Intensive Care Med (2020) 46:116–118
https://doi.org/10.1007/s00134-019-05874-w

EDITORIAL

Trials on oxygen supplementation in sepsis: better late than never

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Oxygen supplementation is one of the most frequently used interventions in critically ill patients. In addition, most ICU patients with sepsis receive oxygen supplementation irrespective of the presence or absence of hypoxia [1]. In the 2016 iteration of the Surviving Sepsis Campaign (SSC) guideline [2], there was no guidance on the use of supplementary oxygen or on oxygenation targets for these patients, alongside recommendations for further research [3].

To our knowledge, at least one randomised trial has been conducted on oxygen therapy in sepsis, the Hyper2S-trial [4]. This two-by-two factorial, multicentre, randomised trial allocated mechanically ventilated patients with septic shock to an FiO_2 at 1.0 (hyperoxia) vs. an FiO_2 targeting an oxygen saturation of 88–95% (normoxia) during the first 24 h. The other allocation was to isotonic vs. hypertonic saline infusion. The trial was stopped prematurely for safety reasons when 442 of the planned 800 patients had been enrolled. The primary outcome, 28-day mortality, had occurred in 43% in the hyperoxia group vs. 35% in the normoxia group (hazard ratio 1.27, 95% CI 0.94–1.72; $p=0.12$). The incidence of serious adverse events, including atelectasis and intensive care unit-acquired weakness, appeared to be higher in the hyperoxia vs. the normoxia group. While this caused some concern, the use of FiO_2 at 1.0 in clinical care of patients with sepsis appeared to be quite rare; the baseline FiO_2 in two sepsis trials combined ($n=1770$) was reported to be 0.51 (inter-quartile range 0.40–0.70) [1].

The results of the Hyper2S trial did support the notion of harm from more liberal use of oxygen as observed in observational studies in general ICU patients [5, 6] and in those with sepsis [1]. A post hoc analysis of Hyper2S-trial highlighted potential harm only in patients meeting the sepsis-3 defined septic shock, which is hypotension requiring vasopressor therapy and raised lactate concentrations. The implication being harmful effects of oxygen may be exaggerated in sepsis patients with evidence of cellular and metabolic abnormalities [7], likely to be mediated by reactive oxygen species, in the context of impaired mitochondrial function and lower antioxidant concentrations seen in sepsis [8]. The other larger trial done in ICU patients, the OXYGEN-ICU trial [9], included 480 adult ICU patients expected to stay at least 72 h, among whom 40% had documented infection at baseline. Again, the results suggested that higher use of oxygen caused harm, but the single-center design and the stopping of the trial after an unplanned interim analysis hamper the interpretation.

On that background, it is more than welcome to read the publication of the sub-group of patients with sepsis from the ICU-ROX trial in *Intensive Care Medicine* [10]. The ICU-ROX trial was a multicentre randomized trial allocating 1000 adult ICU patients who were expected to be mechanically ventilated for > 24 h to receive conservative or usual oxygen therapy. In the conservative-oxygen group, the upper limit of SpO_2 was 97%; FiO_2 was decreased to 0.21 if the $SpO_2 > 90\%$. In the usual-oxygen group, there were no specific measures limiting the FiO_2 or the SpO_2. In the full trial cohort, there was no difference in the number of ventilator-free days, which was the primary outcome. There were four predefined subgroup analysis, among which patients with suspected hypoxic–ischemic encephalopathy appeared to have worse outcome with usual oxygen therapy. The present study is a post hoc sub-group analysis of 251 patients adjudicated to have sepsis at baseline. There was no statistically significant treatment effect heterogeneity

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Table 1 Ongoing ICU trials likely randomising subgroups of patients with sepsis to higher vs. lower oxygenation targets

Trial acronym	Identifier	Population	Sample size	Higher O_2 target	Lower O_2 target	Status
HOT-ICU	NCT 03174002	ICU patient with acute hypoxia within 12-h of ICU admission	2928	PaO_2 90 mmHg	PaO_2 60 mmHg	Recruiting-estimated completion June 2020 Interim analysis past (50% of patients)
O2-ICU	NCT 02321072	ICU patients with ≥ 2 positive SIRS-criteria and an expected ICU stay > 48 h	385	PaO_2 120 (105—135) mmHg	PaO_2 75 (60-90) mmHg	Recruiting-estimated completion Dec 2019
LOCO2	NCT 02713451	ICU patients with ARDS ventilated < 12 h	206 planned 850	PaO_2 (90–105) mmHg	PaO_2 (55—70) mmHg	Terminated for safety reasons
TOXYC	NCT 03287466	ICU patients who are expected to be mechanically ventilated > 24 h	60	Standard care	SpO_2 (88–92%)	Recruiting-estimated completion Dec 2019

ARDS acute respiratory distress syndrome, *SIRS* systemic inflammatory response syndrome; Data obtained from clinicaltrials.gov (Webpage accessed on 11 November 2019)

between conservative vs. usual-care oxygen therapy on 90-day mortality (36.2% vs. 29.2% [absolute difference, 7.0% points; 95% CI, −4.6 to 18.6]; *p* value for interaction = 0.35 for sepsis vs. non-sepsis). None of the secondary outcomes differed between group, but all point estimates favoured usual-care oxygen. The investigators conclude that clinically important harm is possible with conservative oxygen therapy in patients with sepsis, but benefit cannot be excluded. The interpretation of these findings is hampered by the post hoc design, the lack of stratification for sepsis at allocation, in fact many of the patients presented had to identified in registers post hoc, the small samples size as acknowledged by the investigators and use of 90-day mortality as the outcome instead of the primary outcome of ventilator-free days used in the ICU-ROX trial.

Clearly these results call for more trials on oxygen in this patient group as suggested by the ICU-ROX investigators. There are several ongoing randomized trial enrolling ICU patients to different oxygenation strategies (Table 1); several of these trials are likely enrolling at fair number of patients with sepsis. However, none of the trials are focused specifically on sepsis; the enrol patients with acute hypoxia, systemic inflammatory response syndrome or ARDS (Table 1). And none of the ongoing trials are likely to provide a large sub-group of patients with sepsis to substantially increase the certain of the effect estimates observed in the ICU-ROX sub-group; the HOT-ICU trial is the only large trial ongoing, but the presence of sepsis is not registered at baseline in that trial [11]. A large subgroup of patients with sepsis will likely be included in the MEGA-ROX trial planned by the ICU-ROX investigators. When finalised, MEGA-ROX will have enrolled 40,000 ICU patients and likely provide reliable estimates on the effects of conservative oxygen therapy in sepsis.

How much oxygen shall we give to patients with sepsis until further evidence is available?

Oxygen is a drug—as such it has beneficial effects and side-effects. The balance between the benefit and harm of higher vs. lower targets for oxygen supplementation in patients with sepsis is still unknown. Until we have better evidence from large randomized trials, a strategy that avoids both hypoxia and hyperoxia may be aimed for. Such a strategy was recommended in a recent clinical practice guideline on oxygen therapy in acutely ill medical patients. The strong recommendation was to aim for peripheral capillary oxygen saturation (SpO_2) of ≤ 96%, for acutely ill medical patients receiving oxygen therapy. The authors also highlight that it is reasonable to aim for a target range of 90–94% in most patients [12].

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Author contributions
AP wrote the first draft. All authors contributed to the critical revision of the manuscript for important intellectual content.

Compliance with ethical standards

Conflicts of interests
AP is in the steering committee of the HOT-ICU trial and receives research funding from the Innovation Foundation and Novo Nordisk Foundation, Denmark.

This work was supported by the National Institute for Health Research Clinician Scientist Award (CS-2016-16-011 for MSH). The views expressed in

this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health and Social Care. All authors are on the Editorial Board for ICM and declare no other competing interests.

Publisher's Note

Received: 12 November 2019 Accepted: 16 November 2019
Published online: 26 November 2019

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