MEDICAL GAS RESEARCH
www.medgasres.com

Oxygen targets in critically ill patients: from pathophysiology to population enrichment strategies

Claudio Ripa[1], Laveena Munshi[2, 3, 4], Wolfgang M. Kuebler[5, 6, 7, 8, 9], Aurora Magliocca[10], Fabio S. Taccone[11], Lorraine B. Ware[12, 13], Giuseppe Citerio[1, 14], John G. Laffey[15, 16], Emanuele Rezoagli[1, 17, *]

https://doi.org/10.4103/mgr.MEDGASRES-D-24-00120

Date of submission: November 12, 2024

Date of decision: December 28, 2024

Date of acceptance: December 3, 2024

Date of web publication: April 17, 2025

Abstract

Oxygen supplementation is widely used to enhance oxygen delivery and to treat or prevent hypoxia; however, it requires careful management to avoid the harmful effects of excessive oxygen exposure. Both hyperoxia (inspiratory oxygen fraction exceeding 0.21) and hyperoxemia (arterial oxygen tension oxygen partial pressure [PaO_2] > 100 mmHg) can contribute to lung injury, promote systemic vasoconstriction, and increase the production of reactive oxygen species, which can impair macromolecular and cellular functions. Conversely, in certain situations, hyperoxemia may provide benefits, such as hemodynamic stabilization in hyperdynamic shock, immunomodulation, and bactericidal effects. The literature presents conflicting evidence regarding the impact of different oxygen targets (i.e., PaO_2 and/or peripheral saturation of oxygen [SpO_2]) on both short- and long-term outcomes in patients with acute critical conditions, such as acute respiratory distress syndrome, sepsis, cardiac arrest, and acute central nervous system injuries. These discrepancies may stem from the small differences between the oxygenation targets used in randomized trials, the physiological limitations of PaO_2 and SpO_2 targets, which reflect blood oxygen content rather than oxygen delivery, the lack of measurements of microvascular function or oxygen delivery, and the heterogeneity in treatment response. Furthermore, advanced analytical methods (e.g., machine learning) are emerging as promising tools to implement population enrichment strategies. By refining patient sub-group identification, these approaches can significantly optimize precision medicine, enabling more personalized oxygen therapy tailored to individual patient characteristics.

Key Words: critical care; hyperoxemia; hyperoxia; hypoxemia; hypoxia; machine learning; oxygen delivery; oxygen; population enrichment; precision medicine; reactive oxygen species

Introduction

Around 3 billion years ago, the ability of some microorganisms to generate oxygen (O_2) from light slowly enriched the air. During the Great Oxidation Event, about 2.4 billion years ago, the O_2 tension in the earth´s atmosphere abruptly increased from 10 to 150 mmHg, leading to the development of mitochondria, that enabled the production of adenosine triphosphate (ATP) through the reduction of O_2 in the respiratory chain.[1] Since then, atmospheric O_2 has exerted its influence on aerobic organisms through a sophisticated balance between O_2 availability and O_2 tissue supply.[2] Since this time, humans have developed new tools for management of conditions of hypoxemia. In hypoxic patients, supplemental O_2 is a life-saving treatment that has been around for just over a century and developed to maintain adequate O_2 tissue delivery. Nonetheless, while the dangers of tissue hypoxia are well known, the implications of exposure to elevated O_2 levels with excessive oxidative stress, both for the lungs (which are the primary exposure site) and for all organs, are somehow underappreciated.

In this narrative review, we examined the current evidence on outcomes associated with different oxygenation targets in critically ill patients, highlighting the limitations of the existing literature and identifying key areas for improvement to support the development of personalized management strategies.

Search Strategy

We conducted a literature search using the MEDLINE database, focusing on articles published in English since January 2000 to December 2024 that provided full-text availability. The primary emphasis was on human studies, encompassing both healthy volunteers and patients, while data from mammalian models were incorporated where relevant to enhance clarity and context regarding pathophysiologic mechanisms. The search strategy utilized specific keywords, including “oxygen,” “hyperoxia,” “hyperoxemia,” “hypoxia,” “hypoxemia,” “oxygen delivery,” “reactive oxygen species,” “critical care,” “precision medicine,”

[1]School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy; [2]Interdepartmental Division of Critical Care Medicine, Sinai Health System/University Health Network, University of Toronto, Toronto, Canada; [3]Department of Medicine, Sinai Health System and University Health Network, Toronto, Canada; [4]Mount Sinai Hospital, Toronto, Canada; [5]Institute of Physiology, Charité-Universitätsmedizin, Berlin, Germany; [6]German Center for Cardiovascular Research, Berlin, Germany; [7]Department of Surgery, University of Toronto, Toronto, Canada; [8]Department of Physiology, University of Toronto, Toronto, Canada; [9]Keenan Research Center, St Michael’s Hospital, Toronto, Canada; [10]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [11]Department of Intensive Care, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium; [12]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [13]Department of Pathology, Microbiology and Immunology, Vanderbilt University, Nashville, TN, USA; [14]Department of Neuroscience, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [15]Department of Anaesthesia and Intensive Care Medicine, Galway University Hospitals, Galway, Ireland; [16]Anaesthesia, School of Medicine, College of Medicine, Nursing and Health Sciences, and CÚRAM Center for Research in Medical Devices, University of Galway, Galway, Ireland; [17]Department of Emergency and Intensive Care, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Gerardo dei Tintori, Monza, Italy

***Correspondence to:** Emanuele Rezoagli, MD, PhD, emanuele.rezoagli@unimib.it.

https://orcid.org/0000-0002-4506-7212 (Emanuele Rezoagli); https://orcid.org/0009-0009-3114-828X (Claudio Ripa); https://orcid.org/0000-0003-0551-9533 (Laveena Munshi); https://orcid.org/0000-0003-4100-2961 (Wolfgang M. Kuebler); https://orcid.org/0000-0002-3908-3857 (Aurora Magliocca); https://orcid.org/0000-0003-0830-1628 (Fabio S. Taccone); https://orcid.org/0000-0002-9429-4702 (Lorraine B. Ware); https://orcid.org/0000-0002-5374-3161 (Giuseppe Citerio); https://orcid.org/0000-0002-1246-9573 (John G. Laffey)

Funding: *This work was supported by Institutional funds of the University of Milano-Bicocca, Monza, Italy. Emanuele Rezoagli was supported by the Bicocca Starting grant 2020 from the University of Milano-Bicocca.*

How to cite this article: *Ripa C, Munshi L, Kuebler WM, Magliocca A, Taccone FS, Ware LB, Citerio G, Laffey JG, Rezoagli E. Oxygen targets in critically ill patients: from pathophysiology to population enrichment strategies. Med Gas Res. 2025;15(3):409-419.*

"population enrichment" and "machine learning" to identify pertinent publications. References were further refined based on specific syndromes and pathologies of different organs such as acute respiratory distress syndrome, acute myocardial infarction, and traumatic brain injury, ensuring a focused and comprehensive exploration of the literature. Representative articles were systematically screened to synthesize existing evidence, aiming to highlight the current state of knowledge and identify potential knowledge gaps, thereby providing insights for future research and practical advancements in critical care.

Complexities of Oxygen Supplementation to Treat Cellular Hypoxia

Hypoxia is the insufficient supply of O_2 to tissues, possibly leading to cellular death. The aim of O_2 supplementation in hypoxic patients is to optimize oxygen delivery (DO_2) – as millilitres per minute of O_2 delivered to tissues, to avert cellular hypoxia (**Figure 1**).[3,4] This is essential to maintain the mitochondrial respiratory chain function, which can operate with PO_2 levels as low as 0.3–0.7 mmHg.[5,6] DO_2 is the product of cardiac output and arterial oxygen content (CaO_2). Thus, O_2 supplementation primarily seeks to increase CaO_2 as long as tissue blood flow remains stable. Since measuring cellular hypoxia is challenging, clinicians rely on proxies such as the blood O_2 content. CaO_2 is determined by three key factors: dissolved O_2, haemoglobin concentration (Hb), and the percentage of O_2-saturated Hb. O_2-saturated Hb monitoring offers the advantage of being a continuously accessible "at-a-glance" parameter. The arterial dissolved O_2, instead, needs invasive arterial blood. These two parameters are related through the O_2-Hb dissociation curve.[7] The affinity to O_2 of haemoglobin is influenced by many factors, including pH, which affects the haemoglobin-O_2 affinity through the Bohr effect, where low pH levels promote O_2 release to metabolically active tissues. Other influencing factors include partial tension of carbon dioxide, temperature and 2,3-biphosphoglicerate which is produced at increased amount at elevated altitudes.

However, the relationship between DO_2 and CaO_2 may be a source of misunderstanding. For instance, a low CaO_2 due to hypoxaemia (defined as arterial blood O_2 partial pressure (PaO_2) < 60 mmHg) does not necessarily lead to hypoxia, as in high-altitude physiology when O_2 delivery is guaranteed despite the low O_2 tension in the air. Furthermore, a high CaO_2 due to hyperoxemia (PaO_2 > 100 mmHg) does not reduce the risk of tissue hypoxia, as in conditions of extreme cardiac output compromise.

Oxygen Supplementation – Are There Any Associated Risks?

Whether there is a single optimal level of oxygenation to achieve the most favorable outcome in critically ill patients remains unclear. Recent critical care recommendations[8] suggest an upper peripheral saturation of oxygen (SpO_2) target of 96% for all patients during O_2 supplementation, with a common target range of SpO_2 90–94%. These clinical recommendations have been developed based on recent evidence on the risks of excessive O_2 supplementation and aim to provide pragmatic guidance to avoid unnecessary support in patients with normal SpO_2. The choice of oxygenation targets should be balanced against benefits and risks at an individual patient level. Targeting lower oxygenation may expose patients to the risk of tissue hypoxia due to arterial hypoxaemia. Conversely, higher oxygenation targets may pose serious safety risks, including hyperoxia – e.g., high inspiratory O_2 fraction (FiO_2) > 0.21 – and hyperoxemia (e.g., PaO_2 > 100 mmHg).

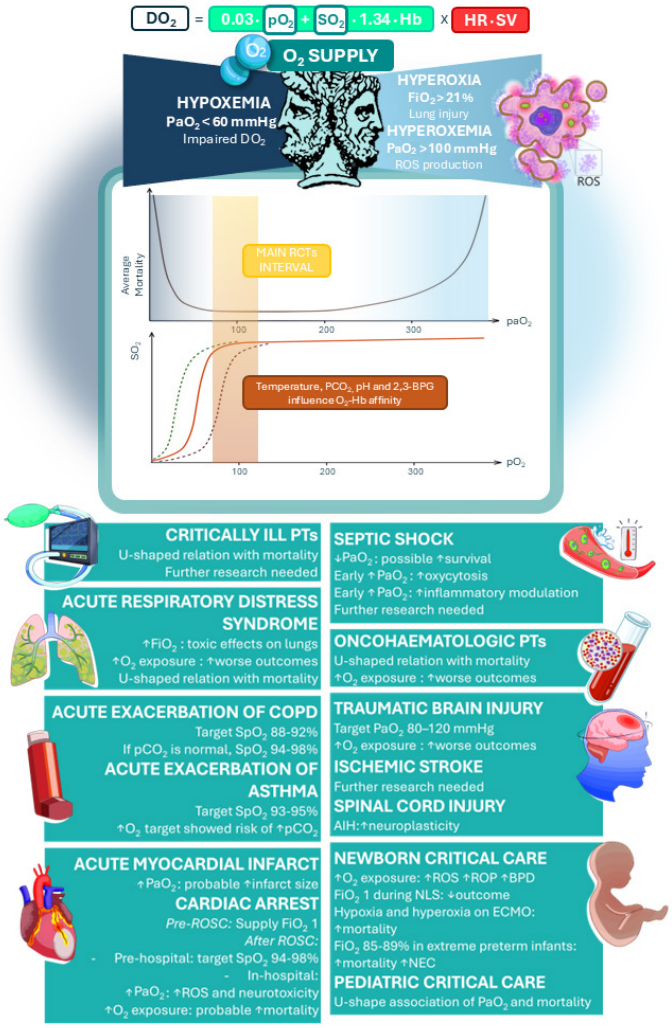

Figure 1 | DO_2 can be optimized through adjustments in oxygen supply, Hb levels, and cardiac output, as shown in the equation above.
Manipulating oxygen supply carries two major risks: hypoxemia, where O_2 levels are insufficient to fulfil tissue demands (hypoxia), and hyperoxemia, which can lead to lung injury and systemic oxidative stress due to ROS production. This relationship highlights the delicate balance between the two-edged features of O_2 supply, both of which may impact mortality. As adapted from Martin et al.[3], key RCTs comparing survival outcomes in ICU patients with different O_2 targets tend to fall within a PaO_2 range (yellow box) where the U-shaped relationship between PaO_2 and mortality (as described by Helmerhorst et al.[4]) has a plateau with a low mortality proportion. Additionally, the sigmoid feature of the ODC and the variability of SpO_2 in response to multiple factors (orange box) hinders the reliability of SpO_2 itself and the comparability between studies. The boxes on the bottom summarize the clinical findings and the knowledge gaps across different clinical conditions of critical illness. Created with Clip Studio Paint 1.5 and Microsoft Power Point (2021). 2,3-BPG: 2,3-Biphosphoglicerate; ABG: arterial blood gas analysis; AIH: acute intermittent hypoxia; AMI: acute myocardial infarction; ARDS: acute respiratory distress syndrome; BPD: bronchopulmonary dysplasia; CO_2: carbon dioxide; COPD: chronic obstructive pulmonary disease; DO_2: delivery of oxygen; ECMO: extra-corporeal membrane oxygenation; FiO_2: inspiratory fraction of oxygen; Hb: haemoglobin; HBOT: hyperbaric oxygen therapy; HR: heart rate; ICU: intensive care unit; O_2: oxygen; NEC: necrotizing enterocolitis; NLS: newborn life support; ODC: oxygen–hemoglobin dissociation curve; pCO_2: partial tension of carbon dioxide; pH: power of hydrogen; pO_2: partial tension of oxygen; PTs: patients; ROS: reactive oxygen species; SCI: spinal cord injury; SO_2: oxygen saturation; SV: stroke volume; RCT: randomized clinical trial; ROP: retinopathy of prematurity; ROS: reactive oxygen species; TBI: traumatic brain injury.

Hyperoxia can damage airway mucosa and alveoli. Animal models of hyperoxia-induced acute lung injury have shown that a FiO_2 > 0.7 over 3–6 days can significantly impact lung function and may lead to death from progressive respiratory failure. This emphasizes a dose-response effect dependent on both FiO_2 levels and duration

of exposure. Histopathological examinations revealed increased alveolar-capillary membrane permeability and acute exudative pulmonary oedema followed by a fibroproliferative phase, pulmonary surfactant dysfunction along with epithelium thickening, reduced mucociliary clearance, neutrophil infiltration and the release of pro-inflammatory mediators. These findings were exacerbated in animal models concurrently exposed to non-protective mechanical ventilation. However, interspecies and intraspecies variability suggest variable genetic susceptibility, which limits the generalizability of these results.[9] After more than 12 hours of FiO_2 > 0.75, healthy human volunteers developed symptoms such as cough, mucosal irritation, chest discomfort, and atelectasis. Additional symptoms included dyspnoea, paraesthesia, headache, nausea and vomiting. Bronchoalveolar fluid from healthy subjects exposed to FiO_2 > 0.50 for 17–45 hours showed signs of early alveolar injury and increased vascular permeability.[9,10] During the second half of the 20th century, reports described severe pulmonary pathology in patients mechanically ventilated for more than 10 days with an FiO_2 > 0.9. Those findings closely resembled descriptions from the animal models of hyperoxia-induced acute lung injury, including characteristic exudative lung injury. However, even the authors cautioned that factors such as ventilatory pressure and volume regimens, along with the primary causes of respiratory failure, could interfere with any further interpretation of casuality.[11] More recent ventilatory strategies, especially positive end-expiratory pressure titration, along with technological advancements, have reduced the need for high FiO_2 exposure, likely leading to a substantial reduction of additional risks associated with hyperoxia.[9] Along with endothelial derangement and alveolar exudative damage, hyperoxia can produce atelectasis through intra-alveolar de-nitrogenation.[12] These effects exacerbate the shunting of non-oxygenated blood, further compromising gas exchange and worsening overall lung function.[13]

Hyperoxemia can exacerbate the production of reactive oxygen species (ROS), mainly through the incomplete mitochondrial reduction of O_2. ROS are capable of altering the structure of organic macromolecules, impairing their function. If not carefully regulated, oxidative stress can intensify the inflammatory response through the activation of various kinases and signalling pathways. This is even more pronounced in the presence of mitochondrial dysfunction,[14] which by itself generates ROS. Moreover, oxidative stress is recognized as a key contributor to a wide array of pathologies, such as cancer, atherosclerosis, cardiovascular diseases, chronic neurological (e.g. Alzheimer's disease) and pulmonary diseases.[15] While hyperoxemia is defined by PaO_2 > 100 mmHg, there is no threshold for tissue hyperoxia, which depends on perfusion and tissue metabolic activity.

Therefore, although tissue hypoxia may be harmful, hyperoxemia may also have risks. Of note, eukaryotic organisms have evolved mechanisms to protect themselves against harm from both hypoxemia and hyperoxemia. For instance, during foetal development, hypoxia inducible factor 1 subunit alpha is expressed to counteract the detrimental effects of hypoxia by promoting erythropoiesis and neo-angiogenesis.[16] Analogously, enzymatic and non-enzymatic antioxidant mechanisms (e.g., superoxide dismutase, glutathione, and thioredoxin) are activated at later stages of the foetal development to support the newborn's adaptation to the sudden increase in PaO_2 (from 40–50 mmHg to 70–80 mmHg) following the first breath, which leads to an acute increase in ROS production.

Hyperoxemia Definition – Targeting Partial Arterial Tension of Oxygen or Peripheral Saturation of Oxygen?

Arbitrary cut-offs for defining hyperoxemia undermine the generalizability of the results of recent studies. Different opinions persist regarding the optimal variables to define the levels of oxygenation targeted in each study, such as PaO_2, SpO_2, or composite targets.[17] As already noted, those oxygenation targets are measures of blood oxygen content which are in reality only a proxy for oxygen delivery. Furthermore, SpO_2 measurement may not provide a reliable estimate of actual PaO_2, which is the determinant of hyperoxemia and ROS production.[18] Moreover, the PaO_2-SpO_2 relation (described by the sigmoidal O_2-Hb dissociation curve) comes with inherent limitations: SpO_2 changes very little (reaches a plateau) with increases in PaO_2 above 120 mmHg, and O_2-Hb affinity can vary substantially in the presence of several conditions generally affecting intensive care unit (ICU) patients. Furthermore, SpO_2 measurement may be affected by factors such as poor peripheral perfusion, cold skin or dark skin pigmentation, which reduce its reliability.

A more reliable approach likely lies in measuring cumulative exposure to high oxygen levels. This emphasizes the importance of the dose and the time spent above a critical threshold rather than relying solely on single time-point data. In addition, the lack of tissue oxygenation measurements significantly limits our understanding of the complex interactions between oxygen exposure and patient outcomes, which may vary unpredictably based on local microvascular function.

Oxygen Targets and Outcomes in Critically Ill Patients: Which Patient Subgroups?

As reported below, most of the randomised controlled trials (RCTs) with different oxygenation targets have proved controversial average treatment effects, and largely fail to resolve existing uncertainties. Given the ubiquitous use of oxygen therapy, there exists a growing interest among clinicians to pursue further RCTs to explore this topic. However, the effects of higher or lower oxygen targets in different subpopulations of critically ill patients need to be considered.

Undifferentiated critically ill patient populations

De Jonge et al.[19] observed a U-shape association between PaO_2 within the first 24 hours of ICU admission and hospital mortality in a cohort of 3000 mechanically ventilated ICU patients. The subsequent Oxygen-ICU trial[20] tested the effects of an interventional conservative protocol for O_2 supplementation aiming to maintain a SpO_2 between 94% and 98% or the PaO_2 between 70 and 100 mmHg with the lowest FiO_2 (median PaO_2 87 mmHg) as compared with a control liberal protocol targeting a SpO_2 between 97% and 100% and a PaO_2 up to 150 mmHg (median PaO_2 102 mmHg) in a large cohort of ICU patients. The interventional group had an ICU mortality that was almost halved compared to the control group, along with improved secondary outcomes (i.e. incidence of new shock episodes, liver failure and new bloodstream infections). These considerations were subsequently confirmed by one meta-analysis which took into account 25 RCTs enrolling more than 16,000 patients admitted to the ICUs with various aetiologies.[21] Moreover, other major RCTs did not reproduce the same results.[22-25] Nielsen et al.[22] found a beneficial effect of conservative O_2 supply (targeting a PaO_2 of 60 mmHg) on the median number of days alive without life support (e.g., primary outcome), but no effect on mortality was observed. However, the liberal group, which targeted a PaO_2 of 90 mmHg), rarely exceeded a PaO_2 of 100 mmHg during the study period. In contrast, the ICU-ROX trial[23] and Gelissen et al.[24] did not find a significant difference in mortality (secondary end-point) when patients were randomized to liberal (respectively: SpO_2 > 91% and PaO_2 105–135 mmHg) *versus* conservative oxygenation targets (SpO_2 91–97% and a PaO_2 60–90 mmHg, respectively). In the PILOT trial conducted by Semler et al.[25], patients receiving mechanical ventilation were randomized to three different SpO_2 targets (lower: 90%; intermediate: 94% and higher: 98%), rather than defined PaO_2 ranges. The rate of in-hospital death at 28 days was similar across the different O_2 target groups, as were the rates of other complications.

One limitation of the comparison of these studies is the variable definitions of liberal and conservative oxygen targets and the heterogeneous populations under evaluation (**Table 1**).[20,22-46] These seemingly conflicting results regarding the effect of different oxygenation targets on clinical outcomes in RCTs were elegantly interpreted in an editorial by Martin et al.[3] (**Figure 1**). The authors demonstrated that the oxygenation target ranges from the treatment arms of major ICU RCTs fell within a flat portion of the adjusted probability curve for in-hospital death related to PaO_2 levels, as described by Helmerhorst et al.[4] In this flat region, mortality risk is at its lowest, suggesting that minor differences in oxygen targets may be unlikely to meaningfully impact patient outcomes.

Table 1 | Main characteristics and findings of the RCTs reported in the current review

Trial	Year	Study design	Location	Size	Disease	Endpoint	High O_2 level (HO_2L) group*	Low O_2 level (LO_2L) group*	Primary outcome	Secondary outcomes	Conclusions
Critically ill											
Oxygen-ICU trial[20]	2016	SC RCT	Italy	434	Mixed	60 d	PaO_2 < 150 mmHg and SpO_2 97–100%	PaO_2 70–100 mmHg and SpO_2 94–98%	ICU mortality	New-onset respiratory, cardiovascular, liver, and renal failure	Higher ICU mortality and complication rate in the HO_2L group
ICU ROX trial[23]	2020	MC RCT	Australia and New Zealand	965	Mixed	28, 90 and 180 d	SpO_2 > 90% (PaO_2 108 mmHg) §	SpO_2 90–97% (PaO_2 90 mmHg) §	Ventilator free days at 28 d	Long term mortality, employment, cognitive impairment and quality of life	No difference
HOT-ICU trial[26]	2021	MC RCT	Northern Europe	2928	Mixed with AHRF	90 d and 12 mon	PaO_2 90 mmHg	PaO_2 60 mmHg	Mortality	Serious adverse events, days alive without life support. Mortality and quality of life at 12 mon	No difference
Gelissen et al.[24]	2021	MC RCT	Netherlands	574	Mixed (no ARDS)	14 d	PaO_2 105–135 mmHg	PaO_2 60–90 mmHg	Non-respiratory SOFA	SOFA-derived outcomes, duration of IMV, mortality	No difference
HOT-ICU in COVID-19[27]	2022	MC RCT	Northern Europe	110	Mixed with AHRF and COVID-19	90 d	PaO_2 90 mmHg	PaO_2 60 mmHg	Mortality	Serious adverse events, days alive without life support	No difference
PILOT[25]	2022	SC RCT	USA	2541	Mixed with IMV	28 d	SpO_2 98% (PaO_2 81–95 mmHg) °	SpO_2 90% and SpO_2 94% (PaO_2 74–89 mmHg) °	Ventilator-free days	Mortality	No difference
HOT-COVID trial[22]	2024	MC RCT	Northern Europe	726	Mixed with AHRF and COVID-19	90 d	PaO_2 90 mmHg	PaO_2 60 mmHg	Days alive without life support	Mortality; ICU complications; and days alive out of hospital	More days alive without life support in the LO_2L group
Acute respiratory distress syndrome											
Aggarwal et al.[28]	2018	RCTs secondary analysis		2994	ARDS	90 d	FiO_2 > 0.5 and PaO_2 > 80 mmHg	Not as HO_2L	In-hospital mortality	Ventilator-free and hospital-free days	Higher mortality in the HO_2L group
Acute central nervous injuries											
Stroke O_2 study[29]	2017	MC RCT	UK	8003	Stroke	90 d	Continuous or Nocturnal O_2 supplementation 2–3 L/min	No O_2 supplementation	mRS score	Mortality at 7 d, mortality, neurological and functional outcomes at 90 d	No difference
Cardiac arrest and acute myocardial infarction											
AVOID[30]	2015	MC RCT	Australia	441	STEMI	180 d	O_2 8 L/min	No O_2 supplementation unless SpO_2 < 94%	MI size	Recurrent MI, cardiac arrhythmia, and myocardial infarct size at MRI	Larger MI size at 6 mon in the HO_2L group
DETO2X–AMI trial[31]	2017	SC RCT	Sweden	6629	AMI	30 d and 12 mon	O_2 6 L/min	No O_2 supplementation	Mortality	Death at 30 d, rehospitalization with cardiovascular cause	No difference
COMACARE[32]	2018	MC RCT	Finland and Denmark	120	ROSC after OHCA	2, 3 and 180 d	PaO_2 150–188 mmHg	PaO_2 75–113 mmHg	Serum NSE at 2 d	Serum NSE, S100B, troponin during the first 72 h; rSO_2, NIRS, EEG during the first 48 h, CPC at 6 mon; mechanical ventilation; length of ICU and hospital stay; mortality	No difference
ICU-ROX trial[33]	2020	MC RCT *post hoc* analysis	Australia and New Zealand	176	ROSC after OHCA	180 d	SpO_2 > 90% (PaO_2 88 mmHg) ç	SpO_2 90–97% (PaO_2 84 mmHg) ç	Mortality or unfavourable neurological outcome	ICU and hospital LOS, ventilator-free days, and vasopressor-free days	Higher ventilator-free days and vasopressor-free days in the LO_2L group
COMACARE[34]	2021	MC RCT *post hoc* analysis	Finland and Denmark	112	ROSC after OHCA	ICU admission, 24, 48, and 72 h after OHCA	PaO_2 150–188 mmHg	PaO_2 75–113 mmHg	Plasma NfL concentration at 48 h	Plasma NfL concentration at 24 and 72 h; plasma S100 concentration at 24, 48 and 72 h; cardiac troponin concentration at 24, 48 and 72 h; NIRS during the first 48 h; CPC at 6 mon; ICU LOS; IMV length; hospital LOS; survivorship	No difference
Bernard EXACT trial[35]	2022	MC RCT	Australia	425	ROSC after OHCA	At ICU and hospital discharge, 12 mon	SpO_2 98–100% (PaO_2 130 mmHg)	SpO_2 90–94% (PaO_2 95 mmHg)	In-hospital mortality	Hypoxic episodes and serious adverse events	Higher hypoxia rate in the LO_2L group
BOX trial[36]	2022	MC RCT	Denmark	791	ROSC after OHCA	90 d	PaO_2 98–105 mmHg	PaO_2 68–75 mmHg	CPC 3–5	NSE levels, neurological outcome	No difference
TTM2 trial[37]	2022	MC RCT secondary analysis	Australia, Europe and USA	1418	ROSC after OHCA	180 days	PaO_2 > 300 mmHg	PaO_2 60–300 mmHg PaO_2 < 60 mmHg	mRS 4–6	Mortality and Neurological outcome at 6 mon; threshold of oxygenation associated with mortality and poor neurological outcome; cumulative dose of oxygen related with mortality and poor neurological outcome; effect of PaO_2 on outcome	Both hypoxia, hyperoxia and the time exposure to hyperoxia are associated with mortality
HOT-ICU trial[38]	2023	MC RCT *post hoc* analysis	Northern Europe	335	ROSC after OHCA	90 d and 12 mon	PaO_2 90 mmHg	PaO_2 60 mmHg	Mortality	Serious adverse events, days alive without life support. Mortality and quality of life at 12 mon	Fewer serious adverse events in the LO_2L group

Table 1 | Continued

Trial	Year	Study design	Location	Size	Disease	Endpoint	High O_2 level (HO_2L) group*	Low O_2 level (LO_2L) group*	Primary outcome	Secondary outcomes	Conclusions
Sepsis and septic shock											
HYPER2S trial[39]	2017	MC RCT	France	442	Septic shock	28 and 90 d	FiO_2 1 for 24 h (51%)#	SpO_2 88–95% (56%)#	Mortality at 28 d	Mortality at 90 d; SOFA, days alive without support, ICU LOS	Higher serious adverse event in the HO_2L group
HYPER2S trial[40]	2018	MC RCT *post hoc* analysis	France	230	Septic shock (Sepsis-3 definition)	28 and 90 d	FiO_2 1 for 24 h (56.5%)#	SpO_2 88–95% (59%)#	Mortality at 28 d	Mortality at 90 d	Higher mortality in HO_2L group
Acute exacerbation of chronic obstructive disease and asthma											
Rodrigo et al.[41]	2003	MC RCT	Uruguay	74	Asthma	20 min	PaO_2 257 mmHg	PaO_2 99.4 mmHg	$PaCO_2$	pH, peak expiratory flow (PEFR), PaO_2, heart rate and respiratory rate	$PaCO_2$ increases and PEFR decreases in the HO_2L group
Perrin et al.[42]	2011	MC RCT	New Zealand	106	Severe exacerbation of asthma	20, 40 and 60 min	FiO_2 8 L/min	SpO_2 93–95% mmHg	$PaCO_2$	–	PCO_2 increases in the HO_2L group
Nielsen et al.[43]	2024	MC RCT subgroup analysis	Northern Europe	563	COPD	90 d and 12 mon	PaO_2 90 mmHg	PaO_2 60 mmHg	Mortality	Serious adverse events, days alive without life support. Mortality and quality of life at 12 mon	No differences
Newborn and pediatric critical care											
Vento et al.[44]	2009	MC RCT	Spain		Resuscitated infants of ≤ 8 wk of gestation	28 d and 36 wk	FiO_2 1	FiO_2 0.3	Neonatal death and BPD incidence	Durations of oxygen support, IMV and use of surfactant	Lower oxygen support and risk of BPD in the LO_2L group
Tataranno et al.[45]	2015	MC RCT	Australia	119	Resuscitated infants of ≤ 2 wk of completed gestation	2 and 12 h	FiO_2 1	FiO_2 0.21	Oxidative stress markers	–	Lower oxidative stress in the LO_2L group
Peters et al.[46]	2024	MC RCT	UK	2040	Children > 38 wk admitted to PICU for IMV	30 d	SpO_2 > 94%	SpO_2 88–92%	Duration of organ support and survival	Mortality, IMV duration; organ support duration; functional status at discharge; PICU and hospital LoS	Better outcome in the LO_2L group

* Mean PaO_2 (or surrogate) levels, if not specified by randomization criteria, are indicated in brackets; ˚ Mean values during day 1 to 7; ç time-weighted PaO_2 over the first 10 days of mechanical ventilation; § higher mean value during 90 days; # rate of patients with PaO_2 > 120 mmHg. AHRF: Acute hypoxic respiratory failure; AMI: acute myocardial infarction; ARDS: acute respiratory distress syndrome; BPD: bronchopulmonary dysplasia; CA: coronary angiography; CPC: cerebral performance category; EEG: electroencephalography; FiO_2: inspiratory fraction of oxygen; HO_2L: high oxygen target; ICU: intensive care unit; IMV: invasive mechanical ventilation; LO_2L: low oxygen target; LOS: length of stay; MI: myocardial infarction; MC: multi-center; MRI: magnetic resonance imaging; mRS: modified Rankin Score; NfL: neurofilament light; NIRS: Near infra-red spectroscopy; NSE: neuron specific enolase; OHCA: out-of-hospital cardiac arrest; PaO_2: partial arterial tension of oxygen; PICU: Pediatric Intensive Care Unite; RCT: randomized controlled trial; ROSC: return to spontaneous circulation; rSO_2: regional saturation of oxygen; SC: single-center; S100B: S100 calcium-binding protein B; SOFA: Sequential Organ Failure Score; SpO_2: peripheral saturation of oxygen; STEMI: ST-elevation myocardial infarction.

Acute respiratory distress syndrome

In acute respiratory distress syndrome (ARDS), inflammation and protein-rich lung oedema impair gas exchange, while exposure to high FiO_2 can injure the airway mucosa and alveoli.[5,9] Although hyperoxemia is considered relatively uncommon,[47] given the challenges in achieving it, the optimal oxygenation target remains uncertain. A longitudinal analysis of 10 trials performed by the ARDS Network introduced the concept of a dose-response relationship between the cumulative above-goal O_2 exposure – calculated as the FiO_2 exceeding 0.5 among participants with a PaO_2 > 80 mmHg – and worsened clinical outcomes in patients with different severities of ARDS.[28] Similarly, Boyle et al.[48] found a U-shape association between average time-weighted PaO_2 within the first 7 days and mortality in 202 prospectively enrolled ARDS patients. These data suggest that the cumulative oxygen dose might contribute to clinical outcomes in patients with acute lung injury Although Madotto et al.[47] did not find a relation between hyperoxemia and mortality risk, their analysis of 2005 patients with ARDS from the LUNG SAFE study revealed that hyperoxemia (PaO_2 > 100 mmHg) occurred in 30% of patients, particularly among those with mild ARDS. Of these hyperoxemic patients, two-thirds were exposed to FiO_2 > 0.6 (e.g., excess FiO_2 administration). By day 2, however, median FiO_2 levels had decreased, and fewer than half of the hyperoxemic patients experienced sustained hyperoxia. Notably, excess FiO_2 administration was transient in nearly 80% of cases, probably suggesting a rapid improvement after ventilatory support. Nonetheless, approximately one-third of patients remained hyperoxaemic at each FiO_2 decile by day 2, underscoring the potential for further FiO_2 reduction and more tailored oxygen exposure.

Acute central nervous injuries

O_2 supplementation in patients with acute brain injury aims to enhance tissue oxygen delivery and prevent secondary brain injury. However, ROS production, cerebral excitotoxicity, microglial activation, and vasoconstriction raise questions regarding the safety of hyperoxia and its relationship to patient outcomes.

Rezoagli et al.[49] reported an independent association between high oxygen exposure during the first week of hospitalization—measured by FiO_2 levels or PaO_2—and unfavorable outcomes, such as mortality and a GOSE score ≤ 4 at 6 months in traumatic brain injury (TBI) patients.

Similarly, a *post hoc* analysis of the observational ENIO study[50] found that PaO_2 values above 156 mmHg were associated with an increased probability of in-hospital mortality in TBI patients. Interestingly, recent small studies using cerebral micro-dialysis have shown that hyperoxia reduces brain lactate levels and the lactate-to-pyruvate ratio after TBI.[51,52] While it remains unclear if a specific high PaO_2 threshold is safe for TBI patients, the European Society of Intensive Care Medicine guidelines currently recommend targeting normoxia (PaO_2 80–120 mmHg),[53] regardless of intracranial pressure elevation.

Despite preclinical evidence suggesting the potential benefits of hyperoxia in acute ischemic stroke, clinical studies lack solid evidence of the protective effects of oxygen therapy in those patients. The stroke oxygen study,[29] which enrolled 8003 patients, examined the effects of O_2 supplementation (mean highest SpO_2 99.1%) and found no difference in morbidity (assessed via the modified Rankin Scale at 90 days) or mortality at seven days compared to the control group (mean highest SpO_2 98.3%). Furthermore, the modulation of O_2 exposure seems to affect the recovery from spinal cord injury. While the primary damage in spinal cord injury is typically irreversible, the secondary injury is a dynamic process involving oxidative stress, inflammation and apoptosis. These phenomena contribute to the

degeneration of the spinal cord function and seem to be exacerbated by acute intermittent hypoxia exposure.[54]

Cardiac arrest and myocardial infarction

During cardiac arrest O_2 delivery is critically impaired along with O_2 to the brain, leading to neuronal death over a few minutes. Currently, the International Liaison Committee on Resuscitation recommends the use of the highest dose of O_2 during cardiopulmonary resuscitation to maximise brain O_2 delivery[55] and maintain the use of 100% FiO_2 until the SpO_2 or the PaO_2 can be measured reliably in adults after return of spontaneous circulation (ROSC).[56]

After cardiac arrest, ischemia leads to endothelial activation and increases microvascular permeability to fluid and proteins as well as the recruitment of inflammatory leukocytes.[57] After reperfusion, the activated leukocytes release ROS and exacerbate the inflammatory response.[58] Subsequently, the regional inflammatory reaction can activate a generalized inflammatory syndrome. In this setting, hyperoxia could exacerbate the production of ROS with potential neurotoxic effects and increase reperfusion brain injury. At this stage, clinicians are advised to maintain SpO_2 levels between 94% and 98% if arterial blood oxygen saturation can be assessed reliably, or a PaO_2 of 75 to 100 mmHg.[55,59] While these recommendations are weak and based on very low-certainty evidence, our understanding of how oxygenation influences outcomes after ROSC has advanced rapidly over the past decade. The potential risks of inadequate or excessive O_2 supplementation on patient survival after cardiac arrest are becoming increasingly evident.[35,60] The Reduction of Oxygen After Cardiac Arrest (EXACT) trial assessed O_2 titration among adult patients with ROSC after out-of-hospital cardiac arrest and advanced airways in the prehospital setting.[35] In this trial patients with stable ROSC and a SpO_2 > 94% on 100% FiO_2, were randomized into one of the two SpO_2 targets: 90–94% and 96–98% until the first arterial blood gas in ICU. The primary outcome of survival to hospital discharge was lower in the lower SpO_2 group (38.3% *vs*. 47.9%; difference, –9.6% [95% confidence interval (CI), –18.9% to –0.2%]; unadjusted odds ratio, 0.68 [95% CI, 0.46–1.00]; P = 0.05). A higher proportion of patients randomised to the lower SpO_2 arm experienced a hypoxemic episode (SpO_2 < 90%) before ICU admission and required an increase in FiO_2 to 1 (31% *vs*. 16%, P < 0.001), with no differences in other secondary outcomes between the two groups. Although the study was halted because of the COVID-19 pandemic, possible harm from lower SpO_2 titration in the prehospital setting emerged from this data.

In the in-hospital setting, two observational studies showed that hyperoxemia within 24 hours after cardiac arrest was linked with impaired neurological recovery and increased mortality.[61,62] Roberts et al.[61] identified an exponential increase in poor neurological outcomes with PaO_2 exceeding 300 mmHg after ROSC in 280 comatose patients after both in-hospital and out-of-hospital cardiac arrest. It is noteworthy that approximately 40% of their cohort had a PaO_2 exceeding this threshold. However, in the largest randomized trial comparing blood pressure and oxygenation targets after cardiac arrest (BOX trial) with a 2-by-2 factorial design, Schmidt et al.[36] found no difference in mortality or any of the secondary endpoints between a restrictive oxygenation target (PaO_2 68–75 mmHg) and a liberal oxygenation target (PaO_2 98–105 mmHg). Additionally, the COMACARE trial[32] compared two different PaO_2 targets (PaO_2 75–113 mmHg *vs*. PaO_2 150–188 mmHg) and found no differences in the serum concentrations of neuron-specific enolase at 48 hours following out-of-hospital cardiac arrest. No differences were also observed in the levels of the new biomarker of brain injury neurofilament light chain among the two groups.[34] Several sub-studies of phase III clinical trials have been conducted to assess the associations between oxygen targets and outcomes. In 166 patients randomized in the ICU-ROX trial[33] with suspected hypoxic-ischaemic encephalopathy, the rate of death or unfavourable neurological outcome at 6 months was 55.1% (43 of 78 patients) in the conservative oxygen group (targeting SpO_2 < 97%) and 68.1% (49 of 72 patients) in the more liberal (SpO_2 > 90%) oxygen therapy group (odds ratio 0.58; 95% CI 0.3–1.12; P = 0.1). Additionally, the conservative group had more vasopressor-free days and ventilator-free days. In a pre-planned sub-analysis of 335 post-ROSC cardiac arrest patients enrolled in the HOT ICU trial,[38] the adjusted difference in mortality between the lower and the higher oxygen group was 5.6% at 3 months (95% CI –4.88 to 16.05), with similar results at 1 year (adjusted relative risk (RR) 1.05, 95% CI 0.90– 1.21, P = 0.53). Finally, a secondary analysis of the targeted hypothermia versus targeted normothermia after Out-of-Hospital Cardiac Arrest (TTM-2) trial explored the association of hypoxemia (PaO_2 < 60 mmHg) or hyperoxemia (PaO_2 > 300 mmHg) with death and neurological dysfunction at 6 months.[37] The authors showed that 24.9% of patients had at least one episode of hypoxaemia while 7.6% of patients had at least one episode of hyperoxaemia, and prolonged exposure to hyperoxemia was significantly associated with mortality (P = 0.003).

In acute myocardial infarction current guidelines of the European Society of Cardiology recommend against routine O_2 therapy in patients without hypoxemia (SpO_2 ≥ 90%), while oxygen therapy is advised only in patients with oxygen saturation < 90%.[63] These recommendations are based on evidence from large, randomized trials evaluating supplemental O_2 *versus* ambient air in patients presenting with suspected myocardial infarction who were not hypoxemic at baseline.[31,64] The Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction (DETO2X-AMI) trial[64] enrolled 6629 patients and showed no significant effect of supplemental oxygen, as compared with ambient air, on all-cause mortality at 1 year or on the incidence of rehospitalization with myocardial infarction. Stub et al.[30] demonstrated that those who received oxygen at 8 L/min (median SpO_2 98%) experienced worse outcomes—including higher rates of acute myocardial infarction recurrence, cardiac arrhythmias, larger infarct sizes, and increased mortality—compared to patients who received oxygen at 4 L/min (median SpO_2 100%). However, this study included the patients with STEMI evidence at ambulance arrival and the enrollment was restricted only to those with a SpO_2 > 94% at baseline.

Sepsis and septic shock

Evidence regarding the safety of hyperoxia in sepsis or septic shock is conflicting. Oxidative stress plays a crucial role in bacterial clearance through oxycytosis, where oxygen release from oxyhaemoglobin aids in bacterial killing. These “antimicrobial” benefits were also demonstrated in surgical patients who experienced a reduced incidence of surgical wound infections when exposed to higher oxygen levels (mean PaO_2 286 mmHg) during the perioperative period.[65]

Moreover, some evidence suggests that the outcomes may depend on the timing of oxygen exposure. Early use of oxygen therapy has shown promise in modulating the immunologic response to insults in septic shock.[66] In a murine model of polymicrobial infection by caecal ligature and puncture,[67] dose-dependent hyperbaric O_2 therapy (253.31 kPa of FiO_2 1 every 12 hours) improved survival through mechanisms largely independent of direct bacterial toxicity. Instead, these benefits were attributed to elevated interleukin-10 levels, a B-cell modulator, and presumably by a reduction in bacterial dissemination, as suggested by bacterial load analysis. Additional evidence from models of sterile inflammation triggered by ischemia/reperfusion injury[66] indicates that hyperbaric O_2 therapy could modulate the proinflammatory cascade. This happens due to the downregulation of nuclear factor-κB E-selectin, and intercellular

adhesion molecule-1, as well as reducing levels of proinflammatory cytokines like interleukin-6. Additionally, early hyperoxia has shown beneficial effects on hemodynamic stabilization in the initial stages of porcine sepsis models by improving tissue oxygenation and exerting systemic vasoconstriction (median PaO_2 levels at 12, 18, and 24 hours after peritonitis induction were 80 mmHg *vs*. 490 mmHg, 74 mmHg *vs*. 337 mmHg, and 71 mmHg *vs*. 286 mmHg, respectively, in the control and interventional groups).[68] However, a physiological study of induced septic response in healthy human volunteers found no significant differences in hemodynamics or cytokine levels between the control group (peak PaO_2 125 mmHg) and the hyperoxemic group (peak PaO_2 525 mmHg).[69]

While hyperoxia may benefit systemic organs, modulate immune responses, and exert bactericidal effects, it also poses risks to the lungs. Thus, O_2 therapy demands a careful approach to maximize benefits while minimizing pulmonary harm. Data on the beneficial effects of hyperoxia during sepsis are conflicting, primarily stemming from animal models of hyperdynamic shock. A *post hoc* analysis of the HYPERS2S trial[40] suggested a potential survival benefit from restricted O_2 therapy, aligning with the hypothesis that excessive oxygen may exacerbate the high ROS production and mitochondrial dysfunction characteristic of sepsis. This theory posits that high O_2 exposure could worsen these conditions. Nevertheless, the optimal application of hyperoxia in this context has yet to be thoroughly explored.

Onco-hematologic patients

With oncologic therapeutic advancements and improved patient outcomes, the number of onco-hematologic patients admitted to ICUs has risen over the past decades – mainly for septic shock or pneumonia. In this cohort of patients, cellular hypoxia is known to promote cancer cell survival and angiogenesis,[70] and is further investigated to be a prognostic factor and therapeutic target. However, hyperox(em)ia may also contribute to pulmonary toxicity and exacerbate lung injury. Under these premises, Dumas et al.[71] identified a significant U-shaped relationship between day PaO_2 levels and 28-day mortality in a cohort of 11,249 ICU patients with hematologic malignancies and acute respiratory failure admitted to the ICU. Of these patients, 56% had acute leukaemia, while 38% had lymphoma or multiple myeloma. ICU admissions were primarily for ARDS (43%), sepsis (40%), cardiac arrest (5.5%), and neurological conditions (7%). Notably, hyperoxemia was highly prevalent among patients ventilated with FiO_2 1.0, and approximately one-third of patients in each FiO_2 decile were hyperoxaemic. Excess oxygen use, defined as $FiO_2 \geq 0.6$ in hyperoxaemic patients, was observed in 20% of patients on day one (median PaO_2 163 mmHg) and 10% of patients by day three. Although further research is needed to understand the biological relationship between oxygenation levels and outcomes in patients with malignancies, these findings suggest that modifying clinical practices could significantly impact mortality rates potentially without clinical hazard.

Long-Term Outcomes in Intensive Care Unit Discharged Patients

The clinical interest of intensive care practitioners has included long-term disability following ICU admission, often referred to as post-intensive care syndrome.[72] This has led to investigations of whether different oxygenation targets might influence long-term outcomes. The ICU-ROX trial[23] was among the first to explore this question, finding no significant differences between groups at 6 months in terms of mortality or cognitive impairment. However, patients receiving oxygen therapy to target $SpO_2 > 97\%$ had better scores for Personal Care and Mobility on the European Quality of Life - 5 Dimensions - 5 Levels (EuroQoL-5D-5L) questionnaire. Notably, the trial showed no differences between groups in days free from ventilatory support, a known risk factor for post-intensive care syndrome. Additional researchers conducted a 1-year follow-up via telephone interviews to investigate potential differences in long-term outcomes. The HOT-ICU trial[26] focused on ICU patients with mixed aetiologies admitted for acute hypoxemic respiratory failure. Participants were randomized to receive oxygen therapy targeting either a PaO_2 of 60 or 90 mmHg for up to 90 days post-randomization. Subsequently, the *post hoc* analysis of the HOT-ICU trial[27] and the HOT-COVID trial,[22] examined outcomes differences in critical ill patients with COVID-19 when supplied with different oxygenation targets (PaO_2 60 or 90 mmHg). Although no significant intergroup differences were observed in short-term outcomes, Nielsen's analysis showed a greater number of days alive without life support in the low-oxygen treatment harm. Crescioli et al.[73,74] further evaluated 1-year health-related quality of life in the cohorts of these studies. Both analyses showed that targeting different oxygenation levels did not result in improved survival or health-related quality of life at 1-year follow-up.

Acute Exacerbation of Chronic Obstructive Disease and Asthma

Oxygen therapy is a cornerstone treatment for acute exacerbations of chronic obstructive pulmonary disease (AECOPD). However, the administration of oxygen must be carefully titrated to prevent the risks associated with over-oxygenation, particularly in patients at risk of hypercapnic (type 2) respiratory failure. These patients often have chronic hypercapnia, and excessive oxygen can suppress hypoxic drive, leading to worsening hypercapnia, respiratory acidosis, and potential respiratory failure.[75]

In patients with AECOPD, the British Thoracic Society recommends to target an SpO_2 range of 88–92% using a 28% Venturi mask at 4 L/min.[76] Arterial blood gases should be checked within 30–60 minutes to assess the presence of hypercapnia and acidosis.[77] For patients who show normal $PaCO_2$ levels on arterial blood gases, oxygen can be titrated to achieve a SpO_2 of 94–98%. If hypercapnia and acidosis persist despite optimal oxygen therapy, non-invasive ventilation should be initiated to provide ventilatory support.

The dangers of overoxygenation in AECOPD have been well documented. Echevarria et al.[78] investigated the impact of admission oxygen saturation levels on inpatient mortality in 1027 hospitalized AECOPD patients receiving supplemental oxygen. The study analyzed data grouping patients by oxygen saturation levels: ≤ 87%, 88–92%, 93–96%, and 97–100%. The results revealed that oxygen saturations above the guideline-recommended 88–92% were associated with significantly increased mortality. Specifically, compared to the 88–92% group, the adjusted odds ratio for mortality was 1.98 (95% CI 1.09–3.60, $P = 0.025$) and 2.97 (95% CI 1.58–5.58, $P = 0.001$) for saturations of 93–96% and 97–100%, respectively.

A pre-planned secondary analysis of 536 patients enrolled in the HOT-ICU trial[43] investigated whether a lower oxygenation target (PaO_2 60 mmHg, SpO_2 88–92%) reduced mortality compared to a higher target (PaO_2 90 mmHg, SpO_2 94–98%). No statistically significant differences in 90-day mortality were observed between the two oxygenation groups (RR: 0.98, 95% CI: 0.82–1.17, $P = 0.67$). However, both groups maintained tight control of $PaCO_2$, and no significant differences in secondary outcomes, including length of ICU stay or readmission rates, were found. These results suggest that both lower PaO_2 target may be safely used if $PaCO_2$ levels are closely monitored.

Oxygen therapy is a critical intervention during acute exacerbations of asthma. However, evidence underscores the importance of titrated oxygen delivery to avoid complications associated with

excessive oxygen administration. The 2023 update from the Global Initiative for Asthma emphasizes maintaining SpO_2 between 93% and 95%. This approach has been associated with better outcomes than uncontrolled, high-concentration oxygen therapy, especially in patients with impending respiratory failure.[79]

Studies comparing oxygen delivery strategies highlight the risks of uncontrolled oxygen administration. In a randomized trial of 74 patients with acute severe asthma, Rodrigo et al.[41] demonstrated that FiO_2 1 led to significant increases in $PaCO_2$ levels (P = 0.03) and reductions in peak expiratory flow rate (PEFR, P = 0.001), particularly in patients with baseline $PaCO_2$ > 40 mmHg, when compared with patients receiving FiO_2 0.28. Similarly, a randomized controlled trial by Perrin et al.[42] compared high-concentration oxygen (8 L/min) with titrated oxygen (93–95% SpO_2) in 106 patients with severe asthma exacerbations. The high-concentration group exhibited a significantly higher risk of hypercapnia, showing a $PaCO_2$ rise ≥ 4 mmHg (RR 2.3, 95% CI 1.2–4.4, P < 0.006). Severe cases with a final $PaCO_2$ ≥ 45 mmHg were exclusively in the high-concentration group, underscoring the potential of higher levels of administered oxygen to leas to hypercapnic respiratory failure. Chien et al.[80] also reported that uncontrolled oxygen delivery exacerbated hypercapnia in asthmatic patients, with 46.7% of participants developing hypercapnic respiratory failure after 20 minutes of FiO_2 1. Taken together, the data strongly support the use of titrated oxygen therapy in acute asthma exacerbation for optimizing outcomes.

Newborn and Pediatric Critical Care

Oxygen therapy is a critical intervention in neonatal care, and its use is associated with significant both benefits and risks. Excessive oxygen exposure contributes to oxidative stress, a key factor in neonatal morbidities such as retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis.[81-83] These risks are particularly pronounced due to their immature antioxidant systems.[84]

In term newborns, research underscores the efficacy of resuscitation with room air FiO_2 0.21.[45,85] Term infants generally require only positive pressure ventilation with air to achieve normal cardiorespiratory adaptation without significant oxidative complications. In contrast, preterm infants, particularly those born before 32 weeks of gestation, frequently require higher FiO_2 for stabilization.[86,87] However, this increases their susceptibility to oxidative stress and associated pathologies. Further research by Vento et al.[44] demonstrated that initial resuscitation of preterm neonates with FiO_2 0.3, as opposed to FiO_2 0.9, reduced oxidative stress markers (P < 0.01), leading to fewer days of mechanical ventilation (13 *vs*. 27 days, P < 0.01) and a lower incidence of bronchopulmonary dysplasia (15.4% *vs*. 31.7%, P < 0.05).

The NEOPROM meta-analysis[88] examined the impact of oxygen saturation targets in extremely preterm infants (< 28 weeks). Targeting a low saturation range (85–89%) reduced severe retinopathy of prematurity (RR 0.74, 95% CI 0.59–0.92) but significantly increased mortality (RR 1.41, 95% CI 1.14–1.74) and necrotizing enterocolitis (RR 1.25, 95% CI 1.05–1.49).

In newborns with respiratory failure undergoing extracorporeal membrane oxygenation support, both early hypoxia or moderate hyperoxia after ECMO initiation are each associated with greater odds of 28-day mortality.[89]

In summary, oxygen therapy requires precise titration based on gestational age and clinical condition. Recent studies emphasize the critical impact of oxygen management on outcomes in pediatric ICUs. As reported in a cohort study and systematic review, Raman et al.[90] reported that PaO_2 has a U-shape association with mortality in critically ill children admitted to the ICU. Therefore, both low and high levels of oxygenation may be negatively associated with outcome in this patient population.

A systematic review by Lilien et al.[91] highlighted that, in a meta-analysis of 11 studies encompassing 23,204 patients, hyperoxia was associated with mortality with an odds ratio of 1.59 (I^2 = 92%). Despite these findings, the included studies varied in their definitions and assessments of hyperoxia, with the majority utilizing PaO_2 as a primary variable of oxygen exposure. In an observational study, Ramgopal et al.[92] reported that severe hyperoxemia, defined as PaO_2 greater than 300 mmHg, was independently associated with increased in-hospital mortality. Their data revealed an increasing dose-exposure association with in-hospital mortality, with adjusted odds ratios of 1.47 (95% CI, 1.05–2.08; P = 0.03), 2.01 (95% CI, 1.27–3.18; P = 0.002), and 2.53 (95% CI, 1.62–3.94; P < 0.001) after exposure to one, two, and three or more severe hyperoxemic events, respectively. Similarly, Numa et al.[93] demonstrated that patients with PaO_2 ≥ 250 mmHg had an adjusted odds ratio of 2.66 for mortality. In the Oxy-PICU trial, Peters et al.[46] compared the role of conservative (SpO_2 88–92%) versus liberal (SpO_2 > 94%) oxygenation targets on major outcomes. Their findings suggested that conservative oxygenation targets slightly reduced the duration of organ support and mortality probability. However, adherence to the conservative protocol faced challenges due to clinical priorities, such as acute deterioration episodes or physiotherapy, and staffing issues, including lack of trial awareness. These studies collectively highlight the complex relationship between oxygenation levels and patient outcomes in pediatric ICUs.

Targeting Oxygen Exposure to the Right Patients: Population Enrichment Strategies

Critical illness is complex and heterogeneous; assessing treatment effects through the difference in average outcomes may be an ineffective approach in this setting. Focussing on the "average" blinds clinicians to the singularity of each patient. In critical care, it is common to treat "clusters" of clinical syndromes – e.g., ARDS, septic shock, and cardiogenic shock. However, clinicians are aware that each of these clusters includes a variety of clinical presentations, where even the guidelines fail to address all possible "sub-phenotypes." Classically, after performing an RCT, the first research effort aims to conduct *post-hoc* subgroup analyses, which however often provide less reliable insights due to intrinsic study limitations. Furthermore, a multitude of patients' intrinsic characteristics, both for clinical presentation and demographic characteristics, can unpredictably affect the outcome of treatment.

Population enrichment aims to identify patient sub-phenotypes that are more likely to respond to interventions, thereby overcoming trial limitations and increasing the efficiency of cause-effect inference. Distinguishing sub-phenotypes within a cohort of patients with the same clinical condition would allow a deeper understanding of specific treatment effects on outcomes and facilitate the implementation of precision medicine.[94] New tools for predictive modelling, such as machine learning, enable the integration of prognostic, clinical, and biochemical data to enhance population enrichment.[95]

The remarkable work of Buell et al.[96] elegantly demonstrates that a one-size-fits-all approach is inadequate and provides an innovative approach to pragmatically aim for population enrichment strategies taking advantage of the potential of artificial intelligence. The authors developed a machine learning model predicting the effect of lower versus higher SpO_2 targets on mortality in patients from the PILOT trial that was used as a derivation cohort. The authors designed a machine learning model capable of predicting the

complex interactions between various patient characteristics with different oxygenation targets. Ultimately, they identified clusters of patients who could benefit from different SpO_2 targets. For instance, older male patients with a higher prevalence of acute brain injury were predicted to benefit from a lower SpO_2 target. Conversely, patients with a higher prevalence of sepsis, respiratory disease, and extremely altered vital signs were predicted to benefit from a higher SpO_2 target. This model was validated using data from patients enrolled in the ICU-ROX trial. The findings in the validation cohort strongly confirmed the results obtained in the derivation cohort. The researchers estimated that implementing their machine learning model in the ICU-ROX trial would have resulted in a 6.4% absolute reduction in the overall mortality. However, prospective validation of this interpretation is needed.

Future Directions – The Right Oxygen Dose to the Right Patient

Call for a personalized oxygen therapy strategy

The recent findings on population enrichment strategies underscore that advancing efforts toward personalized oxygenation target guidelines is a prudent path forward. Addressing the pathophysiologic mechanisms of oxygen toxicity, alongside innovations in phenotyping and artificial intelligence will enable more precise stratification of target population subgroups. Future research can leverage advanced tools for population enrichment to provide more nuanced interpretations of oxygen supplementation and tissue exposure in critical care.

While preventing tissue hypoxia is crucial, excessive oxygenation (hyperoxia) poses significant risks, particularly to lung tissue. It should be limited to specific scenarios where it may confer benefits to systemic organs or exert bactericidal effects. Current guidelines, which define oxygen targets primarily as safety measures applied broadly across populations, lack of this personalization. Additionally, oxygen over-supplementation remains prevalent, often exceeding both physiological needs and established recommendations. Avoiding unnecessary O_2 exposure, once oxygen delivery (DO_2) is optimized, could improve patient outcomes. Careful monitoring of PaO_2 and SpO_2 in clinical practice is essential to prevent exposing critically ill patients to unnecessary – and potentially harmful – hyperoxemia.

O_2 targets, O_2 monitoring and long-term outcomes in critically ill patients

Initial research efforts should prioritize standardizing the definitions and detection methods for hyperoxemia. Variability in oxygenation targets across the literature complicates monitoring practices and the exposure of patients to hyperoxemia. New studies should also prioritize underexplored oxygen physiological markers such as DO_2, tissue oxygenation, and microvascular function, which offer valuable physiological insights. Moreover, recent investigations began to highlight the importance of evaluating long-term outcomes associated with different oxygenation targets. Studies with follow-up assessments after ICU discharge have already provided intriguing insights on link between oxygen exposure and long-term outcomes, laying a foundation for future research.

As this is an invited narrative review, it does not encompass systematically all the possible literature on the topic. However, according to the authors' perspective and critical revision of the investigated literature we highlight significant gaps in research methodology and emphasize the need to enhance research approaches aimed at personalizing oxygen therapy in critical care. A critical evaluation of current practices and future strategies are necessary to address the complexities of this clinically relevant topic and to advance the goal of truly personalized medicine.

Author contributions: *CR and ER conceptualized and wrote the original draft, conceived and created the original figure and table. All authors reviewed and edited the paper for important intellectual content. All authors read, discussed and approved the final version of the manuscript to be published.*

Conflicts of interest: *None declared.*

Data availability statement: *Not applicable.*

References

1. Rich P. Chemiosmotic coupling: The cost of living. *Nature.* 2003;421:583.
2. Pogge von Strandmann PA, Stüeken EE, Elliott T, et al. Selenium isotope evidence for progressive oxidation of the Neoproterozoic biosphere. *Nat Commun.* 2015;6:10157.
3. Martin D, de Jong A, Radermacher P. Is the U-shaped curve still of relevance to oxygenation of critically ill patients? *Intensive Care Med.* 2023;49:566-568.
4. Helmerhorst HJ, Arts DL, Schultz MJ, et al. Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med.* 2017;45:187-195.
5. Singer M, Young PJ, Laffey JG, et al. Dangers of hyperoxia. *Crit Care.* 2021;25:440.
6. Sjöberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. *J Intern Med.* 2013;274:505-528.
7. Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve. *Breathe (Sheff).* 2015;11:194-201.
8. Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ.* 2018;363:k4169.
9. Kallet RH, Matthay MA. Hyperoxic acute lung injury. *Respir Care.* 2013;58:123-141.
10. Davis WB, Rennard SI, Bitterman PB, Crystal RG. Pulmonary oxygen toxicity. Early reversible changes in human alveolar structures induced by hyperoxia. *N Engl J Med.* 1983;309:878-883.
11. Nash G, Blennerhassett JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artificial ventilation. *N Engl J Med.* 1967;276:368-374.
12. Aboab J, Jonson B, Kouatchet A, Taille S, Niklason L, Brochard L. Effect of inspired oxygen fraction on alveolar derecruitment in acute respiratory distress syndrome. *Intensive Care Med.* 2006;32:1979-1986.
13. Rezoagli E, Laffey JG, Bellani G. Monitoring lung injury severity and ventilation intensity during mechanical ventilation. *Semin Respir Crit Care Med.* 2022;43:346-368.
14. Ferrari M, Jain IH, Goldberger O, et al. Hypoxia treatment reverses neurodegenerative disease in a mouse model of Leigh syndrome. *Proc Natl Acad Sci U S A.* 2017;114:E4241-E4250.
15. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev.* 2017;2017:8416763.
16. Berra L, Medeiros KJ, Marrazzo F, et al. Feasibility of delivering 5-day normobaric hypoxia breathing in a hospital setting. *Respir Care.* 2024;69:1400-1408.
17. Buell KG, Semler MW, Churpek MM. Individualized treatment in critical care: the oxygenation paradigm. *Intensive Care Med.* 2024;50:1327-1330.
18. Athale J, Suffredini AF. Pulse oximetry: a necessary imperfect tool in critical care. *Crit Care Med.* 2023;51:1246-1248.
19. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care.* 2008;12:R156.
20. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-icu randomized clinical trial. *JAMA.* 2016;316:1583-1589.
21. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet.* 2018;391:1693-1705.

22. Nielsen FM, Klitgaard TL, Siegemund M, et al. Lower vs higher oxygenation target and days alive without life support in COVID-19: the HOT-COVID randomized clinical trial. *JAMA.* 2024;331:1185-1194.
23. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med.* 2020;382:989-998.
24. Gelissen H, de Grooth HJ, Smulders Y, et al. Effect of low-normal vs high-normal oxygenation targets on organ dysfunction in critically ill patients: a randomized clinical trial. *JAMA.* 2021;326:940-948.
25. Semler MW, Casey JD, Lloyd BD, et al. Oxygen-saturation targets for critically ill adults receiving mechanical ventilation. *N Engl J Med.* 2022;387:1759-1769.
26. Schjørring OL, Klitgaard TL, Perner A, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med.* 2021;384:1301-1311.
27. Rasmussen BS, Klitgaard TL, Perner A, et al. Oxygenation targets in ICU patients with COVID-19: A post hoc subgroup analysis of the HOT-ICU trial. *Acta Anaesthesiol Scand.* 2022;66:76-84.
28. Aggarwal NR, Brower RG, Hager DN, et al. Oxygen exposure resulting in arterial oxygen tensions above the protocol goal was associated with worse clinical outcomes in acute respiratory distress syndrome. *Crit Care Med.* 2018;46:517-524.
29. Roffe C, Nevatte T, Sim J, et al. Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: the stroke oxygen study randomized clinical trial. *JAMA.* 2017;318:1125-1135.
30. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation.* 2015;131:2143-2150.
31. Hofmann R, James SK, Jernberg T, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med.* 2017;377:1240-1249.
32. Jakkula P, Reinikainen M, Hästbacka J, et al. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Med.* 2018;44:2112-2121.
33. Young P, Mackle D, Bellomo R, et al. Conservative oxygen therapy for mechanically ventilated adults with suspected hypoxic ischaemic encephalopathy. *Intensive Care Med.* 2020;46:2411-2422.
34. Wihersaari L, Ashton NJ, Reinikainen M, et al. Neurofilament light as an outcome predictor after cardiac arrest: a post hoc analysis of the COMACARE trial. *Intensive Care Med.* 2021;47:39-48.
35. Bernard SA, Bray JE, Smith K, et al. Effect of lower vs higher oxygen saturation targets on survival to hospital discharge among patients resuscitated after out-of-hospital cardiac arrest: the EXACT randomized clinical trial. *JAMA.* 2022;328:1818-1826.
36. Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med.* 2022;387:1467-1476.
37. Robba C, Badenes R, Battaglini D, et al. Oxygen targets and 6-month outcome after out of hospital cardiac arrest: a pre-planned sub-analysis of the targeted hypothermia versus targeted normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial. *Crit Care.* 2022;26:323.
38. Crescioli E, Lass Klitgaard T, Perner A, Lilleholt Schjørring O, Steen Rasmussen B. Lower versus higher oxygenation targets in hypoxaemic ICU patients after cardiac arrest. *Resuscitation.* 2023;188:109838.
39. Asfar P, Schortgen F, Boisramé-Helms J, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med.* 2017;5:180-190.
40. Demiselle J, Wepler M, Hartmann C, et al. Hyperoxia toxicity in septic shock patients according to the Sepsis-3 criteria: a post hoc analysis of the HYPER2S trial. *Ann Intensive Care.* 2018;8:90.
41. Rodrigo GJ, Rodriquez Verde M, Peregalli V, Rodrigo C. Effects of short-term 28% and 100% oxygen on PaCO2 and peak expiratory flow rate in acute asthma: a randomized trial. *Chest.* 2003;124:1312-1317.
42. Perrin K, Wijesinghe M, Healy B, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. *Thorax.* 2011;66:937-941.
43. Nielsen MB, Klitgaard TL, Weinreich UM, et al. Effects of a lower versus a higher oxygenation target in intensive care unit patients with chronic obstructive pulmonary disease and acute hypoxaemic respiratory failure: a subgroup analysis of a randomised clinical trial. *BJA Open.* 2024;10:100281.
44. Vento M, Moro M, Escrig R, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics.* 2009;124:e439-449.
45. Tataranno ML, Oei JL, Perrone S, et al. Resuscitating preterm infants with 100% oxygen is associated with higher oxidative stress than room air. *Acta Paediatr.* 2015;104:759-765.
46. Peters MJ, Gould DW, Ray S, et al. Conservative versus liberal oxygenation targets in critically ill children (Oxy-PICU): a UK multicentre, open, parallel-group, randomised clinical trial. *Lancet.* 2024;403:355-364.
47. Madotto F, Rezoagli E, Pham T, et al. Hyperoxemia and excess oxygen use in early acute respiratory distress syndrome: insights from the LUNG SAFE study. *Crit Care.* 2020;24:125.
48. Boyle AJ, Holmes DN, Hackett J, et al. Hyperoxaemia and hypoxaemia are associated with harm in patients with ARDS. *BMC Pulm Med.* 2021;21:285.
49. Rezoagli E, Petrosino M, Rebora P, et al. High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury: insights from CENTER-TBI and OzENTER-TBI. *Intensive Care Med.* 2022;48:1709-1725.
50. Robba C, Battaglini D, Cinotti R, et al. Individualized thresholds of hypoxemia and hyperoxemia and their effect on outcome in acute brain injured patients: a secondary analysis of the ENIO study. *Neurocrit Care.* 2024;40:515-528.
51. Giannì G, Minini A, Fratino S, et al. The impact of short-term hyperoxia on cerebral metabolism: a systematic review and meta-analysis. *Neurocrit Care.* 2022;37:547-557.
52. Ghosh A, Highton D, Kolyva C, Tachtsidis I, Elwell CE, Smith M. Hyperoxia results in increased aerobic metabolism following acute brain injury. *J Cereb Blood Flow Metab.* 2017;37:2910-2920.
53. Robba C, Poole D, McNett M, et al. Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. *Intensive Care Med.* 2020;46:2397-2410.
54. Pearcey GEP, Afsharipour B, Holobar A, Sandhu MS, Rymer WZ. Acute intermittent hypoxia increases maximal motor unit discharge rates in people with chronic incomplete spinal cord injury. *J Physiol.* 2024;602:5699-5711.
55. Greif R, Bray JE, Djärv T, et al. 2024 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. *Resuscitation.* 2024;205:110414.
56. Soar J, Berg KM, Andersen LW, et al. Adult advanced life support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation.* 2020;156:A80-A119.
57. Bro-Jeppesen J, Johansson PI, Hassager C, et al. Endothelial activation/injury and associations with severity of post-cardiac arrest syndrome and mortality after out-of-hospital cardiac arrest. *Resuscitation.* 2016;107:71-79.
58. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care.* 2004;10:208-212.
59. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Intensive Care Med.* 2021;47:369-421.
60. Awad A, Nordberg P, Jonsson M, et al. Hyperoxemia after reperfusion in cardiac arrest patients: a potential dose-response association with 30-day survival. *Crit Care.* 2023;27:86.

61. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: prospective multicenter protocol-directed cohort study. *Circulation.* 2018;137:2114-2124.
62. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA.* 2010;303:2165-2171.
63. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42:1289-1367.
64. Hofmann R, James SK, Svensson L, et al. DETermination of the role of OXygen in suspected acute myocardial infarction trial. *Am Heart J.* 2014;167:322-328.
65. Belda FJ, Aguilera L, García de la Asunción J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA.* 2005;294:2035-2042.
66. Calzia E, Asfar P, Hauser B, et al. Hyperoxia may be beneficial. *Crit Care Med.* 2010;38:S559-568.
67. Buras JA, Holt D, Orlow D, Belikoff B, Pavlides S, Reenstra WR. Hyperbaric oxygen protects from sepsis mortality via an interleukin-10-dependent mechanism. *Crit Care Med.* 2006;34:2624-2629.
68. Barth E, Bassi G, Maybauer DM, et al. Effects of ventilation with 100% oxygen during early hyperdynamic porcine fecal peritonitis. *Crit Care Med.* 2008;36:495-503.
69. Kiers D, Gerretsen J, Janssen E, et al. Short-term hyperoxia does not exert immunologic effects during experimental murine and human endotoxemia. *Sci Rep.* 2015;5:17441.
70. Wilson WR, Hay MP. Targeting hypoxia in cancer therapy. *Nat Rev Cancer.* 2011;11:393-410.
71. Dumas G, Morris IS, Hensman T, et al. Association between arterial oxygen and mortality across critically ill patients with hematologic malignancies: results from an international collaborative network. *Intensive Care Med.* 2024;50:697-711.
72. Hiser SL, Fatima A, Ali M, Needham DM. Post-intensive care syndrome (PICS): recent updates. *J Intensive Care.* 2023;11:23.
73. Crescioli E, Klitgaard TL, Poulsen LM, et al. Long-term mortality and health-related quality of life of lower versus higher oxygenation targets in ICU patients with severe hypoxaemia. *Intensive Care Med.* 2022;48:714-722.
74. Crescioli E, Riis J, Weinreich UM, et al. Long-term cognitive and pulmonary functions following a lower versus a higher oxygenation target in the HOT-ICU and HOT-COVID trials: a protocol update. *Acta Anaesthesiol Scand.* 2024;68:575-578.
75. Abdo WF, Heunks LM. Oxygen-induced hypercapnia in COPD: myths and facts. *Crit Care.* 2012;16:323.
76. O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax.* 2008;63 Suppl 6:vi1-68.
77. Kane B, Decalmer S, Ronan O'Driscoll B. Emergency oxygen therapy: from guideline to implementation. *Breathe.* 2013;9:246-253.
78. Echevarria C, Steer J, Wason J, Bourke S. Oxygen therapy and inpatient mortality in COPD exacerbation. *Emerg Med J.* 2021;38:170-177.
79. Asthma GIf. 2023 GINA report, global strategy for asthma management and prevention. https://ginasthma.org/2023-gina-main-report/. Accessed December 6, 2024.
80. Chien JW, Ciufo R, Novak R, et al. Uncontrolled oxygen administration and respiratory failure in acute asthma. *Chest.* 2000;117:728-733.
81. Torres-Cuevas I, Parra-Llorca A, Sánchez-Illana A, et al. Oxygen and oxidative stress in the perinatal period. *Redox Biol.* 2017;12:674-681.
82. Saugstad OD. Oxygen and retinopathy of prematurity. *J Perinatol.* 2006;26 Suppl 1:S46-50; discussion S63-64.
83. Darlow BA, Morley CJ. Oxygen saturation targeting and bronchopulmonary dysplasia. *Clin Perinatol.* 2015;42:807-823.
84. Saugstad OD, Sejersted Y, Solberg R, Wollen EJ, Bjørås M. Oxygenation of the newborn: a molecular approach. *Neonatology.* 2012;101:315-325.
85. Saugstad OD, Ramji S, Soll RF, Vento M. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. *Neonatology.* 2008;94:176-182.
86. Madar J, Roehr CC, Ainsworth S, et al. European Resuscitation Council Guidelines 2021: Newborn resuscitation and support of transition of infants at birth. *Resuscitation.* 2021;161:291-326.
87. Aziz K, Lee HC, Escobedo MB, et al. Part 5: Neonatal Resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2020;142:S524-S550.
88. Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. *Neonatology.* 2014;105:55-63.
89. Brohan O, Chenouard A, Gaultier A, et al. Pa o2 and mortality in neonatal extracorporeal membrane oxygenation: retrospective analysis of the extracorporeal life support organization registry, 2015-2020. *Pediatr Crit Care Med.* 2024;25:591-598.
90. Raman S, Prince NJ, Hoskote A, Ray S, Peters MJ. Admission PaO_2 and Mortality in Critically Ill Children: A Cohort Study and Systematic Review. *Pediatr Crit Care Med.* 2016;17:e444-e450.
91. Lilien TA, Groeneveld NS, van Etten-Jamaludin F, et al. Association of arterial hyperoxia with outcomes in critically ill children: a systematic review and meta-analysis. *JAMA Netw Open.* 2022;5:e2142105.
92. Ramgopal S, Dezfulian C, Hickey RW, et al. Association of severe hyperoxemia events and mortality among patients admitted to a pediatric intensive care unit. *JAMA Netw Open.* 2019;2:e199812.
93. Numa A, Aneja H, Awad J, et al. Admission hyperoxia is a risk factor for mortality in pediatric intensive care. *Pediatr Crit Care Med.* 2018;19:699-704.
94. Gordon AC, Alipanah-Lechner N, Bos LD, et al. From ICU syndromes to ICU subphenotypes: consensus report and recommendations for developing precision medicine in the ICU. *Am J Respir Crit Care Med.* 2024;210:155-166.
95. Graham Linck EJ, Goligher EC, Semler MW, Churpek MM. Toward precision in critical care research: methods for observational and interventional studies. *Crit Care Med.* 2024;52:1439-1450.
96. Buell KG, Spicer AB, Casey JD, et al. Individualized treatment effects of oxygen targets in mechanically ventilated critically ill adults. *JAMA.* 2024;331:1195-1204.