stahl in 1731, stated that all combustible substances were made up of two parts, one part, a “fire-like” element called “phlogiston”, was released into the air when the substance was burned, while the other “dephlogisticated” part was thought to be its true form, growing plants were thought to absorb “phlogiston”, which is why air did not spontaneously combust and also why plant matter (dried wood, leaves, etc) burned well when ignited [10,11]. Between the 17th and 18th centuries, the scientists Mikhail Vasilyevich Lomonosov of Russia, Robert Hooke of England, Ole Borch of Denmark, and Pierre Bayen of France all conducted experiments on combustion that produced oxygen in minute quantities but none of them were able to recognize it as an element, as many scientists still favoured the phlogiston theory [10,12]. The phlogiston theory was eventually abandoned before the end of the 18th century following experiments by Antoine Lavoisier and others, nevertheless it remains an important milestone in the history of oxygen, as it led many scientists to conduct experiments which ultimately concluded with the discovery of oxygen.

Carl Wilhelm Scheele, a Swedish-German pharmacist in Uppsala, Sweden, produced oxygen by heating mercuric oxide and various nitrates in 1771-72 and gave it the name “Fire Air” as it was the only known agent that supported combustion. He described it in his book *‘Treatise on Air and Fire’* , which he sent to his publisher in 1775, but the manuscript was not published till 1777 [5,12]. The British chemist and clergyman Joseph Priestley of Wiltshire, England was the second to isolate oxygen by focussing sunlight on mercuric oxide in a glass tube, which liberated a gas he called “dephlogisticated air”, which we know as oxygen today. He noted that candles burned brighter in the gas and that a mouse was more active and lived longer while breathing it. He even breathed the gas himself and described his own experience as follows :

"The feeling of it to my lungs was not sensibly different from that of common air, but I fancied that my breast felt peculiarly light and easy for some time afterwards" .

Priestley claimed that only two mice and himself had the privilege of breathing this new gas. Priestley published his findings in a paper titled *‘An Account of Further Discoveries in Air’* published in 1775 [13], which was included in the second volume of his book titled ‘*Experiments and Observations on Different Kinds of Air’* [14]. As Priestley’s findings were published before those of Scheele, he is usually given priority in the discovery of oxygen [5,12,13,14].

Priestley paid a visit to the French chemist Antoine-Laurent Lavoisier in October 1774, during which he revealed his experiment in which he had isolated the new gas. Scheele had also dispatched a letter to Lavoisier on September 30, 1774, in which he described his discovery of the gas [12]. The contributions of Lavoisier in the discovery of oxygen are plentiful. Firstly, it was Lavoisier who discredited the phlogiston theory [15]. Secondly, it was Lavoisier who first coined the term “Oxygen” for this gas, and thirdly, it was he who correctly identified the vital role it plays in combustion, though he later on claimed to have discovered it independently. Lavoisier conducted the first quantitative experiments on oxidation and in one of them observed how there was no overall increase in weight when tin and air were heated in a closed container, moreover, he noted that air rushed in on opening the container, which indicated that part of the trapped air had been consumed, and, furthermore, the tin had increased in weight by a quantum same to that of the air that rushed back in. This and other experiments on combustion in which he proved that air is a mixture of two gases, one of which he called “Vital Air”, essential for respiration and combustion, and the other “Azote” (Greek for "lifeless"), which did not support either process, were documented in his book ‘*Sur la combustion en généra’l’*, published in 1777. Azote was later given the name “Nitrogen” in English, although it has retained the earlier name in French and several other European languages [5].

In 1777, Lavoisier renamed “Vital Air” to “Oxygène*”* which means literally, “acid former” or “acid producer” [derived from the words *“*oxy” - "sharp, acid" (from Greek “oxys” which means "sharp, sour", used to describe the sour taste and corrosive nature of acids) and “-gène” - "one that produces or generates" (from Greek “-gen s” which means "born, generated")] [10], because he incorrectly believed that oxygen was a constituent of all acids, a belief later disproved by the eminent British scientist Sir Humphry Davy who showed that the acid of Scheele's substance, called at the time “oxymuriatic acid”, contained no oxygen [16]. However, by then the name “Oxygen” had become too well established in the English language and continues to stick to this day, inspite of opposition by English scientists and the fact that it was Priestley who successfully isolated the gas and first published his discovery about it, partly due to a poem praising oxygen in the popular book ‘*The Botanic Garden’* published in 1791 by Erasmus Darwin, the grandfather of Charles Darwin [10,12,17].

<u>Chemical properties of Oxygen [18] :</u>

1. Symbol : O
2. Atomic number : 8
3. Atomic weight 15.9994 (approx. 16) $g.mol^{-1}$
4. Electronegativity : 3.5
5. Density : 1.429 kg/m^3 at 20°C
6. Specific Gravity : 1.1
7. Melting point : -219 °C
8. Boiling point : -183 °C

Oxygen exists as a gaseous chemical element in natural form as a diatomic molecule O_2, and also as a triatomic molecule O_3 (Ozone). A total of seventeen different isotopes of oxygen have been identified [19], out of which three stable isotopes exist in

natural form, namely ^{16}O, ^{17}O, and ^{18}O, with ^{16}O being the most abundant (99.762% natural abundance) [10,20]. Under normal conditions oxygen is a colourless, odourless and tasteless gas which condensates as a light blue liquid. Unlike most gases which are slightly diamagnetic, meaning that they are repelled out of a magnetic field, oxygen is paramagnetic and is attracted by a magnetic field. Of the small group of gases including nitrogen and argon that are paramagnetic, oxygen is the most paramagnetic gas of all, and this paramagnetic property is extended to its liquid form as well [21,22]. Oxygen is reactive and readily forms compounds, called oxides with all other elements except helium, neon, argon and krypton [23].

Oxygen gas (O_2) is moderately soluble in water. As the content of oxygen in atmospheric air is 20.9%, the partial pressure of oxygen at sea level (1 atm) is 0.209 atm. The water solubility of oxygen at an ambient temperature of 25°C and atmospheric pressure of 1 bar is 40 mg/L water, therefore, in atmospheric air in which the partial pressure of oxygen is 0.209 atm, 40 x 0.209 = 8.36 mg of oxygen will dissolve in each liter of water that comes in contact with air. Like all gases, the solubility of oxygen is strongly affected by temperature and pressure, being lower at higher temperatures and vice-versa. Oxygen solubility is also inversely proportional to the amount of dissolved solids. Consequently, oxygen solubility in freshwater exceeds that of seawater by 1 to 3 mg/L, depending on the temperature. The saturation constant of oxygen in rivers and lakes in highlands, hilly and mountainous areas is usually lower than those in the lowlands, being pressure dependent [24].

Evolution of Oxygen Therapy in Medicine :

In 1783 the French physician Caillens reported the first case in which oxygen was actually employed as a remedy, and in the following year the Swiss physician Jurine, of Geneva, published an essay, in which reported the case of one of his patients ,a young lady afflicted with tuberculosis, who benefited from daily inhalations of oxygen [25]. In 1789 the physician Chaptal, of Montpellier, France reported his experience of two of his patients suffering from tuberculosis who were administered oxygen, which produced immense relief in one of them but not the other [26]. However, it was the work of two societies in England, formed towards the end of the 18th century that gave oxygen its current status as a drug in medicine. The Lunar Society of Birmingham was an exclusive group formed by eminent scientists who met once every month on the night of the full moon (allegedly so to allow them to walk home safely by moonlight, through the dark and unpatrolled streets of the city) with the objective to encourage transfer of new scientific knowledge to industry. Its prominent members included Joseph Priestley, Josiah Wedgwood, Erasmus Darwin (the grandfather of Charles Darwin) and the Scottish inventor James Watt. It was at one such meeting of the Lunar society that Watt learned from Priestley about his experiences with the new "dephlogisticated air", this may have been the reason why Watt joined Thomas Beddoes, an English physician and scientific writer when he founded the Pneumatic Institution in Bristol in 1799 along with Sir Humphry Davy, who also served as its superintendent (Figure 1). Beddoes believed that oxygen therapy was beneficial for the treatment of certain medical disorders, and in others, even if it did no good, it could do no harm [27] . Out-patients were administered oxygen at the pneumatic institution for treatment of a variety of diseases such as consumption, scrofula or King's evil (tuberculosis), asthma, palsy, dropsy, venereal disorders, and others, which conventional treatment failed to relieve or cure (Figure 1).

BRISTOL GAZETTE and PUBLIC ADVERTISER, March 21, 1799

NEW MEDICAL INSTITUTION

This institution is fixed at the upper end of Dowry-Square, Hotwells, corner house. It is intended among other purposes for treating diseases, hitherto found incurable, upon a new plan. Among the subscribers are almost all the Medical professors at Edinburgh, and a large portion of the Physicians in England, who have done anything to improve the practice of their art.

At present it is only ready for out-patients, and the attendance of persons in Consumption, Asthma, Palsy, Dropsy, obstinate Venereal Complaints, Scrophula or King's Evil, and other diseases, which ordinary means have failed to remove is desired.

Patients will be treated gratis. The application of persons in confirmed consumption is principally wished at present; and though the disease has heretofore been deemed hopeless, it is confidently expected that a considerable portion of such cases will be permanently cured.

It has been perfectly ascertained by experience, that none of the methods to be pursued are hazardous or painful.

Attendance will be given from Eleven till One o'clock by Thomas Beddoes or Humphry Davy.

Subscriptions for the support of this Institution received by John Savery, Esq., Narrow Wine Street, Bristol.

Figure 1. First public notice of the Pneumatic Institution , appearing in the *"Bristol Gazette"*
(From : http://www.lakesidepress.com/pulmonary/papers/ox-hist/ox-hist1.html)

Beddoes, Davy, Watt and their colleagues at the Pneumatic Institution made no claim for cure; they merely informed patients that their aim was to investigate the efficacy of oxygen either for the treatment of disease or relief of its symptoms. Typical therapy was described as “a pint of oxygen in a bagful of common air”, that is to say, diluted 20 to 40 times its bulk in air, with a tendency to gradually increase the dose (oxygen concentration) as symptom relief directed, it is estimated that such a mixture must have contained approximately 23 to 28% oxygen, with higher concentrations administered on a case-to-case basis for specific conditions [25,27] . Many techniques and devices for oxygen delivery similar to those developed at the Pneumatic Institution are still used today, including corrugated non-crushable breathing tubes, mouthpieces and the method for mass production of gases devised by Watt [25,26] . In 1800, the pneumatic institution was converted into a hospital to cope with the Typhus outbreak in Bristol, which brought the chapter of rational and scientific investigation into the efficacy of oxygen therapy to a nearly abrupt end for over a century, until it was revived by the work of Haldane and others.

During the 1800s, the physician S. B. Birch in England published papers advocating the use of oxygen therapy for different conditions, these doses were usually small, typical therapy being “four gallons in the morning and evening”, usually delivered by wafting oxygen from a bucket towards the face of the patient [25,26,28,29,30] . In one such publication in *The Lancet* in 1869, Birch even advocated the use of “oxygenated bread and water” [28,30] .

Throughout the 19th century there were very few instances of oxygen therapy administered rationally, however, several instances of “Compound Oxygen” therapy, often advertised as a cure-all magic remedy are on record [25,31]. This, instead of pure oxygen, was often nitrous oxide, mixed with ferric carbonate or potassium chlorate to give it colour and convince patients that they were obtaining benefit, much in the same way oxygen in modern oxygen parlours is bubbled through coloured water [25]. Such irrational commercial practices were heavily criticized by the American physician Samuel S. Wallian, who strove to advocate rational use of oxygen therapy with a scientific basis for medical purposes [25,26,32].

The first cylinders for storing oxygen were developed in 1868, which permitted its use during general anaesthesia [33,34]. Prior to 1868 the administrator of oxygen always had to manufacture his own gas. Many accomplished this in the same manner as Beddoes and Watt, although highly portable apparatus was available such as that described by Wallian in which potassium chlorate and manganese dioxide in the proportion of seven to one were heated together. To purify the gas, it was initially passed through two bottles of caustic soda solution and then through another weak solution of silver nitrate, pure water and finally a layer of cotton wool before being collected in a rubber bag for administration to the patient. An important development occurred in 1868, in which George Barth, the proprietor of a firm manufacturing nitrous oxide and oxygen transferred 15 gallons of freshly produced oxygen from a bag into a copper cylinder by compression through a hand pump to a maximum allowable pressure of 450 p.s.i.. Steel cylinders were introduced by Barth for nitrous oxide in 1868 but were not used for oxygen until a later date. The availability of compressed oxygen gas removed the need for self-manufacture by the physician or administrator [26,34].

In 1855 the German physician and physiologist Adolph Eugen Fick described the law of diffusion for gases, named after him and in 1870 described the principle, also named after him, which was a defining moment in the development of physiology and the quantitative measurement of blood flow. Fick described oxygen tension in terms of units of partial pressure, and used this to explain the difference in oxygenation between arterial and venous blood, relating this difference to tissue oxygen consumption and cardiac output [35,36].

In 1878, Paul Bert, a French physician and physiologist in his work ‘*La Pression barometrique’* described comprehensively the physiological effects of air pressure, both above and below the normal. He showed that oxygen was toxic to insects, arachnids, myriapods, molluscs, earthworms, fungi, germinating seeds, birds, and other life-forms. Central nervous system toxicity at high oxygen tension was first described by Bert and is sometimes referred to as the "Paul Bert effect" [37,38].

In 1885, George Holtzapple, an American physician was the first to use oxygen to save a young boy dying of pneumonia. A year after graduating in 1884 and setting up practice in the community of Loganville, he was called to a farmhouse to treat a very ill 16-year-old boy suffering from pneumonia, who, already struggling for breath and cyanosed by the time, frantically appealed to Holtzapple to give him more “air”, which Holtzapple correctly assumed to be oxygen. Assuring the worried family that he would be back, Holtzapple rushed back to his carriage, whipped up his horse and sped back to town, only to return later with a spirit lamp, rubber tubing, large test tubes, corks, chlorate of potash and manganese oxide. While setting up his apparatus, Holtzapple gave instructions to the family to fetch a bucket of water and place it near the patient’s head. He carefully mixed and heated the explosive chemicals over the spirit lamp, as the oxygen released travelled up the tube into the bucket of water and bubbled onto the surface, one of the men fanned it onto the patient’s face. Holtzapple remained with the patient, administering oxygen every few hours, and the young boy made an excellent recovery. Holtzapple published this experience as a case report with a reasoned physiological explanation of oxygen therapy for the treatment of pneumonia and was thus the first to document the role of oxygen in the acute care setting [39,40] (Figure 2).

Figure 2. Illustration of Dr. George Holtzapple administering Oxygen therapy to a sick boy with pneumonia from the 1945 edition of *"York – The story of a dynamic community"*
(From : https://www.ydr.com/story/opinion/2020/05/11/york-and-history-oxygen-medicine/3108248001/)

The first record of continuous oxygen therapy in medicine was reported in 1890 by the physician Albert Blodgett of Boston, America, as a last resort for the treatment of a young lady with pneumonia whom he deemed "irrevocably doomed." In the hopes of merely easing her final moments, he hooked her up to an oxygen cannister, turned on the gas, and left it running. To his astonishment, the woman stabilized and her breathing became more regular. He described his experience in his own words as below [25] :

"For a time there was no appreciable benefit from the gas, but gradually the color of the surface improved, the respiration was less embarrassed, the patient could swallow, and the immediate symptoms were again relieved. When I directed the continuous administration of the gas, I did so under the positive conviction that the patient was irrevocably doomed, and the best result that I looked for, was simply relief to the sensation of suffocation, and not any curative action. At this time I had only employed the gas in the manner ordinarily directed, that is, two or three gallons at a time, several times daily. I now directed its use without cessation, and to my great surprise, the patient not only obtained the relief desired, but was enabled to carry on the function of respiration. The amount of gas employed was not far from two hundred gallons in twenty four hours. The dealer who supplied the gas was astonished at the amount required, and, thinking to do me a service, sent me a cautionary message, implying that no human being could possibly stand so great an amount of oxygen, on account of the dangerous degree of stimulation to the system and the increased combustion of tissue" .

The dose of oxygen described above, though considered excessive at the time, would be the modern equivalent of 6 L/min. Blodgett published his results, arguing that oxygen could save lives [41]. This first description of a paradigm shift in oxygen therapy was published at the time when several other papers advocated bizarre methods and routes of oxygen delivery via the stomach for resuscitation, via the urethra for inflammatory conditions and by enema for the treatment of gallstones [42] .

Oxygen therapy took a quantum leap in the years after Holtzapple's and Blodgett's publications, attributable to advances in physiology and medicine, as well as the outcome of gas warfare used during the First World War. Sir William Osler, the Canadian physician, in the first edition of his famous textbook *'The Principles and Practice of Medicine'* published in 1892, commented on the utility of oxygen therapy for different conditions as follows [26] :

Diabetes Mellitus (p. 305) – "The coma is an almost hopeless complication. Inhalations of oxygen have been recommended, and lately the intravenous injections of a saline solution, as practised by Hilton Fagge".

Asthma (p. 501) – "The use of compressed air in the pneumatic cabinet is very beneficial, oxygen inhalations may also be tried".

Emphysema (p. 549) – "Inhalation of oxygen may be used and the remedies given already mentioned in connection with bronchitis".

Anemia (p. 696) – "Dilute hydrochloric acid, manganese, phosphorus, and oxygen have been recommended".

In the third edition of the same book, published in 1898, Osler's comments about oxygen therapy in diabetic coma, asthma, emphysema and anemia remained unchanged, however, for the first time, he added a comment on oxygen therapy for pneumonia (p. 137), as follows [26] :

"It is doubtful whether the inhalation of oxygen in pneumonia is really beneficial. Personally, when called in consultation to a case, if I see the oxygen cylinder at the bedside I feel the prognosis to be extremely grave. It does sometimes seem to give transitory relief and to diminish the cyanosis. It is harmless, its exhibition is very simple, and the process need not be at all disturbing to the patient. The gas may be allowed to flow gently from the nozzle directly under the nostrils of the patient, or it may be administered every alternate 15 minutes through a mask".

These comments suggest that while Osler did use oxygen therapy for some patients, he was not too keen to recommend it to all. In 1899 another physician in the United States Dr. W. L. Conklin described that oxygen therapy was gaining wider acceptance, but there still existed considerable doubt among physicians regarding its efficacy, and described his own experience as follows [26,43] :

"I will not weary you with a detailed account of my own experience with oxygen. I have used it in a variety of pathological conditions accompanied by dyspnoea, with uniform relief so far as that distressing symptom was concerned, and with marked benefit to the patient as well, in nearly every case.

I have always used the mixture prepared by the Walton Oxygen Works and kept constantly in stock by the Paine Drug Company. This is made according to the formula of the London Oxygen Hospital and consists of one part of oxygen and two of nitrogen non-oxide. The latter gas has anaesthetic properties which make it of value, and the mixture is not irritating to the lung tissue, as pure oxygen is said to be.

In looking over current medical literature I find many cases reported in which the results obtained from oxygen inhalations are so evidently favorable as to furnish, it seems to me, strong clinical proof of its therapeutic value.

Believing, as I do, that there are no facts in physiological chemistry which really discredit this clinical evidence, or prove that the use of oxygen is unscientific, I feel confident that it will steadily grow in favor and come in time to be considered of definite and positive therapeutic value by all who will give it a fair trial".

In 1899, 21 years after Paul Bert first described oxygen toxicity in the central nervous system, the Scottish pathologist James Lorrain Smith described his experiments on birds and mice in which he discovered that oxygen at a pressure of 0.43 bar (43 kPa) had no effect but at 0.75 bar (75 kPa) behaved like a pulmonary irritant. Consequently, pulmonary oxygen toxicity is referred to as the "Lorrain Smith effect" [44].

The physician who is credited with giving rational and scientific basis to oxygen therapy and bringing it to its forefront in modern medicine was John Scott Haldane of Scotland [45,46], who, while still a reader in physiology at Oxford University published his landmark paper *'The therapeutic administration of oxygen'* in 1917, in which many of the concepts explained at the time still remain valid and largely unchallenged even today [45,47]. In 1892, Haldane and Lorrain Smith launched a study on the blood oxygen levels in various pathophysiological conditions [48]. In 1898, guided by the Danish physiologist Christian Bohr, Haldane devised an improved blood gas analyser [49,50]. The enhanced affinity of deoxygenated hemoglobin to bind with carbon dioxide was named the "Haldane effect" [50,51]. In 1906, Haldane, working along with the British physiologist John Gillies Priestley (J G Priestley, different from J B Priestley) proved that the respiratory reflex was triggered by an excess of carbon dioxide and not by a deficit of oxygen in blood and they described in detail the regulation of respiratory drive by carbon dioxide and its effects on blood hydrogen ion concentration [52,53] . Haldane also described the concept of anoxemia, which he classified into three types - lack of oxygen (hypoxic), lack of hemoglobin (anemic), or lack of circulation (stagnant) [54]. In addition, Haldane also described the physiologic effects of carbon monoxide poisoning at tissue level [45,46,55] and well as oxygen toxicity in the lungs and central nervous system [56]. He was the first to identify the concept of calculating the percentage of oxygen inspired, far beyond the technology of his time, and pioneered the concept of ventilation-perfusion matching. In 1907 he developed a decompression chamber to help make deep-sea diving safer and produced the first decompression tables after extensive experiments with animals [57,58]. In addition, Haldane led an expedition to Pike's Peak in 1911 and described the physiological adaptation to low oxygen pressures experienced at high altitudes [59,60].

Haldane also investigated mining deaths and asphyxia in coal miners, sometimes subjecting himself to great risk by inhaling toxic gases in self-experimentation. He demonstrated carbon monoxide poisoning to be the major cause of death in coal miners, and advised that miners carry small animals like mice or canaries along with them to detect dangerous levels of gases in mines, apart from being small, lightweight and easily portable, these animals also had a higher basal metabolic rate, which meant that the symptoms of gas poisoning became evident in them well before the gases accumulated to reach levels toxic to workers, this practice was followed till the 1980s, when the animals were replaced by electronic gas detectors. He was a noted authority on the effects of different pulmonary diseases, such as silicosis and toxic gas inhalation in miners [45,46] and published the book *'Respiration'* in 1922 [52]. Apart from respiratory physiology, Haldane also studied the physiology of sweating and suggested ways to treat heat stroke in miners and oil rig workers [45,46]. Haldane described the physiological derangements that occur in pneumonia in his own words as follows [25] :

"When a portion of the lungs, including even the greater portion of both lungs, is entirely blocked by consolidation, there is commonly no cyanosis. This indicates that there is very little blood passing through the consolidated parts. What passes through the healthy portion is sufficient for respiratory requirements during rest. When cyanosis due to a lung affection exists, in spite of the fact that air is entering the whole or a great part of the lungs freely, we seem driven to the conclusion that the entry of oxygen in the blood through the alveolar walls is impeded by exudation and increase in the thickness of the alveolar walls".

Haldane went on to prove how, in the latter situation, blood levels of carbon dioxide concentration do not rise because carbon dioxide is more soluble than oxygen. His solution for "hindered passage of oxygen through alveolar walls" was to raise the percentage of oxygen in the alveolar air by increasing the concentration (fraction or percentage) of oxygen in inspired air, thereby increasing the diffusion pressure. He was a strong advocate for oxygen therapy in the critically ill, best described in his own words below [25] :

"It may be argued that such measures as the administration of oxygen are at best only palliative and are of no real use, since they do not remove the cause of the pathological condition. As a physiologist, I cannot for a moment agree with this reasoning. The living body is no machine, but an organism constantly tending to maintain or revert to the normal, and the respite afforded by such measures as the temporary administration of oxygen is not wasted, but utilized for recuperation".

This great leap forward made by Haldane is noteworthy, given the fact that a chasm existed between him and his contemporaries in medicine, to cite one example, when he was writing in terms of ventilation-perfusion, others were recommending treatment with subcutaneous administration of oxygen gas [61]. In view of his landmark contributions, Haldane is rightly considered to be the "Father of Oxygen Therapy" and was honoured by the Royal Society with the award of the Queen's Medal in 1916 and the Copley Medal in 1934 [45].

Haldane's expertise came to the fore with gas warfare techniques deployed during the first World War, when oxygen was used for the treatment of poisoning by phosgene (a gas first synthesized by Sir Humphry Davy). Phosgene could be used alone, as well as in combination with other poison gases like chlorine as "white star". Phosgene being more dense and heavier than air, once sprayed would form a dense white cloud that would easily roll down hills and plains into trenches and suffocate soldiers hiding either there (trench warfare) or under camouflage. Phosgene is known to form hydrochloric acid as it combines with water in the lungs, causing direct corrosive action as well as alveolar damage. The effects of phosgene poisoning ranged from mild cough and exertional dyspnea at lower concentrations to frank pulmonary edema and acute respiratory distress at higher concentrations [25, 62].

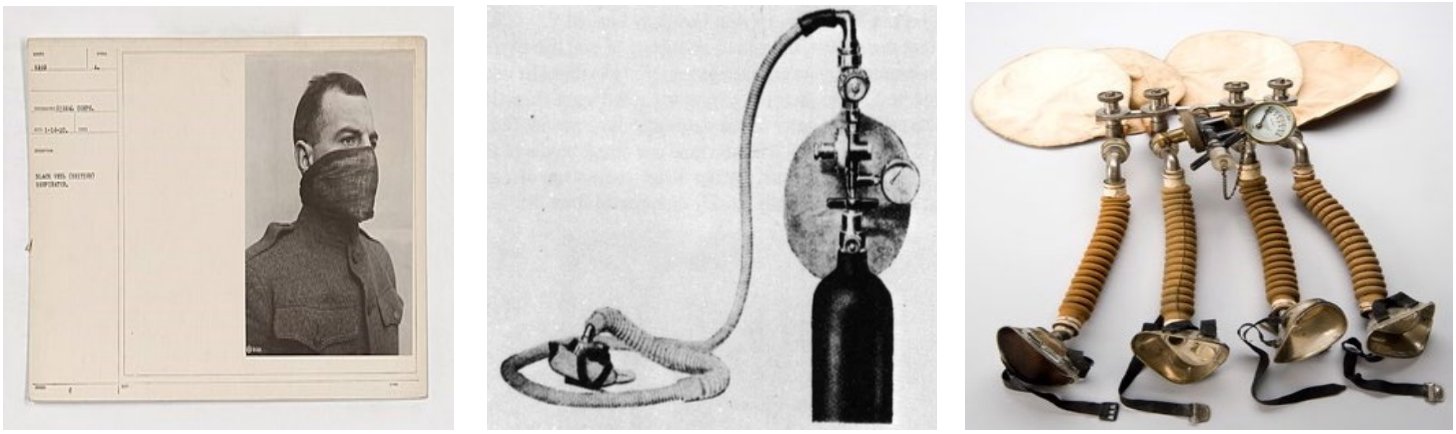
Between 1916-17 more than 17,000 casualties from gas warfare were reported and it is interesting to know that the matter might have been brought to Haldane's attention by his own son, John Burdon Sanderson (JBS) Haldane who enlisted in the third battalion of the Black Watch regiment of the British army and served at the battlefront, first as a trench-mortar instructor and later on as an instructor of grenades during the war, and who later became known for his contributions to physiology, Neo-Darwinism, evolutionary biology, genetics and mathematics. In 1916, after an enemy bomb attack severely wounded him, JBS Haldane was relieved from duty and sent to India for recuperation till 1919, after which he returned to England. It may surprise the reader(s) to know that JBS Haldane became an Indian citizen in 1961 after renouncing British citizenship and worked at the Indian Statistical Institute, Kolkata and later on at Bhubaneshwar, Odisha, India till his death in 1964. He willed his body to the Rangaraya medical college, Kakinada, Andhra Pradesh in India for medical research and teaching [63,64,65,66,67]. JBS Haldane was described in print on 25th June 1962 by Groff Conklin as a "Citizen of the World", to which he responded as follows [68] :

"No doubt I am in some sense a citizen of the world. But I believe with Thomas Jefferson that one of the chief duties of a citizen is to be a nuisance to the government of his state. As there is no world state, I cannot do this. On the other hand, I can be, and am, a nuisance to the government of India, which has the merit of permitting a good deal of criticism, though it reacts to it rather slowly. I also happen to be proud of being a citizen of India, which is a lot more diverse than Europe, let alone the U.S.A, the U.S.S.R or China, and thus a better model for a possible world organisation".

Dr. John Scott Haldane went to the war front at the request of Lord Kitchener and attempted to identify the gases being used, apart from inventing the chemically treated "Black Veil" gas mask to reduce exposure to poison gases, he also experimented with oxygen therapy for the treatment of soldiers and other defence personnel in both the acute and the chronic phases of gas poisoning and devised the first portable respirator as well as an "Oxygen Tent" that could simultaneously administer oxygen to four people at a time [34,69,70,71,72] (Figure 3).

Acute poisoning, after initial triage, was managed by administering oxygen as close to the site of exposure as possible, with the portable respirator devised by Haldane, which consisted of a pressurized cylinder, pressure regulator, a reservoir bag attached to the regulator, and a tight-fitting mask with non-return valves [25,34]. The necessity to administer oxygen continuously for as long as the symptoms of anoxemia persisted was identified, and the earlier practice of giving it only for few minutes every hour was discarded [25]. A common complaint was that oxygen was wasted as it leaked into the air.

Another problem was that in severe cases, secretions from profuse lung edema filled the masks; consequently the face mask was replaced by nasal prongs, developed by Captain Adrian Stokes of the 10th Hussars regiment [25,72]. Persistent nocturnal dyspnea and poor exercise tolerance were identified in many gassed soldiers, long after their recovery from acute exposure, for treatment of which a large facility was established in Cambridge, consisting of large air-tight wards, each sized approximately 1,000 square feet by volume and containing three beds, aerated with an atmosphere of 40 to 50% oxygen, maintained by removing carbon dioxide, water vapour and most of the nitrogen from air by passing it through soda-lime, calcium chloride and potassium permanganate. It is also described how experiments on oxygen therapy were single-blinded at the time, as in some cases, the patient believed that he was getting treatment, while in reality he was not doing so, sometimes he complained that the treatment did him no good, whereas he improved once the oxygen treatment really began. This treatment from single-blinded experiments was known to improve survival in acute gas poisoning and reduce morbidity in the chronic phase [25,28].



A. **B.** **C.**

Figure 3. Equipment devised by Dr. John Scott Haldane during the First World War

A. Black veil gas mask respirator (From : https://en.wikipedia.org/wiki/Black_Veil_Respirator)
B. Oxygen therapy apparatus (From : Leigh JM. The evolution of Oxygen therapy apparatus. Anaesthesia 1974;29: 462-85)
C. Oxygen tent for 4 people (From : https://wellcomecollection.org/works/jmymssca)

In addition to phosgene poisoning, oxygen was also found to be useful for the treatment of pulmonary edema resulting from trench nephritis, acute purulent bronchitis, and severe hemorrhage [25]. The success of oxygen therapy during the First World War was documented, with a report published in the *British Medical Journal* after the war, which highlighted practical difficulties in oxygen supply and administration, some of which remain valid concerns even today [73]. Phosgene is still commercially used in the plastic and dye industry today, with the potential threat of being employed as a bioweapon for terrorism [25].

During the First World War, sufficient knowledge and experience were gained regarding the principles and practice of oxygen therapy, including, but not limited to, storing and administering oxygen from a pressurized cylinder via interfaces such as nasal prongs or masks, with or without a reservoir bag to increase inspired oxygen concentration, following which rational practice of oxygen therapy began to gain acceptance across the world [25,73,74]. However, there still existed reluctance and hesitation to accept continuous oxygen therapy from some members of the medical profession, many of whom still favoured intermittent oxygen therapy. The effect of therapeutic oxygen on survival was described in 1928, and, thereafter, as more evidence evolved to support the utility of oxygen in acute trauma and critical care, intermittent oxygen therapy slowly receded into the background [25,28,74]. In 1962, it was proved that intermittent oxygen therapy was followed by worsening of arterial hypoxemia as compared to that before treatment [75].

Oxygen was used mainly in hospitals for treatment and relief of hypoxemia in patients suffering from a variety of respiratory and other illnesses. It wasn't until the 1950's that the first form of portable medical oxygen was invented, and even then its use was restricted to ambulances and on the scene of medical emergencies [76]. The physician Alvan Leroy Barach is credited for refining the application of oxygen therapy in the United States and laying down the foundation for ambulatory oxygen therapy for chronic lung diseases [74,77]. In 1935 Barach was the first to use helium-oxygen mixture (Heliox) for the relief of dyspnoea in adults and children with asthma and upper airway obstruction [78]. In 1936 he noted that oxygen when administered to select cases of chronic lung disease relieved difficult breathing, restored strength, and reduced limb oedema and designed the first portable oxygen devices for patients with emphysema, as well as transfilled oxygen bottles for ambulatory patients with exertional dyspnea during the 1950's [79,80]. During the same period, the physicians Coats, Gilson [81] and Pierce [82] also used oxygen stored in small, portable, compressed gas cylinders for patients with lung diseases and documented subjective symptom improvement.

At the time, medical oxygen for domiciliary use was provided either by pre-filled heavy pressurized gas cylinders or smaller cryogenic liquid oxygen systems, both of which were cumbersome and inconvenient as they necessitated frequent home visits by suppliers for refilling [76]. The Union Carbide Corporation in the United States invented the molecular sieve in the 1950s which made possible the development of oxygen concentrators and this was followed by the first cryogenic liquid home medical oxygen system in the 1960s [83]. The first oxygen concentrators were manufactured in the early 1970s by both Union Carbide and the Bendix corporations and were large, bulky and expensive units, unlike the concentrators of today [83]. In the mid-1980s, Medicare, the federal health insurance program in the United States switched from a fee-for-service payment to a flat monthly rate for home oxygen therapy, this reimbursement policy change led to an industry driven switch in home oxygen delivery systems from the conventional pressurized gas and liquid oxygen systems previously in use to the more preferred oxygen concentrators, principally to bring down the long-term cost [83]. Since the early 2000s, many companies have produced small portable oxygen concentrators for domiciliary use and travel.

In 1968, two physicians Thomas Petty and Micheal Finigan published the results of the first study documenting the beneficial effects of long-term oxygen therapy (LTOT) administered to twenty patients of chronic obstructive pulmonary disease (COPD) in Denver, Colorado, U.S.A [84]. Thereafter, two landmark randomized clinical trials, the Nocturnal Oxygen Therapy Trial (NOTT) in the United States [85] and the Medical Research Council (MRC) trial in the United Kingdom [86], published in 1980 and 1981 respectively, demonstrated that LTOT significantly decreased mortality among patients of COPD with severe resting hypoxemia.

In 1974, a Japanese engineer Takuo Aoyagi invented the first pulse oximeter to measure oxygen saturation in blood [87]. V. Courtney Broaddus, professor emeritus of medicine and associate director of the Lung Biology Center at the University of California, San Francisco in the United States, and the Editor-in-Chief of the seventh edition of *Murray and Nadel's Textbook of Respiratory Medicine*, during an interview with the New York Times, remarked that oxygen saturation by pulse oximetry in addition to temperature, pulse rate, respiratory rate and blood pressure, has become the fifth vital sign of health [88].

Evolution of Assisted Ventilation :

A. Negative pressure ventilation :

The use of assisted ventilation can be traced back to ancient times, with references dating to the Bible as well as the works of the Greek physician Galen and the anatomist Andreas Vesalius of Denmark, both of whom referred to assisted ventilation by observing distension of the lungs of animals by blowing air through a reed or cane inserted in the trachea [89,90]. Way back in 1670, John Mayow thought of negative pressure ventilation, and constructed a ventilator model from bellows and a bladder to pull in and expel air [91]. The first negative pressure ventilator was devised by the British physician John Dalziel in 1832 [92]. Improved prototypes developed by Eugene Woillez of France in 1876, Alexander Graham Bell of the United States in the 1882, F. Sauerbruch of Germany in 1904 and W. Stueart of South Africa in 1918 followed [91,92,93]. The first of the negative pressure ventilators to be of clinical value, the "Iron Lung" was built by Philip Drinker and Louis Agassiz Shaw Jr., professors of industrial hygiene at the Harvard School of Public Health in the United States in 1928 [91,93,94,95]. It was powered by an electric motor with air pumps from two vacuum cleaners and the first of these devices was used at Boston Children's Hospital, Massachusetts to save the life of an eight-year-old girl afflicted with poliomyelitis. Further improvements to the iron lung were made by August Krogh of Denmark and John Haven Emerson of the United States in 1931, Robert Henderson of the United Kingdom in 1934 and Edward Both of Australia in 1937 [91,93]. These ventilators rose to prominence during the polio epidemic in the 1950s, and were used to treat patients who developed respiratory failure due to diaphragmatic paralysis, who would typically spent two weeks inside an iron lung while recovering (Figure 4). Subsequently, as national universal immunization programmes led to the elimination of polio, interest in negative pressure ventilators dwindled, and they have now largely been replaced by positive pressure ventilators.

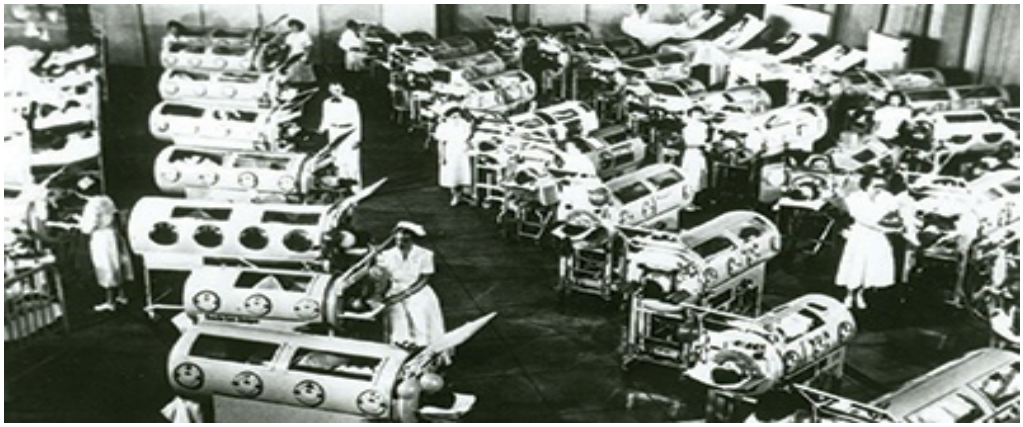


Figure 4. Patients ventilated in Iron Lungs during the Polio epidemic in the United States
(From : https://www.hsph.harvard.edu/news/magazine/centennial-infectious-diseases-pandemics/)

B. Positive pressure ventilation :

In 1773, the English physician William Hawes began publicizing the power of artificial ventilation to revive survivors of drowning. Hawes offered a reward paid out of his own pocket to any one bringing him a body rescued from the water within a reasonable time of immersion. Thomas Cogan, another English physician, joined Hawes in his crusade, and in 1774 both Hawes and Cogan each brought fifteen friends to a meeting at the Chapter Coffee-house, St Paul's Churchyard, where they founded the Royal Humane Society as a campaigning group for first aid and resuscitation [90,96]. Towards the later part of the 18th century, the Royal Humane Society of England began advocating the use of bellows, similar to those used by blacksmiths for artificial respiration, on the recommendation of the Scottish surgeon John Hunter [90,97,98]. One of the first manually operated non-invasive positive pressure ventilators was devised by Francois Chaussier, a French obstetrician in 1780 [93,98]. George Edward Fell, a physician in Buffalo, New York, U.S.A. devised an apparatus from bellows, a face mask and a breathing valve to drive air through a tracheotomy, which was successfully applied clinically in a landmark case in 1887. Another American physician Joseph O'Dwyer modified Fell's face mask-tracheotomy system by incorporating an intralaryngeal tube, this “Fell-O'Dwyer” apparatus was used successfully to provide assisted ventilation for patients of neurosurgery in 1894 and thoracic surgery in 1899 [90,93,97,99]. In 1907, Johann Heinrich Dräger, a German entrepreneur received the patent for his “Pulmotor”, a pneumatically operated positive pressure ventilator known for saving the lives of several thousand individuals [93,96]. In 1910, two American doctors Nathan Green and Henry Harrington Janeway devised a “rhythmic inflation apparatus” for intermittent positive pressure ventilation [93,96]. The bag-valve-mask concept for assisted ventilation was developed in 1953 by the German physician Holger Hesse and his colleague, the Danish anaesthetist Henning Ruben, following their initial work on a suction pump, and named “AMBU” (Artificial Manual Breathing Unit), a name which still sticks to this day [97].

Forrest Morton Bird, an American pilot and biomedical engineer is credited with designing the first successful prototype of the modern positive pressure ventilator, named the "Bird Universal Medical Respirator" in 1957 (Figure 5A) [96,100,101,102]. Bird had served in the United States Army Air Corps during the Second World War as a technical air training officer due to his advanced qualifications, which provided him the opportunity to pilot nearly every aircraft in service, including some of the advanced jet planes which were capable of flying to ‘hypoxic’ altitudes beyond which it became difficult for pilots to breathe, even with oxygen supplementation [100,101,102]. Bird discovered a pressure breathing circuit in an oxygen regulator found in a crashed German Junkers-88 bomber which he was flying back to the United States for study and worked on it with the objective of making it functional, ultimately it became the standard design for high-altitude oxygen regulators for most Allied military aircraft, enabling their pilots to fly upto altitudes of 37,000 feet, far higher than the earlier limit of 28,000 feet permitted by the conventional breathing regulators that had been used previously [100,101,102].

Bird studied physiology and medicine at different schools without taking a degree, in order to understand the response of the human body to the stress it experienced during flight, this knowledge, coupled with his technological prowess and years of experience as an aviator helped him develop efficient ventilators [100,101,102]. Bird’s first prototype was a crude transparent device rigged from strawberry shortcake tins and a doorknob for controlling air pressure [101,102], further revision and refinement of which ultimately led to the Bird Universal Medical Respirator (sold commercially as the Bird Mark 7 Respirator and informally called the "Bird"), a small transparent green box (Figure 5A) that became the prototype for modern positive pressure mechanical ventilators [100,101,102] . Bird also developed subsequent models such as the Bird Mark 8, which added the provision for negative pressure during expiration [100,102], the Bird Mark 9 which allowed much higher pressure and flow during inspiration and was famously used to ventilate an elephant an the San Diego zoo [102], the Bird Mark 10 with a flow accelerator or leak compensating system [102] and another ventilator for infants, nicknamed the “Babybird” (Figure 5B) which considerably brought down breathing-related infant mortality in the United States from 70% to 10% [100,102] .

A. **B.**

Figure 5. Ventilators developed by Forrest Morton Bird

A. The Bird Mark 7 Respirator (From : https://www.woodlibrarymuseum.org/museum/bird-mark-7-respirator/)

B. Main Body of the Baby Bird Ventilator (From : http://www.neonatology.org/pinups/coen/coen.html)

In 1980, the first non-invasive positive pressure ventilator with continuous positive airway pressure (CPAP) was invented by Colin Sullivan, an Australian physician, his invention was the outcome of his interest in the upper airway and its role in sudden infant death syndrome (SIDS). After successfully treating his dog's breathing issues with a vacuum cleaner, the idea struck him that human patients could possibly benefit from similar therapy. He built an experimental prototype from a vacuum cleaner motor attached to a hose and nasal mask, and used it successfully for the very first time to treat a patient of severe obstructive sleep apnea scheduled to undergo a tracheostomy, when the patient, hesitant for the operation, enquired regarding an alternative [103,104].

The Future of Oxygen Therapy :

Science and technology are inextricably linked with medicine, and advances in one follow the other. As technology evolves, more and more novel methods of oxygen delivery are under research. New interfaces and delivery systems, such as the high-flow nasal cannula (HFNC), extra-corporeal membrane oxygenation (ECMO) and pulsed delivery systems, described later by authors of different chapters in this newsletter, intravenous oxygen (IVOX) [105] as well as special entrainment devices have been developed [106]. The potential of nanoparticles to improve oxygen delivery to hypoxic tissues has been studied in diseases such as myocardial infarction, tumors and acute respiratory distress syndrome with interesting implications [107,108,109,110]. Novel engineered proteins such as OMX-CV [111] as well as molecules such as perfluorocarbons (PFCs) [112,113] have also been tested as biotherapeutics for oxygen delivery.

Summary :

- The journey of Oxygen therapy in medicine has progressed over a long and arduous path ever since its inception, taking a quantum leap during the 19th and 20th centuries to achieve its current status, where it has become an integral part of the management of respiratory failure, trauma and critical care, anaesthesia, and the treatment of several acute and chronic conditions.

- In modern medicine, there exists considerable scope for short-term, intermittent and long-term oxygen therapy in several respiratory and non-respiratory illnesses, not only in the acute setting but also for long-term management, backed by robust data from observational, as well as experimental studies.

- Oxygen therapy acts by several mechanisms, apart from relieving hypoxia at cellular, tissue and organ levels, it also confers significant physiologic benefits, such as pulmonary vasodilatation and systemic vasoconstriction, anti-inflammatory and anti-infective effects, and promotes organ rest and tissue repair.

- One must not forget that above atmospheric concentrations, oxygen acts like a drug, and therefore, it should be considered as such and prescribed accordingly for specific conditions, after judiciously considering its merits and demerits for each patient on a case-to-case basis. Every prescription of oxygen therapy with regards to dose, delivery and duration should be specific and tailor-made for the patient, rather than administered in a straight-jacket or blanket manner, as there still exist safety concerns about both over-and-under use of oxygen in patients with critical illnesses and other acute or chronic respiratory and non-respiratory diseases.

- In today's era, oxygen therapy is used and prescribed frequently, often with a tendency to casually take it for granted. In this regard, it is important to acknowledge the pioneering work and efforts of all scientists and physicians who contributed to the discovery, applications and effects of oxygen, and applaud their courage in sometimes taking the road less travelled to conduct difficult experiments that were often fraught with trial and error. It must be appreciated that each of them, in his own way, contributed step-by-step to oxygen therapy and assisted ventilation attaining their current status in modern medicine today. For this purpose, the author has compiled a gallery to honour each of them (Figure 6).


Michael Sendivogius


John Mayow


Carl Wilhelm Scheele


Joseph Priestley


Antoine Lavoisier


James Watt


Thomas Beddoes


Sir Humphry Davy


Adolf Eugen Fick

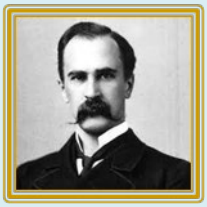

Paul Bert


George Holtzapple

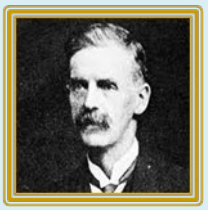
Photograph Not Available
Albert Blodgett

Photograph Not Available
S. B. Birch

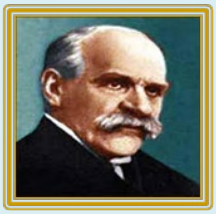
Photograph Not Available
Samuel Wallian


William Osler

Photograph Not Available
W. L. Conklin


James Lorrain-Smith

Photograph Not Available
John G. Priestley


John Scott Haldane


Alvan L. Barach


Thomas L. Petty


Takuo Aoyagi

Nocturnal Oxygen Therapy Trial
NOTT Investigators

Medical Research Council Trial
MRC Investigators

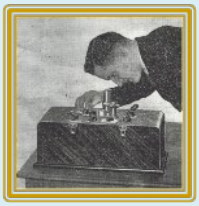
Photograph Not Available
John Dalziel

Photograph Not Available
W. Stueart


Philip Drinker


Louis Agassiz Shaw Jr.


John H. Emerson


Edward Both


William Hawes


Thomas Cogan


Francois Chaussier


George Fell


Joseph O'Dwyer

Photograph Not Available
Nathan Green


Henry Janeway


Johann Drager


Holger Hesse


Henning Ruben


Forrest Bird


Colin Sullivan

Figure 6. Gallery dedicated to All whose Efforts elevated Oxygen Therapy and Assisted Ventilation to their Current Status in Modern Medicine *

** The author wishes to clarify that this photo gallery is by no means complete. It is quite possible that even after research, some names might have been unintentionally left out. Spaces for photographs that could not be found or retrieved are left blank above the names.*

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Natural Sources of Oxygen

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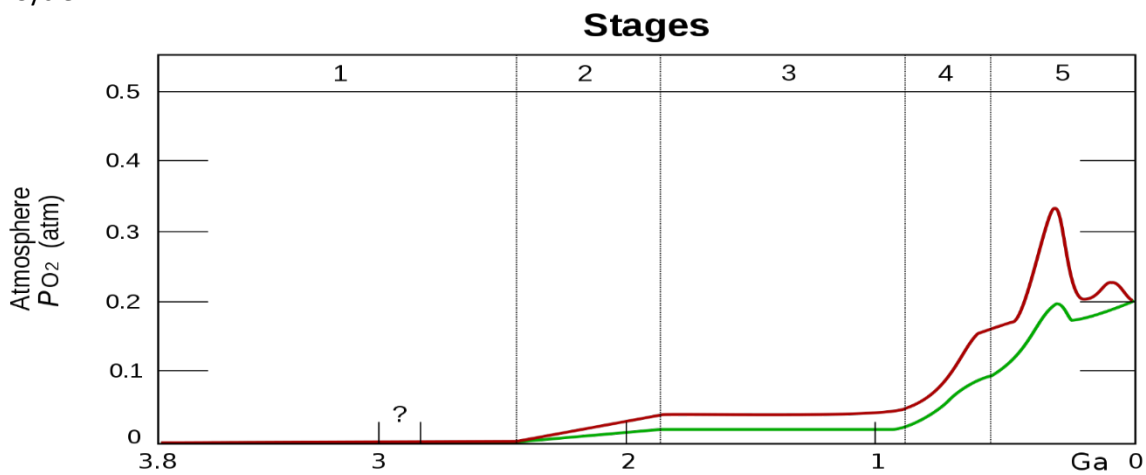
Introduction :

Oxygen (O_2) is the most crucial element in nature, compatible with life. All aerobic organisms depend on oxygen to produce energy from carbon substrates. The current concentration of oxygen in ambient (atmospheric) air is 209460 ppm (parts per million), or 20.95%. However, this concentration has never been constant, rather, it has changed several times in the history of our planet. The age of Earth is estimated to be about 4.5 billion years ever since it was formed, at that time, its' primitive atmosphere was devoid of oxygen and consisted mainly of hydrogen, with traces of ammonia and methane, to which nitrogen and carbon dioxide were added later by subsequent volcanic eruptions. It is estimated that Oxygen was first produced on Earth about 2.7 to 2.8 billion years ago. It took up residence in the Earth's atmosphere around 2.45 billion years ago, where it was first released by cyanobacteria, unicellular organisms which were the precursors of plants. They were the first organisms to generate energy by absorbing carbon dioxide from the atmosphere and replacing it with oxygen, in the presence of sunlight by the process we know as photosynthesis. It is also seen that there was a significant time interval between the appearance of oxygen-producing organisms and the actual oxygenation of the atmosphere. Why did it take another one billion years for oxygen levels to rise high enough to enable the evolution of life and how did the proportion of atmospheric oxygen reach its present level and how does the controlling system work at maintaining a proportion of 21 percent is still not well understood [1,2]. The event of production of oxygen through photosynthesis, called the "Great Oxidation Event" (Figure 1) transformed our planet from a world of barren rock, lava and volcanic gases to a world of greenery, teeming with life. As forms of life evolved, oxidation became the predominant mechanism for energy to be generated by non-photosynthesizing cells, through oxidative phosphorylation in mitochondria. An equilibrium was established from the beginning of the Cambrian period 540 million years ago till date, where the concentration of oxygen in the atmosphere hovered between 15 to 35%, a range compatible with life, with rise in oxygen concentration associated with a new burst of life and fall with downscaling and extinction of species [1,2,3,4]. The oscillation of Earth's atmospheric oxygen concentration around a level that optimally promotes the development of multicellular living organisms is termed the "Global Oxygen Cycle".



O_2 build-up in the Earth's atmosphere. Red and green lines represent the range of the estimates while time is measured in billions of years ago (Ga).
Stage 1 (3.85–2.45 Ga): Practically no O_2 in the atmosphere. The oceans were also largely anoxic with the possible exception of O_2 in the shallow oceans.
Stage 2 (2.45–1.85 Ga): O_2 produced, rising to values of 0.02 and 0.04 atm, but absorbed in oceans and seabed rock.
Stage 3 (1.85–0.85 Ga): O_2 starts to gas out of the oceans, but is absorbed by land surfaces. No significant change in oxygen level.
Stages 4 and 5 (0.85 Ga – present): Other O_2 reservoirs filled; gas accumulates in atmosphere

Figure 1. The Great Oxidation Event

(From : By Oxygenation-atm.svg: Heinrich D. Holland derivative work: Loudubewe (talk) - Oxygenation-atm.svg, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=12776502)

Oxygen in Air, Water and Soil :

The oxygen that we currently find in the air has two main sources. The first and major source is oxygen which is liberated as a by-product of photosynthetic chemical reactions. The second source occurs in the atmosphere itself when water molecules are split apart after being struck with ultraviolet radiation. This process is called photolysis. The water molecule is broken down into one molecule of diatomic hydrogen and one of free oxygen. The hydrogen molecule is light, and has a quick thermal velocity, so it can escape Earth's atmosphere leaving behind the free oxygen to form a diatomic oxygen molecule. Before photosynthesis began on a large scale, free oxygen molecules in the atmosphere were used up in oxidation reactions with free metal ions on the Earth's surface, mainly iron. Even when oxygen released by photosynthetic organisms was taking control of the atmosphere, these free oxygen molecules were placed into the rock involved in oxidation reactions. This has been responsible for the formation of red coloured rocks as may be seen in some geographical areas like in the southwestern United States and other places. Because of this, early Earth had a reducing atmosphere, composed mainly of methane, carbon dioxide, water, carbon monoxide, and nitrogen [5].

The Earth today is unusual among planets in that it has as abundance of oxygen. However, this essential element was not plentiful on our planet until microorganisms known as cyanobacteria began to produce it by photosynthesis [5,6,7]. The principal source of natural oxygen presently is photosynthesis. All of the Earth's oxygen does not come from trees and plants. Rather, the atmospheric oxygen that we depend on as humans, and other living things, comes predominantly from the ocean. It is produced via plankton - drifting plants, algae, some bacteria, crustaceans, molluscs, and more that can photosynthesize. Their extremely small size precludes them from swimming against ocean currents, so they drift. The amount of plankton in, and the oxygen released by the earth's water bodies is not constant but varies with the tide, the temperature and the time of the day.

More than half of the world's oxygen is produced by phytoplanktons (unicellular plants) that float on the surface of the water in the seas, lakes, rivers, and oceans, whereas the remainder is produced by terrestrial green vegetation (trees, plants, and grasses) and algae (Figure 2). When these wither and die a small fraction of their organic carbon gets buried in the ground or ocean floor and gets converted eventually by the process of decay into coal, oil and shale (Figure 3). In a way, we owe the ocean for oxygen, that comes from land plants as well, as all land plants have evolved from green marine algae.

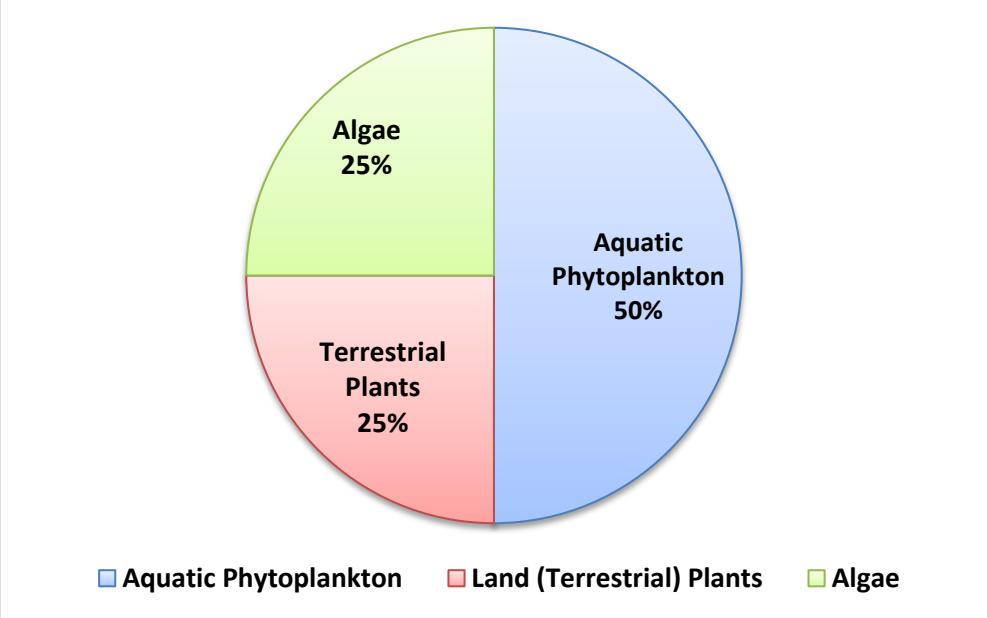


Figure 2. Environmental Sources of Oxygen

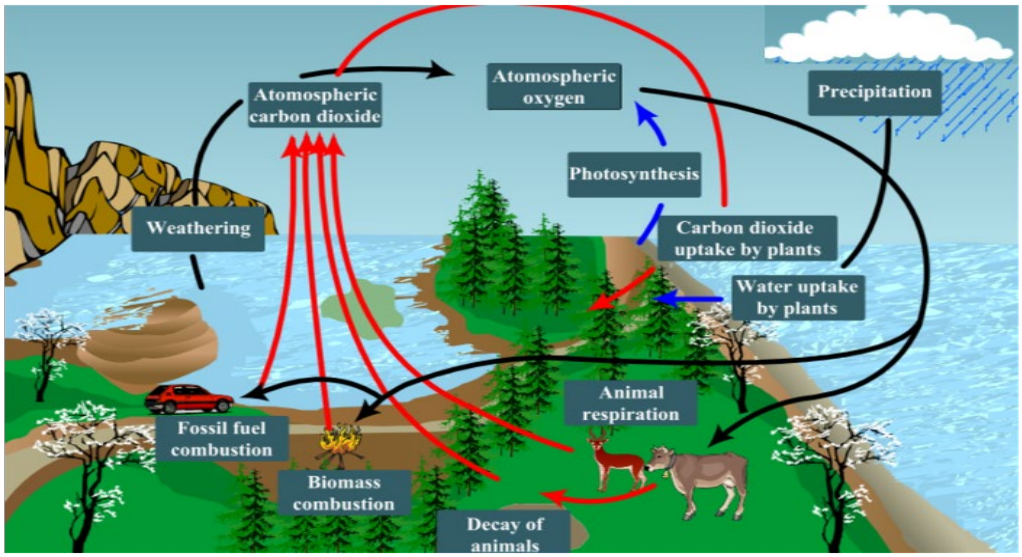


Figure 3. Oxygen and Carbon cycles

(From : https://www.pngkey.com/maxpic/u2t4t4u2a9y3t4t4/ [Free license])

One species of phytoplankton, *Prochlorococcus* (Figure 4) which is invisible to the naked eye has great contribution in production of oxygen. Prochlorococcus is the smallest photosynthetic organism on earth but this little bacteria produces up to 20% of the oxygen in our entire biosphere. That's a higher percentage than all the tropical rainforests on land combined. *Prochlorococcus which* releases countless tons of oxygen into the atmosphere is so small that millions can fit in a drop of water. *Prochlorococcus* has achieved fame as perhaps the most abundant photosynthetic organism on the planet. It is estimated that Prochlorococcus provides the oxygen for one in every five breaths we take. They are also responsible for drawing down significant portions of the carbon dioxide from the air, and thus are helpful both ways [8].

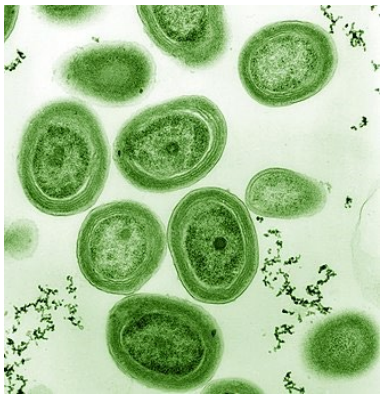


Figure 4. Prochlorococcus marinus

Phytoplankton, also known as microalgae, are the grass of the sea, and are similar to terrestrial plants in that they contain chlorophyll and require sunlight in order to live and grow. Most phytoplankton are buoyant and float in the upper part of the ocean, where sunlight penetrates the water. These phytoplankton also require inorganic nutrients such as nitrates, phosphates, and sulphur which they convert into proteins, fats, and carbohydrates. Thus besides producing oxygen, in a balanced ecosystem, phytoplankton provide food for a wide range of sea creatures including shrimp, snails and jellyfish [9,10,11] .

It is the phytoplankton and terrestrial green plants that maintain the proportion of oxygen in the atmosphere at 20%, as their production and expenditure of oxygen are nearly equal. For example, a clump of trees in a forest absorb carbon dioxide from the atmosphere during photosynthesis and convert it to oxygen to support new growth, but also generate a nearly equal amount of carbon dioxide when the older trees die. This balance of atmospheric oxygen is currently maintained as our oceans and forests are not taking in more carbon dioxide or letting off more oxygen, however, activities such as burning coal and oil for domestic, transport and industrial purposes add to the carbon dioxide released into the atmosphere, causing the Earth to warm up, a phenomenon we know as "Global Warming" (Figure 3).

Though the oceans produce more than 50% of the oxygen on Earth, a great amount of it is also consumed by marine life. Like land animals, marine animals also require oxygen for respiration while they live and it is also consumed when dead plants and animals decay in the ocean. This is particularly problematic when the decomposition consumes oxygen faster than it can be replenished, giving rise to zones where oxygen concentration is too low to support marine life, called “dead zones”.

Oxygen from Plants and Trees :

Plants and trees release oxygen during photosynthesis, when they produce glucose in the presence of sunlight and chlorophyll using carbon dioxide and water as substrates. They also consume oxygen when glucose is split to release energy for their metabolism. More oxygen is produced than consumed. During photosynthesis, six molecules of oxygen are released when six molecules of cardon dioxide combine with six molecules of water to produce one molecule of glucose by photosynthesis, a net gain of one molecule of oxygen for every atom of carbon added to the tree. An averagely growing tree produces nearly one kilogram of oxygen for each kilogram of wood gained by weight or about 100 kg of oxygen per year. Trees that grow faster produce more oxygen. One person breathes approximately 9.5 tonnes of air in a year, of which oxygen is 21 percent, and, of this, only a quarter is extracted during each respiratory cycle, this works out to a total of 740 kilograms of oxygen per year, the equivalent amount produced by 7-8 trees. The world’s population is on the rise requiring a greater number of trees to meet the oxygen demand but unfortunately the number of plants and trees is on the decline. Besides this, urbanization leading to the cutting down of trees as well the recent forest fires around the world have destroyed a large number of trees in rainforests disturbing this balance. This could have been a cause of greater concern had there not been a larger source of oxygen in form of the ocean [6].

National Geographic cited a study from 2010 that said land plants are responsible for 34 percent of photosynthesis on the planet [6]. However, an ecosystem ecologist at Oxford University, calculated these figures in 2019, after the wildfires, and said that the Amazon produces only 9 percent oxygen in the atmosphere. According to the National Ocean Service, with organisms like phytoplankton producing around 20 percent of oxygen in the biosphere, it is currently higher than all of the tropical rainforests on land combined [7].

Banyan, Peepal, Neem and Tulsi trees all provide a high amount of oxygen for more than 20 hours of the day. Peepal is considered to be the largest oxygen provider, along with Neem and Tulsi. It releases 24 hours of oxygen and determines atmospheric carbon dioxide (CO2). Bamboo is one of the fastest growing plants which releases about 30 % more oxygen than most other trees. No tree releases oxygen at night. We also know that most plants mostly take up carbon dioxide and produce oxygen during the day (photosynthesis), and this process is reversed at night (respiration).

Rainforests are responsible for around 28 percent of the Earth's oxygen and the marine plants produce more than 70 percent of the oxygen in the atmosphere. The remaining 2 percent of Earth's oxygen comes from other sources.

Figure 5. Oxygen producing Plants and Trees - Bamboo, Peepal, Neem and Tulsi (left to right, clockwise)

Indoor Environments and Oxygen :

Fresh air is not something we get enough of in modern life, especially as most of us seem to be increasingly stuck indoors. Indoor air can be stale, and thanks to modern synthetic materials and temperature regulation, it also contains pollutants and is also often well below recommended humidity levels. Synthetic furniture, paints, and computers, to name a few, silently pump chemical vapours into the air, while your heating system will dry out your air.

What is polluting Your Home ?

Pollutant	Source
Benzene	Glues, paints, furniture wax and detergents
Formaldehyde	Emissions, disinfectants and fixatives, or preservatives in consumer products, furniture and pressed wood products, tobacco smoke
Trichloroethylene	Homes undergoing renovation
Xylene and Toluene	In a variety of household sprays and consumer products
Ammonia	Aerosols and sprays used in the home
Pesticides	Sprays
Second-hand tobacco smoke	Indoor smoking
Oxides - Carbon monoxide Nitrogen Dioxide Sulphur Dioxide	Combustion products from gas and kerosene stoves, wood and coal burning, fireplaces

Table 1. Sources of Indoor Air Pollution

(based on Indoor air pollution, WHO Training Package for the Health Sector, 2008)

The humble indoor plant can make all the difference to the air we breathe indoors. They work hard at cleaning our air of these toxins and releasing oxygen and humidity back into the ambient indoor atmosphere. Studies by NASA prove that certain plants help keep the air in your house cleaner and increase oxygen levels. But not all plants are the same. Some like more light or heat than others, and some clean the air better so it is important to get the right one. To help you choose the right indoor plants for your house, here are our top ten air-purifying plants that will clean and provide oxygen to the air inside your home (Table 2) [12] :

1. Aloe Vera
2. Chlorophytum comosum (Spider plant)
3. Sanseveria trifasciata (Snake plant)
4. Spathiphyllum wallisii (Peace Lily)
5. Dracena marginate (Dragon tree)
6. Dypsis lutescens (Areca palm)
7. Boston Fern
8. Ficus Elastica (Rubber plant)
9. Ficus Benjamin (Weeping Fig)
10. Scindapsus
11. Epipremnum sp. (Golden Pothos)
12. English Ivy
13. Philodendron
14. Orchids (Orchidaceae)

Table 2. List of Indoor Plants that purify Air and generate Oxygen

(From : http://www.huffingtonpost.com/2015/07/29/best-houseplants-destress_n_2964013)

Figure 6. Indoor Plants that produce Oxygen

(From : https://www.dailyexcelsior.com/purifying-power-of-indoor-plants/)

Oxygen dissolved in Water :

Dissolved oxygen (D.O.) refers to the level of free, non-compound oxygen present in water or other liquids. The level or content of oxygen dissolved in water is one of the most important parameters in aquatic systems, being essential for the survival of all aquatic organisms, apart from being a measure of water quality, as it affects biochemical as well as physical factors like odor, appearance and taste. Due to its chemical properties, oxygen by itself is poorly soluble in water. Phytoplankton and aquatic plants produce oxygen when they photosynthesize. In addition, some oxygen from air also gets dissolved at the water surface. D.O. levels depend on several factors, whether water is flowing or still, turbulence when water flows over rocks, bends or other obstacles, the temperature of water, the climate and the population density of native aquatic plants and animals. The D.O. content is highest in cold water flowing through many obstacles and a moderate amount of plants. Turbulent or running water, such as that of a river, waterfall or stream, or flowing in waves dissolves more oxygen than the still water of a pond or lake [13,14]. Aquatic plants add to the D.O. by taking up carbon dioxide and releasing oxygen, but paradoxically if there are too many plants, then more D.O. will be depleted when these plants die and bacteria decompose them (Figure 7).

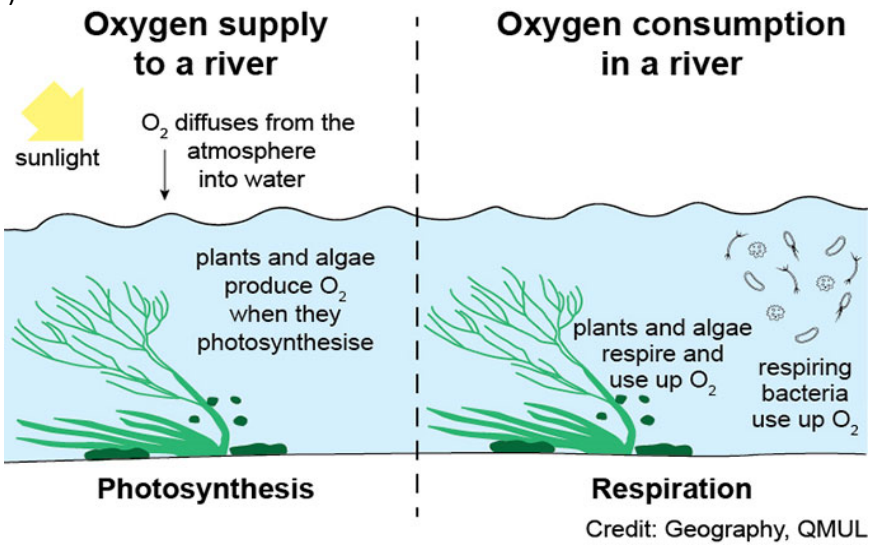


Figure 7. Oxygen Supply and Consumption in a River

(From : Geography, Queen Mary University of London)

Photosynthesis in aquatic plants adds to the D.O during the daytime, and respiration in them depletes the D.O. at night (Figure 8) . The rate of photosynthesis also changes according to the intensity and duration of sunlight, therefore, on a bright sunny day the D.O. level will be higher as compared with rainy or cloudy days. Temperature and climate also affect D.O. levels which are higher in cold than warm water. This might make us think that in the winter season D.O. level might be higher, however, it must be remembered that during winter ice may form on the water surface, effectively sealing the air-water interface, as a result of which very little oxygen enters the water from the atmosphere. D.O. level is also dependent on the depth of the water body, being highest at the water surface and decreasing with depth. In deep lakes that are not aerated or do not receive much wind, D.O. level is lowest at the bottom where water meets the sediment or mud, as many bacteria, aquatic fungi and animals live in this sediment and decompose dead fish, aquatic plants and animals that sink to the bottom, thereby consuming a lot of the dissolved oxygen[13,14,15] . Lakes and ponds that are stocked with fish or dumped with sewage also have low D.O. levels, due to excessive oxygen consumption [16,17].

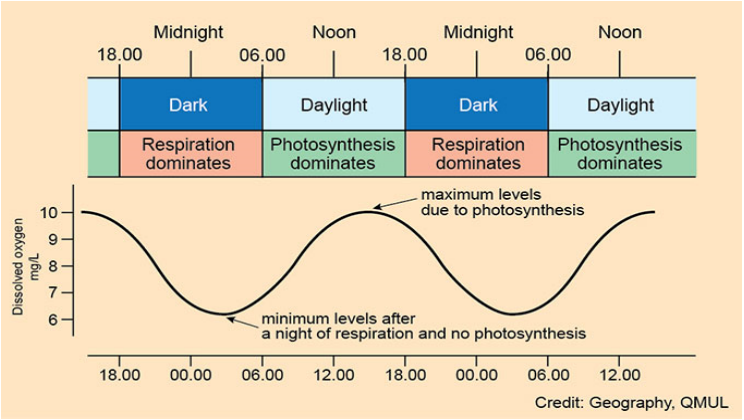


Figure 8. Diurnal and Nocturnal Variations in Dissolved Oxygen

(From : Geography, Queen Mary University of London)

D.O. level is measured in milligrams per litre (mg/L) directly in the water using a calibrated dissolved oxygen sensor. For aquatic life to exist, water should contain a minimum concentration of dissolved oxygen. The amount of dissolved oxygen an aquatic animal requires also varies according to its size, complexity, stage of life cycle and the depth at which it lives. Fish consume the most of dissolved oxygen in water while bacteria consume the least. Worms and clams that live at the bottom of the river or ocean bed, where the oxygen level tends to be low, require D.O. concentrations of at least 1 mg/L, whereas crabs, oysters and other fish require concentrations of about 3 mg/L and spawning fish, their eggs and larvae require concentrations up to 6 mg/L during these sensitive life stages. A healthy level of D.O. in water is estimated to be above 6.5 - 8 mg/L or between 80 to 120 percent. (Figure 9). Moreover, D.O. levels, even in the same water body do not remain constant but can fluctuate over the years (Figure 10).

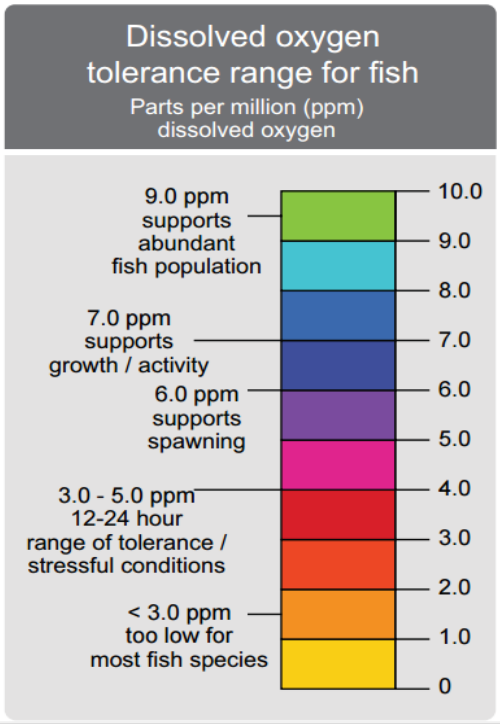


Figure 9. Healthy Level of Dissolved Oxygen in Water

(From : https://www.leaffin.com/dissolved-oxygen-aquaponics/)

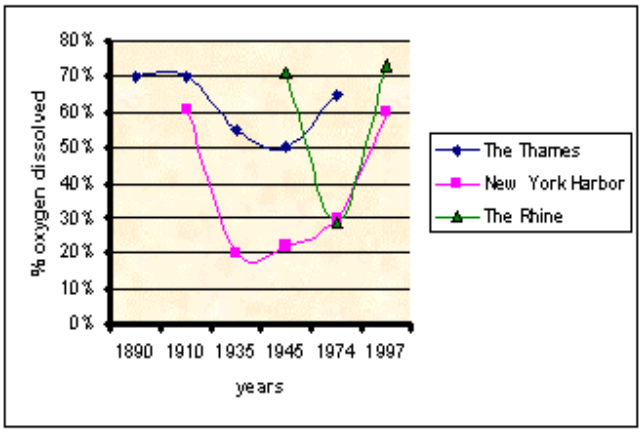


Figure 10. Dissolved Oxygen (D.O.) level variation in 3 different water bodies across time

(From : https://www.change.org/p/supreme-court-of-india-inviting-supreme-court-india-to-set-river-development-project-norms-suo-moto)

Oxygen in Soil :

Oxygen in soil is essential for respiration of the roots of trees and plants as well as organisms in soil like bacteria, fungi, saprophytes, insects, and parasites, as well as nutrient and water uptake of plants (Figure 11). The composition of soil air at the surface is very similar to that of the atmosphere and there is only a slight decrement in the oxygen content in soil air (20.6%) as compared to atmospheric air (20.9%). Like water, the oxygen content in soil decreases with depth and at the bottom of the soil bed may be as low at 5%. Oxygen transport in the soil occurs by diffusion and is influenced by physical properties like structure and composition, texture, porosity, and water content. The presence of any organic matter (e.g. vegetation, biofertilizer, compost) in the soil affects its' structure and porosity, which are determinants of oxygen transport. More compact and less porous soils hinder oxygen transport. Since oxygen diffuses through pores, any change in the soil composition and porosity will have a positive impact on oxygen transport if pore connectivity increases and vice versa. Gases diffuse in water much slower than they do in air, hence in soils with a high-water content or during flooding where soil aeration is impacted, and water accumulates in the pores, oxygen diffuses much more slowly (Figure 12) [18,19].

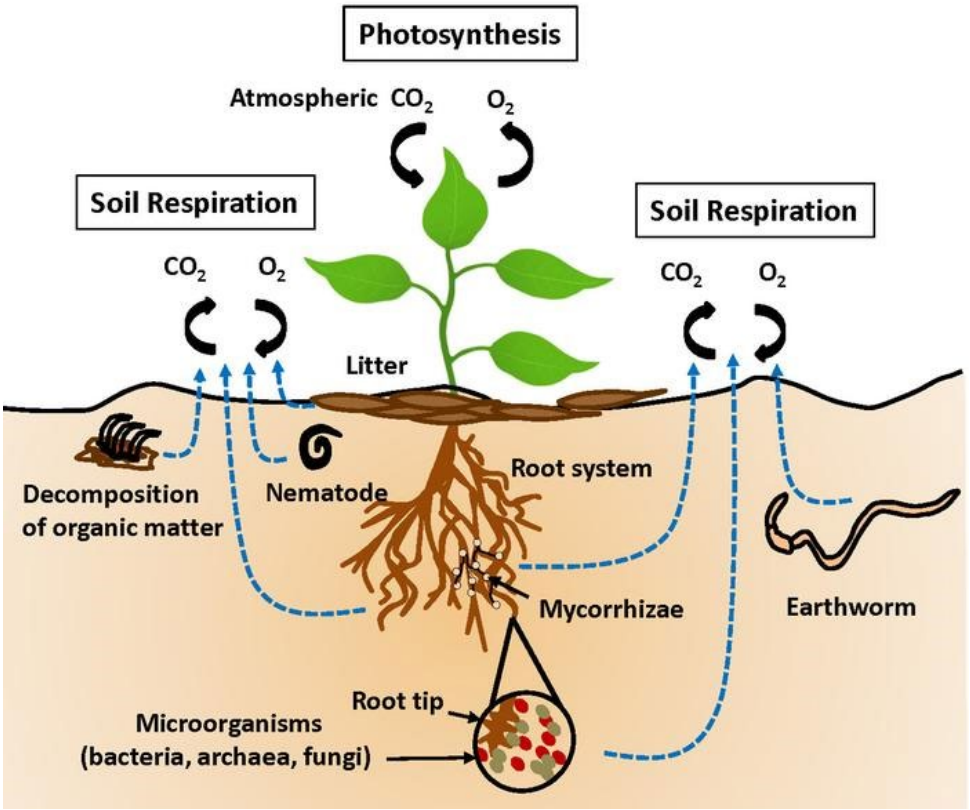


Figure 11. Soil Flora and Fauna and Gas Exchange

(From : https://permies.com/t/66829/process-carbon-released-atmosphere-soil)

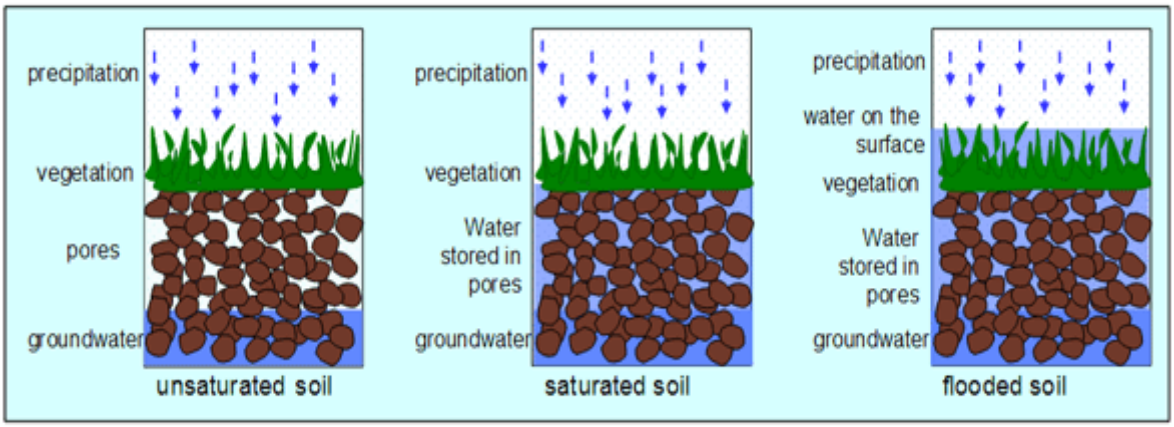


Figure 12. How Water Saturation and Flooding affect Soil Oxygen Content

(From : http://www.floodsite.net/juniorfloodsite/html/en/student/thingstoknow/hydrology/waterstorage2.html)

Impact of Geostationary, Dynamic and Gravitational effects on the Global Oxygen Cycle :

Earth's rotation period is 24 hours at present but may have been much lower at the time of creation. It has been postulated that the rotation period, or the length of one day might have been as low as 6 hours more than 4 billion years ago and the rotation and the illumination period may have increased more than threefold since the origin of photosynthesis, due to slowing down of the earth's rotational speed, giving rise to increased rotation period or daylength, could be one of the triggers for the global oxidation events. Other abrupt events that can affect oxygen production and consumption include shifting of tectonic plates during massive earthquakes or continent formations giving rise to hydrogen escape, exposure of phosphorus-bearing rocks to the forces of weathering, absorption of solar radiation, continental growth, or volcanic eruptions. As Earth's rotation rate, governed by planetary physics, is independent of these geological or biological triggers, the daylength effect on oxygen cycle operates in parallel to these other Earth-bound mechanisms [20].

Better Oxygenation through a Balanced Diet :

Certain foods, though they do not contain oxygen, help in oxygen transport and delivery in the body (Table 3). Foods that are rich in Vitamins A, B2, B3, B5, B9, B12, and D, minerals like iron and copper, nitric oxide, antioxidants and have an alkaline pH, help to maintain optimal oxygenation through indirect mechanisms like regulating hemoglobin, red cell mass and hemopoieses and blood flow. Consumption of such foods is associated with a reduced risk of stroke, diabetes, and hypertension, and improved respiratory, cardiac and circulatory function [21].

FRUITS	VEGETABLES
• Apples • Berries • Citrus fruits (Oranges, lemons) • Dates • Figs • Kiwis • Pears (Avocado) • Pineapples • Peaches • Pomegranates	• Beetroot • Beans • Broccoli • Carrots • Lettuce • Garlic • Mushrooms • Onion • Spinach • Sweet Potato
MEAT	**FISH**
• Eggs • Chicken • Fowl • Liver • Brain • Tongue	• Carp • Mackerel • Salmon • Sardines • Tuna
DAIRY PRODUCTS	**NUTS AND SEEDS**
• Milk • Ghee • Yogurt	• Almonds • Walnuts • Pecan • Sunflower seeds

Table 3. Foods that are rich in Anti-oxidants and help to maintain Oxygenation in the body

The Last Word - Oxygen Conservation :

Oxygen is crucial for the survival of life on earth. Ever since the dawn of the twentieth century, fuel combustion, pollution, and global warming, themselves inevitable consequences of the industrial revolution which began two centuries ago, have

led to oxygen depletion, a phenomenon which is increasing day by day. Each year, nearly 100 gigatons of oxygen are depleted from the earth's atmosphere, and, at this rate, it has been estimated that by the year 2100, the atmospheric concentration of oxygen would decrease further to 20.825 % from its current level of 20.946 % . We have entered a new era in Earth's history in which humans, rather than environmental forces, are the primary drivers of environmental change. Life must take a full circle, as in the past it has been observed that a fall in atmospheric oxygen concentration has been associated with downscaling and extinction of species. It is high time to take a note of this impending threat and enforce corrective measures to preserve oxygen, not only in the atmosphere, but also in the land and the sea. Oceanic plankton must be conserved by decreasing pollution, saving energy, urging individuals and industries to stop destroying habitat on land and in the ocean, and encouraging others to stop overharvesting ocean wildlife. Other measures include substitution of fossil fuels by green energy, recycling of industrial and domestic waste and strategies using anaerobic microorganisms to decompose organic matter. Governments of all countries must work hand in hand with each other to redefine our relationship with Earth to one where both people and nature can peacefully co-exist in harmony [22,23].

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Medical and Industrial Oxygen – Sources, Supply, Storage, Safety and Transport

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Introduction :

Oxygen is essential for life, having its main role at the cellular level, which is essential for the myriad of metabolic processes that keep us alive. Oxygen is probably the commonest drug used in the care of patients who present with medical emergencies and its importance in the field of healthcare cannot be underestimated. Oxygen is widely used in every healthcare setting, with applications from resuscitation to inhalation therapy. Apart from the health care industry, Oxygen is used in diverse applications covering various industries like in steel-making and refining and fabrication processes of other metals, in chemicals, pharmaceuticals, petroleum processing, glass and ceramic manufacture, pulp and paper manufacture. It is also used for environmental protection in municipal and industrial effluent treatment plants and facilities.

Medical Oxygen :

Medical oxygen is high purity oxygen that is used for medical treatments and developed for use in the human body. Oxygen therapy is an essential medicine and core component of hospital systems that has been a standard of care for more than a hundred years. Though Oxygen was known to be the only element that supports respiration as early as 1800 and was first used in the medical field in 1810, it took about 150 years for the gas to be used throughout medicine. In the early to mid- twentieth century oxygen therapy became rational and scientific, and today modern medicine could not be practiced without the support that oxygen supplies.

Medical oxygen is used to :

- Restore tissue oxygen tension by improving oxygen availability in a wide range of conditions such as chronic obstructive pulmonary disease (COPD), cyanosis, shock, severe hemorrhage, carbon monoxide poisoning, major trauma, cardiac/respiratory arrest
- Provide a basis for virtually all modern anaesthetic techniques
- Aid resuscitation
- Provide life support for artificially ventilated patients
- Aid cardiovascular stability

Industrial Oxygen :

Industrial oxygen is focused on uses in industrial plants including combustion, oxidation, cutting and chemical reactions. The industrial oxygen purity levels are not appropriate for medical use, as there could be impurities from dirty equipment or industrial storage that could make people ill. Oxygen in Industries serves a complimentary role to create actions that are carried out in these facilities.

The steel industry is the largest consumer of oxygen (consumes 55% of commercially produced oxygen) in “blowing” high-carbon steel - that is, volatilizing carbon dioxide and other non-metal impurities in a more rapid and more easily controlled process than if air were used. Apart from the steel industry, Oxygen is required in various micro, small and medium enterprises, infrastructure projects, food processing units, as well as continuous process industries such as furnaces, refineries, aluminium, copper processing plants (Table 1).

Metal production - Ferrous and Non-ferrous	Pulp and Paper
Aerospace and Aircraft	Refining
Automative and Transport	Water and Waste Management
Chemicals	Welding and Metal Fabrication
Energy	Electronics
Glass	Food and Beverages
Pharmaceuticals and Biotechnology	Laboratories

Table 1. Various Industries requiring Oxygen

Sources and Supply of Oxygen :

Oxygen is an important element constituting 21% of Earth's atmosphere and is crucial for sustenance of life. Molecular oxygen, O_2, is found only in the atmosphere and for industrial applications of oxygen, high purity of 99.7% is needed. The procedure for generating medical and industrial oxygen is same. However, medical oxygen is generated with high purity and the oxygen system for generation of medical oxygen is fabricated with the highest quality standards. Medical oxygen is distilled in the air separation till it meets medical specifications. The daily production capacity (including for industry use) of oxygen in India currently is 7,127 MT (metric tonnes) per day. Most of this is utilized in various industries and only 10-20% is required for the medical needs in hospitals. Oxygen supply is typically achieved using :

A. Oxygen plants (piped directly or distributed via cylinders) : An oxygen plant is a large, onsite central source of oxygen. The oxygen is piped directly or can be distributed via cylinders. Oxygen plant requires a reliable source of power. There are mainly two industrial processes for on-site oxygen generation, as follows :

1. Cryogenic distillation : Is the process originally developed in 1895,and is considered the most efficient and popular for industrial production of oxygen. Moreover, it is also the process that is best suited for continuous interrupted production of oxygen with high purity up to 99.7%ppm.

2. Pressure swing adsorption (PSA) : A PSA oxygen plant employs a technology that absorbs nitrogen from ambient air to concentrate oxygen for supply to hospitals. They operate at near-ambient temperatures and use specific adsorbent materials (that trap a substance on their surface) like zeolites, activated carbon, molecular sieves etc., to trap oxygen at high pressure.

B. Oxygen cylinders (filled at an oxygen plant) : Medical oxygen is stored in high pressure gas cylinders at ambient temperature. Most oxygen storage cylinders are made of steel. Aluminium is used for MRI suite cylinders. They have a black body and white shoulders. Care is needed in the handling and use of compressed medical oxygen gas cylinders. Under no circumstances should oils or grease be used to lubricate any part of the compressed gas medical oxygen cylinder or the associated equipment used to deliver the gas to the patient. Cylinders must not be exposed to extremes of temperature.

C. Oxygen concentrators (concentrating oxygen from air on-site) : Smaller volumes of oxygen (upto 10 Litres) of lower concentrations (up to a maximum of 95%) are produced on site using portable electric-driven concentrating units (Figure 1). Air is separated at ambient temperature. Units are used for home or remote field use. Oxygen concentrators require a constant electricity supply in order to operate. Apart from a small reservoir in the circuit, there is no way in which to store the produced oxygen, so a cylinder back-up is necessary to cover electricity or machine failure.

Figure 1. An Oxygen Concentrator

D. Liquid Oxygen (delivered from a specialized gas plant and stored on-site at very high pressure) : Oxygen is generally liquefied so that it can be more effectively transported and stored in large volumes . Liquid oxygen is a cryogenic liquid. Cryogenic liquids are liquefied gases that have a normal boiling point below -238°F (-150°C). Liquid oxygen has a boiling point of -297.3°F (-183.0°C). One litre of liquid oxygen is equivalent to 840 litres of gaseous oxygen. Because the temperature difference between the product and the surrounding environment is substantial, even in the winter, keeping liquid oxygen insulated from the surrounding heat is essential. The product also requires special equipment for handling and storage. Liquid storage is less bulky and less costly than the equivalent capacity of high-pressure gaseous storage.

E. Oxygen Pipeline Systems : These supply oxygen at high pressures to equipment such as anesthetic machines and ventilators. A key advantage of pipeline systems is that they obviate the need for handling and transporting heavy cylinders between wards.However,these system of oxygen delivery requires installing centralzied oxygen sources with copper pipelines and needs high level of maintenance especially for medical use.

Figure 2. An Oxygen Pipeline in a hospital

Storage :

Oxygen can either be stored in cylinders, a vacuum insulated evaporator or a manifold cylinder bank.

A. Oxygen Cylinders : Oxygen is stored in various sizes of cylinders according to requirements (Figure 3). The sizes and specifications of cylinders used are shown in Table 2. A pin index system is utilised, with the pins being placed at positions 2 and 5. The gauge pressure indicates how much gas is present, assuming that oxygen behaves like a perfect gas (i.e. it obeys all the three gas laws at room temperature).

Figure 3. Different Sizes of Oxygen Cylinders

Size	Capacity (L)	Pressure (psi)	Weight(Kg)
B	200	1900	2.3
D	400	1900	3.4
E	660	1900	5.4
F	1360	1900	14.5
G	3400	1900	34.5
H	6900	2200	53.2
M	3450	2200	29.0

Table 2. Various Sizes and Capacities of Oxygen Cylinders

C. Vacuum-insulated evaporator (VIE) or cryogenic tank : A VIE is basically a huge thermos flask that is used to store liquid oxygen on site (Figure 4). It is used at large hospitals which require oxygen at > 300 litres per second or > 7,000,000 litres annually. One litre of liquid oxygen is equivalent to 840 litres of gaseous oxygen.

Figure 4 . A Cryogenic Tank

D. Manifold cylinder gas system (bank) : A manifold cylinder gas system has two banks of at least 10-G-size (46.5 kg/7600 L) cylinders, connecting five cylinders on each side by a manifold of piping (Figure 5). This system is used in smaller hospitals which do not have a VIE, or as a backup for the period during which a VIE is being filled at a larger hospital. One bank is used at a time. In a hospital, size J cylinders are commonly used, which are capable of holding 6,800 litres of oxygen.

Figure 5. A Manifold Cylinder Bank

Medical Oxygen versus Industrial Oxygen :

The process of generation of medical as well as industrial oxygen are the same and the oxygen generated is of high concentration in both. However there are few key differences between the two as highlighted in Table 3.

Medical Oxygen	Industrial Oxygen
High purity oxygen used for medical treatments and is developed for use in the human body	Industrial oxygen is focused on uses in industrial plants including combustion, oxidation, cutting and chemical reactions
Stringent criteria regarding high purity of oxygen	No stringent criteria for purity
Medical compressors come in oil-free or oil-less varieties	Industrial oxygen can be generated by oil-lubricates, oil less or oil -free compressors.
Entire supply chain strictly controls the presence of water to prevent the rusting process inside the cylinders	No such criterion required
Strict regulations and setting parameters pertaining to tank cleanliness in order to eliminate the possibility of any potentially harmful contaminants and infections	Industrial oxygen isn't regulated as strictly as it is used to accelerate or support some sort of industrial function
Considered as a drug and mandatory to have proper drug licenses and comply with standard operating systems	Used as raw material to increase performance and capital efficiency in many industries and to improve productivity

Table 3. Differences between Medical and Industrial Oxygen

Safety and Precautions :

Being a flammable gas, Oxygen strongly supports combustion and hence it becomes really essential to follow strict guidelines regarding its storage and use.

1. Store oxygen under cover in a well-ventilated area, kept dry and clean and not subjected to extremes of heat or cold
2. Do not permit smoking or open flames in any areas where oxygen is stored or handled
3. Oxygen must be separated from flammable and combustible items by a 20-feet or a half-hour (30-minute) fire-resistant wall
4. Oxygen in contact with oils, greases and tarry substances creates a highly dangerous environment due to the risk of spontaneous combustion
5. Electrical equipment capable of sparking or generating extreme heat should not be used in the vicinity of patients receiving oxygen
6. The recommended personal protective equipment for handling should be used while handling liquid oxygen
7. Oxygen cylinders must be fitted with an appropriate pressure-reducing device; Do not plug, remove, or tamper with any pressure-relief device.
8. Under no circumstances should oils or grease be used to lubricate any part of the compressed gas medical oxygen cylinder or the associated equipment used to deliver the gas to the patient
9. Maintain separation between full and empty cylinders
10. Use cylinders in strict rotation so that cylinders with the earliest filling date are used first
11. Store separately from other medical cylinders within the store

Transporting Oxygen across Air, Land and Water :

The recommended method of transporting gas cylinders is to let a professional gas transport company handle it, but such options may not always be available or feasible, in such cases, standard recommendations that need to be followed to ensure safety during transport are :

Recommendations for loading and securing cylinders :

- Limit the number of cylinders at a time.
- Ensure the cylinder is clearly labelled, and the valve is locked in the 'fully closed' position and use valve protection caps before moving. A pressure relief device must be in communication with the vapor space of the cylinder.
- Use cylinder dollies or other mechanical lifting devices to load the cylinders to the vehicle.
- Load and transport cylinders preferably in the upright position and secured to flat floors or platforms, taking care never to drop them or allow other cylinders or objects or hard surfaces to collide with or bang into them.

- Secure the cylinders in place to prevent any movement or collision during transit. Cylinders should not be allowed to shift relative to each other or the supporting structure. If the cylinders are secured to a pallet, it is recommended that the pallet must be able to transport 3,500 lbs per pallet, and the cylinders must be secured by a web strap rated at 10,000 lbs.

Requirements for Vehicles transporting cylinders :

- The vehicle must have an open body with a support capable of holding the cylinder(s) upright when subjected to an acceleration of 2G.
- It is recommended to avoid closed or restricted routes e.g. long tunnels while driving.
- Any vehicle transporting gas cylinders must also possess the following papers, within reach of the driver at all times :

✓ Shipping papers (hazard manifests or trip sheets). These contain information on the type, size, and quantity of hazardous materials. This requirement does not apply to cases when the material transported is used as a material of trade - e.g. a welder transporting gas to a job site. Medical oxygen does not fall under this exception. When transporting medical oxygen for home health use, shipping papers are typically referred to as “oxygen manifests”. If the vehicle is transporting more than one litre of a material poisonous by inhalation or a compressed gas with a methane content of at least 85%, a safety permit should also be issued by the competent authority

✓ Emergency Response Guide or equivalent

Requirements for the Driver or Company transporting cylinders :

Any employee that comes in contact with or drives a vehicle transporting 1,001 or more pounds of hazardous materials must :

- Undergo training, sometimes referred to as commercial driver's license (CDL) training. In the United States, it is recommended that such training must occur within 90 days of employment and be renewed every three years.
- Drivers must receive drug and alcohol information, with their supervisor trained in drug testing.
- Haulers for hazardous materials must provide insurance liability depending on the cargo.

Recommendations for Health care workers and patients carrying oxygen cylinders :

- Use a cart or holster, open at the top to carry portable oxygen units and avoid placing them in closed bags or backpacks.
- Secure the storage device while travelling so they do not roll in a car. Tanks or cylinders containing liquid oxygen should be placed upright and never be laid side-by side. Portable cylinders can be laid on their sides, but their valves must be protected from collision. Cylinders or tanks should never be placed in a tightly closed space like a trunk.
- When using oxygen, sit in a open place, far from the vehicle or adjacent a partially opened window to prevent oxygen and heat from building up in the vehicle.
- When traveling by bus, give the bus service advance notice that you will be traveling with oxygen. Some bus services permit that patient to carry a fixed amount of oxygen e.g. 4 cylinders – 2 on board and 2 in the cargo hold compartment.

Transporting (airlifting) oxygen by air :

Oxygen, being a flammable and combustible gas, is classified as a dangerous commodity by the ICAO (International Civil Aviation Organization) and hence its transport by air is subject to full compliance with applicable ICAO regulations for carriage of dangerous goods. ICAO permits oxygen cylinders to be transported by air both in passenger and or cargo/freight aircraft, with limits of upto 75 kg and 150 kg for passenger and freight planes respectively. Since during the COVID-19 pandemic, much larger quantities of oxygen were required to be airlifted at a time, governments had to explore other options, like using defence aircraft for this purpose, which were exempted from The Aircraft Rules, 1937 and The Aircraft (Carriage of Dangerous Goods) Rules, 2003, to airlift oxygen on a priority basis in intermediate bulk containers meant for transportation of oxygen and other gases that could accommodate thousands of tonnes at a time. In India, the Indian Air Force (IAF) came to the rescue during the oxygen crisis during the second wave of COVID-19 in the country (Figure 6). A statement by the Ministry of Defence said the IAF's C-17 and IL-76 heavy-lift aircraft were used to airlift large empty oxygen tankers from their place of use to filling stations across the country to speed up the distribution of medical oxygen. Once refilled, they were transported by road or rail to various hospitals or states across the country.

Transporting oxygen across water :

Like aircraft, oxygen is classified as a dangerous cargo by the International Maritime Dangerous Goods (IMDG) code and its carriage on ships is subject to compliance with IMDG and Medical First Aid Guide (MFAG) international safety regulations. For basic medical requirements the IMDG and MFAG codes require shipping operators to carry a minimum of 44 litres of medical oxygen at a pressure of 200 bar on board to ensure sufficient oxygen supply in the event of passengers and crews becoming ill with a respiratory infection. These cylinders have to be hydrostatically tested every five years or at an interval

specified by the manufacturer, whichever is earlier and their contents to be checked and changed as required per the manufacturer's requirements, or every three years, whichever is earlier, the entire system to be inspected annually by a competent person in accordance with the manufacturer's instructions. To comply with this requirement most vessels carry a large (stationary) oxygen cylinder with a capacity of 40 litres (or two cylinders of 20 litres or four of 10 litres capacity each) and two (one portable and one spare) smaller 2 litre cylinders, each equipped with one flow meter unit and two ports each for supplying oxygen to two persons simultaneously. However, during the COVID-19 pandemic there were demands from various quarters, including maritime safety specialists to raise this limit, as a 40 litre cylinder operating at 200 bar with a flow rate of max 25 litres per minute would last for 5.3 hours, insufficient to treat more than one COVID-19 patient if medical evacuation could not be effected or if the cylinders could not be quickly refilled or replaced. During the second wave of COVID-19 in India, the Indian Navy deployed as many as nine warships to ferry medical supplies, including liquid oxygen-filled cryogenic containers and entire tankers from countries like Bahrain, Qatar, Kuwait and Singapore to meet the high demand for oxygen in the country.

The COVID-19 Pandemic and Oxygen Supply Crisis :

The COVID-19 pandemic has highlighted and un-earthed the deficiencies in hospital oxygen systems globally and it hit really hard in India during the second wave in May 2021. A host of problems have contributed to this crisis, from inadequate production, logistics snarls and issues relating to transport and last-mile delivery. Besides, Oxygen access was challenged by low quality and poorly maintained equipments, lack of clinical and technical training and protocols, and deficiencies in local infrastructure and policy environment. The daily production capacity (including for industry use) of oxygen was 7,127 MT while the demand reached upto 6,600 MT per day. This was several times higher than the demand for medical oxygen in pre-COVID times, which was around 700 MT per day. Because of the several fold increase in medical oxygen requirement almost all of the oxygen produced, even that for industrial purposes had to be diverted to medical use to combat the acute crisis. Though industrial oxygen is never used for medical purposes, the impurities found in industrial oxygen were taken care of to make it suitable for medical use. The pandemic taught us an important lesson in that we need to strengthen our health care system including hospital oxygen supply and storage as well as optimize use of oxygen therapy. However, a comprehensive pandemic response is going to need more than just oxygen. It will require ensuring access to the devices needed to deliver oxygen to patients, ranging from pulse oximeters to ventilators, and health workers that are trained to use such devices effectively. A strong political commitment, effective contingency planning and a strong healthcare infrastructure with people centric policies is needed to fight and save mankind against such deadly emergencies.

Figure 6. Mass Transport of Oxygen during the Second COVID-19 Wave in India

Top Left : Indian Railways running "Oxygen Express" to transport Oxygen to states across the country
Top Right : Oxygen tankers escorted under Police protection
Bottom Left and Right : Indian Air Force airlifting Oxygen tankers
(From : https://www.businessinsider.in/india/news/checkout-in-images-how-oxygen-is-being-transported-across-the-country-by-air-rail-and-road/slidelist/82212220.cms)

Summary – Points of Interest :

- Oxygen is an essential drug for health care industry and essential component for diverse applications in various other industries
- The process for generating medical and industrial oxygen is the same
- Medical oxygen is generated with high purity and the oxygen system for generation of medical oxygen is fabricated with the highest quality standards
- The ongoing COVID-19 pandemic unearthed many deficiencies of healthcare systems including oxygen supply
- An effective long-term contingency plan is warranted to face such pandemic situations in future

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Gas Exchange in the Lungs

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Introduction :

The basic principles surrounding the concept of pulmonary gas exchange was established more than 60 years ago. Lungs help in the exchange of the respiratory gases Oxygen (O_2) and Carbon dioxide (CO_2) between inspired ambient air and blood, by transferring the oxygen from inhaled air into the bloodstream and carbon dioxide from the blood through exhaled air, during respiration.

Organs involved in Gas Exchange :

Atmospheric air enters the body through the mouth or nasal cavity and enters into the pharynx, or throat. From there, it passes through the larynx and enters the trachea. Finally it enters the lungs, where trachea branches into the left and right bronchi. These branches further divide into smaller and smaller branches, which are collectively known as bronchioles. The smallest (terminal) bronchioles end in tiny air sacs called alveoli. These alveoli inflate when a person inhales and deflate when a person exhales (Figure 1).

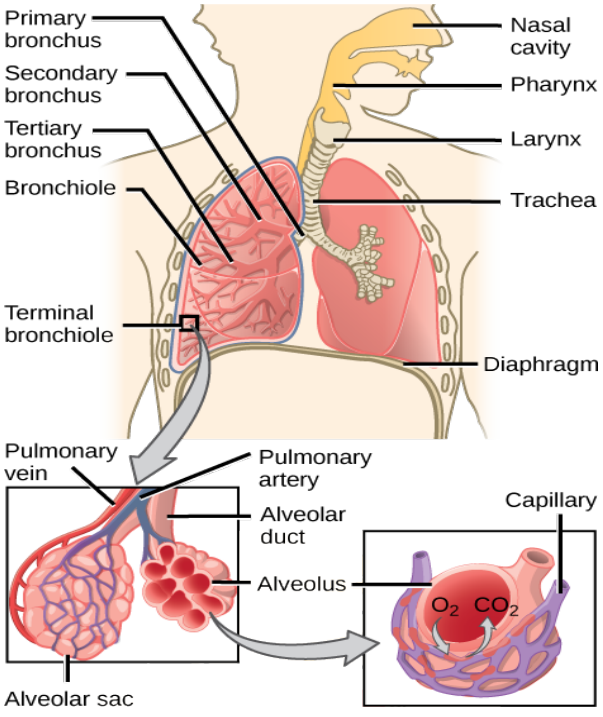

Figure 1. The Human Respiratory System

When gas exchange takes place, oxygen travels from the lungs and flows into the bloodstream. At the same time carbon dioxide passes from the blood and reaches to the lungs. This process takes place in the lungs between the alveoli and a network of tiny blood vessels called capillaries, which are located in the walls of the alveoli. These walls share a membrane with the capillaries (alveolo-capillary membrane), where the red blood cells are flowing inside. This paves the way for oxygen and carbon dioxide to diffuse, or move freely, between the respiratory system and the bloodstream.

Oxygen molecules attached to these red blood cells then travel back to the heart, for distribution to other organs. At the same time, carbon dioxide molecules in the alveoli are released out of the body through exhaled air the next time the person exhales. Thus, this process of gaseous exchange allows the lungs to replenish the oxygen in the body and eliminate carbon dioxide at the same time.

Gas Exchange in the Alveoli :

The lungs are a collection of some 300 million very small gas-filled polyhedral cells (alveoli), the walls of which are made up of a rich capillary network supported by a very thin interstitial matrix. Alveoli are the site of exchange, where blood and gas are brought into very close proximity, within a distance of approximately 1 micron (1µ). Each alveolus expands with fresh gas (high in O_2 and low in CO_2 content) that flows down the bronchial tree from the nasopharynx during inspiration. The alveoli then reduce in volume during expiration, returning gas (lower in O_2 and higher in CO_2 content) up the bronchial tree to the mouth. This process is called ventilation. The capillaries in the alveolar wall are fed with pulmonary arterial blood returned from the tissues (Figure 2). This requires two conduits with appropriate pumps : the pulmonary vascular system driven by the right heart bringing mixed venous blood to the region of exchange, and the tracheo-bronchial tree, with ventilation driven by the respiratory muscles exchanging gas between the alveolar space and the ambient air.

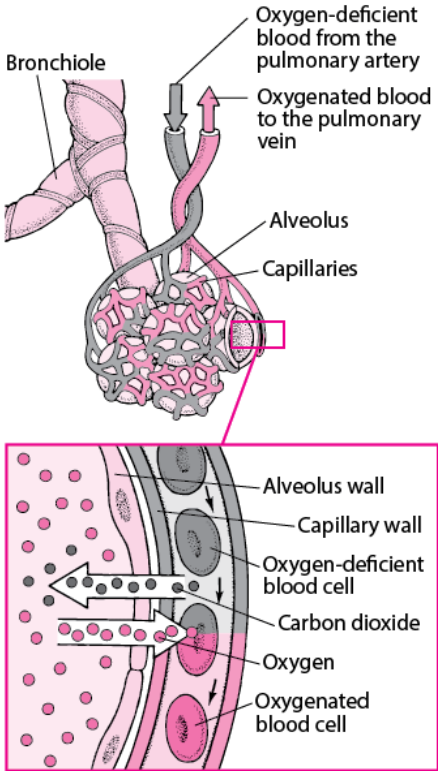

Figure 2. Gas Exchange in Alveoli

This blood is lower in O_2 and high in CO_2 , but after it flows through the alveolus and reaches the pulmonary veins, the O_2 level increases while CO_2 level decreases through the process of gas exchange. Usually, all alveoli are both ventilated as well as perfused. While these statements may be self-explanatory to most, they become the central concept behind how gas exchange occurs and therefore how blood gases can be interpreted clinically. The exchange of O_2 with CO_2 between the alveolar gas and the blood occurs by simple, passive diffusion (Figure 3).

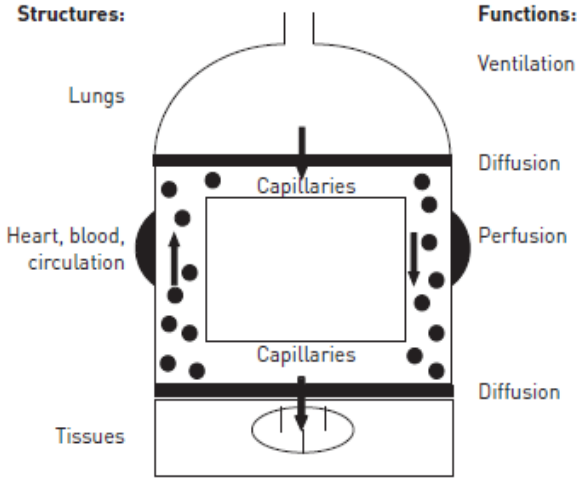

Figure 3. Schematic representation of the O_2 transport pathway

(Note : CO_2 transport pathway from the tissues to the lungs mirrors that for O_2)

Principles of pulmonary gas exchange :

Based on the above, pulmonary gas exchange is considered as a continuous process involving :
1) Ventilation,
2) Diffusion (including both physical diffusion throughout the pulmonary blood : gas barrier and subsequent chemical reactions (between O_2 and haemoglobin (Hb) and for CO_2 conversion to bicarbonate), and,
3) Perfusion (blood flow in the pulmonary circulation)

The fundamental principle that brings these three separate physical processes together quantitatively is called conservation of mass. This implies that within the lungs, every O_2 molecule that is inhaled but not exhaled diffuses from alveolar gas to blood and can be found within the same blood.

In quantitative terms, the product of minute ventilation (V'E, L·min¯1) and the difference between inspired and mixed expired O_2 concentrations (FiO_2 and FEO_2 respectively) quantifies the amount of O_2 ($V'O_2$) that leaves the alveolar gas and enters the pulmonary capillary blood per minute. The O_2 entering the pulmonary capillaries is quantified by the product of pulmonary blood flow (Q', L·min¯1) and the difference between pulmonary venous ($CpvO_2$) and pulmonary arterial (Cv^-O_2) O_2 concentrations. In this section, it is assumed, as stated above, that the lungs are homogeneous, meaning the concentration of O_2 in the blood leaving every alveolus is the same, and, passing unchanged into the systemic arterial blood, is thus equal to the systemic arterial O_2 concentration (CaO_2). This can be expressed by the following simple mass conservation equations :

$$\mathbf{V'O_2 = V'_E \times (FiO_2 - FEO_2) = V'_A \times (FiO_2 - FAO_2)}$$

and

$$\mathbf{V'O_2 = Q' \times (CaO_2 - CvO_2)}$$

In the right hand part of equation 1, it is recognised that the conducting airways do not themselves take part in air/blood gas exchange. This allows minute ventilation and mixed expired O_2 concentration to be replaced by alveolar ventilation (V'A) and alveolar O_2 concentration (FAO_2), respectively.

Because the process of diffusional transport described above usually comes to rapid completion well within the red cell transit time (at rest at sea level)[3], the partial pressure of O_2 in the alveolar gas (PAO_2) and the capillary blood leaving the alveolus can be considered to be the same. This means that $CpvO_2$ (and thus CaO_2 in equation 2) is that O_2 concentration that can simply be read off the Oxygen-haemoglobin dissociation curve at the value of PAO_2 , noting that :

$$\mathbf{PAO_2 = FAO_2 \times k}$$

where k is a constant , calculated as follows : **k = (barometric pressure - saturated water vapour pressure) / 100.**

The Alveolar Gas Equation :

The equation for CO_2 corresponding to that for equation 1 for O_2 is now presented :

$$\mathbf{V'CO_2 = V'A \times (FACO_2 - FICO_2)}$$

If this equation is simply divided by equation 1, and ignoring $FICO_2$ as negligible, we get :

$$\mathbf{V'CO_2 / VO_2 = R = FACO_2 / (FiO_2 - FAO_2) = PACO_2 / (PiO_2 - PAO_2)}$$

Here R stands for the respiratory exchange ratio, and the change from fractional concentration to partial pressure (P) follows Dalton's law of partial pressures, thus if we now rearrange this equation we have :

$$\mathbf{PAO_2 = PiO_2 - PACO_2 / R}$$

This is the simple form of the well-known alveolar gas equation that relates alveolar PO_2 to alveolar PCO_2.

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Oxygen Uptake, Delivery and Utilization

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Introduction :

Oxygen is the vital substrate for energy production and survival. Aerobic respiration is the most efficient mechanism for adenosine triphosphate (ATP) production which serves as the fuel to maintain cellular homeostasis and metabolism. Since the tissues have no storage system for oxygen, a continuous supply of oxygen at a rate that matches their metabolic demand is necessary to maintain aerobic metabolism and normal cellular function. For oxygen to be utilized for the production of energy in the tissues, it is first taken up by the lungs from the atmosphere, from where it is delivered to the tissues via blood. This process is dependent on the pulmonary and systemic circulation. Once oxygen reaches the tissues, it is utilized by the mitochondria to produce ATP. Transport of oxygen from environment to the cells of the body tissues depends on the integrated functioning of three organ systems namely the lungs, heart, and vascular system for circulation of blood.

Oxygen Uptake :

The primary function of the lungs is gas exchange. Oxygen is taken up from ambient air into the alveoli and then diffuses across the alveolo-capillary membrane into the pulmonary circulation in exchange for carbon dioxide which is removed from the circulation to the alveoli and finally exhaled into the atmospheric air. Oxygen in the alveolus diffuses across the alveolar-capillary membrane by simple passive diffusion, as the gas travels from an area of high to low partial pressure. This diffusion is based on the principle of Fick's law which states that the amount of gas that moves across a membrane or tissue sheet is directly proportional to the area but inversely proportional to the thickness of the membrane. The average thickness of the alveolar-capillary membrane is 0.3 μm and the surface area of the respiratory membrane between 50 and 100 m^2. Once oxygen is inside the pulmonary capillaries the next step is transport of oxygen to tissues.

The partial pressure of a gas is found by multiplying its concentration by the total pressure. The partial pressure of oxygen at sea level can be calculated thus : $\mathbf{PO_2 = FiO_2 \times (P_B - P_H)}$
where PO_2 is the partial pressure of oxygen, FiO_2 is the concentration of oxygen in the inspired air which is 20.9%, P_B is the atmospheric pressure at sea level which is 760 mm Hg and P_H (47 mm Hg) the water vapor pressure as the air is saturated with water vapor. The PO_2 of moist inspired air is therefore 20.9/100 x (760 – 47) = 149 mm Hg.

By the time oxygen reaches the alveoli, its partial pressure falls to about 100 mm Hg, which is determined by a balance of alveolar ventilation and removal of oxygen by pulmonary blood flow. The arterial blood when it reaches the peripheral tissues, a substantial fall in PO_2 occurs. The PO_2 of venous blood returning from the tissues is only about 40 mm Hg.

Oxygen Delivery :

Oxygen is carried in the blood in two forms, a small amount (free form) is dissolved but the major component (bound form) is in combination with hemoglobin. Normal arterial blood with a PaO_2 of about 100 mm Hg contains only 0.3 ml of dissolved oxygen per 100 ml, whereas about 20 ml is combined with hemoglobin. Blood is able to transport large amounts of oxygen because it forms an easily reversible combination of oxygen with hemoglobin - oxyhemoglobin. The relationship between the partial pressure of oxygen and the number of binding sites of hemoglobin that have oxygen attached is known as the oxygen dissociation curve. Each gram of pure hemoglobin can combine with 1.39 ml of oxygen, and in the blood of a normal healthy individual with 15 grams of Hemoglobin per 100 ml of blood, the oxygen carrying capacity (when all the binding sites are full) is 1.39 x 15, or about 20.8 ml O_2/100 ml of blood.

The total oxygen concentration of a sample of blood, which includes the oxygen combined with hemoglobin and the dissolved oxygen is calculated as follows :

Oxygen concentration (CaO_2) = (1.39 x Hb) x SaO_2 + (0.003 x PaO_2)

where Hb is the hemoglobin concentration, SaO_2 is the percentage hemoglobin saturated with oxygen and PaO_2 is the partial pressure of oxygen in arterial blood.

The shape of the oxygen dissociation curve is sigmoid (S-shaped) with the upper portion being relatively flat (Figure 1). This means that a fall of 20 to 30 mm Hg in arterial PO_2 in a healthy subject with an initial normal value (100 mm Hg) causes only a minor reduction in arterial oxygen concentration. However, this also means that monitoring non-invasively with a pulse oximeter will fail to identify a substantial fall in arterial PO_2. The steep lower portion of the oxygen dissociation curve means that considerable amounts of oxygen can be unloaded to the peripheral tissues with only a small drop in capillary PO_2, a factor that favours oxygen delivery to tissues under stress .

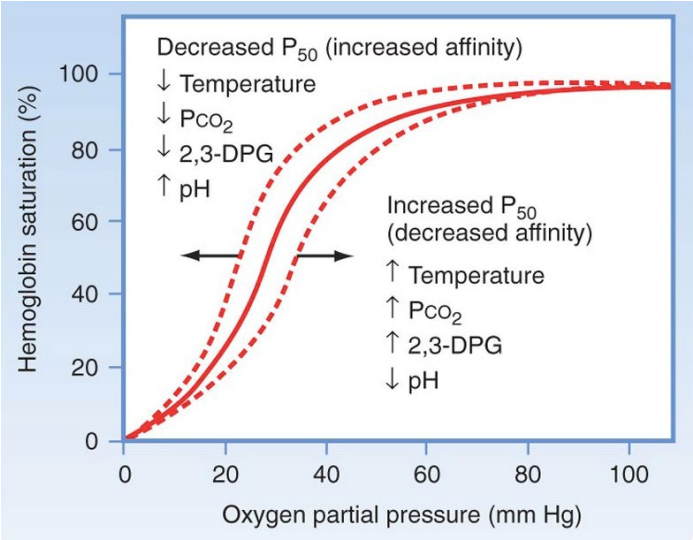

Figure 1. Oxygen Hemoglobin Dissociation Curve

Various factors affect the position of the oxygen dissociation curve. An increase in temperature, partial pressure of carbon dioxide (PCO_2), concentration of 2,3-diphosphoglycerate (2,3-DPG) in the red blood cell and a fall in the hydrogen ion concentration (or decrease in pH), shifts the curve to the right. This indicates that the affinity of oxygen for hemoglobin is reduced. As peripheral blood loads carbon dioxide, the unloading of oxygen is assisted. 2,3-diphosphoglycerate is an end product of red cell metabolism. Chronic hypoxia tends to increase its concentration which in turn also assists in unloading oxygen from hemoglobin to tissues. Global oxygen delivery is the amount of oxygen delivered to the tissues in each minute which is the product of cardiac output and oxygen content, as follows :

Oxygen delivery (DO_2) = Qt x CaO_2 x 0.01

where Qt is the cardiac output in ml of blood/min CaO_2 is the oxygen concentration in ml of O_2/100ml of blood.
This is an overall measure of oxygen delivery and does not take into account regional differences in blood flow and tissue perfusion. Oxygen flux to each tissue bed is not constant throughout the body. The microcirculation responds to altering tissue metabolic demands by varying the regional and local blood flow. Thus, alterations in cardiac output, arterial oxygen saturation and hemoglobin concentration in blood, will all affect oxygen delivery. Under resting conditions with normal distribution of cardiac output, the total oxygen requirements of the tissues is met and aerobic metabolism is maintained. It is clear from the equation above that the global oxygen delivery is dependent upon the cardiac output and the oxygen concentration of blood which in turn is dependent upon the Hemoglobin level, SaO_2 and PaO_2.

Failure of Oxygen delivery :

Failure of oxygen delivery to cells leads to cellular dysfunction which could cause cellular death and organ dysfunction and finally death of the person. Oxygen consumption drives the oxygen delivery requirements. But, failure of oxygen delivery to meet tissue or cellular oxygen demand will result in reduction of aerobic metabolism and energy production, necessitating ATP production by the less efficient glycolytic pathway. The critical level of oxygen delivery below which the oxygen consumption (VO_2) declines is 300 ml/min. This situation commonly arises due to failure of circulation which is described as shock. However, failure to meet the oxygen demand could also occur due to various other pathological mechanisms either singly or in combination as enumerated in Table 1.

Type of Hypoxia	Pathophysiological mechanisms	Conditions
Hypoxic Hypoxia	Reduced supply of oxygen due to low oxygen	• Low ambient oxygen (high altitude) • Ventilatory failure (respiratory arrest, drug overdose) • Pulmonary shunt (VSD with right to left flow, pneumonia, pneumothorax, pulmonary edema etc.)
Anemic Hypoxia	Low hemoglobin with normal oxygen tension	• Severe anemia • Blood loss • Carbon monoxide poisoning
Stagnant Hypoxia	Inadequate blood circulation	• Left ventricular failure • Pulmonary embolism • Hypovolemia
Histotoxic Hypoxia	Impaired cellular metabolism of oxygen	• Cyanide poisoning • Alcohol intoxication

Table 1. Types of Hypoxia and their pathophysiological mechanisms

The impact of a low oxygen delivery could be worsened by increased oxygen demand. Oxygen demand increases due to exercise, trauma (surgery, burns), inflammation, sepsis, fever, shivering, pain, agitation, thyrotoxicosis and physiotherapy which all lead to increased metabolic demand. On the other hand, therapeutic interventions like mechanical ventilation, hypothermia, sedation, analgesia, neuromuscular blocking agents, antipyretics and state of shock decrease oxygen demand. In critical illness, when oxygenation is inadequate, it is important to look into all the factors that contribute to and affect DO_2 and VO_2. Markers of tissue hypoxia, such as acidosis and lactate in conjunction with assessment of mixed venous oxygen saturation ($ScvO_2$) and hemodynamic measurements to assess adequate circulation are useful in such situation.

Inadequate Oxygen delivery :

In normal subjects at rest, the oxygen delivery (DO_2) is in excess of oxygen consumption (VO_2). The tissues consume only about a quarter of the available oxygen. With this large reserve in supply, oxygen consumption is a reflection of the metabolic demand and does not depend on the oxygen supply. Mild to moderate reductions in oxygen delivery are well tolerated and do not compromise the VO_2. However, when oxygen delivery is critically reduced below a certain level (called the critical DO_2), the oxygen extraction can no longer compensate to match VO_2 (Figure 2). This is when the limit of maximal oxygen extraction is reached.

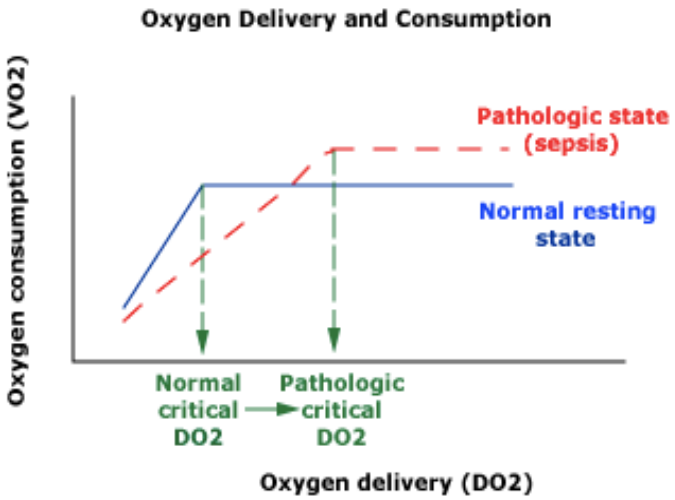

Figure 2. Oxygen Delivery and Consumption in the normal resting state and in the critically ill

At any level of oxygen concentration, the circulatory system affects tissue oxygen delivery through either variation in cardiac output or altering individual organ blood flow and oxygen delivery. In most tissues, blood flow and oxygen delivery is controlled in proportion to the tissue metabolic demands. For example, skeletal muscle blood flow increases with exercise; gastrointestinal blood flow increases following feeding and respiratory muscle blood flow increases with increased work of breathing. In general, blood flow through an organ matches its metabolic demand. Blood flow to the kidneys and skin are usually in excess of their demand because the kidneys have to continuously filter and skin has to transfer heat constantly to regulate body temperature. When DO_2 is reduced, systemic neurohumoral mechanisms are activated to redistribute the blood and oxygen flow in order to increase oxygen extraction. This is done predominantly by the sympathetic nervous system which causes redistribution of blood flow by differential organ vasoconstriction (and vasodilation).

Diagnosis and monitoring of Inadequate Oxygen delivery :

Early recognition and treatment of failure or inadequacy of oxygen delivery is important for preserving organ function. Traditional methods of assessment of DO_2 and VO_2 like heart rate, blood pressure or urine output can be misleading. In young healthy patients, the oxygen utilization can increase by 70-80 % with increased demand, meaning that such variables can change very late when DO_2 is decreased. These clinical parameters must be correlated with other technical values like hemoglobin saturation with oxygen (SaO_2), partial pressure of oxygen (PaO_2), acid base and mixed venous oxygen saturation ($ScvO_2$) and they should be continuously re-evaluated to plan treatment for the patient.

Oxygen concentration in the blood depends on both SaO_2 and PaO_2. Both these parameters do not reflect true tissue oxygenation, and oxygen extraction may vary between organs. In general, supplementary oxygen is required when PaO_2 falls below 60 mm Hg or SaO_2 is below 88%. Measurement of arterial acid base status may also be used to assess global oxygen delivery. The presence of acidosis and a base deficit of less than -2 may be used to detect inadequate DO_2 presuming this reflects lactate accumulation. However, serial assessments of lactate as a marker are needed to know the trend in oxygen delivery and utilization in conjunction with other parameters. Mixed venous oxygen saturation of hemoglobin ($ScvO_2$) can also be used as a marker of oxygen utilization by the tissues. A lower $ScvO_2$ (<70%) in the blood returning to the right heart with normal SaO_2 indicates increased extraction of oxygen in the tissues. Conversely a raised $ScvO_2$ (>75%) implies low demand (hypothermia, or a cellular utilization problem) like in cyanide poisoning when the cellular phosphorylation is inhibited. The value of $ScvO_2$ should also be used in conjunction with other markers of oxygen delivery and clinical context. Progressive metabolic acidosis, hyperlactatemia, falling mixed venous oxygen saturation as well as organ specific features such as oliguria and impaired level of consciousness suggest inadequate oxygen delivery. Serial lactate measurements can indicate both progression of the underlying problem and response to treatment.

Oxygen Uptake and Utilization :

Global oxygen consumption measures the total amount of oxygen consumed by the tissues per minute. It can be measured directly from the inspired and mixed expired oxygen concentrations and expired minute volume, or derived from the cardiac output and arterial and venous oxygen contents, as follows :

$VO_2 = Qt\ (CaO_2 - CvO_2)$

where VO_2 is the Oxygen consumption, Qt is cardiac output, CaO_2 and CvO_2 are the arterial and venous oxygen contents.

The amount of oxygen consumed (VO_2) as a fraction of oxygen delivery (DO_2) defines the oxygen extraction ratio (OER).

$OER = VO_2/DO_2$.

OER can also be expressed as the proportion of oxygen that is removed from the arterial blood as it passes through microcirculation. It could thus be calculated as

$OER = CaO_2 - CvO_2/CaO_2$

where CaO_2 is the oxygen content of the arterial blood and CvO_2 is the oxygen content of venous blood. Normal oxygen extraction ratio varies from 25-30%. In a normal 75 Kg adult undertaking routine activities, VO_2 is approximately 250ml/min with an OER of 25% which increases to 70-80% during maximal exercise in the well trained athlete. The oxygen not extracted by the tissues returns to the lungs and the mixed venous saturation (SvO_2) measured in the pulmonary artery represents the pooled venous saturation from all organs. It is influenced by changes in both global DO_2 and VO_2 and provided the microcirculation and the mechanisms for cellular oxygen uptake are intact, a value above 70% indicates the global DO_2 is

adequate. A mixed venous sample is necessary because the saturation of venous blood from different organs varies considerably. For example, the hepatic venous saturation is usually 40-50% but the renal venous saturation may exceed 80%, reflecting the considerable difference in the balance between the metabolic requirements of these organs and their individual oxygen deliveries.

Most of the cellular aerobic metabolism takes place in the mitochondria. The rate of diffusion of oxygen from bound oxyhemoglobin to the mitochondria follows the same principle as diffusion of oxygen from alveoli to blood. Once delivered to the cell, oxygen generates ATP by the electron transport chain, utilizing the power of NADH and $FADH_2$ generated from the citric acid cycle.

Cellular Hypoxia :

Human cells can reduce metabolic rate and increase oxygen extraction from surrounding tissues when oxygen delivery is compromised. Anaerobic metabolism is actively utilized by some tissues when oxygen demand is not met. In patients with organ dysfunction in critical illness, function may be compromised in the short term but structural damage is not seen following recovery.

Regional Hypoxia :

In critical illness, it is possible for tissue hypoxia to exist with associated organ dysfunction despite normal global oxygen distribution (DO_2) and $ScvO_2$ values. Few of the clinical methods commonly used for assessing DO_2 can identify changes in either organ or regional distribution of oxygen. Not only can the DO_2 of each organ system be manipulated to meet demand, but also, within each organ, regional demands may vary and can be varied. The effects of disordered or diverted regional blood flow can be important. In shock, splanchnic blood flow is often reduced, with the potential for gut ischemia. Hence, detection of gut ischemia could be used to influence management of oxygen delivery with the objective to reduce the likelihood of multi-organ failure. Also, vasoactive drugs are often used to increase oxygen delivery in the hope that this will optimize delivery to all tissues. However, such therapy may not increase oxygen delivery in all regions alike.

Conclusion :

The uptake, delivery and utilization of oxygen for metabolic demand of an individual is complex. Each step is affected by multiple factors. It is important to understand how our respiratory system, blood and the cardiovascular system function in an integrated manner to facilitate the movement of oxygen from the atmosphere to the pulmonary capillary to the mitochondria to be able to manage the critically ill patient.

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Hypoxia and Respiratory Failure

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Introduction :

Hypoxia and hypoxemia are commonly used interchangeably to describe the deficiency of oxygen. The two terms however have different meanings. **Hypoxia** is defined as a condition characterized by lack of or insufficient oxygen supply at the tissue level. On the other hand, **hypoxemia** is an alternate term which refers specifically to low arterial oxygen content and therefore low arterial oxygen supply to a particular tissue. Hypoxia can be further classified as generalized when the whole body is affected and localized when there is low oxygen supply to a particular region. Complete deprivation of oxygen is referred to as **anoxia.**

Local Hypoxia :

Deficient blood supply to a particular region, such as due to arterial blockade causes local ischemia and oxygen deficiency. An ischemic organ appears pale which on surface feels cold and appears cyanosed. Severe hypoxia or anoxia will result in gangrene of the affected tissue.

Generalized Hypoxia :

Generalized tissue hypoxia is classified into the following four types :

1. **Hypoxic hypoxia :** Hypoxia of this type is caused by inadequate oxygen in the blood either due to low inspired oxygen (which may result from deficient oxygen in the inhaled /ambient environmental air such as at high altitude, fires and smoke) or due to lung diseases (hypoventilation or ventilation-perfusion disturbances).
2. **Anemic hypoxia :** Presence of severe anemia i.e. low haemoglobin saturation and low oxygen delivery is an important cause of hypoxia.
3. **Stagnant (or circulatory) hypoxia** : There is inadequate blood flow to the hypoxic tissue. This is commonly seen due to hypotension or low cardiac output due to any cardiopulmonary or systemic disease.
4. **Histotoxic hypoxia** : There is an adequate amount of inhaled oxygen but the tissues are unable to use the oxygen. This is commonly seen in cases of poisoning.

Besides these true forms of hypoxia, a state of **relative hypoxia** can occur when there is greater than usual demand for oxygen by the tissues such as during sepsis or other conditions of high stress. This is sometimes referred to as **metabolic hypoxia**.

Hypoxia and Respiratory Failure :

Essentially speaking, hypoxia indicates the presence of respiratory failure i.e failure of the respiratory system to efficiently perform one or both of its gas exchange functions - the uptake of oxygen and removal of carbon dioxide. Respiratory failure can therefore be classified as either **hypoxemic (type I)** or **hypercapnic (type II) .**

In type I respiratory failure, the arterial oxygen tension (PaO_2) is lower than 60 mm Hg with a normal or low arterial carbon dioxide tension ($PaCO_2$). On the other hand, type II failure is characterized by hypoxia and hypercapnia ($PaCO_2$ higher than 50 mm Hg). Respiratory failure may also be classified as acute or chronic based on the duration of the underlying disease and onset of failure (Table 1). Acute respiratory failure may often be characterized with life-threatening abnormalities of arterial blood gases and acid-base status. Chronic respiratory failure occurs in patients with chronic and protracted illnesses with gradual onset and relatively poorly distinguished clinical features.

Acute Respiratory Failure	Chronic Respiratory Failure
Develops within minutes to hours	Develops over a longer period
History of an acute illness : Pneumonia, sepsis, poisoning, intoxication	History of a chronic illness : chronic respiratory or neuromuscular illness
CO_2 retention : may or may not be there. Severe acidosis : pH is less than 7.3	Hypercapnia is almost always present. Decrease in pH is usually not severe
Usually, no evidence of a chronic illness. Acute exacerbation of a chronic illness such as COPD or asthma is also an important cause of acute respiratory failure.	Features of chronic hypoxemia such as polycythemia or cor pulmonale

Table 1. Clinical Characteristics of Acute and Chronic Respiratory Failure

Pathophysiology of Respiratory Failure :

The respiratory system consists of a central control component in the central nervous system and a peripheral component which comprises of the airways and alveoli as well as the peripheral nervous system, respiratory muscles, and the chest wall. Abnormalities of structure and/or function of any of these components can lead to respiratory failure. In addition, tissue hypoperfusion resulting in hypoxia can also cause respiratory failure. Hypoperfusion may occur secondary to a number of conditions including hypovolemia, septic shock and cardiogenic shock. Respiratory failure may also occur due to an increase in ventilatory demand, minute ventilation and/or the work of breathing.

Movement of oxygen from the environment to the tissues involve the following physiological processes :

1. Ventilation – movement of air and oxygen to the lung alveoli.
   This is best represented by the alveolar air equation :
   $VA = K \times VCO_2 / PaCO_2$
   where K is a constant, VA is alveolar ventilation, and VCO_2 is carbon dioxide ventilation).
2. Diffusion – uptake of oxygen by the pulmonary capillary blood and elimination of CO_2 from the blood to the alveoli
3. Ventilation-perfusion distribution or ratio (V/Q ratio)
4. Transport – carriage of oxygen in the arterial blood to the tissues
5. Utilization of oxygen by the metabolizing tissues.

Distribution of Ventilation and perfusion : It is also important that both ventilation and perfusion are evenly distributed to different parts of the lungs for adequate gas exchange (i.e. oxygen uptake and CO_2 removal). V/Q ratio is the amount of air or oxygen that reaches the alveoli divided by (or expressed as a fraction of) the amount of blood that flows through the pulmonary capillaries. Approximately four litres of oxygen and five litres of blood pass through the lungs every minute, therefore a V/Q ratio of about 0.8 per minute is considered normal. Ventilation-perfusion (V/Q) mismatch occurs when either the ventilation (airflow) or perfusion (blood flow) in the lungs is impaired, preventing the lungs from optimally delivering oxygen to the blood. Diseases that obstruct airflow in the tracheo-bronchial tree or reduce alveolar oxygenation result in a decreased V/Q ratio, whereas those that obstruct pulmonary capillary blood flow result in an increased V/Q ratio.

In blood, oxygen binds to hemoglobin; 1.36 mL of oxygen combines with 1 gram of hemoglobin depending on the oxygen level in blood, the partial pressure of which is represented by the PaO_2. This relationship is expressed as the sigmoid-shaped oxygen-hemoglobin dissociation curve.

CO_2 is transported in 3 main forms :

i. dissolved in plasma,
ii. as bicarbonate, and;
iii. combined with hemoglobin (carbamino compound).

Hypoxia and respiratory failure results whenever there is significant disturbance of any of these processes :

1. Hypoventilation
2. Ventilation-perfusion disturbances or mismatch : an area in the lung may be adequately ventilated but poorly perfused (Relative hypoventilation), or an area may be adequately perfused but poorly ventilated (Shunt effect).
3. Diffusion defects due to defects of the alveolo-capillary membrane
4. Oxygen transport problems
5. Problems of metabolism and tissue utilization of oxygen

Causes of Respiratory Failure :

Respiratory failure can occur in a large number of respiratory as well as non-respiratory diseases (Table 2). Type I or hypoxic failure can occur almost due to all acute diseases of the lung which cause alveolar filling (pneumonia, cardiogenic or noncardiogenic pulmonary edema, pulmonary hemorrhage) or collapse (acute airways obstruction). Common causes of hypercapnic respiratory failure (type II) include drug overdose, neuromuscular disease, severe kyphoscoliosis and diffuse, severe airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). Causes of either type I or type II respiratory failure are not mutually exclusive. For example, acute exacerbation of a chronic disease such as COPD, bronchial asthma and interstitial lung disease (ILD) can cause acute failure which is sometimes referred to as acute-on-chronic respiratory failure.

Type I (Hypoxemic) Respiratory Failure	Type II (Hypercapnic) Respiratory Failure
Acute pulmonary illnesses : • Pneumonia • Severe asthma • Pulmonary edema • Acute respiratory distress syndrome (ARDS) • Pulmonary embolism • Fat embolism syndrome • Pneumothorax • Pulmonary fibrosis **Non-pulmonary conditions :** • Cardiogenic and non-cardiogenic pulmonary edema • Aspiration pneumonia • Systemic vasculitides causing extensive pulmonary hemorrhage	**Chronic respiratory diseases (CRDs) :** • COPD • Severe asthma • Pulmonary fibrosis **Central nervous system (CNS) diseases :** • Drug overdose and poisonings • Myasthenia gravis • Polyneuropathy • Head and cervical cord injury • Obesity-hypoventilation syndrome and Primary alveolar hypoventilation **Peripheral nervous system involvement in :** • Guillain-Barré syndrome • Muscular dystrophy • Severe kyphoscoliosis

Table 2 : Causes of Respiratory Failure

Diagnosis of Respiratory Failure :

1. **Clinical Features :**

Diagnosis is suspected from the presence of an underlying illness involving the respiratory system (Table 2) and clinical features suggestive of hypoxemia and / or hypercapnia (Table 3). Frequently there is an overlap of signs and symptoms of hypoxemia and hypercapnia. Acute onset of symptoms of chest pain, fever, cough, dyspnea, and orthopnea suggest pneumonia and sometimes pulmonary edema. Acute respiratory distress syndrome (ARDS) which can complicate acute, severe conditions such as sepsis, trauma, aspiration, pneumonia, pancreatitis or toxins and drug toxicity is an important cause of acute respiratory failure. Chronic lung disease is often characterized by the presence of chronic cough, phlegm and breathlessness. Weight loss and other constitutional symptoms may also be present. Physical findings include the presence of cyanosis which occurs when at least 5 g/dL or more of hemoglobin is deoxygenated. Diagnosis is further substantiated by signs of acute (consolidation, pulmonary edema or acute asthma) or chronic lung disease (COPD, bronchiectasis, kyphoscoliosis). Clinical features may also be seen due to complications of respiratory failure, both acute and chronic. Polycythemia, pulmonary hypertension, right ventricular enlargement and failure (known by the syndromic term of chronic cor pulmonale) are common complications of long-standing hypoxemia and chronic respiratory disease. Respiratory failure can also occur as a result of pulmonary embolism, nosocomial pneumonia, barotrauma, cardiovascular, gastrointestinal (GI), renal, or nutritional disorders or infections.

Hypoxemia	Hypercapnia
• Cyanosis • Tachypnoea • Tachycardia (terminally bradycardia) • Sweating, restlessness, anxiety, sleeplessness • Atrial and ventricular arrhythmias • High systolic blood pressure (later hypotension) • Mental confusion, disorientation and incoordination, progressing to convulsions, coma	• Headache, confusion, drowsiness • Sleep disturbances • Personality changes and disorientation. • Pulse is fast, bounding and collapsing with warm extremities • High systolic blood pressure. • Flapping tremors (asterixis) • Papilloedema • Seizures • Coma

Table 3. Common Clinical Features of Respiratory Failure attributable to the presence of hypoxemia and hypercapnia.

Common cardiovascular complications include tachycardia, arrhythmias, hypotension due to reduced cardiac output, and acute myocardial ischemia. Hypoxemia frequently leads to acute renal failure and abnormalities of electrolytes and acid-base balance. This may commonly result from renal hypoperfusion and use of nephrotoxic drugs.

Gastrointestinal complications are also common – include gastric hemorrhage due to stress ulceration, distention, ileus and sometimes diarrhea. Hepatic hypoxemia may be characterized with jaundice and hepatic necrosis.

Malnutrition is frequently present in these patients. Besides the underlying chronic disease, malnutrition is caused by a multitude of factors such as the complications related to enteral or parenteral nutrition, abdominal distention and diarrhea. Infections, hypoglycemia, electrolyte imbalance further add to the problem.

2. Blood gas and acid-base assessment :

Diagnosis of respiratory failure is finally confirmed by analysis of arterial blood gases (Oxygen and carbon dioxide) and acid-base balance. Arterial blood gas pressures (i.e. partial pressures, pO_2 and pCO_2) are measured from arterial blood samples which is an invasive procedure. Non-invasive assessment is preferred for routine monitoring. It includes pulse oximetry to measure arterial oxygen saturation (SaO_2 %) and end-tidal breath capnometry for assessment of carbon dioxide pressure (ET pCO_2 or ET-CO_2). Hypoxemia is an essential character of both acute and chronic respiratory failure whereas hypercapnia may or may not be present. Hypercapnia is essentially a manifestation of hypoventilation which can be present during both acute and chronic respiratory failure. Hypercapnic respiratory failure occurs secondary to a variety of causes, including respiratory muscle fatigue, impaired neuromuscular function, and decreased respiratory drive caused by central nervous system depression.

The distinction between acute and chronic respiratory failure requires interpretation of acid-base status. Chronic respiratory failure develops over a longer period of several days to weeks allowing time for renal compensation and alterations in bicarbonate concentration. Assessment of acid-base status requires estimation of pH, pCO_2, bicarbonate concentration, serum electrolytes and anion-gap.

3. Pulmonary Imaging :

Chest x-ray and sometimes computed tomographic (CT) scanning to help diagnose lung parenchymal and pleural conditions such as consolidation, collapse, effusion, or pneumothorax. Radiology also helps to distinguish between cardiogenic and non-cardiogenic pulmonary edema which may be otherwise difficult. Cardiac or hydrostatic edema is suggested by the presence of increased heart size, vascular redistribution, peribronchial cuffing, pleural effusions, septal lines, and perihilar bat-wing distribution of infiltrates (Figure 1) **.** On the other hand the lack of these findings suggests acute respiratory distress syndrome (ARDS). Failure to detect an obvious abnormality on chest radiograph in hypoxemic respiratory failure may suggest the possibility of right-to-left shunting.

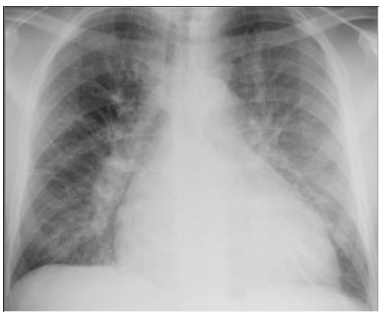

Figure 1. Chest radiograph of a patient with cardiogenic pulmonary edema

Cardiac functional status is determined with the help of electrocardiography (ECG) and Echocardiography (ECHO). Both ECG and ECHO provide important information about the presence of any rhythm disturbance, myocardial contractility, valvular function and underlying cardiovascular cause of respiratory failure. The findings of left ventricular dilatation, regional or global wall motion abnormalities, or severe mitral regurgitation support the diagnosis of cardiogenic pulmonary edema. A normal heart size and normal systolic and diastolic function in a patient with pulmonary edema would suggest ARDS. ECHO also provides an estimate of right ventricular function and pulmonary artery pressure in patients with chronic hypercapnic respiratory failure.

4. Assessment of Pulmonary Function :

Pulmonary functions tests (PFTs) such as spirometry and diffusion capacity are difficult to perform during acute respiratory failure. Moreover, these are not required to confirm the diagnosis of respiratory failure but are more important for the diagnosis of the underlying chronic respiratory disease. PFTs provide both diagnostic and prognostic help in diseases such as asthma, COPD and interstitial lung disease. Obstructive pattern is characterized by a decrease in the FEV_1-to-FVC ratio (FEV_1/FVC) whereas restrictive pattern is suggested by a reduction in both FEV_1 and FVC and a fairly preserved FEV_1/FVC ratio. Restrictive lung function pattern may also be present in both chest-wall and neuro-muscular diseases. Normal values for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) suggest a disturbance in respiratory control.

5. Other investigations :

Detailed investigations are required for the diagnostic assessment of respiratory failure as well as to know the functional status of different organ systems. Such an assessment requires general hematological, biochemical, microbiological and immunological tests as well as chest radiography. Presence of polycythemia may indicate chronic hypoxemic respiratory failure. It is a common feature of chronic conditions such as COPD. Abnormal renal and hepatic function, as well as abnormal serum concentrations of electrolytes (sodium, potassium, magnesium, and phosphate) may either indicate the etiology of, or the complications associated with respiratory failure.

Right-sided heart or pulmonary artery catheterization (Swan-Ganz catheterization) and measurement of pulmonary capillary wedge pressure is an invasive procedure. It is rarely done only when there is strong suspicion about cardiac dysfunction. It may be required to distinguish between cardiogenic and non-cardiogenic edema.

Management of Respiratory Failure :

Management of respiratory failure involves a multi-pronged approach. Hypoxemia as well as the ventilatory and hemodynamic status along with maintenance of acid-base balance needs immediate correction. It is also important to identify and manage the underlying pathophysiologic processes and aggravating factors that led to respiratory failure in the first place. The specific treatment depends on the etiology of respiratory failure. Management steps can be broadly classified as follows :

1. Correction of hypoxemia, hypercapnia
2. Management of aggravating / precipitating factors responsible for respiratory failure and Management of underlying lung and / or other diseases
3. Treatment of complications
4. General care

1. Correction of hypoxemia and hypercapnia : Reversal of hypoxemia is important to prevent damage to different tissues especially of vital organs such as the brain, heart, liver and kidneys. Hypercapnia alone is relatively well tolerated even though the severe acidosis due to hypercapnia requires urgent attention. PO_2 below 40 mmHg and PH below 7.2 are poorly tolerated. Patient with acute respiratory failure or acute worsening of chronic respiratory failure should be immediately shifted to a respiratory care unit or intensive care unit (ICU). Arterial blood gas analysis is most important in making an overall assessment of the patient condition. It is not at all uncommon to miss a diagnosis of early and incipient respiratory failure is sometimes delayed. The dangerous levels of hypoxia, hypercapnia and acidosis may vary with the underlying condition.

It is important to remember that oxygen is required in all hypoxic conditions even in the absence of demonstrable hypoxemia. Hypoxia, based on pO_2 levels is classified as either hypoxemic (i.e. associated with low arterial PO_2) or normoxemic when the arterial PO_2 is normal. Hypoxemic hypoxia occurs due to pulmonary diseases while normoxemic hypoxia is commonly seen in non-pulmonary condition.

2. Oxygenation : Correction of hypoxemia is aimed at achieving an arterial oxygen tension of 60 mm Hg or arterial oxygen saturation of about 90% which is essential for tissue oxygenation. This is achieved with high concentrations of inspired oxygen (FiO_2) in cases of acute respiratory failure for a rapid recovery from hypoxemia. To avoid the risk of oxygen toxicity, it is important to reduce the FiO_2 as soon as possible to a level sufficient to maintain good oxygenation. This is even more important in patients with chronic respiratory failure and hypercapnia. There is a significant risk of respiratory depression due to CO_2 retention with administration of high concentrations of oxygen and a rapid increase in arterial PO_2. This rapid increase in arterial carbon dioxide tension, also called as carbon dioxide narcosis causes severe respiratory acidosis, somnolence, and coma. This occurs as a result of reversal of pulmonary vasoconstriction, increase in dead space ventilation and hypoventilation.

A number of devices are available which can be employed for oxygen delivery from the oxygen source to the patient. These include nasal cannulae, simple face masks, non-re-breathing masks or high flow nasal cannulae. Soft nasal catheters and prongs to obtain a flow rate of 0.5 to 2 L/min are most commonly used. The use of masks allows delivery of a known and fixed concentration of O_2 for patients with chronic respiratory failure and hypercapnia. Venturi masks (for fixed concentration of 24%, 28%, 32% delivery) are usually employed. Masks are sometimes poorly tolerated by dyspneic patients who may feel suffocated with their use.

Finally, one may resort to the use of assisted respiratory support (ARS) and mechanical ventilation if there is no or poor response to conventional methods of oxygen administration and the hypoxemia is persistent and progressive. ARS should be employed as early as possible to avoid serious hypoxic damage to vital organs. Ventilatory assistance not only helps to raise PO_2 and lower PCO_2 but also provides rest to the fatigued respiratory muscles. Ventilatory assistance generally requires endotracheal intubation or tracheostomy and attachment of the patient to a ventilator machine. Intubation is associated

with several complications and should therefore be undertaken only in the presence of persistent hypoxemia despite receiving maximum oxygen therapy. Mechanical ventilation is also required to manage hypercapnia with impairment of consciousness and to avoid respiratory muscle fatigue in patients with respiratory failure.

Non-invasive positive pressure ventilation (NIV) is also available for patients with in relatively milder forms of respiratory failure and those with hypercapnia. NIV is provided with the help of a tight-fitting face mask without tracheal intubation / via upper airway. There are different modes of NIV which include the bi-level positive airway pressure (BiPAP) and continuous positive airways pressure (CPAP) ventilation. It is essential that the patients should be conscious and have an intact airway with the presence of airway protective reflexes. NIV lowers the reduce complications rate, duration of ICU stay and mortality in patients with mild to moderate respiratory failure. It is more effective in acute respiratory failure due to COPD than in other causes. Extracorporeal membrane oxygenation (ECMO) may be needed in refractory cases. ECMO is likely to be more effective than mechanical ventilation and conventional management for patients with severe but potentially reversible respiratory failure. It is however costlier as well as requires greater expertise.

Lowering of arterial pCO_2 and correction of respiratory acidosis are achieved with management of underlying cause of hypoventilation and other complicating factors. Ventilatory assistance is often necessary for this purpose.

There are small differences in the principles or delivery of oxygen therapy for different clinical conditions. A brief account of different clinical indications for oxygen therapy is discussed as under :

I. Oxygen therapy for respiratory failure due to pulmonary disorders :

1. Acute Respiratory Tract Infections – bronchopneumonia and acute respiratory distress syndrome : Hypoxemia may develop in severe acute upper and lower respiratory tract infections. Upper respiratory tract infections such as acute laryngitis (especially in infants and young children) may cause respiratory stridor and a picture of acute upper airway obstruction. If severe, this may prove to be fatal. Lower respiratory tract infections such as bronchiolitis and severe bronchopneumonia cause hypoxemia requiring high concentrations of oxygen. Hypoxemia may be severe and often oxygen-resistant if there is acute respiratory distress syndrome, which frequently complicates bronchopneumonia.

2. Chronic Obstructive Pulmonary Disease (COPD) : Respiratory failure characterized by the presence of hypoxia and hypercapnia is a common complication seen in COPD disease during an exacerbation of the underlying disease. While hypoxia is primarily attributed to ventilation-perfusion (V/Q) mismatch, hypercapnia results from hypoventilation contributed by airway obstruction, chronic respiratory muscle fatigue and central hypoventilation. Oxygen in these patients is required both during hospitalizations for acute exacerbations and on long-term domiciliary basis for maintenance therapy for management of hypoxia.
The goal of oxygen therapy in COPD is to maintain a PaO_2 of 55 to 60 mm Hg which corresponds to arterial oxygen saturation (SpO_2) of 89-92%. This is usually achieved with controlled low-flow of oxygen since an excess of oxygen can blunt the ventilatory drive precipitating hypoventilation, worsening of hypercapnia and acute respiratory acidosis. Controlled oxygen is best delivered with high-flow devices such as a venti-mask.

3. Acute Severe Bronchial Asthma : Respiratory failure in asthma may occur due to the presence of persistent airway obstruction or acute exacerbation characterized by ventilation - perfusion mismatch. Typically, there is mild hypoxemia, hypocapnia and respiratory alkalosis during an acute attack. Hypercapnia is generally absent and even normo-capnia is considered as a sign of CO_2 retention. Oxygen administration for acute asthma exacerbation should ideally start from home for correction of unrecognized hypoxemia. Initially, oxygen is administered via a face mask or a nasal cannula at a flow rate of 4-6 L/min to achieve an FiO_2 of 35-40%. Flow rate is adjusted to maintain SaO_2 of at least 92% and a PaO_2 of about 60 mmHg. Oxygen should be humidified to prevent dryness of nasal mucus membrane. Rapid bronchodilation following aggressive treatment with bronchodilators may paradoxically worsen gas exchange and V/Q mismatch precipitating hypoxia. It is therefore important to administer O_2 along with pharmacotherapy to avoid the worsening of hypoxia. Oxygen also helps to reduce pulmonary hypertension due to hypoxic pulmonary vasoconstriction, and may also exert a dilatatory effect on the severely constricted bronchi.

4. Interstitial Lung Disease (ILD) : Hypoxemia in ILDs especially pulmonary fibrosis is characteristically induced after exercise. The alterations in gas exchange are contributed by both ventilation-perfusion mismatch and impaired diffusion. The V/Q mismatch results from small tidal volumes but high breathing frequencies because of intrinsic stiffness of lungs. Hypoxemia at rest occurs during an acute infective episode or acute exaggeration. Oxygen administration is required usually in higher concentrations for correction of hypoxemia without any significant fear of hypercapnia. Oxygen requirements are generally high and increase with the severity of illness. There are no clear indications for long term oxygen therapy for maintenance treatment. While there is some evidence to suggest symptomatic relief from breathlessness and cough as well as improved quality of life, there are no reliable survival data to suggest effectiveness of domiciliary oxygen therapy for ILD.

5. Chronic destructive, fibro-cavitary lung diseases : Hypoxemia results whenever there is extensive lung destruction due to chronic cavitary diseases such as bronchiectasis, tuberculosis and cystic fibrosis. Reduced lung volume and pulmonary

hypertension which invariably result in the due course of time are both responsible for hypoxia. Excessive mucus formation causes plugging of airways contributing to hypoventilation and hypoxemia. Acute worsening, for example due to an infectious pneumonia, causes precipitation of acute respiratory failure. Oxygen administration is required whenever there is any such exacerbation of symptoms or worsening. Not enough literature is available on experience with long term domiciliary oxygen although it has been shown to improve exercise performance in patients with extensive pulmonary disease in cystic fibrosis.

II. Oxygen therapy for non-pulmonary diseases :

Most of the non-pulmonary diseases for which oxygen is frequently administered do not show any demonstrable hypoxemia. Some of these conditions are characterized by tissue hypoxemia while the indication for others is entirely empirical. Some such conditions are discussed as under :

1. Cardiac disorders : Except for the presence of pulmonary edema due to left heart failure, hypoxemia is often not demonstrable in cardiac diseases. Presence of left ventricular failure with pulmonary congestion and/or edema is a definite indication. Oxygen administration may also help to improve cardiac muscle function and tissue oxygenation in patients with acute myocardial infarction even though there is no arterial hypoxemia. Oxygen may relieve breathlessness even though excess administration can lead to systemic vasoconstriction and increased after-load. Use of 100 % FiO_2 is especially useful for patients with complicated infarction such as with congestive heart failure or cardiogenic shock, may also improve myocardial oxygenation and contractility. There is no clear evidence on the role of oxygen during uncomplicated episodes of angina or myocardial infarction. Similarly, no definite conclusion can be drawn whether O_2 administration reduces the extent of acute myocardial ischemia. Long term oxygen therapy is found to be useful for severe cardiac failure. There are a few reports which show significant improvements in quality of life as well as in sleep disordered breathing in these patients with nocturnal oxygen therapy.

2. Cerebrovascular Disorders : Supplemental oxygen administration provides no benefit to most patients of ischemic stroke. Oxygen administration may also help in the treatment of cluster headaches and migraine. It does not benefit the management of seizures except for management of aspiration pneumonia which may complicate an episode of seizure or unconsciousness.

3. Other Medical Disorders :

i. Hemoglobin abnormalities : There is poor oxygen transport and tissue hypoxia in the presence of low hemoglobin (anemia), abnormalities of hemoglobin (sickle cell disease), low intravascular volume (hypovolemia shock) and/or inadequate blood flow (hypotension). Most patients with chronic anemias do not show any benefit with oxygen therapy but it is required for conditions in which a sudden fall in hemoglobin level is seen following an episode of massive bleeding or intravascular hemolysis. There is no established role of oxygen for conditions associated with hemoglobin abnormalities such as methemoglobinemia or sickle cell disease. It may be temporarily useful in acquired methemoglobinemia following toxic exposure to drugs or chemicals such as nitrates, nitrites, sulfonamides and chlorates. Carboxy-hemoglobinemia (COHb) due to acute carbon monoxide poisoning is a definite indication. Hyperbaric oxygen therapy (HBO) is most helpful in such a situation. It involves breathing pure oxygen in a hyperbaric chamber in which the air pressure is higher than normal, this accelerates the replacement of carbon monoxide with oxygen in blood in patients with severe carbon monoxide poisoning and also protects cardiac and brain tissues, which are particularly vulnerable to injury from carbon monoxide poisoning.

ii. Problems of blood volume and cardiac output : Oxygen transport and delivery to the tissues is impaired in conditions with reduced cardiac output such as in the presence of hypovolemia due to any cause, sepsis or myocardial dysfunction. This can happen due to cardiac ischemia, myocarditis and pulmonary thromboembolism. Supplementary oxygen at FiO_2 of 60 to 100 percent is useful in addition to primary treatment of the underlying problem. However prolonged therapy is likely to cause problems of oxygen toxicity without accruing any significant benefit.

iii. **Palliative Care :** Oxygen is often used for patients with advanced malignancies and other end stage diseases to reduce breathlessness. Oxygen diminishes the anxiety, pain and discomfort associated with respiratory distress. The Working Party of the Association of Palliative Medicine Science Committee suggests the need to tailor the administration of O_2 to an individual patient to reduce the level of breathlessness and improve the quality of life. It is also comforting for the patient and his near and dear ones to see a breathless patient on oxygen even if it does not provide any physiological benefit.

iv. **Surgical indications :** Oxygen is routinely administered during anesthesia and surgery. It is also given during endoscopic and interventional procedures especially when these procedures are prolonged. Peri-operative oxygen at FiO_2 of about 70-80% is helpful to reduce the rate of post-operative complications such as post-operative nausea, vomiting and wound infection. Similarly, it may be helpful for women in labor especially to lessen fetal distress even though data is yet inconclusive in patients with history of respiratory disease to reduce the level of anxiety and improve the oxygen reserves. There is mild to moderate hypoxemia in the immediate post-operative period. Post-operative administration of oxygen is therefore required for the first few hours after surgery, usually at low flow rates. More prolonged administration may be

required in patients who have undergone surgery for a prolonged period or are suffering from a co-morbid cardio-pulmonary condition. Post-operative oxygen is also recommended after pulmonary or cardiothoracic surgery for longer periods. Therapy is guided by monitoring of the patients' vital parameters and oxygen saturation and pressure measurements.

Long-term Oxygen therapy :

Use of long-term oxygen therapy (LTOT) on a domiciliary basis for patients with COPD and chronic respiratory insufficiency was shown to improve quality of life and reduce mortality in the early 1960s in two landmark trials – the Medical Research Council (MRC) Oxygen Therapy Trial and Nocturnal Oxygen Therapy Trial (NOTT) undertaken in the United Kingdom and United States respectively. Several subsequent studies from several countries have substantiated these findings. In addition, LTOT has been tried for almost all chronic respiratory diseases characterized by hypoxemia and sometimes even for patients who do not demonstrate resting hypoxemia but develop the same during sleep or exercise. Besides COPD, some of the other important indications for LTOT may include interstitial pulmonary fibrosis, extensive bronchiectasis or cystic fibrosis, kyphoscoliosis and sleep apnea syndrome. Although data is inconclusive, patients with severe cardiac failure and other end-stage chronic conditions may also benefit to a variable extent. The benefit is largely symptomatic as a palliative measure for many of these non-pulmonary disorders. There are however, definite criteria and indices used for selection of patients for long term domiciliary oxygen use.

General Management of Respiratory Failure :

Besides oxygen therapy, some of the other important steps of management of respiratory failure are discussed as under :

1. Securing the airways :

It is important to secure patency of airways for an adequate ventilation. A number of factors are responsible for an increased production due to infection and inflammation and retention of secretions in the upper airways. Poisoning due to organophosphates or other toxins, scorpion stings and severe hypothermia are generally associated with excessive bronchorrhea. Presence of dehydration causing drying of secretions as well as the muscular weakness and altered level of consciousness makes it difficult for patients to cough out the thick and dry secretions. Airway blockage finally results in hypoventilation, hypoxemia and increased work of breathing. It is therefore important to maintain adequate hydration and a good bronchial hygiene. Humidification of inspired air/gases and nebulisation of hypertonic saline solutions helps to achieve liquefaction of secretions. Chest Physical therapy with chest percussion and vibration methods is also used to promote bronchial hygiene and assist the drainage of respiratory secretions.

2. Management of underlying lung disease and/or aggravating/ precipitating factors responsible for respiratory failure :

Respiratory failure may occur in a large number of conditions, both respiratory and systemic diseases (Table 2) and may be triggered most commonly following an infection such as pneumonia or sepsis. Simple upper respiratory viral catarrh, urinary tract, gastrointestinal or skin infections, malaria or other febrile illnesses may also trigger respiratory failure. Besides infection, other acute stressful condition such as an injury, surgery, drug overdosage, poisoning and exposure to toxins, snake bites or other poisonous stings, hemorrhage or thrombo-embolic phenomena may also precipitate respiratory failure. Respiratory failure may also occur along with a concurrent cardiac, gastrointestinal, renal, hepatic or neurological illness.

Essentially, the treatment depends upon the cause of precipitating or aggravating factors. For example, Infection requires treatment with appropriate antibiotics/anti-microbial agents and other drugs. The choice of antibiotics is made on the basis of culture reports, local microbiological epidemiology and other empiric factors. Problems of accumulation of secretions, bronchospasm and infection in patients with relative hypoventilation due to obstructive lung disease should be appropriately handled. Bronchospasm should be treated with nebulized bronchodilators and corticosteroids wherever indicated. Left ventricular failure and pulmonary embolism should be treated as needed. Problems like drug overdosage should be managed with dialysis and other means to enhance drug excretion. Similarly, patients of myasthenia gravis and myxoedema would require specific therapy. Patients with Guillain-Barre syndrome require ventilatory support till the disease runs its course.

3. Treatment of complications :

Early detection of complications is essential since many of them may prove to be fatal. Any worsening in respiratory failure should be immediately investigated for the presence of complications and treated accordingly. Some of the important complications include the following :

i. Pulmonary complications :

a. Pulmonary infection is most common. Strict aseptic techniques in all manipulations of the patients should be used.
b. Pulmonary Embolism and Pneumothorax : Occur in patients on ventilators. Sudden deterioration in a stable patient demands a search for this complication.

c. Blockade of endotracheal or tracheostomy tubes by inspissated secretions or improper position may cause atelectasis and may be fatal.

d. Tracheal injury may occur due to excessive pressure of the cuff of the endotracheal – tracheostomy tubes.

e. Pulmonary oxygen toxicity occurs due to excessive O_2 delivery. It presents like acute pulmonary oedema. Therefore the FiO_2 must be kept as low as possible.

ii. Cardiac complications :

a. Heart failure : Acute right ventricular failure occurs due to pulmonary hypertension and hypoxia. Left ventricular failure may occur from over hydration and increased pulmonary capillary permeability.

b. Cardiac arrhythmias : Hypoxaemia, wide variations in pH, electrolyte disturbance, uses of drugs like adrenoceptor agonists, xanthines and digitalis are all responsible for various types of arrhythmias in respiratory failure. Cardiac rhythm should therefore be monitored carefully.

iii. Central nervous system complications :

a. Convulsions may occur due to brain hypoxia or due to sudden induction of respiratory alkalosis in a patient on a ventilator.

b. Altered consciousness and coma.

iv. Gastrointestinal haemorrhage : is frequent from stress ulcers and from the use of corticosteroids, aspirin, theophylline and anticoagulants.

General Care :

Patients with respiratory failure are bed-ridden, often connected to a ventilator. They require comprehensive management for not only the disease and its complications, but also for prevention of other general problems.

Fluid balance : Adequate fluid balance is necessary for haemodynamic maintenance and adequate renal perfusion. Excess of fluid can lead to cardiac dysfunction and pulmonary oedema. Adequate attention to nutrition, fluids and electrolyte balance should be given.

Maintenance of nutrition : It is important to maintain nutrition including the caloric intake, essential vitamins, minerals and electrolytes. Regular monitoring is done for their levels and replacements given as per requirement. Caloric intake is similarly important for prevention of muscle mass and body weight.

Prevention of bed-sores : Change in body position is frequently required to prevent the formation of pressure sores. Appropriate air mattresses are also helpful.

Care of bladder and bowels : Bed-ridden patients often have urinary and/or faecal incontinence. Adequate attention should be given for their care. Urinary catheterization is necessary to take care of incontinence. Regular cleaning and change of bed sheets is also necessary. Bowel enema may be required in case of constipation.

Exercises : It is important to maintain muscle tone and strength, joint mobility and flexibility. Regular limb exercises (passive, active-assisted and active) will reduce the effects of immobility as well as help to optimize oxygen transport. Inspiratory muscle training will aid improvement of inspiratory muscle strength and facilitate weaning. Lastly, early mobilization should be encouraged as it improves overall body function and mobility.

Pharmacological Treatment :

Drug treatment for the underlying diseases should continue as usual. Blood pressure, ischemic heart disease and diabetes should be appropriately controlled.

i. Pulmonary edema is treated with diuretics, nitrates, analgesics, and inotropes. Sublingual nitroglycerin tablets and spray are particularly useful in acute pulmonary edema with a systolic blood pressure of at least 100 mm Hg. Morphine IV is an excellent adjunct in the management of acute pulmonary edema.

ii. Inotropic Agents : Hypotension and shock are commonly present in these patients requiring treatment with inotropic agents such as dopamine, dobutamine, milrinone, dopexamine, and digoxin. Dopamine and dobutamine are most commonly used for patients with hypotension who present with congestive heart failure. Dopamine is a positive inotropic agent that stimulates both adrenergic and dopaminergic receptors. Its hemodynamic effects depend on the dose. Lower doses stimulate mainly dopaminergic receptors that produce renal and mesenteric vasodilation; higher doses produce cardiac stimulation and renal vasodilation. Nor epinephrine is used in protracted hypotension after adequate fluid replacement. It stimulates beta-1 - and alpha - adrenergic receptors, which leads to increased cardiac muscle contractility and heart rate, as well as vasoconstriction. Dobutamine produces vasodilation and increases the inotropic state. At higher dosages, it may cause increased heart rates, thus exacerbating myocardial ischemia. It is a strong inotropic agent with minimal chronotropic effect and no vasoconstriction.

iii. Analgesics and sedatives to relieve pain and discomfort.

iv. Antibiotics to treat an infection : Choice of antibiotic and other anti-microbial drugs is an important decision. This will normally depend upon the hospital policy, culture and sensitivity reports of blood, endo-tracheal secretions and/or other specimens and the local microbial epidemiology. Different hospitals normally follow an antibiotic-stewardship policy to prevent misuse of and development of drug resistance to antibiotics.

v. Anticoagulant prophylaxis : For prevention of deep venous and pulmonary artery thrombo-embolism.

vi. Corticosteroids : Glucocorticosteroids are often useful for the treatment of those forms of hypoxemic respiratory failure which are mediated through the immune system or which occur as a result of irritant gas or chemical or thermal injuries. High dosages of corticosteroids should be used such as hydrocortisone (100-200 mg), 2 to 4 hourly. Methyl prednisolone is usually given IV in the emergency department (ED) for initiation of corticosteroid therapy, although in theory, oral administration should be equally efficacious.

vii. Bronchodilators : Bronchodilators are an important component of treatment in respiratory failure caused by obstructive lung diseases. Nebulized bronchodilators are required to manage bronchospasm and airway hygiene. These agents act to decrease muscle tone in both small and large airways in the lungs. This category includes beta-adrenergics, methylxanthines, and anti-cholinergics. Inhalational drugs and oral xanthine derivatives such as oral theophylline are given for maintenance treatment of diseases such as COPD and asthma. Nebulized treatment is considered better during acute illness.

Summary :

- In summary, respiratory failure is a serious and life-threatening condition secondary to a large number of respiratory and other systemic diseases.
- The diagnosis essentially depends upon the presence of hypoxia demonstrable on oximetry and blood gas examination even though it is suspected on the basis of clinical signs and symptoms.
- Oxygen therapy constitutes the corner-stone of management. General care and stabilization as well as the management of the underlying condition are equally important. Oxygen is essential for the life of all human cells. It is therefore important to maintain adequate oxygenation. Assisted ventilation with non-invasive or invasive methods is frequently required to obtain this goal.
- Treatment of the underlying cause(s) and prevention of complications also necessitate equal attention.

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Hypoxia at High Altitude and during Deep Sea Diving in Health and Disease

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Introduction :

Air is a mixture of gases composed of 78 % nitrogen, 21 % oxygen, 0.9 % argon and 0.1% of other gases such as carbon dioxide, water vapour and neon. The atmospheric pressure of air at sea level is one atmosphere absolute (1 ATA) which exponentially decreases at higher regions of the atmosphere in accordance with Boyle's law of pressure volume relationship. Consequently, the partial pressure of inspired oxygen (PIO_2) which is 149 mmHg at sea level drops to 43 mmHg on the summit of Mount Everest at an altitude of 29,028 feet, making the atmospheric air at that altitude severely oxygen deficient for a given volume (28 % of sea level) without change in its composition (Table 1).

Height in Metres	Corresponding Height in Feet	Partial pressure of Oxygen (PO_2)	Percentage (%) Sea level FIO_2
0	0	149	100%
1000	3281	132	89%
2000	6562	117	79%
3000	9843	103	69%
4000	13123	90	60%
5000	16404	78	52%
6000	19685	67	45%
7000	22966	58	39%
8000	26247	51	3%
9000	29528	42	28%

Table 1. Barometric pressure and PO_2 at different altitudes

On the other hand, the underwater environment is a hyperbaric environment leading to volume contraction with compression of the air that is proportionate to the height of descent from the surface. At higher pressures entrapped gases become more soluble in order to remain dissolved in a liquid state, which re-expand on decompression at lower pressures. Both hyperbaric underwater and hypobaric atmospheric milieu are hypoxic, affecting the oxygen transportation cascade and oxygen utilization by tissues.

High Altitude :

An elevation between 1500 to 2500 metres above the mean sea level is considered as moderate altitude or intermediate altitude. High altitude is defined as an elevation above 2500 metres above the mean sea level, this is further classified as very high and extremely high altitudes (Table 2).

Level of Altitude	Height in Metres	Corresponding Height in Feet
Moderate	1500 - 2500	5000 - 8000
High-altitude	2500 - 3500	8000 - 11500
Very High-altitude	3500 - 5500	11500 - 18000
Extreme High-altitude	≥ 5500	≥ 18000

Table 2. Classification of different levels of altitude in the atmosphere

Mountains cover nearly one-fifth of the earth's surface. Nearly 400 million people live in regions located at an altitude above 1500 metres from the mean sea level, with more than one-third among them living above 2500 metres. It is estimated that about 100 million people travel annually to high altitude regions for military, scientific, adventure and recreational purposes.

High Altitude Hypoxia :

Adaptive changes to Hypoxia [1,2,3] : High altitude atmosphere is characterized by hypobaric hypoxia, hypothermia, intense solar radiation and strong winds. Though the composition of air remains the same, due to low partial pressures, high altitude is air-thin, cold and light. Despite breathing air that is low in inspired PO_2, the tissue oxygen pressure is maintained within the physiological range as required for aerobic metabolism by the lowlander due to a series of adaptive changes by the body on exposure to a high-altitude environment. Native Tibetans and people residing in the south American Andes region have lived for several generations in very high-altitude environments leading a normal life by virtue of this remarkable adaptation process. Lowlanders, used to normo-baric conditions have stayed indefinitely in regions above 2500 metres from the sea level after going through a due process of acclimatization. Many have climbed peaks above 8000 metres considered to be a 'death zone' without oxygen after adequate body conditioning. Nevertheless, adaptation to extreme altitudes remain poor with individual variation in the susceptibility to hypobaric hypoxia.

1. Hypoxic ventilatory response (HVR) : The most important adaptive change to hypoxia is hyperventilation that improves the alveolar PO_2 (PAO_2) by reducing the alveolar PCO_2. The role of hyperventilation in maintaining PAO_2 as normal as possible at an extreme altitude is better understood by applying the alveolar gas equation on the top of Mount Everest with a PCO_2 of 40 mmHg, a respiratory quotient (RQ) of 1 and an inspired PO_2 (PIO_2) of 43 mmHg with or without hyperventilation (Figure 1).

Step 1 : The Alveolar gas equation : $PAO_2 = PIO_2 – PCO_2 / RQ$

Step 2: Applying the alveolar gas equation on the summit of the Mount Everest, expected PO_2 with normal ventilation will be $43 – 40 / 1 = 3$ mmHg

Step 3 : After the adaptive 5-fold increase in the minute ventilation, the PCO_2 drops to 8 mmHg, and thus the PAO_2 becomes 35 mmHg as follows :

$43 – 8 / 1 = 35$ mmHg

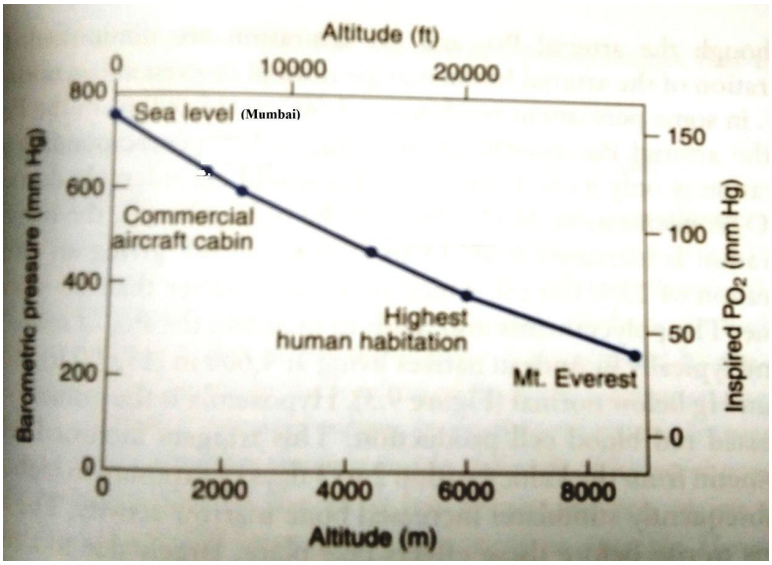


Figure 1. Relationship between Barometric pressure and Inspired PO_2 at various altitudes

Hypoxia is a powerful stimulant for inducing ventilation by increasing both the rate as well as the depth of breathing. This hypoxic ventilatory response is mediated by peripheral chemoreceptors located in the carotid body. It has been observed that oxygen sensing glomus cells of the carotid body become active with enhanced neuronal activity when arterial PO_2 (PaO_2) is around 60 mmHg, sending strong afferent inputs via the carotid sinus nerve to the respiratory centers for augmenting ventilation. Further, acidotic cerebrospinal fluid (CSF) due to CO_2 influx from the blood, stimulates the central chemoreceptors inducing hyperventilation to wash out CO_2 that has been raising in the blood following enhanced tissue CO_2 production. Consequent hypocapnia and CSF alkalosis, inhibits central chemoreceptors, leading to hypoventilation that aggravates hypoxemia. Therefore, it is essential to sustain HVR by keeping the pH of CSF slightly acidotic, in the face of mounting respiratory alkalosis due to hyperventilation, and this is achieved by enhanced urinary loss as well as CSF clearance of bicarbonates within a few days of high-altitude stay by the lowlander. Furthermore, in response to sustained hypoxia, the glomus cells undergo structural changes enhancing the HVR. HVR is influenced by genetic factors and those with poor

ventilatory response to hypoxia fail to adapt even to moderately high altitude conditions. Native Tibetans have a better HVR due to changes in genes encoding hypoxia inducible factor - 2 alpha (HIF-2α) . High altitude exercise performance may also be influenced by angiotensin converting enzyme (ACE) polymorphism that is more prevalent in elite athletes and climbers.

2. Respiratory Mechanics and Lung Function : Hypoxia leads to various compensatory changes in the respiratory system for improving tissue oxygenation. Initially due to hyperventilation, there is a decline in the vital capacity due to an increase in the end-expiratory residual volume. However, the work of breathing is expected to be low due to lowered airway resistance associated with breathing high altitude air that is lighter and less polluted. Though the diffusion of gases across the alveolar-capillary membrane is limited by the low transit time due to tachycardia, impairment of diffusion is minimal due to compensatory improvements in ventilation and perfusion of the lung following hypoxia. Lung functions of new high-altitude inductees return to near normal level after a few months of high altitude stay.

3. Periodic breathing and sleep apnea : Many low landers develop periodic breathing during sleep on arrival to an altitude above 1600 metres. Central sleep apnea is common especially at greater elevations affecting both sleep quality and architecture. High altitude sleep among low landers is characterised by delayed sleep onset, frequent nocturnal awakening, lack of slow wave sleep, poor sleep efficiency and reduced total sleep time. Many experience lethargy and day time somnolence. Delayed circulation time due to cardiac dysfunction and lag in the equilibration of CSF hydrogen ions due to the blood brain barrier aggravate respiratory instability, characterised by episodes of Cheyne-Stokes breathing or cyclical breathing of hyperpneas and hypopneas.

4. Pulmonary Blood flow and Perfusion : Hypoxia causes severe pulmonary vasoconstriction through sympathetic stimulation leading to acute pulmonary hypertension and increase in the right heart work load. There is redistribution of blood by opening up of the pulmonary capillary bed, resulting in perfusion of better ventilated lungs. Hypoxemia in the long run induces angiogenesis, increased blood viscosity and permanent pulmonary vascular changes that are commonly seen after several months of high altitude stay.

5. Oxygen Dissociation Curve : Oxygen saturation (SaO_2) decreases with altitude and at the top of Mount Everest, SaO_2 is just 50 % of the sea level value (Figure 2). The fall in SaO_2 with declining arterial PO_2 is not uniformly linear and is depicted by the sigmoid shaped oxygen dissociation curve. At moderate altitudes, SaO_2 is well maintained since PIO_2 values fall within the upper flat portion of the curve. However, there is disproportionate fall of SaO_2 in relation to PIO_2 at greater altitudes corresponding to the steeper portion of the oxygen dissociation curve. The position of the oxygen dissociation curve as determined by the p50 (PO_2 at 50% hemoglobin saturation) shifts to the right at moderate altitudes, increasing the unloading of oxygen from the venous blood for a given PO_2. This right ward shift occurs due to increased CO_2 production, low PH, elevated levels of 2,3 diphosphoglycerate (2,3 DPG) and elevated local temperature due to hypoxemia. On the other hand, there is an augmented oxygen uptake by the blood in the pulmonary capillaries due to shift of the oxygen dissociation curve to the left by the local increase of blood pH following CO_2 elimination by lungs. At extreme altitudes, the pulmonary uploading of oxygen is at its premium, enabling greater availability of oxygen for actively metabolic tissues.

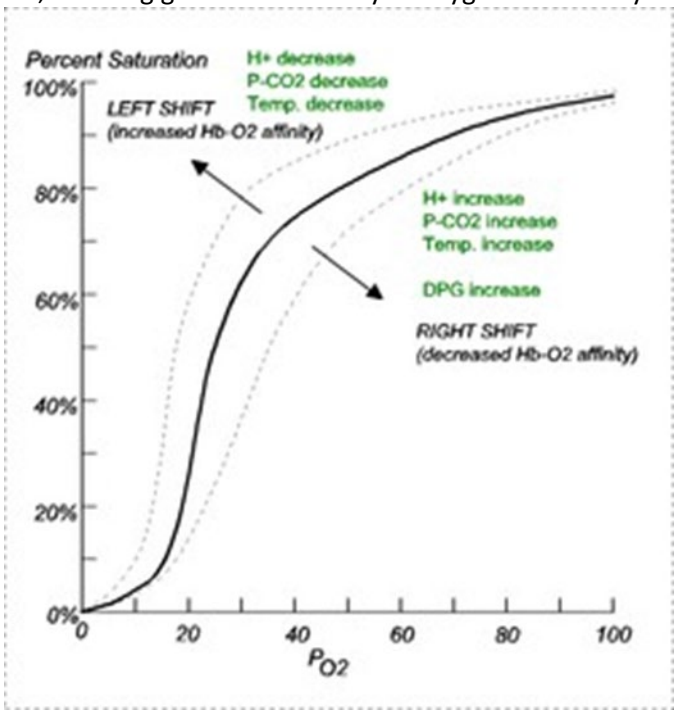


Figure 2. The Oxygen – Hemoglobin Dissociation Curve

6. Cardiac Output : Hypoxia induced sympathetic stimulation along with partial decrease in the vagal tone increases both heart rate and cardiac contractility. Cardiac output initially declines due to decreased plasma volume and decreased preload as a result of hypoxic pulmonary vasoconstriction. With acclimatization, there is gradual stabilization of both heart rate and cardiac output.

7. Blood and Bone Marrow : Initially on induction to high altitude, there is hemoconcentration due to dehydration as a result of reduced plasma volume consequent to hypoxia induced diuresis, besides increased insensible loss due to breathing dry and cool high-altitude air. Within a few days of high altitude stay, erythropoiesis by the bone marrow increases significantly due to enhanced renal secretion of erythropoietin in response to tissue hypoxia. For achieving the maximum bone marrow response, many months of high altitude stay are required. Permanent residents of high altitude have very high erythroid mass to compensate for environmental hypoxia. The average hemoglobin level in chronic high-altitude residents residing at an elevation of 15,000 feet is around 19 gm/dL, a substantial elevation above the normal sea level value of 15 gm/dL with a hematocrit of 45 and this helps greatly in maintaining oxygen content of the blood above the sea level value despite a low PO_2, since each gram of extra hemoglobin increases blood oxygen content by about 1.34 mL. Furthermore, the mixed venous PO_2 remains almost normal with only a minimal fall below the corresponding sea level value (Figure 3). Hematological adaptation is much more pronounced in native South American Andeans as compared to the Tibetans.

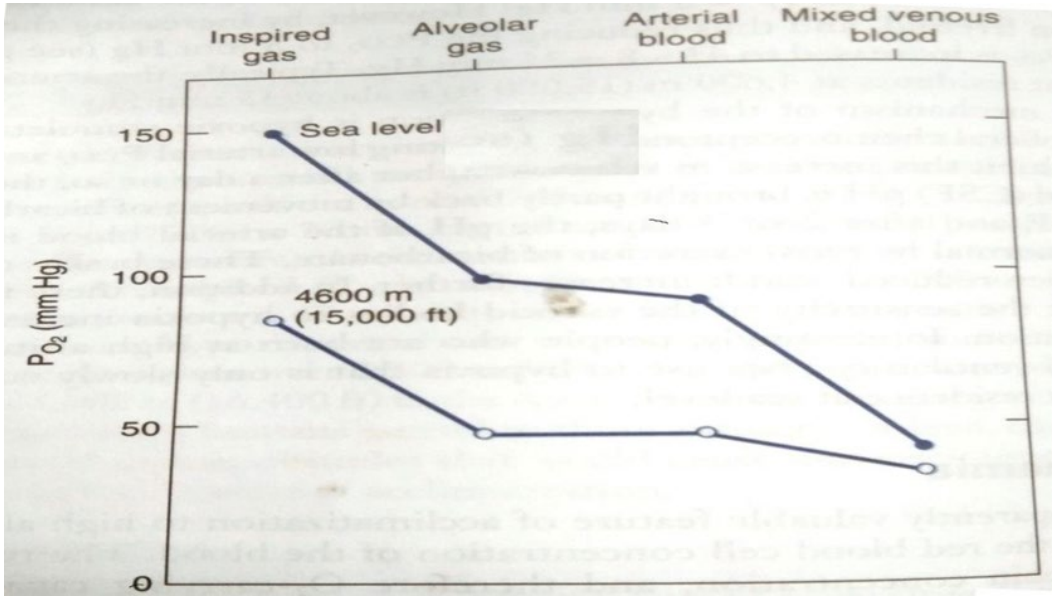


Figure 3. PO_2 levels in Inspired Air, Alveoli, Arterial and Venous Blood both at sea level and at an altitude of 4600 metres

Adverse effects of High altitude Hypoxia [1,2,3,4] :

1. Exercise capacity and Body Weight : High altitude impacts exercise capacity, metabolic functions and body mass index (BMI). Maximum rate of oxygen consumption (VO_2 max), a measure of aerobic exercise capacity, declines by about 10 % for every 1000 metres altitude gain above 1600 metres. Consequently, at higher altitudes the VO_2 max is significantly reduced with a poor exercise tolerance. Say for example at an altitude of 5,000 metres, VO_2 max is reduced by about 40 % of the sea level value, resulting in muscle fatigue even at rest despite increase in the oxygen content of blood. This has been postulated to be due to augmented blood flow to vital organs to meet metabolic demands with disproportionately less blood flow to exercising skeletal muscles [5]. At sea level oxygen demand of exercising tissue is met by hyperventilation. At high altitudes hyperventilation generated PO_2 gain is insufficient to meet the oxygen demand of the exercising tissue and as a result mild exercise aggravates hypoxemia as evidenced by significant desaturation on minimal physical activity. Sustained hypoxia at extreme altitudes leads to muscle atrophy and low oxidative activity. Protein synthesis is impaired. Poor appetite, increased catabolism, impaired intestinal functions and loss of body water all contribute to loss of weight that is more pronounced by extended stay above 5000 metres.

2. Mental functions : Brain consumes more oxygen per gram of tissue as compared to rest of the body (20% of total consumption), as a result of which brain tissue is highly sensitive to oxygen deprivation. Hypoxemia of the nervous system causes neuronal injury that can be severe and irreversible depending upon the duration and the degree of hypoxia.
Impaired neurological functions manifesting with restlessness, poor memory, cognitive dysfunction, incoordination, impaired motor skills, mental fatigue and mood changes are commonly observed above an altitude of 3000 metres. Ascent to very high-altitude regions may lead to irreversible neuronal changes. Climbers have been found to develop cortical atrophy and subcortical lesions on ascending to extreme altitudes.

Physiological Benefits of High Altitude [1,2,3] :

Staying at moderate altitudes of less than 3000 meters may offer several health benefits. Lower incidences of atherosclerosis, ischemic heart disease, stroke and certain cancers have been observed among high altitude residents. Even asthmatics show better control by virtue of breathing high altitude air that is more thin, less polluted and low in allergen content, notwithstanding the adverse effects of cold air on airway resistance. However, high altitude stay will be detrimental to patients of underlying lung disease with already compromised lung functions, due to worsening of hypoxemia [5].

Regular physical activity and exercise training at moderate heights also help since exercise induced intermittent hypoxia has been known to exert cardiovascular, neurovascular and anti-cancer protective effects. These protective effects of hypoxia are attributed to activation of hypoxia inducible factor - 1 alpha (HIF-1α), a key regulator of erythropoiesis, angiogenesis, apoptosis and metabolism of atherogenic cholesterol. Exercise induces release of the vasodilator nitric oxide (NO) from the vascular endothelium. NO is known to be both neuro and cardio-protective. Another high-altitude factor is the abundance of ultraviolet radiation that is postulated to play both an immunomodulatory as well as a thrombo-prophylactic role by enhancing the synthesis of Vitamin D in the skin.

Hypoxia induced High Altitude Illnesses [3,4,6,7] :

Various types of altitude sicknesses have been described that are both acute and chronic among those who fail to acclimatize to high altitude environments. Adaptation to high altitude is influenced by several factors including prior physical conditioning, pre-existing illness, age, gender, oxygen saturation, prior stay, rate of ascent, arrival altitude, sleeping altitude, physical activity and genetic make-up. Re-inductees remain susceptible. Even the young and previously healthy are not spared. Symptoms develop within the span of a few hours to few days of stay while chronic illness takes several months to develop. Altitude illnesses improve with rest and de-induction to lower heights. The severity of high altitude illness may be classified as mild, moderate or severe. Those who exhibit severe symptoms can progress to develop life threatening high altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE), or both, warranting emergency care. The incidence of HACE or HAPE is much lower than that of acute mountain sickness (AMS) and is estimated to be in the range of 0.1% to 4%.

1. Acute Mountain Sickness (AMS) :

AMS is characterized by headache, nausea, loss of appetite, insomnia, dizziness, lack of energy. The Lake Louise Scoring system (LLSS) is based on a self-assessment questionnaire and a score card is also available to guide evaluation of the following symptoms of AMS :

- Headache
- Gastro-intestinal symptoms such as nausea and vomiting
- Fatigue and weakness
- Dizziness and light-headedness
- Difficulty sleeping

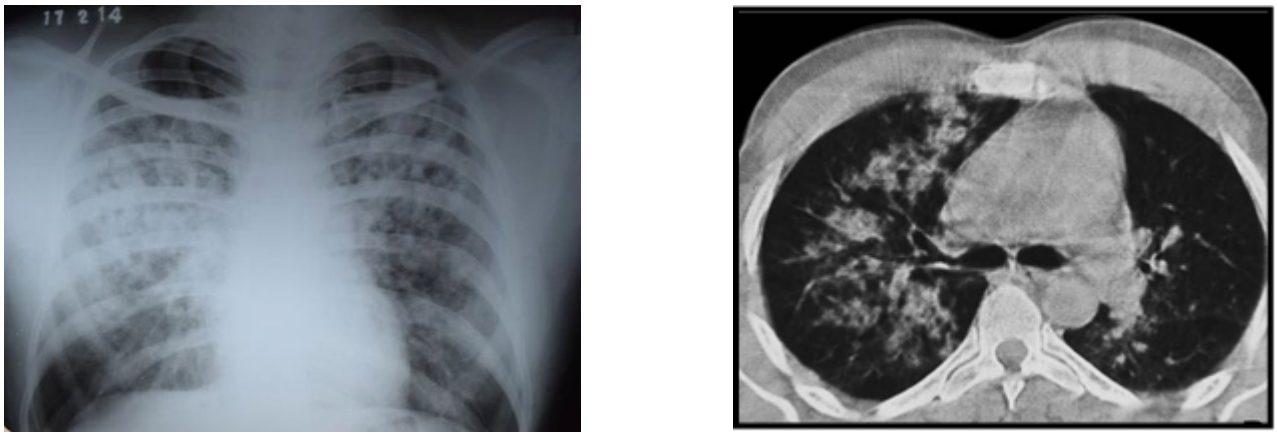
Each symptom is rated with a Score : 0 - no discomfort, 1 - mild, 2 – moderate, and 3 - severe / incapacitating.
Diagnosis of AMS is suggested by the presence of headache and one other symptom with an LLSS score or 3 or more. A score of 3 to 5 indicates mild AMS and a score ≥ 6 suggests severe AMS.

Mild AMS : is self-limiting with mild symptoms which remit spontaneously in a day or two. About 50 % experience mild AMS on arrival to high- altitude regions.
Moderate AMS : symptoms are progressive with worsening on exertion. Severe headache, nausea, difficulty in walking and incoordination should prompt one to seek immediate medical attention. Affected individuals experience difficulty in performing routine activities. Immediate de-induction (descent) to lower heights will relieve symptoms.
Severe altitude sickness : is an emergency. Symptoms are present even at rest and are distressing. This condition can progress rapidly to high-altitude cerebral edema, high-altitude pulmonary edema or both. Emergency care includes oxygen supplementation and administration of dexamethasone 8 mg IV/IM/Oral stat followed by 4 mg administered once every 6 hours for the next few days. Early evacuation to a lower altitude improves the condition.

2. High-altitude pulmonary edema (HAPE) [4,6,7] :

It is a potentially fatal condition, usually occurring 2 to 4 days after arrival to altitudes above 2500 metres and may not be preceded by AMS. It is a high permeability non-cardiogenic pulmonary edema.
Susceptible individuals have exaggerated pulmonary reactivity to hypoxia with pulmonary vasoconstriction leading to acute and severe elevation of pulmonary arterial pressures. Inhomogeneous hypoxic vasoconstriction with stress failure of weak thin walled pulmonary capillaries lead to capillary leak, a hallmark feature of HAPE. Affected individuals develop incapacitating fatigue, chest discomfort, severe breathlessness, orthopnea, cough and pink frothy sputum. It can progress rapidly to acute right heart failure. Fever may be present, not necessarily due to infection. Early diagnosis of HAPE may be

difficult since many of its symptoms may occur in high altitude sojourners without this illness. Examination reveals cyanosis, tachypnea, tachycardia and bilateral rales. Chest X-ray film reveals the characteristic features of non-cardiogenic pulmonary edema (Figure 4).



A. **B.**

Figure 4. A. Chest radiograph; and, B. Computed tomography section showing bilateral alveolar opacities

Treatment : Immediate hospitalisation is a must. Descent to a lower altitude of less than 4000 feet should be done quickly and safely as possible. Emergency care includes oxygenation and management inside a hyperbaric chamber. Placing the patient inside a portable hyperbaric chamber (Figure 5) improves the condition dramatically by ambient pressure changes, similar to descent to altitudes of 1500 metres (5000 feet). In a remote setting, oral or sublingual administration of 10 mg of short-acting Nifedipine, followed by 30 mg of the extended release formulation twice daily is recommended. The Phosphodiesterase type-5 inhibitor drug Tadalafil 10 mg twice daily is another alternative.

Figure 5. A Portable Hyperbaric Chamber used by the Indian Army

3. High-altitude cerebral edema (HACE) :

HACE is a very severe form of AMS characterised by altered sensorium and ataxia. The disease can lead to deep coma and at times can be fatal due to herniation of the brain. Severe cerebral hypoxemia induces vasoconstriction with extracellular exudation of proteinaceous fluid through damaged capillaries. The vasogenic origin of HACE from the disruption of blood-brain barrier (BBB) is evidenced by the magnetic resonance imaging (MRI) finding of a preferential spread along the white matter of the brain with corpus splenium involvement. Diagnosis of HACE is essentially clinical. All cases should be given emergency therapy with 8 mg of Dexamethasone administered by the oral/IM/IV route, followed by 4 mg every 6 hours, besides oxygenation and specialised care at a lower height of less than 4000 feet.

4. High-altitude pulmonary hypertension (HAPH) :

HAPH is a subacute form of mountain sickness with severe pulmonary hypertension and cardiac failure which has been observed among lowlanders living at altitudes over 5500 metres. Features develop after a few weeks of high altitude stay. The initial response to high altitude hypoxia is exaggerated pulmonary vasoconstriction. Chronic hypoxia leads to vascular remodelling with muscularisation of pulmonary capillaries without plexiform lesions. HAPH is observed in about 10% of

residents especially of Himalayan and Tibetan regions of high altitude. This condition is similar to "Brisket Disease" found in animals. Treatment includes de- induction to lower altitudes and supportive care along with oxygenation [8].

5. Chronic mountain sickness (Monge disease) : This condition was first described by Dr. Carlos Monge in 1925 among Andes high altitude residents. It is a progressive, incapacitating disease with multi-systemic involvements seen among chronic high-altitude dwellers who reside at heights above 2500 metres. Incidence is much higher among the high-altitude residents of the South American region. It is characterised by exaggerated erythroid response with hemoglobin values greater than 21 gm/dL, many have higher hemoglobin values even up 28 gm/dL and hematocrit values exceeding 80%. It is frequently associated with pulmonary hypertension. The disease is more common among males, the elderly and those who are obese with sleep apnea syndrome. Patients exhibit features of multi-organ dysfunction with gross physical and mental disabilities. Neurological symptoms predominate over pulmonary symptoms. Headache, altered sensorium, excessive somnolence and personality changes are common. De-induction to lower altitudes, oxygenation and supportive therapy along with phlebotomy improves symptoms. Acetazolamide therapy offers some benefit.

Prevention and Treatment of High Altitude Illnesses [9,10] :

Prophylactic medication, gradual ascent, avoiding physical exertion on arrival, proper rest, sleeping at lower heights *("Climb high and Sleep low")* and adequate intake of fluid and calories are known to prevent altitude sickness. One should abstain from alcohol, tobacco and sedative drugs. Driving by road or climbing to reach the high-altitude area with a day's rest in between at an intermediate height is always better than arriving by flight, as it gives more time for the body to get acclimatized. Prior medical consultation is recommended for the elderly and those with comorbid conditions before travel to high altitude regions.

Acclimatization : On arrival to a high-altitude area, a low lander is advised to follow an acclimatization schedule in different stages according to the height to be climbed, as follows :

Stage I : 8000 - 12000 feet
Days 1 & 2 : Rest except for short walks without any climbs
Days 3 & 4 : Walk for 1.5 - 3 km, avoid steep climbs
Day 5 : Walk up to 5 km
Day 6 : Walk up to 5 km and climb 300 m at a slow pace

Stage II : 12000 - 15000 feet
Days 1 & 2 : Slow walk up to 1.5 - 3 km, avoid steep climbs
Day 3 : Slow walk up to 3 km, climb up to 300 m
Day 4 : Slow walk up to 3 km, climb 300 m without equipment

Stage III : 15000 - 18000 feet
Days 1 & 2 : Walk up to 1.5 - 3 km, avoid steep climbs
Day 3: Walk up to 3 km, climb up to 300 m
Day 4: Walk up to 3 km, climb 300 m without equipment.

Absence from high altitude (re-inductees) : Re-inductees are required to undergo acclimatization depending upon the duration of absence from high altitude, generally, for absence of less than ten days, acclimatization is not required and for absence more than 28 days, complete acclimatization is advised. For the intermediate period of absence, a modified acclimatization schedule as given below is recommended as below :

10 to 28 days (re-inductees) :
Days 1 & 2 : Rest, except short walk
Day 3 : Walk at slow pace 1 - 2 km, avoid steep climbs
Day 4 : Slow walk for 1 - 2 km, climb up to 300m

Prophylactic drugs :

Acetazolamide (Diamox) : is a carbonic anhydrase inhibitor. It is time-tested drug with proven benefit in preventing acute mountain sickness, HACE and HAPE. By its inhibitory action on carbonic anhydrase, it not only enhances the urinary excretion of bicarbonate but also lowers CSF bicarbonates. It acts on the carotid body to enhance the hypoxic ventilatory response (HVR). Being a structural analogue of sulfonamides, allergic reactions are known to occur. Its safety in pregnancy is not clear. Side effects are higher with doses of 250 mg twice daily and include circum-oral paraesthesia, nausea and vomiting besides

allergic reactions. The drug is given one day prior to arrival at high altitude and then continued for the next 2-5 days at a standard dosage of 125mg twice daily. It has also been used to treat acute mountain sickness, subacute mountain sickness and chronic mountain sickness, for treatment of these conditions, the dose recommended is 250 mg twice daily.

Dexamethasone : is a corticosteroid which less effective than acetazolamide as a prophylactic drug. For prophylaxis, the dose recommended is 2 mg 6 hourly or 4 mg twice daily. It is given one day prior to induction to high altitude and then continued for the next few days. In the treatment of HACE, it has been observed to produce symptomatic relief without substantial reduction in cerebral edema, thereby giving a false sense of benefit. It is only recommended for the emergency care of HACE and severe AMS in remote locations, where immediate evacuation is not possible.

Tadalafil : is a phosphodiesterase type 5 inhibitor that increases the half-life of nitric oxide (NO) by preventing enzymatic degradation. NO is a pulmonary vasodilator and is secreted by the vascular endothelium in response to hypoxia. It is known to improve pulmonary gas exchange and reduce pulmonary hypertension. The prophylactic dose recommended is 10 mg oral tablet twice daily.

Nifedipine : is a calcium channel blocker and a pulmonary vasodilator. It reduces acute pulmonary hypertension. It is used for the emergency treatment of HAPE in a dose of 30 mg slow release (SR) twice daily, after giving 10 mg of the drug by the oral or sublingual route. The prophylactic dose is 30 mg SR twice daily.

Deep Sea Diving :

The Hyperbaric underwater environment [11,12] :

70 % of the earth's surface is covered by water bodies, namely seas and oceans. The average depth of the sea is 3.7 Km (3,700 metres or 12,100 feet) with a maximum depth of 11 Km (11,000 metres or 36,200 feet). The underwater environment is hyperbaric and cold. Water being denser than air exerts more pressure than air on any given surface area; and; therefore, underwater pressure is hyperbaric which is defined as a pressure higher than the atmospheric pressure at sea level, called atmospheric pressure absolute (ATA) that is equivalent to 101.3 kPa / 1 atmosphere (ATM) / 760 mm Hg. The ATA (atmospheric pressure, absolute) unit is used in place of ATM (atmospheric pressure) to indicate the total pressure of the system, compared to a vacuum. For example, underwater pressure of 3 ATA would mean that this pressure includes 1 ATM of air pressure and 2 ATM due to the water.

There is progressive increase of hydrostatic pressure by one atmosphere for every 10.06 metres (33 feet) descent into the sea from the surface. Therefore, a diver who descends to a depth of 30 metres below the surface, experiences the weight of 4 atmospheric pressure absolute (4 ATA) on his/her body from all sides (3 ATM hydrostatic pressure + 1 ATM of the sea surface pressure).

As the pressure increases, body gases get compressed and lung volume reduces in accordance with Boyle-Marriotte's law of inverse relationship between pressure and volume, for example, at a depth of 20 metres below the sea surface, the lung volume of the diver is reduced by 50 %. At higher pressures, gases inside the body dissolve and remain in a liquid state that is in accordance with Henry's law of gas solubility. Most of the recreational scuba (self-contained underwater breathing apparatus) divers descend up to a depth of 40 metres of 130 feet below sea level to avoid nitrogen narcosis due to formation of dissolved nitrogen in the blood at higher pressures on further descent. As the underwater pressure decreases during ascent, there is proportionate increase in the lung volume and release of dissolved gases from the tissue.

Hyperbaric Illnesses [11,12,13] :

The hyperbaric underwater environment is injurious to health with catastrophic consequences due to rapid pressure changes during diving - both descent as well as ascent. Due to extremely high pressures, a greater part of the oceanic depths remains largely unexplored. Various syndromes have been described due to exposure to a hyperbaric sea environment, as follows :

1. Caisson Disease
2. Barotrauma
3. Nitrogen Narcosis
4. High pressure Neurological Syndrome
5. Oxygen Toxicity
6. Cold Water Immersion Syndrome

1. Caisson Disease : This condition is also called decompression sickness (DCS), dysbarism, divers disease, "the bends" or aerobullosis . This was initially described among caisson workers. A Caisson is a watertight retaining structure used in for work in water environments (e.g. construction of dams, bridge piers or repair of ships). Caissons are constructed in such a way that the water can be pumped out, keeping the work environment dry. DCS is also common in scuba divers after a rapid ascent. During deep-sea diving, nitrogen gas which form about 80 % of body air dissolves in body tissues due higher pressures encountered during the descent. As the diver ascends, much of this dissolved nitrogen reverts back to gaseous form which then slowly diffuses out from the nitrogen gas supersaturated tissue to reach an equilibrium state. If the diver ascends too fast, consequent to rapid decompression, bubbling of nitrogen from these supersaturated tissues occurs on returning to the surface. Though bubbles can form anywhere in the body including heart, lung, brain, skin and joints, they are more often observed in the joints and venous circulation. Symptoms and signs of the disease are mainly due to mechanical effects of the gas bubbles - distortion of tissue and vascular obstruction. Inflammatory syndrome may occur. A myriad of symptoms and signs may be present including joint pains, fatigue, low backache, neck pain, numbness and weakness of limbs, dizziness, confusion, tinnitus and vomiting. Early descriptions of DCS used the terms "bends" for joint or musculoskeletal pain, "chokes" for breathing problems, and "staggers" for neurological problems. Symptoms may be Mild [Type I (simple)] when only the skin, musculoskeletal system, or lymphatic system are involved or Severe [Type II (serious)] when other organs are involved (Table 3). Type II DCS is considered more serious and usually has worse outcomes. The onset of clinical features of decompression sickness might be delayed for up to 48 hours after surfacing.

Organ	Severity	Clinical Features
Skin	Type I (Mild)	Purpura, erythema
Musculoskeletal	Type I (Mild)	Myalgia, joint pains improving with bends
Ear	Type I (Mild)	Dizziness, loss of hearing, vertigo, nausea, vomiting
Respiratory	Type I (Mild) - Type II (Severe)	Chest pain, breathlessness, cough
Nervous System	Type II (Severe)	Unconsciousness, convulsions, paralysis, spinal cord injury, incontinence

Table 3. Clinical Features of Decompression Sickness

Treatment : DCS is treated by administering oxygen at a concentration (FiO_2) of 100 %, fluid resuscitation and hyperbaric oxygen therapy for 5 - 6 hours as per the standard protocol. Recompression occurs in a hyperbaric chamber where the patient breathes 100 % oxygen at a pressure higher than one atmosphere absolute (1 ATA). As a result, there is an increase in the dissolved oxygen content and the partial pressure of oxygen (PO_2) in blood . Normally at a PO_2 of 100 mmHg, about 0.3 mL of dissolved oxygen is present per dL (100 mL) of blood, by increasing the pressure to 3 ATA, it increases to 6 mL per dL of blood. Hyperbaric oxygen therapy (HBOT) was originally used to treat decompression sickness among caisson workers and divers by preventing bubble formation by recompression. This is the preferred method of treatment in DCS since it is more efficient and less risky. However, in severe cases, in order to eliminate bubble formations, recompression to pressures that are associated with significant (even unacceptable) oxygen toxicity may be required. Over the years the use of HBOT has expanded to cover far diverse applications not only in many medical and surgical conditions but also in diving, aviation and space flight barometric disorders.

2. Barotrauma : During ascent, compressed gas in body cavities such as the lung, hollow viscus, middle ear and sinuses expands. High pressure as such is not harmful so long as the pressure inside the cavity is balanced with the ambient atmospheric pressure. Barotrauma of the lung is more common among divers and may lead to arterial embolism with serious circulatory disturbances. Various complications of barotrauma are grouped as follows :

- Pulmonary barotrauma - Pneumomediastinum, pneumopericardium, pneumothorax, subcutaneous emphysema.
- Arterial Gas embolism - Coronary and cerebral artery embolism
- Hollow viscus barotrauma - Perforation, intestinal obstruction
- Face, teeth, ear, nose, teeth barotrauma - Facial edema, conjunctival haemorrhage, epistaxis, trigeminal nerve palsy (maxillary), tooth fracture, vertigo, tinnitus, tympanic membrane rupture and hearing loss

3. Nitrogen Narcosis : Nitrogen is a poorly soluble gas that forms about 80 % of body air (78% of atmospheric air). Under high pressure nitrogen is converted to dissolved (liquid) form in the body tissue, especially in fat. The content of dissolved nitrogen in blood increases under high pressure. The effects of dissolved nitrogen are similar to anaesthetic agents. Divers experience euphoria and impairment of judgement at a depth of 50 metres (160 feet). Further descent can lead to severe incoordination and coma. The narcotic effects dissipate without a lasting effect on ascent to the surface.

4. High-pressure Nervous Syndrome (HPNS) [14] : For deep sea diving at a depth exceeding 40 metres or 130 feet, divers use helium gas mixture for breathing since helium is lighter and least narcotic compared to nitrogen. Helium narcosis is expected to occur in divers at depths of approximately at 300 metres (1000 feet). However, many divers experience symptoms other than narcosis such as tremors, myoclonic jerks, somnolence, nausea, dizziness and decreased mental performance at shallow depths of 150 metres (500 feet) when using breathing gas mixtures containing helium. This is termed as high pressure nervous syndrome or high pressure neurological syndrome. Its occurrence is related to the speed of compression (rapid descent) and absolute pressure (depth of the dive), besides the percentage of helium used for breathing. All effects are reversible on returning to shallower depths.

5. Oxygen Toxicity : Prolonged oxygenation at high partial pressures is harmful. The human body can safely tolerate fraction of inspired oxygen (FiO_2) of about 0.5 (50%) administered under a normobaric pressure for long periods without significant toxicity. Administration of oxygen at FiO_2 of 100% for prolonged periods causes absorption atelectasis of proximally blocked alveoli due to widening of the oxygen gradient between alveoli and the venous blood of pulmonary capillaries. In premature infants, retrolental fibroplasia (retinopathy of prematurity) occurs. In underwater conditions, oxygen toxicity occurs when the partial pressure of oxygen (PO_2) underwater exceeds atmospheric pressures. Divers experience convulsions within 30 minutes when PO_2 is about 4 atmospheric pressures. Therefore, in scuba divers, the fraction of oxygen in the breathing mixture is kept very low.

6. Immersion Pulmonary Edema (Cold Water Immersion Syndrome) : Immersion in water under cold conditions causes central redistribution of blood flow with an increase in central venous pressure due to peripheral vasoconstriction. Rarely, in some swimmers and divers, particularly under cold conditions, pulmonary edema may occur, which resolves spontaneously within a few hours to a few days in surface conditions.

Prevention of Hyperbaric diving injuries [11,12] :

Divers use self-contained underwater breathing apparatus (scuba) to breathe air from a pressurised bottle using a pressure regulator to achieve pressure equilibration during deep sea diving. In order to mitigate the compressive effects, gases with low solubility that are far lighter than nitrogen are used in the breathing gas mixture. Even oxygen in air mixture has to be kept under a low partial pressure in accordance to an increase depth of diving, in order to minimise oxygen toxicity. The selection of a gas mixture in the breathing apparatus is based on the depth of diving from the surface. Nitrox mixture with less nitrogen and more oxygen is mainly used for recreational diving in shallow depths of up to 40 metres (130 feet). Helium and nitrox mixture is used for diving in depths up to 150 metres (500 feet) for depths beyond that a combination of oxygen, helium and hydrogen is used (hydreliox).

Nitrogen narcosis can be mitigated by breathing air containing far lighter and easily diffusing helium that is about 50 % less soluble than nitrogen. Slow and gradual ascent in a staged manner is to be followed strictly during deep sea diving to prevent decompression sickness. The incidence of decompression sickness can be reduced by breathing low oxygen - helium (heliox) mixture. 'Saturation Diving' is used by commercial divers for working in sea depths to prevent acute pressure changes. In this method, divers do not return to normobaric conditions and they remain in hyperbaric chambers of the ship when not working. These divers undergo gradual decompression while returning to ambient atmospheric conditions.

Summary :

Pressures changes from the ambient sea level have profound influence on human physiology, more importantly on the oxygen transportation cascade from atmosphere to mitochondria. Both hypo and hyperbaric atmospheres are harmful to human beings with the regulatory systems of body physiology failing at extreme conditions resulting in catastrophic consequences. Hypobaric hypoxia is a unique feature of high altitude environment, producing acute, subacute and chronic effects. Hyperbaric underwater milieu leads to compressive and decompressive effects during decent and ascent respectively. Pressure related hypoxia is both preventable and correctable. Induction to a normobaric condition as quickly and safely as possible, without adversely impacting the homeostasis by avoiding acute changes is the key to hasten recovery from the harmful effects of hypoxia related to pressure changes in the environment.

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Assessment of Tissue Oxygenation

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Introduction :

Internal respiration or tissue oxygenation is the process of transport of oxygen (O_2) from the atmosphere to the cells which involves the exchange of gases between capillaries and tissue cells. The delivery of oxygen to tissues for cellular metabolism is a three-step process, involving :

1. Oxygen uptake in lungs (External respiration)

2. Oxygen transport in blood

3. Diffusion of oxygen from capillaries to cells (Internal respiration/tissue oxygenation)

Tissue oxygenation is often impaired in critically ill patients with poor cardiopulmonary reserve. Optimising oxygen delivery to meet oxygen demand has the potential to improve outcomes in these patients. The main determinant of this is a balance between oxygen delivery and oxygen consumption [1,2].

Oxygen Delivery and Consumption [2,3,4] :

Oxygen delivery (DO_2) depends on two factors :

1. Arterial oxygen content (CaO_2) : It is the total amount of O_2 present in blood i.e. combined with Hb and those dissolved in plasma

$CaO_2 = (1.34 \times Hb\% \times SaO_2) + (0.0031 \times PaO_2)$ = ~ 20 mL of O_2 per dL (100 mL) of blood in a normal healthy individual

[Hb% - Haemoglobin expressed in %, SaO_2 - Arterial oxygen saturation, PaO_2 - arterial partial pressure of oxygen]

and

2. Cardiac output (Q) = Heart rate x stroke volume

Oxygen consumption (VO_2) refers to the rate of uptake of oxygen by tissues from the microcirculation. It is a product of cardiac output and the difference in oxygen content between arterial and venous blood and is calculated as follows :

$VO_2 = Q \times 1.34 \times Hb \times (SaO_2 - SvO_2)$. The normal range is 110 - 160 mL/min/m^2.

Factors influencing VO_2 :

a. Common causes of decreased VO_2 include :

1. Decreased blood supply to tissues (e.g. cardiogenic or hypovolemic shock)

2. Increased cellular/tissue oxygen demand /metabolic rate (e.g. fever, burns, sepsis, acute pancreatitis or inflammation)

3. Impaired tissue utilization of oxygen in cytotoxicity, poisoning and other disorders (e.g. cyanide and carbon monoxide poisoning, sepsis)

b. Common causes of increased VO_2 include :

Fever, increased respiratory rate, shivering, seizures, even chest physiotherapy, positional change, minimal activity and tracheal suctioning in a sick patient can increase oxygen consumption.

Early correction of VO_2 deficit is therefore warranted to limit the severity of tissue ischemia

Assessment of Tissue Oxygenation :

Partial pressure of oxygen in tissues (PO_2) cannot be routinely measured at the bedside since there are no normal values for it like PaO_2. The blood tests that are used to detect tissue hypoxia (lactate, pH, oxygen transport/oxygen consumption, mixed venous oxygen saturation, venous arterial carbon dioxide gradient) are normally obtained from systemic venous, arterial or pulmonary arterial sources and, hence, must be considered as "global", rather than specific measurements of tissue oxygenation.

Oxygen transport, measured as the product of cardiac output and the arterial oxygen content, is a commonly evaluated clinical indicator of adequate tissue oxygenation. Normal tissue oxygen levels vary within and among organs but typically fall in a range of 3 - 9 %, substantially less than the 21% present in air. Within cells this fraction is even lower, ranging from 1.3 - 2.5 %. In vitro, extracellular pO_2 levels of 2 % or less are commonly considered to be hypoxic.

Parameter	Equation	Normal range
Arterial O_2 content(CaO_2)	$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$	20 mL / dL
Cardiac output (Q)	Q = HR x SV	4 - 8 L / min
Cardiac index (CI)	CI = Q / BSA	2.4 - 4.0 L / min / m^2
Oxygen delivery (DO_2)	Q x 1.34 x Hb x SaO_2	900 - 1000 mL / min
Oxygen delivery index (DO_2 index)	DO_2 / BSA	520 - 570 mL / min / m^2
Oxygen uptake (VO_2)	Q x 1.34 x Hb x (SaO_2 – SVO_2)	180 - 280 mL / min / m^2
Oxygen uptake index (VO_2 index)	VO_2 / BSA	110 - 160 mL / min / m^2
Oxygen extraction ratio (O_2ER or OER)	(SaO_2 - SVO_2 / SaO_2) x 100	20 - 30 %

Table 1. Normal Values and Equations of Tissue Oxygenation Parameters

(BSA = Body Surface area, Hb = Hemoglobin, HR = Heart rate, PaO_2 = Partial pressure of O_2 in arterial blood, SaO_2 = Arterial O_2 saturation, SVO_2 = Mixed venous O_2 saturation, SV = Stroke Volume)

Continuous, uninterrupted and sufficient supply of oxygen to all tissues is necessary for the efficient production of ATP, and this supply is considered sufficient when aerobic metabolism is maintained. The methods currently available or under development for assessing the adequacy of tissue oxygenation include :

1. Blood gas analysis
2. Transcutaneous oxygen measurement
3. Gastric tonometry
4. Pulse oximetry
5. Near-infrared spectroscopy
6. Functional magnetic resonance imaging (MRI)
7. Nuclear magnetic resonance (NMR) spectroscopy
8. Electron paramagnetic resonance
9. Positron emission tomography (PET)
10. Single photon emission computed tomography (SPECT)

Assessment of Tissue Hypoxia by clinical and biochemical methods in the critically ill [1,4,5,6] :

Tissue hypoxia is defined as a decrease in oxygen utilisation and is usually associated with a switch to anaerobic metabolism from the normal aerobic pathway. Decreased oxygen transport and low blood flow often precede the onset of anaerobic metabolism, hence early detection of this physiological abnormality (e.g. serum lactate) and its correction could possibly prevent tissue hypoxia, thus it is important to prevent such patients going towards a relatively low-flow state.

1. Clinical assessment : This should be the first approach taken to assess the critically ill patient. Although signs of tissue hypoxia are somewhat insensitive and nonspecific, several signs (mental obtundation, abnormal skin perfusion, decreased urine output, hypotension, abnormal vitals, delayed capillary refill etc.) often indicate organ dysfunction caused by tissue

hypoxia, and therefore, should prompt a search for reversible causes of tissue hypoxia. However these signs become clinically apparent often late during the course of tissue hypoxia.

Central venous pressure (CVP) is often incorrectly used as a parameter for replacement of intravascular volume. Its validity as an index of right ventricular reload is now redundant and moreover, it correlates poorly with the cardiac index, stroke volume, left ventricular end-diastolic volume and right ventricular end-diastolic volume. Instead of CVP, physiological and biochemical tests for tissue hypoxia should be used to complement clinical assessment.

2. Arterial pH and Serum lactate : A common abnormality in patients with tissue hypoxia is metabolic acidosis, often as a result of lactic acidosis. Blood lactate levels increase when tissue hypoperfusion results in anaerobic metabolism and when there is delayed clearance of lactate due to liver diseases, thiamine deficiency (blocks pyruvate metabolism) and metabolic alkalosis (stimulates glycolysis). The major reasons to measure arterial lactate are to assess tissue hypoxia and to investigate metabolic acidosis. The advantages of plasma arterial lactate is that it is easy to measure, is a better prognostic indicator (than oxygen derived physiological variables) and can be followed sequentially to assess the patient's response to therapy designed to reverse tissue hypoxia. A blood lactate value higher than 2 mmol/L is generally taken as abnormal and more than 4mmol/L is strongly associated with worse outcomes. More important is the lactate clearance time, which if less than 24 hours correlates with better survival, whereas if prolonged to more than 48 hours denotes higher probability of infection, organ dysfunction and death.

3. Arterial blood gases (ABG) : ABG is a clinical test that involves measurement of the pH of arterial blood and the amount of oxygen and carbon dioxide dissolved in arterial blood and is routinely used in the diagnosis and monitoring of predominantly critically/acutely ill patients. ABG allows assessment of two related physiological functions, namely pulmonary gas exchange and acid-base homeostasis. pO_2(a) is a measure of the pressure exerted by the very small fraction (1 - 2 %) of total oxygen in arterial blood that is dissolved in blood plasma, whereas sO_2(a) reflects the remaining 98 - 99 % of total oxygen in arterial blood that is bound to hemoglobin in red blood cells. To be specific, sO_2(a) is the percentage of hemoglobin in arterial blood that is capable of binding oxygen, and is saturated with oxygen :

$$sO_2(a) = O_2Hb / (O_2Hb + HHb) \times 100$$

[O_2Hb = concentration of oxygenated hemoglobin in arterial blood, HHb = concentration of deoxygenated hemoglobin in arterial blood]

sO_2(a) obviously cannot possibly be greater than 100 %. pO_2(a) is the major determinant of sO_2(a), and the relationship between the two parameters is described by the oxygen dissociation curve.

4. Mixed venous oxygen saturation (SvO_2) and mixed venous arterial carbon dioxide gradient : Mixed venous blood represents blood returning from all venous beds of the body mixed together in the right ventricle. It is obtained from blood at the distal end of the pulmonary artery with the help of a specialised pulmonary artery catheter, the tip of which emits infrared light and records light reflected back from hemoglobin in circulating erythrocytes (reflectance spectrophotometry). Where pulmonary artery catheters are not placed routinely, the central venous oxygen saturation ($ScvO_2$) can be used as a surrogate marker for SvO_2.

Decreased mixed venous oxygen saturation and pressure can be caused by decreased oxygen transport and/or increased oxygen demand. However, a normal or increased value does not rule out significant tissue hypoxia, especially in sepsis. Therefore, decrease in mixed venous oxygen saturation and pressure are more likely to occur in cardiogenic and hypovolemic shock rather than septic shock. A critical level of mixed venous oxygen saturation that defines inadequate oxygen delivery is difficult to define. Therefore SvO_2 is a marker of the balance between whole body oxygen delivery and oxygen demand and is normally between 65 – 75 % i.e. oxygen demand is usually about 25 - 35 % that of oxygen delivery, values below 60 % indicate cellular oxidative impairment and below 50% are associated with anaerobic metabolism

Causes of decreased SvO_2 :

a. Decreased oxygen delivery - Hypovolemia, decreased cardiac output, low Hb (anemia), low PaO_2 and SaO_2 (hypoxemia)

b. Increased oxygen demand - Critical illness, sepsis, thyrotoxicosis, etc

Causes of increased SvO_2 :

a. Increased oxygen delivery - Increased cardiac output, use of ionotropes, increased Hb etc.

b. Decreased oxygen demand - Deep sedation and paralysis in ventilated patients

c. Decreased tissue (cellular) oxygen utilization - Cyanide and CO poisoning, sepsis

d. Left to right shunts

$ScvO_2$: It is the venous oxygen saturation near the junction of the superior vena cava and right atrium which is obtained from subclavian or internal jugular central venous catheter. Since $ScvO_2$ neglects venous return from the lower body, values for $ScvO_2$ are 3 – 5 % less than SvO_2 . Values < 65 % indicate ongoing oxidative impairment and above 80% reflect cellular dysfunction with impaired oxygen consumption, as seen in the late stages of shock. $ScvO_2$ has to be considered as a "global" marker of tissue hypoxia in context with other markers of tissue perfusion like lactate.

5. Oxygen transport and Oxygen consumption relationship : The measurement of changes in oxygen consumption in response to changes in oxygen transport has been suggested as a sensitive method to determine whether tissue hypoxia exists. There are several problems with this approach including uncertainty that the patient's underlying oxygen demand has remained constant, difficulty in accurately measuring the pertinent variables involved, mathematical coupling of shared variables, and the thermogenic effects of adrenergic agents administered to increase cardiac output. Because of these methodologic issues, difficulties in making appropriate measurements and the fact that many studies have not found dependency of oxygen consumption on oxygen transport (when measured by independent techniques), this approach is not particularly useful in the care of the critically ill patient.

The oxygen extraction ratio (OER) as obtained from capillary blood is about 25 % in the resting state and it may increase upto 70 - 80 % during exercise. Factors affecting OER include the rate of oxygen delivery to capillaries, oxygen-hemoglobin dissociation relationship, relation between the size of the capillary to cellular PO_2, diffusion distance to cells and the rate of oxygen utilization by cells. The survival time of different tissues with hypoxia varies as follows (Table 2).

Organ(s)	Survival time in Hypoxia
Brain	< 3 minutes
Heart	30 minutes
Kidney and liver	15 - 20 minutes
Skeletal muscle	60 - 90 minutes
Vascular smooth muscle	24 - 72 hours
Hair and nails	Upto several days

Table 2. The Survival Time of Tissues and Organs in Hypoxia

6. Pulse oximetry :

Adequate oxygen delivery to tissue depends on sufficient oxygen content in arterial blood and blood flow to the tissue. Oximetry is a technique for the assessment of blood oxygenation by measurement of light transmission through blood, which is based on the different absorption spectra of oxygenated and deoxygenated hemoglobin (transmission spectrophotometry). Oxygen saturation in arterial blood provides information on the adequacy of respiration and is routinely measured in clinical settings, utilizing pulse oximetry. Oxygen saturation in venous blood (SvO_2) and in the entire blood in a tissue (StO_2) are related to blood supply to the tissue, and several oximetric techniques have been developed for their assessment. SvO_2 can be measured non-invasively in the fingers, making use of modified pulse oximetry, and in the retina, using the modified Beer-Lambert Law. StO_2 is measured in peripheral muscle and cerebral tissue by means of various modes of near infrared spectroscopy (NIRS), utilizing the relative transparency of infrared light in muscle and cerebral tissue. The primary problem of oximetry is the discrimination between absorption by hemoglobin and scattering by tissue elements in the attenuation measurement, and the various techniques developed for isolating the absorption effect.

Dual oximetry : By simultaneously measuring SaO_2 by pulse oximetry and the SvO_2 one can get continuous measurement of whole body oxygen extraction, i.e. $SaO_2 – SvO_2$, the normal value being 20 – 30 %

The different blood tests that are used to detect tissue hypoxia (lactate, pH, oxygen transport/oxygen consumption, mixed venous oxygen saturation, venous arterial carbon dioxide gradient) are normally obtained from systemic venous, arterial or pulmonary arterial sources and hence must be considered as global measurements. The resulting values are flow-weighted averages. This has two consequences :

1. Because of the diluting effect brought about by the contribution of blood from normoxic tissues, regional hypoxia may not always result in measurable changes in global indices; and,
2. Abnormalities in these tests cannot identify the site of hypoxia.

Despite the lack of specificity, an unexplained high lactate should prompt a search for the source of the abnormality (e.g., ischemic bowel, etc). As the conventional global measurements of tissue hypoxia are not specific for particular organs, and may not be sensitive enough to detect regional hypoxia, there is a need to consider regional indices. Approaches that may enable a regional analysis in the future include the use of polarographic oxygen and luminescent probes, infrared and near infrared spectrometry, nuclear magnetic resonance spectroscopy and positron emission tomography.

Monitoring Regional Hypoxia [1,2,4,5,6,7] :

1. Sublingual Capnometry : The sensor is placed under the tongue to measure partial pressure of carbon dioxide in the sublingual tissue($PslCO_2$).The normal value is 43 - 47 mmHg. $PslCO_2$ >70 mmHg correlates with elevated lactate levels. A difference or gap between $PslCO_2$ and $PaCO_2$ of > 25 mmHg identifies patients at a high risk of mortality.

2. Gastric intra-mucosal pH : Gastric intra-mucosal pH appears to be a good prognostic indicator of patient outcome in the intensive care unit in a selected series of patients, but it is not certain that it is much better than other predictors in unselected patients. It employs a balloon in the stomach to measure intramucosal pH (pHi) . However, this technique is complex, relatively expensive, operator skill-dependent and time consuming to measure. The gastric mucosal-arterial carbon dioxide difference is more specific than gastric intramucosal pH. Because increased gastric arterial carbon dioxide difference can be secondary to decreased gastric flow (carbon dioxide stagnation) and anaerobic metabolism (non-specific) and because of inadequate data regarding reproducibility, response to therapy, and definition of the abnormal gradient, further studies are required before we can recommend this potentially promising technique for routine clinical use.

3. Orthogonal Polarisation Spectroscopy (OPS) : OPS uses polarised light to visualise the microcirculation directly. Hemoglobin absorbs polarised light and real-time images are reflected to video microscope and functional capillary density is measured. OPS is a sensitive marker of tissue perfusion and an indirect measurement of oxygen delivery. The tissues evaluated include oral, sublingual, rectal and vaginal mucosa. Movement artifacts, presence of saliva and observer related bias are few limiting factors of OPS.

4. Near Infra Red Spectroscopy (NIRS or NIS) : It measures the concentrations of hemoglobin, oxygen saturation and cytochrome aa3.Cytochrome aa3 is the final receptor in the electron transport chain responsible for 90 % cellular oxygen consumption. It remains in a reduced state during hypoxia. NIS is used primarily to evaluate the perfusion of skeletal muscles. The problems faced with NIS include signal contamination by light scatter, variable interpretations of data and the lack of a reference standard for comparison.

5. Transcutaneous oxygen tension : It measures transcutaneous oxygen or carbon dioxide. Increased mortality is seen in patients with low transcutaneous oxygen or high transcutaneous CO_2. It is a marker of regional tissue hypoperfusion by using heated probes placed on the skin. The limitations include tissue trauma from probe insertion, thermal injury if the probes are not moved every 4 hours and lack of established critical values to guide resuscitation.

6. Magnetic Resonance Spectroscopy (MRS) : MRS which uses radiolabelled molecules to determine metabolite concentrations and quantify tissue enzyme kinetics, may be readily combined with MRI which uses signals from protons to form anatomic images. It is used clinically for various conditions particularly within the brain, infectious diseases and metabolic pathologies as the detected metabolites are sensitive to hypoxia, energy dysfunction neuronal injury, membrane turnover and inflammation.

7. Electron Paramagnetic Resonance (EPR) : To monitor the pO_2 levels in vivo, continuous wave (CW) and time-domain (TD) EPR spectroscopy method was used, in which surface coil resonator and Lithium phthalocyanine (LiPc) as the oxygen sensor were crucial. Once LiPc particles are embedded in a desired location of organ/tissue, the pO_2 level can be monitored repeatedly and non-invasively. This method is based on the effect of oxygen concentration on the EPR spectra of LiPc which offers several advantages as follows :

i. High sensitivity
ii. Minimum invasiveness

iii. Repeated serial measurements
iv. Absence of toxicity (non-toxic)
v. Measurement in a local region of the tissue with embedded LiPc

8. Positron Emission Tomography (PET) : Hypoxia has been identified as a major adverse prognostic factor for tumor progression and for resistance to anti-cancer treatment. Various approaches have been evaluated to assess tumor hypoxia in vivo. PET imaging in particular has emerged as a promising non-invasive tool to accurately characterize tumor oxygenation, thus offering the potential to optimize and individualize therapy for patients suffering from cancer. Special emphasis is placed on human PET studies assessing tumor hypoxia in patients with different tumor entities, various anti-cancer therapies (chemotherapy, radiation therapy, hypoxia targeting chemotherapy) as well as studies deriving prognostic factors and outcome data [8].

9. Single Photon Emission Computed Tomography (SPECT) : Pilot clinical studies with SPECT and PET detection of radiolabelled markers to tumor hypoxia have been reported. Preclinical studies with "microSPECT" and "microPET" will be important to define the optimal radiodiagnostic(s) for measuring tissue oxygenation and for determining the time after their administration for optimal hypoxic signal acquisition. Radiolabelled markers of growth kinetics and intrinsic radiosensitivity of cells in solid tumors are also being developed [8].

10. Functional Magnetic Resonance Imaging (Functional MRI) : A quantitative estimate of cerebral blood oxygen saturation is of critical importance in the investigation of cerebrovascular disease. While positron emission tomography can map *in vivo* the oxygen level in blood, it has limited availability and requires ionizing radiation. Magnetic resonance imaging offers an alternative through the blood oxygen level-dependent contrast. The *in vivo* and non-invasive approach to map brain tissue oxygen saturation (StO_2) with high spatial resolution correlated well with results from blood gas analyses for various oxygen and hematocrit challenges. Thus, the MRI technique may improve our understanding of the pathophysiology of several brain diseases involving impaired oxygenation [9].

Implications of Tissue Hypoxia [4,6,7] :

Although the tolerance of the normal human body to hypoxemia and anemic hypoxia is impressively high, severe hypoperfusion or extreme hypoxemia can lead to organ dysfunction and eventually to cell death and tissue necrosis. During hypodynamic shock, blood flow redistribution causes tissue hypoxia , the most affected organs being the gut and the kidney. The direct role of tissue hypoxia in the pathogenesis of multiple organ dysfunction syndrome secondary to sepsis and/or the systemic inflammatory response syndrome is less well defined. Tissue hypoxia or hypoperfusion of one organ may lead to dysfunction or failure of a distant organ. For example bowel ischemia, or at least maldistribution of blood flow between the mucosa and the muscularis, may cause translocation of bacteria and increased endotoxin levels in portal blood. This can cause a systemic inflammatory response which alters the microcirculation leading eventually to organ dysfunction, perhaps before tissue hypoxia bas occurred. Sepsis and the systemic inflammatory response syndrome (SIRS) are associated with increased oxygen consumption which is usually met by a hyperdynamic cardiovascular response. Inadequacy of this response has been suggested to cause tissue hypoxia. Minimally elevated blood lactate levels cannot however be taken as proof of tissue hypoxia in sepsis, since alternative mechanisms can be at play, such as increased aerobic metabolism or inhibition of pyruvate dehydrogenase by endotoxins. Direct endothelial cell injury by inflammatory mediators, microcirculatory plugging by circulating cells, and increased microvascular permeability combine to impair microcirculatory perfusion and tissue oedema, further altering oxygenation and nutrition of cells. The role of tissue hypoxia in the critically ill is therefore a complex one. First, hypoxia of one organ may cause dysfunction or failure of a distant one. Second, sepsis and the systemic inflammatory response syndrome cause organ dysfunction that is only partially explained by tissue hypoxia per se. Third, maldistribution of microperfusion and alteration of the microvasculature by the systemic inflammatory response appears to play a major role in organ dysfunction.

Correction of Tissue Hypoxia [3,4,6,7] :

Approaches to correct tissue hypoxia are optimisation of delivery of oxygen to the tissues and reduction in oxygen demand. For most patients with tissue hypoxia the management approach or therapeutic plan requires hemodynamic assessment and monitoring, usually with a pulmonary artery catheter.

a. Optimizing Oxygen Delivery :

Early resuscitation by expanding the circulating volume is crucial for patients in hypovolemic and distributive shock since delays can be associated with the development of refractory tissue hypoxia. The adequacy of fluid resuscitation is more important than the type of fluid administered. Blood transfusions should be considered when the hematocrit is below 30 %

(hemoglobin < 10 g/dl). If signs of inadequate perfusion persist despite volume loading, vasoactive drugs are recommended. Given the typical septic profile of low peripheral vascular resistance, dopamine is an appropriate first choice. If the response is inadequate or a high lactate persists, dobutamine should be considered. In situations of very low peripheral vascular resistance with low mean arterial pressure, norepinephrine may be useful.

b. Reducing Oxygen Demand :

Sedation should be used at the lowest dose that commensurates with the abolition of pain, stress and anxiety. Increased sympathetic activity should be reduced but not abolished as some sympathetic activity is necessary to preserve microcirculatory control. Muscle relaxants may occasionally be required. In patients with evidence of persistent tissue hypoxia, mechanical ventilation should be considered even if arterial oxygen pressure and carbon dioxide pressure are acceptable, since placing the respiratory muscles at rest decreases respiratory muscle oxygen consumption and thus may improve the oxygenation of other hypoperfused organs.

Several studies have demonstrated that critically ill patients with normal or supranormal oxygen transport are more likely to survive than patients with less than normal oxygen transport. In addition, these patients are less likely to develop multiple organ dysfunction syndrome (MODS). These findings formed the basis for a number of studies which investigated whether increasing oxygen transport to supranormal values could decrease mortality. Post-hoc analysis of randomized controlled trials of improving oxygen transport suggests that mortality is lower in subsets of patients who achieve and, perhaps, maintain, supranormal oxygen transport. However, it is likely that patients who are capable of achieving supranormal oxygen transport are more likely to survive and it is their ability to respond to the manipulations, rather than the result of the manipulations themselves, that accounts for the improvement in survival. Thus, continued aggressive attempts to increase oxygen transport to supranormal values in all patients are unwarranted. However, timely resuscitation and achievement of normal hemodynamics is essential.

Summary :

Technical advances in tissue oximetry have rendered possible better knowledge of hypoxia at cellular and tissue level. With the current emphasis on microvascular function, regional tissue perfusion and oxygenation in the critical care setting, strategies have evolved for the application of different invasive as well as non-invasive modalities for assessment of tissue oxygen supply and demand, with objectives to identify the presence of hypoxia in tissue, predict response to and monitor efficacy of oxygen therapy, as well as determine the management approach. Currently, correction of tissue hypoxia in the critically ill patient is based on the implementation of strategies that ensure sufficient global oxygen delivery and avoid oxygen debt. Several modalities, each with its own merits and demerits, including pulse oximetry, analysis of blood gases, transcutaneous oxygen measurement, gastric tonometry, near-infrared spectroscopy, magnetic resonance spectrometry, functional magnetic resonance imaging, electron paramagnetic resonance, positron emission tomography and single photon emission computed tomography are either available or under evaluation for their efficacy towards assessing the adequacy of tissue oxygenation. It is of paramount importance to recognize their individual advantages and limitations in this regard, in order to optimize management strategies for correction of hypoxia in the critical care setting.

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Pulse Oximetry

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Introduction :

Early detection of hypoxia and its correction is essential for reducing morbidity and mortality. Even though central cyanosis is a reliable physical sign of hypoxia, it appears late when the patient develops profound hypoxia. Pulse oximetry is a useful non-invasive method to measure oxygen saturation and detect hypoxia early. The instrument, called pulse oximeter (Figure 1), being small, lightweight and battery operated is portable and can be used anywhere. In this review we discuss regarding the use of pulse oximetry in a self-assessment Question-Answer format.

Figure 1 : Pulse Oximeter

Question 1. *Which of the following is a* ***WRONG*** *statement regarding the pulse oximeter ?*

A. It measures hemoglobin that is saturated with oxygen in peripheral arterial blood.
B. It works based on the principle of Beer-Lambert law.
C. It consists of a light emitting diode and a photodetector.
D. Two separate wavelengths of light illuminate oxygenated and deoxygenated hemoglobin.
E. It measures the ventilatory function of the lung.

Answer : E. Ventilatory function includes inspiration and expiration. It is measured by spirometry. Inadequate ventilation may lead to hypoxia, hypercapnia or both which can be measured non-invasively by capnography.

Pulse oximeter uses a sensor device which consists of two light sources (red and infrared) and a photo detector to measure the absorption of visible light. Deoxyhemoglobin absorbs light maximally in the red band of the spectrum (600 to 750 nm), and oxyhemoglobin absorbs maximally in the infrared band (850 to 1000 nm). Thus, the emitters emit light at 660 nm and 940 nm for optimal detection of deoxyhemoglobin and oxyhemoglobin in blood respectively. The amount of dissolved oxygen in the blood determines the number of oxygen molecules bound to hemoglobin. The ratio between the amplitude of the red and infrared wavelength is used to determine oxygen saturation by the pulse oximeter. Pulse oximeter measures the difference in light absorption by oxygenated and deoxygenated hemoglobin, and then calculates the percentage of hemoglobin that is saturated with oxygen. Ratio of oxyhemoglobin to the total concentration of hemoglobin in the blood is known as oxygen saturation which is referred to as SpO_2.

The sensor (detector) and emitters are positioned facing each other through interposed tissue. Probes are most frequently placed on the fingers, toes, ear lobes, or nasal ala. In infants, probe can be placed on the palms, feet, arms, cheeks, tongue,

penis, nose, or nasal septum. These sites are preferentially used since they contain a high density of vascular tissue. In addition to SpO_2, many pulse oximeters also display pulse rate and relative pulse amplitude.

Pulse oximetry estimates peripheral SpO_2 using the principle of Beer-Lambert law, which states that "*the absorptive capacity of a dissolved substance is directly proportional to its concentration in a solution*". Pulse oximeter reading is calibrated using reference tables of actual arterial oxygen saturation (SaO_2) measurements performed using co-oximetry. This is compiled using data from exposing healthy volunteers to decreasing fractions of inspired oxygen (FiO_2) to yield SaO_2 ranging from 100 to 75 percent. Since it is unethical to intentionally generate lower saturations in volunteers, values for an SaO_2 less than 75 percent are obtained by extrapolation from these volunteer data.

Question 2. *Which of the following is a* ***WRONG*** *statement regarding the pulse oximeter ?*

A. Can detect hypoxia before the onset of cyanosis
B. Reliable in all patients
C. Portable
D. Simple to use
E. Can be used to monitor for hypoxia

Answer : B. The Pulse oximeter will function properly only when it is able to detect a modulation in the transmitted light. In conditions where perfusion is decreased and pulse amplitude is small, the signal will be decreased. In such situations the device will be liable to error or may be unable to obtain a reading.

Central cyanosis is a late indicator of hypoxia and is subjective, depending on the experience and eyesight of the observer. A good ambient lighting is essential for early detection of cyanosis. It may be missed in people with skin pigmentation. Pulse oximetry when used appropriately, is more accurate and can detect hypoxia early compared to central cyanosis.

Pulse oximetry provides continuous data. Hence it is often used to monitor for hypoxia and oxygen therapy can be easily adjusted to a target SpO_2 level. Since it is a small, portable instrument and simple to use which requires no special training, it is useful in a variety of settings for monitoring SpO_2 in less seriously ill patients. Pulse oximeter is often used for patient monitoring in emergency departments, operating rooms, emergency medical services (EMS) systems, postoperative recovery areas, endoscopy suites, sleep and exercise laboratories, oral surgery suites, cardiac catheterization suites, facilities that perform conscious sedation, labor and delivery wards, inter-facility patient transfer units, high altitude, aerospace medicine facilities, and patients' homes. In the present covid pandemic the instrument has gained crucial role in monitoring for hypoxia.

SpO_2 will be reliable only when the pulse oximetry waveform is normal. A normal pulse oximeter waveform has a dicrotic notched appearance typical of an arterial waveform which synchronizes with a palpable or observed heart rate.

In most patients with SpO_2 values of 90 percent or higher, the value lies within 2 to 3 percent above or below the true arterial saturation (SaO_2) reference standard. However, the accuracy worsens when the SaO_2 is < 90 percent, and especially below 80 percent. Thus, SpO_2 is less reliable in critically ill patients where oxygenation can rapidly fluctuate and desaturation is common (Table 1).

SpO_2 (%)	PaO_2 (mmHg)	Oxygenation status
95 - 100	80 - 100	Normal
91 - 94	50 - 60	Mild hypoxia
86 - 90	50 - 60	Moderate hypoxia
Less than 85	Less than 50	Severe hypoxia

Table 1. Pulse Oximetry and PaO_2 correlation with Oxygenation status

In most patients, peripheral oxygen saturation as measured by pulse oximetry (SpO_2) provides accurate information on tissue oxygenation. Clinicians should also pay attention to trends in oxygenation in addition to absolute values. When treating patients with supplemental oxygen for hypoxemia, they should target SpO_2 levels that are desirable for the specific etiology and should avoid oxygen toxicity. The clinician should be aware of the limitations and errors associated with pulse oximetry. Normal SpO_2 range is 96 to 99%. Resting oxygen saturation ≤ 95 percent or exercise desaturation of ≥ 5 percent is considered abnormal. Trends in oxygen saturation over a period of time and the underlying disease process are also important for

interpretation i.e. a resting oxygen saturation of 96 percent could be abnormal if a patient previously had a resting oxygen saturation of 99 percent. A target level of 88 to 92 percent may be sufficient in a patient with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). A target saturation of > 95 percent may be considered optimal in acute hypoxic respiratory failure. Oxygen toxicity, particularly in premature neonates can be limited by titrating oxygen to an SpO_2 of 90 percent, which usually reflects a PaO_2 of approximately 60 mmHg at a pH of 7.4.

Question 3. *In which of the following conditions is pulse oximetry reading* ***MOST RELIABLE*** *?*

A. Acute exacerbation of obstructive airway disease
B. Severe pneumonia
C. Septic shock
D. Severe anaemia
E. Atrial fibrillation

Answer : A. In patients with hypotension (septic shock), poor peripheral perfusion (severe pneumonia), poor pulse wave and strength (atrial fibrillation), pulse oximeter measurements will not be reliable. Low hemoglobin concentrations can lead to falsely low readings when SaO_2 is below 80 percent.

Pulse oximetry is subject to artifactual and patient-related sources of error (Table 2). The best defence against error is a high index of suspicion. If a saturation reading is in doubt, equipment error can be quickly ruled out by putting the probe on the healthcare worker's own finger. Once assured that equipment is functioning, the clinician should investigate for other potential sources of error, most of which are readily identified and resolvable.

Question 4. *Which of the following conditions* ***DOES NOT*** *interfere with pulse oximetry reading ?*

A. Hemoglobinemia
B. Nail polish
C. Methylene blue
D. Prolonged exposure to smoke in fire hazard
E. Foetal hemoglobin in new-borns

Answer : E. Foetal hemoglobin does not interfere with pulse oximetry readings. Hence pulse oximetry is reliable in new-borns.

Carboxyhemoglobin : Carboxyhemoglobin (COHb) absorbs approximately the same amount of 660 nm light as oxyhemoglobin. Pulse oximetry reading represents summation of oxyhemoglobin and carboxyhemoglobin. Hence in carbon monoxide poisoning SpO_2 will be normal. Arterial oxygen tension (PaO_2) measurements tend to be normal because PaO_2 reflects the oxygen dissolved in blood, and this process is not affected by COHb. In contrast, hemoglobin-bound oxygen (which normally comprises 98 percent of arterial O_2 content) is profoundly reduced in the presence of carboxyhemoglobin. Hence, whenever carboxyhemoglobinemia is suspected, co-oximetry (not pulse oximetry) is recommended for the measurement of carboxyhemoglobin levels.

Methemoglobin : Methemoglobin absorbs light at wavelengths of both 660 and 940 nm. Methemoglobinemia should be suspected in those with cyanosis and a normal PaO_2. Up to a methemoglobin level of 20 percent, SaO_2 drops by about one-half of the methemoglobin percentage. At higher methemoglobin levels, SaO_2 trends toward 85 percent regardless of the true percentage of oxyhemoglobin, thus leading to over- or underestimation of the true SaO_2. When methemoglobinemia is suspected, co-oximetry should be used to accurately determine the methemoglobin level.

Sulfhemoglobin : Sulfhemoglobin absorbs light at 660 nm, similar to oxyhemoglobin. Sulfhemoglobinemia is most commonly caused by the ingestion of oxidizing drugs (e.g. dapsone, sulphonamides, metoclopramide, nitrates). Patients present in a similar fashion to those with methemoglobinemia (cyanosis and normal PaO_2). However, unlike methemoglobin, sulfhemoglobin shifts the hemoglobin-oxygen dissociation curve to the right, thereby "unloading" oxygen in the periphery such that the adverse effects are not as clinically significant as with methemoglobinemia. High levels can falsely reduce the SpO_2, trending towards 85 percent, similar to methemoglobin. However, multi-wavelength co-oximetry does not accurately distinguish it from methemoglobin. If suspected, specialized biochemical testing available in a limited number of centres is required. While testing is ongoing the offending agent should be stopped, if feasible. Patients do not respond to methylene blue therapy (i.e. therapy for methemoglobinemia) which may also be a diagnostic clue. There is no known antidote, however, severe cases may respond to exchange transfusion.

Inherited forms of abnormal hemoglobin (Hemoglobinopathies) : Inherited forms of abnormal hemoglobin (Hb) are rare but have been reported to result in falsely low SpO_2 readings (e.g. Hb Lansing, Hb Bonn, Hb Koln, Hb Hammersmith, and Hb Cheverly).

Severe Anemia : Pulse oximetry readings may be affected by profoundly decreased hemoglobin level is less than 5 g/dL

Nail polish : The use of nail polish can potentially affect pulse oximeter readings if the polish absorbs light at 660 nm and/or 940 nm A small study of volunteers wearing black, green, and blue nail polish revealed a drop in SaO_2 of 3, 5, and 6 percent, respectively. Red nail polish does not appear to have an effect on pulse oximetry readings. Newer devices appear to be less affected with the greatest reductions in SpO_2 found in those with black or brown polish not exceeding 2 percent.

Vital dyes : Vital dyes, such as methylene blue (used to treat methemoglobinemia, or during endoscopic polypectomy), indocyanine green (used for measuring cardiac output, for ophthalmic angiography, or for measuring liver blood flow), fluorescein (ophthalmic angiography) and isosulfan blue (used intraoperatively to mark breast and melanoma tumors) can cause erroneously low pulse oximetry readings due to absorption of light at 660 nm or 940 nm. Methylene blue has the greatest impact as it absorbs significantly at 670 nm. However, these effects tend to be transient and resolve rapidly as the dyes are diluted and metabolized.

Defect	Causes
Inability to record SpO_2	**Inadequate perfusion** • Hypotension • Vasoconstriction • Low Cardiac output • Low volume pulse • Irregular heartbeat (Arrhythmia) • Elevation of probe above the level of heart
Falsely normal or elevated SpO_2	• Carbon monoxide poisoning • Sickle cell anemia with vasoocclusive crises • Sulfhemoglobin • Methemoglobin • Bright light
Falsely low SpO_2	• Venous pulsations • Excessive movement • Intravenous pigmented dyes • Application of nail polish • Severe anemia (with concomitant hypoxemia)
Falsely low or high SpO_2	• Poor probe positioning • Sepsis and septic shock • Edema • Arterio-venous fistula

Table 2. Causes for Unreliable SpO_2 Readings.

Question 5. *Which Patients will require initial Arterial Blood Gas (ABG) estimation regardless of a normal pulse oximetry ?*

Answer :

1. Cardiac or respiratory arrest
2. Hypotension
3. Sepsis and shock
4. Polytrauma
5. Patients who are apnoeic or who require assisted ventilation or are on mechanical ventilation
6. Patients with suspected or confirmed carbon monoxide poisoning or smoke inhalation
7. Neonates in distress

8. Patients with suspected sickle cell crisis

9. Near drowning patients

10. When an acid-base abnormality is suspected

11. For pH measurement - Hypercapnic respiratory failure, COPD in acute exacerbation, altered sensorium

Summary :

- Pulse oximeter measures peripheral arterial oxygen saturation (SpO_2) as a surrogate marker for tissue arterial oxygenation (SaO_2).
- Pulse oximetry uses spectrophotometry to determine the proportion of hemoglobin that is saturated with oxygen in peripheral arterial blood.
- Pulse oximetry is a rapid, non-invasive tool that can provide continuous assessment of oxygenation.
- However, it cannot detect hyperoxemia or arterial oxygen or carbon dioxide tension.
- Pulse oximetry is indicated in any setting where hypoxemia may occur.
- It provides accurate assessment of tissue oxygenation in most patients.
- Pulse oximetry is subject to artifactual and patient-related sources of error. Once assured that equipment is functioning, the clinician should investigate for other potential sources of error, most of which are readily identified and resolvable.

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Oxygen as a Drug

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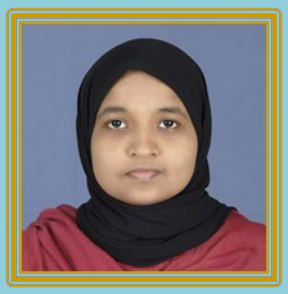

Introduction :

Oxygen (O_2) is the most commonly used drug in emergency medicine. Oxygen saves lives when used appropriately to correct hypoxemia and is an essential component in resuscitation of the critically ill. 34% of ambulance patients receive oxygen during transit and 15-17% of hospital inpatients will be receiving oxygen at any given time [1,2]. Supplemental oxygen as a medical treatment became common early in the twentieth century for patients who suffered discomfort or difficulty breathing, mainly helping them recover from a hypoxic state and relieve dyspnea. Like any other drug, oxygen should be prescribed, administered and monitored by trained staff. In this chapter, we have tried to provide a concise overview of and describe Oxygen as a drug, by its mechanism of action, rationale, therapeutic benefits, effects, indications and adverse effects.

Indications of Oxygen therapy :

Historically, oxygen has been administered for three main indications, of which only one is evidence-based. First, oxygen is given to correct hypoxemia because severe hypoxemia is clearly harmful to the human body. Second, oxygen has been administered to ill patients in case they might become hypoxemic. Recent evidence suggests that this practice may actually place patients at increased risk if impaired gas exchange does actually develop. Third, a very high proportion of medical oxygen was administered because most clinicians believed that oxygen can alleviate breathlessness in most circumstances. However, oxygen has not been proven to have any consistent effect on the sensation of breathlessness in non-hypoxemic patients.

Rationale of Oxygen therapy :

Oxygen therapy is usually defined as the administration of oxygen at concentrations greater than those found in ambient air. It is usually undertaken to treat or prevent hypoxemia, thereby preventing tissue hypoxia which may result in tissue injury or even cell death. Clinicians must bear in mind that supplemental oxygen is given to improve oxygenation but it does not treat the underlying causes of hypoxemia which must be diagnosed and treated as a matter of urgency.

Physiological benefits of Oxygen therapy :

Oxygen therapy increases partial pressure of oxygen in the alveoli (PAO_2) and is therefore only effective when alveolar capillary units have some functional ventilation. Oxygen therapy is ineffective if there is a pure shunt (such as pulmonary arteriovenous malformations) where mixed venous blood does not pass through an alveolar capillary unit. There will only be a small overall increase in PaO_2 due to an increase in dissolved oxygen in the pulmonary venous blood from ventilated alveolar capillary units, which is small compared with the content of oxygen carried by hemoglobin. In poorly ventilated units (low V/Q ratio), PAO_2 will be low. Increasing FiO_2 (fraction of oxygen in inspired air) will increase PAO_2 and therefore the PaO_2 (arterial partial pressure of oxygen).

Hypoventilation disorders can be considered as those in which low V/Q units are predominantly functioning within the lungs . When there is diffusion limitation due to increased alveolar capillary membrane thickness such as in fibrotic lung disease, increasing PAO_2 will augment the rate of diffusion across the alveolar capillary membrane by increasing the concentration gradient. Increasing dissolved oxygen in plasma by oxygen therapy may also be used to offset the effects of hypo perfusion to some extent (stagnant hypoxia) and may well be important in certain situations (cardiogenic shock), although the effect is only marginal.

Target Oxygen saturation in acute illness :

According to British Thoracic Society guidelines for oxygen use in adults in healthcare and emergency settings 2017 update [3], target oxygen saturation range for acutely ill patients not at risk of hypercapnic respiratory failure is 94–98%. For most patients with known COPD or other known risk factors for hypercapnic respiratory failure (eg, morbid obesity, Cystic Fibrosis,

chest wall deformities or neuromuscular disorders or fixed airflow obstruction associated with bronchiectasis), a target saturation range of 88–92% is suggested pending the availability of blood gas results.

Appropriate positioning of a patient can maximise V/Q matching. In the healthy self-ventilating adult lung, V/Q matching improves from non-dependent to dependent areas. In lung disease, there is a disruption of this pattern and, in these instances, appropriate positioning may be advantageous in optimizing V/Q matching, therefore improving gas exchange, oxygenation and carbon dioxide clearance. Even in healthy participants the PO2 is 0.7 kPa (5 mm Hg) lower in the supine position than in the upright position [4]. Fully conscious hypoxemic patients should ideally be allowed to maintain the most upright posture possible (or the most comfortable posture for the patient) unless there are good reasons to immobilise the patient (eg, skeletal or spinal trauma).

Initial choice of equipment for Oxygen therapy in patients without critical illness :

For acutely breathless patients not at risk of hypercapnic respiratory failure who have saturations below 85%, treatment should be started with a reservoir mask at 15 L/min in the first instance. The oxygen concentration can be adjusted downwards (using nasal cannulae at 1–6 L/min or a simple face mask at 5–10 L/min) to maintain a target saturation of 94–98% once the patient has stabilized. In other cases of acute hypoxemia without critical illness or risk factors for hypercapnic respiratory failure, treatment should be started with nasal cannulae (or a simple face mask if cannulae are not tolerated or not effective) with the flow rate adjusted to achieve a saturation of 94–98% . If medium-concentration therapy with nasal cannulae or a simple face mask does not achieve the desired saturation, change to a reservoir mask and getting specialist advice is warranted.

Oxygen therapy in critical illness :

It is advisable to use the highest feasible inspired oxygen for ventilation during cardiopulmonary resuscitation [5]. Once spontaneous circulation has returned and arterial blood oxygen saturation can be monitored reliably, aim for a target oxygen saturation (SpO_2) range of 94–98% and take an arterial blood gas (ABG) sample to guide ongoing oxygen therapy. If the blood gas shows hypercapnic respiratory failure, reset the target range to 88–92% or consider mechanical ventilation. In critical illness, including major trauma, sepsis, shock and anaphylaxis, initiate treatment with a reservoir mask at 15 L/min and aim for a saturation range of 94–98%. In cases of carbon monoxide poisoning, an apparently “normal” oximetry reading may be produced by carboxyhemoglobin [6], so aim at an oxygen saturation of 100% and use a reservoir mask at 15 L/min irrespective of the oximeter reading and arterial oxygen tension (PaO_2).

Oxygen therapy for specific conditions that frequently require oxygen therapy :

In respiratory conditions with low risk of hypercapnic respiratory failure like acute asthma, pneumonia, acute breathlessness in lung cancer and interstitial lung diseases, the target SpO_2 range is 94-98%. In patients with pneumothorax having hospital observation without drainage, the use of high-concentration oxygen (15 L/min flow rate via reservoir mask) is recommended unless the patient is at risk of hypercapnic respiratory failure [7].

Common medical emergencies for which Oxygen therapy is indicated only if hypoxemia is present :

In patients with myocardial infarction, angina and stroke, there is no evidence of benefit from the administration of supplemental oxygen to non-hypoxemic patients and there is some evidence of possible harm [8], especially when used at high-flow rates. High concentrations of oxygen should be avoided in patients with stroke, unless required to maintain normal oxygen saturation. Oxygen should be given via nasal cannulae, unless there are clear indications for a different oxygen delivery system [9]. In most poisonings, aim to maintain an oxygen saturation of 94 – 98% unless the patient is at risk of hypercapnic respiratory failure. However in poisoning by paraquat [10] and bleomycin [11], give oxygen only if the saturation falls below 85% and reduce or stop oxygen therapy if the saturation rises above 88%, due to the potential risk of oxygen toxicity.

Oxygen therapy in patients with hypercapnic respiratory failure :

Chronic obstructive pulmonary disease (COPD) is the best known condition that can predispose to hypercapnic (type 2) respiratory failure with acidosis. Other conditions which can render patients vulnerable to hypercapnic respiratory failure include Cystic fibrosis (CF), Non-CF bronchiectasis (often in association with COPD or severe asthma), Severe kyphoscoliosis or severe ankylosing spondylitis, Severe lung scarring from old tuberculosis (especially with thoracoplasty), Morbid obesity (BMI > 40 kg/m^2), Musculoskeletal disorders with respiratory muscle weakness, especially if on home ventilation, Overdose of opioids, benzodiazepines or other respiratory depressant drugs. For patients with prior hypercapnic failure (requiring NIV or intermittent positive pressure ventilation) who do not have an alert card, it is recommended that low concentration oxygen treatment should be started using a 24% Venturi mask at 2–3 L/min (or a 28% Venturi mask at 4 L/min or nasal cannulae at 1–2 L/min if a 24% mask is not available) with an initial target saturation of 88–92% pending urgent blood gas results. Patients with a respiratory rate > 30 breaths/min should have the flow rate from Venturi masks set above the minimum flow rate specified for the Venturi mask packaging to compensate for the patient’s increased inspiratory flow.

Oxygen therapy during pregnancy :
Women who suffer from major trauma, sepsis or acute illness during pregnancy should receive the same oxygen therapy as any other seriously ill patients, with a target oxygen saturation of 94–98%. The same target range should be applied to women with hypoxemia due to acute complications of pregnancy (e.g. collapse related to amniotic fluid embolism, eclampsia or antepartum or postpartum hemorrhage). The use of oxygen during labour is only required when there is evidence of maternal hypoxemia (oxygen saturation < 94%). The use of oxygen supplementation during intrauterine fetal resuscitation during labour was widespread in the past but there is no evidence of benefit [12, 13].

Oxygen therapy in perioperative care and during procedures requiring conscious sedation :
Hyperoxemia is not recommended routinely in the perioperative and postoperative period to reduce the incidence of postoperative nausea and vomiting or postoperative infection [14]. A target saturation of 94–98% is recommended for most surgical patients except those at risk of hypercapnic respiratory failure when a range of 88–92% should be achieved. Pulse oximetry monitoring is recommended for postoperative patients.

Oxygen therapy in palliative care :
Oxygen use in palliative care patients should be restricted to patients with SpO_2 consistently < 90% or patients who report significant relief of breathlessness from oxygen. In non-hypoxemic patients, opioids and non-pharmacological measures should be tried before oxygen.

Potential benefits of hyperoxemia and supplemental Oxygen therapy in non-hypoxemic patients :
Hyperoxemia has been shown to be beneficial in the following clinical situations :

- Carbon monoxide and cyanide poisoning
- Spontaneous pneumothorax
- Some postoperative complications
- Cluster headache

Oxygen admixtures with other gases for medical purposes :

Helium - Oxygen mixtures (Heliox) : Helium has been mixed with oxygen (Heliox), usually in a ratio of 80:20 or 70:30 to treat adults and children with upper and lower airway disease as the reduced gas density can decrease resistance to airflow and therefore reduce the work of breathing in narrowed airways. There is insufficient evidence to support the use of Heliox either as an inhaled gas or as the driving gas for nebulizer therapy in adult patients with acute exacerbations of asthma or AECOPD except as part of randomised clinical trials or in exceptional circumstances [15]. A therapeutic trial of Heliox is reasonable in patients with mechanical upper airway obstruction or postoperative stridor.

Nitrous oxide - Oxygen mixtures (Entonox) : Entonox is a 50:50 mixture of oxygen and nitrous oxide that has been widely used as an inhalational analgesic agent for many years. The use of Entonox gas mixture for analgesia should be avoided if possible in patients at risk of hypercapnic respiratory failure.

Delivering Oxygen to patients who require nebulized bronchodilator therapy :
In patients with acute severe asthma, especially in the pediatric population, oxygen should be used as the driving gas for the nebulised bronchodilators whenever possible at a gas flow rate of 6–8 L/min because these patients are at risk of hypoxemia. However, in adults, oxygen driven nebulization is not usually recommended. This is more so in patients with chronic Type II respiratory failure like COPD. When an oxygen-driven nebuliser is given to patients with COPD there is a risk of hypercapnia and acidosis due to the high FiO^2 which is delivered. Hence this is strongly discouraged. When nebulized bronchodilators are given to hypercapnic patients, they should ideally be given using an electrical compressor or ultrasonic nebuliser and, if necessary, supplementary oxygen should be given concurrently by using nasal cannulae at 1–4 L/min to maintain an oxygen saturation of 88–92%.

Administration and monitoring of Oxygen therapy :

Oxygen prescriptions should include initial mode of delivery, flow rate and interface (e.g., 4 L/min via nasal cannulae). But the most important aspect of the prescription is to give a target range (e.g. 88 – 92 % SpO_2 in patients with chronic respiratory diseases). The effects should be monitored using pulse oximetry, monitoring of respiratory rate and close observation of the patient. Arterial or capillary blood gas analysis should be repeated if clinical progress is not satisfactory and in all cases of hypercapnia and acidosis. All patients should have their oxygen saturation observed for at least 5 min after starting oxygen therapy or for patients who require an increased concentration of oxygen and after oxygen therapy has been decreased or stopped.

Oxygen toxicity :

Oxygen is a powerful drug and should be handled with care. The oxidative stress induced by hyperoxia on pulmonary, cardiovascular, and neurological systems have been demonstrated in several in vitro, animal and human studies. Hyperoxic acute lung injury is the most known form of oxygen-related toxicity but many other organs and systems may be impaired. Sustained hyperoxia exerts detrimental effects at the cellular level, particularly in the mitochondria that usually plays a key role in detoxifying cells from reactive oxygen species (ROS) [16]. For detailed information the reader is advised to refer to an article exclusively dedicated to this topic in this very issue of Lung Bulletin.

Hyperbaric Oxygen therapy :

Hyperbaric oxygen is a treatment in which a patient breathes 100% oxygen intermittently while inside a treatment chamber at a pressure higher than at sea level pressure (i.e. > 1 atm). In certain circumstances, hyperbaric oxygen therapy (HBOT) is the primary treatment modality, whereas in others, it is an adjunct to surgical or pharmacologic interventions [17]. Common indications include air or gas embolism, carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning, gas gangrene, decompression sickness, arterial insufficiencies.

Summary :

In medicine, whenever Oxygen is administered, it is to be considered like a prescribed drug with specific biochemical and physiological actions, an adequate range of effective doses and well-known adverse effects at excessively high doses [18]. The safe use of oxygen includes careful consideration of the appropriate delivery device (mask, cannulae, etc) together with an appropriate source of oxygen and an appropriate oxygen flow rate. An oxygen target range should be prescribed for all hospital patients. A good understanding of the principles of oxygen therapy is essential for judicious use of oxygen as a drug.

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Oxygen Therapy for Acute Respiratory Conditions



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Introduction :

Oxygen is a colorless, odorless and tasteless gas which is essential for the survival of all human beings. It has been in use as a supplemental therapy for many centuries, for patients of respiratory failure, for prevention or treatment of hypoxemia, in concentrations greater than what is found in ambient air. The main objective of Oxygen therapy is to maintain normal oxyhemoglobin saturation to ensure adequate oxygen delivery to all tissues in the body. A decrease in oxygen levels in the body can result in a plethora of adverse effects on different organs of the body. In the respiratory system it can cause increased ventilation, pulmonary vasoconstriction resulting in pulmonary hypertension and respiratory failure. In the cardiovascular system it can result in coronary vasodilation, decreased systemic vascular resistance, increased cardiac output, tachycardia resulting in myocardial ischemia, infarction ischemia or infarction of other critically perfused organs, hypotension and arrhythmias. It can also result in acute tubular necrosis of the kidneys as also confusion, delirium progressing to coma and at times irreversible brain injury and death.

Oxygen therapy should be used only to correct hypoxia or hypoxemia but not to relieve breathlessness without assessing the cause. No study has found the benefit of its use in patients with dyspnea due to non-cardiorespiratory causes like metabolic acidosis, anxiety, or pain. Oxygen therapy also is associated with certain risks and adverse effects and therefore, like any other drug, it should be prescribed rationally, administered appropriately and monitored scientifically and judiciously. The goals of this article are to briefly describe the indications, the various commonly used oxygen delivery devices, administration, monitoring and the risks associated with oxygen therapy in acute care settings.

Indications :

Hypoxemia is defined as presence of an abnormally low oxygen tension in the blood. According to studies published long prior to the COVID-19 pandemic, 34% of ambulance patients during transit, 25% of patients in the emergency room and 15 – 17% of indoor patients are hypoxic and require oxygen at any given point in time [1,2]. COVID-19 pandemic has changed the scenario completely and the use and prescription of oxygen therapy has gone up manifolds, across the globe.

As stated before, the main indication for oxygen therapy is hypoxemia and not merely breathlessness or dyspnea. No study so far, has shown any benefit of using oxygen supplementation to relieve dyspnea without hypoxemia. Hypoxemia frequently occurs in clinical conditions like lower respiratory tract infections, diffuse parenchymal lung diseases or interstitial lung diseases, bronchiectasis, bronchiolitis, upper airway obstruction, severe obstructive airways disorders like bronchial asthma and chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute pulmonary edema, pulmonary vascular diseases like pulmonary embolism and pulmonary hypertension, pleural disorders like pneumothorax and pleural effusion, lung malignancies, neuromuscular disorders and chest wall disorders, cardiac arrest, trauma, carbon monoxide poisoning, and obstetric and perioperative emergencies and common neonatal conditions like birth asphyxia.

Other indications include Pre-oxygenation in induction of anaesthesia and difficult intubation, pre and post-suctioning, Post-operative oxygenation especially in abdominal and chest surgeries, hyperbaric oxygen therapy for decompression

sickness, gas embolism, gas gangrene and carbon monoxide poisoning. An indication in which oxygen may be given without actual hypoxia is in patients with pneumothorax in whom an intercostal tube is not being inserted. It helps accelerating resolution of the pneumothorax.

Delivery Devices for Oxygen therapy :

Oxygen can be delivered to a patient using a wide range of inexpensive and easily available delivery devices depending upon the clinical scenario (Table 1). Oxygen delivery systems can be classified into Hyperbaric and Normobaric. Hyperbaric oxygen therapy involves breathing pure oxygen under high atmospheric pressures ranging from 1.4 to 2.0 atmospheres absolute pressure (atm). Its indications include carbon monoxide poisoning, arterial gas emboli, decompression sickness, necrotising soft tissue infections such as gas gangrene, non-healing radiation injuries, crush injury and compartment syndrome, refractory osteomyelitis etc. Normobaric oxygen is the one which is commonly used in day-to-day medical practice. It can be delivered through variable performance (also called low flow) devices or fixed performance devices (also called high flow) devices (Table 1). The choice of delivery system is based upon the degree of hypoxemia, requirement for consistent and precise oxygen delivery and patient comfort. Depending upon which device is selected for oxygen delivery, an inspired oxygen (FiO_2) starting from 26% till upto 90% (FiO_2 0.26 to 0.90) can be achieved.

Low Flow Delivery Systems	High Flow Delivery Systems
1. Nasal Cannulae **2. Nasal Catheters** **3. Simple Masks** **4. Reservoir Masks *** • *Re-breathing or Partial Re-breathing Masks** • *Non-Rebreathing Mask (NRBM)** 5. **Oxygen Conserving devices** • *Transtracheal catheters* • *Cannulae (Oxymizer, pendant, Oxyspec)* • *Demand devices*	1. **Venturi masks** 2. **Air - Oxygen blenders** **3. High-Flow Nasal Cannula**

Table 1. Oxygen Delivery Systems

** Sometimes, partial rebreathing and non-rebreathing masks are also classified as high-flow devices, depending on whether the device flow exceeds the patient's minute ventilatory requirement.*

Low Flow devices : Using a low flow oxygen delivery device does not mean providing low flow rate or low concentration of oxygen, rather it means that the gas flow is insufficient to meet the entire inspiratory demand of the patient. Low flow systems provide only a fraction of the patient's minute ventilatory requirement as pure oxygen and the remainder by adding another gas, most commonly room air. Thus they mix oxygen with entrained room air, such that the fraction of oxygen in the inspired air (FiO_2) will be dependent on the patient's anatomic reservoir and minute ventilation, of which even small fluctuations can cause significant variations in the amount of entrained air and the resultant air-oxygen ratio, thereby making it difficult to deliver a consistent FiO_2 to the patient. Low flow devices include (Figure 1) :

1. Nasal Cannulae (or nasal prongs) : Consists of two soft prongs attached to a tubing which can deliver upto 1 to 6 litres of O_2 per minute (L/min) with the ability to achieve an FiO_2 of 0.24 to 0.44 (i.e., 20% + 4% per additional litre of flow). FiO_2 decreases as the ventilation rate increases. While using nasal cannulae, neither is the dead space increased nor is there any rebreathing. The nasopharynx acts as a reservoir and if the patient breathes through the mouth, air flow produces a Venturi effect in the posterior pharynx entraining oxygen from the nose. It is light-weight and comfortable and allows the patient to eat, drink or speak without having to remove it. In addition to adults, it can be used in children aged less than 5 years and is ideal for long term oxygen therapy. However, it cannot deliver high flow oxygen, cannot be used in the presence of nasal obstruction and can cause irritation [3].

2. Nasal Catheter : This is a single lumen catheter, which is inserted into the nostrils to be lodged just above the uvula. It is uncomfortable to the patient, must be repositioned every 8 hours and offers no additional advantages over the nasal cannula. If used in the presence of nasal mucosal tear, it could result in surgical emphysema and if inserted too deeply, could result in gastric distension. With oxygen flows of 2 – 3 L/min an FiO_2 of 35 to 40% can be achieved.

3. Transtracheal Catheter : Is a small delicate polythene catheter introduced into the trachea between the 2nd and 3rd rings surgically under local anaesthesia or percutaneously by the Seldinger technique. It bypasses the anatomical dead space of upper airways , effectively using the upper airway as an oxygen reservoir during expiration.

4. Simple Mask : Is an inexpensive, transparent mask with side holes which has a reservoir capacity of 100 – 250 ml. It can deliver upto 5 – 10 litres of O_2 per minute achieving an FiO_2 of 0.35 – 0.55 [15]. Flow rates greater than 8L/min do not increase FiO_2 any further. It may cause patient discomfort if not fitted properly and also slightly increases the dead space. It Interferes with eating, drinking, communication, requires a tight seal to function effectively and there is a high chance of rebreathing if the oxygen flow rates are less than 2 L/min. While the FiO_2 varies with the breathing efforts of the patient, it cannot deliver a very high FiO_2 .

5. Reservoir Masks :

Partial Rebreathing mask : Is the one which, with the help of a reservoir bag is able to deliver an FiO_2 of upto 0.6 to 0.8. As the name suggests, it captures the exhaled gases, thus allowing rebreathing of part the exhaled gases during the initial part of exhalation from the dead spaces. Unlike the non-rebreathing mask, it does not have one-way valves, therefore the expired air mixes with inhaled air. The reservoir bag has a capacity of 1 litre and requires a minimum oxygen flow rate of 8 litres per minute to keep it functional. The bag must be partially inflated to one-third or half of its capacity at all times, to ensure delivery of high FiO_2 with adequate CO_2 evacuation. It interferes with speaking, eating and drinking but is of great use when oxygen supplies are limited or needs to be conserved, like in an acute supply crisis. It is to be used short term for patients who require high levels of oxygen.

Non-Rebreathing mask (NRBM) : Non-rebreathing masks ensure that the inspired gas does not contain any portion of expired gas volume as they are fitted with one way valves which prevent rebreathing of the exhaled air to a large extent. It can deliver higher FiO_2 of 0.95 with oxygen at flow rates of 10 – 15 L/min. A tight seal between the mask and the patient's face ensures good results.

Sometimes, partial rebreathing and non-rebreathing masks are also classified as high-flow devices, depending on whether the device flow exceeds the patient's minute ventilatory requirement.

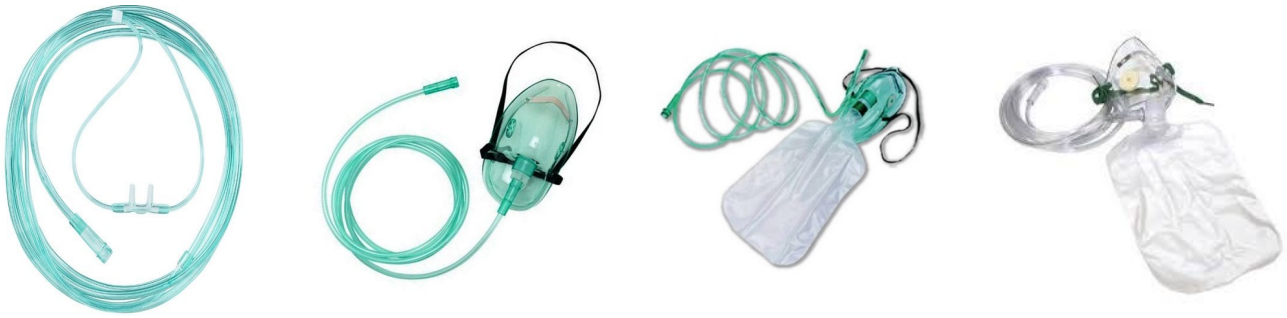

Figure 1. Low-flow Oxygen Delivery Devices (Interfaces)
(Left to right : Nasal Cannulae, Simple Oronasal mask, Re-breathing mask, Non-Rebreathing mask)

Calculation of FiO_2 in low flow systems :

FiO_2 delivered to the patient by a low flow oxygen delivery device is dependent on 3 factors, namely :
1. The patient's tidal volume, respiratory rate and ventilatory pattern – dependent on the patient and illness
2. Size (volume) of the available reservoir
3. Oxygen flow rate (L/min)

Since minor variations in any of the above factors can effect great fluctuations in the FiO_2 delivered, it is of paramount importance to the treating physician to estimate the FiO_2 delivered at any point in time. An example is given below.

Suppose an otherwise young healthy adult male patient without comorbidities, diagnosed with pneumonia who presents with mild respiratory distress (respiratory rate = 20 cycles/min) and hypoxemia of acute onset is prescribed Oxygen at a flow rate of 6 litres/min through nasal cannulae, the FiO_2 is estimated as follows :

- Tidal volume (V_T) = 500 ml (average)
- RR = 20, so each cycle = 3 seconds with the inspiratory time = 1 second and expiratory time = 2 seconds
- 6 Litres of O_2 per minute = 6000 ml/min, therefore 6000 / 60 seconds = 100 ml per second (cannula flow rate)
- 50 ml of 100% O_2 from anatomic reservoir (nasopharyngeal dead space)
- So 100 ml (from cannula) + 50 ml from dead space = 150 ml of the Tidal volume
- The remaining 350 ml (500 ml – 150 ml) fraction of the patient's tidal volume is from room air (which contains 21% oxygen), so the oxygen content of this fraction will be 0.21 x 350 ml = 72 ml of 100% O_2
- Thus, the total volume of Oxygen (in ml) = 150 ml (as calculated before) + 72 ml (from room air) = 222 ml of O_2
- Hence , a Tidal Volume of 500 ml in this patient contains 222 ml of 100% O_2
- Therefore, the FiO_2 provided to this patient is 222 ml per 500 ml = 0.44 (44%)

High Flow devices : High flow oxygen delivery systems are based on the Venturi modification of Bernoulli principle. In High flow systems, the gas flow is sufficient to meet the entire inspiratory demand, they achieve this by incorporating a larger reservoir whose size exceeds the patient's anatomic dead space. The flow usually exceeds 4 times the patients minute volume (at less ratios, entrainment of room air at peak inspiration occurs). They provide consistent and predictable FiO_2 which is unaffected by the patient's ventilatory pattern, in addition to better control of humidity and temperature, and both high as well as low concentrations of Oxygen can be administered with precision. High flow devices include :

1. Venturi Masks : These are used when it becomes necessary to provide consistent and fixed FiO_2 . The masks have holes on either side attached to a colour-coded Venturi device which has markings for the recommended oxygen flow rate to achieve the desired FiO_2. These devices are precise in delivering an FiO_2 ranging from 0.24 to 0.6 . Oxygen flows like a jet through a fixed constrictive orifice past open side ports in the Venturi device. As it flows through the central orifice of the mask its velocity increases, and simultaneously the lateral pressure adjacent and perpendicular to the vector of flow decreases, causes a drop in pressure along the sides of the jet, which draws in room air into the face mask via side ports. (Figure 2). The amount of air entrained which affects the FiO_2 depends on the size of the side ports and the flow of oxygen,
Since both these parameters are constant, the resultant Air : Oxygen entrainment ratio is also constant, delivering a well controlled consistent FiO_2 . Venturi masks are ideal for use for the management of respiratory failure in patients with blunted hypercarbic respiratory drive (e.g. respiratory acidosis), patients with hypoxemia who are dependent on their hypoxic drive to breathe but require controlled increments in FiO_2 and those with hypoxemia who have abnormal ventilatory pattern and whose ventilatory requirements exceed the delivery capabilities of low flow systems.

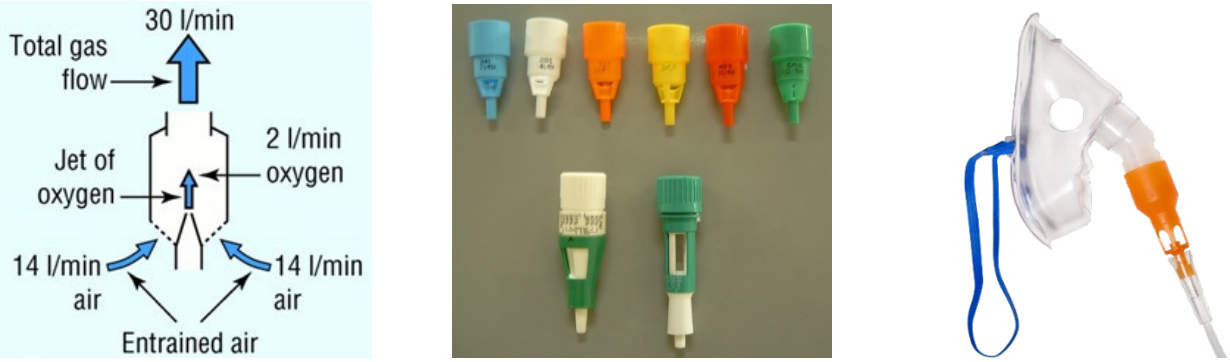

Figure 2. Venturi Masks (Left : Principle of Entrainment, Middle : Different devices, Right : Attached to mask)

2. High flow nasal cannula (HFNC) : High-flow nasal cannula (HFNC) oxygen therapy has gained a lot of attention in the recent past. It has the capacity to achieve FiO_2 ranging from 0.21 to 1.0 (21 to 100%) with flows of upto 60 L/min. It comprises an air-oxygen blender, an active humidifier, a single heated circuit, and a nasal cannula. It has numerous physiological benefits which include reduction of anatomical dead space, PEEP effect, constant fraction of inspired oxygen, and heated humidification [4]. For detailed information the reader may refer to an article exclusively written on this topic in this issue of Lung Bulletin.

3. Air-Oxygen blenders : These are precision metered devices that convert high pressure (50 – 70 p.s.i.) wall sources of compressed air and oxygen to usable predictable flows upto 100 L/min with a constant FiO_2 that ranges between 0.21 – 1.0. However, they are expensive, noisy and require pressure reduction valves and inlet pressure monitors to ensure constant FiO_2 against fluctuations in pressure from the source.

Oxygen Conserving devices : Nearly two-thirds of the respiratory cycle is expiration, whereas alveolar ventilation occurs only during early part of inspiration. This means that most of the oxygen delivered with continuous oxygen flow is wasted as it is lost to the ambient air. Oxygen conserving devices improve the efficiency of O_2 administration by minimizing this wastage and enhancing patient compliance. This can be achieved by several devices such as the transtracheal catheter described earlier, reservoir nasal cannulae (Oxyspec, Oxymizer, pendant, moustache etc) which have a small reservoir that can store O_2 during exhalation and deliver this as a small bolus during the onset of inspiration or electronic devices (Pulsed – fixed volume, or demand – variable volume) which deliver a short bolus of O_2 in early inspiration on triggering of the sensor by negative nasal pressure.

Other devices : Tracheostomy collars, T-tube adapters, helmets and face tents are other devices that can be used for delivering oxygen. Different oxygen delivery devices along with their merits and demerits are summarized in Table 2.

Device	FiO_2 / Flow rate	Merits	Demerits
Nasal Cannulae **or Nasal Prongs (N.P.)**	0.24 @ 1 L/min 0.28 @ 2 L/min 0.32 @ 3 L/min 0.36 @ 4 L/min 0.40 @ 5 L/min 0.44 @ 6 L/min	• Simple • Inexpensive • Well tolerated • Permits eating, drinking talking and patient interaction	• Some oxygen leaks into ambient air • Flows > 6 L/min don't increase FiO_2 above 0.44 • Higher flows may cause drying of mucous membranes, rhinitis and sinusitis
Simple Oxygen Masks	0.4 @ 5-6 L/min 0.5 @ 6-7 L/min 0.6 @ 7-8 L/min	• Comfortably fits on patient's face • Additional reservoir of 100-200ml facilitates higher FiO_2 than nasal cannula	• Requires flows > 5-6 L/min to avoid CO_2 accumulation • Interfere with eating, drinking, talking, sleeping • Less well tolerated than nasal cannula • Increased risk of aspiration • Claustrophobia and Aerophagia • Drying of mucous membranes
Mask with Reservoir Bag	Upto 0.85 for Rebreathing mask and 0.9 to 1.0 for NRBM, depending on the flow rates	• Reservoir of 600-1000 ml facilitates FiO_2 > 0.6	• Similar disadvantages of simple masks (above) • Tight-fitting mask , hence may be more uncomfortable • Requires flows > 5-8 L/min to distend the reservoir bag and avoid CO_2 accumulation
Transtracheal catheter	0.25 to 0.45 depending on the flow rates between 0.5 to 4 L/min	• Small and inconspicuous • Lack of nasal or facial irritation • Patient can eat, sleep, drink, talk comfortably • Reduction in total oxygen usage by upto 50-75% (Most cost effective)	• Risk of infection • Can get blocked by potentially fatal mucus balls or plugs • Small and thin catheters are prone to displacement and breakage
Venturi Masks	0.24 @ 2 L/min 0.28 @ 4 L/min 0.31 @ 6 L/min 0.36 @ 8 L/min 0.40 @ 10 L/min 0.60 @ 15 L/min	• Deliver a precise, fixed and consistent FiO_2 • Ideal for patients with blunted hypercarbic respiratory drive or with hypoxemia who require controlled increments in FiO_2 or have inconsistent breathing patterns	• Expensive • Relatively uncomfortable • Since the entrainment and exhalation ports are small and narrow, can get blocked by moisture or humidification or secretions, causing reduction in FiO_2 and hypercarbia • Back pressure by occluded exhalation ports may decrease entrained room air and thus inadvertently increase FiO_2
High Flow Nasal Cannula (HFNC)	0.21 to 1.0 depending on the flow rates	• Better patient comfort as it provides heated and humidified gas • Decreases work of breathing • Reduces dead space • Improves gas exchange • Improves lung compliance • Provides PEEP • Allows for patient interaction	• Consumes large quantities of oxygen • Unsuitable in patients with structural abnormalities of the upper airway • Potential risk of transmission of airborne infections, including COVID-19 by aerosolization due to humidified gas at high pressure
Air – Oxygen Blenders	0.21 to 1.0	• Convert high pressure wall sources of compressed Air and Oxygen to predictable flows • Precision metered devices that deliver low or high flows at precise FiO_2	• Require pressure reduction valves and inlet pressure monitors to ensure constant FiO_2 against fluctuations in wall pressure • Expensive to set up • Require specialized personnel to install and monitor • Noisy

Table 2. Brief Description, Advantages and Disadvantages of different Oxygen Delivery Devices

Administration and Monitoring of Oxygen therapy in the Acute Care setting [5] :

Like any other drug, oxygen should also be prescribed and documented in the drug chart. While prescribing oxygen, it is important to set a target oxygen saturation range. The level of hypoxemia that is dangerous to an individual varies according to the premorbid state of the patient. Patients with chronic lung diseases are often used to living with low oxygen levels [even upto SaO_2 (arterial oxygen saturation) of 80% or PaO_2 (arterial partial pressure of oxygen) of 45 mm Hg] while other patients with no underlying lung disease may be harmed by short- term exposure to $SaO_2 < 90$ % or $PaO_2 < 60$ mm Hg. As per the evidence available, saturations of 96 – 98% in healthy non-smoking adults and 94% in those over the age of 70 years with underlying lung disease or heart failure, are considered to be normal. Fine-tuning on an individual level may be required depending upon the clinical condition, along with the selection of an appropriate oxygen delivery device and flow rate. Such patients are usually dynamic in their clinical state and abrupt clinical worsening can happen anytime, hence they should be closely monitored using at least pulse oximetry, preferably continuously in the first few hours, or till stabilisation of the clinical condition occurs, following which the oxygen saturation may be monitored every 4 hours. It is also important to monitor, and document in the case records, the usual vital signs which include – pulse rate, respiratory rate, blood pressure, consciousness status and presence of cyanosis as also the oxygen flow rates. An arterial blood gas (ABG) especially in patients with suspected type II respiratory failure, metabolic conditions like diabetic ketoacidosis, renal failure or if there is deterioration in the clinical state of the patient, should be performed immediately and then periodically as and when indicated. it is also important to check the oxygen supply and connections from time to time, as serious incidents due to disconnection or misconnection of oxygen supplies are known to happen. Adequate oxygen backup and appropriate monitoring should be ensured during patient transfers and while patients are waiting for diagnostic/therapeutic procedures or interventions.

Adjustments in oxygen flow rates are to be made based on the clinical response of the patient. Reduce the flow rate if the oxygen saturation is exceeding the set target or increase it if the saturations show a declining trend or if tachycardia, tachypnoea or increased work of breathing is present. If the patient continues to deteriorate then high flow nasal cannula or non-invasive ventilatory (NIV) support or mechanical ventilation (MV), as felt appropriate, may need to be considered depending upon the clinical state.

According to the British Thoracic Society (BTS) guidelines for oxygen use in emergency and healthcare settings, patients requiring oxygen supplementation can be divided into the following groups :

1. **All patients of critical illness requiring high levels of supplemental oxygen :** Patients should be given high concentration of supplemental oxygen upto 15 L/min via non-rebreathing reservoir bag during the initial stages of resuscitation. Early administration of oxygen may reduce organ dysfunction and the length of ICU stay and improve survival. The recommended target range for oxygen saturation in intensive care units is 94 – 98% as research has shown an impaired median-term survival with oxygen saturation < 90%; keeping the target saturation between 94 – 98% also allows a margin of safety (90 – 94%) for any inaccuracies in monitoring and a buffer to allow for variation in the oxygen saturations. Once the patient stabilises, further need for oxygen should be determined using pulse oximetry and ABGs if required. These conditions include situations like cardiac arrest or resuscitation in which highest possible oxygen flows should be given till spontaneous circulation is restored. For emergencies like shock, sepsis, major trauma, drowning, anaphylaxis, major pulmonary haemorrhage, status epilepticus, major head injury, Carbon monoxide poisoning, etc., patient-specific treatment for the underlying condition must also be instituted immediately and early intubation and mechanical ventilation considered if the patient is comatose. Even in a critically ill patient suspected of having type II respiratory failure, initial oxygen saturation targets will be the same till an ABG is available for confirmation.

2. **Serious illness requiring moderate amounts of oxygen if the patient is hypoxic :** The target oxygen saturation should be 94 – 98% and an escalating strategy has been recommended, starting with a nasal cannula at a flow rate of 2 – 6 L/min or a face mask at a flow rate of 5 – 10 L/min, and escalating to a reservoir mask at a flow rate of 10 – 15 L/min if oxygen saturation remains or initially is around 85% . These conditions usually include acute hypoxemia (cause not yet determined), acute bronchial asthma, pneumonia or any other lower respiratory tract infection, lung cancer, acute exacerbation of interstitial lung disease, pleural diseases like pneumothorax and massive pleural effusions, pulmonary embolism, cardiogenic pulmonary oedema, severe anemia and post-operative hypoxemia due to various causes. Attempts to initiate treatment of the underlying cause should be made simultaneously.

3. **Conditions for which patients should be monitored closely but oxygen therapy is not required unless the patient is hypoxemic :** In the presence of myocardial infarction and acute coronary syndromes, if the patient is not hypoxemic,

supplemental oxygen may actually increase the size of infarct. In patients with stroke also, oxygen therapy may be harmful if given to a non-hypoxemic patient with mild to moderate stroke. These patients should ideally be nursed in the upright position and be given oxygen supplementation only after clearing the airways, with minimal possible flows to maintain oxygen saturation between 94 – 98% or 88 – 92% if the risk of type II respiratory failure is present. Patients with hyperventilation or dysfunctional breathing are unlikely to benefit from oxygen supplementation and should undergo evaluation for any organic illness that may be responsible for it. Most poisonings and drug overdoses result in respiratory depression and will benefit with the use of antidotes like naloxone for opiate poisonings. ABG should be obtained and checked to rule out type II respiratory failure. Even in patients with acid aspiration, oxygen supplementation should be avoided as theoretically it can cause harm to such patients. The target oxygen saturations in patients with poisoning with paraquat or bleomycin should be 85 – 88 %, as higher levels can be harmful.

Metabolic and renal disorders can cause breathlessness and don't need oxygen supplementation until hypoxemia sets in. Giving oxygen to a normoxemic pregnant lady can be harmful to the foetus. In the event of major trauma, sepsis or any other acute illness in pregnancy like collapse related to amniotic fluid embolus, eclampsia or antepartum or postpartum hemorrhage, the target saturation should be 94 – 98% unless there is a clinical condition causing risk of type II respiratory failure which would then necessitate a target saturation of 88 – 92%.

Women who are more than 20 weeks pregnant, if they develop hypoxemia with altered sensorium and require respiratory or cardiovascular support or cardiopulmonary resuscitation should ideally be nursed in left lateral tilt or manual uterine displacement (ideally to the left) positions, in order to improve cardiac output and oxygen delivery. Patients with acute and subacute neurological and muscular conditions producing muscle weakness need ventilatory support more often as they usually have type II respiratory failure. For all patients undergoing any procedure in which a reduction of oxygen saturation is commonly seen or expected (SpO_2 < 90% or fall of 4% or more for > 1 minute during the procedure), like flexible bronchoscopy or upper gastrointestinal tract endoscopy, or any other procedure involving conscious sedation, the oxygen saturation should be monitored routinely using at least a pulse oximeter during the procedure, and in the recovery period. The target oxygen saturation range should be 94 – 98%, or 88 – 92% in those at risk of hypercapnic respiratory failure. The same holds true during peri-operative care. Oxygen supplementation during palliative care should only be given if the oxygen saturation is < 90% or to those who feel significantly relieved of their breathlessness with its use. Monitoring of oxygen saturation, in a terminally ill patient, in comfort-focused care, in the last few days of life, is not recommended.

4. **Patients with exacerbation of COPD or other conditions at risk of type II respiratory failure** : Patients with risk of type II (hypercapnic) respiratory failure like bronchiectasis, cystic fibrosis, morbid obesity, neuromuscular or chest wall deformities should be initiated on low flow controlled oxygen therapy, keeping the target levels for oxygen saturation around 88 – 92%. Studies have shown that an SpO_2 saturation > 85% prevents death and since hypercapnic patients thrive on their hypoxic drive, a target range of 88 – 92% is recommended. A 24% Venturi mask at 2 – 3 L/min or a 28% Venturi mask at 4 L/min or a nasal cannula at 1 – 2 L/min may be used for this purpose. ABG should be performed at the earliest and then monitored periodically to guide regarding the need for ventilatory support.

Humidification of Oxygen [5,6] :

Humidification of oxygen is not required when delivering low flow oxygen or delivering it for a short duration. It is of benefit in patients with thick viscous secretions, those requiring prolonged oxygen support or those on tracheostomy or any other artificial airway. However, use of bubble bottles, which allow a stream of oxygen to bubble through water, should be discouraged used as there exists little in their favour and on the contrary they could increase the risk of infections.

Oxygen during Nebulisation [5] :

It is preferred especially in patients with Type II respiratory failure (such as those with acute exacerbations of asthma or COPD) to provide nebulised bronchodilators using ultrasonic or jet nebulisers while concurrently giving oxygen through a nasal cannula targeting a saturation range of 88 – 92%. If oxygen driven nebulisers are used in such patients, the duration of their use should be restricted to not more than 6 minutes, to prevent the build-up of pCO_2. However, in patients with asthma with normal pCO_2 levels, piped oxygen or oxygen cylinders capable of delivering > 6 L/min flow or electronically driven nebulisers may be used for this purpose.

Weaning from, and Discontinuation of Oxygen therapy [5] :

Supplemental oxygen is to be weaned off gradually as sudden cessation can result in rebound hypoxemia which may be to a level even lower than when what was present prior to initiation of oxygen therapy. Once the patient has achieved clinical stability with resolution of the underlying illness and oxygen saturation has remained above the target range for at least

4 – 8 hours, then it is time for the treating physician to consider reducing the patients' oxygen support. It is recommended to reduce the flow rate on the same device that was initiated first and then change the device and continue reducing flow rates as per stability of the patient. Oxygen therapy should be completely stopped once the requirement is down to flow of < 2 L/min (through nasal cannula) and the oxygen saturations are within the target range on two consecutive observations. The patient should continue to be monitored at 5 minutes and then again at the end of 1 hour. If the patient remains stable then oxygen can be discontinued, however the patient should continue to be monitored for saturation and physiology on a regular basis depending upon clinical status. If oxygen saturation drops after cessation of therapy then oxygen should be restarted from the lowest levels that maintained the target saturation previously. However, if higher flows are needed then a thorough clinical review and assessment to establish the cause of desaturation must be made. Some patients after discontinuation of oxygen therapy may experience a transient drop in saturation levels like during minor exertion or due to mucus plugs blocking the airways. Such patients should be provided oxygen on an as per need basis.

Risks associated with Oxygen therapy :

Oxygen therapy like all other therapies is also fraught with certain complications, especially when given in excess. This was recognised by Lavoisier, way back in the 18th century, that excess of oxygen, when given to animals led to a severe illness.

1. Pulmonary Oxygen toxicity : High-flow oxygen is commonly used in critically ill patients [7] especially cardiac arrest survivors [8] without realising that hyperoxemia is linked to worse outcomes than normoxemia. A retrospective observational study of 36,307 consecutive patients who were mechanically ventilated, showed that in-hospital mortality was increased with both abnormally low and abnormally high oxygen levels within the first 24 hours of admission in the ICU [9]. Another observational study of more than 6000 adult post-cardio-pulmonary resuscitation survivors from 120 ICUs, showed that arterial hyperoxemia was independently associated with increased in-hospital mortality when compared with either hypoxemia or normoxemia. A dose-dependent association between supranormal oxygen levels and the risk of in-hospital death has also been noted [10].

Over-oxygenation or supranormal oxygen levels or Hyperoxia is known to produce free oxygen radicals (such as superoxide, activated hydroxyl ions, singlet O_2 and hydrogen peroxide). These cause cellular injury, impair the function of essential intracellular processes, increase permeability of the capillaries with resultant oedema and trigger an inflammatory cascade that ultimately leads to damage to the alveolar-capillary membrane, cell death and capillary and tissue damage resulting in pulmonary fibrosis. Prolonged periods of mechanical ventilation with a high concentration of inspired oxygen (FiO_2) in patients with acute respiratory distress syndrome (ARDS) has been described to result in progressive alveolar damage. Decreased production of surfactant and nitrogen washout in the presence of high concentrations of oxygen resulting in absorption atelectasis may be the other factors responsible. The exact level of FiO_2 and the duration that can result in the damage are unclear. Studies conducted in normal volunteers in the 1950s suggested a threshold of 60%, above which if ventilation was continued for a prolonged period, damage was bound to happen. However, it is extremely difficult to discern this from so many other causes that result in ventilator-induced lung injury (VILI) , and also the newer emerging concept of Patient self-inflicted lung injury (P-SILI). Nevertheless, an attempt should be made to minimise FiO_2 to the least possible level which is sufficient to maintain $PaO_2 > 60$ mm Hg and $SpO_2 > 90\%$ [11].

2. Depression of Ventilation and Worsening of ventilation-perfusion (V/Q/) mismatch : This is known to occur in patients with type II respiratory failure like those diagnosed with COPD, severe asthma, cystic fibrosis, bronchiectasis, chest wall disorders, neuromuscular disease and obesity hypoventilation syndrome (OHS). These patients suffer from chronic carbon-dioxide (CO_2) retention and are dependent on their hypoxic respiratory drive to breathe. Hyperoxia can result in loss of this hypoxic drive resulting in further retention of CO_2 and worsening of their respiratory failure [12]. In addition, oxygen is known to possess a dilatatory effect on the pulmonary arterial system but a vasoconstrictive effect on the systemic circulation. Therefore, when given in excess, it may paradoxically worsen the ventilation-perfusion mismatch and hypercapnia in such patients.

The first randomised trial of controlled oxygen therapy in patients with acute exacerbations of COPD confirmed that the mortality was higher in high oxygen concentration group (9%) as compared to the controlled oxygen group (4%) with target oxygen saturations of 88 – 92% [13]. Similarly, a randomised placebo-controlled trial in patients with obesity hypoventilation syndrome showed that breathing 100% oxygen worsened hypercapnia in stable patients [14].

3. Fire hazard : Oxygen, being a flammable gas, is combustible. It can be both a saviour and a killer. It is one of the elements of the fire triangle (heat, fuel and oxygen), and hence carries the potential to perpetuate fires and injure or kill a patient. Cigarette smoking while on oxygen therapy is the most common cause of fire, which leads to thermal or burn injuries or even death of patients. Another common event that could lead to fire in the airways is use of heat generating devices such as laser or cautery during bronchoscopy with high flows of oxygen being administered during the procedure. It is recommended to keep the FiO_2 to the least possible levels and certainly less than 40% at all times during such procedures [17].

4. Absorption atelectasis : Since oxygen is rapidly absorbed from the alveoli, therefore, when given in pure form it results in the collapse of the dependent portions of the lungs. Patients when given oxygen at high FiO_2 during mechanical ventilation or during induction and maintenance of anaesthesia, are prone to developing atelectasis and hence a shunt. Therefore it is recommended to either use low FiO_2 or use positive end-expiratory pressure (PEEP) to prevent atelectasis [18].

5. Retinopathy of prematurity (ROP) : The association between hyperoxia and retrolental fibroplasia or what is now called retinopathy of prematurity was recognised more than 70 years back. It is usually known to occur in low birth weight and very premature infants. It involves the growth of abnormal and fragile blood vessels throughout the retina, which can leak, causing scar formation and retinal detachment thereby leading to visual impairment and blindness. With newer technology and methods available to monitor the oxygen levels of infants, it is strongly recommended to target PaO_2 levels not more than 50 – 80 mm Hg in neonates or infants receiving oxygen [19].

6. Bronchopulmonary dysplasia (BPD) : Bronchopulmonary dysplasia in newborns is attributed to hyperoxia or mechanical ventilation in the very low birth weight (usually less than 2 pounds) premature neonates (born > 10 weeks before their due dates). Free oxygen radicals, especially superoxide, result in fibrosis and destruction of acinar structures, resulting in scarring and emphysematous changes. Infections that occur before or shortly after birth also can contribute to BPD.

7. Bacterial contamination : Microbial contamination associated with certain nebulization and humidification systems is a possible hazard [12]. Inhaling dry oxygen can result in mucosal dryness and irritation in the respiratory tract. Hence humidifiers are used to add moisture to the gas. But these humidifiers, especially the reusable ones often get colonised with various bacteria and fungi and hence become a source of nosocomial infections. Small water particles, mixed with oxygen provide an excellent vehicle for the transmission of microorganisms into the lower respiratory tract [20].

8. Paraquat poisoning and Bleomycin therapy : While Oxygen therapy is contra-indicated in patients of paraquat poisoning [21], it should be given carefully to those receiving bleomycin or have previously used bleomycin as it may potentiate bleomycin-induced lung injury [22].

9. Ischemia - Reperfusion injury : Hyperoxemia is known to cause coronary vasoconstriction, hence, if oxygen is administered in excess at the time of acute myocardial infarction it may increase the size of and worsen the infarct, resulting in increased mortality [23] . The Air versus Oxygen in ST-Segment–Elevation Myocardial Infarction (AVOID) study, was a multicentre, prospective, randomized, controlled trial comparing oxygen (8 L/min) with no supplemental oxygen in patients with ST-elevation–myocardial infarction (STEMI). It revealed that patients in the oxygen group had a significant increase in mean peak creatine kinase levels (1948 versus 1543 U/L), increased rate of recurrent myocardial infarction (5.5% versus 0.9%; p = 0.006), increased frequency of cardiac arrhythmia (40.4% versus 31.4%; p = 0.05) and at 6 months, an increase in myocardial infarct size on cardiac magnetic resonance imaging (cardiac MRI) (n=139; 20.3 versus 13.1 g; p = 0.04) [24]. In a similar fashion, high oxygen concentration may result in cerebral vasoconstriction resulting in increased infarcted area and increased mortality [25].

Case Report :

A 55 years old, obese female with body mass index 45, a known case of diabetes, hypertension and hypothyroidism presented to the emergency department (E.D.) with complaints of laboured breathing and decreased sensorium for 2 days. On examination she was dull but responding to verbal commands. Signs of meningism were absent. Her pulse rate was 120/minute, blood pressure was 120/72 mm Hg, temperature was 98.4 °F, and SpO_2 was 72% on room air. Her random blood sugar was 150 mg%. She had mild cyanosis, mild pedal edema and no wheeze. Oxygen was administered immediately in the E.D. and the SpO_2 improved to 98%. However, she became more dull and started to respond only to deep painful stimuli. At this stage, an arterial blood gas (ABG) sample was drawn which showed evidence of respiratory acidosis (pH = 7.2, pCO_2 = 72 mmHg, PaO_2 = 110 mmHg and HCO_3 = 27 meq/L). Patient was then provided non-invasive ventilatory (NIV) support and controlled oxygen therapy to target her SpO_2 around a range of 88 to 92%. An ECG was done which showed evidence of *p* pulmonale with right heart strain pattern. Her cardiac enzyme levels were normal. Two-dimensional echocardiography (2D-ECHO) revealed dilated right atrium and ventricle with increased pulmonary arterial pressures and tricuspid regurgitation. After verifying that the creatinine levels were normal, a computerized tomographic pulmonary angiography (CTPA) was performed, which showed normal lung parenchyma and no evidence of pulmonary embolism. She was diagnosed to be a case of obesity hypoventilation syndrome (OHS) with pulmonary hypertension, currently in decompensation and was continued on NIV support with controlled oxygen therapy. 12 hours later, she became alert and a repeat ABG was performed which showed improvement over the previous one (pH = 7.31, pCO_2 = 62 mmHg, PaO_2 = 58 mmHg and HCO_3 = 30 meq/L). This case highlights the perils of overzealous oxygen supplementation in patients with type II respiratory failure which initially led to deterioration of her clinical condition.

Summary :

Oxygen therapy like any other therapy should be used judiciously. While oxygen is life saving in most situations, it can also exert deleterious effects in certain other situations. Selection of the appropriate delivery device depending upon the clinical condition and nature of illness will ensure a successful outcome. The recommended target oxygen saturation in a patient with no risk of hypercapnia is 94 to 98%, but in a patient at risk is 88 to 92%. Patients need to be monitored carefully while on oxygen therapy and weaned off gradually, once they clinically stabilize and their oxygen requirement falls. However, a drop in oxygen saturation levels or an increasing oxygen demand indicate deterioration and necessitate urgent medical re-evaluation of the patient.

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Oxygen Therapy in Chronic Respiratory Diseases

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Introduction :

Since more than a century, Oxygen has been acknowledged as a "therapeutic agent" for the treatment of hypoxia, however, it still has to be accepted as a "pharmacological agent", though its indication, dose, mechanisms of action, method of delivery and duration of therapy are all in concurrence with those of other pharmacological drugs. Oxygen remains the mainstay in management of respiratory failure to correct hypoxia, both for Acute as well as Chronic lung diseases. Chronic Obstructive Pulmonary Disease (COPD) is a prototype of chronic respiratory diseases (CRDs) for which treatment has been prescribed with oxygen therapy; both in the acute setting for exacerbations (short-term oxygen therapy) in the hospital, as well as in the domiciliary setting at home (long-term oxygen therapy or LTOT) since a long time. COPD being a progressive disease, in its advanced stages hypoxia sets in necessitating the use of domiciliary oxygen. This being one the most common chronic respiratory diseases, has been studied richly to evaluate when, where and how to use oxygen in the management of COPD. Affirmative results of Long-term home oxygen trials conducted in patients with COPD since the last four decades led the clinicians to use home oxygen in patients of COPD with chronic respiratory failure. However, the burden of chronic respiratory diseases leading to respiratory failure has significantly increased in the last two decades in India as well, expanding the need for oxygen therapy. Patients with chronic respiratory failure due to other CRDs like Interstitial Lung Disease (ILD), Pulmonary Arterial Hypertension (PAH), Chest Wall and Muscle Disorders (CMD), etc. are also increasingly being prescribed long term oxygen despite lack of similar evidence of its beneficial outcomes as in COPD. Since the pathophysiology of hypoxia is different in various non-COPD chronic lung diseases, it is prudent to understand the mechanisms as well as expected outcomes of oxygen therapy in such diseases in order to prescribe an appropriate dose, duration and mode of its delivery, as well as evolve appropriate indications for the future. Despite evidence favouring the beneficial effects of oxygen, its utilization in clinical practice is limited even in developed nations. The objective of this review is to focus on use of oxygen in chronic respiratory diseases which requires 'Home Oxygen Therapy' and it will be discussed in detail.

Case Report :

A 67-year-old male current smoker with a body-mass index of 23 and smoking index of 34 packs/years has been having breathlessness on exertion with cough and expectoration for a total duration of 10 years. He was diagnosed with COPD and had episodic worsening's during winter seasons which was managed with a short course of antibiotics along with oral corticosteroids on an out-patient basis. He was hospitalized twice over the previous twelve months for acute exacerbations; the first lasting for five days in the respiratory ward and the second for seven days in the intensive care unit in the previous month. The patient is currently on treatment with triple therapy through a metered-dose inhaler with spacer and has never used oxygen at home. His breathlessness persists and currently is graded as mMRC III.

Examination revealed normal vitals with oxygen saturation (SpO_2) at room air being 92% which desaturated to 89% on walking into the out-patient clinic, mild pallor, pitting pedal edema and fine tremors without cyanosis or clubbing. Chest appeared hyperinflated with scattered rhonchi and crackles in both lungs. Per abdominal and cardiovascular examination did not reveal any abnormality. The patient exhibited some cognitive issues and forgetfulness, apart from these, CNS examination was otherwise normal. The chest radiograph revealed mild hyperinflation of the lung fields bilaterally. The patient and his son enquired whether they should give oxygen at home.

(All Answers to the Questions that follow are provided in the Key at the end of this article)

Question 1 . Is this patient a suitable candidate for home oxygen therapy? Why ?

Answer Options :

A. Not at present.
B. Yes, for exertional desaturation as short-burst oxygen therapy (SBOT)
C. Yes, for long-term home oxygen therapy
D. Yes, for short term till recovery from acute exacerbation of COPD (AECOPD)

The patient underwent pulmonary function testing (PFT) and six-minute walk test (6MWT) for assessment, after a month, with the results as follows :

PFT

PFT Parameter	Predicted	Pre-bronchodilator	Post-bronchodilator	Change
FVC	3.09	1.82 L (59% predicted)	1.84 L (60% predicted)	1%
FEV_1	2.48	1.04 L (42%predicted)	1.10 L (44% predicted)	6% (60ml)
FEV_1/FVC	-	57.3%	59.9%	5%
DL_{CO}	21.92	6.98 (36% predicted)	-	-

6MWT

Distance covered (m)	Baseline SpO_2 (%)	Minimum SpO_2 (%)	End of Test SpO_2 (%)	Recovery time (min)
146	92	87	88	2

Electrocardiogram showed no evidence of 'p pulmonale'.

Question 2. Which of the following is indicative of the need for LTOT in this patient ?

Answer Options :

A. FEV_1 < 50% of predicted
B. DL_{CO} < 40% of predicted
C. 6MWT distance < 150 meters
D. Minimum saturation on exercise < 88%
E. None of the above

Question 3. For LTOT, this patient fulfills which of the following criteria ?

Answer Options :

A. Baseline SpO_2 < 94%
B. Baseline SpO_2 < 94% with anemia
C. Baseline SpO_2 < 92% with exercise desaturation of 4%
D. Baseline SpO_2 < 92% with breathlessness
E. Criteria not met and needs review later

The patient was reviewed two months later and his baseline SpO_2 had improved to 94%. A two-dimensional echocardiography (2-D ECHO) done at this point showed evidence of mild pulmonary hypertension. He underwent a polysomnography which showed nocturnal hypoxemia.

Question 4. Does this patient fulfill the criteria for LTOT ?

Answer Options :

A. Yes
B. No
C. Needs arterial blood gas (ABG) to confirm
D. Needs oxygen administration during sleep

Follow-Up : The patient underwent an ABG on room air, which revealed pH 7.35, PO_2 58 mmHg, PCO_2 48 mmHg, Hematocrit 50%.

Question 5. All of the following statements are correct regarding prescribing LTOT to this patient, EXCEPT :

Answer Options :

A. PaO_2 criteria is met
B. $PaCO_2$ shows hypercapnia, but the patient can still be given LTOT
C. pH is acidotic hence LTOT is contraindicated
D. Hematocrit criteria is not met

Counselling with discussion about smoking cessation was done with the patient in the presence of the caregiver, following which he agreed to use nicotine-replacement therapy (NRT) to help him quit smoking, following which he returned two months later and confirmed that he has quit smoking.

The patient was prescribed LTOT.

Question 6. Which is TRUE of the following ?

Answer Options :

A. Liquid oxygen is compact and ideal for home oxygen therapy
B. Oxygen concentrator is good if the patient requires Oxygen at a flow rate < 6 L /min
C. To start with, an Oxygen cylinder can be prescribed initially for home use and later on substituted with another device
D. Patient needs an oxygen conserving device during exercise only initially.

Question 7. The recommended oxygen delivery device (interface) for this patient would be :

Answer Options :

A. Nasal cannula
B. Nasal Mask
C. Trans-tracheal oxygen
D. Venturi mask

Question 8. Routine follow-up of patients on LTOT at home should include ALL, EXCEPT :

Answer Options :

A. Safety issues
B. Urinary cotinine
C. Exhaled CO
D. Nasal bleeds
E. Repeat ABG

Question 9. Follow-up visit after three months in the clinic should be with the following objectives, EXCEPT :

Answer Options :

A. Need for withdrawal of LTOT
B. Compliance check for LTOT
C. Readjusting flow rates of oxygen
D. Assessments for hypercapnia
E. Re-assessment sleep study

At three months, a repeat ABG on room air, after withholding oxygen for 30 minutes shows : pH 7.33, PaO_2 58 mmHg, PCO_2 51 mmHg

Question 10. What should be the next step ?

Answer Options :

A. Withdraw LTOT
B. Consider non-invasive ventilation (NIV)
C. Consider NIV with LTOT
D. Reassess at 12 months

Evolution of Oxygen Therapy and its Application from the Clinician's Perspective :

Oxygen prescription in clinical practice needs the documentation of hypoxia, which in the last century required Arterial Blood Gas (ABG) analysis, requiring the expertise of arterial puncture as well as expansive equipment to measure partial pressure of oxygen in blood (pO_2), both being possible in hospital settings only. The advent of compact finger pulse oximeters as well as portable oxygen delivery systems has helped domiciliary oxygen therapy to become easy and widely available. Prescribing practices too changed from conventional COPD cases to a much broader group of patients with chronic respiratory diseases with resting and / or exertional hypoxemia. Although home oxygen does correct hypoxemia, it comes at the cost of limitation of activity as well as impact on the psychosocial health of the patient, thereby instigating non-compliance. The cost of long-term home oxygen therapy is also a deterrent in our country where the major burden of chronic respiratory diseases is borne by poor and rural patients.

COPD and ILD together form the most common indications for domiciliary oxygen use all across the world. Though breathlessness and exercise limitation are common to both diseases, their etiopathogenesis and natural history are widely different. Recommendations for Long Term Oxygen Therapy (LTOT) has clear evidence based guidelines/recommendations in COPD and are often extrapolated to other chronic respiratory diseases with similar oxygenation status. Besides resting hypoxia, patients with chronic respiratory disease might suffer from exercise or sleep-induced hypoxia, where therapeutic oxygen targets and strategies are different and mostly based on limited research. Hence, there exists an unmet need to understand and optimize home oxygen use in our country while maximizing benefit, availability and compliance to deserving patients.

Terminologies used in Oxygen Therapy :

Various terminologies are used interchangeably to describe use of oxygen by patients at home but need clarification as provided by ATS guidelines in 2020 (Table 1). Home oxygen is using oxygen at home for any indication and is synonymous with Domiciliary Oxygen Therapy (DOT) and includes LTOT as well as short term use of oxygen at home (e.g. during exercise, nocturnal, palliative, etc.) but excludes its use in acute care in the hospital or emergency settings.

Long Term Oxygen Therapy	Oxygen prescribed for minimum use for 15 hours /day in patients with chronic hypoxia and is prescribed for rest of life of the patient
Nocturnal Oxygen Therapy	Oxygen given during sleep only
Palliative Oxygen Therapy	Oxygen used to relieve dyspnea without hypoxia and can be used continuously, nocturnally or during brief activities
Short Term Oxygen Therapy	Oxygen provided temporarily to treat hypoxia which is expected to improve over days e.g. recovering from Acute Exacerbations of COPD
Short Burst Oxygen Therapy	Transient and intermittent oxygen delivered during or after exercise / strenuous activity (bathing, etc.) induced hypoxia but with no resting hypoxemia

Table 1. Terminologies used for various forms of Home Oxygen Therapy

Pathogenesis and Consequences of Hypoxemia :

Hypoxemia immediately effects ventilation and peripheral circulation by increasing both to compensate for fall in oxygenation when PaO_2 becomes < 55 mm Hg. As a consequence there is drop in arterial carbon dioxide tension ($PaCO_2$) with compensatory increase in heart rate and cardiac output to increase oxygen delivery to tissues. Also, ventilation-perfusion mismatch is improved by regional pulmonary vasoconstriction secondary to alveolar hypoxia to further meet the goal of improving oxygen levels. Oxygen carrying capacity of blood is also increased gradually by hypoxic stimulation of erythropoietin release and increasing the number of circulating red blood cells. Hence, it is prudent to consider resting hypoxemia when arterial oxygen tension of $\leq$ 55 mmHg or between 56 – 59 mmHg with evidence of end-organ damage (Polycythemia, Pulmonary Hypertension or Congestive Heart Failure, all being consequences of long standing hypoxemia). Further, decreased availability of oxygen to cells and tissues shifts energy production from aerobic to anaerobic metabolism with accumulation of lactate. Consequently, patients may develop poor decision making with deficit in cognitive and motor functions. Unconsciousness occurs with severe hypoxemia. Some nonspecific symptoms of hypoxemia may manifest as breathlessness, palpitations or chest pain (Figure 1).

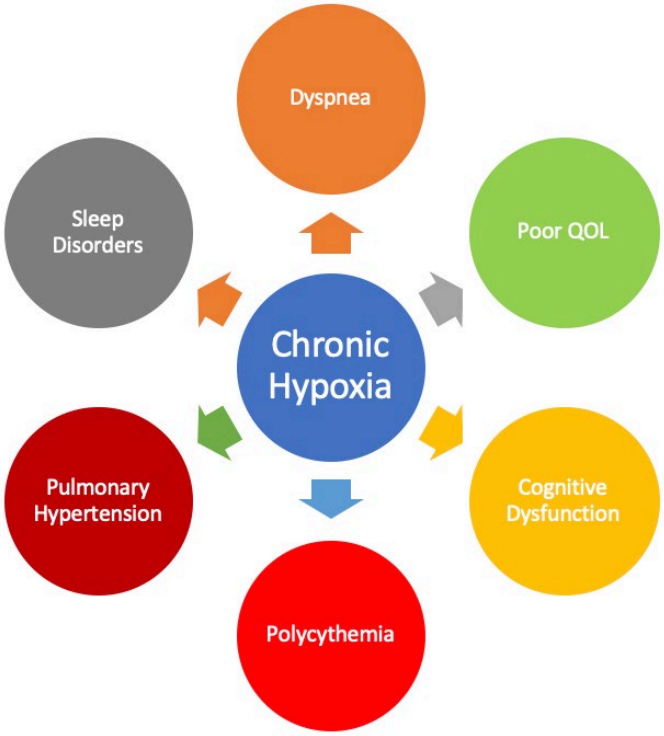

Figure 1 . Clinical Consequences of Chronic Hypoxia

Severe Hypoxemia	$SpO_2 \leq 88\%$ or PaO_2 of $\leq$ 55 mm Hg on room air
Moderate Hypoxemia	SpO_2 89–93% or PaO_2 of 56–65 mm Hg on room air
Nocturnal Hypoxemia	$SpO_2 < 90\%$ for > 12 minutes of monitored sleep time
Exercise Hypoxemia	$SpO_2 \leq 88\%$ during exercise

Table 2. Definitions of Hypoxemia
(used in clinical trials to investigate effects of oxygen supplementation in these conditions)

Physiological Effects of Oxygen :

Pulmonary Circulation :

Cor Pulmonale is the consequence of chronic hypoxemia with subsequent mortality varying from 30 – 100%. Improving survival has always been a hard end point of clinical trials investigating the beneficial effects of long term domiciliary oxygen therapy. Results of earlier trials showed beneficial effects in patients of COPD with severe hypoxemia but similar results are lacking in patients with mild to moderate hypoxemia. However, favorable outcomes in patients of COPD with severe hypoxemia have not shown significant changes in pulmonary hemodynamics at rest or exercise. This is contradictory to acute changes observed in pulmonary arterial (PA) pressures on administration of oxygen in hypoxic persons, however, still patients of chronic respiratory diseases with pulmonary hypertension are the candidates most likely to benefit from long term oxygen therapy.

Hematocrit :

Hematocrit in any individual with hypoxia is the outcome of balance between erythropoietin stimulation by low oxygen versus suppression by ongoing inhibitory factors (e.g. inflammation, infection or other co-morbid illnesses like coronary artery disease, diabetes mellitus, obesity, etc.). Although a reduction in hematocrit has been reported in some trials using oxygen, this remains mostly unclear. On the contrary, a low hematocrit in patients with hypoxemia at the beginning of long term oxygen therapy has been linked to poor survival.

Cognitive Function :

Cognitive dysfunction is multifactorial in patients with chronic respiratory diseases with hypoxemia. COPD patients are 2.4 times more likely to develop cognitive abnormalities and those with baseline $SpO_2 \leq 88\%$ are 5.5 times more likely to develop these neural issues. LTOT has been shown to improve alertness and coordination with increase in cerebral blood flow and reduces this risk (Odds ratio 0.14, 95% CI 0.07-0.27, $p < 0.001$)

Lung Function (FEV_1) :

No evidence exists to demonstrate that LTOT either improves/stabilizes or decreases the decline in lung function associated with chronic respiratory diseases with hypoxia, like COPD. However, negative influences of comorbidities with chronic respiratory diseases like cor pulmonale, heart failure, stroke, etc. are attenuated by the use of oxygen, though prevalence of these comorbidities is more likely in patients with severely affected lung functions but a differential response to such patients is not reported.

Dyspnea :

Breathlessness at rest and exercise are two different aspects of chronic lung diseases and the results of supplementation oxygen are less clear on reduction of dyspnea at rest , however, where oxygen is given to treat dyspnea on ambulation, there are multiple trials showing beneficial effects showing less grades of breathlessness if exercise is done with oxygen therefore increasing effort tolerance in patients if CRDs. Multiple mechanisms are likely to contribute to this, however, the effects of supplemental oxygen on improving dyspnea in non-hypoxic patients is not clear.

Quality of Life :

Using long term oxygen in chronic hypoxic respiratory patients to improve quality of life has conflicting results and is mostly compounded by hindrances related to the oxygen delivery device (e.g. portability of equipment and its impact on patient mobility). Ambulatory oxygen has been shown to improve the quality of life in COPD but it was neither related to either the severity or chronicity of hypoxia nor predicted on the correction of hypoxia. However, any improvement in quality of life in patients of chronic respiratory diseases with hypoxia is worth considering as hardly any alternative therapeutic options are available.

Exercise Tolerance :

Exercise intolerance is common feature of chronic respiratory diseases and is linked to hypoxemia as a “cause-effect” though four elements : respiratory, cardiac, muscular and metabolic , which are required to coordinate in performing exercise. Conventionally, mismatch of ventilatory capacity versus ventilatory demand gives rise to the sensation of respiratory discomfort leading to development of symptom of dyspnea on exercise, initially during exertion and which later on progresses to dyspnea at rest.

Supplemental oxygen improves exercise tolerance when given to such patients who are hypoxic at rest or develop hypoxia on exertion. Patients who are hypoxic at rest have shown improvement in exercise time, distance travelled, as well as level of dyspnea on oxygen supplementation during exercise. There are multiple mechanisms likely to contribute this beneficial effect of oxygen on exercise performance, predominantly by decreasing the sensation of dyspnea by tilting the balance in favor of reduced minute ventilation (mainly due to reduction in tidal volume while breathing oxygen versus room air) with decrease in disturbing signal inputs to brain. However, the exact magnitude of this positive effect is variable.

Exercise induced hypoxia (EIH) is a feature of chronic respiratory diseases, with COPD and ILD’s being the two main causes. This signifies normoxia at rest with hypoxemia setting on physical activity. It has been shown that oxygen administration during exercise enhances performance in healthy patients as well as those with COPD and is likely due to be multifactorial too. Exertional desaturation has been linked to lower diffusion capacity (DL_{CO}) and is reported in COPD patients with emphysema, ILD’s and pulmonary hypertension. However, prescribing supplemental oxygen in patients with only EIH has not been shown to improve survival though EIH has been shown to decrease survival in some studies in COPD. Also, predicting EIH in chronic respiratory diseases is a challenge as it depends upon the pathophysiology of the underlying disease. In COPD, resting oxygen saturation, lung function, diffusion capacity and cut offs are for negative results e.g. no patient exhibited EIH with $DL_{CO} > 55\%$ of predicted.

The six minute walk test (6MWT) is generally used to demonstrate EIH but the shuttle walk test (SWT) performs significantly better in predicting EIH as drop in oxygenation is more in the paced walk test. Similarly lower limb cycling in COPD exhibits EIH in 75% of patients with COPD and $FEV_1 < 35\%$. $DL_{CO} < 50\%$ with baseline $SpO_2 < 95\%$ also predicts EIH. However, no single parameter in lung function tests or the 6MWT can predict eligibility for LTOT with a high degree of sensitivity and specificity.

Sleep :

Sleep induces drop in ventilation with a slight fall in oxygen levels and increase in CO_2 but the effects are more pronounced in patients with baseline marginal hypoxia and during rapid eye movement (REM) sleep. Oxygen therapy during sleep has been shown to improve the quality of sleep and decrease cardiac rhythm abnormalities in patients with nocturnal hypoxemia (NH) which has been reported in about 25% of COPD cases without daytime hypoxia. NH has been linked to persistent PH during the daytime and supplementing oxygen in these patients has been shown to decrease PA pressures. However, evidence to support nocturnal oxygen in NH in COPD is not so forthcoming. It is important to realize that when sleep apnea is associated with chronic lung diseases, the effect on nocturnal desaturations is more profound and treatment may merit combined use of positive airway pressure therapy (PAP) and oxygen, since this overlap is common (~ 30%), a high index of suspicion is warranted.

Harmful Effects of Oxygen :

Uncontrolled and Excessive Oxygen therapy can adversely affect lung parenchyma in diseased lungs by potentially causing oxidant injury via the release of free oxygen radicles which was first reported in patients with IPF. However, in a later multivariate analysis, oxygen therapy was not shown to be independently associated with shortened survival in these patients and only indicated disease severity.

An increase in carbon dioxide (CO_2) levels while breathing oxygen is possible in patients with chronic hypercapnia and is due to blunting of the hypoxic respiratory drive as in these patients main respiratory input is the hypoxia itself, giving more oxygen can inhibit this drive. Also giving oxygen to such patients can aggravate hypoxia by worsening the ventilation-perfusion (V/Q) mismatch secondary to relieving of hypoxic pulmonary vasoconstriction which was compensatory to poor ventilation in these patients. Typically patients with COPD, Obesity-hypoventilation syndrome and advanced respiratory diseases with chronic respiratory failure are prone to this effect of oxygen administration. Hence, caution with monitoring of blood gases is required while initiating oxygen therapy in these cases.

Indications of Oxygen Therapy in Chronic Lung Diseases :

1. Chronic Obstructive Pulmonary Disease (COPD) :

This is the most common chronic respiratory disease where domiciliary oxygen is advised either long term oxygen therapy (LTOT) indicated for resting severe hypoxia or ambulatory short bursts to correct exercise induced hypoxemia or nocturnal oxygen therapy to correct sleep hypoxia. Role of LTOT in COPD in research has reported improved survival in patients with chronic hypoxemia where continuous oxygen therapy (24 hours) improved survival by 1.92 times as compared to nocturnal oxygen (12 hours) in the NOTT trial and another randomized controlled trial, the Medical Research Council (MRC) trial, where patients who were given oxygen for at least 15 hours per day reported improved survival as compared with patients without oxygen . Other reported benefits of Oxygen in COPD are improving :

1. *Pulmonary artery pressures at 6 months on starting LTOT*
2. *Sleep quality and quantity*
3. *Quality of life*
4. *Neuropsychological functions*

But no decrease in either the number of COPD exacerbations or related hospitalizations on LTOT has been reported. LTOT trials did not find any difference in outcomes whether baseline carbon dioxide was normal or high and no oxygen toxicity was reported over 5 years of LTOT in hypercapnic patients. On the contrary, a better survival benefit was reported in hypercapnic patients who also fulfilled hypoxia criteria for LTOT. Patients with baseline hypercapnia should undergo titration for oxygen requirement with ABG's to evaluate degree of hypercapnia and respiratory acidosis. If PCO_2 rises by more than 7.5 mmHg on two occasions while administering LTOT, its recommended to add NIV support during sleep also.

Potential ill effects e.g. nose bleeds, tripping on the equipment, fires, etc. are very rare.

Indications : Stable COPD patients with resting hypoxia, defined as :

1. $PaO_2 \leq 55$ mmHg or
2. Resting $PaO_2 \leq 60$ mmHg with evidence of peripheral edema (secondary to cor pulmonale), hematocrit >55 or pulmonary hypertension
3. Resting hypercapnia along with oxygenation criteria 1 or 2

It is recommended by GOLD to initiate LTOT on SpO_2 though related trials did not use oxygen saturation as inclusion criteria. Equivalence between oxygen saturation versus arterial blood gas tensions cannot be universalized due to characteristics of the oxygen-hemoglobin dissociation curve and external influences which can alter it. Also target saturation required on using oxygen cannot be confirmed with repeated ABG's.

Recommendations :

- LTOT is recommended for at least 15 hours a day with target oxygen saturation to achieve $SpO_2 \geq 90\%$.
- Revaluation of patients started on LTOT needs to be done early within one month and later at 3-4 months and besides trouble shooting of issues, it is also recommended to assess the efficacy.
- Since LTOT trials did not show survival benefit in cases of COPD with moderate hypoxia at rest or on exercise, they need to be evaluated on a case-to-case basis.

2. Interstitial Lung Diseases (ILD) :

Chronic hypoxia is seen in most cases with ILD, the prototype being IPF. The ILD India Registry showed that nearly 50% of ILD cases at diagnosis were already hypoxic and 20% of these were already on domiciliary oxygen therapy. Pulmonary hypertension is also a common complication, necessitating the supplementation of oxygen. There are no clinical trials in ILD patients regarding the efficacy of LTOT and the results of COPD related research are often extrapolated to justify oxygen therapy in hypoxic ILD patients. It is assumed that LTOT may improve survival and prevent complications (e.g. worsening pulmonary hypertension). Other benefits of LTOT expected in these patients include relief of breathlessness, improved quality of life and disability limitation is expected. Practices to prescribe oxygen in ILD's are institution or center-based. 24-hour ambulatory oxygen saturation studies in ILD patients to estimate 'hypoxic burden' is one way to advise home oxygen to them.

Prescribing ambulatory oxygen in ILD patients who develop hypoxemia on exertion led to improvement in health-related quality of life (HRQoL) as well as exercise capacity in some studies and is recommended. However, oxygen equipment related difficulties as well as the emotional turmoil of developing oxygen dependence are challenges that limit its use.

Indications : LTOT is advised in ILD when baseline PaO_2 is $\leq$ 55 mmHg OR with $PaO_2 \leq 60$ mmHg with peripheral edema, polycythemia or pulmonary hypertension, and also recommended in patients with severe breathlessness with severe exertional hypoxia (and sometimes with moderate hypoxia) in predefined settings.

Other chronic respiratory conditions where LTOT or ambulatory oxygen for exercise induced hypoxia are :

- Cystic Fibrosis (CF) and Non-CF bronchiectasis
- Neuromuscular and Chest wall diseases
- Obesity Hypoventilation and Overlap syndromes
- Pulmonary Hypertension

However, research is unavailable in these conditions and again it is the data obtained from COPD trials that is used as a pretext for LTOT being likely to improve survival and quality of life (QoL) and prevent complications. Neuromuscular diseases (NMD) and obesity related chronic hypoxemia are indications for non-invasive ventilation (NIV) but additional oxygen is required in many for correcting residual hypoxia on PAP (positive airway pressure) devices.

Correction of nocturnal hypoxemia alone in patients with COPD, ILD, Neuromuscular diseases or Obesity – hypoventilation syndrome (OHS) by using nocturnal oxygen therapy (NOT) has either not been either studied in detail, or whatever little evidence exists does not show survival benefits. However, in NMD and OHS where NIV support is being also prescribed, add-on oxygen therapy may help to maintain oxygenation and hence can be considered.

Exercise induced hypoxia alone in chronic respiratory diseases may need ambulatory oxygen therapy (AOT) as oxygen in such patients may improve oxygen transport and utilization by exercising muscles leading to increase in exercise capacity, but its long term benefits are not demonstrated. Role of AOT during pulmonary rehabilitation is more clear with >10% improvement in exercise capacity in such patients undergoing PR. Hence, AOT is not routinely recommended in patients with chronic respiratory diseases with isolated EIH, but can be considered for pulmonary rehabilitation (PR) or exercise programs.

Screening Patients with Chronic Respiratory Diseases for Domiciliary Oxygen Therapy :

Although both SpO_2 by oximetry and SaO_2 by ABG estimate PaO_2, but in patients with chronic respiratory diseases presence of hypercapnia shifts the oxygen-hemoglobin dissociation curve making SpO_2 overestimate PaO_2. Hence, if $SpO_2 < 88\%$ is used

as the criteria to prescribe LTOT, it has been estimated that nearly 56% of eligible patients would be denied oxygen therapy due to this discrepancy. Hence SpO_2 can be considered a screening tool but confirmation would require ABG.

Indications :

- Patients having resting $SpO_2 \leq 92\%$
- Patients having resting $SpO_2 \leq 94\%$ with peripheral edema, Hematocrit $\geq 55\%$ or pulmonary hypertension

An acute exacerbation of COPD with residual hypoxia should be reassessed for LTOT at 8 weeks post discharge as 30 – 58% such cases improve and don't meet the criteria for LTOT.

Technical Usage Recommendations :

- Rule of using oxygen for a minimum of 15 hours per day is recommended. Use of oxygen for 24 hours per day adds additional benefit in severe cases with higher $PaCO_2$ or Hematocrit or PA pressures as well as patients with greater neurocognitive impairment.
- LTOT initiation should start with oxygen at 1L / min flow rate and titrated upwards till target of $SpO_2 > 90\%$ is met and repeat ABG is recommended to confirm $PaO_2 \geq 60$ mmHg.
- Sleep induces hypoxemia and it is recommended that LTOT patients should increase oxygen flow by an additional 1 L/min during sleep above their baseline requirement.
- Exercise-induced desaturation also requires an increase in oxygen delivery and hence ambulatory patients should be reassessed for augmentation of oxygen during activity/exercise to tailor oxygen therapy to individual patient demands.
- Ambulatory and / or nocturnal oximetry can be used to individualize prescriptions of oxygen in such patients. Patients prescribed LTOT as well as their caregivers should be trained to handle their machines, flow rates and warned about complications in detail.

Palliative Oxygen Therapy :

Palliative oxygen therapy (POT) is used to alleviate dyspnea in patients with advanced chronic diseases with a limited life expectancy, with the aim to reduce suffering, provided all treatable causes have been addressed optimally. Since oxygenation status does not match with the degree of breathlessness and baseline oxygen saturation may be normal in these cases, it is not recommended to use oxygen in such cases. Terminal malignancies and chronic cardio-respiratory diseases constitute the main diseases in this category and POT is occasionally considered to treat intractable breathlessness to improve the Quality of Life (QOL), when other pharmacological as well as non-pharmacological therapies fail.

Equipment for Domiciliary Oxygen use :

Home oxygen is provided to patients by :

1. Oxygen Concentrators
2. Oxygen Cylinders
3. Liquid Oxygen

Oxygen Concentrators *:* Are the most frequently used by patients as no refilling is required but the equipment is bulky and cannot be used for ambulatory use beyond few meters and being electricity driven, needs constant electric supply. By removing nitrogen from room air they provide oxygen at FiO_2 of 85-95% with high levels of oxygen at low flow rates (< 4-5 L/min) and FiO_2 is flow as well as equipment dependent. Flow can be either in continuous or pulsed mode with the latter providing higher flow rates for a longer time on battery power. The equipment requires regular maintenance and adequate length of tubing to allow patient mobility without tripping or disconnecting it from the machine. Home machines weigh around 4.5 – 8.6 kg and run on electric supply or batteries. Portable oxygen concentrators are light weight and mostly supply pulsed mode and hence unsuitable for patients who are sleeping or with higher oxygen demands. They may be recommended to any patient who is using oxygen for > 1.4 hours/day.

Oxygen Cylinders : Use metal containers of varying sizes, coded with different colors to store compressed oxygen at high pressures given with regulator adjusted to the flow rates required. Nowadays light-weight metals are used to make them more portable for ambulatory use and big cylinders are usually recommended as a standby on account of equipment or electricity failures.

Liquid Oxygen : Uses cooled and condensed oxygen to liquid in insulated containers called flasks and smaller containers can be filled from it. It requires training for this filling process and mishaps can cause cold burns or blasts. Also, these systems need proper and hazard-proof storage facilities.

Humidification : Is sometimes needed to counter the drying effect of oxygen in patients dependent on higher flow rates (e.g. ILD) or with those with plenty of respiratory secretions (e.g. bronchiectasis). Humidifiers bubble oxygen through sterile water. However, no evidence exists to support the routine use of humidification in non-tracheostomized patients, moreover, it adds to the risk of infection.

The choice of equipment for oxygen delivery to every patient needs to be individualized, balancing cost, efficacy, needs, safety and resources.

Safety for Home Oxygen Use :

Fire and personal injury are the two reported downsides of home oxygen therapy. Hence, smoking cessation is recommended and closely followed for all smokers. Lighting a cigarette has been reported as a major cause followed by other open flammable systems, E-cigarettes can also ignite fires and are not safe. These fires not only be fatal for the patients but have also been reported as a threat to care givers as well as fire fighters. Hence, care givers need to be counselled too against smoking in the vicinity of patients on home oxygen. In current smokers who are candidates for home oxygen therapy, risk assessment needs to be done prior to prescribing oxygen at home to avoid fire accidents. Tripping related to oxygen equipment or tubing is reported due to impaired mobility and / or cognitive issues in patients with chronic respiratory diseases and needs regular monitoring / repositioning of tubing.

Follow Up :

Routine follow-up at 3 months after initiation of LTOT is recommended to ensure the need to continue and review LTOT as well as any safety issues and complications of therapy. Compliance to smoking cessation as well the number of hours of oxygen use per day needs to be checked. ABG is done to reassess continuation of need for LTOT and development or worsening of hypercapnia and acidosis.

Conclusion :

Home oxygen is prescribed frequently in patients with chronic respiratory diseases. Strong evidence based recommendations exist for patients of COPD with severe resting hypoxemia or moderate hypoxemia and cor pulmonale as defined in clinical trials (NOTT, MRC) with favorable results. Here, the recommendation is to use oxygen for at least 15 hours per day to improve survival, quality of life, sleep, neurocognitive function and pulmonary hemodynamics. Although no studies have been done in similar clinical conditions with hypoxia e.g. ILD, CF, PH and NMD, the use of LTOT is nevertheless recommended by extrapolating data to similar levels of hypoxic indications as in COPD. However, no evidence exits to support LTOT use in mild to moderate resting hypoxia in COPD. Exertional hypoxia in COPD without resting hypoxemia does improve on using short burst of oxygen (AOT) while exercise and is recommended during exercise training (e.g. pulmonary rehabilitation). Isolated nocturnal hypoxia per se has also not shown significant benefit in clinical studies and hence oxygen during sleep to correct hypoxemia during sleep (NOT) is only recommended when required along with NIV support in cases with MND, CWD, OHS, etc. Palliative oxygen therapy (POT) is sparingly recommended in patients with preterminal chronic cardio-pulmonary diseases or malignancies to alleviate breathlessness even without hypoxia to decrease the sensation of dyspnea. Measuring arterial oxygen saturation using oximeters is used to screen patients for home oxygen but is inaccurate and an ABG on room air is recommended before prescribing LTOT. It has been shown that if $SpO_2 < 92\%$ is used as screening value it will be 100% accurate in identifying candidates for LTOT on ABG but will miss 31% cases on ABG showing $PaO_2 \leq 60$ mm hg. Resting hypercapnia with hypoxia criteria being met is not a contraindication but would need close monitoring while initiating LTOT. No worsening of $PaCO_2$ was reported in LTOT clinical trials. Target oxygenation is to maintain levels of SpO_2 90 – 92% during home oxygen therapy. Oxygen concentrators are the most frequently used devices for home oxygen therapy and portable devices are available for ambulatory use being easy to maintain vis a vis oxygen cylinders or liquid oxygen. Patients prescribed home oxygen need to be explained about the potential benefits as well as accidents and harmful effects and safety checks need to be in place.

Answer Key :

1 A
2 E
3 E
4 C
5 B
6 D
7 A
8 E
9 E
10 C

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Oxygen Therapy in Pediatric Clinical Practice




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Introduction :

Oxygen is one of the most important therapeutic agents used in the clinical management of pediatric patients suffering from cardiopulmonary diseases. Despite its importance in pediatric acute severe illnesses, oxygen therapy remains an inaccessible luxury for a large proportion of severely ill children admitted to hospitals in developing countries [1]. The gap between knowledge and practice of Oxygen therapy is a common phenomenon and there is wide variation in approaches to oxygen therapy within pediatric clinical practice. Oxygen therapy within pediatric clinical practice is predominantly determined by institutional or individual practice or preference and arises from a lack of understanding of the relative merits and demerits of the different techniques of oxygen monitoring in children who are different from adults. This comprehensive review briefly summarizes the current and best available evidence regarding the oxygen therapy in pediatric clinical practice, and for the benefit of the reader, is systematically organized into the following sections :

- Introduction
- Historical Aspects of Oxygen Therapy in Pediatric clinical Practice:
- Hypoxia and Assessment of Inadequacy of Oxygen Delivery
- Physical and Physiologic Effects of Oxygen Therapy
- Indications of Oxygen Therapy
- Oxygen Delivery Devices
- High-Flow Oxygen versus Low-Flow Oxygen in Hospitalized Pediatric Patients
- Monitoring and Maintenance of Oxygen Therapy
- Contra-indications of Oxygen Therapy
- Oxygen Toxicity
- Complications of Oxygen Therapy
- Weaning and Discontinuation of Oxygen Therapy
- Oxygen Therapy in Children with COVID-19
- Clinical Pearls in Oxygen Therapy in Pediatric Clinical Practice

Historical Aspects of Oxygen Therapy in Pediatric Clinical Practice : Oxygen was first discovered by Joseph Priestley in 1775, later named as oxygen by Antoine Lavoisier in 1778 [2]. Oxygen therapy has its origins in the Pneumatic Institution founded in Bristol (UK) in 1779 by Thomas Beddoes, the aim of which was to explore the potential efficacy of this gas for the treatment of diseases [3]. The pediatric use of inhaled oxygen was first initiated by Julius Hess in 1934 [4]. Later on, by 1940, oxygen therapy for treatment of cyanosis, apnea and periodic breathing in the newborn became a standard of care.

Hypoxia and Assessment of Inadequacy of Oxygen Delivery :

Continuous and adequate supply of oxygen to the organs and tissues are required for normal physiological function for adequate metabolism of carbohydrates and the production of adenosine triphosphate (ATP). Inadequate oxygen delivery to tissues leads to hypoxia. Tissue hypoxia in children causes a myriad of undesirable problems, such as localized vasodilation, pulmonary vasoconstriction, metabolic acidosis, tissue necrosis, increased risk of kernicterus, and impairment of surfactant production, especially in the newborn [5]. Persistent tissue hypoxia can ultimately lead to serious and permanent brain injury and even death [6]. The oxygen carrying capacity of blood is determined by the concentration of hemoglobin present in the blood; its oxygen saturation and diffusion to the organs and tissue and is largely affected by the rate of blood flow; and the efficiency with which oxygen is unloaded from hemoglobin to the tissues. Conditions like pulmonary disease, hypoventilation, uneven matching (mismatch) of ventilation to perfusion, diffusion defects, intrapulmonary shunts or "right to left" cardiac shunts, or reduced oxygen carrying capacity due to anemia or abnormal blood hemoglobin can all lead to hypoxia.

The term hypoxia and hypoxemia are not synonymous. Hypoxemia is defined as a decrease in the partial pressure of oxygen in the blood whereas hypoxia is defined as reduced level of tissue oxygenation, which can be due to either defective delivery or defective utilization of oxygen by the tissues. Hypoxemia and hypoxia do not always coexist. Patients can develop hypoxemia without hypoxia if there is a compensatory increase in hemoglobin level and cardiac output (CO). Similarly, there can be hypoxia without hypoxemia. To identify and assess a child's need for oxygen therapy, several physical signs and laboratory values can be assessed. Physical signs, such as cyanosis, confusion, tachycardia, retractions, nasal flaring and expiratory grunting (infants) can be indications that the child needs oxygen therapy [6].

A simple non-invasive device, pulse oximetry is now most commonly used to identify hypoxemia in the clinical setting. In the child with a normal pH, PCO_2, temperature and diphosphoglycerate, non-invasive oxygen saturation (SpO_2) value of approximately 90 and 95% corresponds to arterial pressures (PaO_2) of 60 and 80 mm Hg respectively [7]. Pulse oximetry has its limitations and is known to be inaccurate in carbon monoxide poisoning and other conditions where the oxyhemoglobin dissociation curve shifts either to the left (increased affinity for O_2) or the right (decreased affinity for O_2). In an anemic child, SpO_2 might be in the normal range despite a reduced PaO_2. Many pulse oximeters are affected by movement artifact and impaired peripheral perfusion [8, 9]. Arterial Blood Gas (ABG) analysis is an invasive but a very accurate method used to measure partial pressure of oxygen (PaO_2) for detecting hypoxemia in children.

Physical and Physiologic Effects of Oxygen Therapy in Pediatric Clinical Practice :

Individual responses to oxygen therapy in the pediatric age group vary greatly, depending on the particular cause of hypoxia and the degree of impairment. Hypoxia caused by hypoventilation and ventilation/perfusion anomalies associated with pulmonary disease is most responsive to oxygen therapy [7], on the other hand; oxygen supplementation in hypoxia caused by cardiac shunts, shock or hemoglobin deficiency /dysfunction might lead to only small increases in tissue oxygenation, though even this small increment may prevent life-threatening hypoxia in the child [10]. Medical oxygen, when administered to the patient is a dry gas and to preserve ciliary function and minimize atelectasis and tracheitis, it needs to be humidified before providing it to children.

Indications of Oxygen Therapy in Pediatric Clinical Practice :

The therapeutic indication for providing oxygen in children is similar to adults, i.e. when the PaO_2 falls to below 60 mm Hg. However PaO_2 alone is not sufficient to determine oxygen delivery to tissues. The rational for oxygen therapy is to prevent or correct cellular hypoxia, caused by hypoxemia (low PaO_2), and thus prevent potentially irreversible damage to vital organs. Simply stated, oxygen therapy is a modality to provide oxygen according to target saturation rates (as per the age of the child and nature or pattern of the disease) in order to achieve normal or near normal oxygen saturation levels for ill children by increasing the concentration of inhaled oxygen. The World Health Organization (WHO) recommends oxygen administration in children if oxygen saturation (SpO_2) level < 90% with signs of respiratory distress [11].The WHO Emergency Triage Assessment and Treatment (ETAT) guidelines recommend a target SpO_2 of 94% for children with emergency signs for severe disease(severe pneumonia, septic shock, severe anemia, central nervous system infection or heart failure) where oxygen delivery from the lungs to body tissues is impaired, or where vital organs may be susceptible to low oxygen levels [12,13]. Common indications for oxygen therapy in pediatric clinical practice are enumerated in Table 1 below.

Acute Hypoxemia
Acute Respiratory Infections Shock Sepsis Asthma Meningitis Cardiac failure
Abnormalities in quality or type of hemoglobin
Acute blood loss Carbon monoxide poisoning Trauma
Others
Pneumothorax Perioperative Emergencies Post-operative state resulting in hypoxemia

Table 1. Common Indications for Oxygen Therapy in Pediatric Clinical Practice

Oxygen therapy in pediatric clinical practice must be provided at accurate and safe levels with the lowest possible fractional concentration of inspired oxygen (FiO_2) by careful selection of the oxygen delivery device. The target range of oxygen saturation is different for different age groups of children (preterm newborn, newborn, infant, children and adolescent), disease pattern (acute or chronic) and/or type of disease.

In hospitalized children, oxygen should be administered and weaned to achieve target SpO_2 level between 94% and 99% [14] . Most of the critically ill newborn babies require oxygen. The ideal oxygen saturation target for extremely low birth weight (LBW) infants remains unknown and is likely to be patient specific and dependent on various factors, including gestational age, chronologic age, underlying disease and transfusion status. Current delivery room resuscitation guidelines recommend the use of room air for term newborns and preterm newborns of greater than or equal to 35 weeks' gestation and FiO_2 of 0.21 to 0.3 for preterm infants of less than 35 weeks' gestation. Most appropriate evidence-based strategies advocate targeting oxygen saturation for newborns to 91% to 95% with close monitoring [4,15]. A target saturation of 94% during the resuscitation phase will compensate for the potential of reduced oxygen delivery, as well as compensate for the error of the test inherent with the use of some pulse oximeters [12].

Oxygen Delivery Devices in Pediatric Clinical Practice :

Methods of Oxygen delivery in children can be Non-Invasive (through a face mask, head box, incubator or tent or holding tubing close to an infant's face), semi-invasive (insertion of prongs or catheters into the upper airway) or Invasive (Ventilators). Oxygen delivery systems are categorized as low-flow (variable performance) systems or high-flow (fixed performance) systems. With low-flow systems, 100% oxygen mixes with room air during inspiration and the room air is entrained, making the proportion (percentage) of delivered oxygen variable. High-flow devices provide a high flow of premixed gas such that the child is not required to inhale room air and the proportion of oxygen delivered is consistent. The methods used for administration of oxygen to children should be safe, simple and effective. It is also important to select an oxygen delivery system that suits the child's age, size, needs, clinical condition and therapeutic goals. Different devices and methods for Oxygen therapy in Pediatric Clinical Practice are summarized in Table 2 below.

Oxygen Delivery Device	Type of Flow	Flow Rate	FiO_2 achieved	Advantages	Disadvantages
Nasal Cannula	Low Flow	0.5-11/min for neonates 1-2 L/min for infants 1-4 L/min in preschool children 6 L/ min in school children	0.24 at 1L/min to 0.44 at 6L/min	Most commonly used device when FiO_2 required is between 22 to 60% Allows the child to eat, talk, and cough without interruption Humidification is not required at low flow rates	FiO_2 inconsistent. May cause drying of nasal mucous membranes at high flow rates
Simple Face Mask	Low Flow	6 L/min	Up to 0.6	Useful for acute situations and short term use only (set at 6-10L/min) Snugly fits on patient's face without much discomfort Increases the size of the oxygen reservoir beyond the limit of anatomic reservoir	Inconsistent FiO_2 delivery Minimum of 6L/min to be maintained for avoiding hypercarbia Mask must be removed for eating and drinking
Nasopharyngeal Catheters	Low Flow	0.5 L/min for neonates 1 L/min for infants	Higher PEEP is achieved	Most economical of all the methods Better oxygenation with moderate PDDP is achieved with a lower oxygen flow than with nasal prongs.	Requires close supervision Prone to blockage If displaced downwards into the esophagus causes gagging, vomiting and gastric distension
Head Boxes, Incubators and Tents	Low Flow	7-10 L/min	> 0.5	Actual FiO_2 can be determined precisely with an oxygen analyzer No increased risk of airway obstruction or gastric distention Humidification is not necessary	Requires high oxygen flows to achieve adequate concentrations of oxygen and to avoid carbon dioxide accumulations Interferes with feeding
Non - Re-breather Mask (NRBM)	Low Flow	10-15 L/min	0.8 to 0.95	Works as a high flow system as it provides high FiO_2 Good for short-term oxygen therapy	Inconsistent FiO_2 delivery Can cause hypercarbia
Venturi Masks	High Flow	2-4 L/min = 24% O_2 12-15 L/min = 60% O_2	Fixed FiO_2	Guarantees delivery of a fixed and consistent FiO_2	Can cause hypercarbia Humidification can alter oxygen concentration
High-Flow Nasal Cannula (HFNC)	High Flow	1-2 L/min 4L/min in infants up to 40L/min or more in adolescents	Adjustable 21 to 100%	Used when a higher FiO_2 with some end-expiratory pressure is required and ventilation is adequate Delivers a mixture of air and oxygen More comfortable Incidental delivery of positive end-expiratory pressure (PEEP)	Not suitable in upper airway abnormalities that may make HFNC ineffective or potentially dangerous such as severe hypoxia, hemodynamic instability, facial bone or skull base trauma and pneumothorax Should be applied carefully in patients with a decreased level of consciousness, congenital heart disease, acute asthma, or chronic respiratory failure

Table 2. Oxygen Delivery Devices and Interfaces used in Pediatric Clinical Practice.

High-Flow Oxygen versus Low-Flow Oxygen in Hospitalized Pediatric Patients :

The use of High-Flow Nasal Cannula (HFNC) oxygen delivery systems to provide respiratory support to children has increased over the past decade. HFNC is an oxygen supply system capable of delivering humidified and heated oxygen at a flow rate of up to 60 liters per minute. This delivery of oxygen at an adjustable FiO_2 (between 21 to 100 %), heated ($34\ ^0C - 37\ ^0C$) with nearly 100 % relative humidity can avoid mucosal injury, patient discomfort from cold, dry air and encourage the clearance of secretions and reduce bronchoconstriction. The basic principle of HFNC is to set a higher oxygen flow than the inspiratory demand flow according to the clinical situation [16]. HFNC systems also provide washout of the nasopharyngeal dead space, decrease inspiratory resistance, improve airways conductance and pulmonary compliance, as well as decrease metabolic work by providing heated and humidified gas [16]. HNFC can be initiated as the first-line therapy for all age groups of children with various etiologies of acute respiratory distress. HFNC in neonates and preterm babies is non-inferior to CPAP in preventing intubation and invasive ventilation; however, HNFC should only be used for moderate to severe bronchiolitis in the pediatric ward and intensive care unit (PICU) for the best results [17]. Humidification of Oxygen, either heated or unheated is recommended and used while providing high flow oxygen therapy. Many high-flow nasal cannula systems are designed with in-built warming and humidification systems that provide oxygen at appropriately humidification and as close to normal body temperature which is non-irritating to the mucosa of the upper airways, thereby increasing patient comfort.

Monitoring and Maintenance of Oxygen Therapy in Pediatric Clinical Practice :

Children who are on oxygen therapy should be regularly monitored by regular pulse oximetry to determine whether they still need oxygen and whether those who are already on oxygen have developed worsening of respiratory distress. It is unlikely that a child who has normal oxygen saturation while breathing room air has impaired ventilation; however, once oxygen is administered, SpO_2 can be maintained at normal levels despite severe hypercapnea. As pulse oximetry cannot indicate the adequacy of ventilation, children receiving oxygen therapy must be also be assessed clinically for respiratory effort, respiratory rate and the level of consciousness to check for the adequacy of ventilation. A child with inadequate ventilation will have slow or shallow breathing and will be lethargic. Any concern about the adequacy of ventilation should prompt efforts to ensure that the airway is clear and protected; and the child is positioned to facilitate chest expansion (e.g. sitting in a semi-recumbent position at $20 - 30\ ^0$, head-up to reduce diaphragmatic splinting).

Contra-indications of Oxygen Therapy in Pediatric Clinical Practice :

There are no absolute contra-indications to oxygen therapy in Pediatric Clinical Practice if indications are judged to be present clinically. Supplemental O_2 should be administered with caution in children presenting with paraquat poisoning and with acid inhalation. The administration of oxygen can lead to pulmonary vasodilation and subsequent system ischemia in some congenital heart defects because of an unbalanced circulation. In children with chronic carbon dioxide retention, oxygen administration may cause further increases in carbon dioxide and respiratory acidosis [18]. Children with chronic neuromuscular disorders, chest wall deformities, cystic fibrosis, morbid obesity and chronic lung disease of prematurity are at higher risk.

Oxygen Toxicity :

There is a Janus-faced dimension to Oxygen Therapy in Pediatric Clinical Practice in that in addition to being essential, it is toxic under certain conditions. Oxygen toxicity in children can be divided into two groups; one in which the child is exposed to very high concentrations of oxygen for a short duration, and the second where the child is exposed to lower concentrations of oxygen but for a longer duration, which can result in acute and chronic oxygen toxicity, respectively.

Acute oxygen toxicity manifests generally with central nervous system (CNS) effects, while chronic oxygen toxicity has mainly pulmonary effects. Severe cases of oxygen toxicity can lead to cell damage and even death. It has been shown that exposure to high concentrations of oxygen first damages the capillary endothelium, followed by interstitial edema (0 to 12 hours), worsening pulmonary compliance and vital capacity (12 to 30 hours), followed by thickening of the alveolar-capillary membrane (30 to 72 hours) [19,20] . If the process continues, Type 1 alveolar cells are destroyed, and Type II cells proliferate [21]. An exudative phase follows, resulting in a low ventilation/perfusion ratio, physiologic shunting, and worsening hypoxemia. $FiO_2 > 0.50$ presents a significant risk of absorption atelectasis [21]. The risk of absorption atelectasis may be greatest in children breathing at low tidal volumes [7]. Unrestricted or unmonitored administration of oxygen to preterm infants is associated with a disastrous increase in the incidence of retinopathy of prematurity, chronic lung disease and necrotizing enterocolitis. The onset and rate of progression of oxygen toxicity in children is influenced by a variety of conditions, procedures and drugs.

Oxygen toxicity is managed by reducing the exposure to increased oxygen levels. The lowest possible concentration of oxygen that alleviates tissue hypoxia is optimal in most decompensated neonates. Treatment for oxygen toxicity is purely symptomatic, therefore it is imperative to monitor for early recognition of toxicity. Abrupt or sudden discontinuation of oxygen at the onset of toxicity may at time aggravate symptoms. Damage due to oxygen-induced pulmonary toxicity is reversible in most children. Infants who have survived bronchopulmonary dysplasia will ultimately recover near-normal lung function, since the lungs continue to grow during the first 5 – 7 years of life.

Complications of Oxygen Therapy in Pediatric Clinical Practice :

CO_2 Narcosis : This occurs in children who have chronic respiratory obstruction or insufficiency which results in hypercapnea (i.e. raised $PaCO_2$). In these children the respiratory center relies on hypoxemia as the stimulus to maintain adequate ventilation. If these children are given oxygen with a high FiO_2, it can blunt their respiratory drive, causing respiratory depression and further rise in $PaCO_2$ [18]. Therefore, one must be cautious while using high FiO_2 in the presence of reduced minute ventilation [19].

Pulmonary Atelectasis : High concentrations of oxygen (FiO_2 > 60%) may damage the alveolar membrane when inhaled for more than 48 hours resulting in pathological lung changes [19].

Retinopathy of Prematurity : Neonates exposed to high levels of oxygen are at risk for developing retinopathy of prematurity (ROP), as oxygen promotes neovascularization of the retina and can cause vision loss or blindness. Mild Retinopathy of prematurity (ROP) in infants frequently reverses without intervention and the eyesight may become normal in later years [22,23].

Weaning and Discontinuation of Oxygen Therapy in Pediatric Clinical Practice :

A weaning trial in children on oxygen therapy should be best done in the morning, when there are likely to be adequate staff to observe the child throughout the day. If weaning is initiated and/or supplemental oxygen is discontinued in the late evening or night, then oxygen desaturation that sometimes occurs during sleep might increase the risk for hypoxemia, which may go unrecognized during the night. For children on oxygen therapy who are in a stable condition (Stable vital signs, with no respiratory distress, feeding adequately and normal level of consciousness, and with SpO_2 > 90%), oxygen should be interrupted once a day for 10 – 15 minutes and the children carefully examined for changes in clinical signs and SpO_2 to assess whether supplemental O_2 still required [11]. Children should receive supplemental oxygen until their SpO_2 on room air is 90%. If the SpO_2 is 90% after a trial on room air, they should remain off oxygen, and their SpO_2 should be rechecked after 1 hour, as late desaturation can sometimes occur. Continuous pulse oximetry monitoring needs to be done for at least 30 minutes post cessation of oxygen therapy [11].

Oxygen Therapy in Children with COVID-19 :

The child with COVID-19 infection should receive oxygen supplementation to achieve a target $SpO_2 \geq 94\%$ during resuscitation if the child has emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) and once the child is stable, the target should be set at SpO_2 > 90% [12].

The preferred mode of oxygen delivery in children with COVID-19 infection is nasal prongs or nasal cannula for infants and children less than 5 years of age. It is recommended that only those children having respiratory distress should receive oxygen when their SpO_2 < 90% [24]. Initially oxygen should be administered by nasal prongs at a standard flow rate (0.5 - 1 L/min for neonates; 1 - 2 L/min for infants; 2 - 4 L/min for older children and 4 - 6 L/min for adolescents) or through an appropriately sized face mask (> 4 L/min) to reach an SpO_2 of $\geq$ 94% . If severe hypoxemia persists despite maximal flow rates then oxygen should be given by continuous positive airway pressure (CPAP) or by a face mask with a reservoir bag. HHHFNC (Heated Humidified High Flow Nasal Cannula) or HFNC can be tried in children with mild ARDS without evidence of hemodynamic instability, altered mental status or multi-organ failure though it is known to generate aerosol, thereby increasing the risk of transmission of COVID-19 [25]. With all these non-invasive methods if the child's oxygenation status does not improve or respiratory status deteriorates then he/she should be considered for invasive mechanical ventilation.

Summary - Clinical Pearls for Oxygen Therapy in Pediatric Clinical Practice :

- Supplemental oxygen only relieves hypoxemia, it does not improve ventilation or correct the underlying cause of respiratory failure.
- SpO_2 is a measure of oxygenation and not ventilation. Therefore, beware of oxygen therapy at high FiO_2 in the presence of reduced minute ventilation.
- Many children in the recovery phase of an acute respiratory illness are characterized by ventilation/perfusion mismatch and can be managed by maintaining their SpO_2 % within the low 90's range as long as they are clinically improving, feeding well and don't have obvious respiratory distress.
- Normal SpO_2 values may be found despite rising blood carbon dioxide levels (hypercapnea).
- Oxygen therapy at high FiO_2 has the potential to mask signs and symptoms of hypercapnea.
- Therapeutic procedures and handling may increase the child's oxygen consumption and lead to worsening hypoxemia therefore, it is mandatory to closely monitor and assess children on Oxygen therapy at regular intervals.
- Children with cyanotic congenital heart disease normally have SpO_2 between 60 to 90 % at room air. Strategies to increase SpO_2 > 90 % with supplemental oxygen are not recommended except in emergency situations due to the risk of causing ventilation-perfusion mismatch by increasing circulation to the pulmonary system while adversely decreasing systemic circulation.
- Unless clinically contra-indicated, an attempt to wean the child off oxygen therapy and/or ventilation should be attempted at least once per shift.
- Although a pediatrician may consider specific methods and devices for oxygen administration and initially select the most appropriate one at the onset of therapy, it is important to understand that with therapy individual patients change, and their medical conditions evolve too. Therefore, constant re-evaluation of the child on oxygen therapy is critical to ensure the necessity for continued oxygen administration as well as decide which method or device is the best possible for each child from time to time.

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Long-term Oxygen Therapy and Oxygen Delivery Devices

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Introduction :

The United Kingdom Medical Research Council (MRC) Multicentre trial and the United States Nocturnal Oxygen Therapy trial (NOTT) have clearly demonstrated decreased cardiovascular complications and increased survival of patients with chronic obstructive pulmonary disease (COPD) exhibiting severe resting hypoxemia, following treatment with oxygen supplementation [1]. The concept of Long-term oxygen therapy (LTOT) gained support from the results of the above landmark studies [2].

Indications :

Long-term oxygen therapy is indicated in the following situations [3]:

1. Patients with arterial oxygen tension (PaO_2) ≤ 55 mm Hg at rest despite optimal treatment of underlying condition
2. Patients with PaO_2 < 55 mm Hg demonstrating features of neurological dysfunction, cor pulmonale, secondary pulmonary hypertension or polycythemia
3. Patients exhibiting a fall in PaO_2 below 55 mm Hg and desaturation during sleep and/or exercise.

Patients with advanced COPD exhibiting severe resting hypoxaemia are to be considered for continuous oxygen therapy. Those exhibiting an arterial PO_2 of less than 55 mm Hg three weeks or more while in a stable clinical state, or having pulmonary hypertension, cor pulmonale or secondary polycythemia or impaired neuropsychiatric function, with a PaO_2 between 55 and 59 mm Hg in a stable state are considered candidates for long-term oxygen therapy. It is indicated in patients who do not have the ability to adapt to even a moderate degree of hypoxemia. These patients should exhibit the above findings on two separate occasions preferably three weeks apart under optimal medical therapy and after discontinuing smoking and while breathing room air. The goal of long-term oxygen therapy is to allow the patients to be as active as possible and to encourage exercise and ambulation outside the home.

The progressive course of COPD leads to marked limitation of exercise tolerance in some individuals and they become respiratory cripples with profound hypoxemia at rest and during exercise. Long-term oxygen therapy appears to be beneficial to these chronically hypoxemic individuals as it enables them to carry out their activities of daily living. Supplemental oxygen can reverse many of the adverse effects of chronic hypoxemia. It reduces hematocrit, improves neuropsychiatric function, and reduces pulmonary artery pressure. LTOT also improves the overall survival and quality of life of many patients.

There is no proof that supplemental oxygen prolongs life in pulmonary fibrosis, however, ambulatory oxygen significantly improves exercise capacity in patients with idiopathic pulmonary fibrosis.

Oxygen has to be delivered by nasal cannula at a flow rate of 1 to 2 litres per minute with additional 1 litre per minute flow during conditions of exercise and while sleeping to prevent hypoxemic episodes. Such therapy has shown to improve the survival and quality of life of most patients. It should be noted that some patients develop significant hypoxemia only with exercise or during sleep; and; accordingly, they require oxygen during physical activity or during sleep due to an increased metabolic demand of exercise and to a modest degree of hypoxemia respectively. Survival is better with supplementation of either 12 or 15 hours oxygen and best with more continuous (20 hours) oxygen in selected patients with advanced COPD. The administration of oxygen is generally begun at night as hypoxemia worsens in the reclining position and during sleep.

Oxygen Delivery Devices :

A variable amount of oxygen has to be administered to patients suffering from pulmonary diseases, cardiovascular ailments, neuromuscular disorders, post-operative conditions, acute and chronic respiratory failure using oxygen delivery systems.

Oxygen delivery systems are classified as low-flow and high-flow systems. Low-flow oxygen delivery systems provide lower oxygen flow than the actual inspiratory flow. During inspiration by the patient, oxygen gets diluted with room air. As the degree of dilution depends on the inspiratory flow, there is difficulty to calculate the inspired oxygen fraction (FiO_2). High-flow oxygen delivery systems provide higher oxygen flow, in which the FiO_2 remains stable and does not get affected by the type of breathing (ventilatory pattern) by the patient [4].

Oxygen can be administered conveniently by oronasal devices such as nasal catheter, nasal cannula and different types of masks. The oronasal devices enrich the inspired air and fulfil the demands commonly encountered in clinical practice. These devices are simple, less expensive and more comfortable.

Oxygen must be administered in such a concentration as to achieve an arterial oxygen tension (PaO_2) of 50 to 80 mm Hg. The PaO_2 when related to the fraction of inspired oxygen tension (FiO_2) reflects the efficiency of oxygenation. Oxygen ratio is estimated by dividing PaO_2 in mmHg by the inspired oxygen concentration in per cent (PaO_2/FiO_2). Normally it is 4.

The administration of oxygen is vital in all situations associated with hypoxemia. It is administered in high or low concentrations depending on the co-existence of hypercapnia. When there is no danger of CO_2 retention, higher concentration of oxygen can be given safely. A low concentration of oxygen is used in situations of chronic retention of CO_2 as seen in COPD.

In any acute lung conditions without underlying chronic lung disease, such as pulmonary embolism, pneumonia, tension pneumothorax, acute severe asthma, pneumonia due to influenza, COVID-19, or other infections, pulmonary edema or myocardial infarction, a higher concentration of oxygen can be administered. Similarly, in conditions associated with disorganisation of parenchymal and alveolar structure of peripheral gas exchange (idiopathic pulmonary fibrosis), higher concentration of oxygen can be safely given as there is no retention of CO_2. In these situations, there is no danger of induction of hyperventilation as the patient is not breathing primarily on anoxia reflexes (hypoxic respiratory drive). Oxygen is administered to achieve a target PaO_2 greater than 60 mm Hg and it will give an oxygen saturation of approximately 90 per cent.

Severe airways obstruction is associated with CO_2 retention and hypoxemia. While the arterial oxygen tension falls linearly, the level of CO_2 ($PaCO_2$) rises in a hyperbolic way. During acute exacerbations of COPD following infection, or uncontrolled administration of oxygen or use of sedatives, the chemoreceptor drive for ventilation is eliminated and there is reduced alveolar ventilation. As the hypoxemia is extremely severe it has to be relieved immediately by administering oxygen through ventimask. Generally, administration of oxygen is begun with an initial concentration (FiO_2) of 24 per cent. In such a concentration, it is only 3 per cent higher than that of fresh atmospheric air. It is sufficient to improve oxygenation without losing the respiratory stimulant effect. A minimal dose of oxygen raises the arterial oxygen tension as the gas exchange occurs on the steep part of the oxygen dissociation curve. Moreover, it does not have detrimental effects on the ventilation/perfusion (V/Q) distribution (e.g. increasing blood flow to poorly ventilated areas of the lungs), and does not significantly raise the $PaCO_2$.

Low-flow Oxygen delivery systems :

1. Nasal catheter : The light rubber nasal catheter is a simple effective device for administration of oxygen. It has to be inserted after lubricating its tip with liquid paraffin, through the nose, until its tip is visible behind the uvula in the oropharynx. Oxygen supply is less affected by the degree of mouth breathing or the position of the head of the patient (Figure 1A).

2. Nasal cannula : A Nasal cannula is a device used to deliver supplemental oxygen. It comes as soft, lightweight, short two-pronged plastic tube. The prongs are placed in the nostrils, from which a mixture of air and oxygen flows. The other end of the tube is connected to an oxygen supply source such as a portable oxygen generator or a wall connection via a flowmeter. It is commonly used to deliver oxygen to patients with mild-to-moderate hypoxia. The prongs are held in place by an elastic head band and the prongs are protruded 1 cm into each nostril. They deliver oxygen into the nasopharyngeal space, at a flow rate of 1 to 6 litres per minute. FiO_2 increases by 4% with each additional litre of oxygen per minute. They are comfortable to the patient and are well tolerated. They facilitate eating, drinking, coughing, talking and patient interaction without interrupting the flow of oxygen. They are widely used in domiciliary oxygen therapy. The nasal cannula is not suitable to administer oxygen flow at a rate ≥ 6 litres/minute as it causes dryness of the nasal mucosa. It may occasionally disturb sleep (Figure 1B).

These devices provide a fixed FiO_2 which varies inversely with the total ventilation of the patient. Oxygen has to be humidified to prevent nasal mucosal dryness and irritation. These devices are generally employed in patients without hypercapnia who require supplementary oxygen up to an FiO_2 of not more than 40 per cent. They are also used in the management of domiciliary oxygen therapy.

3. Simple face mask : A simple face mask can be recommended when a moderate amount of oxygen is needed. It can deliver 5 to 10 litres of oxygen per minute. It fits over the nose and mouth of the patient. There are side exhalation ports through which the patient exhales carbon dioxide. The efficiency of the mask is determined on how well it fits. It interrupts eating and drinking as it has to be removed during these actions. The patient may sometimes develop claustrophobia or an irrational fear of confined place (Figure 1C).

4. Non-rebreather mask (NRBM) : Another low-flow device to administer high FiO_2 is a non-rebreather mask. It has a reservoir bag of 1000 mL capacity facilitating delivery of a higher concentration of oxygen. There is a one-way valve between the mask and the reservoir bag that facilitates prevention of the patient from inhaling expired air. It is possible to deliver 10 to 15 litres of oxygen/minute (FiO_2 of 80 – 90%). FiO_2 depends on the pattern of breathing by the patient. These masks can be used in severely hypoxic patients who are ventilating properly. However, there is danger of carbon dioxide retention (Figure 1D).

5. Rebreather masks : Unlike the NRBM, these do not have one-way valves between the mask and the reservoir bag. The inspired oxygen and expired air get collected in the reservoir bag. The reservoir bag has a capacity of 1 litre and requires a minimum oxygen flow rate of 8 litres per minute to keep it functional, it must be partially inflated to at least one-third or half capacity at all times, to ensure oxygen delivery at a high FiO_2 while at the same time avoiding CO_2 accumulation (Figure 1E).

Sometimes, rebreathing and non-rebreathing masks are also classified as high-flow devices, depending on whether the device flow will exceed the patient's minute ventilatory requirement.

6. Transtracheal oxygen catheters : The small inconspicuous transtracheal oxygen catheter (TTOC) bypasses the anatomical dead space of the mouth and upper airways and delivers oxygen directly into the trachea. It is inserted percutaneously using the Seldinger technique. Oxygen flow through a TTOC ranges between 0.5 and 4 litres per minute. As oxygen flows directly into the traches, it reduces the overall oxygen needed during rest and exercise. However, TTOC placement has not gained widespread popularity as only a few physicians are trained to insert the TTOC, and there also exists widespread reservation towards performing this invasive procedure in hypoxemic, elderly, frail patients. Moreover the small fragile transtracheal catheters are easily prone to displacement or breakage, as well as the formation of potentially fatal 'mucus balls'.

A. Nasal Catheter **B. Nasal Cannula** **C. Simple Face Mask** **D. Non-Rebreather Mask** **E. Rebreather Mask**

Figure 1. Low-flow Oxygen Delivery Devices

Different masks are available to deliver a low fixed concentrations of oxygen at 24, 28 and 35 per cent. A low-flow oxygen therapy with stepwise increments in the fraction of inspired oxygen helps to prevent respiratory acidosis in patients with chronic obstructive pulmonary disease (COPD). The masks are somewhat uncomfortable to the patient and it has to be removed while eating, drinking, talking and coughing. Those who do not like masks or when masks are not available, oxygen can be given through nasal catheter or nasal cannula or double nasal prong. A low concentration of oxygen has to be administered continuously. If oxygen is given at a flow rate of 1, 2, and 3 litres per minute, a concentration of 24, 28 and 35 per cent respectively can be reasonably achieved. However, FiO_2 delivered to the lungs varies with patient's breathing pattern. The FiO_2 in these situations is calculated as : $20 + 4 \times O_2$ flow (litres/minute)

High-flow Oxygen delivery systems :

1. Venturi mask : A Venturi mask is a high-flow device that is able to deliver a known fixed concentration of oxygen to the patient regardless of the oxygen flow rate to the mask and the minute ventilation of the patient. It fits lightly over the nose and the mouth and gives a blast of fresh air over the face. It has a soothing effect.

Oxygen flowing at a high velocity (4 to 8 litres per minute) in the form of a jet through a narrow orifice to the base of the mask creates a negative pressure entraining atmospheric air through the perforations in the face piece and there is no rebreathing. It works on the Venturi modification of the Bernoulli's principle. As air gets mixed with oxygen there is no necessity of additional humidification (Figure 2A).

2. High-flow nasal cannula : A high-flow nasal cannula includes a flow generator, an air-oxygen blender and a humidifier. It is possible to generate a gas flow up to 60 litres/minute by the flow generator. The oxygen blender increases FiO_2 up to 100% and the humidifier saturates the gas mixture. This device delivers heated humidified oxygen to a wide-bore nasal prong. Depending on the patient's flow and FiO_2 it is possible to titrate flow rate. High-flow nasal cannula possesses the capacity to reduce the work of breathing by improving functional residual capacity (FRC) and mucociliary clearance (MCC) of secretions, as well as provide additional positive end-expiratory pressure (PEEP) to open up and distend collapsed alveoli (Figure 2B).

3. Polymask and Pneu Mask : These masks have a face piece as the interface, an air mix apparatus and a rebreathing storage bag for oxygen. The individual inhales oxygen from the bag and air through the aperture. During expiration, the dead space air containing a high concentration of oxygen fills the reservoir bag with some CO_2 (2 to 3 per cent) and the rest of the gas is expired through the aperture. As there is rebreathing, it is necessary to administer oxygen at a higher flow rate (6 to 8 litres/minute). These devices are useful in giving a high inspired oxygen concentration (60 per cent) and are effective in raising the arterial oxygen tension in patients with acute myocardial infarction, cardiogenic shock, and heart failure. The presence of a reservoir bag causes rebreathing of expired CO_2, thus making them unsuitable for patients with COPD .

A. Venturi Mask **B. High flow nasal cannula**

Figure 2. High-flow Oxygen Delivery Devices.

Oxygen Concentrator :

Two types of oxygen systems - stationary (compressed gas high pressure cylinders or tanks and oxygen concentrators) and portable (transfilling gaseous or liquid system) are available for home use in the domiciliary setting for patients who require long-term oxygen therapy. Patients who are bedridden or confined to their homes do not require a portable system, and for them a stationary source with a 13-metre-long extension tube is adequate. Oxygen concentrators are electrically powered and cost-effective in the long-term setting. They separate oxygen from room air by the adsorption principle of a molecular sieve, which removes the nitrogen fraction (78% of atmospheric air) from ambient air, leaving behind an air mixture that is rich in oxygen. They are somewhat bulky and generate a lot of noise, as well as require a back-up tank system in the event of power failure [5]. Some of the newer generation oxygen concentrators are smaller and more portable than the earlier devices. Since the oxygen concentrator draws room air through a series of filters, dust, bacteria and other particulate matter is also removed. It utilises the principle of rapid pressure swing adsorption (PSA) technology to provide oxygen in homes or clinics where using liquid or pressurized oxygen might be dangerous or inconvenient to persons with moderate-to-severe hypoxemia. Oxygen concentrators provide a cost-effective source of oxygen. They are safe and convenient alternatives to pressurized cylinders or cryogenic oxygen tanks. Oxygen concentrators may be stationary or portable. Stationary concentrators provide an uninterrupted oxygen supply. The plug is connected to the main electricity supply at home and a continuous flow of oxygen up to 10 to 15 litres per minute can be obtained. They are used by patients on LTOT. They are safer compared to compressed gas cylinders. Portable oxygen concentrators work on lithium-ion batteries, and are designed as small, lightweight and mobile units that carry and administer oxygen in a comfortable and compact manner, useful for ambulatory patients who wish to live an active life. For detailed information the reader may refer to an article exclusively written on this topic in this issue of Lung Bulletin.

Monitoring :

Oxygen therapy is necessary for treatment in all situations of hypoxemia and respiratory failure. Oxygen therapy has to be monitored carefully, and the dose, flow rate, FiO_2 and duration all have to be selected carefully. Arterial oxygenation is assessed by measuring the partial pressure of oxygen in arterial blood (PaO_2) [6]. The dose of oxygen selected must be of such

concentration as to raise adequate tissue oxygen levels. It is uncommon to find rapid rise in PaO_2 when the inspired concentration of oxygen is less than 40 per cent and rare when FiO_2 is less than 30 per cent.

Oxygen should be administered in low concentrations to begin with. Small increments of concentration of inspired oxygen are to be made on further assessment and/or improvement. The patient has to be watched carefully after commencement of oxygen therapy. Records of pulse, temperature, blood pressure, respiratory rate, consciousness and pulse oximetry are to be kept. The mental clarity, level of consciousness, frequency and depth of respiration, cough and sputum production are to be noted. Repeated measurement of blood gases helps in judging the safe limits of oxygen administration.

It is important to pay attention to the manner in which oxygen is delivered to patients. Oxygen delivery must be continuous and should not be stopped abruptly until the patient has recovered. Intermittent administration of oxygen in patients with CO_2 retention is dangerous. If oxygen is withheld even for a short while, it results in washing out of meagre body reserve of oxygen and there is a fall in alveolar oxygen tension. CO_2 is eliminated slowly and its level in the alveoli continues to remain high. It dilutes the alveolar gas causing a decline in oxygen tension. In other words, the level of PaO_2 becomes lower than what it was prior to the administration of oxygen. Hence it is recommended that oxygen therapy should be continuous to increase PaO_2. The level of oxygen has to be built up slowly thus relieving hypoxemia. It must be remembered that severe hypoxemia causes death within four minutes whereas severe CO_2 retention is not usually lethal.

Attempts to achieve complete saturation of hemoglobin in arterial blood by high fraction of inspired oxygen and even by use of positive end expiratory pressure (PEEP) are not necessary and may even prove detrimental to the patient. An arterial PO_2 of 60 mm Hg provides approximately 90 per cent saturation of arterial blood if the acid-base status is normal. In the presence of acidosis, a PaO_2 greater than 80 mm Hg is required to achieve the same level of oxygenation.

Even a small increment in arterial oxygen tension results in significant rise in the saturation of hemoglobin with oxygen, due to the sigmoid shape of the oxygen-hemoglobin dissociation curve. It can stimulate respiration without losing its respiratory stimulant effect (hypoxic respiratory drive). Under normal situations, no additional benefit is secured by raising PaO_2 to a level greater than 60 to 80 mm Hg. An increase of even 1 per cent of inspired oxygen concentration elevates the oxygen tension (PaO_2) by 7 mm Hg. It is necessary to maintain normal hemoglobin levels in the presence of respiratory failure as proper oxygen transport to the tissues has to be maintained. Because of this variation, there is minimal rise in CO_2 level whereas oxygen saturation shows a marked change.

Summary - Key Points of Interest :

- Long-term oxygen therapy is recommended for patients with $PaO_2 \leq 55$ mm Hg despite optimal medical treatment of the underlying condition
- Long-term oxygen therapy is needed for those patients with hypoxemia with neurological dysfunction, cor pulmonale, secondary pulmonary hypertension or polycythemia
- Oxygen delivery systems may be either low flow or high flow
- Oxygen can be administered by oronasal devices such as nasal catheter, nasal cannula and different types of masks
- Oxygen concentrators are useful for domiciliary management of patients receiving long-term oxygen therapy at home
- Oxygen therapy has to be carefully monitored
- Oxygen delivery must be continuous and should not be stopped abruptly until the patient has recovered
- A small increment in arterial oxygen tension results in a significant rise in the saturation of hemoglobin

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High Flow Nasal Oxygen

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Introduction :

High Flow Nasal Oxygen (HFNO) popularly known as high flow nasal cannula (HFNC), is a high flow oxygen therapy modality. As the name suggests, it delivers oxygen at high flows, 40 – 80 litres/min (depending on the manufacturer) in comparison to up to 15 litres/min by the conventional low flow oxygen therapy systems like an oxygen mask.

HFNO comes as a portable machine that includes an air-oxygen blender, a humidifier, inspiratory tube and wide bore nasal cannula. Because it provides oxygen at high flow rates that can dry the upper airway mucosa, it comes with a humidifier that provides heated (31 to 37 degrees C) and humidified air. The air-oxygen blender has a flow meter in situ by which FiO_2 (21% to 100%) and flow (20 to 80 L/min) can be titrated independently as required. In the article, we will be addressing some of the common questions that might arise in the minds of physicians about the use of HFNO.

How does HFNO work ?

The mechanism of action of HFNO is multi-fold [1]:

1. During respiratory distress and tachypnea, the patient's ventilatory demand/minute ventilation increases at which low flow oxygen devices cannot deliver a fixed and desirable FiO_2, that is when HFNO comes in handy because of its ability to deliver oxygen at higher flows (up to 60 – 80 L/min), it can meet the patient's ventilatory demand and thus can provide fixed FiO_2 and decrease the work of breathing.

2. Physiological dead space in the nasopharynx is around a third of the tidal volume. It allows for the accumulation of CO_2 and provides lesser oxygen for diffusion. This effect increases in patients with tachypnea with a decrease in tidal volume. HFNO, by delivering inspiratory air at higher flow than the patient's demand, washes out CO_2 that has accumulated within the physiological dead space and thus increases ventilation and alveolar oxygen.

3. HFNO, by delivering high flow air, creates a positive pressure environment that leads to dilatation of the nasopharyngeal airway, which by decreasing nasopharyngeal airway resistance increases ventilation.

4. HFNO creates a positive end-expiratory pressure (PEEP) to the lower airways also, that improves ventilation and oxygenation by alveolar recruitment and by increasing functional residual capacity. Though PEEP is itself dependent on the delivered inspiratory flow to the patient, closure of mouth and the size of the patient (obese, adult, child), researchers have shown that HFNO provides ~ 1 cmH_2O PEEP for every 10 L/min flow with the mouth closed.

5. Low flow oxygen devices provide dry, cool air to the airways, which causes desiccation of the airway mucosa and may lead to irritation, bleeding and increase risk of infection. HFNO, by providing heated and humidified air, improves the comfort and compliance of the oxygen therapy that further enhances the outcome.

What are the different components of HFNO equipment ?

HFNO components include the following (Figure 1) :

1. A flow generator to provide gas flow rates up to 60 – 80 litres per minute
2. An air-oxygen blender that achieves an FiO_2 of 21% to 100%
3. A humidifier that maintains the gas (oxygen) mixture at a temperature of 31 to 37 degrees C.
4. Tubing to deliver the gas
5. Wide-bore nasal prongs as the patient interface

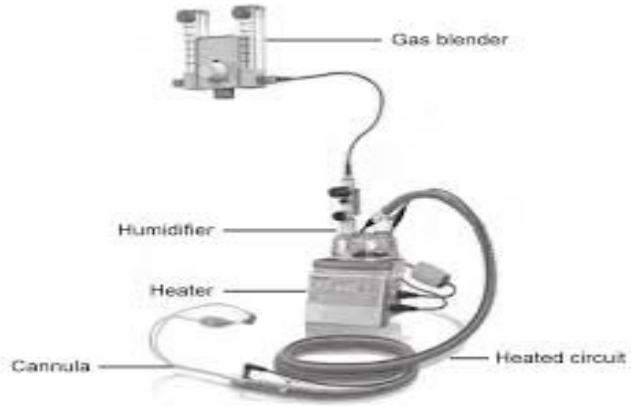

Figure 1. Components of HFNO equipment

What are the indications of HFNO ?

HFNO can be used as an oxygen therapy device where low flow devices can't meet the demand. It can be used for following indications [1] :

1. Acute Hypoxemic Respiratory Failure

HFNO is helpful in patients with acute hypoxemia, even in mild to moderate acute respiratory distress syndrome (ARDS), Pneumonia and acute exacerbation of interstitial lung disease (ILD). Studies have found that in patients with acute hypoxemic respiratory failure without hypercapnia, HFNO improves outcome in terms of ventilator-free days, comfort, compliance with the therapy, dyspnea severity, all-cause mortality in the intensive care unit (ICU) and 90-day mortality in comparison to non-invasive ventilation (NIV) without any significant adverse effects. HFNO is superior to NIV in terms of patient compliance, whereas the NIV mask interface and tight belts may render patients uncomfortable during respiratory distress.
The ability to titrate FiO_2 and flow independently is also helpful in acute hypoxemic respiratory failure with prone positioning.

2. Post-Surgical Respiratory Failure

HFNO is helpful in the patients post-surgery when there is an increased oxygen requirement. HFNO, by the effect of providing PEEP, also prevents post-surgery atelectasis to some extent and improves oxygenation and respiratory distress.

3. Acute Heart Failure /Pulmonary edema

Pulmonary edema sometimes requires positive pressure to clear the alveoli and to improve oxygenation. HFNO is better in cautiously chosen patients for the above benefit, but if the patient is not improving with the low PEEP with HFNO, upgrading respiratory support with NIV or Invasive ventilation can be considered.

4. Pre and Post-extubation Oxygenation

For pre-oxygenating a patient for intubation, HFNO can be used effectively as it can give 100% Oxygen with high flow and negates the need of applying a tight-fitting mask of NIV for oxygenation over the face of an already apprehensive patient. HFNO has the advantage over the non-rebreathing mask (NRBM) or NIV in that it can provide oxygenation during intubation and thus give more time for intubation before the patient desaturates. For Post-extubation oxygenation, HFNO has been found to be associated with lesser tachycardia and tachypnoea compared to lower flow oxygen modalities.

5. Oxygenation during flexible bronchoscopy [2]

HFNO can be effectively used as an oxygenation modality during flexible bronchoscopy procedures. It has the edge over low flow oxygen devices (nasal cannula, oxygen mask, non-rebreathing oxygen mask) by having a facility to provide 100% oxygen with some PEEP effect and without a mask covering the nasal and oral opening that is required for bronchoscope insertion.

6. In the emergency department for rapid improvement in dyspnea and hypoxia

In the emergency room, respiratory distress is the most common complaint to deal with. HFNO is found superior to low flow oxygen delivery devices in the rapid correction of hypoxemia, dyspnea and respiratory discomfort.

7. Do Not Intubate (DNI) patients

HFNO has been found to provide adequate oxygenation in patients of hypoxemic respiratory failure with DNI status and could be an alternative to NIV for these patients.

8. Hypercapnic Respiratory Failure [3]

Patients of COPD with hypercapnic respiratory failure are usually managed with NIV, though the compliance of NIV because of poor mask intolerance is an issue for many of them. HFNO has been found to increase the tidal volume in these patients; in some, it reduces breathing frequency, and in others, it decreases $PaCO_2$. For carefully chosen patients, because of comfortable application, HFNO can be tried, especially after stabilization of the acute event. Close monitoring of the effectiveness of HFNO is needed in these patients, and upgradation of ventilatory support in the form of NIV or mechanical ventilation is advisable if the patient is deteriorating.

8. Obstructive Sleep Apnea [3]

Positive airway pressure (PAP) therapy is the mainstay of obstructive sleep apnea (OSA) treatment, but compliance is a barrier for many to adopt the modality. Studies have found that HFNO for OSA reduces Apnea-Hypopnea Index (AHI), desaturation index, arousals and improves slow-wave sleep and quality of sleep. However, more studies are needed before we can start using HFNO for OSA as a definitive treatment, and even if used, its' effectiveness must be ensured and monitored.

When should we NOT use HFNO ?

Because of inadequate data to support the use of HFNO for various clinical indications, the absolute contraindication of HFNO is also not known [3]. Most of the relative contra-indications of NIV like altered consciousness, hemodynamic instability or maxilla-facial injury are also an issue of concern with HFNO. It should be carefully used with close monitoring in the conditions where NIV is contra-indicated (except claustrophobia where HFNO is very helpful) or failed to improve the clinical condition of the patient.

What should be the initial settings of HFNO ?

At the start, after explaining the utility and working of the HFNO to the patient, the initial setting could be the following :
Flow – 40 to 50 Litres/min
Temp – 37 degrees C
FiO_2 – As per oxygen deficit, for moderate to severe hypoxemia start with 100% and titrate thereafter as needed

How do we assess its success in managing the patient ?

Close monitoring is needed on vital parameters for the initial one hour during the use of HFNO. It improves respiratory rate and hemodynamic parameters within the first hour of use in most cases. Non-decreasing respiratory and pulse rate, poor SpO_2 despite high flow and oxygen support, an increasing $PaCO_2$, alteration in mental status, hemodynamic instability, and continued thoraco-abdominal asynchrony are signs of HFNO failure.[4]

Roca et al.[5] proposed and studied ROX (respiratory rate oxygenation) index, a ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate per minute in adult patients with hypoxemic respiratory failure caused by pneumonia and found it to be a simple and valuable tool to predict the outcome of HFNO (need intubation or not) and monitor progression.

ROX index = (SpO_2 / FiO_2) / RR (Respiratory rate)

The authors suggested :

1. ROX index greater than or equal to 4.88 measured at 2, 6, or 12 hours of initiation of HFNO is a determinant of HFNO success.
2. ROX index lesser than than 2.85, 3.47, and 3.85 at 2, 6, and 12 hours of HFNO initiation predicts HFNO failure with the specificities of 99.2%, 99.2%, and 98.4%, respectively.
3. If the difference between ROX index at 2 hours and 12 hours is > 2 (an increase), it predicts the success of HFNO.

As this study was carried out in a specific population and with specific criteria for intubation, the use of ROX index is currently limited and it needs to be studied in greater detail before it can be generalised.

How safe is HFNO ? What are its adverse effects ?

HFNO is a safe and comfortable mode of oxygen therapy, but not free from side effects, which include :

1. Inadvertently given high flow may cause headache in few patients.
2. It may lead to dryness of the upper airway and epistaxis if high flow is used without humidification.
3. Higher flows increase the likelihood of ineffective sealing of the passageways leading to air leaks, waste of oxygen and loss or reduction of the beneficial positive airway pressure effect
4. Because of its good compliance, it may delay intubation and mechanical ventilation and this may be associated with poorer outcomes in an inappropriately chosen subset of patients, especially during the acute phase of exacerbation of the underlying disease, e.g. COPD.

How useful was HFNO during the COVID-19 pandemic ?

During the first wave of the COVID-19 pandemic, there was a global concern of transmission of infection with the use of HFNO so the trend was to avoid its use which led to early intubation in a very high number of covid patients and the high morbidity and mortality associated with intubation followed. Down the course, studies found that the dispersion of smoke (considered droplets as surrogate) with the use of HFNO was equal to that of an oxygen mask at 15 L/min flow. This dispersion can be further reduced with the use of three-ply mask over the nasal interface of HFNO. Following this, HFNO became popular and increasingly used for the management of hypoxemia secondary to COVID-19, where it was found to be very effective not only in managing respiratory failure but also in conserving precious resources like mechanical ventilators and ICU beds, however, it also consumes oxygen resources because of the large volumes of oxygen required, necessitating an oxygen audit .

Studies have shown that :

- HFNO increases the compliance of the use of non-invasive modality.
- HFNO has a more than 60% success rate in managing severe COVID-19 patients.[6]

In conclusion, it can be said that HFNO can be a therapeutic modality of choice in patients with severe COVID-19 pneumonia, along with the other indications mentioned above, provided patients are carefully selected and monitored well.

Summary :

- HFNO is an oxygen supply system capable of delivering up to 100% heated and humidified oxygen at a flow rate of up to 80 litres per minute.
- HFNO is evolving as a therapeutic modality for respiratory failure and has many potential clinical applications.
- Since HFNO is a relatively new modality, it is recommended to organise training and demonstration sessions for physicians, nurses and respiratory therapists to familiarize them with its use and application in appropriate conditions and judiciously preserve oxygen supply and avoid waste.
- Advantages of HFNO compared with conventional oxygen delivery systems include higher flow rates at more precisely controlled FiO_2, improved efficiency of ventilation by CO_2 washout from the nasopharyngeal dead space, enhanced patient comfort, humidification of respiratory secretions and provision of PEEP.

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Oxygenation during Mechanical Ventilation

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Abstract :

Hypoxemia is the most common indication of mechanical ventilation and admission to intensive care unit (ICU). However, hypoxemia is the result of a myriad of pathophysiological alterations that result from various diseases. Understanding the underlying basic pathophysiology of hypoxemia is of paramount importance for choosing the optimum strategy for treatment of hypoxemia and respiratory failure. Increasing fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP), prone positioning, recruitment manoeuvres and few other strategies have been used to improve oxygenation status. However, each of these interventions is associated with some or the other adverse effects and some of these are not well supported by the published data. The utility of these potential interventions should be understood by all ICU physicians. This article discusses in brief the pathophysiology, interventions for correction, and monitoring of hypoxemia in the ICU.

1. Introduction :

If we observe a desaturating critically ill patient in our ICU, the most common reflex action would be to start supplemental oxygen or increase the fraction of inspired oxygen (FiO_2). Can we generalize this treatment strategy of giving more oxygen to all patients with hypoxemic respiratory failure? Patients with methemoglobinemia have an oxygen saturation (SpO_2) on pulse oximeter of approximately 85%, which does not increase after oxygen supplementation [1]. Patients suffering from pulmonary diseases with shunt physiology have minimal response to supplemental oxygen. In fact, there is a risk of oxygen toxicity, absorption atelectasis and worsening of hypoxemia if high FiO_2 is given for long duration [1]. Thus, understanding the pathophysiology of underlying disease(s) to decide appropriate treatment strategies is of utmost importance rather than just increasing supplemental oxygen. The terms hypoxia and hypoxemia are often used interchangeably but it is important to recognize the difference between the two. Hypoxia is defined as a reduction in oxygen at tissue level, whereas hypoxemia refers to a reduction in the partial pressure of oxygen in the blood. Various types of hypoxia and severity of hypoxemia based on measurable parameters are mentioned in Tables (Boxes) 1 and 2.

The importance of knowledge of the pathophysiology of different types of hypoxia can be understood with example that anemic hypoxia caused by low hemoglobin is due to low oxygen carrying capacity of the anemic patient's blood and the best treatment would be correction of the anemia with blood products. Circulatory hypoxia occurs when the patient's cardiac output and tissue perfusion are reduced as in cases of shock (e.g. hypovolemic shock). The treatment involves interventions which normalize the patient's cardiac output and tissue perfusion. Cyanide poisoning can lead to histotoxic hypoxia, where cyanide interferes with a person's ability to utilize oxygen to produce energy (cellular respiration). The treatment involves administration of a cyanide antidote (e.g., hydroxycobalamin). Hypoxemic hypoxia occurs due to lower than normal PaO_2 which can be a result of low FiO_2, hypoventilation, V/Q mismatch, shunt, diffusion limitation [1]. Thus, understanding the pathophysiology of hypoxia is essential before treating critically ill patients We will discuss the pathophysiology of hypoxemic hypoxia in greater detail in the next section.

BOX 1 : TYPES OF HYPOXIA	
Types of Hypoxia	**Common Causes**
Hypoxemic hypoxia	Low PaO_2, high altitude, hypoventilation
Anemic hypoxia	Lower than normal red cell count, abnormal hemoglobin, carboxyhemoglobin
Circulatory hypoxia	Reduced cardiac output, decreased tissue perfusion (e.g., shock)
Histo-toxic hypoxia	Cyanide poisoning

Table 1. Types and Common Causes of Hypoxia

BOX 2 : SEVERITY OF HYPOXEMIA			
Severity	**PaO_2 value**	**PaO_2 range**	**Oxygen saturation**
Mild	< 80 mmHg	60 to 79 mmHg	90 to 94 %
Moderate	< 60 mmHg	40 to 59 mmHg	75 to 89 %
Severe	< 40 mmHg	< 40 mmHg	< 75 %

Table 2. Severity of Hypoxemia with corresponding PaO_2 and SpO_2

2. Pathophysiology of Hypoxemic Hypoxia:

2.1 Low FiO_2 : High altitude dwellers suffer from chronic hypoxia and polycythemia (body's compensation to increase the oxygen carrying capacity) due to low FiO_2 at high altitudes. If they shift to an altitude near sea level (where FiO_2 increases), hypoxia and polycythemia get corrected gradually [2].

2.2 Hypoventilation : Ventilation can be defined as exchange of air between lungs and the atmosphere so that oxygen can be exchanged for carbon dioxide. During hypoventilation, this gaseous exchange decreases, which in turn leads to hypoxemia and hypercarbia (rise in $PaCO_2$). Hypoventilation can be due to abnormalities in the central nervous system, respiratory system or musculoskeletal system.

Minute Ventilation = Tidal volume X Respiratory rate.

Thus, minute ventilation is the amount of ventilation (gas entering/coming out from the lung) in a minute. The treatment of hypoventilation will be to increase minute ventilation in order to correct hypoxemia and hypercarbia. Increasing FiO_2 without increasing minute ventilation may correct hypoxemia, but will not correct hypercarbia, in fact it may worsen it [2].

2.3 Ventilation/Perfusion (V/Q) mismatch : In a normal upright person, the lung apex has more negative intrapleural pressure than the lung base. Thus, the alveoli at the lung apex are more distended as compared to those at the lung base. It is more difficult to distend an already distended alveoli at the apex. Thus, more ventilation (gas entering/coming out from the lung) occurs at the base as compared to the apex. Due to the effect of gravity, pulmonary blood flow (perfusion) is significantly greater at the bases as compared to the apex. Actually, the ventilation/perfusion ratio (V/Q) is < 1 at lung base but > 1 at lung apex. It implies that perfusion is more as compared to ventilation at lung base and when we move towards the apex, the fall in perfusion is significantly greater as compared to the fall in ventilation. This is the V/Q relationship in a normal lung. A V/Q of < 1 at lung base suggests a perfusion reserve i.e. pulmonary blood flow can increase its' oxygen carrying capacity if ventilation increases upto a point where V/Q = 1. A good example will be respiratory mechanics during exercise where lung reserves are utilized to match the increased oxygen demand. The amount of V/Q inequality (mismatch) decreases during exercise because of the more uniform topographical distribution of blood flow. If V/Q is > 1, it implies that perfusion has reached the level of its' maximum oxygen carrying capacity. If perfusion remains constant, there will be minimal increase in oxygen carrying capacity irrespective of the increase in ventilation.

Disorders of the airways (COPD, Asthma) and of the pulmonary circulation (pulmonary embolism, pulmonary arterial hypertension) have significant V/Q mismatch. This can be corrected by correcting the primary disorder (e.g. bronchodilators for airway obstruction, anticoagulation for pulmonary embolism, vasodilators for pulmonary arterial hypertension). There is significant perfusion limitation in critically ill patients with shock. Thus, if these patients have refractory hypoxemia, a supine position will negate the effect of gravity and cause a uniform topographical distribution of blood flow. This will optimize the V/Q ratio [2].

2.4 Shunt : Shunt is an important cause of hypoxemic hypoxia which is usually not corrected by supplemental oxygen. It occurs because a portion of blood is shunted from the oxygenation process in the lung and this deoxygenated blood eventually mixes with the oxygenated blood, lowering its PaO_2 [2]. The cause of a shunt can be pulmonary or extrapulmonary. It can be due to the involvement of airway (lung collapse), alveoli (pneumonia, ARDS, pulmonary edema), pulmonary vessels (pulmonary arterio-venous malformation), heart (septal defects) [1]. Contrast echocardiography with agitated saline can be used to differentiate intracardiac from intrapulmonary shunts. After administering agitated saline, appearance of bubbles in the left heart early (within three to five beats) after right chamber opacification suggests an intracardiac shunt. Later appearance of bubbles in the left heart (> 5 beats after first seeing bubbles in the right atrium) suggests pulmonary arterio-venous shunting [3]. Shunt will be corrected by treating the primary pathology. (e.g. removal of retained airway secretions which cause lung collapse, using positive end expiratory pressure (PEEP), higher mean airway pressure, recruitment manoeuvre to open the fluid filled and collapsed alveoli of ARDS, Coiling pulmonary arterio-venous malformation (PAVM), closing intra cardiac septal defects) [3]. The amount of shunt can be calculated from the equation :

$$\frac{Qs}{Qt} = \frac{(Cc'O2 - CaO2)}{(Cc'O2 - CvO2)}$$

where Qs is the shunted portion; Qt is total cardiac output, $Cc'O_2$ is the content of oxygen of the alveolar capillary (also called pulmonary end-capillary), CaO_2 is the arterial O_2 content, and CvO_2 is the mixed venous oxygen content [1].

3. Strategies to Improve Oxygenation during Mechanical Ventilation :

3.1 Supplemental Oxygen therapy : Increasing FiO_2 as a treatment strategy can treat most cases of hypoxemic respiratory failure, however the response to oxygen may be minimal in few patients (e.g methemoglobinemia, shunt, significant V/Q abnormalities). In cases of hypoventilation, supplemental oxygen may correct hypoxemia, but will not correct hypercarbia. While giving supplemental oxygen, every attempt should be made to maintain the FiO_2 below 0.6 to prevent complications of oxygen toxicity while keeping the PaO_2 between 60 and 90 mm Hg. This goal is not always possible, and sometimes a higher FiO_2 is required. Breathing 100% oxygen can lead to absorption atelectasis which can increase intrapulmonary shunting (i.e., shunt fraction), further contributing to hypoxemia. Target PaO_2 of 60 mm Hg and SpO_2 of 90% are acceptable lower limits for most adult patients. The desired FiO_2 can be set based on the formula [1] :

$$\frac{Known\ PaO2}{FiO2\ (known)} = \frac{Desired\ PaO2}{FiO2\ (desired)}$$

3.2 Mean airway pressure (Paw) : One approach that can be used to increase the PaO_2 involves increasing the Paw. Paw is the average pressure above baseline during a total respiratory cycle (I + E). Factors that affect Paw during positive-pressure ventilation include peak inspiratory pressure (PIP), total PEEP (auto-PEEP plus extrinsic or set PEEP), inspiratory-to-expiratory (I : E) ratios, respiratory rate (RR), and inspiratory flow pattern. A high PIP and PEEP, higher RR, higher inspiratory flow and greater inspiratory time will lead to increase in Paw. Paw is a major determinant of oxygenation in patients with ARDS because it affects mean alveolar pressure and alveolar recruitment and, therefore, oxygenation. The formula for calculation Paw and its graphical representation are mentioned below.

$$\bar{P}aw = \frac{1}{2}\left[PIP \times \left(\frac{\text{inspiratory time}}{\text{total respiratory cycle}}\right)\right]$$

When PEEP is used, the equation is as follows:

$$\bar{P}aw = \frac{1}{2}(PIP - PEEP) \times \left(\frac{\text{inspiratory time}}{\text{total cycle time}}\right) + PEEP$$

In the Pressure-time curve (Figure 1), a sum of pressure readings (i.e area under the curve) divided by the cycle time will give the value for mean airway pressure (Paw) [1].

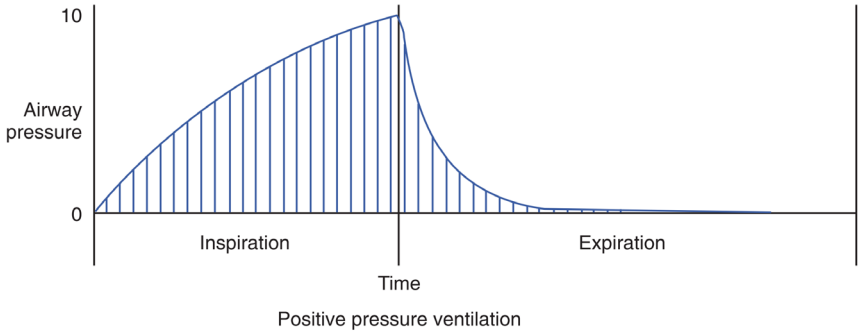

Figure 1. The Pressure-time curve

3.3 Positive end-expiratory pressure (PEEP) :

i) Indications : Functional residual capacity (FRC) usually decreases when a patient is intubated or placed in a supine position. The reduction in FRC is due primarily to the abdominal contents moving upward and exerting pressure on the diaphragm. Minimum level of PEEP (3 – 5 cm H_2O) will help preserve a patient's normal functional residual capacity (FRC). Therapeutic PEEP (5 cm H_2O or greater) is useful in the treatment of refractory hypoxemia caused by increased intrapulmonary shunting, decreased FRC and pulmonary compliance (e.g. ARDS, pulmonary edema, atelectasis, sleep apnea). PEEP helps to recruit collapsed alveoli while avoiding overdistention of already open alveoli. Both overdistention (volutrauma) and repeated collapse and re- expansion of alveoli (atelectatrauma) are associated with ventilator-induced lung injury (VILI) [1].
The following are the goals of PEEP/CPAP therapy [1]:

- Enhance tissue oxygenation to reduce the FiO_2 to safer levels (<0.6) as PEEP becomes effective.
- Maintain a $PaO_2 \geq 60$ mm Hg and SpO_2 at 90% or greater, at an acceptable pH.
- Recruit alveoli and maintain them in an aerated state.
- Restore functional residual capacity.

An effort is made to accomplish these goals while simultaneously sustaining cardiovascular function and avoiding lung injury. High levels of therapeutic PEEP (e.g., ≥ 15 cm H_2O) are beneficial for a small percentage of the patients with ARDS, but are often associated with cardiopulmonary complications (such as decreased venous return, decreased cardiac output, decreased blood pressure (BP), barotrauma and volutrauma), hence physiological response to therapy must be monitored carefully. For adults, PEEP is usually increased in increments of 3 to 5 cm H_2O. Approximately 15 minutes after an increase in PEEP, all ventilatory and available hemodynamic parameters are reassessed. Optimum PEEP is when target oxygenation is achieved at $FiO_2 < 0.40$ without profound cardiopulmonary side effects [1].

BOX 3 : INDICATIONS FOR POSITIVE END-EXPIRATORY PRESSURE (PEEP) THERAPY
• Bilateral infiltrates on chest X-ray film
• Recurrent atelectasis with low functional residual capacity
• Reduced lung compliance
• PaO_2 less than 60 mmHg on FiO_2 more than 50%
• PaO_2/FiO_2 ratio less than 300 for ARDS
• Refractory hypoxemia: PaO_2 increase less 10 mmHg with FiO_2 increase of 20%

Table 3. Indications for Positive End-Expiratory Pressure (PEEP) therapy

ii) Contra-indications : Disorders which lead to an increased risk of hemodynamic compromise and pneumothorax are contraindications to PEEP therapy.
Relative contra-indications : Hypovolemia, recent lung surgery
Absolute contra-indications : Untreated significant pneumothorax or a tension pneumothorax, bronchopleural fistulas, elevated intracranial pressures (ICP) [1].

iii) Interface : Positive pressure is commonly applied to the airway with a mask, nasal prongs, endotracheal tube, or tracheostomy tube. Each of these interfaces have their advantages and disadvantages. The common hazards of masks include skin necrosis, vomiting and aspiration, claustrophobia. With nasal CPAP, loss of pressure from the system can occur through the mouth, especially at high pressures (> 15 cm H_2O). Problems of nasal CPAP include gastric distention, pressure necrosis, swelling of nasal mucosa, and abrasion of the posterior pharynx [1].

3.4 Prone positioning : In most patients with ARDS, gravitational and geometric factors contribute to more uniform pulmonary aeration in the prone position as compared to supine position. This leads to decreased shunting and clinically significant improvements in oxygenation. In the prone positioning in severe acute respiratory distress syndrome (PROSEVA) trial where adults with PaO_2/FiO_2 (P/F ratio) < 150 who were intubated/ventilated for < 36 hours were included. The intervention arm received prone position ventilation for at least 16 consecutive hours, for 28 days, or until improvement to set standard. The primary outcome of all-cause mortality at 28-days was 16% in prone vs. 32.8% in supine arm ($p < 0.001$) [4]. Thus, early application of prolonged prone-positioning sessions has mortality benefit and should be given to all patients with severe ARDS. Similar benefits of awake prone ventilation and increase in oxygenation have been seen in cases of mild-to-moderate COVID-19 ARDS as well.

3.5 Recruitment manoeuvre (RM) : A recruitment manoeuvre is a sustained increase in pressure in the lungs with the goal of opening as many collapsed lung units as possible. It is performed in the management of patients with Acute Lung Injury (ALI) and ARDS. There are various ways of performing a RM. The most commonly used method is sustained inflation where in a well sedated patient, the ventilator is set to CPAP/spontaneous mode (mandatory rate = zero), and CPAP is increased to 30 to 40 cm H_2O for about 40 seconds. RM may improve oxygenation but is associated with its own hazards, hence it should be used in selected patients with refractory hypoxaemia as a rescue therapy. Potential complications of RM are barotrauma, such as pneumothorax, pneumomediastinum, subcutaneous emphysema and hypotension [1].

3.6 Inverse ratio ventilation (IRV) : Inverse ratio ventilation (IRV) which is usually given with pressure controlled mode of ventilation (PCV), called PCV-IRV or PC-IRV, is based upon the principle where inspiratory time (I) is greater than expiratory time (E), that is, I:E >1. Lengthening the inspiratory time increases mean airway pressure because more of the respiratory cycle is spent in inspiration, which may translate into improvements in oxygenation. However, IRV also limits the time for exhalation, potentially resulting in dynamic hyperinflation, auto-PEEP and hypercarbia. While increasing auto-PEEP may translate to improved oxygenation, it also results in high pulmonary pressures that may not be lung-protective. IRV with auto-PEEP plus applied PEEP may also compromise cardiac output. PCV–IRV should only be used as a "salvage" mode of ventilation in cases of refractory hypoxemia [3].

3.7 Extra-corporeal membrane oxygenation (ECMO) : ECMO is a form of Extra-corporeal Life Support (ECLS), a form of therapy that utilizes an external artificial membrane and a mechanical pump to provide gas exchange and systemic perfusion in patients with failure of lung and/or heart function. It is based on the hypothesis that more patients will survive if the lung is allowed to recover from its injury by a temporary rest period given by extracorporeal gas exchange [3]. In ECLS, venous blood is drained from a central vein via a cannula, pumped through a semipermeable membrane that permits diffusion of oxygen and carbon dioxide, and returned via a cannula to a central vein (VV ECMO) or major artery (VA ECMO). VV ECMO may be considered in patients with severe ARDS whose oxygenation or ventilation cannot be maintained adequately with best practice conventional mechanical ventilation and adjunctive therapies, including prone positioning. VA ECMO provides both respiratory and hemodynamic support, hence it can be used in patients with refractory cardiogenic shock and cardiac arrest. In an individual patient data meta-analysis of 429 patients from 2 major RCT's (CESAR and EOLIA) which compared ECMO to conventional management in patients with severe ARDS, 90-day mortality was 36% in the ECMO-group and 48% in the control group [relative risk - 0.75, 95% confidence interval (CI) - 0.6–0.94; p = 0.013; I^2 = 0%]. The authors concluded that ECMO had mortality benefit when compared to conventional ventilation in cases of severe ARDS [5]. Although ECMO is a promising intervention, it is associated with complications like bleeding, thrombosis, neurological injury and requires expertise, which is available in only few centres. Thus, ECMO is a safe and viable strategy for severe ARDS only when performed in experienced centres.

3.8 High-frequency oscillatory ventilation (HFOV) : HFOV is a mode of ventilation in which patients are supported with rapid pressure oscillations (300 cycles/min) that generate very small tidal volumes (1–2 mL/kg). Theoretically, the very small tidal volume prevents ventilator induced lung injury. In spite of the theoretical benefits of HFOV, the Oscillation for Acute Respiratory Distress Syndrome (ARDS) Treated Early (OSCILLATE) trial was stopped early, as the HFOV group appeared to have a higher in-hospital mortality compared with a low tidal volume, high PEEP control group [6]. Few clinicians use it as salvage therapy even if it is not supported by clinical trials [3].

3.9 Other interventions : Theoretically, inhalation of nitric oxide (NO) reduces pulmonary vascular resistance and selectively vasodilates pulmonary capillaries and arterioles that serve ventilated alveoli, diverting blood flow away from areas of shunt to these alveoli. Rapid inactivation of NO by hemoglobin warrants continuous delivery of gas through the ventilator circuit. If continuous delivery of NO is interrupted (e.g. during patient transport or due to NO supply exhaustion), precipitous and life threatening hypoxemia and right-sided heart failure may occur due to rebound increase in pulmonary vascular resistance. While demonstrating improvements in oxygenation in some patients, inhaled NO did not improve survival in any of the trials. Although Inhaled NO is not recommended as a treatment strategy for ARDS, it can be used as a salvage intervention [3].

Helium-oxygen gas mixture (Heliox) has a lower density than does oxygen, room air, or a mixture of the two, resulting in conversion of the predominantly turbulent flow to a more laminar pattern which decreases the work of breathing. It may be useful in management of upper airway obstruction when the obstruction is temporary and reversible The major limitation is an inability to deliver gas with an inspiratory fraction of oxygen (FiO_2) of more than 40%. Despite physiologic evidence and clinical reports of efficacy, prospective, randomized studies demonstrating improved outcome in patients receiving heliox are lacking [3].

4. Monitoring Oxygenation status in patients on Mechanical Ventilation :

4.1 PaO_2/FiO_2 (P/F) ratio : According to the Berlin definition, ARDS has been classified based on a ratio of arterial partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2). PaO_2/FiO_2 ratio < 100 in severe ARDS, 100 – 200 in moderate ARDS and 200 – 300 in mild ARDS [3]. Thus, by using the PaO_2/FiO_2 ratio, we can objectively define the severity of ARDS and monitor the oxygenation status. Despite the above classification, a PaO_2/FiO_2 threshold of 150 mm Hg has been used to define severe ARDS in various randomized trials. The goal of our therapy is to keep this ratio to its maximum value with lung protective ventilation strategy.

4.2 Oxygenation saturation (SpO_2) : SpO_2 is the most common non-invasive parameter monitored using a pulse oximeter, where the relative light absorption of oxyhemoglobin and deoxyhemoglobin is analyzed by the device and an oxygen saturation is calculated. To interpret the readings of a pulse oximeter, it is important to understand the physiology behind the S-shaped oxygen dissociation curve (Figure 2) . The upper flat portion of the curve suggests that even though there is a significant fall in PaO_2 (dissolved oxygen) from the maximum to 60 mm Hg, the oxygen carrying capacity does not decrease as proportionally because SpO_2 (percentage of haemoglobin bound to oxygen) falls to approximately 90%. If the PaO_2 falls further to 30 mm Hg, we reach the steep phase of the curve, where SpO_2 (oxygen carrying capacity) decreases significantly to approximately 60%. This correlation between SpO_2 and PaO_2 is known as the 30-60-90 rule of the oxygen dissociation curve. Thus, in hypoxemic conditions, fall in oxygen carrying capacity is gradual till the SpO_2 reaches 90% but not below. Hence, it is necessary to supplement oxygen if SpO_2 is less than 90%. Also, at SpO_2 less than 90%, the pulse oximeter may provide inaccurate readings of SpO_2 and the oxygen carrying capacity. In disorders of abnormal hemoglobin such as methemoglobinemia, SpO_2 is not reliable as the light absorption spectrum of hemoglobin changes [3].

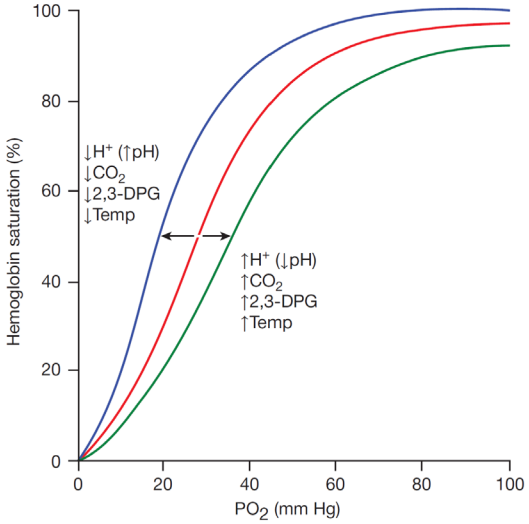

Figure 2. Oxygen Dissociation Curve : Normal curve (red), shift of curve to right (green) and left (blue) with causes of the shift. [2,3-DPG → 2,3 diphosphoglycerate] [3]

4.3 ROX index : ARDS has a high mortality rate ranging from 30 – 50%. As the disease severity increases, it is important to prevent both early and delayed intubation to maximize our chances of a favourable treatment outcome. ROX index has been studied to determining high flow nasal cannula (HFNC) failure (need or not for intubation). ROX index is defined as the ratio of oxygen saturation as measured by pulse oximetry/FiO_2 to the respiratory rate. It is easy to calculate and does not require a blood gas analysis. As per a study done by Roca et. Al., a ROX < 2.85, < 3.47, and < 3.85 at 2, 6, and 12 hours of HFNC initiation, respectively, were predictors of HFNC failure, whereas a ROX > 4.88 at 12 hours of HFNC initiation had a lower risk of HFNC failure [7]. ROX index is an additional tool to assess the oxygenation status. It has an additional advantage as it objectively guides us regarding the need for intubation and mechanical ventilation.

$$\text{ROX} = \frac{SpO2 \,/\, FiO2(\%)}{Respiratory\ rate}$$

5. Weaning from Assisted Ventilation :

Candidates for possible discontinuation and removal of mechanical ventilation should have adequate gas exchange in the lungs (i.e., PaO_2/FiO_2 > 150 – 200 mm Hg and a normal or baseline arterial $PaCO_2$) while breathing non-toxic concentrations of oxygen (FiO_2 < 50%) and at low levels of PEEP (< 8 cm H_2O). In addition, there should be no evidence of myocardial

ischemia, severe tachycardia (> 140 beats/min), circulatory shock, or ongoing sepsis (e.g., fever). Once a candidate is ready to wean, a spontaneous breathing trial (SBT) is given for 30 to 120 minutes using pressure support (5 cm H_2O) or a T-piece. Patient is weaned from the ventilator after a successful SBT [8].

6. Conclusion :

Hypoxemia is the common physiological end result of myriad of pathological conditions. Identification of the underlying pathophysiology of hypoxemia is of paramount importance in the management of respiratory failure. Hypoxemia may be corrected with just oxygen supplementation in some cases whereas in many other cases it requires highly sophisticated equipments such as high flow nasal cannula, non-invasive ventilation, endotracheal intubation and mechanical ventilation, and extra-corporeal membrane oxygenation in extreme cases. FiO_2, PEEP/CPAP, prone positioning and recruitment manoeuvres are useful strategies for improvement of oxygen levels.

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Oxygenation during Bronchoscopy and other Pulmonary Interventions

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Introduction :

Interventions in pulmonary medicine either involve intubating the central airway or negotiating into the pleural space. The former includes rigid and flexible bronchoscopy, including the newer flexible interventional modalities such as endobronchial ultrasound (EBUS), whereas the latter includes pleural drain insertion and medical thoracoscopy. Primarily, these pulmonary interventions are indicated in patients who present with respiratory symptoms due to diseases that have already compromised the existing respiratory mechanics. Hence, achieving adequate ventilation and oxygenation during these interventions, in such patients who already have an overburdened respiratory system, is often challenging. In this chapter, we will review the literature available on the effects of various pulmonary interventions on oxygenation, and discuss methods to achieve adequate oxygenation during these procedures.

Flexible Bronchoscopy in the non-critically ill patient :

Simple flexible bronchoscopy alone, without any diagnostic sampling, performed under local anaesthesia and in the absence of oxygen supplementation, is associated with peri-procedural transient hypoxemia [1,2] . Additional performance of bronchoalveolar lavage (BAL) during diagnostic flexible bronchoscopy is associated with a further decline in arterial oxygen saturation, and the degree of hypoxemia may increase with larger volumes of saline instillation for BAL procedure [2,3]. Likewise, other diagnostic interventions during flexible bronchoscopy, such as endobronchial biopsy and bronchial washings, are also associated with hypoxemia [4]. The arterial oxygen concentration, in most cases, however, returns to its initial normal baseline values, usually within ten minutes of completion of the procedure [3,5]. Hypoxia during bronchoscopy may be attributed to upper airway obstruction by pre-existing lesions, mechanical obstruction of airways by the bronchoscope, suctioning and ventilation-perfusion mismatch, excessive sedative-hypnotic use, patient position during bronchoscopy and baseline lung function [4,6]. Interestingly, intraprocedural and post procedural hypoxemia is documented, albeit less profound, even when bronchoscopy is performed under the cover of nasal oxygen with flow rates upto 3 L/min, under local anaesthesia and without any sedation [4].

Sedation during awake bronchoscopy performed with oxygen supplementation, is not significantly associated with greater hypoxemia as compared to flexible bronchoscopy without sedation. Contrary to popular belief, moderate sedation, in addition to reducing procedure duration and improving patient tolerance during the procedure, is not associated with increased respiratory depression when given for flexible bronchoscopy performed with oxygen supplementation. However, in the absence of oxygen supplementation, performing flexible bronchoscopy with moderate sedation is associated with significant hypoxemia [7]. Hence, it is recommended that awake bronchoscopy with local anaesthesia, should routinely be performed with supplemental oxygen delivered via either nasal cannulae or a pharyngeal catheter, especially in patients who already have low baseline oxygenation or possess risk factors for desaturation during the procedure [8,9,10] . It may be argued that oxygen supplementation during flexible bronchoscopy may not prevent oxygen desaturation during the procedure [8]. However, in the setting when desaturation occurs, the availability of supplemental oxygen helps to reduce the intensity and duration of desaturation, as well as hastens recovery to baseline oxygenation levels [1,8] . In the event that significant hypoxemia does develop during awake bronchoscopy with or without moderate sedation, it can be corrected with remedial measures which include increasing oxygen flow via nasal cannulae or insertion of an intratracheal catheter for oxygen delivery, reversal of sedation, withdrawal of the bronchoscope from the airway, bag and mask ventilation, and rarely, endotracheal intubation [8].

Oxygen delivery through high-flow nasal cannula (HFNC) has been studied as an alternative to standard conventional oxygen therapy by nasal cannula in patients undergoing flexible bronchoscopy on an outpatient basis. Compared to conventional oxygen therapy, HFNC improves gas exchange, prevents loss of end-expiratory lung volume, as well as prevents any increase in diaphragm activation [11]. Endobronchial ultrasound (EBUS), an advanced flexible bronchoscopic procedure, when performed under moderate intravenous sedation, may be associated with hypoxemia and hence is traditionally performed under cover of oxygenation via conventional nasal cannulae. HFNC has been studied in patients without baseline hypoxemia undergoing EBUS, and has not been found to reduce either the occurrence or the degree of desaturation when compared to conventional oxygen therapy [12,13].

Flexible Bronchoscopy in the critically ill hypoxemic patient :

Flexible bronchoscopy in the intensive care settings is even more challenging, considering that these patients are already hypoxemic, and are on supplementary oxygenation or ventilation via invasive or non-invasive mechanical ventilation. These patients are at risk of developing worsening hypoxemia during the procedure [14,15,16,17] . In intubated patients on mechanical ventilation, diagnostic flexible bronchoscopy with performance of protected specimen brushings and bronchoalveolar lavage, is associated with hypoxemia, irrespective of the volume of saline instilled for lavage [15,16,17,18]. Underlying lung disease, higher positive end-expiratory pressure (PEEP) requirement, and ventilator-patient dyssynchrony were predictors of procedure related hypoxemia in intubated patients [15,16]. Often, the hypoxemia is transient, easily manageable, and responds well to increased oxygen delivery or a transient change in ventilatory settings, and is usually associated with complete recovery within 24 hours [16,17,19]. To reduce the occurrence and severity of procedure related hypoxemia, it is recommended to increase the delivered oxygen flow rate to 100% for preoxygenation prior to the procedure, and to continue the higher flow rate during the procedure and in the immediate post bronchoscopy period. The ventilator settings should be in control mode, ideally volume control with pressure alarm limits raised to permit adequate delivery of gas without pressure cycling [20].

In the critically ill non-intubated patients with hypoxemic respiratory failure, bronchoscopy is often associated with a post procedural increase in oxygen and ventilatory support requirement, and occasionally necessitates endotracheal intubation as well [21]. In a non-intubated patient with hypoxemia already on supplementary oxygenation, bronchoscopy can be performed by either increasing the flow of oxygen delivered by existing nasal cannula, or switching to alternative oxygen delivery devices, which include laryngeal mask airway with continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), and high flow nasal cannula. In the former, we must remember the limitations in terms of maximum oxygen that can be effectively delivered by the existing nasal cannula, and also anticipate possible oxygen desaturation once the bronchoscope is negotiated into the central airway, local lignocaine is instilled, and suctioning is performed, and the available leverage that the existing nasal cannula can compensate for, by increasing the oxygen flow rate [22,23]. However, when the baseline oxygen saturation is just about maintained in near low normal range with reasonably adequate oxygen flow rates by the nasal cannula, then it would be advisable to switch to alternative oxygen delivery devices during flexible bronchoscopy. A retrospective single center experience of flexible bronchoscopy procedures performed in patients with severe hypoxemia under laryngeal mask airway (LMA) with CPAP demonstrated high diagnostic yield without significant hypoxemia and requirement for endotracheal intubation [14]. Non-invasive positive pressure ventilation is less invasive when compared to LMA, and is now the favoured oxygen delivery device in patients with moderate hypoxemia, and also in immunocompromised patients with severe hypoxemic respiratory failure undergoing flexible bronchoscopy, and is associated with a favourable diagnostic yield without any procedure related emergent endotracheal intubation [24,25,26] . Nowadays, NIPPV masks with bronchoscope ports are easily and readily available. Both LMA with CPAP and NIPPV improve oxygenation by increasing mean airway pressure, which in turn increases the tidal volume, alveolar recruitment, and subsequently improve ventilation-to-perfusion (V/Q) ratios [23,24]. Though bronchoscopy under NIPPV support in patients with moderate-to-severe hypoxemia is relatively safe, caution must be taken to monitor hemodynamic and respiratory parameters very closely during the procedure as these patients are prone to develop sudden worsening hypoxemia that may warrant endotracheal intubation [26,27]. For patients with mild-to-moderate hypoxemia already receiving NIPPV, bronchoscopy with BAL can be performed under NIPPV cover, albeit with risk for subsequent endotracheal intubation in a small percentage of patients [27]. Other diagnostic procedures such as bronchial and transbronchial lung biopsies have been performed in patients with moderate hypoxemia under NIPPV cover, and may carry a higher risk of worsening oxygenation [28,29].

Apart from the above techniques, high flow nasal cannula (HFNC) can also be considered for oxygenation during flexible bronchoscopy. HFNC is superior to conventional nasal cannulae by generating higher flows that can meet the inspiratory demands of the patient, which in turn generates a positive end-expiratory airway pressure, reduces dead space, and increases alveolar ventilation [23]. HFNC can prevent hypoxemia and provide adequate oxygenation, albeit less effectively when compared to NIPPV during bronchoscopy and bronchoalveolar lavage in patients with moderate hypoxemia, but may sometimes be insufficient to achieve adequate ventilation, especially so after administration of sedation or in patients with poor oxygenation at baseline [30,31,32]. HFNC can also provide adequate oxygenation in other procedures apart from

bronchoalveolar lavage, such as endobronchial biopsy, evacuation of mucus plugs or blood clots and EBUS [33]. Overall, though HFNC is superior to conventional oxygen therapy via nasal cannula in patients with mild to moderate hypoxemia, it ranks inferior to NIPPV especially in the setting of patients with severe hypoxemic respiratory failure, co-existing cardiac failure or hemodynamic instability [34].

Rigid Bronchoscopy :

Rigid bronchoscopy is superior to flexible bronchoscopy in terms of intra procedural airway management and oxygenation. Hence, the issues related to oxygenation and procedure related hypoxemia are less as when compared to flexible bronchoscopy. Prior to intubation with a rigid bronchoscope, preoxygenation is performed with induction of general anaesthesia, which generally provides an adequate oxygenation window for the bronchoscopist to intubate with the rigid bronchoscope. Occasionally, at the time of induction with general anaesthesia, even with adequate preoxygenation, there may be failure to achieve adequate levels and period of oxygenation long enough for the bronchoscopist to intubate and secure the airway with the rigid bronchoscope. At this critical conjuncture, HFNC can be considered as an alternative delivery device to achieve adequate oxygenation during the apneic state at the time of induction with general anaesthesia and before intubation with the rigid bronchoscope [35].

Medical Thoracoscopy :

Medical thoracoscopy procedure is usually performed with a combination of local anaesthetic infiltration along with moderate intravenous sedation. Considering that patients who undergo medical thoracoscopy are either having pleural effusion or pneumothorax that result in ineffective ventilation, the addition of moderate intravenous sedation may lead to hypoxemia during the procedure. Anticipating intraprocedural hypoxemia, medical thoracoscopy is commonly performed under supplemental conventional oxygen therapy delivered by a nasal cannula or face mask [36]. There are no studies that have compared performance of medical thoracoscopy with and without supplementary oxygen therapy. An alternative to conventional oxygen therapy is HFNC, which has been demonstrated to be of utility in maintaining oxygen saturation in patients undergoing non-intubated video assisted thoracoscopic lung surgery (VATS). This raises the possibility of considering HFNC in patients undergoing medical thoracoscopy as well.

Summary - Key Points :

- In non-critically ill patients without baseline hypoxemia and with risk factors for desaturation, it is recommended to perform flexible bronchoscopy under oxygen cover with conventional nasal cannula with a flow of 2 – 3 L/min.
- In non-critically ill patients with mild hypoxemia, it is recommended to perform bronchoscopy under oxygen cover via conventional nasal cannula, or high flow nasal cannula.
- In critically ill patients with moderate-to-severe hypoxemia who are not intubated and are receiving conventional oxygen therapy, it is recommended to consider performing bronchoscopy under the cover of NIPPV. HFNC is an alternative option in these patients. However, facility for NIPPV and endotracheal intubation should ideally be available as a backup in the event of worsening oxygenation or ventilation with HFNC.
- In critically ill patients with moderate-to-severe hypoxemia who are already on HFNC or NIPPV, the same oxygen delivery device can be continued during bronchoscopy. However, all precautions for possible emergent airway endotracheal intubation should be readily available by the bedside in the event of an emergency, including ineffective oxygenation, ventilation, or cardiorespiratory arrest.
- In critically ill intubated patients on mechanical ventilation, it is recommended give 100% preoxygenation prior to and during the procedure.
- For rigid bronchoscopy, HFNC can be considered as an alternative for oxygen delivery during induction with general anaesthesia prior to intubation with the rigid bronchoscope.
- For medical thoracoscopy under moderate intravenous sedation, it is recommended to provide the patient with supplemental oxygen if the patient is hypoxemic, or has risk factors for developing hypoxemia during the procedure.

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Oxygen Concentrators




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Abstract :

Oxygen supplementation is a crucial add-on therapy for patients with acute respiratory failure as well as for those with chronic lung diseases and hypoxemia. The aim of supplemental oxygen is to ensure adequate oxygenation of arterial blood thereby facilitating normal oxygen supply to peripheral tissues, assuming a normal cardiac output. Oxygen therapy can be short-term (acute) or long-term. Unique issues related to long-term oxygen therapy for chronic hypoxemic conditions include limitation of costs of treatment, ensuring steady maintenance of supply without need for repeated procurement of manufactured oxygen, conservation of available resources etc. The advent of oxygen concentrators has revolutionalized domiciliary oxygen therapy and has proved to be cost-effective, efficacious, safe and convenient. This article summarises the technical aspects, ancillary equipments, advantages and disadvantages of oxygen concentrators and provides practical tips for practitioners with regard to prescription of these devices for their hypoxic patients.

Keywords : Oxygen therapy, hypoxemia, oxygen concentrators, domiciliary oxygen devices

Introduction - Oxygen as a life-saving gas :

Oxygen is a life-saving and life supporting gas. Aerobic metabolism and energy derivation in humans hugely depends on an adequate oxygen supply to tissues. Cellular respiration in aerobic organisms results in release of electrons from an energy substrate. The released electrons are delivered to molecular oxygen through a series of exchange reactions constituting the respiratory chain. Cytochromes, flavin enzymes, non-heme iron proteins, etc are crucial members of the electron transport chain. Surplus energy is liberated during this process and is trapped as ATP, which in turn is consumed at cellular level by the organisms for various life sustaining activities. Lack of adequate oxygen supply at the cellular level shifts metabolism towards an anaerobic path, which is far less efficient as an energy source and not sustainable for the long term. Hence, sustenance of life in humans mandates a constant and adequate oxygen supply.

Oxygen delivery to tissues depends on the content of atmospheric oxygen, alveolar ventilation, efficiency of gas exchange, and patency of the circulation. Tissue hypoxia results within a span of as little as 4 minutes of malperformance of any of these mechanisms because the oxygen reserve in the body tissues is meagre. Increased tissue oxygen demand or inability to utilise available oxygen can also result in inadequate energy generation. The hallmark of any indication that necessitates supplemental oxygen therapy is the presence of tissue hypoxia, which can be either acute or chronic. The indications for oxygen therapy have broadened from in-patient care to out-patient settings also for patients with severe and progressive chronic pulmonary diseases and resultant chronic hypoxemia. As opposed to healthcare in acute care settings, long-term treatment with oxygen presents unique challenges. Cost of therapy, conservation of oxygen consumption and portability of equipments (source and delivery device) are of paramount concern while considering or prescribing chronic oxygen therapy, both for the physician as well as the patient. Oxygen concentrators merit a special place in domiciliary or long-term oxygen therapy as they fulfil the previously mentioned requirements. The present review attempts to familiarise the clinician with the basic functioning, advantages and recent developments in the field of oxygen concentrators.

What are the Various Sources of Oxygen ?

Delivery of oxygen in acute care setting is typically from pre-manufactured and stored oxygen. In contrast, oxygen for chronic domiciliary use may either be delivered from a manufactured source (Oxygen tank or cylinder) or produced at the place of utilisation (Oxygen concentrator). Oxygen gas is manufactured by commercial gas producers under strict safety conditions and stringent norms, with guidelines for purity as well as packaging. Regulatory systems advocate monitoring and tracking each time oxygen is repackaged, to ensure the quality of the gas. Oxygen produced in the domiciliary setting is made possible with devices that filter out nitrogen from atmospheric air, leaving oxygen as the main component of the residual gas. The regulation on purity of gas production is suboptimal, with no monitoring facilities for gas quality other than manufacturer recommendations. The utility of stationary concentrators is well established, with reasonable reliability of performance. Portable oxygen concentrators (POCs) are newer additions whose performance and convenience of usage are increasingly being recognised.

What are the Basic Features of Oxygen Concentrators ?

Stationary concentrators are a convenient source of oxygen in the domiciliary setting, with reasonably acceptable and reliable gas quality. The major limitations are the requirement of uninterrupted power supply and the capabilities of the device. Oxygen concentrators for home use are well established and are emerging as the standard of care for stationary use. These units are capable of producing oxygen with 90% ± 5% purity at flow rates of 1 to 10 litres per minute. The weight of present generation devices is approximately 10 kg, much less than the weight of earlier models (in the mid-1970s), which used to weigh as much as 80 pounds. Advantages of the newer generation devices are lower power consumption, reduced noise, improved performance, and lesser maintenance costs. They are equipped with up to 100 feet long tubing to the patient, to allow for mobility within the home. A device that supplies flow rates of up to 10 L/min can address the needs of a sicker patient and is marketed with only slight increase in size, weight, power consumption and operational costs. Oxygen concentrators that can refill cylinders have also been developed.

How do Oxygen Concentrators generate Oxygen ?

Oxygen concentrators ensure a safe, convenient, environment friendly and continuous supply of oxygen-enriched air. They are sometimes also referred to as oxygen generators. Oxygen concentrators consist of a series of filters or sieves mounted within them. These filters remove dust, bacteria and other particulates as atmospheric air circulates through them. For oxygen generation Pressure Swing Adsorption Technique with two Zeolite filters is used. These filters are fed with pressurized ambient air drawn from the atmosphere which moves through Zeolite filters, which trap nitrogen within their micro pores. This affinity of Zeolite for nitrogen is a property by virtue of the chemical nature of zeolite and the atomic structure of nitrogen. The residual portion of the ambient air, which contains mainly Oxygen along with other air constituents pass through the filter. Since the major constituent of ambient air is nitrogen (78%) and oxygen (21%), the de-nitrogenised effluent air coming out of the filter is made up predominantly of oxygen. A schematic model of oxygen generation in oxygen concentrator is shown below in Figure 1. While Filter 1 filters the air, Filter 2 purges out nitrogen through the vent. The system operates until it generates acceptable oxygen levels. A typical oxygen concentrator is capable of generating oxygen flows of 0.5 to 5 litres per minute (low-flow supply oxygen concentrators), while some models may generate up to 10 litres per minute (high-flow supply oxygen concentrators).

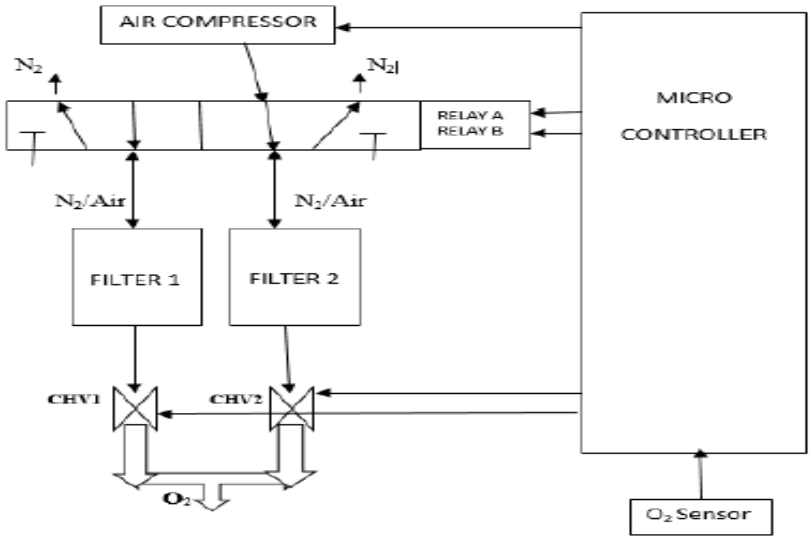

Figure 1. Schematic explanation of Oxygen generation in an Oxygen Concentrator

(Source : Sameer SK, Eswaran P. Development and integration of oxygen generator for home air conditioner. IOP Conference Series: Materials Science and Engineering 912; 2020: 042054. Reproduced under the terms of the Creative Commons Attribution 3.0 license)

What are the Merits and Demerits of Stationary versus Portable Oxygen Concentrators ?

Portable oxygen concentrators are the newest arrival in the commercial market for patients who prefer a compact, lightweight and easy-to-carry oxygen source. They vary in weight, size, maximum sustainable flow rates, battery backup duration, as well as other parameters. The differences in performance between stationary and portable concentrators revolve around :

1) Maximum oxygen delivery
2) Dimensions and weight
3) Power options
4) Cost of device

Stationary oxygen concentrators provide higher oxygen flow rates, but have a higher procurement cost. Portable oxygen concentrators have the charm of smaller size and less weight; greater flexibility with regard to power sources are also afforded by POCs. For patients who are frequent travellers, a portable oxygen concentrator is the preferred choice. Most POCs use lithium-ion batteries, which degrade over time. Most of these batteries can be recharged approximately 300 times without significant degradation.

What is "Pulsed Oxygen Delivery" ?

The traditional domiciliary oxygen therapy is via low-flow continuous oxygen delivery systems, which are simple to use and design; but these systems have the inherent disadvantage of being wasteful with regard to oxygen consumption. Flow of oxygen during the entire expiration period of the respiratory cycle is useless with regard to its availability for gas exchange, except a small amount which may be retained for subsequent inhalation (Figure 2). Moreover, oxygen supplied during the late inspiratory phase also reaches only the conduit airways rather than gas-exchanging lung units, and can also be considered to be wasted, since it does not participate in gas exchange. Technology has made it possible for oxygen to be delivered intermittently and selectively only during those phases of the respiratory cycle where gas exchange is feasible, which ensures that oxygen is conserved rather than wasted. An oxygen source when coupled with an oxygen conserving device releases oxygen only when inspiration is detected and delivers a quantum of oxygen. Such devices are known as pulsed oxygen delivery systems (PODs). Portable oxygen concentrators (POCs) can detect the patients' inspiratory effort as a negative pressure fluctuation within the cannula or interface and deliver an oxygen pulse to the patient only when inhalation is sensed in the above manner. Their triggering technology is highly sophisticated and is more sensitive than that of the older oxygen conservers. Hence, POCs may be grouped under oxygen conserving devices.

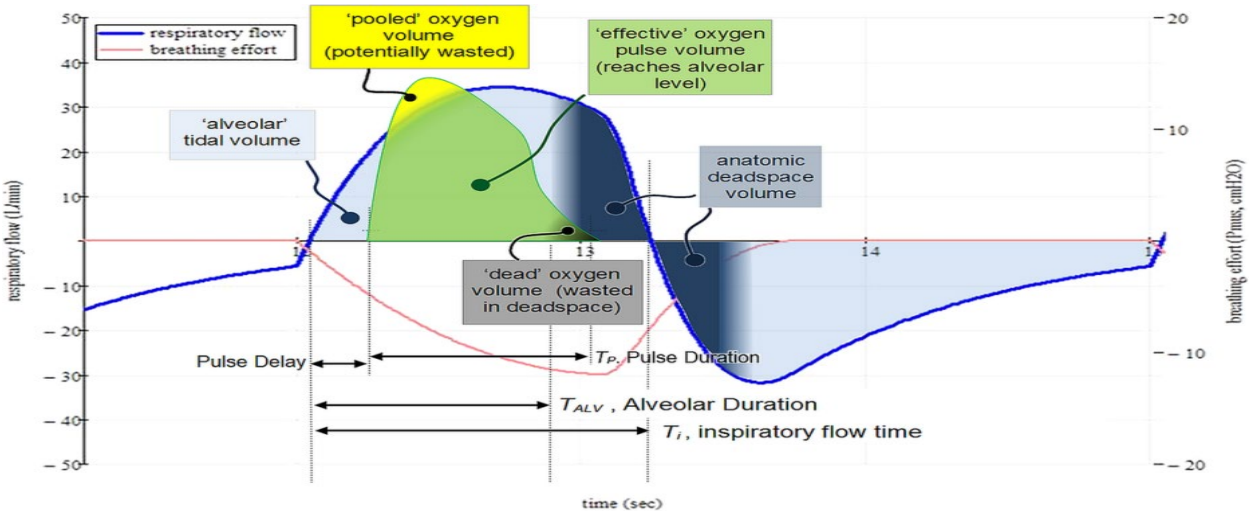

Figure 2 . Respiratory flow and Oxygen flow for a single breath during pulsed dose oxygen delivery

(Source : Martin DC. Contemporary portable oxygen concentrators and diverse breathing behaviours -- a bench comparison. BMC Pulm Med. 2019 Nov 19;19(1):217. Reproduced under the terms of the Creative Commons Attribution 4.0 International License)

What are the Advantages of Oxygen Concentrators over Oxygen Cylinders ?

Oxygen concentrators may be viewed as manufacturing units which produce oxygen by removing nitrogen and concentrating the oxygen received from ambient atmospheric air. They do not require refilling, unlike oxygen cylinders. The cost and effort involved in refilling or replacing oxygen cylinders is substantial, and this is a premier advantage of using a concentrator . Oxygen concentrators use electricity to "extract" oxygen and hence ensure an unlimited supply of oxygen. Portable concentrators are capable of delivering oxygen during travel and transit since they have inbuilt rechargeable batteries. Some

of these models provide up to 12 hours of continuous supply after which the battery needs to be charged. Over a longer period of months to years, concentrators are far more cost-effective and conservative than compressed gas cylinders.

The major limitation of oxygen concentrators is their mandatory dependence on an electrical power source, without which they cannot function. Furthermore, the economical investment is a one-time lumpsum amount, which may prove challenging in countries like India where healthcare equipment expenses need to be borne out-of-the pocket by patients. Unexpected power outages are common in our country and one needs to provide an alternative, either by setting up a backup power generator at home or a backup oxygen cylinder. Although not substantial, device maintenance and services involve nominal expense. Patients using stationary oxygen concentrators are advised to clean filters weekly and regularly service the concentrators at intervals. The generation of heat and substantial noise, which was a routine phenomenon in old models, is substantially reduced with the later-generation models. Flow rates more that 3 – 4 litres per minute may necessitate incorporation of a humidifier. Table 1 summarises the advantages and disadvantages of oxygen concentrators as compared to oxygen cylinders.

Parameter	Oxygen Concentrator	Compressed Oxygen Cylinder
Requires power source	Yes	No
Transportation	Only at the time of installation	Yes, regularly for refilling/replacement
Exhaustion of O_2 supply	No, as long as power supply uninterrupted	Yes
Day-to-day care	Moderate, includes cleaning of device and filters	Minimal care only needed
Initial (Procurement) cost	Higher	Lower, but subsequent refilling or replacement adds to the net cost
Recurring costs	Small, restricted to maintenance and electricity charges	High – cylinder refilling and transportation
Check list	Check for low O_2 output	Check for pressure leaks
Precautions	Care of tubing, filter	Flammable

Table 1 . Comparison of Oxygen Concentrator with Compressed Oxygen Cylinder

What are the Specifications of commonly used Oxygen Concentrators ?

Although many models of stationary and portable oxygen concentrators are available in the market, the authors have chosen to focus on a couple of models as prototype examples for descriptive discussions. We, the authors clarify that we do not have any conflict of interest with any particular company's products or models; selection of a particular brand and model is solely based on commercial availability, procurement cost, services etc, and that we are not endorsing any model or company. The Everflo Q marketed by Philips has operating variables as specified in Table 2 and has the advantage of being lightweight with the comfort of low noise and the economy of low power consumption. The add-on accessories to be acquired include compressor intake filter, micro disk filter, humidifier and humidifier connector tube, stand-alone or integrated low-flow flow meter, flow meter locking kit etc. Filter change is usually not required for two years. Installation and setting-up is easy and the user manual is patient friendly, and the maintenance costs are economical.

Parameter	Everflo-Q (Philips)	Nuvo-Lite (Nidek)
Oxygen concentration (FiO_2) provided	93% + / - 3% @ flow rate 3 litres / minute	90% (+ 6.5% / -3%) @ flow rate 5 litres / minute
Flow rate generated	0.5 – 5 litres per minute	0.125 – 5 litres per minute
Input Voltage	12 VAC + / - 10%	230 VAC
Average power consumption (Watts)	350	290
Noise generated (Decibels)	45	< 40
Weight (Kg)	13	13.6
Dimensions (mm)	584 x 381 x 241	580 x 360 x 220

Table 2 . Comparison of two commercially available Oxygen Concentrators

Simply Go is Philips' first oxygen concentrator that offers the benefits of a continuous flow mode in a lightweight, easy-to-carry design and weighs as little as 4.5 kg. SimplyGo has a pulsed mode which detects respiratory effort and delivers the necessary volume of oxygen during inspiration, and a sleep mode which has a lower trigger sensitivity. Competing features are offered by Nidek Nuvo Lite model with a smaller size and lower power consumption and is summarised in Table 2 (above)**.** A careful choice of individual patient requirements and resources needs to be considered before acquiring/purchasing a particular model and this needs a detailed patient – doctor – caregiver discussion.

Figure 3. An Oxygen Concentrator

What are the Therapeutic Gaps, Current Challenges and Future Directions ?

The challenges associated with oxygen concentrators include the initial procurement cost, the upper ceiling to the rate of oxygen that can be delivered, bulk of the device, power consumption, noise levels etc. Many of these gaps have already been addressed in the modern generation devices. One specific need from a patient perspective will be the availability of a handy portable device which can ensure oxygen delivery at a substantial flow rate, and which can be procured at an affordable price. Marketing industries may be directed to focus their research on this particular arena to bridge this unmet need, from patients and physicians alike.

Summary :

- Oxygen concentrators have cemented their place in chronic domiciliary oxygen therapy in our country.
- Attractive features include the lack of need for any separate oxygen source, portability, longevity of the device and excellent performance.
- Technological advancements have made new generation devices more patient friendly.
- Further research to address unmet patient needs might overcome the shortcomings of existing devices.

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Oxygen Crisis in Pandemics

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Introduction :

The World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) as an outbreak a Public Health Emergency of International concern on 30th January 2020 and with the rising number of cases and its high infectivity, declared it as a pandemic on 11th March 2020. It is a global crisis that has burdened healthcare systems worldwide. The pathogen responsible for COVID-19 has been identified as a novel member of the enveloped RNA beta-coronavirus genus of the family Coronaviridae and due to morphological and genetic similarities with coronaviruses that cause Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV), has been named the Severe Acute Respiratory Syndrome - Coronavirus - 2 (SARS-CoV-2).

We have seen the effects of COVID-19 as a multiple system disorder with increased understanding and data from multiple studies and case reports coming from different parts of the world. Amongst these, the most important is the involvement of lungs, which causes the most devastating effects, ranging from a simple upper respiratory tract infection to full-blown respiratory failure. From these studies we do know about the clinical characteristics and epidemiology of the disease, what we don't know completely yet is its impact on lung pathophysiology. The clinical spectrum of the disease is quite varied and has been classified into mild (81%), moderate (14%) and critically ill (5%) [1,2].

Complications of COVID-19 :

- The most common complication in patients with severe COVID-19 is severe pneumonia
- Other complications may include Acute Respiratory Distress Syndrome (ARDS), Sepsis and Septic Shock and Multiple Organ Failure (including Acute Kidney Injury and Cardiac Injury)
- Complications are more prevalent in at-risk groups including : Older Age (> 70 years); those with co-morbid conditions such as cardiovascular disease, lung disease, diabetes and those who are immunosuppressed [3] . In a small proportion of these, the illness may be severe enough to lead to death.

Most patients with severe pneumonia present with progressive Type 1 respiratory failure and have pronounced hypoxemia, sometimes with no signs of dyspnea or sense of breathlessness. This phenomenon is called as silent or happy hypoxemia [4]. This disproportionate severity of hypoxemia and relatively mild respiratory symptoms are seen in multiple studies from around the world. One such study comes from China where Guan et. al. reported that out of 1099 hospitalised COVID-19 patients, only 18.7% of patients reported dyspnea, despite low PaO_2 / FiO_2 ratios and abnormal computed tomography (CT) chest scans with requirement of supplemental of oxygen seen in 41% of patients [5]. A study from New York showed that 27.8% of patients admitted for COVID-19 required supplemental oxygen therapy and 12% of hospitalised patients required invasive ventilation, among which 88% of them died [6]. Studies have shown that hypoxemia is independently linked with in-hospital mortality [7] . Thus, oxygen administration at the right time can be life saving.

There are three important steps involved in oxygenation. These include:

1. Transfer of oxygen via alveoli
2. Transfer of oxygen to the tissues
3. Removal of carbon dioxide from blood into alveoli and from them into the environment

A disturbance in any of these three processes leads to Respiratory failure

Pathophysiological Mechanisms of Tissue Hypoxia

Arterial hypoxemia

- Low inspired oxygen partial pressure (high altitude)
- Alveolar hypoventilation (sleep apnea, opiate overdose)
- Ventilation perfusion mismatch
- Right to left shunts

Failure of oxygen hemoglobin transport system

- Inadequate tissue perfusion
- Low hemoglobin concentration
- Abnormal oxygen disassociation curve (hemoglobinopathies, high carboxyhemoglobin)
- Histotoxic poisoning of intracellular enzymes (cyanide poisoning, septicemia)

Table 1. Mechanisms and Causes of Hypoxia

Oxygen Delivery systems :

A wide variety of cheap oxygen delivery systems are available. The flow rates of mask and valve design allow delivery of inspired oxygen of concentrations ranging from 24 to 90% (FiO_2 24 – 90%). The two main parameters on which the flow of oxygen depends are the minute volume (MV) and the flow rate of ventilation. The greater the ventilation the lower the FiO_2 for a given flow rate of supplemental oxygen. A fixed FiO_2 cannot be achieved in a patient with a varying ventilatory requirement unless the total ventilatory minute volume is provided at the required FiO_2 .There are two basic types of masks which either deliver the entire (high flow mask) or proportional (low flow mask) requirement of the patients ventilatory requirement. High flow systems can deliver upto 40 litres/min flow of gas and ensure that the patients breathing pattern, which may at times be irregular does not affect the FiO_2. Venturi valves (based on Bernoulli's principle) are used in these masks and the inspired oxygen levels are controlled from FiO_2 between 24 – 60% .

Oxygen masks :

High flow, jet mixing masks : are useful for accurately delivering low concentrations of oxygen (24 – 35%). Delivery of FiO_2 doesn't get affected by pattern of ventilation. They are better in Type 2 respiratory failure (as in chronic obstructive pulmonary disease) as they improve hypoxemia but reduce the risk of retaining carbon dioxide. As the mask is flushed with high flow rates rebreathing of expired gas is not a problem.

Low flow masks : are useful for achieving a concentration of up to 60% with moderate oxygen flow rates (6 – 10 L/min). These are mainly used for patients with Type 1 respiratory failure (e.g. pulmonary oedema, pulmonary embolism). The flushing is not adequately done in these type of masks, expired air can accumulate and hence these cannot be used in Type 2 respiratory failure as they may lead to further carbon dioxide retention.

Rebreathing and anaesthetic type oxygen masks : Partial rebreathing masks incorporating non-rebreathing valves and reservoir bags are being used more and more in cases of Type 1 respiratory failure (especially in COVID-19 pneumonia) and can provide concentrations greater than 60% at low oxygen flow rates.

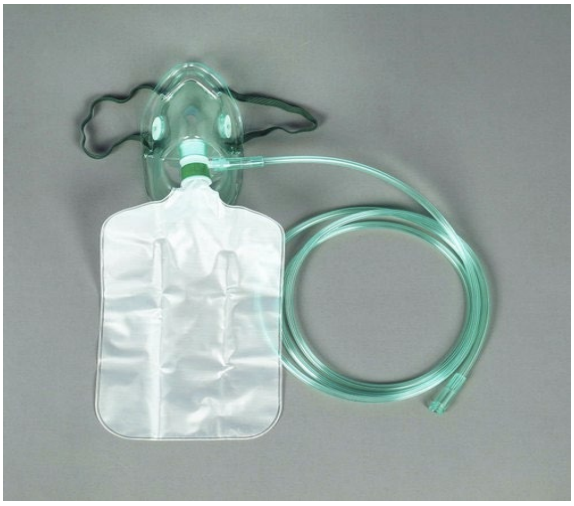
Other interfaces and devices :

Nasal prongs : are simple and convenient to use. FiO_2 depends on the flow rate of oxygen (1 – 6 L/min) and varies according to ventilatory minute volume. At an oxygen flow rate of 2 L/min the oxygen concentration in the hypopharynx of a resting subject is 25 – 30%.

Non-invasive ventilation (NIV) : NIV refers to delivery of ventilatory support without the need for an invasive artificial airway (an endotracheal or tracheostomy tube). There are two types of NIV : Continuous (CPAP) and Bi-Level Positive Airway Pressure (BiPAP or BPAP). It is generally accepted that NIV is often used in short-term life-threatening respiratory conditions, such as pulmonary oedema or when intubation carries a greater risk than other benefits, for example, patients with chronic Type 2 respiratory failure arising from Chronic Obstructive Pulmonary Disease (COPD). It avoids intubation by assisting in alveolar ventilation and improves gas exchange parameters. Other uses of NIV are in nocturnal hypoventilation where it has also been proven to be effective.

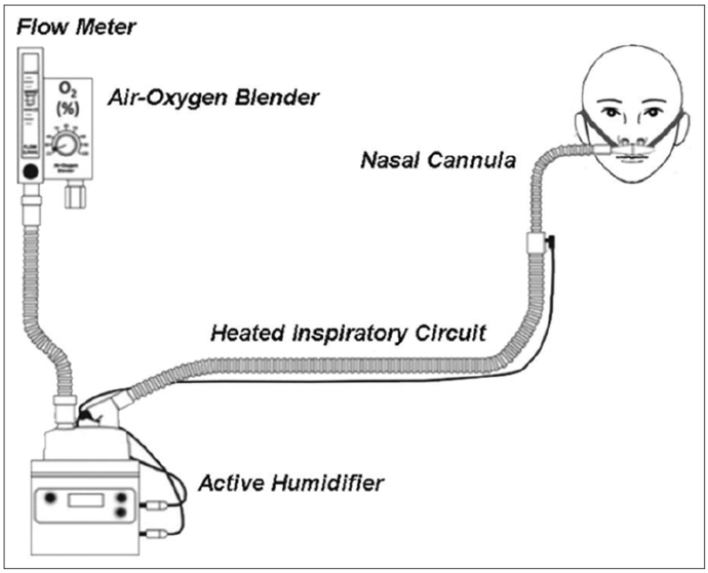
High flow nasal oxygen / cannula (HFNO or HFNC) : involves using nasal cannulae and positive pressure is provided to the airways. Advantages of using HFNO over other methods include the humidification of oxygen to prevent dehydration of the airway passages, high flow rates to provide carbon dioxide "washout", a reduction in the anatomical dead space, provision of Positive end-expiratory pressure (PEEP) and delivery of oxygen at an FiO_2 close to 100%.

A. Face Mask



B. Non-Rebreathing Bag Mask (NRBM)

C. Oro-nasal Mask used for Non-Invasive Ventilation



D. High Flow Nasal Oxygen (HFNO)

Figure 1. Different Interfaces and Devices used for Oxygen Delivery

Modality	What you set	What you get	Notes
Simple Nasal cannula	1 – 6 L/min	25 – 45% FiO_2	Easy, typical first line
Simple Face mask	6 – 10 L/min	40 – 50% FiO_2	Not typically used
Venti-mask	4 – 15 L/min, different valves	25 – 50% FiO_2	Not typically used
Non-rebreathing mark (NRBM)	10 – 15 L/min	~ 100% FiO_2	Short term rescue therapy
HFNC (HFNO)	Any FiO_2 , Flow rates up to 60 L/min	Any FiO_2 ? PEEP	Excellent longer-term choice, consider in all extubated patients
BiPAP (BPAP)	Any FiO_2 , IPAP, EPAP	Pressure support ventilation without intubation	Last line before intubation

Table 2. A Brief Comparison of different Oxygen Delivery Devices and Interfaces

Use of NIV in the COVID era :

During the initial outbreak in China, it was suggested that early intubation and invasive ventilation should be done in patients with COVID-19 pneumonia rather than using NIV [3] . Later on, in countries such as Italy which faced a shortage due to limited number of ventilators and other resources being exhausted, continuous positive airway pressure (CPAP) was used and appeared to have a better and significant effect than initially thought [8]. CPAP is usually started at a higher levels than the intrinsic levels of around 5 cm H_2O. In severe COVID 19 patients, initial settings for CPAP suggested are 10 cm H_2O with FiO_2 60% [9]. Positive End Expiratory Pressure (PEEP) is the pressure which prevents alveolar collapse by maintaining pressure in the patient's airway, which distends the alveoli to such an extent that it improves gaseous exchange. BiPAP is usually used in patients with chronic respiratory disease, such as COPD, so it may be useful in COVID-19 for patients who have co-morbidities such as COPD in addition to COVID-19 [10]. BiPAP has two settings for pressure namely IPAP (inspiratory positive airway pressure) and EPAP (expiratory positive airway pressure). In most studies done in NIV, it has been found that to achieve adequate tidal volumes, the IPAP can range from 12 to 35 cm H_2O of pressure. Expiratory Positive Airway Pressure (EPAP) works on the same principles as PEEP in CPAP devices, preventing alveolar collapse on expiration, at a pressure which is maintained above the atmospheric pressure. A risk of volu-trauma (over-distension) and barotrauma is present if the patient is not monitored properly. Emerging evidence from Italy showed that NIV may not be sufficient in all cases of type 1 respiratory failure due to severe COVID 19 pneumonia [11]. Review of some early studies suggests more than 50% of patients required re-intubation and it is now thought that NIV support may, at best provide a bridge for respiratory support for this group of patients where fatigue remains a significant symptom, and assistance in breathing is needed to aid recovery.

Use of HFNO in the COVID era :

The use of HFNO in COVID has two main issues : its effectiveness and safety. Early studies from China showed that there was risk of aerosolization of virus with use of HFNO and NIV, but overall data suggesting that is scarce. In 2012 during the epidemic of SARS (severe acute respiratory syndrome) a meta-analysis showed there was no increased risk of healthcare workers (HCWs) being infected with SARS-CoV when using HFNO [12]. Recently some studies have recommended use of HFNO in hypoxemia due to severe COVID-19 pneumonia which leads to lesser rates of intubation or may delay it [13]. Several studies have shown that HFNO was found to be more comfortable in comparison to other non-invasive strategies [14]. However, given the high efficacy of HFNO to oxygenate patients, closely monitoring its use in COVID-19 patients is crucial to avoid any delay in intubation. Monitoring respiratory rates and pulse oximetry, apart from clinical assessment, is essential.

Can Two be better than One ? Use of HFNO and NIV alternatively in COVID-19 :

Initially in view of COVID-19 being a contagious infectious disease which spreads by the inhaled route via aerosolization of virus particles, NIV and HFNO were not being preferred and early intubation was the way to go in critically ill patients with hypoxia and respiratory failure. But as evidence emerged that the prognosis of these patients was not very good with failure

to extubate them, NIV and HFNO were considered, and, subsequently with this evidence many studies were done where the first line of treatment was given as HFNO or NIV. A retrospective study from China showed that in patients where HFNO was used as the first-line treatment and had HFNO failure they were shifted to NIV; and, conversely; in patients where NIV was used as first-line therapy and had NIV intolerance they were shifted to HFNO. It was found that in critically ill patients of COVID-19, the duration of HFNO plus NIV (HFNO + NIV) didn't increase intubation or mortality rates [15].

Advantages of HFNO :

1. Oxygen delivery is comfortable, decreasing risk of treatment failure
2. Easy to implement with good patient comfort as the soft nasal cannulae are usually well tolerated
3. Work of breathing is reduced
4. Patient can be fed orally and oral hygiene can be easily maintained
5. No risk of aspiration as compared to full face mask interfaces (in BiPAP)
6. Accurate FiO_2 delivery

Disadvantages of HFNO :

1. Some patients are unable to tolerate the high flow rates because of nasal discomfort
2. Irritation of the nasal mucosa
3. Low flow oxygen is not humidified and leads to dry nose, dry throat and nasal pain.

Pitfalls in oxygen therapy with BiPAP :

1. Effective clearance of secretions is impaired.
2. Cannot be used in patients with drowsiness or impaired level of consciousness
3. Mask-face interface is difficult to manage - *"one size fits all"* masks do not, in fact, fit all; and patients with unusual facial anatomy or paucity of facial soft tissue (e.g. in cachexia) will have more difficulty
4. Mask leak is uncomfortable and decreases the effectiveness and compliance of the therapy
5. Work of breathing may be increased (i.e. mandatory mechanical breaths are usually impossible or dangerous)

Oxygen Crisis before reaching the hospital during the COVID-19 pandemic :

Most patients contracting COVID-19 don't require oxygen support and can be managed by self isolation at home and monitoring their symptoms. Inspite of that many patients who went on to develop hypoxemia did require special attention and monitoring due to the exceptionally high number of these cases and the current infrastructure unable to cope with the load, this became particularly evident during the second wave of COVID-19 in 2021, when patients were unable to find vacant hospital beds. These patients were being managed at home in consultation with their respective doctors, with oxygen supplied from oxygen cylinders or concentrators. Patients were also advised to do awake proning whenever possible and it has been shown to be a very effective measure in improving oxygenation. However, managing these COVID-19 patients at home has the following disadvantages :

1. Monitoring of patients is not uniform and proper
2. Oxygen concentrators and cylinders are sometimes not sufficient to improve hypoxemia, particularly in severe cases of COVID-19
3. In case of deterioration, patient may need to be shifted to a better equipped setting which includes Intensive care unit (ICU)

Pros and Cons of Oxygen Concentrators versus Oxygen Cylinders :

OXYGEN CONCENTRATORS	
Pros	**Cons**
Unlimited supply of oxygen as it produces oxygen from compressing room air. Will never run out of oxygen	Continuous power is required either through electrical power outlet or batteries.
Lightweight and portable	Often noisy due to many mechanical components working at a single time
Good for home as well as hospital use	Expensive but single time cost (unlike cylinders)
OXYGEN CYLINDERS	
Pros	**Cons**
Power is not required. Pressurized oxygen present inside cylinder	Heavy and lifting the cylinder can be a tedious task. Not easily portable
Lower initial cost. Can be taken on rent and refilled as per the need	Contains a limited amount of oxygen, which will invariably finish and get exhausted at some point
Mostly silent and makes no sounds or beeps	Greater long-term cost due to repeated refilling

Table 3. Advantages and Disadvantages of Oxygen Concentrators and Oxygen Cylinders

Oxygen Crisis in hospital settings during the COVID-19 pandemic :

The single most important life-saving intervention for moderate to severe COVID-19 cases with hypoxemia is administration of medical oxygen. In the face of the COVID-19 pandemic, particularly the second wave, whose impact in many nations was far more devastating than the first pandemic, the world dealt with shortages of oxygen supply leading to national and global oxygen crisis, which was more due to non- anticipation of the oxygen demand, and interruption of the supply chain, rather than a shortage or lack of production of medical oxygen. As the number of cases rose rapidly and no one anticipated the sharp steep rise, the supply chain for providing oxygen was found to be lacking in many situations, under different circumstances. The oxygen crisis was made worse with compounding issues like black marketing of oxygen cylinders, so much so that several oxygen cylinders and concentrators were being hoarded by these black marketeers and the cost of medical oxygen rose rapidly. The other problem faced during the pandemic was oxygen rationing wherein all the hospitals were given at least some regular oxygen supply but it was under calculated, or inappropriately used, thereby discouraging these facilities to admit more critically ill patients who required admission. These requirements were calculated on the patient load basis, however the oxygen requirement of a patient doesn't remain static during his/her illness, and can increase from 2 L/min to as much as 15 L/min within minutes to hours. Therefore this concept of oxygen rationing was fundamentally flawed and unscientific. To keep up with the demand oxygen was airlifted from other countries, liquid oxygen was diverted from industries to hospitals, cryogenic oxygen tankers were imported and all the medical oxygen plants in the country were running to their full capacity. In India, the demand for medical oxygen, which in pre-COVID times, was around 700 MT per day sharply escalated to 6,600 MT per day during the second wave of the COVID-19 pandemic and the judiciary had to step in to direct all sources of oxygen, including industrial sources, to be reserved for medical use. The COVID-19 pandemic taught us several important lessons, for one, never to take oxygen, a gas abundantly found in the air we breathe for granted, and; secondly, the necessity to strengthen our health care system with special attention to oxygen supply and storage as well as strategies to optimize oxygen usage and avoid wastage.

Use of Awake Proning (at home and hospital) :

As targeted and other therapies are being developed for COVID-19, optimisation of supportive management needs to be done. Awake proning is one such strategy for supportive management of COVID-19 which helps in improving oxygenation, by redistribution of regional blood flow and perfusion to the lungs. It is now being implemented in COVID-19 guidelines and has become a standard of care in patients with suspected or confirmed COVID-19 disease [16].

The physiological advantages of awake proning are as follows :

1. Decreases ventilation-perfusion mismatch
2. Decreases pleural pressure gradient between the dependent and non-dependent areas of lungs
3. Decreases shunting, with more a homogenous distribution of oxygenation

Using awake proning in COVID-19 patients with hypoxemia oxygen requirement can decrease their overall oxygen requirement and helps to conserve oxygen for other patients who may be in greater need of it. This can help in preventing another oxygen crisis in the future by judiciously using oxygen for only those patients who require it.

Key Learning Points – Possible Solutions for Prevention of further similar situations and Better Preparedness :

- Setting up (installation) of oxygen plants and cryogenic tank facilities (preferably nearer to hospital sites) which should be managed properly and not fall prey to disuse.
- Oxygen supply chain to be made more robust and to remain ready for any such need arising in the near future.
- Titration of oxygen given to the patient should be done regularly by the doctors and nursing staff to avoid wastage of oxygen and to ensure that it is administered only when needed.
- An Oxygen audit (described separately in another chapter in this newsletter) should be carried out by all hospitals/treatment facilities on a regular basis.
- Hoarding and black marketing of oxygen cylinders and concentrators should be made strictly punishable and strict laws should be enacted to ensure punitive action taken against the culprits.

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Oxygen Audit for Respiratory Health Services

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Introduction and Objectives :

The gas Oxygen is used in Medicine for the treatment of hypoxia, not dyspnea. Antoine Lavoisier (France) coined the term "Oxygen" in 1777. Carl Scheele (Sweden) and Joseph Priestley (England), in the 1770s, also made valuable contributions towards its' discovery.

Oxygen Audit : Why ?

Oxygen, as a drug, has been used to treat patients for over a century now, however, it still remains one of the most inappropriately prescribed drugs leading to considerable misuse with significant ramifications. The ongoing COVID-19 pandemic has caused immense pressure on already fragile healthcare system, especially in the developing countries, which has since then been under extreme scrutiny from all sections of society, including print, electronic and social media. Hospitals have struggled to keep up with increasing oxygen requirements to cope with the deluge of patients in respiratory failure. An oxygen audit committee was set up by the Hon'ble Supreme Court of India in May 2021 to assess overall medical oxygen requirement in different states and union territories and whether demand was being matched by supply from Centre. The interim report of this committee sparked a huge controversy by allegedly reporting a significant disparity between demand and supply in certain places with the supply outweighing demand in some states and being insufficient to match demand in others. The matter remains under judicial scrutiny.

This highlights the importance of treating Oxygen as any other drug with a finite resource and reserve. Following established protocols for oxygen prescription and use will result in appropriate use of Oxygen as a precious resource and reduce wastage.

The objective of this article is to provide guidance on appropriate and safe use of oxygen in patients.

An Overview of Oxygen Use and Administration :

Oxygen is mainly used therapeutically, to treat hypoxia. Use of oxygen in a palliative context to abate breathlessness in terminal conditions (advanced cancer/cardiorespiratory illness) is not recommended unless there is clear evidence of hypoxia, however, it could be considered in rare situations exclusively by specialist teams, with formal assessment of its' effects on symptoms or the quality of life [1]. Hyperbaric oxygen (Oxygen delivered at pressures greater than 1 Atmospheric pressure) is used in uncommon conditions to further augment tissue oxygen delivery, e.g. Air embolism, Decompression sickness, carbon monoxide poisoning, acute trauma/crush injury, non-healing ulcers, wound healing, etc.

Hypoxemia is defined as partial pressure of arterial O_2 (PaO_2) < 60 mm Hg or arterial Oxygen saturation (SpO_2) < 90%, in subjects breathing room air [2]. Supplemental oxygen is used in patients whose PaO_2 or SpO_2 falls below these levels. British Thoracic Society (BTS) guidelines, suggest use of oxygen for SpO_2 < 94%, unless there is underlying chronic lung disease with risk of hypercapnic respiratory failure, wherein supplemental oxygen is indicated if SpO_2 < 88% on room air [3].

Oxygen therapy is usually prescribed as one of the following :

- Short-term or Acute Oxygen therapy
- Long-term Oxygen therapy (LTOT)
- Short burst Oxygen therapy
- Ambulatory therapy
- Travel Oxygen

LTOT is defined as supplemental oxygen used for at least 15 hours per day. Information derived from the landmark NOTT (Nocturnal Oxygen Therapy Trial) and U.K. MRC (Medical Research Council) trial helped outline the criteria for LTOT [1,4] :

- Resting PaO_2 < 55 mm Hg or SpO_2 < 88%
- PaO_2 55 – 59 mm Hg or SpO_2 88 – 90% with evidence of Cor Pulmonale or Polycythemia [Hematocrit (Hct) > 55%]

The above criteria only applies to patients with stable underlying cardio-respiratory disease. LTOT assessment should not be carried out during an acute exacerbation [1]. Pulse oximetry alone is not ideal for LTOT assessment [1]. Patients should undergo formal assessment for LTOT after a period of stability of at least 8 weeks from their last exacerbation. Two blood gas measurements, at least three weeks apart, should be performed to confirm need for LTOT [1].

Patients who have failed oxygen weaning in-hospital but are otherwise stable may be prescribed LTOT if their resting SpO_2 $\leq$ 92%, to facilitate discharge. These patients will need short interval follow-up with further blood gas results [1]. Additionally, domiciliary oxygen may also be used for Sleep desaturation, Exercise desaturation or for palliative purposes, as mentioned above.

Oxygen Delivery Systems are classified as :

1. Low flow – variable FiO_2 delivered, maximum flow rate 8 L/min (nasal prongs, pillows, face masks)
2. High flow – Fixed, precise, controlled FiO_2 delivered, flow rates 8 – 15 L/min (Venturi masks, hoods, tents, High Flow Nasal Oxygen)
3. Reservoir (essentially low flow) – variable FiO_2 delivered, useful for acute/short term management, flow rate required 8-15 L/min (Re-breathing or Non-re-breathing masks [NRBM]).

A Review of Literature and Related Guidelines :

Basic guidelines on oxygen treatment, its' indications and implementation have been laid down by the BTS [1,3]. A literature search on Oxygen Audit globally revealed numerous articles, a few of which are summarized below.

Surveys :

1. Shankar and Muthaiah, 2000. Audit on prescription of long-term oxygen treatment, Bassetlaw District General Hospital, NHS, 1993-1998 on 34 patients. 70% patients were prescribed when clinically unstable (exacerbation of underlying respiratory condition). Only 53% underwent repeat ABG documenting successful correction of PaO_2 to > 60mm Hg without unacceptable $PaCO_2$ rise. No patients were re-assessed after 3 weeks. 32 out of 34 patients continued using O_2 concentrator when reviewed 6 months later [5].

2. Singh *et al*, Adequacy Assessment of Oxygen Therapy, Jaipur, 2000. In 35.5% patients there was no oxygen flow from the source at all, despite being connected whereas in 35.2% cases the oxygen flow rate was found to be below the rate prescribed [6].

3. Jamil A and Pratibha B, 2011. Oxygen prescription and oxygen therapy on the wards according to British Thoracic Society guidelines : Experience of an acute trust in the U.K. A study on 740 patients. 11% were on supplemental oxygen. Only 30% had proper prescription and mode of delivery documented [7].

4. Szulc A *et al*, 2012. Audit of oxygen prescribing practices in a district general hospital, 2012 : 21 out of 51 patients (41%) had oxygen prescribed correctly. 13 patients had COPD, 6 of whom (46%) were found to have SpO_2 within appropriate range and only 3 (23%) had the target range correctly specified and documented [8].

5. BTS Emergency Oxygen Audit Report 2015 : An audit of 55,208 patients. 7741 patients (14%) were using oxygen. 52.7% had a prescription for oxygen within the documented target range. 42.5% received supplemental oxygen without a proper prescription. In patients within the prescribed target range, 9.5% were saturating at below range and 21.5% were above [9].

6. Ward based oxygen therapy audit, Telford's Princess Royal Hospital, NHS, 2015 on 70 patients. 61% patients had a formal O_2 prescription documented. 95% of those with a prescription had a target SpO_2 range documented. 63% of those with documented range were appropriately oxygenated as per target [10].

7. Sieber and Osterwalder, 2016. Data collected before and after implementation of oxygen treatment algorithm. After intervention, there was a relative reduction of 18% patients receiving supplemental oxygen [11].

8. Erwan L'Her *et al,* 2017 found out that automated O_2 administration reduced incidence of hyperoxia and duration of oxygen therapy, improved time spent within SpO_2 targets and helped quicker weaning off O_2 [12].

9. Abhilash KP *et al*, 2020. In a large cohort, the number of patients receiving oxygen reduced from 9.6% to 4.8% after implementation of strict prescribing protocol, as found in a study conducted in the Emergency Department at Christian Medical College, Vellore, India in 2016-17 [13].

Excerpts from a few surveys organised by The Royal Liverpool and Broadgreen University Hospitals, University of Liverpool, U.K. [29] are as follows :

- Despite established national protocol, 50% of survey participants (health care workers) said Oxygen was rarely prescribed on a drug chart or equivalent.
- 75% health care workers said they were aware of a local Specialist Oxygen assessment team, to whom they could refer patients to in need.
- Nasal cannulae were the most accessible consumable on a regular basis, followed by Venturi masks.
- Oxygen prescriptions most commonly mentioned the FiO_2 range (57%), rather than flow rate in L/min (14.3%).
- 65% said Oxygen was prescribed for patient comfort.

There is a dearth of information in the Indian healthcare system. One of the ways forward would seem to be the formulation of a central patient information database, accessible by doctors and health care workers at different corners of the country, similar to the National Health Services (NHS) in the U.K., which could make data compilation and analysis relatively simpler. It is also very difficult to cater to the massive population of our country and maintain follow-up appropriately and according to protocols. COVID-19 has posed a huge challenge on our healthcare system with oxygen deficits occurring all over the country. This has highlighted the importance of reliable data on oxygen consumption and the need to follow strict oxygen treatment protocols.

Home Oxygen Compliance *:*

Compliance remains an issue, as with any other drug that needs regular consumption. Even with the most modern portable concentrators, oxygen does pose a burden on an individual's mobility. Also, the landmark trials have shown that LTOT results in survival benefit and improves cardio-pulmonary hemodynamics, only when used for a minimum of 15 hours per day. This could easily translate to a patient feeling "tethered" to oxygen tubes for at least 15 hours a day.

A few studies which looked into patient compliance with LTOT are summarized as follows :

1. Pepin *et al*, 1996. A study of 930 patients. Only 45% patients adhered to the instructions of oxygen use for $\geq$ 15 hours per day. The patients who were significantly more hypoxic, hypercapnic and showed greater airflow obstruction on Spirometry were the ones who used LTOT more effectively. A follow-up home visit with further supplementary education was found to improve oxygen use [14].

2. Peckham *et al*, 1998. Two groups, one with formal assessment and training provided by the Respiratory department. The second group (control) had been prescribed LTOT from outside the department without formal training. 82% in the formal training group used LTOT for greater than 15 hours compared to 44% in the other group. Both groups had similar understanding of the risks of smoking but 2% of the first group were actively smoking compared to 15% in the control group [15].

3. Walshaw *et al*, 1998. A study on 61 patients. Only 46% patients used concentrators for the recommended minimum of 15 hours per day. 49% patients had inappropriate oxygen prescriptions, for less than 15 hours per day [16].

4. Nasilowski *et al*, 2009. A study on 30 patients with a 14-month follow-up. 11 out of 30 patients (37%) adhered to the prescription through the entire follow-up duration. Mean oxygen use in the non-compliant group was 9.6 +/ -2.7 hours/day. Compliance reduced from 48% in the first month to 30% in the second month [17].

5. Gauthier *et al*, 2018. Compliance to home oxygen studied in 115 patients. 40% patients had suboptimal Oxygen usage. Compliance also decreased over time [18].

Oxygen for Palliative Care :

Consensus for use of supplemental oxygen in palliative care, purely for symptom relief, is fairly unequivocal in that it is not recommended up front. Evidence suggests no beneficial effect of oxygen over air in refractory dyspnea. However, in absence of documented hypoxia and where other modalities of pharmacological (opioids, benzodiazepines) and non-pharmacological treatment (relaxation techniques, hand-held fans) have been exhausted, BTS recommends administration of oxygen in select cases under the care of specialist teams with proper documentation of its' effect(s) on symptoms and/or quality of life.

Surveys :

1. Bruera *et al*, 2003. No significant difference observed between 2 groups (Oxygen vs air) in terms of dyspnea, fatigue or distance walked [19].

2. Philip *et al*, 2006. No significant difference observed in symptomatic relief of dyspnea on a visual analogue scale or preferences expressed. Oxygen saturation measures did not correlate to ratings of dyspnea [20].

3. Currow *et al*, 2009. The study population was a cohort of patients (advanced cancer or life-limiting illness) referred to Hospice Care service. No clinically significant improvement observed in SAS (symptom assessment score) despite oxygen administration [21].

4. Abernethy *et al*, 2010. No additional symptomatic relief of breathlessness seen in patients subjected to nasal oxygen compared to room air via a concentrator [22].

5. Davidson and Johnson, 2011 . A Review article. Palliative oxygen therapy is not recommended without evidence of reversibility of symptoms. If considered on an individual basis, a clinical review should be performed after 3 days to assess clinical benefit and merit of treatment continuation [23].

Oxygen Safety :

Despite being a lifeline for a huge proportion of patients who seek healthcare for various reasons, oxygen treatment comes with its own share of risks and side-effects.

- Free radical induced tissue damage : In hyperoxic conditions, generation of free radicals overcomes the cell's natural capability of neutralising them quickly. The highly reactive oxygen-derived free radicals are superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^{\cdot-}$).
- Absorption atelectasis : It has been shown that FiO_2 > 50% increases the risk of absorption atelectasis. At higher FiO_2, Oxygen replaces the alveolar Nitrogen. Because of its' high affinity for Hemoglobin, O_2 gets quickly absorbed into blood causing alveolar collapse/atelectasis.
- Hypercapnia in at-risk patients
- Dry nose/mouth
- Pressure sores
- Mobility issues (tubings/cylinders/concentrators), risk of falls by tripping over tubes/connectors
- Fire risk and burn injuries

Oxygen and Fire Risk - Surveys and Reports :

1. Chang *et al*, 2001. A cohort of patients admitted to a Burn Center. 23 patients were found to have burn injuries related to home oxygen use. 13 patients required intubation eventually and 2 patients died. Both fatalities were injured while smoking during oxygen use at home [24].

2. Robb *et al*, 2003. A retrospective review of 2939 burn patients. 25 patients identified to have suffered injuries secondary to oxygen therapy. 22 of the 25 were smoking while using oxygen. Inhalation injury seen in 2 patients, subsequently requiring intubation [25].

3. Murabit and Tredget, 2012. A retrospective review of 1199 adult burn patients, 17 of whom sustained injuries due to smoking while using home oxygen [26].

4. From 2011 to 2012, there have been 29 instances of newspaper reported hospital fires in India, including the tragic fire at AMRI hospital, Kolkata, West Bengal, India that cost 93 lives. Amongst other causes, an Oxygen-rich environment in the wards and ICUs make these areas fire-prone [27].

5. On 24th April 2021, 82 people were killed in a hospital fire in Baghdad. There have been reports of over 20 other instances of fires in oxygen rich environments in hospitals since the beginning of the COVID-19 pandemic [28].

Recommendations :

1. Healthcare workers need to be more proficient with Oxygen prescription and abide by protocols laid down by the BTS. Multiple studies found improper prescription to be one of the many reasons for poor compliance to home oxygen use. For in-patients, oxygen MUST be prescribed either on a paper chart or electronically, just like any other drug with proper adjunctive instructions on flow rates/FiO_2 required and target SpO_2 range. This will help patients achieve desirable oxygenation more effectively while reducing wastage.

2. Patients going home with LTOT need proper counselling and training with regards to the risks and benefits involved. Paper information leaflets should be provided. Studies have shown that follow-up at home by specialist Oxygen assessment teams/nurses improve compliance, reduce risk of side-effects. Patients should be strictly encouraged to quit smoking prior to initiating LTOT, however in extreme circumstances, it can still be prescribed but a thorough risk assessment should be performed and documented. Operational smoke detectors or fire alarms are mandatory and local fire authorities should be made aware accordingly.

3. In the context of palliative care, in the absence of hypoxia, supplemental oxygen could be considered for intractable dyspnea when other modalities have been exhausted but its' merit needs to be judged on a case-to-case basis and it should not be routine practice.

4. Oxygen assessment teams specialising in assessing blood gas reports, obtaining blood/capillary gas samples and providing training and education at patient's homes are a vital cog in the wheel.

5. There is need for further studies on oxygen use in India. Only then can we assess the efficacy of our current practice and aim for improvement thereafter.

Oxygen Audit and the COVID-19 Pandemic :

With regard to the ongoing COVID-19 pandemic, in an attempt to optimize our resources, Institutional Oxygen Audit Committees should **:**

1. Compile and maintain data for oxygen requirement and daily consumption.
2. Liaise with local authorities with regards to details of audit findings, including number of patients on various oxygen support systems.
3. Select the right patient for the right oxygen support system.
4. HFNO should be used judiciously, only after approval from hospital critical care team/medical board.
5. Benefits of awake proning has already been extensively studied and it should be implemented for all in-patients with hypoxic respiratory failure, for at least 16 hours per day.

6. Wastage and leakage from apparatus should be assessed and addressed regularly.
7. While using Non-invasive ventilation/CPAP, attempts should be made to apply higher airway pressures with lower FiO_2, as tolerated.
8. Correct size of NIV/CPAP masks is crucial. Same applies for endotracheal tubes and cuff pressures, to minimise leak and improve oxygenation as much as possible.
9. Appropriate care should be taken to turn off oxygen equipments and switch non-invasive and mechanical ventilators to Stand-by mode when not in use.
10. Wean down FiO_2 as appropriate.

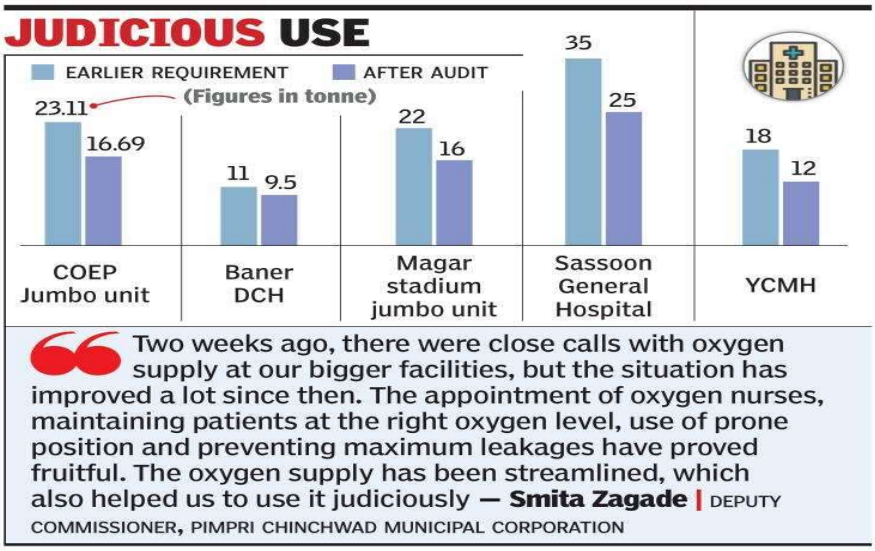

Figure 1. Effects of Oxygen Audit on Oxygen consumption in the city of Pune, Maharashtra, India during the second wave of COVID-19

(From : The Times of India, Pune dated May 8, 2021)

Summary :

- It needs to be appreciated by physicians, patients and policy-makers that medical oxygen is a precious finite resource.
- Regular review of the requirement for oxygen therapy in patients, coupled with assessment of their oxygen levels by pulse oximetry or blood gases can significantly reduce the burden of oxygen supply in acute-care settings.
- Attempts should be made to improve the quality and delivery of oxygen therapy and avoid indiscriminate use of oxygen, particularly in non-ICU or less supervised healthcare settings.
- An oxygen prescription should enlist the delivery device(s) as well as guide the healthcare staff to administer oxygen for specific indications and at an appropriate flow rate and concentration.

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Oxygen Toxicity – The Double-Edged Sword

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Introduction :

Oxygen is indispensible to life. Without oxygen, life can neither be sustained nor carry on. However, if oxygen therapy is inappropriately administered, especially higher concentrations or for a prolonged time period, then like any other drug it will exert adverse outcomes with the potential to damage cells and tissues [1]. This damage can be done by both low and high oxygen concentrations. We all know about the effects of low oxygen concentrations, however high oxygen concentrations can be equally harmful. The clinical setting in which oxygen toxicity occurs can be broadly categorized into two groups; the first is one where the patient is given very high concentrations over a short time and the second is where a lower concentration is maintained over a long period. Severe cases of oxygen toxicity can result in irreversible tissue damage and death.

History :

Oxygen was discovered in the 1770's by Carl Wilhelm Scheele of Sweden and Joseph Priestley of England in 1774. The harmful effects of breathing oxygen at higher concentrations or partial pressures were first recognized in the 19th century. Paul Bert was the first to describe the side effects of hyperbaric oxygen on the central nervous system in 1878 while J. Lorrain Smith was the first to report the pulmonary effects in 1899.

Oxygen Delivery systems :

Oxygen is a drug, like any other prescribed medication with specific biochemical and physiological actions and has a defined therapeutic range beyond which it has side effects as any other drug would have, thus it should be prescribed judiciously and appropriately, a fact which we often tend to forget after initiating a patient on oxygen therapy. Generally oxygen is provided at the atmospheric pressure of ambient room air (normobaric oxygen) with different masks and nasal cannulas with concentration (FiO_2) ranging between 24 to 90%. Masks with reservoirs, positive airway pressure masks, high flow nasal oxygen devices, non-invasive and invasive mechanical ventilators all can all deliver higher concentrations of oxygen. A hyperbaric chamber delivers oxygen at pressures above the atmospheric pressure.

Delivery of oxygen to cells and tissues depends on three factors : adequate ventilation, proper gas exchange, and, finally patent circulation. Most of the oxygen in blood is bound to haemoglobin (bound form) and very little is dissolved in blood (free form) at atmospheric pressure. Oxygen has poor solubility in blood, therefore by increasing fraction of inspired oxygen (FiO_2) to 100% also only a third of the resting oxygen demand is fulfilled [2].

Etiology :

Prolonged exposure to oxygen concentration or short exposure to very high oxygen concentration can cause cellular damage due to oxidative stress and result in cytotoxic cell wall damage and ultimately collapse of alveoli, leading to absorption atelectasis in the lung.

Pulmonary symptoms of oxygen toxicity can present within 24 hours of breathing pure oxygen which range from pleuritic chest pain and substernal heaviness to coughing and dyspnea secondary to tracheobronchitis and absorptive atelectasis leading to pulmonary edema. These symptoms typically abate within 4 hours after stopping high flow oxygen in the vast majority of patients.

Central nervous system (CNS) symptoms manifest earlier than pulmonary symptoms but are often difficult to recognize as patients who are receiving mechanical ventilation may be sedated or paralysed. Early symptoms are variable but nearly always consist of twitching of the perioral muscles and small muscles of hand. If oxygen toxicity continues then nausea, tinnitus, dysphoria and generalized convulsions can occur. Oxygen toxicity can be precipitated by hypercapnia, stress, fatigue and cold [3] .

Pathophysiology :

Oxygen causes vasodilation of the pulmonary circulation and vasoconstriction of the systemic circulation. Free oxygen radicals (intermediate oxygen species , most common ones being hydroxyl ion (OH^-) and peroxynitrite ($ONOO^-$), and also superoxide (O_2^-) and hydrogen peroxide (H_2O_2) inundated by oxygen are believed to be the causes of oxygen toxicity (Figure 1). Free radicals are generated by oxidoreductive processes in the mitochondria and are also produced by function of enzymes such as xanthine and urate oxidases at extra-mitochondrial sites, by phagocytes killing the bacteria and auto oxidative reactions.

In the body, oxygen (O_2) is utilized by cells for generation of ATP as well as a cofactor in intermediate metabolic reactions involving oxidation or hydroxylation of various substrates. During normal cellular metabolism, almost all molecular O_2 is converted completely to water and the enzymes responsible (Cytochrome P450, Cytochrome oxidase, dopamine β- hydroxylase) release very few or no oxygen intermediates (free radicals). However under certain conditions these enzymes (and other enzyme systems) may serve as incomplete electron donors (releasing < 4 electrons to molecular O_2), thereby releasing free radicals, the rate of formation of which is directly proportional to partial pressure of oxygen (PaO_2) (Figure 1). The sources and fates of free oxygen radicals are summarized in Table 1.

These free radicals cause lipid peroxidation, inhibit nucleic acid and protein synthesis, and placate cellular enzymes. Continued exposure to high oxygen concentration leads to increased production of free radicals, which damage pulmonary epithelium and inactivate alveolar surfactant leading to intra-alveolar edema, interstitial thickening, fibrosis and ultimately pulmonary atelectasis [4]. The deleterious effects of free radicals are summarized in Table 2.

Last but not the least, oxygen causes lethal physiological effects in patients of chronic obstructive pulmonary disease (COPD), who when administered oxygen at high FiO_2 develop hypercapnia and type II respiratory failure leading to respiratory acidosis, coma and finally death. This is because of two reasons, namely that it blunts their hypoxic respiratory drive on which they are dependent to breathe resulting in further carbon dioxide (CO_2) retention, and in addition due to selective pulmonary arterial dilatation addition it worsens ventilation-perfusion mismatch by increasing blood flow to poorly ventilated regions of the lungs.

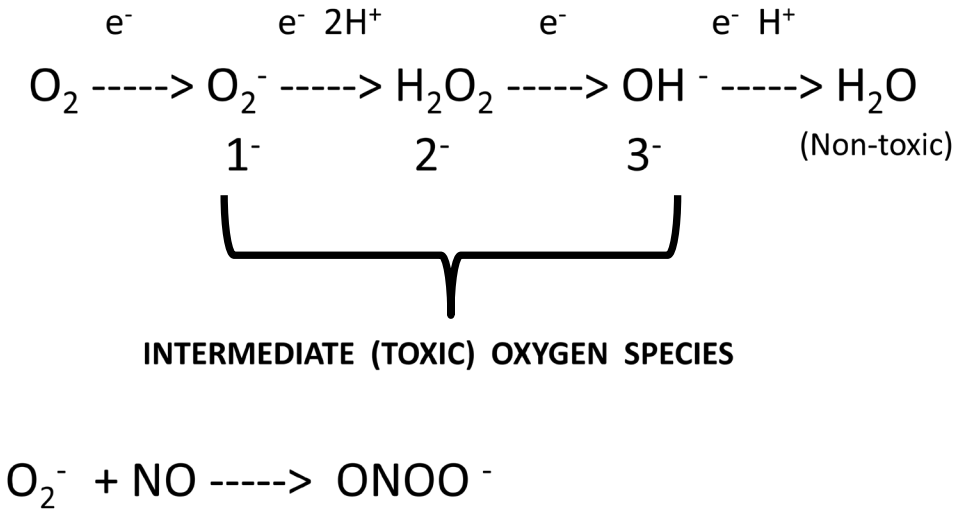

Figure 1. Free Oxygen Radicals

(O_2 – Oxygen, O_2^- – Superoxide, H_2O_2 – Hydrogen peroxide, OH^- – Hydroxyl, $ONOO^-$ – Peroxynitrite, NO – Nitric Oxide)

Free Radical	Symbol	Source	Fate
Superoxide	**O_2^-**	A. In Mitochondria by : 1. *Oxidation of Ubisemiquinone during the mitochondrial electron transport chain* 2. *Auto-oxidation of NADH dehydrogenase* B. In Endoplasmic reticulum (E.R.) and Microsomes by : 1. *Auto-oxidation of flavins (Cytochrome P450)* 2. *Turnover of NADPH Cytochrome C reductase* C. In Plasma membranes by : auto-oxidation of cytochromes during prostaglandin synthesis	Cleared by the enzyme Superoxide dismutase (S.O.D.) which catalyzes dismutation of O_2^- to H_2O_2 at very high reaction rates
Hydrogen Peroxide	**H_2O_2**	Produced in mitochondria, endoplasmic reticulum (E.R.) peroxisomes, microsomes and cell membranes by : *1. Dismutation of Superoxide by S.O.D.* *2. Urate Oxidase activity*	Cleared by 2 enzymes : 1. GSH (Glutathione) redox cycle, in which GSH peroxidase removes lipid peroxides and H_2O_2 at the expense of GSH oxidation 2. Catalase, which converts H_2O_2 to water and oxygen
Hydroxyl	**OH^-**	Generated at production sites of Superoxide and Hydrogen peroxide in the presence of Ferric ions where their concentrations are maximum	Cannot be eliminated by natural enzymatic reactions, hence the most reactive and dangerous of all free radicals
Peroxynitrite	**$ONOO^-$**	Formed by the reaction of Superoxide with Nitric Oxide at physiological pH at any cellular site that contains significant amounts of both, at a rate 3 times faster than the clearance of Superoxide by S.O.D.	Cleared by reactions with : 1. Electron-rich donor molecules : a. *Sulfhydryl groups (active sites in tyrosine phosphatases and other enzymes)* b. *Zinc thiolates* c. *Iron-sulphur centers* 2. Superoxide dismutase catalyzed tyrosine nitration
Singlet Oxygen	**O=O**	Generated during : • Photosensitization reactions in the retina and skin • Phagocytosis by macrophages and neutrophils and oxidation of halide ions by myeloperoxidase (MPO) in phagocytes • CYP-catalyzed hepatic microsomal oxidative reactions of phenolic and other compounds • Reaction of Superoxide with H_2O_2	Quenched by β-carotene, histidine, porphyrins, tocopherol and quinones
Ozone	**O_3**	Sources include : • Exogenous : Ozone, in the atmosphere • Endogenous : Antibodies and amino acids catalyze the conversion of singlet oxygen to ozone, during bacterial killing by activated neutrophils	Detoxified by Tocopherol into less toxic aldehydes and acids and quenched by Ascorbic acid, glutathione and thiols

Table 1. Production and Metabolism of Free Radicals

Histopathological Changes :

Oxygen toxicity leads to development of histological changes in the lung, which can be detected by microscopic examination of cells and tissues. Changes include pulmonary edema, intra-alveolar haemorrhage, congestion and pulmonary capillary injury and leak. Tissue examination reveals that surfactant loss and epithelial injury lead to a spill-over of pro-inflammatory cytokines which aggravate tissue damage by upregulating the inflammatory cascade. Higher oxygen concentrations leads to an increase in the number of free oxygen radicals generated thus modifying the endothelial function. Microscopic examination reveals alveoli filled with floccular pink material which is characteristic of pulmonary edema and capillaries in the alveolar walls are found to be clogged with red blood corpuscles [5].

FOR SUPEROXIDE, HYDROGEN PEROXIDE AND HYDROXYL IONS	
Cellular Component	**Effects**
Lipids	• Damage to cell & organelle membranes • Lipid peroxidation
Proteins	• Inactivation of Enzymes and Transport proteins • Altered cellular and intercellular permeability
Carbohydrates	• Altered recognition of macromolecules
Nucleic Acids	• Inhibition of cell growth and division
Pyridine Nucleotides	• Altered intermediary metabolism
Prostaglandins and Eicosanoids	• Changes in cellular metabolism and intercellular signalling
Surfactant	• Altered Lung mechanics • Decreased pulmonary compliance
FOR PEROXYNITRITE	
Cellular Component	**Effects**
Lipids	• Peroxidation of membrane phospholipid • Damage to cell and cell organelle membranes
Proteins	• Inactivation of Enzymes and Transport proteins
Nucleic Acids	• Cell death
FOR SINGLET OXYGEN AND OZONE	
Cellular Component	**Effects**
Lipids	• Damage to cell and cell organelle membranes
Proteins	• Activation of transcription factors NF-κB and AP-2 and c-Jun-N-terminal kinases (JNK/SAPK) • Reduced level of sirtuin-1, associated with obesity, insulin resistance and aging
Nucleic Acids	• Damaged mitochondrial and chromosomal DNA leading to mutagenesis and cancer • Triggering of caspase cascades and programed cell death • Senescence

Table 2. Cellular and Metabolic Effects of Free Radicals

Clinical Features :

Oxygen toxicity rarely occurs if the FiO_2 is maintained below 50%. The latent period of oxygen toxicity is inversely proportional to the level (FiO_2) of inspired oxygen [6] and varies from 4 to 22 hours at $FiO_2 \geq 95\%$ [2]. At partial pressures of oxygen as high as 200 to 300 kPa, symptoms may begin to manifest within as early as 3 hours (Tables 3 and 4).

CENTRAL NERVOUS SYSTEM (CNS)	RESPIRATORY
• Anxiety • Irritability • Dizziness • Headache • Hyperventilation • Hiccups • Limb tingling and numbness • Tinnitus and hearing disturbances • Tonic clonic seizures	• Hyperemia of nasopharynx • Tickling and burning sensation on inhalation • Uncontrollable coughing • Hemoptysis • Dyspnea • Chest Pain • Crackles • Absorption atelectasis • Bronchopulmonary dysplasia in the newborn
OCULAR	**OTHERS**
• Visual disturbances such as tunnel vision and blurring • Retinal edema • Retrolental fibroplasia (Retinopathy of prematurity) in the newborn	• Fever • Cold shivering • Fatigue

Table 3. Clinical Features and Effects of Oxygen Toxicity

FiO_2 at 1 atm	Duration	Effects of Exposure
28 %	Months	• Subclinical pathological changes • No clinically significant toxicity
60 %	7 days	• Mild Chest discomfort • Possible change in morphometry • No change in Lung mechanics
100 %	< 6 hours	• None
	> 12 hours	• ↓ Tracheobronchial clearance • ↓ Forced Vital Capacity • Cough • Chest Discomfort
	> 24 hours	• Altered Endothelial function
	> 36 hours	• ↓ Diffusion capacity (DLco) • ↑ Alveolar-arterial oxygen gradient [(A-a) DO_2]
	> 48 hours	Pulmonary Edema due to • ↓ Surfactant formation • ↓ Static Lung compliance • ↑ Surfactant inactivation • ↑ Alveolar and capillary permeability
	> 60 hours	• Acute Respiratory Distress Syndrome (ARDS)

Table 4 . Physiological and Clinical Effects of Pulmonary Oxygen Toxicity over Time

Evaluation :

Patients who are at risk of oxygen toxicity should closely monitored for any symptom or sign of appearing toxicity. Their FiO_2, arterial oxygen saturation (SpO_2) and, if monitored, partial pressure of oxygen in arterial blood (PaO_2) all should be kept in a closely monitored range depending on the oxygen concentration being provided. The most widely applied index of oxygen toxicity in humans has been decrease in vital capacity, followed by progressive abnormalities in the carbon monoxide diffusing capacity (DLco) [7]. Onset of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) should be monitored by chest radiography in patients on mechanical ventilation. Similarly ocular assessment should be done to check

for lens opacification to detect early ocular toxicity. CNS toxicity will often be associated with diaphoresis and tachycardia but then these are difficult to detect as most patients with hypoxemia and respiratory failure will already have tachycardia [8].

Differential Diagnosis :

There is a significant overlap of symptoms so it becomes very difficult to narrow down to a single diagnosis as there are many confounding factors. Below is a list of diseases which may mimic or have an overlap with oxygen toxicity (Table 5) [9] :

- Carbon dioxide narcosis
- Carbon monoxide poisoning
- Hyperventilation
- Envenomation or toxin ingestion
- Cerebrovascular event
- Migraine
- Seizure disorder
- Infection
- Multiple sclerosis
- Hypoglycemia

Table 5. Mimics of Oxygen Toxicity

Potentiators of Oxygen Toxicity :

These include chemicals, drugs and dietary factors, as follows :

Bleomycin produces superoxide, and Nitrofurantoin and Paraquat produce superoxide and hydroxyl radicals, whereas disulfiram inhibits superoxide dismutase, hence patients who have received or are currently on any of these therapies need to be given oxygen very judiciously in the event it is indicated. Protein energy malnutrition and dietary deficiency of Sulphur containing amino acids (e.g. tyrosine) which are necessary for glutathione (GSH) synthesis leads to deficiency of glutathione, an important anti-oxidant and free radical scavenger of peroxide, with the possible potential to aggravate the effects of oxygen toxicity. Deficiency of Vitamins A (β-carotene), C (L-Ascorbic acid) and E (α-tocopherol), which are extrinsic anti-oxidants derived and replenished only from diet may also potentiate the effects of oxygen toxicity.

Management :

The best management is to detect impending oxygen toxicity early and reduce the oxygen concentration provided, however, this only sounds much easier than it actually is, as these patients of respiratory failure are often critically ill and require high FiO_2 to correct their hypoxemia and maintain oxygenation. Once the underlying disease process is under control and the patient's clinical and physiological parameters have stabilized, it is of paramount importance to assess the need for continued oxygen therapy and/or consider weaning by decreasing the level of ventilatory support and FiO_2. Oxygen induced seizures are usually self-limiting and do not require any treatment. Patients who are being treated with hyperbaric oxygen therapy can be safeguarded by breaks in between, anti-epileptic therapy and limited treatment pressures. Introduction of air breaks have reduced seizures due to oxygen toxicity by a factor of 10 [10].

Deep sea divers breathe lower oxygen concentrations of oxygen (< 21%) to reduce the toxicity risk. The gaseous mixture is also changed from nitrogen to helium. Underwater seizures require immediate ascent to the ground level as there is a very high risk of fatal drowning.

Treatment :

The treatment for oxygen toxicity is purely symptomatic so it is necessary to recognize the symptoms early. Superoxide dismutase, an anti-oxidant enzyme, has shown promising results in animal studies, and is currently being evaluated in clinical trials for treating non-lethal hyperoxia in humans [11]. Vitamins A, C and E, naturally occurring dietary anti-oxidants have been shown to lower the incidence of retrolental fibroplasia in premature infants on oxygen therapy. Rats treated with dexamethasone have shown greater oxygen induced lung injury with decreased activity of antioxidant enzymes [12]. It is unsure whether these effects are the same in human subjects, however, it does become an important point for concern, as adult and pediatric patients of hypoxic respiratory failure are very often administered higher doses of corticosteroids for refractory hypomexia and shock, in addition to oxygen therapy.

Prognosis :

In adults, the neurological complications are temporary and are usually reversed with withdrawal and removal of the inciting agent (oxygen) [7]. Damage due to pulmonary toxicity is also reversible in most adults. However retinopathy of prematurity rarely goes back without any intervention. When the disease has advanced to a stage that requires surgery then it has been shown that results with stage 3 are the best, but this is not the case for later stages [13].

Long-term Complications :

CNS effects include prolonged amnesia and tonic-clonic seizures. Pulmonary sequelae range from mild tracheobronchitis and atelectasis to diffuse alveolar damage which becomes indistinguishable from ARDS. Ocular complications consist of delayed cataract to reversible myopia to retrolental fibroplasia in children.

Summary – Clinical Pearls :

- Oxygen concentration (FiO_2) of upto 1.0 (100%) can be administered for management of hypoxemia and respiratory failure during initial management of emergencies and transport of critically ill patients, till other modalities like ventilatory support can be arranged.
- In patients on mechanical ventilation, an FiO_2 of upto 1.0 (100%) can be safely used in the first 24 hours without significant risk of lung injury.
- During this period, management should be directed towards strategies to improve gas exchange, optimize oxygen delivery and decrease the patient's oxygen consumption/demand so that FiO_2 can be reduced subsequently.
- The maximum safe duration for Oxygen administration at an FiO_2 between 0.5 to 1.0 is unclear, but it can be tolerated for > 24 hours.
- Oxygen at an $FiO_2 \leq 0.5$ can be safely administered to most patients for weeks.
- The maximum safe duration for chronic or long-term Oxygen therapy in the ambulatory setting remains undefined.
- Oxygen, like any other drug, must be used judiciously, prescribed appropriately, monitored carefully and discontinued when it is no longer required. Patients who are on oxygen therapy should be assessed for clinical, physiological and laboratory parameters of recovery, and weaning should be considered once the hypoxemia is corrected, the underlying pathology has resolved and the patient is clinically stable.

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Anti-Oxidants

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Introduction : What are Anti-Oxidants ?

An anti-oxidant can be defined as any substance that, when present in low concentrations compared to that of an oxidisable substrate, significantly delays or inhibits the oxidation of that substrate. We know that oxidative stress due to production of free oxygen radicals, also called free radicals plays an important role in cellular metabolic process, injury and inflammation. Most of the time, free radicals have a very short half-life and are cleared by endogenous homeostatic and physiological processes, discussed later in this manuscript. However, in certain diseases and pathological processes, the rate of production of free radicals can exceed their clearance by the body, leading to oxidative stress and damage. Anti-oxidants prevent free radical induced damage by clearing free radicals from cells and tissues, promoting their conversion to less toxic (or non-toxic) molecules or substrates, or inhibiting their formation [1,2].

What are Free Radicals ? How are they Formed ? What are their Damaging Effects ?

In the body, oxygen (O_2) is utilized by cells for ATP (adenosine triphosphate) generation as well as a cofactor in intermediate metabolic reactions involving oxidation or hydroxylation of various substrates. Free radicals (reactive oxygen or nitrogen species) are generated by oxidoreductive processes in the mitochondria and are also produced by the action of enzymes such as cytochrome P450, xanthine and urate oxidases, nitric oxide synthase at extra-mitochondrial sites, by auto-oxidative reactions, during infection and phagocytosis and intracellular killing of infective organisms, and inflammation (cyclooxygenase and lipoxygenase). During normal cellular metabolism, almost all molecular oxygen is converted completely to water and the enzymes responsible (cytochrome P450, cytochrome oxidase, dopamine β-hydroxylase, etc) release very few or no oxygen intermediates (free radicals). However under certain conditions these enzymes (and other enzyme systems) may serve as incomplete electron donors (releasing < 4 electrons to molecular O_2), thereby releasing free radicals, also known as intermediate oxygen species, which have unpaired electrons due to incomplete reduction of oxygen, the rate of formation of which is directly proportional to the partial pressure of oxygen (PaO_2) (Figure 1). Free radicals of interest are :

1. Superoxide (O_2^-) – contains 1 unpaired electron
2. Hydrogen Peroxide (H_2O_2) – by definition itself not a free radical as it contains no unpaired electrons, but the peroxide ion (O_2^{2-}) component, the deprotonated form of H_2O_2 and is the reactive component, contains 2 unpaired electrons
3. Hydroxyl ion (OH^-) – contains 3 unpaired electrons and is the most reactive of all free radicals.
4. Peroxynitrite ($ONOO^-$) – a reactive oxygen as well as reactive nitrogen species.

In addition, there are reactive oxygen species that have no unpaired electrons but are yet unstable, such as singlet Oxygen (O=O) and Ozone (O_3), which can react with organic material in the body [2,3,4].

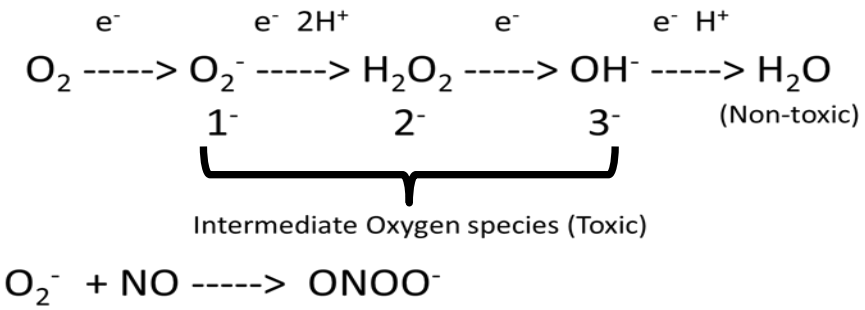

Figure 1. Free Radicals

(O_2 – Oxygen, O_2^- – Superoxide, H_2O_2 – Hydrogen peroxide, OH^- – Hydroxyl, $ONOO^-$ – Peroxynitrite, NO – Nitric Oxide)

The term "free radical" can be applied to any molecular species capable of independent existence that contains unpaired electron(s) in its atomic orbital, which makes it unstable, in order to attain stability, it searches for and "steals" electrons from any cellular or extracellular substance in the vicinity, the loss of which changes the donor's structure and function in a detrimental manner, for example, altering DNA transcription and cellular signalling, membrane permeability, etc. If not cleared or quenched by the body, a disproportionate amount of free radicals causes a condition termed "oxidative stress". The sources and fates of free radicals in the human body are summarized in Table 1 below :

Free Radical	Symbol	Source	Fate
Superoxide	**O_2^-**	A. In Mitochondria by : • Oxidation of Ubisemiquinone during the mitochondrial electron transport chain • Auto-oxidation of NADH dehydrogenase B. In Endoplasmic reticulum (E.R.) and Microsomes by : • Auto-oxidation of flavins (Cytochrome P450) • Turnover of NADPH Cytochrome C reductase C. In Plasma membranes by : auto-oxidation of cytochromes during prostaglandin synthesis	Cleared by the enzyme Superoxide dismutase (S.O.D.) which catalyzes dismutation of O_2^- to H_2O_2 at very high reaction rates
Hydrogen Peroxide	**H_2O_2**	Produced in mitochondria, endoplasmic reticulum (E.R.) peroxisomes, microsomes and cell membranes by : • Dismutation of Superoxide by S.O.D. • Urate Oxidase activity	Cleared by 2 enzymes : 1. GSH (Glutathione) redox cycle, in which GSH peroxidase removes lipid peroxides and H_2O_2 at the expense of GSH oxidation 2. Catalase, which converts H_2O_2 to water and oxygen
Hydroxyl	**OH^-**	Generated at production sites of Superoxide and Hydrogen peroxide in the presence of Ferric ions where their concentrations are maximum	Cannot be eliminated by natural enzymatic reactions, hence the most reactive and dangerous of all free radicals
Peroxynitrite	**$ONOO^-$**	Formed by the reaction of Superoxide with Nitric Oxide at physiological pH at any cellular site that contains significant amounts of both, at a rate 3 times faster than the clearance of Superoxide by S.O.D.	Cleared by reactions with : 1. Electron-rich donor molecules : • Sulfhydryl groups (active sites in tyrosine phosphatases and other enzymes) • Zinc thiolates • Iron-sulphur centers 2. Superoxide dismutase catalyzed tyrosine nitration
Singlet Oxygen	**O=O**	Generated during : • Photosensitization reactions in the retina and skin • Phagocytosis by macrophages and neutrophils and oxidation of halide ions by myeloperoxidase (MPO) in phagocytes • CYP-catalyzed hepatic microsomal oxidative reactions of phenolic and other compounds • Reaction of Superoxide with H_2O_2	Quenched by β-carotene, histidine, porphyrins, tocopherol and quinones
Ozone	**O_3**	Sources include : • Exogenous : Ozone, in the atmosphere • Endogenous : Antibodies and amino acids catalyze the conversion of singlet oxygen to ozone, during bacterial killing by activated neutrophils	Detoxified by Tocopherol into less toxic aldehydes and acids and quenched by Ascorbic acid, glutathione and thiols

Table 1. Sources and Fate of Free Radicals

These free radicals cause lipid peroxidation, inhibit nucleic acid and protein synthesis, and activate intra-cellular enzymes or enzyme systems that trigger on a cascade of cell damage, ultimately culminating in cell death. During mechanical ventilation, prolonged exposure to high oxygen concentration (FiO_2) leads to increased production of free radicals, which damage the pulmonary epithelium and inactivate alveolar surfactant leading to intra-alveolar edema, interstitial thickening, fibrosis and ultimately atelectasis in animal models [5]. The deleterious effects of free radicals are summarized in Table 2 below. For information about pulmonary and systemic oxygen toxicity, the reader is advised to refer an earlier article written exclusively on this topic in this issue of the newsletter.

SUPEROXIDE, HYDROGEN PEROXIDE AND HYDROXYL IONS	
Cellular Component	**Effects**
Lipids	• Damage to cell and cell organelle membranes • Lipid peroxidation
Proteins	• Inactivation of Enzymes and Transport proteins • Altered cellular and intercellular permeability
Carbohydrates	• Altered recognition of macromolecules
Nucleic Acids	• Inhibition of cell growth and division
Pyridine Nucleotides	• Altered intermediary metabolism
Prostaglandins and Eicosanoids	• Changes in cellular metabolism and intercellular signalling
Surfactant	• Altered Lung mechanics • Decreased pulmonary compliance
PEROXYNITRITE	
Cellular Component	**Effects**
Lipids	• Peroxidation of membrane phospholipid • Damage to cell and cell organelle membranes
Proteins	• Inactivation of Enzymes and Transport proteins
Nucleic Acids	• Cell death
SINGLET OXYGEN AND OZONE	
Cellular Component	**Effects**
Lipids	• Damage to cell and cell organelle membranes
Proteins	• Activation of transcription factors NF-κB and AP-2 and c-Jun-N-terminal kinases (JNK/SAPK) • Reduced level of sirtuin-1, associated with obesity, insulin resistance and aging
Nucleic Acids	• Damaged mitochondrial and chromosomal DNA leading to mutagenesis and cancer • Triggering of caspase cascades and programed cell death • Senescence

Table 2. The Cellular and Metabolic Effects of Free Radicals

What are the Effects of Anti-Oxidants on Free Radicals ?

Anti-oxidants perform one of more of the following functions :

1. Prevent or inhibit free radical formation
2. Convert free radicals to less reactive species
3. Compartmentalise (Quarantine) or Scavenge free radicals away from vital cellular structures
4. Upregulate clearance of free radicals by natural or endogenous enzymatic processes
5. Repair the injury caused by free radicals at cellular or molecular level

What are the Different Types of Anti-Oxidants and how do they Work ?

Antioxidants are categorized into the following three types [2,3] :

1. Enzyme Scavenging systems, which catalyse removal of free radicals
2. Enzyme Co-Factor systems, which act as renewable substrates to remove or prevent the formation of free radicals
3. Non-enzymatic Scavenging systems, which either re-reduce free radicals or quench free radical producing reactions

1. Enzyme Scavenging systems :

The most important enzyme scavenger in the respiratory system is superoxide dismutase (SOD), which is present in 3 forms : Copper-Zinc SOD, present in the cytosol and organelles, Manganese SOD, present in the mitochondria and Copper SOD, present in plasma. These are ubiquitous, occurring in nearly all mammalian cells. Cyanide affects Copper-Zinc SOD but not the other two forms. The extracellular form of SOD is released by vascular endothelium into the circulation, following heparin therapy, and is believed to play an important role in the regulation of vascular tone, as nitric oxide (a potent vasodilator, also released by endothelium) is neutralised by superoxide. Superoxide dismutase is the major free radical scavenger in the lungs and other tissues and catalyzes the dismutation of Superoxide (O_2^-) to hydrogen peroxide (H_2O_2) at very high rates. H_2O_2 is subsequently cleared by Catalase, by which it is split into Oxygen and water or by the Glutathione (GSH) redox cycle [6,7,8,9].

Catalase was the first anti-oxidant enzyme to be characterised and is present in nearly all tissues, within cells in the peroxisomes, which also contain other enzymes responsible for generating hydrogen peroxide. It consists of four protein subunits, each containing a heme group and a molecule of NADPH. Catalase activity is greatest within the peroxisomes of erythrocytes and hepatocytes. It catalyses the conversion of hydrogen peroxide to water and oxygen in a two-stage chemical reaction, in the presence of Ferric ions, at a very high rate constant (107 M/sec), making it extremely difficult to saturate catalase as an enzyme in vivo [10,11,12].

2. Enzyme Co-Factor systems :

At the cellular level, the Glutathione (GSH) redox cycle is the most important scavenger of H_2O_2 and consists of two enzyme systems (GSH peroxidase and reductase) working in tandem, using glutathione as a renewable low-molecular weight (LMW) scavenger. GSH peroxidase removes lipid peroxides and H_2O_2 at the expense of GSH oxidation. GSH peroxidases are ubiquitious, present in nearly all tissues, in the plasma, within the cytosol and mitochondria. The plasma form of GSH peroxidase is synthesized in the kidney and the highest intracellular concentration is found in the liver. GSH peroxidase activity is dependent on the presence of selenium and reduced glutathione at the reaction site, and is greatly hampered in selenium deficiency. It catalyses the oxidation of glutathione at the expense of a peroxide, which might either be hydrogen peroxide or another peroxide like lipid hydroperoxide (in cell walls and membranes) by the reaction :

$2GSH + ROOH \rightarrow GSSG + ROH + H_2O$

(GSH : Glutathione, GSSG : Glutathione disulfide, ROOH : Hydroperoxide, ROH : Reduced hydroperoxide)

GSH is then regenerated by GSH reductase using NADPH as a cofactor by the reaction :

$GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+$

(NADPH : Nicotinamide adenine dinucleotide phosphate , $NADP^+$: Nicotinamide adenine dinucleotide phosphate, oxidized form)

GSH reductase is a flavine nucleotide (NADPH) dependent enzyme with tissue distribution similar to that of GSH peroxidase. GSH reductase maintains a high ratio of reduced to oxidised glutathione, on which GSH peroxidase activity is critically dependent. To replenish the supply of reduced glutathione by GSH reductase, NADPH is provided by the pentose phosphate pathway. Therefore, in certain disorders, activation of any alternate pathway that utilises NADPH (such as the aldose reductase pathway) might lead to a deficiency of reduced glutathione and hence impair the action of GSH peroxidase. Thus, NADPH also functions as an anti-oxidant by regenerating reduced glutathione, and, apart from this, it is also known to provide electrons to the thioredoxin (Trx) system, which is important in gene expression by specific transcription factors.

Other enzymes, such as glutaredoxins, generate GSSH through thiol-disulfide exchange with protein disulfide bonds or other low molecular mass compounds, such as coenzyme A disulfide or dehydroascorbic acid by the reaction :

2 GSH + RSSR → GSSG + 2 RSH
(GSH : Glutathione, GSSG : Glutathione disulfide, RSSR and RSH : intracellular small molecular weight thiol disulfide couples)

The GSH:GSSG ratio is therefore an important indicator of cellular health, with a higher ratio signifying less oxidative stress. The drug n-Acetylcysteine (NAC) is a source of the essential amino acid l-cysteine and a precursor of Glutathione [13,14,15,16].

3. Non-enzymatic free oxygen radical scavengers :

These are further categorized into chain-breaking anti-oxidants and transition metal binding proteins.

3. 1. Chain-breaking Anti-Oxidants :

When a free radical interacts with another molecule or substrate, it has the potential to create secondary radicals that can further react with other targets to produce yet more free radical species and propagate the chain of free radical generation. A classic example of such a chain reaction is lipid peroxidation. The chain is broken when two radicals combine to form a stable product or are themselves neutralised by a chain-breaking anti-oxidant. Chain-breaking anti-oxidants are scavenger molecules that either receive from, or donate electrons to a free radical to form another stable molecule that is either non-reactive or less reactive than the radical itself, in the process, they take away or dissipate the charge associated with the unpaired electron(s) in the free radical so that the resultant molecule does not readily accept from or donate electron(s) to other molecules. Chain-breaking anti-oxidants are further categorized into lipid phase and aqueous phase anti-oxidants [2] .

3. 1. 1. Lipid phase chain breaking anti-oxidants :

These include Vitamins E and A, Flavonoids and Ubiquinol-10 and scavenge radicals in membranes and lipoproteins and inhibit peroxidation of phospholipids.

The most prominent amongst these are the lipid soluble Vitamins E (tocopherols and tocotrienols) and A (carotenoids and retinoids). Tocopherols, the naturally occurring forms of Vitamin E, react rapidly with peroxides and peroxyl radicals to form tocopheroxyl and inhibit lipid peroxidation and phosphorylation of membrane phospholipid, hence, in addition to being anti-oxidants, they also exert a membrane stabilising effect and help to maintain the integrity of cell and plasma membranes. α-tocopherol, once consumed, is then either regenerated by reaction with Vitamin C (ascorbic acid) or another chain-breaking anti-oxidant like reduced glutathione (GSH) or urate, or alternatively two tocopheroxyl radicals might combine to form a stable dimeric molecule, or may be completely oxidised to tocopherol quinone [17,18].

The Vitamin A group, which consists of the 20-carbon carotenoids and 40-carbon retinoids, protect plants as well as animals against oxidative stress. The most important anti-oxidants belonging to this group are β-carotene and retinol. Carotenoids are present in membranes and certain lipoproteins and prevent photo-oxidative damage by diminishing exposure to light. Their anti-oxidant properties are conferred by the hydrophobic chain of polyene units in their structure and the longer the polyene chain, greater is their anti-oxidant activity. Carotenoids can auto-oxidize when oxygen tension increases, and thus are most effective at tissue level at low oxygen tensions. β-carotene is not only an efficient scavenger of singlet oxygen, but can also detoxify peroxyl radicals with an efficiency comparable to tocopherols under hypoxic conditions and is believed to prevent in-vivo lipid peroxidation of cell membranes during hypoxia. In addition, it can also neutralize thiyl radicals [19,20,21]. Retinol functions as an anti-oxidant as it donates electrons, but can also behave like a pro-oxidant by generating hydroxyl radicals. The anti-oxidant properties of retinol, unlike β-carotene, are believed to be independent of oxygen concentration [22,23] .

Flavonoids are a heterogenous group of polyphenolic secondary metabolites widely distributed in many plants and are commonly consumed in the diet. They are classified into three subgroups, namely isoflavonoids, bioflavonoids and neoflavonoids and together number more than 5000, making them a very large and diverse group. Sources of flavonoids include grapes, blueberries, citrus and other fruits, parsley, green leafy vegetables, peanuts, cocoa, black tea and red wine. Some studies have correlated reduced incidence of chronic inflammatory and degenerative diseases such as atherosclerosis and coronary artery disease to a diet rich in flavonoids, however, this evidence is challenged as the data is scarce and the result does not take into effect the presence of confounding factors [24, 25,26,27].

Ubiquinol-10, the reduced form of coenzyme Q10, is the only known lipid-soluble anti-oxidant that animal cells can synthesize de novo, although available in lower concentrations than tocopherol, it detoxifies peroxyl radicals with greater efficiency than Vitamins E or A, and also replenishes membrane bound α-tocopherol from the tocopheryl radical. It is the first

line of defence against oxidative stress due to free radical-induced peroxidation of lipids and lipoproteins such as low density lipoprotein (LDL) cholesterol [28,29,30].

3. 1. 2. Aqueous phase chain-breaking anti-oxidants :

These include Vitamin C, Urate, Glutathione, sulfhydryl and other thiols and the proteins albumin and bilirubin. They are responsible for quenching free radicals present in the fluid compartment, such as plasma and cytosol.

Vitamin C (ascorbic acid) is known to be the cofactor for prolyl and lysyl oxidases during the synthesis of collagen and also for other enzymes involved in hydroxylation. In addition, it is a broad -spectrum scavenger of many reactive oxygen species, namely superoxide, hydrogen peroxide, hypochlorous acid, hydroxyl and peroxyl radicals, and singlet oxygen. While quenching free radicals, it undergoes a two phase transformation, losing one electron in each phase, initially to semidehydroascorbic acid, which is relatively stable and subsequently to dehydroascorbic acid (DHA), which is itself unstable and hydrolyses to 2,3-diketogulonic acid, which is ultimately metabolised to oxalic acid. Dehydroascorbic acid may itself be reduced back sequentially to ascorbate radical and ascorbic acid by reduced glutathione or directly to ascorbic acid by thioredoxin reductase. Paradoxically, under suitable conditions (millimolar concentrations of ascorbic acid, presence of metal ions), Vitamin C can also generate free radicals, as electrons from ascorbate can reduce metals such as copper and iron, leading to the formation of superoxide and hydrogen peroxide. [31,32,33,34,35,36].

Uric acid, an end-product of purine metabolism is another aqueous phase anti-oxidant that efficiently scavenges peroxide, singlet oxygen and hydroxyl radicals. At physiological concentrations in plasma, where it chiefly exists as monosodium urate, it reduces oxo-heme formed by the reaction of peroxide with hemoglobin and protects immature and mature erythrocytes against lipid peroxidation. It is more readily oxidized than deoxynucleosides by singlet oxygen and is destroyed by hydroxyl radicals at a comparable rate. It is also believed to confer protection against ozone, an oxygen species believed to be associated with ageing and cancer, and it has been postulated that the increase in the life span of humans during evolution might at least be partly attributed to the protective effect of uric acid, whose levels in plasma (4 – 8.5 mg/dl or 0.24 – 0.51 mmol/L) far exceed that of Vitamin C [37,38,39].

Albumin is the predominant circulating protein in plasma and contributes nearly half of the total protein content. It is the main extracellular molecule responsible for maintaining the plasma redox state. It possesses multiple ligand-binding and free radical-trapping properties, both linked to its complex molecular structure, constituted by 6 methionine and 35 cysteine residues involved in the formation of 17 disulfide bonds, of which the Cys-34 residue is the only free cysteine residue in the entire molecule. It is this Cys-34 residue that contributes maximally towards the anti-oxidant properties of albumin as it is able to scavenge many reactive oxygen and nitrogen species, including superoxide, hydrogen peroxide, peroxynitrite and hypochlorous acid. Albumin detoxifies peroxyl radicals during the transport of free fatty acids, and also binds copper and ferrous ions, thereby inhibiting the formation of hydroxyl ions and peroxidation of lipids, two processes which are dependent on the presence of copper ions, and other oxidative processes such as the Fenton reaction, responsible for the conversion of hydrogen peroxide to the more toxic hydroxyl radical, and the Haber-Weiss reaction, where hydroxyl and hydroxide ions are generated from the reaction of superoxide with hydrogen peroxide, both of which are catalyzed by iron. Albumin also binds with bilirubin, homocysteine, and lipids and exerts indirect anti-oxidant effects through these actions. Albumin-bound complexes with bilirubin, homocysteine, polyunsaturated fatty acids (PUFA) and sterols inhibit lipid peroxidation. In addition, albumin also detoxifies hypochlorous acid, another reactive oxygen species which is a product of phagocytosis. A third of the albumin pool exists as disulfides linked with cysteine, homocysteine, or glutathione and the remaining two-thirds exists in reduced form (mercaptalbumin) with a free thiol in the Cys-34 residue, which accounts for 80% of thiols in plasma, constituting the major extracellular source of reactive free thiol, itself a potent free radical scavenger. Albumin is consumed and itself gets damaged whenever it acts as an anti-oxidant and hence, it is considered to be a sacrificial molecule that protects more vital molecules or structures from damage, however, since it is abundantly present in plasma in a high concentration (3.5 to 5.5 g/dl) and possesses a half-life of 21 days, any consumption is unlikely to be of physiological significance, like a drop taken from the ocean [41,42,43,44,45,46,47].

Bilirubin, a product of heme metabolism, also possesses anti-oxidant properties. It exists in two forms, the free form, which is lipophilic, and the bound (conjugated) form, bound to albumin and other proteins, which is water soluble. Albumin-bound bilirubin gets oxidized to biliverdin, which is immediately reduced by biverdin reductase back to bilirubin. Water-soluble GSH primarily protects water soluble proteins, whereas lipophilic bilirubin protects the more vulnerable lipids from oxidation. It has been suggested that bilirubin plays a crucial role in protecting neonates, who, at birth, are deficient in chain-breaking anti-oxidants, from oxidative damage. Heme oxygenase is known to inhibit the production of reactive oxygen species through its ability to degrade heme and produce carbon monoxide and bilirubin and biliverdin [48,49,50,51].

The other aqueous phase chain-breaking anti-oxidants in plasma are the protein bound thiol groups, described earlier. Thiols undergo single electron oxidation to form thiyl radicals. Sulphydryl (SH-) groups present on plasma proteins also scavenge free radicals by donating an electron to them, and, in the process, form a protein thiyl radical. The protective and reparative anti-oxidant properties of thiols depends not only on their capacity to scavenge free radicals but also on the reactivity of the thiyl radicals which are generated, which can themselves cause oxidative stress and damage. Thiyl radicals can engage in a variety of reactions including hydrogen atom transfer (HAT), electron transfer (ET), and addition or elimination reactions, with nearly all of the 20 essential amino acids, though different rate constants, which vary with each amino acid structure. Thiyl radicals can also extract electrons from fatty acids to initiate the process of lipid peroxidation and hence require immediate detoxification by reduction back to thiols. Under physiological conditions, thiyl radicals react with thiolate anion yielding disulfide radical anion ($RSSR^-$) as an intermediate and, ultimately disulfides and superoxide, which is inactivated by superoxide dismutase . Thiyl radicals can also be reduced to thiols by reacting with ascorbate to form less reactive ascorbyl radicals. The detrimental oxidative reactions of thiyl radicals are, inhibited by ascorbic acid, retinol and tocopherol (Vitamins C, A and E respectively). The anti-oxidant effects of albumin and other proteins have been shown to decrease at high concentrations and this is believed to be due to the oxidative damage caused by the thiyl radicals formed in the process [52,53,54,55,56,57].

Reduced glutathione (GSH) is a major source of thiol groups in the intracellular compartment but is of little importance in the extracellular space. GSH functions as an anti-oxidant directly by scavenging a variety of free radicals, as well as indirectly through its function as an essential factor for glutathione peroxidase (described above) [58]. Thioredoxins are small proteins with two adjacent cysteine residues that undergo reversible oxidation to form a disulfide bond when oxidized by hydrogen peroxide in an NADPH dependent reaction catalyzed by thioredoxin peroxidase in the cytosol. The thioredoxin system protects cells against oxidative stress, particularly by redox induced activation of transcription factors, and removal of hydrogen peroxide and other free radicals, provided sufficient NADPH is available [59,60,61].

3. 2. Transitional metal binding proteins :

Metallic ions play an important role in the structure and function of proteins, and their presence (or absence) greatly influences the physico-chemical conformation and activity of over a third of all proteins. Transition metal binding proteins are integral components of the anti-oxidant defence mechanism and act by sequestering metallic ions so that they are unavailable for reactions or enzyme systems responsible for the creation of free radicals [62]. To this effect, ions of iron, copper and other metals are bound to these proteins so that they are unavailable for the production of free radicals.
Ferrous ion (Fe^{2+}) is the form of iron that drives the Fenton reaction and the formation of superoxide and hydroxyl radicals, as follows :

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^\bullet$

This reaction can occur in vivo, but may be inhibited by the competing presence of superoxide, itself a source of hydrogen peroxide, in vivo, as superoxide and hydrogen peroxide can directly react with each other together to form hydroxyl radicals, but as the second order rate constant for this reaction in aqueous solution is virtually zero, it requires a catalyst in order to proceed further. This requirement is provided for by transition metal ions such as iron, which catalyze a two-stage reaction sequence to proceed at a rapid rate, as follows [2] :

$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^\bullet$ (Fenton reaction)

Net reaction : $O_2^- + H_2O_2 \rightarrow OH^- + OH^\bullet + O_2$

The net reaction described above is called the Haber-Weiss reaction. It is a three-stage chain reaction, catalyzed by iron ions that generates hydroxyl radicals from the reaction of superoxide with hydrogen peroxide. The first stage (initiation) in this chain is the Fenton reaction, described above. Following this, the reaction is propagated by two successive stages, and is finally terminated when the hydroxyl radical is scavenged by a ferrous ion, as follows :

Propagation (2^{nd} and 3^{rd} stage) reactions :

$OH^- + H_2O_2 \rightarrow H_2O + O_2^- + H^+$

$O_2^- + H^+ + H_2O_2 \rightarrow O_2 + OH^- + H_2O$

Termination of the reaction :

$Fe^{2+} + OH^{-} + H^{+} \rightarrow Fe^{3+} + H_2O$

From the reactions above, it becomes evidently clear that the Haber-Weiss and Fenton reactions are critically dependent on the concentration of both Ferrous (Fe^{2+}) and Ferric (Fe^{3+}) ions in solution. As Fe^{3+} is almost a hundred times less soluble than Fe^{2+} in aqueous solution at the near-neutral pH of body fluids, the concentration of ferric ions becomes a limiting factor for the reaction rate. At high pH, under alkaline conditions, the rate of this reaction is slowed down considerably due to precipitation of ferric hydroxide [$Fe(OH)_3$], which reduces the concentration of available Fe^{3+}. Hence, the Haber-Weiss reaction can only proceed at rapid rates in a pH which is sufficiently acidic. In addition to iron, the Fenton reaction may also be catalyzed by other redox competent metal ions such as copper ('Fenton-like' reactions). Although most of the iron and copper stores in the human body are sequestered in forms that are not biologically available to catalyse this reaction sequence, nevertheless, the Fenton component of the Haber-Weiss reaction is still regarded as an important mechanism for the formation of hydroxyl radicals in vivo.

The main copper binding protein, ceruloplasmin, a copper containing ferroxidase, also functions as an anti-oxidant enzyme that catalyses the oxidation of divalent iron by the reaction :

$4Fe^{2+} + O_2 + 4H^{+} \rightarrow 4Fe^{3+} + 2H_2O$

Rapid oxidation of the reactive toxic Ferrous ion to its less reactive Ferric (Fe^{3+}) form by ceruloplasmin and other proteins can be considered as an anti-oxidant effect that either prevents or reduces oxidative damage to lipids, proteins and DNA. In vivo studies have indicated that ceruloplasmin might be a more effective scavenger of peroxyl radicals than superoxide dismutase and a slightly less effective scavenger than catalase. Paradoxically, ceruloplasmin is also known to exert pro-oxidative effects under certain conditions. Superoxide and hydrogen peroxide have been found to disrupt the binding of copper to ceruloplasmin and impair its protective anti-oxidant function while liberating copper, which, in turn may upregulate oxidative stress, including lipid peroxidation, negation of nitric oxide and apoptosis of endothelial cells. These have been implicated in the etiopathogenesis of chronic inflammatory or degenerative diseases such as atherosclerosis, endometriosis and Parkinson's disease [63,64,65,66,67].

Other important proteins include ferritin, transferrin and lactoferrin.

Ferritin is a globular protein whose primary function is to store iron intracellularly and is composed of two subunits, H, with potent ferroxidase activity to catalyse oxidation of ferrous iron, and L, which plays a role in iron nucleation and protein stability. Transferrin is another glycoprotein, produced mainly in the liver that reversibly binds iron and certain other metal ions and transports them through blood to the liver, spleen and bone marrow. Both ferritin and transferrin sequester and discourage the redox cycling of iron in cytochromes and peroxidases, thereby protecting against the deleterious effects of free iron taking part in the Fenton reaction. Transferrin is also more effective than ceruloplasmin in inhibiting lipid peroxidation. Conversely, just like ceruloplasmin, while ferritin can function as an effective anti-oxidant, it may also, under certain conditions, increase oxidative stress through the Fenton reaction by acting as an iron donor when it is degraded. Higher levels of ferritin have been linked to increased oxidative stress in certain in vivo studies [67,68,69,70,71].

Lactoferrin, an iron-binding glycoprotein found in colostrum, human and bovine milk and in certain body fluids is a scavenger of hydrogen and other peroxides, and inhibits lipid peroxidation and hemolysis of erythrocytes. It also inhibits the production of hydroxyl radicals through the Fenton reaction by virtue of its iron-binding capacity. Intracellular levels of reactive oxygen species have been known to decline after lactoferrin therapy, suggesting its ability to reduce oxidative stress-induced apoptosis [72,73] .

Melatonin (5 methoxy-*N*-acetyl-tryptamine) was originally discovered as a polypeptide hormone synthesized by pinealocytes in the pineal gland from the amino acid tryptophan. Its principal function is to regulate circadian rhythms and the sleep-wake cycle. Apart from the pineal gland, it is also produced in the gastrointestinal tract, periodically released into the blood in response to food intake and stimuli by nutrients, especially tryptophan and can also be found in the cerebellum, retina, skin, bone marrow, lymphocytes and platelets. In addition, it is also found in yeast and plant material, and can be consumed as food which can influence its level in the circulation. In recent years melatonin has also gained attention as a potent anti-oxidant with efficiency nearly twice that of Vitamin E. The special chemical structure of melatonin is responsible for its anti-oxidant effects. It can donate an electron or a hydrogen atom to free radicals, thereby detoxifying them in the process. Melatonin interacts with a variety of reactive oxygen species to form cyclic 3-hydroxymelatonin and other melatonin metabolites. Apart from scavenging reactive oxygen and nitrogen species, melatonin inhibits lipid peroxidation, upregulates the activity of certain anti-oxidants like Vitamins C and E while inhibiting the activity of pro-oxidant enzymes, and, in addition, also chelates transition metals involved in the Fenton and Haber-Weiss reactions, thereby inhibiting the formation of

hydroxyl and other radicals. It has also been found to inhibit oxidative stress and cellular apoptosis and restore tissue function. The anti-oxidant effects of melatonin are most pronounced in the retina and brain. Deficiency of melatonin in premature infants may predispose to free radical induced damage. Studies also suggest that melatonin might render treatment-resistant cancers sensitive to various therapeutic agents and delay the onset of certain age-related and degenerative disorders by virtue of its multiple anti-oxidant effects [74,75,76,77,78,79,80,81,82].

What are the Dietary Sources of Anti-Oxidants ?

Certain foods provide substrates for endogenous anti-oxidant systems in the body (Table 3).

FRUITS	VEGETABLES
• Apples • Berries • Citrus fruits (Oranges, lemons) • Dates • Figs • Kiwis • Pears (Avocado) • Pineapples • Peaches • Pomegranates	• Beetroot • Beans • Broccoli • Carrots • Lettuce • Garlic • Mushrooms • Onion • Spinach • Sweet Potato
MEAT	**FISH**
• Eggs • Chicken • Fowl • Liver • Brain • Tongue	• Carp • Mackerel • Salmon • Sardines • Tuna
DAIRY PRODUCTS	**NUTS AND SEEDS**
• Milk • Ghee • Yogurt	• Almonds • Walnuts • Pecan • Sunflower seeds

Table 3. Foods that are rich in Anti-Oxidants

The low-molecular weight, non-enzymatic vitamins β-Carotene (Vitamin A), L-Ascorbic Acid (Vitamin C) and α-Tocopherol (Vitamin E) are naturally occurring anti-oxidants that can easily be replenished from one's diet. In addition to these, foods that are rich in vitamins B2, B3, B5, B9, B12 and D, minerals like iron, copper, selenium, zinc, manganese and molybdenum, molecules like nitric oxide, sulfhydryl donor substrates, essential and sulphur containing amino acids, glutathione and those which have or promote an alkaline pH help to scavenge free radicals and, in addition, also help to maintain optimal oxygenation through indirect mechanisms like regulating hemoglobin, red cell mass, hematopoieses and blood flow. It has been postulated that increasing consumption of such foods (Table 3) could reduce the risk of stroke, diabetes, hypertension and cancer, improve respiratory, cardiac and circulatory function, and, most importantly, reduce damage due to oxidative stress [83,84].

Is it Beneficial to take Anti-Oxidant Supplements ? Are they Safe ?

The dietary sources of anti-oxidants have been enumerated above. A diet that includes more foods that are rich in anti-oxidants is believed by many to be healthier, and the official national health and nutrition policies of many countries urge their citizens to eat more of such foods. While research has shown that people who eat more green vegetables, fruits, lean meat and milk tend to have a lower risk of several chronic or inflammatory disorders, it is not yet clear whether these results can be correlated with the amount of anti-oxidants consumed, or to other components of these foods, or to other factors in the diets, or to lifestyle differences, which are by themselves potentially confounding factors. Large-sample size scientific studies have examined the hypothesis of whether anti-oxidant supplements can help to either prevent or reduce the incidence and/or prevalence of diseases associated with free radical-induced oxidative stress, such as coronary artery disease and atherosclerosis, COPD, cancer, cataracts, diabetes, Parkinson's disease and many others. While a few isolated studies found at best modest benefit, many others revealed no beneficial effects of anti-oxidants, either when supplemented

as medications, or consumed in their natural form in diet, in either preventing the development of, or reducing the risk, incidence or prevalence of the disease(s) studied [85,86,87]. Some of these studies are briefly discussed below :

- The Physicians' Health Study , which included a total of 22,071 U.S. male physicians aged between 40 to 84 years to study the effects of aspirin and β-carotene on cancer and cardiovascular disease showed neither benefit nor harm from β- carotene supplementation [88].
- The Physicians' Health Study II, which included more than 14,000 male physicians aged ≥ 50 years, found that neither Vitamin E nor C supplements reduced the risk of major cardiovascular events (heart attack, stroke, or death from cardiovascular disease), cancer, or cataracts. In fact, Vitamin E supplements were associated with an increased risk of hemorrhagic stroke. However, in a subset of male participants aged ≥ 65 years, long-term supplementation of 50 mg β-carotene showed significant benefit on cognitive function when compared with placebo [89].
- The Women's Anti-oxidant Cardiovascular Study, which included more than 8,000 female health professionals, aged ≥ 40 years, who were at high risk for cardiovascular disease, found no beneficial effects of Vitamin C, E, or β-carotene supplements on cardiovascular events (heart attack, stroke, or death from cardiovascular diseases) or the likelihood of developing diabetes or cancer, although women with pre-existing cardiovascular disease showed modest benefit with Vitamin E supplementation. Among a subgroup of women aged ≥ 65 years, anti-oxidant supplements also did not slow down decline in cognitive function [90].
- The Women's Health Study, which included almost 40,000 healthy women aged ≥ 45 years, found that Vitamin E supplements did not reduce the risk of heart attack, stroke, cancer, age-related macular degeneration, or cataracts. Although Vitamin E supplements were associated with fewer deaths from cardiovascular causes, they did not reduce the overall mortality of study participants [91].
- The Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) randomized controlled trial, in which 13017 French men and women received either a single-daily anti-oxidant combination supplement capsule of 120 mg Vitamin C, 30 mg Vitamin E, 6 mg β-carotene, 100 mcg selenium and 20 mg zinc, or a placebo, for seven and a half years, found that the vitamins had no effect on the overall rates of cardiovascular disease, however, a reduction in the risk of cancer and all-cause mortality was observed in males but not in females who received the anti-oxidant supplement, probably because the male participants had lower blood levels of β-carotene and other vitamins when compared with their female counterparts at the beginning of the study [92].
- The Selenium and Vitamin E Cancer Prevention Trial (SELECT), a study of more than 35,000 men aged ≥ 50 years or older, found that selenium and Vitamin E supplements, either taken alone or together, did not prevent prostate cancer. An updated analysis from this study in 2011, based on a longer follow-up period of study participants, concluded that Vitamin E supplements increased the occurrence of prostate cancer by 17% in men who received the Vitamin E supplement alone, when compared with those who received placebo (there was no increase in prostate cancer when both Vitamin E and selenium were taken together) [93].
- A randomized trial of selenium in people with skin cancer demonstrated significant reductions in cancer and cancer mortality at various sites, including the lung, colon, and prostate, with the effects most beneficial in those with low selenium levels at baseline [94].
- The Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE) trial followed more than 3700 men aged ≥ 60 years for six years found no protective effect of anti-oxidant supplements of Vitamin E or selenium, either alone or in combination, versus placebo, against dementia [95].
- The Heart Outcomes Prevention Evaluation (HOPE) trial, which evaluated the efficacy and safety of Vitamin E and ramipril for the prevention of myocardial infarction (MI), stroke, or cardiovascular death in 9541 patients aged ≥ 55 years at high risk for cardiovascular events or with diabetes mellitus found that Vitamin E supplementation of 400 IU per day was not associated with a reduction in the primary endpoints of MI, stroke, cardiovascular death or cancer when compared with placebo. On the contrary, the secondary endpoints of heart failure and revascularization or limb amputation were more common in the Vitamin E group. An extended follow-up of 3994 participants, the Heart Outcomes Prevention Evaluation - The Ongoing Outcomes (HOPE-TOO) trial carried out by the same investigators revealed no beneficial effect of Vitamin E supplementation in patients with coronary artery disease, paradoxically, it appeared to increase the incidence of heart failure in these patients [96].
- A meta-analysis of 68 anti-oxidant supplement trials found that taking supplements of β-carotene and Vitamins A and C increased the risk of dying. The evidence was controversial, as most trials included participants with some form of serious illness, although 21 of the trials did include healthy participants. Apart from participant characteristics, due to wide variation in the types (combinations) of supplements, their doses and the duration of administration, it became

difficult to compare the interventions of supplementation and their effects [97]. The same authors conducted another systematic review of 78 randomized clinical trials on anti-oxidant supplements including β-carotene and other forms of Vitamin A, Vitamins C and E, and selenium, either individually or in combination and found a greater risk of death with β-carotene and Vitamin E supplements in both healthy participants , as well as those with disease people who were healthy and those with diseases taking beta-carotene and vitamin E supplements had a higher rate of death. As before, there were wide variations in doses, duration (from 1 month to 12 years) and the health status of study participants at the outset [98].

- The Age-Related Eye Disease Study (AREDS), led by the National Eye Institute showed that a combination of anti-oxidants (Vitamins C and E and β-carotene) and zinc reduced the risk of developing the advanced stage of age-related macular degeneration (ARMS) by 25% in people who had the intermediate stage of this disease or who had the advanced stage in only one eye, and that the anti-oxidant vitamin supplements when used alone reduced the risk by about 17%. However, anti-oxidant supplements did not help either to prevent cataracts or slow their progression.
  A follow-up study, AREDS-2, found that adding omega-3 fatty acids (fish oil) to the supplement combination did not improve its effectiveness, however, adding lutein and zeaxanthin (two carotenoids found in the eye) improved the effectiveness of supplements in people who were not taking β-carotene and those who consumed only small amounts of lutein and zeaxanthin in foods [99,100,101,102].

- The MORGEN study, which was undertaken to investigate the relationships between the intake of the anti-oxidant pro-vitamins C, E and β-carotene and the presence of respiratory symptoms and lung function in 6,555 Dutch adults found that Vitamin C intake was not associated with most respiratory symptoms but was inversely related with cough. The FEV_1 and FVC were found to be higher by an average of 53 ml and 79 ml respectively in subjects with a high intake of Vitamin C as compared to those with a low intake, and by 60 ml and 75 ml respectively in subjects with a high intake of β-carotene as compared to those with a low intake. Intake of Vitamin E was found to have a positive association with productive cough but no association with most other symptoms and lung function, while intake of β-carotene was found to have a positive association with wheeze but no association with other symptoms [103].

- A cross-sectional study on 1616 randomly selected healthy residents of Western New York, USA, aged between 35 to 79 years and free of respiratory disease on the association of FEV_1 and FVC with serum Vitamins C and E, retinol, and carotenoids, after adjustment for covariates like smoking status, pack-years of smoking, weight, eosinophil count, and education found that participants falling within the lowest quartile of each of the serum anti-oxidants had consistently lower FEV_1 and FVC than those in higher quartiles, with Vitamin E and β-cryptoxanthin showing the strongest associations, supporting the hypothesis that anti-oxidant Vitamins play an important role in lung health and that Vitamin E and β-cryptoxanthin appear to be stronger correlates of lung function than other anti-oxidant vitamins [104].

- A study on anti-oxidants, oxidative stress, and pulmonary function in 218 individuals diagnosed with chronic airflow limitation, after adjustment for covariates, found that serum β-cryptoxanthin, lutein/zeaxanthin and retinol, and dietary β-carotene, β-cryptoxanthin, lutein/zeaxanthin, Vitamin C, and lycopene were positively associated with FEV_1 and serum βa-cryptoxanthin, lutein/zeaxanthin, and lycopene, and dietary β-cryptoxanthin, β-carotene, Vitamin C, and lutein/zeaxanthin were positively associated with FVC, whereas erythrocytic glutathione was negatively associated with FEV_1 [105].

To summarize, most clinical studies carried out in adults to assess the beneficial health effects of anti-oxidant supplements have found little evidence to support their use. Several theories to explain the lack of substantial benefits with anti-oxidant supplements have been postulated, including the following :

- It is believed that the beneficial effects of fresh fruits and vegetables or other foods rich in anti-oxidants are a result of not only anti-oxidants alone, but also other nutrients present in the same foods, or variance in lifestyle habits. For example, a cup of fresh strawberries contains about 80 mg of Vitamin C (100% RDA), whereas a supplement containing 500 mg of Vitamin C (667% of the RDA) does not contain polyphenols like flavonoids and proanthrocyanins which are naturally present in strawberries and possess anti-oxidant activity themselves, to complement that of Vitamin C. Again, observational studies do provide clues towards etiological links between dietary or lifestyle factors and disease risk, but they are unable to directly prove cause and effect for possible etiologies, as they do not take into account other confounding factors that are likely to affect outcomes. For example, people who eat or consume more anti-oxidants might also be more likely to exercise and follow stress-free lifestyles and less likely to smoke, and it is quite possible that these factors, rather than anti-oxidants alone, account for the reduced prevalence of diseases in them.

- The larger doses of synthetic anti-oxidants present in supplement capsules or tablets are different from smaller doses of natural or dietary anti-oxidants, and therefore the effects of both are likely to vary considerably. Not only

difference in doses, but also in the chemical structure and composition of natural anti-oxidants in food as compared to those in supplements would affect their activity and beneficial effects. For example, eight different forms of Vitamin E (tocopherols and tocotrienols) are present in foods, whereas supplements usually include only one of these forms, namely α-tocopherol.

- The anti-oxidant supplements may not have been given for a long enough time to prevent chronic diseases, such as cardiovascular diseases or cancer, which develop over decades.
- For patients with certain diseases, specific or locally acting anti-oxidants might be more effective than the ones that have been tested. For example, to prevent ocular diseases, anti-oxidants like lutein, which are present in the eye might be more beneficial than β-carotene, which is not present in the eye.
- It is quite possible that at least some or perhaps even many of the subjects who participated in the clinical trials on anti-oxidants were either members of the general population or people who were at high risk for specific diseases, and not necessarily under conditions of increased oxidative stress, where, perhaps increasing their anti-oxidant intake, either naturally by foods or artificially by supplements, or both, might have helped.
- The relationship(s) between free radicals and health and disease states may be more complex than has previously been studied. Under certain circumstances, free radicals may actually (paradoxically) be beneficial rather than harmful (for example, in phagocytosis), and neutralizing them in such conditions might be undesirable.

Anti-oxidants are regularly added to cereals, sport foods bars, energy drinks, and other processed foods, and promoted as supplements by the nutrition and pharmaceutical industry as "superfoods" with the potential to prevent or reverse aging, heart disease, cancer, cataracts, and others, and improve stamina, memory loss, and many other conditions. While their efficacy is often taken for granted, it is unfortunate that concerns have not yet been raised about the safety of anti-oxidant supplements. A 2009 analysis in the United States using data from the National Health and Nutrition Examination Survey (1999-2000 and 2001-2002) estimated the amount of anti-oxidants adults received from foods and supplements. Supplements were estimated to account for 54% of Vitamin C, 64% of vitamin E, 14% of α- and β-carotene, and 11% of selenium intake [106]. However, high-dose supplements of anti-oxidants are also likely to pose certain risks. For example, it was found that high doses of β-carotene may increase the risk of lung cancer in smokers [107]. High doses of Vitamin E may increase the risk of bleeding in patients already on anti-coagulants and anti-platelet drugs and have been associated with an increased risk of hemorrhagic stroke [108], as well as prostate cancer [109] . Doses of Vitamin C that exceed 1000 mg per day are likely to be associated with gastrointestinal disturbances (abdominal pain, nausea, diarrhea and flatulence) [110]. There is conflicting evidence on the effects of taking different anti-oxidant supplements during cancer treatment, with some studies suggesting benefit and others harm. Studies should assess the utility of a specific combination of anti-oxidant(s) and chemotherapy and/or radiotherapy, and determine optimal doses for a specific cancer setting. It is recommended that patients diagnosed with cancer should consult and discuss with their health care provider regarding nutritional supplements, including anti-oxidants [111].

Summary :

- Free radicals, namely reactive oxygen and nitrogen species are produced from time to time in cells as part of the physiological response to inflammation, infection, trauma, hypoxia or other stresses or injuries.
- Most of the time, free radicals are detoxified, quenched or neutralized by the body's in-built cellular defence mechanisms by different anti-oxidant systems, which may be enzymatic or non-enzymatic.
- However, under certain conditions, the rate of production of free radicals might exceed the rate at which they are neutralized, leading to oxidative stress.
- Anti-oxidants prevent free radical induced cellular and tissue damage either by preventing the formation of radicals or by quenching, or scavenging or promoting the decomposition of free radicals that are already formed, or by converting (detoxifying) them to more stable, less reactive or non-reactive molecules.
- Endogenous anti-oxidant mechanisms exist inside the body and are activated as part of the normal cellular defence mechanism in response to oxidative stress and damage.
- Anti-oxidants have often been promoted and marketed as "superfoods", "magic bullets", "energy boosters", "stamina boosters", "vitality boosters" and by many other fancy names from the consumer angle.
- Just because anti-oxidants are good, it doesn't mean that they are always helpful, or even safe, and their beneficial effects cannot always be taken for granted. Many studies which assessed the efficacy and safety of anti-oxidant supplements for the prevention or treatment of different diseases found no evidence to justify their consumption.
- Natural (dietary) sources of anti-oxidants in food are always preferable to anti-oxidant supplements.

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