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CRITICAL COMMENTARY

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Oxygen use and saturation targets in patients with COVID-19: Are we giving too much or aiming too low?

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1 | INTRODUCTION

Current guidelines for the administration of oxygen in hypoxaemic patients with Covid-19 suggest that targeting an oxygen saturation (SpO_2) between 92% to 96% appears adequate.[1] According to the recommendations by the US National Institutes of Health, indirect evidence from experience with patients without Covid-19 shows that SpO_2 levels <92% or >96% may be harmful.[2] These arbitrary targets, that is, 92%-96%, are based on findings extrapolated from studies performed among non-Covid-19 critically ill patients, in particular, those who had sepsis, myocardial infarction, acute respiratory distress syndrome (ARDS), and trauma, where previous investigations regarding the effects of hypoxaemia have been previously conducted.

More recently, guidelines from the Surviving Sepsis Campaign suggested commencing supplemental oxygen for Covid-19 patients who have an acute hypoxaemic respiratory failure with saturations <92%, to achieve SpO_2 levels not higher than 96%.[3] A population-based cohort study of patients with pneumonia showed that a threshold of 92% appears acceptable, as saturations <90% are associated with increased morbidity and mortality.[4] A recent guideline by the British Thoracic Society (BTS) recommends that lower target saturations of 92%-96% are acceptable for all adults, including those with non-Covid-19 conditions, and levels of 88%-92% for adults with acute on chronic type 2 respiratory failure or chronic respiratory disease, that is, chronic obstructive pulmonary disease (COPD) or obesity hypoventilation syndrome (OHS).[5] The aim of this critical commentary is to examine the current state of knowledge regarding the pathophysiology of hypoxaemia in patients with Covid-19 and to discuss implications regarding the use of oxygen to correct hypoxaemia in adults with Covid-19.

2 | HYPOXAEMIA IN COVID-19

Respiratory involvement in Covid-19 is common and patients manifest varying levels of hypoxaemia which can be overt, subclinical, or silent.[6] The pathophysiologic mechanisms in the development of hypoxaemia in Covid-19 are multifactorial, and are primarily incited by localized inflammatory damage resulting in interstitial lung oedema, and the development of microvascular thrombosis on pulmonary vessels leading to a ventilation/perfusion (V/Q) mismatch.[7] This is further complicated by development of endotheliitis and vascular damage, disrupted vasoregulation, loss of lung perfusion regulation, and enhanced hypercoagulability and thrombogenesis, which contribute to the development of respiratory failure and ARDS.[6–8]

More recently, there is increasing awareness that patients with Covid-19 may suffer from silent, or non-dyspnoeic hypoxaemia whereby patients may manifest hypoxaemia to very low levels but without symptoms of distress or discomfort. [6,9] Several mechanisms underlie the development of this "silent hypoxia" in Covid-19, including the capacity of SARS-CoV-2 to produce various Covid-19 phenotypes, invade cells of the central nervous system, impair interoceptive responses, produce left-to-right intrapulmonary shunting and vascular distress phenomena, and modulate transcription factors involved in hypoxic responses.[7,9]

3 | OXYGEN ADMINISTRATION IN COVID-19

The goals of oxygen supplementation in Covid-19 are to treat and correct hypoxaemia and prevent tissue hypoxia, thereby avoiding end-organ hypoxic tissue damage to vital body organs. The clinical utility of oxygen in the management and treatment of hypoxaemia is well-understood. It has been shown that hypoxia at the cellular level can lead to disruption in mitochondrial activity leading to diminished glycolytic activity, disruption in the electron transport chain, and depletion of cellular adenosine triphosphate (ATP) stores.[10] Furthermore, hypoxia can induce cellular apoptosis, which is primarily driven by the release of reactive oxygen species (ROS), release of apoptogenic proteins such as cytochrome c, direct DNA damage,

inhibition of mismatch repair proteins, activation of the p53 signalling pathway, and upregulation of hypoxia-inducible factor (HIF) responses.[11] Amongst patients with Covid-19, the occurrence of hypoxaemia is associated with increased mortality and poorer survival,[12] and together with a low oxygen saturation in the emergency department, is a marker of poor prognosis in Covid-19.[13]

According to the BTS, the main indications for oxygen administration include correction of hypoxaemia, prevention of hypoxaemia in critically ill and at-risk patients, and alleviation of breathlessness, of which only the first is based on sound scientific evidence.[14] In clinical situations where oxygen is given despite normal SpO_2, including carbon monoxide poisoning and states of increased cellular demand such as shock, sepsis, or major trauma, the need for supplemental oxygen is based on clinical judgment and severity of underlying condition.[5,14] Whilst oxygen is commonly administered to patients complaining of breathlessness, routine, and indiscriminate oxygen supplementation for this indication alone should be avoided unless the dyspnoea is associated with hypoxaemia or is reversible with oxygen administration. Several meta-analyses[15,16] showed that oxygen administration can provide symptomatic relief of breathlessness, particularly among COPD patients where this condition is more common and well-studied. Although oxygen administration should not be routinely used as a first line treatment nor as a substitute for the management and optimization of underlying disease, as it has not been shown to produce a clinically important benefit or an improvement in quality of life. Furthermore, oxygen treatment is not without its risks, and complications including nasal irritation, dry nose and throat, hyperoxia-related vasoconstriction, bacterial contamination of delivery systems, and lung injury, may be common and can be potentially harmful.[17,18]

Studies identifying the optimal arterial oxygen saturation (SaO_2) and partial pressure of arterial oxygen (PaO_2) targets in adults are limited by the heterogeneity of the clinical conditions and/or patient populations among which the studies are conducted, but a general consensus exists that among ventilated patients in the adult ICU, a conservative oxygenation strategy is safe and feasible.[19,20] A more recent study demonstrated that among patients in ICU with acute hypoxaemic respiratory failure, aiming for a lower oxygenation target (ie, 60 mm Hg, 8.0 kPa) did not result in an increase in adverse events and had no effect on 90-day mortality rates than when higher oxygenation levels were targeted (ie, 90 mm Hg, 12.0 kPa). This suggests that lower oxygenation targets confer no increased risks, and should be considered in high-risk critically ill patients.[21] This finding is supported by a previously reported meta-analysis which shows that, compared with a conservative approach, liberal oxygen therapy is associated with increased in-hospital mortality without improving other patient-important outcomes.[22] Studies amongst ventilated Covid-19 patients are lacking and whilst there has been a strong urge to identify oxygenation targets amongst this patient group through randomized controlled trials, a conservative approach where both hypoxaemia and hyperoxygenation are avoided appears to be an appropriate strategy.[1]

4 | NURSING MANAGEMENT OF HYPOXAEMIA IN COVID-19

Achieving a desirable oxygenation target range in acute illness, including among adults with Covid-19, requires that expert and holistic clinical assessment of signs and symptoms of hypoxaemia are promptly made, supplemented by findings derived from oximetry readings and blood gases whenever necessary.[5] Oxygen saturation levels should be checked and continuously monitored in all acutely ill, high risk, and breathless patients, including those receiving supplemental oxygen.[14] Oxygen saturation levels measured by pulse oximetry have been advocated both by BTS and Thoracic Society of Australia and New Zealand to be considered as the 'fifth vital sign' and should be documented with other vital signs in patient assessment and management.[14,23] The use of pulse oximetry, whilst generally accurate and reliable, has important limitations that clinicians should always be aware of, including registering falsely low readings in cases of poor perfusion, hypotension, or shock, or when the patient has tattoos or nail polish,[24] or a falsely elevated reading in darkly pigmented individuals[25] or in the presence of carboxyhaemoglobinaemia.[26] Monitoring the trend of oximetry reading is similarly crucial, and any sudden deterioration, including unexpected increase in oxygen requirement or an acute elevation in early warning score, should be escalated to an appropriately skilled responder for prompt review and intervention.[14,23]

Administration of oxygen in clinical setting should be carried out by staff who are well-trained on delivery of supplemental oxygen.[14] Oxygen saturation targets should be clearly defined and documented at the time of admission so that appropriate therapy can be started in the event of unexpected clinical deterioration.[23] Nurses and clinicians should be competent in the use of adjuncts, modalities, and devices for delivery of supplemental oxygen, including both non-invasive and invasive oxygen delivery devices (eg, mechanical ventilatory devices), and should be able to adjust the flow rates and oxygen concentration in order to achieve target saturation range.[14,27]

Hyperoxia should be avoided because of the risks of complications, including absorption atelectasis, hyperoxic acute lung injury, hyperoxic hypercapnia, central nervous system toxicity, coronary and cerebral vasoconstriction, increase in systemic vascular resistance leading to reduction in cardiac output, free radical and ROS damage, and depression of neutrophilic function, which are all associated with prolonged exposure to high oxygen concentrations.[10,11,18] Furthermore, excessive oxygen supplementation, in the light of the pandemic situation, is not only wasteful and expensive but is not resource-effective, particularly in health care institutions in middle- to low-income countries.[28] According to BTS guidance, oxygen use in hospitals should be well-controlled and wastage should be minimized[5] given that during pandemic, resources may be scarce and the potential loss of oxygen supply puts patients at risk for catastrophic outcomes including unnecessary loss of life.[28] In order to minimize wastage in oxygen use, the lowest possible flow should be given to maintain desired saturation ranges, unused oxygen should be turned off,

leakages in oxygen delivery systems, regulators, and knobs should be minimized, and delivery systems should be judiciously de-escalated depending on clinical need.[14]

5 | CONCLUSION

With a paucity of studies that examine the target oxygen saturation among patients with Covid-19, it is suggested that an oxygen saturation level that is sufficient to meet clinical demands be targeted, that is, 92%-96% in all hospitalised adults, and 88%-92% in patients with chronic type 2 respiratory failure or chronic respiratory disease (COPD and OHS). Hypoxaemia and hyperoxia should be avoided as they are associated with poorer outcomes and increased morbidity. Judicious and appropriate use of supplemental oxygen, guided by individualized targets and regular and continuous oximetry monitoring, should dictate clinical decision-making, including the use of both invasive and non-invasive ventilatory strategies, whenever appropriate.

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