Conservative versus liberal oxygenation targets in critically ill children (Oxy-PICU): a UK multicentre, open, parallel-group, randomised clinical trial

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Summary

Background The optimal target for systemic oxygenation in critically ill children is unknown. Liberal oxygenation is widely practiced, but has been associated with harm in paediatric patients. We aimed to evaluate whether conservative oxygenation would reduce duration of organ support or incidence of death compared to standard care.

Methods Oxy-PICU was a pragmatic, multicentre, open-label, randomised controlled trial in 15 UK paediatric intensive care units (PICUs). Children admitted as an emergency, who were older than 38 weeks corrected gestational age and younger than 16 years receiving invasive ventilation and supplemental oxygen were randomly allocated in a 1:1 ratio via a concealed, central, web-based randomisation system to conservative peripheral oxygen saturations ([SpO_2] 88–92%) or liberal (SpO_2 >94%) targets. The primary outcome was the duration of organ support at 30 days following random allocation, a rank-based endpoint with death either on or before day 30 as the worst outcome (a score equating to 31 days of organ support), with survivors assigned a score between 1 and 30 depending on the number of calendar days of organ support received. The primary effect estimate was the probabilistic index, a value greater than 0·5 indicating more than 50% probability that conservative oxygenation is superior to liberal oxygenation for a randomly selected patient. All participants in whom consent was available were included in the intention-to-treat analysis. The completed study was registered with the ISRCTN registry (ISRCTN92103439).

Findings Between Sept 1, 2020, and May 15, 2022, 2040 children were randomly allocated to conservative or liberal oxygenation groups. Consent was available for 1872 (92%) of 2040 children. The conservative oxygenation group comprised 939 children (528 [57%] of 927 were female and 399 [43%] of 927 were male) and the liberal oxygenation group included 933 children (511 [56%] of 920 were female and 409 [45%] of 920 were male). Duration of organ support or death in the first 30 days was significantly lower in the conservative oxygenation group (probabilistic index 0·53, 95% CI 0·50–0·55; p=0·04 Wilcoxon rank-sum test, adjusted odds ratio 0·84 [95% CI 0·72–0·99]). Prespecified adverse events were reported in 24 (3%) of 939 patients in the conservative oxygenation group and 36 (4%) of 933 patients in the liberal oxygenation group.

Interpretation Among invasively ventilated children who were admitted as an emergency to a PICU receiving supplemental oxygen, a conservative oxygenation target resulted in a small, but significant, greater probability of a better outcome in terms of duration of organ support at 30 days or death when compared with a liberal oxygenation target. Widespread adoption of a conservative oxygenation saturation target (SpO_2 88–92%) could help improve outcomes and reduce costs for the sickest children admitted to PICUs.

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Introduction

Supplemental oxygen is used liberally in paediatric intensive care units (PICUs). Peripheral oxygen saturations (SpO_2) in the range of 95–100% are typical.[1–4] Exposure to high fractions of inspired oxygen (FiO_2) might contribute to oxidative stress.[5] Observational studies describe a U-shaped relationship between oxygenation and harm in adults and children.[1,4,6,7] Conservative oxygen therapy, the approach of targeting oxygen saturations to the lower end of the range currently used in PICUs, might reduce the risk of harm from higher FiO_2 but could increase exposure to potentially harmful hypoxia.[8]

Since 2016, randomised trials in acutely ill adults have not shown consistent benefit or harm with different oxygenation strategies.[9–15] A series of trials demonstrated higher mortality, but less retinopathy, in extremely preterm neonates (infants who were born between 24 weeks +0 days of gestation, and 27 weeks +6 days of gestation) with conservative oxygen targets.[16–18] Randomised trials of

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See Online for appendix

Research in context

Evidence before this study

Evidence from observational studies and a systematic review and meta-analysis have shown associations between high arterial oxygenation and increased paediatric intensive care unit (PICU) mortality, and that current practice is for liberal oxygenation. Trials of conservative oxygenation strategies in critically ill adults have not shown a consistent benefit or harm. We searched PubMed and Clinical Trial Registries from database inception up to Oct 21, 2022, for clinical trials published in English with the terms "oxygen", "oximetry", and "intensive care" in humans aged from birth to 16 years on Oct 21, 2022. We identified three randomised controlled trials of lower oxygenation targets among UK and east African children outside of PICUs, which reported equivalent safety to standard care with a reduced use of resources, and our own multicentre pilot trial, which confirmed safety and feasibility of the proposed Oxy-PICU trial reported here. To our knowledge, there have been no randomised trials investigating the effectiveness of conservative oxygenation targets in critically ill children.

Added value of this study

Oxy-PICU is the first randomised trial of a conservative oxygenation target in critically ill children with sufficient power to inform on clinical effectivness and cost-effectiveness. It demonstrates a small, but significant, greater probability for a better outcome, in terms of fewer days of organ support or death at 30 days with a conservative oxygenation target when compared to current practice of liberal oxygenation targets. The point estimates for each component of the primary outcome favoured conservative oxygenation. Oxy-PICU provides the first trial data in support of the current, expert opinion-based recommendation of a conservative oxygenation target in severe respiratory failure, and suggests that this target should be extended to all emergency PICU admissions who are receiving invasive mechanical ventilation and supplemental oxygen.

Implications of all the available evidence

A peripheral oxygenation saturation target of 88–92% might provide a small but significant greater probability of a better outcome in terms of the duration of organ support or death compared with the current practice of liberal oxygenation among children admitted to PICU as an emergency while receiving invasive mechanical ventilation and supplemental oxygen. The observed effect size is small, but the population who could benefit from this intervention is large. Further research is needed to define the individuals most likely to benefit from conservative oxygenation targets, and the relative advantages of both intermediate and lower oxygenation targets.

lower oxygenation targets among UK[19] and east African children outside of the PICU[20] report equivalent safety to standard care with a reduced use of resources. There is no randomised trial evidence for the optimal oxygenation target for critically ill children. Current guidelines recommend an oxygenation target of SpO_2 of 88–92% in cases of severe paediatric acute respiratory distress syndrome (pARDS),[21,22] but this is not based on randomised clinical trial evidence. Adherence to this guideline is poor.[3]

Following a pilot to confirm feasibility,[23] we conducted the Oxygenation in Paediatric Intensive Care Units (Oxy-PICU) trial. Our aim was to evaluate whether a conservative oxygenation target (SpO_2 88–92%) would reduce duration of organ support or incidence of death when compared with current practice of a liberal oxygenation target (SpO_2 >94%) among children admitted as an emergency who are invasively mechanically ventilated in the PICU receiving supplemental oxygen.

Methods

Study design and participants

Oxy-PICU was a pragmatic, multicentre, open, parallel-group, randomised clinical trial conducted in 15 UK National Health Service (NHS) PICUs across England and Scotland, and their associated emergency inter-hospital transport services.

The protocol, approved by the East of England Research Ethics Committee (19/EE/0362) and the UK Health Research Authority, has been published previously.[24]

The study population comprised children older than 38 weeks corrected gestational age and younger than 16 years, enrolled within 6 h of meeting all the following criteria: accepted for admission to a participating PICU as an emergency; receiving invasive mechanical ventilation with supplemental oxygen; and face-to-face contact with PICU or emergency transport services staff. Exclusions included known or suspected uncorrected congenital cardiac disease, known pulmonary hypertension, or when brain pathology or injury was the primary reason for admission. Full exclusion criteria are given in the appendix (p 5).

As oxygenation targets are selected urgently, a model known as research without prior consent[23] was approved.[25] Written informed consent was sought from parents or legal guardians as soon as appropriate, typically within 24–48 h. In the case of refusal or withdrawal of consent, data collected up to the point of refusal or withdrawal were retained unless the parents or legal guardians requested otherwise. Consent procedures are detailed in the appendix (pp 6–8).

Randomisation and masking

Patients were randomly allocated in a 1:1 ratio to conservative (SpO_2 88–92%) or liberal (SpO_2 >94%) oxygenation targets via a concealed, central, 24-h telephone and web-based randomisation system. The computer-generated randomisation sequence was minimised on age (<12 months *vs* ≥12 months); site; primary reason for

admission (lower respiratory tract infection *vs* other); and severity of abnormality of gas exchange (SpO_2 : FiO_2 [SF] ratio <221 with positive end-expiratory pressure (PEEP) ≥5 cm H_2O *vs* other). Each participant was allocated, with 80% probability, to the group that minimised between-group differences in these factors among all current recruits. No masking was attempted.

Procedures

Use of SpO_2 targets was selected because of the low (and reducing) use of in-dwelling arterial catheters in the target population.[26] During invasive mechanical ventilation, ventilator settings and FiO_2 were adjusted with the intention of achieving a conservative SpO_2 of 88–92% or liberal SpO_2 of greater than 94%. The conservative oxygenation target was selected as acceptable to UK clinicians and reflected guidelines for severe pARDS.[21]

The oxygenation targets were applied immediately from the time of random allocation and throughout invasive mechanical ventilation during the patient's PICU admission. In cases of failed extubation, the patient returned to their assigned treatment. Clinicians were permitted to adjust ventilator parameters with the aim of remaining within the target range. All other care was determined by the clinical team primarily responsible for the participant's care.

Outcomes

The primary outcome was the duration of organ support at 30 days following random allocation, a rank-based endpoint with death either on or before day 30 as the worst outcome (a score equating to 31 days of organ support), with survivors assigned a score between 1 and 30 depending on the number of calendar days of organ support received. Organ support was defined according to the Paediatric Critical Care Minimum Dataset[27] as routinely collected for the Paediatric Intensive Care Audit Network registry. Major components included respiratory support (including invasive and non-invasive positive pressure support); cardiovascular support (including vasoactives and fluid boluses), and renal support. Other components of organ support included analgesia or sedation, exchange transfusion, neurological support, and metabolic support. A full breakdown of the organ support components included in the primary outcome can be found in the appendix (pp 9–10).

Secondary outcomes were mortality at PICU discharge and 30 days; time to liberation from invasive mechanical ventilation (defined as the time from random allocation to the start of a continuous 48-h period free from invasive mechanical ventilation), duration of organ support (as defined for the primary outcome); functional status at PICU discharge (measured by the Paediatric Overall Performance Category [POPC] and Paediatric Cerebral Performance Category [PCPC] scales; appendix p 11–12); length of PICU and acute hospital stay; and incremental costs at 30 days.

The number and percentage of patients having prespecified serious adverse events, including severe lactic acidosis, cardiac ischaemia, acute kidney injury, and seizure, and any unexpected serious adverse events considered to be related to the oxygenation target, between random allocation and either 30 days or PICU discharge (if before 30 days) were reported.

A full description of outcomes is provided in the appendix (pp 9–10). Outcomes are reported up to 30 days and time of hospital discharge. Longer-term outcomes, up to 1 year (including the primary outcomes for cost-effectiveness), will be reported separately.

Statistical analysis

Based on the Oxy-PICU pilot trial,[23] a total of 2040 participants were required to provide 90% power to detect a reduction of 12 h (from 120 h to 108 h) in the mean duration of organ support, assuming no effect on mortality (estimated at 7·5%) and allowing for a withdrawal or refusal of deferred consent of 10% (appendix p 77). An interim analysis, comparing the primary outcome between groups using a two-sided rank-sum test, was undertaken at 50% recruitment using a Peto-Haybittle stopping rule ($p<0·001$) for termination either due to benefit or harm. The Peto-Haybittle stopping rule was chosen, despite a low likelihood of stopping at the interim analysis, as the investigators felt that a trial stopped early at a lower threshold would be unlikely to change clinical practice.

Patterns of exposure in patients randomly allocated to each group were reported using summary descriptive statistics and graphical methods. Separation between groups in terms of SpO_2 was summarised by the median of individual patient mean values. Adherence within groups was defined as adjustment of the ventilator settings and FiO_2 with the aim of maintaining SpO_2 in the target range for both randomly allocated groups. Deviation within groups was defined as failure to adjust ventilator settings, and FiO_2 when SpO_2 was above (conservative) or below (both) the target range for three consecutive hours.

For the **Paediatric Intensive Care Audit Network registry** see https://www.picanet.org.uk

Patients were analysed in their randomised group (intention-to-treat) according to a prespecified statistical analysis plan (see appendix pp 12–13), with the primary analysis population defined as all patients who were randomly allocated except for those where consent to use data pertaining to the primary outcome could not be obtained. The primary outcome was compared between groups using a two-sample rank-sum (Wilcoxon-Mann-Whitney) test with a two-sided p value of 0·05. The primary effect estimate was the probabilistic index (the probability that the intervention is superior to the control for the primary outcome of duration of organ support or death), presented with a 95% CI. A probabilistic index over 0·5 indicates a greater than 50% chance that conservative oxygenation therapy is superior to liberal oxygenation therapy for a randomly selected patient. This analysis of

the rank-based primary outcome allows for identification of differences across the entire distribution of organ support or death, rather than assessing differences in mean or median values, which are highly insensitive to changes in the distribution. Where organ support data were missing it was assumed that organ support was received on the days the patient was in a PICU or high dependency unit, or the location was not known and that organ support was not received on the days the patient was on a ward. Ordered logistic regression was used in a sensitivity analysis in the primary analysis population to estimate the unadjusted and adjusted proportional odds ratio, adjusting for the following baseline covariates: age (<12 months *vs* ≥12 months); primary reason for admission (lower respiratory tract infection *vs* other); severity of abnormality of gas exchange (SF ratio <221 with PEEP ≥5 cm H_2O *vs* other); predicted mortality at PICU admission (measured using the Paediatric Index of Mortality 3 score);[28] and site (as a random effect).

Subgroup analyses were performed to test for inter—actions in the proportional odds model between the effect of allocated treatment group and the following baseline covariates: age (<12 months *vs* ≥12 months); age-adjusted heart rate;[29] and haemoglobin concentration at PICU admission, with missing variables replaced using multiple imputation.

Mortality at PICU discharge and at 30 days was compared between groups using an adjusted odds ratio. Time to liberation from invasive mechanical ventilation was analysed using Cox regression, with patients who died while receiving invasive mechanical ventilated censored, and summarised as the adjusted hazard ratio. Comparisons of duration of organ support and of PICU and hospital stay were summarised by the probabilistic index, stratified by survival status. Functional status at PICU discharge was compared as the number and percentage in each category.

Incremental total costs at 30 days for the two groups were compared using a linear regression model, allowing for clustering of patients at sites, and adjusted for the same baseline covariates as for the clinical effectiveness analysis.

The percentage of patients experiencing one or more adverse events was compared between groups using Fisher's exact test. There was no correction for multiple testing of secondary outcomes; therefore results of secondary outcomes should be treated as exploratory. Statistical analyses were conducted using Stata/MP version 17.0. Details of additional statistical analyses are provided in the appendix (pp 12–13).

The trial was registered before commencement of recruitment with the ISRCTN registry (ISRCTN92103439).

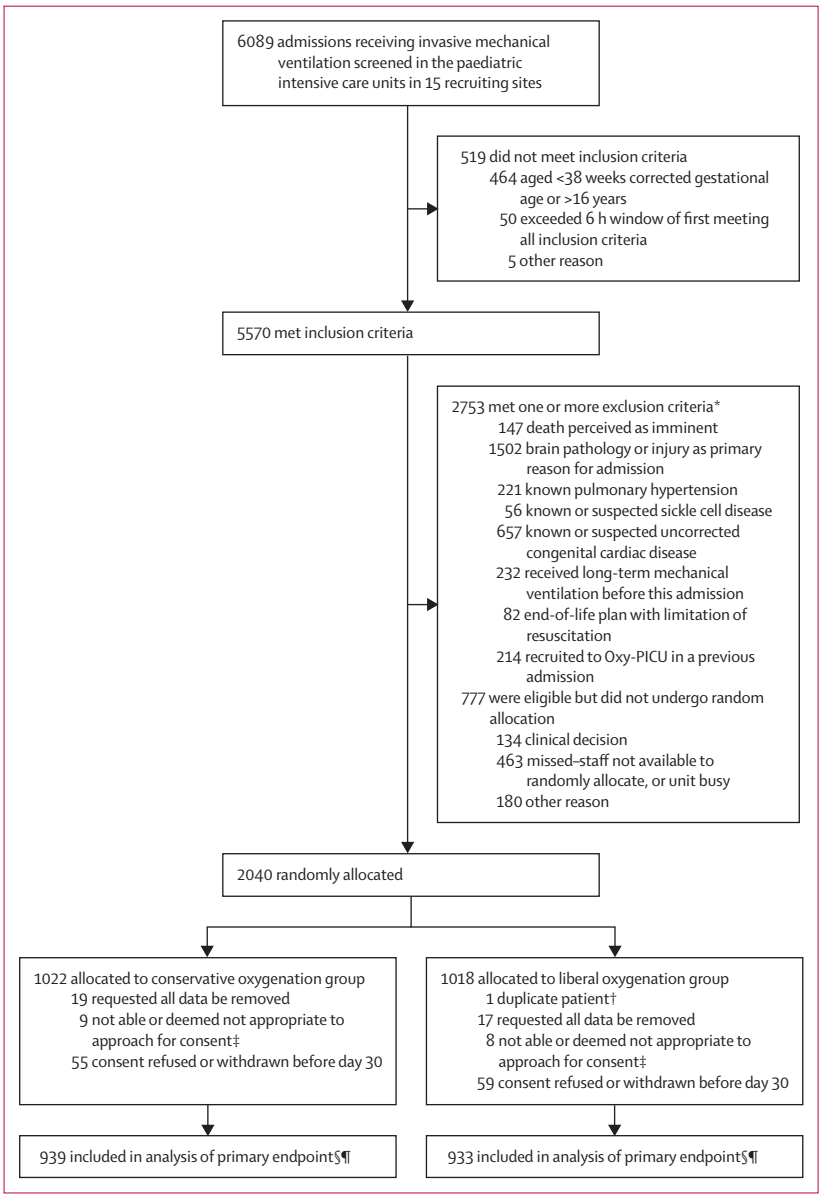

Figure 1: **Trial profile**
A total of 2817 patients met all inclusion and no exclusion criteria, of whom 2040 (72·4%) were randomly allocated without prior consent. One participant was randomly allocated in error, and for 53 participants consent was not subsequently available. In 55 (5.4%) of 1022 participants in the conservative oxygenation group and 59 (5·8%) of 1018 in the liberal oxygenation group consent was subsequently refused or withdrawn before day 30. Primary outcome data were available for all participants who remained in the analysis. *Numbers meeting individual exclusion criteria do not add to the total as some patients met >1 criterion †One patient was identified as having undergone duplicate random allocation after trial recruitment had closed. The first random allocation was retained in the analyses. ‡Approach for consent was deemed not appropriate only in exceptional circumstances. These were where the patient was under the care of social services and an appropriate legal guardian could not be identified; due to language barriers; or an impending inquest or legal action at the participating hospital. As a result, there was not a legal basis for inclusion in the trial. §Includes three patients where consent was refused or withdrawn after day 30 (one in the conservative oxygenation group and two in the liberal oxygenation group). ¶Primary endpoint was assumed based on location of care for 28 patients in the conservative oxygenation group and 32 patients in the liberal oxygenation group.

Role of the funding source
The UK National Institute for Health Care Research funded the trial and convened an independently chaired, majority-independent trial steering committee, and an independent data monitoring and ethics committee. The funder of the study had no role in study design, data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Between Sept 1, 2020, and May 15, 2022, 6089 children who were admitted to a PICU and received invasive mechanical ventilation and supplemental oxygen were screened across 15 NHS PICUs and their associated emergency transport services. Of these, 2817 met the eligibility criteria and 2040 (72·4%) were randomly allocated. Consent for collection of the primary outcome was obtained for 1872 (92%) of the 2040 patients who were included in the primary analysis (939 participants in the conservative group and 933 in the liberal oxygenation group; figure 1). The trial groups had similar characteristics at baseline (table 1 and appendix pp 14–16), and were representative of the wider PICU population (appendix p 17).

The median of the mean SpO_2 and FiO_2 values during invasive mechanical ventilation were lower in the conservative oxygenation group than the liberal oxygenation group. For the conservative group, median mean SpO_2 was 94% (IQR 93–96) versus 97% (96–98) for the liberal oxygenation group. Median mean FiO_2 was 0·27 (0·24–0·33) for the conservative group versus 0·35 (0·30–0·42) for the liberal group (figure 2, appendix pp 18–20). Participants in the conservative oxygenation group spent a greater proportion of their total time in hours on invasive mechanical ventilation with an SpO_2 88–92, with a median of 26% (10–47) compared with the liberal oxygenation group (1% [0–4]). The conservative oxygenation group spent a median of 27% (6–62) of time on invasive mechanical ventilation with both an FiO_2 of 0·21 and an SpO_2 greater than 92%, compared with only 1% (0–18%) in the liberal oxygenation group, and the conservative group also had an overall lower cumulative exposure to oxygen over the first 7 days following random allocation (appendix pp 18–19, 21–22).

During the first 24 h the FiO_2 was reduced in both groups, but more rapidly in the conservative oxygenation group. This was mirrored by a greater reduction in SpO_2 (appendix p 23). Patients in whom mechanical ventilation could be stopped within the first day had a higher mean SpO_2 than those with longer periods of mechanical ventilation and supplemental oxygen (appendix p 23). Mean airway pressure was similar between the groups (appendix p 25). The number of patients experiencing at least one protocol deviation was greater in the conservative oxygenation group; however, overall, the proportion of time spent non-adherent while receiving invasive mechanical ventilation was low in both groups with 3·8% of time receiving invasive mechanical ventilation in the conservative oxygenation group versus 1·5% of hours in the liberal oxygenation group (appendix pp 23–24). The main reasons for non-adherence were acute deterioration episodes, staffing related issues (eg, lack of trial awareness) or other clinical priorities or clinical preference (eg, physiotherapy, pneumothorax). Further details on protocol adherence are reported in the appendix (pp 23–24).

The duration of organ support or death at 30 days was significantly lower in the conservative than the liberal oxygenation group (table 2, figure 3, appendix pp 40–41) with a probabilistic index of 0·53 (95% CI 0·50–0·55; p=0·04 Wilcoxon rank-sum test) indicating a higher probability for a better outcome in the conservative oxygenation group. The unadjusted and adjusted odds ratios for the conservative compared with the liberal oxygenation group were 0·85 (95% CI 0·73–0·99) and 0·84 (95% CI 0·72–0·99), respectively (table 2). These odds ratios were relatively consistent across the mortality and organ support components of the primary outcome (appendix pp 26–28).

Prespecified subgroup analyses by age, age-adjusted heart rate, and haemoglobin concentration at admission did not reveal any significant heterogeneity

	Conservative oxygenation group (n=939)	Liberal oxygenation group (n=933)
Age, years	2·6 (4·1)	2·5 (3·9)
Aged younger than 12 months	450 (48%)	439 (47%)
Sex, assigned at birth		
Female	528/927 (57%)	511/920 (56%)
Male*	399/927 (43%)	409/920 (44%)
Ethnic background†		
White	521/750 (69%)	509/761 (67%)
Asian	101/750 (13%)	109/761 (14%)
Black	55/750 (7%)	57/761 (7%)
Mixed	36/750 (5%)	38/761 (5%)
Other	37/750 (5%)	48/761 (6%)
Time in hours between meeting eligibility criteria and random allocation, median (IQR)	2 (1–3)	2 (1–3)
Any comorbidities‡	456/938 (49%)	490/930 (53%)
Primary reason for admission lower respiratory tract infection	601 (64%)	602 (65%)
Severity of gas exchange (SF ratio <221 with PEEP ≥5 cm H_2O)	557 (59%)	554 (59%)
PIM3 risk of death, % (SD)§	3·7% (6·2)	3·8% (6·3)
Main reason for admission to PICU		
Asthma	46 (5%)	43 (5%)
Bronchiolitis	363 (39%)	336 (36%)
Croup	16 (2%)	16 (2%)
Obstructive sleep apnoea	2 (<1%)	0
Diabetic ketoacidosis	3 (<1%)	0
Recovery from surgery	35 (4%)	52 (6%)
Seizure disorder	54 (6%)	51 (5%)
Other	420 (45%)	435 (47%)
Physiological values recorded at, or within 1 h before, random allocation		
SpO_2 %, median (IQR)	98% (95–100)	98% (95–100)
FiO_2	0·56 (0·22)	0·55 (0·21)
PaO_2, mm Hg¶	98 (60)	101 (83)
Base excess, mEq/L‖	−2·1 (6·1)	−1·2 (6·5)
Blood lactate, mmol/L**	1·8 (1·9)	1·8 (1·7)
Systolic blood pressure, mm Hg††	98·7 (21·8)	97·7 (21·2)
Mean airway pressure, cm H_2O‡‡	12·4 (6·2)	12·4 (5·4)

(Table 1 continues on next page)

	Conservative oxygenation group (n=939)	Liberal oxygenation group (n=933)
(Continued from previous page)		
Age-adjusted heart rate at baseline§§		
5th to <10th percentile	72/914 (8%)	79/910 (9%)
10th to <50th percentile	202/914 (22%)	221/910 (24%)
50th to <90th percentile	364/914 (40%)	345/910 (38%)
90th to <95th percentile	87/914 (10%)	88/910 (10%)
95th to <99th percentile	122/914 (13%)	113/910 (12%)
≥99th percentile	67/914 (7%)	64/910 (7%)

Data are n (%) or mean (SD) unless otherwise stated. FiO_2=fraction of inspired oxygen. mEq/L=milliequivalents per litre. PaO_2=partial pressure of arterial oxygen. PEEP=positive end-expiratory pressure. PICU=paediatric intensive care unit. PIM3=Paediatric Index of Mortality 3. SpO_2=peripheral oxygenation saturation. SF ratio=the ratio of peripheral oxygen saturation to fraction of inspired oxygen. *Sex was obtained from routinely collected data, and was missing for 13 patients in the liberal oxygenation group and 12 patients in the conservative oxygenation group. †Ethnic background was obtained from routinely collected data and was missing for 361 patients (172 [18·4%] in the liberal oxygenation group and 189 [20%] in the conservative oxygenation group) Percentages in the table are of the total patients with ethnicity recorded. ‡Data on comorbidities were not available for 3 patients in the liberal oxygenation group and 1 patient in the conservative oxygenation group. §The predicted risk of death in the PICU was calculated from the PIM3 score.[28] ¶Data were not available for 653 patients in the liberal oxygenation group and 640 patients in the conservative oxygenation group due to patients not having a catheter in place for arterial blood gas measurement. To convert the values for PaO_2 to kilopascals, divide by 7·501. ||Data were not available for 365 patients in the liberal oxygenation group and 366 patients in the conservative oxygenation group. **Data were not available for 356 patients in the liberal oxygenation group and 339 patients in the conservative oxygenation group. ††Data were not available for 158 patients in the liberal oxygenation group and 131 patients in the conservative oxygenation group. ‡‡Data were not available for 568 patients in the liberal oxygenation group and 545 patients in the conservative oxygenation group. §§Data were not available for 23 patients in the liberal oxygenation group and 25 patients in the conservative oxygenation group.

Table 1: **Characteristics of the patients at baseline**

(appendix p 42). Sensitivity analyses of the primary outcome in the per-protocol population, using alternative definitions of the duration of organ support, and using alternative approaches to analysis were all consistent with the main analysis and confirm a significant benefit with a conservative oxygenation target (appendix pp 26–31). The primary outcome was not available for 8% of patients in each treatment group due to lack of consent. Best-case and worst-case analyses for these missing outcomes demonstrated that the missing data could be sufficient to change the primary effect estimate from a small benefit of liberal oxygenation (probabilistic index 0·47 95% CI [0·44–0·50]) to a more substantial benefit of conservative oxygenation (probabilistic index 0·58 [0·55–0·60], appendix pp 26–28).

Mortality at PICU discharge and at 30 days did not differ significantly between groups (table 2). Receipt and duration of each component of organ support and functional status at PICU discharge are presented in the appendix (pp 32–34), and the proportion of days of receipt of combinations of organ support are shown in the appendix (p 43). The proportion of participants receiving non-invasive respiratory support (45·4% for conservative oxygenation group and 46·2% for liberal oxygenation group) and cardiovascular support (32·2% and 36·3%) were similar between groups, as was the median duration of intervention. Receipt of renal support and other types of organ support was low in both groups. Time to liberation from invasive mechanical ventilation was shorter in the conservative oxygenation group (adjusted hazard ratio 1·11, 95% CI 1·01 to 1·21; appendix p 44). At 30 days, mean costs were £32 479 (SD 23 635) in the conservative and £34 725 (26 491) in the liberal oxygenation group. The adjusted mean difference in incremental cost at 30 days was −£2143 (95% CI −£4320 to £34; table 2). Sensitivity analyses of the relevant secondary outcomes were consistent with the main analysis (appendix pp 30–31, 36–37).

Adverse events were reported in 24 (3%) of 939 patients in the conservative oxygenation group and 36 (4%) of 933 patients in the liberal oxygenation group (table 3). Of these, 12 events (two severe lactic acidosis, seven cardia ischaemia, two acute kidney injury, and one critical hypotension and hypoxia) from 12 patients in the conservative oxygenation group and 21 events (six severe lactic acidosis, 11 cardiac ischaemia, two acute kidney injury and two seizures) from 17 patients in the liberal oxygenation group met the criteria for a serious adverse event (table 4).

Discussion

Among children admitted as an emergency to PICU receiving invasive mechanical ventilation and supplemental oxygen the duration of organ support or death at 30 days was improved with a conservative oxygenation target (SpO_2 88–92%) when compared with treatment as usual with a liberal oxygenation target (SpO_2 >94%). Point estimates for both components of this outcome favoured the conservative oxygenation group. We did not detect any clinically important harm associated with the use of conservative oxygenation, and average costs were lower. These findings therefore support an oxygenation target of SpO_2 88–92% for critically ill children receiving invasive mechanical ventilation.

Our results are consistent with observational data of worse risk-adjusted outcomes with hyperoxia.[6] Two randomised trials of conservative oxygenation strategies in children in ward-based settings both reported equivalent safety and reduced resource use with the more conservative intervention.[19,20] Our pilot trial in 107 children admitted as an emergency to PICU demonstrated a similar trend towards reduced length of PICU stay.[23] While the observed effect between groups was small, given the number of critically ill children treated with oxygen each year, a small effect might result in larger clinical effect. To put these findings into context, acknowledging the uncertainty around the point estimates, if the observed change in the distribution of the primary outcome is true then for every 200 patients treated with a conservative oxygenation target this would equate to one fewer death and 123 fewer days of organ support, corresponding to approximately 0·6 days per patient. Although not statistically significant, targeting a conservative oxygenation target is likely to reduce incremental costs at 30 days with the point estimate for

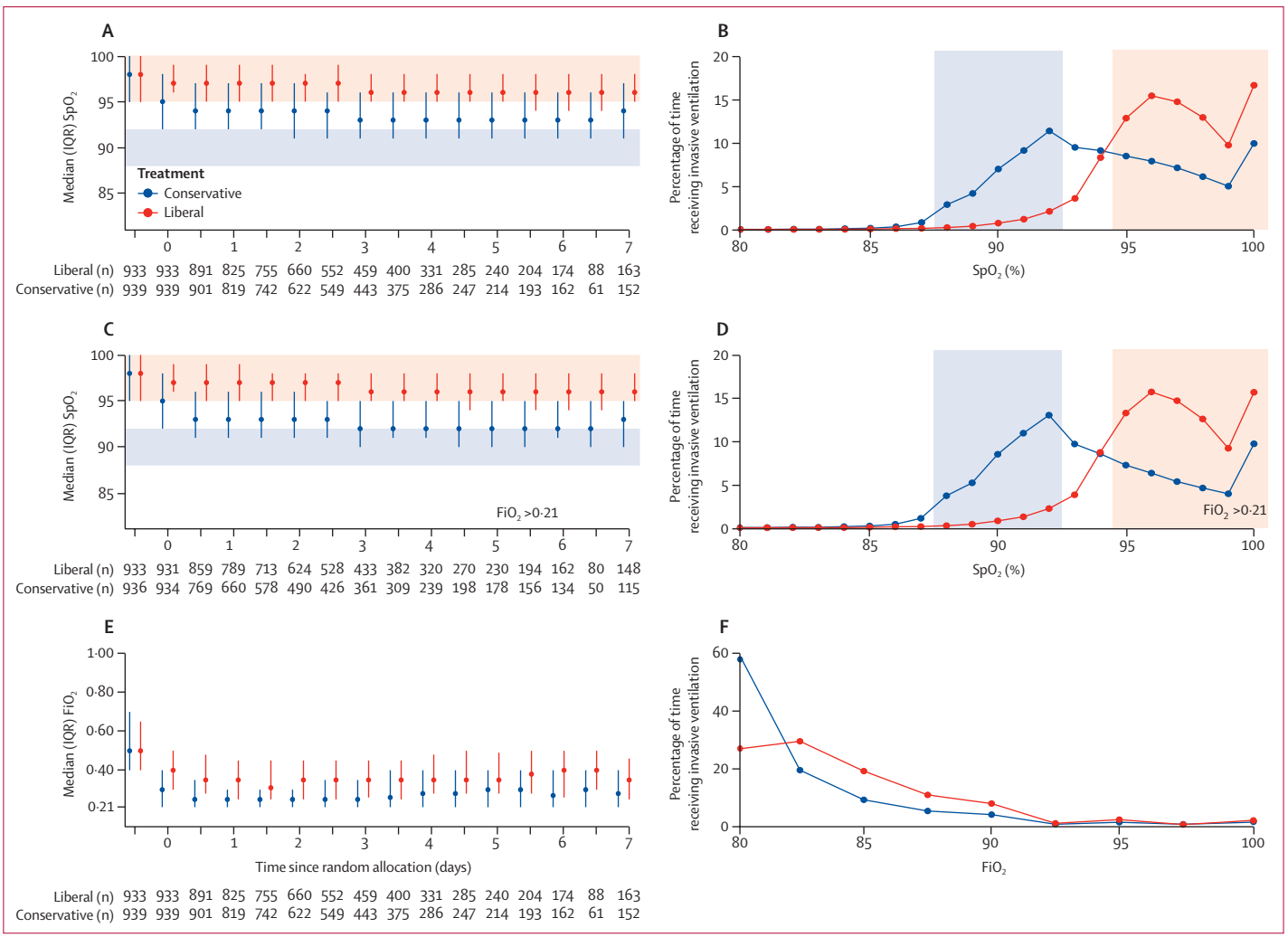

Figure 2: **Distribution of SpO_2 and FiO_2 according to oxygenation target group**
Baseline and subsequently median and IQR SpO_2 (panels A, C) and FiO_2 (panels E, F) measurements at individual timepoints while receiving invasive mechanical ventilation for the first 7 days following random allocation are shown. Panels B and D show the percentage of time at each SpO_2. Panels A, B, E, and F include all ventilated observations, whereas panels C and D show only SpO_2 values in children invasively mechanically ventilated with FiO_2 greater than 0·21. Shaded areas illustrate the treatment group target SpO_2 ranges. SpO_2=peripheral oxygen saturation. FiO_2=fraction of inspired oxygen.

this secondary outcome and confidence intervals both strongly favouring conservative oxygenation.

Trials of conservative oxygenation in critically ill adults have shown variable results.[11–13] Smaller trials have described benefit[10,12] or harm[15] with conservative oxygenation, but larger trials have reported no significant effects to date.[11,13,30] A meta-analysis of recent studies of critically ill adults showed no consistent evidence of benefit or harm.[31,32] While duration of organ support was not consistently described in these trials, similar to the results of our trial, we know from the literature on adult patients that any effects from conservative oxygenation are likely to be small but given the number of critically ill patients (both adults and paediatric patients) treated with oxygen, a small effect could still have a large clinical effect. More extremely premature infants died with a conservative oxygenation target of SpO_2 85–89% in a series of large trials, although there were important reductions in severe retinopathy. A different risk–benefit ratio of oxygenation strategies in critically ill children compared with extremely premature infants[16] or adults is plausible based on differences in case-mix (precipitants to intensive care admission and patterns of comorbid diseases), mortality risk, length of stay, redox status, and fetal haemoglobin concentrations.

The strengths of our trial included the inclusivity of the population, with 15 out of the 28 UK PICUs contributing a high proportion of potentially eligible patients, thus reflecting the UK PICU population, and the pragmatic design reflecting real world practice. The endpoint was chosen in consultation with patients and their families as being of direct relevance to their

	Conservative oxygenation group (n=939)	Liberal oxygenation group (n=933)	Effect estimate (95% CI)	p value
Primary outcome				
Days of organ support or death to day 30*	5 (3 to 9)	5 (3 to 10)	0·53 (0·50 to 0·55)†	0·04‡
Unadjusted odds ratio	..	..	0·85 (0·73 to 0·99)§	..
Adjusted odds ratio	..	..	0·84 (0·72 to 0·99)¶	..
Secondary outcomes				
Mortality at PICU discharge‖	25 (2·7%)	27/932 (2·9%)	0·89 (0·51 to 1·58)¶	0·78**
Mortality by day 30	23 (2·4%)	28 (3·0%)	0·80 (0·45 to 1·41)¶	0·48**
Hours from random allocation to liberation from invasive mechanical ventilation (95% CI)	69·6 (66·1 to 75·2)	73·2 (69·0 to 79·8)	1·11 (1·01 to 1·21)††	0·03‡‡
Days of organ support to day 30 [number of patients]				
30-day survivors	5 (3 to 9) [916]	5 (3 to 9) [905]	0·53 (0·50 to 0·55)†	0·06‡
30-day non-survivors	10 (4 to 20) [23]	7 (4 to 13) [28]	0·41 (0·25 to 0·57)†	0·25‡
Length of PICU stay, days [number of patients]‖‖				
PICU survivors	4 (3 to 8) [914]	5 (3 to 8) [905]	0·52 (0·49 to 0·54)†	0·26‡
PICU non-survivors	15 (5 to 33) [25]	11 (4 to 36) [27]	0·48 (0·32 to 0·64)†	0·78‡
Length of hospital stay, days [number of patients]§§				
Hospital survivors	8 (5 to 15) [898]	8 (5 to 17) [887]	0·51 (0·49 to 0·54)†	0·29‡
Hospital non-survivors	17 (5 to 33) [29]	13 (6 to 49) [37]	0·52 (0·38 to 0·66)†	0·75‡
Health-care costs up to 30 days				
GBP	32 479 (23 635)	34 725 (26 491)	−2143 (−4320 to 34)¶¶	0·05
US$‖‖	47 975 (34 912)	51 293 (39 131)	−3166 (−6381 to 50)¶¶	0·05

Values are median (IQR), n/N (%), or mean (SD) unless otherwise specified. Adjusted analyses are adjusted for: age; primary reason for admission (lower respiratory tract infection *vs* other); severity of abnormality of gas exchange (SF ratio <221 with PEEP ≥5 cm H_2O *vs* other); PIM3 risk of death; and site. PICU=paediatric intensive care unit. SF ratio=the ratio of peripheral oxygen saturation to fraction of inspired oxygen. PEEP=positive end-expiratory pressure. PIM3=Paediatric Index of Mortality 3. *In calculating the median and interquartile range, death is ranked higher than any duration of organ support. †Probabilistic index (the probability that a randomly selected patient receiving conservative oxygenation has a better outcome than a randomly selected patient receiving liberal oxygenation). A value above 0·5 indicates higher probability of better outcome. ‡Wilcoxon rank-sum test. §Unadjusted odds ratio. ¶Adjusted odds ratio. ‖Status at PICU discharge not known for one patient in the liberal oxygenation group. **Fisher's exact test. ††Adjusted hazard ratio. ‡‡Cox proportional hazard p value. §§Length of stay in hospital not known for nine patients in the liberal oxygenation group and 12 patients in the conservative oxygenation group. ¶¶Adjusted mean difference. ‖‖Costs were collected in GBP and converted to US$ using the currency conversion factor $1 equals £0·677.

Table 2: **Primary and secondary outcomes**

experience of PICU.[33] The duration of organ support in the standard liberal oxyenation group was similar to the pre-trial estimate, but mortality at 30 days (3%) was underestimated (pre-trial estimate 7·5%). The conservative assumption in our power calculation of no effect on mortality was therefore important in selecting an appropriate sample size. The pragmatic inclusion criteria resulted in a wide case-mix of children being randomly allocated and a high consent rate (92%). However, we cannot exclude the possibility that results might differ in specific subgroups of patients, for example for severity of baseline gas exchange. We note that extreme values of the primary outcome changed more than the middle values. This might result from different mechanisms, for example additional oxidative injury in the most severely ill longer stay patients, while the less unwell children might benefit from the removal of unnecessary, but not biologically harmful, respiratory support as in the BIDS trial.[19]

Weaknesses of our trial included the somewhat atypical case-mix, which included fewer than expected children with lower respiratory tract infections, reflecting the lockdown and school closures during the COVID-19 pandemic. In addition, we excluded two important sub-populations of children admitted to PICU—those with congenital cardiac disease and acute encephalopathy as primary reasons for admission to PICU, because of a lack of clinical equipoise around oxygen targets. We also excluded a small number of participants because of not being able to obtain deferred consent from the parent or legal guardian; however, this was balanced between groups. In the UK, PICU is provided in regional specialist units. These results might not be generalisable to other settings, eg, to mixed adult and paediatric intensive care units.

As a pragmatic trial designed to be directly relatable to routine clinical practice, and as the intervention required supplemental oxygen to be titrated in response to patients' SpO_2 readings, we did not attempt to mask clinicians to the allocated treatment, similar to other recent trials. Adherence to the conservative oxygenation target was challenging. While the rate of protocol deviations from the conservation oxygenation target was greater than rates of deviation for the liberal oxygenation target, this is similar to patterns of deviation observed in recent trials in adults,

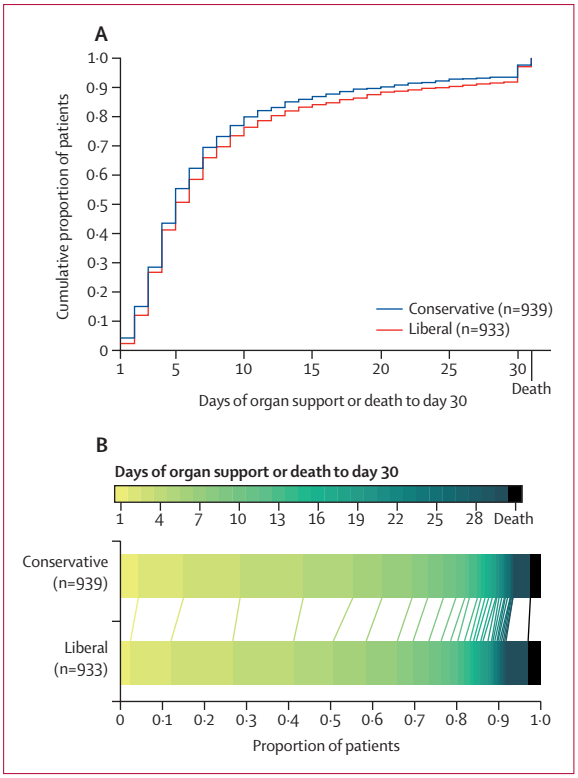

Figure 3: **Distribution of days of organ support and death**
(A) shows the cumulative proportion of patients in each treatment group with each value of number of days of organ support during the first 30 days following random allocation, with death listed last on the axis, corresponding to a value of 31. Curves that rise more steeply indicate a more favourable distribution in the number of days of organ support. The height of the curve at any point from 1 to 30 days indicates the proportion of patients with that number of days of organ support or fewer (eg, the height at day 20 indicates the proportion of patients that survived to 30 days with ≤20 days of organ support). The height of the final step of each curve from 30 to 31 indicates the mortality on or before day 30 in each group. (B) shows the distribution of days of organ support or death as horizontally stacked proportions for each treatment group. Blue represents worse outcomes and yellow represents better outcomes.

	Conservative oxygenation group (n=939)	Liberal oxygenation group (n=933)
Number of patients experiencing one or more adverse events	24 (3%)	36 (4%)
Adverse events		
Severe lactic acidosis	4 (<1%)	10 (1%)
Cardiac ischaemia	7 (1%)	11 (1%)
Acute kidney injury	8 (1%)	15 (2%)
Seizures	5 (1%)*	10 (1%)
Other	1 (<1%%)†	0

Occurrences of the specified, expected adverse events were recorded for all randomly allocated patients from the time of random allocation until 30 days after randomisation or discharge from the paediatric intensive care unit, whichever was later. Considering that at the time of eligibility for Oxy-PICU all children were critically ill, and due to the complexity of their condition were at an increased risk of experiencing adverse events, occurrences of non-specified, unexpected adverse events were only reported if they were, in the investigator's opinion, considered to be related to the trial treatment. Specified, expected adverse events were new onset of severe lactic acidosis (>5 mmol/L) without otherwise known cause; cardiac ischaemia without otherwise known cause; acute kidney injury without otherwise known cause; and seizures without otherwise known cause. *One patient experienced two events. †The event in the "Other" category was an episode of critical hypotension and hypoxia.

Table 3: **Adverse events**

	Conservative oxygenation group (n=939)	Liberal oxygenation group (n=933)
Number of patients experiencing one or more serious adverse events	12 (1%)	17 (2%)
Serious adverse events		
Severe lactic acidosis	2 (<1%)	6 (1%)
Cardiac ischaemia	7 (1%)	11 (1%)
Acute kidney injury	2 (<1%)	2 (<1%)
Seizures	0	2 (<1%)
Other	1 (<1%)*	0

Data are n (%). Serious adverse events include all expected and unexpected adverse events which were reported as being severe (requiring clinical treatment and resulting in significant prolongation of hospital stay, or permanent functional limitation, or both in combination), life threatening (complication that may lead to death, or where the participant died as a direct result of the complication or adverse event), or fatal. *Event was an episode of critical hypotension and hypoxia.

Table 4: **Serious adverse events**

and will probably have reduced the effect of the intervention biasing toward the null. Moreover, the proportion of time spent non-adherent while receiving invasive mechanical ventilation was low in both groups (3·8% and 1·5% in the conservative and liberal oxygenation groups, respectively). However, we cannot exclude the possibility that some of these deviations were protective. Patients were on high levels of supplemental oxygenation before random allocation (combined baseline median FiO_2 0·56), corresponding to SpO_2 levels far exceeding the conservative target range (baseline median SpO_2 98%). While using a conservative oxygenation target was successful as a lever to reduce oxygen exposure, patients in the conservative group still spent a large proportion of their time above the target range, due to the lack of need for supplemental oxygen to maintain higher levels. We cannot say whether an intermediate oxygenation target (eg, SpO_2 92–95%) or more rigorous adherence to the 88–92% target could have been preferable. Additionally, we did not collect baseline POPC and PCPC scores to permit an analysis of change in these categories.

Future research should include defining the mechanisms underlying the observed benefit. These might include a biological effect of oxygen, but also enabling staff to wean oxygen support more quickly by being more tolerant of mildly abnormal physiological oxygen values. Trials of intermediate or lower SpO_2 values in individuals at higher risk are also required.

Among children and young people admitted to PICU as an emergency who receive invasive mechanical ventilation, a conservative oxygenation target of SpO_2 88–92% resulted

in a small, but significant greater probability of a better outcome in terms of the duration of organ support or death at 30 days.

Contributors

MJP, SR, RA, ED, LE-M, JP, PR, KT, KMR, DAH, and PRM conceived, designed, and obtained funding for the trial. All authors oversaw trial conduct and management, and contributed to acquisition, analysis, and interpretation of the data. KT, EG, ZS, and DAH directly accessed and verified the data, and conducted the analyses. MJP, DWG, SR, DAH, and PRM drafted the manuscript. All authors critically revised and approved the manuscript for submission.

Declaration of interests

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Data sharing

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data for scientific research may be granted following review.

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References

1 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**: e444–50.

2 Raman S, Ray S, Peters MJ. Survey of oxygen delivery practices in UK paediatric intensive care units. *Crit Care Res Pract* 2016; **2016:** 6312970–74.

3 Ray S, Rogers L, Raman S, Peters MJ. Liberal oxygenation in paediatric intensive care: retrospective analysis of high-resolution SpO_2 data. *Intensive Care Med* 2017; **43:** 146–47.

4 Balcarcel DR, Coates BM, Chong G, Sanchez-Pinto LN. Excessive oxygen supplementation in the first day of mechanical ventilation is associated with multiple organ dysfunction and death in critically ill children. *Pediatr Crit Care Med* 2022; **23:** 89–98.

5 Brugniaux JV, Coombs GB, Barak OF, Dujic Z, Sekhon MS, Ainslie PN. Highs and lows of hyperoxia: physiological, performance, and clinical aspects. *Am J Physiol Regul Integr Comp Physiol* 2018; **315:** R1–27.

6 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.

7 Chu DK, Kim LH-Y, 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:** 1693–705.

8 Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. *Intensive Care Med* 2015; **41:** 1–4.

9 Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med* 2022; **387:** 1467–76.

10 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:** 180–90.

11 Schjørring OL, Klitgaard TL, Perner A, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med* 2021; **384:** 1301–11.

12 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:** 1583–89.

13 Semler MW, Casey JD, Lloyd BD, et al. Oxygen-saturation targets for critically ill adults receiving mechanical ventilation. *N Engl J Med* 2022; **387:** 1759–69.

14 Panwar R, Hardie M, Bellomo R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. a pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med* 2016; **193:** 43–51.

15 Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med* 2020; **382:** 999–1008.

16 Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010; **362:** 1959–69.

17 Schmidt B, Whyte RK, Asztalos EV, et al. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA* 2013; **309:** 2111–20.

18 Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* 2013; **368:** 2094–104.

19 Cunningham S, Rodriguez A, Adams T, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet* 2015; **386:** 1041–48.

20 Maitland K, Kiguli S, Olupot-Olupot P, et al. Randomised controlled trial of oxygen therapy and high-flow nasal therapy in African children with pneumonia. *Intens Care Med* 2021; **47:** 566–76.

21 Kneyber MCJ, de Luca D, Calderini E, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). *Intensive Care Med* 2017; **43:** 1764–80.

22 Fernández A, Modesto V, Rimensberger PC, et al. Invasive ventilatory support in patients with pediatric acute respiratory distress syndrome: from the second pediatric acute lung injury consensus conference. *Pediatr Crit Care Med* 2023; **24**: S61–75.

23 Peters MJ, Jones GAL, Wiley D, et al. Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. *Intensive Care Med* 2018; **44:** 1240–48.

24 Chang I, Thomas K, O'Neill Gutierrez L, et al. Protocol for a randomized multiple center trial of conservative versus liberal oxygenation targets in critically ill children (Oxy-PICU): oxygen in pediatric intensive care. *Pediatr Crit Care Med* 2022; **23:** 736–44.

25 Woolfall K, Frith L, Dawson A, Gamble C, Lyttle MD, Young B. Fifteen-minute consultation: an evidence-based approach to research without prior consent (deferred consent) in neonatal and paediatric critical care trials. *Arch Dis Child Educ Pract Ed* 2016; **101:** 49–53.

26 Khemani RG, Rubin S, Belani S, et al. Pulse oximetry vs. PaO_2 metrics in mechanically ventilated children: Berlin definition of ARDS and mortality risk. *Intensive Care Med* 2015; **41:** 94–102.

27 NHS Data Model and Dictionary. The Paediatric Critical Care Minimum Data Set (PCCMDS). https://www.datadictionary.nhs.uk/data_sets/supporting_data_sets/paediatric_critical_care_minimum_data_set.html?hl=pccmds (accessed Dec 30, 2022).

28 Straney L, Clements A, Parslow RC, et al. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care. *Pediatr Crit Care Med* 2013; **14:** 673–81.

29 Bonafide CP, Brady PW, Keren R, Conway PH, Marsolo K, Daymont C. Development of heart and respiratory rate percentile curves for hospitalized children. *Pediatrics* 2013; **131:** e1150–57.

30 Mackle D, Bellomo R, Bailey M, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med* 2020; **382:** 989–98.

31 Barbateskovic M, Schjørring OL, Krauss SR, et al. Higher *vs* lower oxygenation strategies in acutely ill adults: a systematic review with meta-analysis and trial sequential analysis. *Chest* 2021; **159:** 154–73.

32 Cumpstey AF, Oldman AH, Martin DS, Smith A, Grocott MPW. Oxygen targets during mechanical ventilation in the ICU: a systematic review and meta-analysis. *Crit Care Explor* 2022; **4:** e0652.

33 O'Hara CB, Canter RR, Mouncey PR, et al. A qualitative feasibility study to inform a randomised controlled trial of fluid bolus therapy in septic shock. *Arch Dis Child* 2018; **103:** 28–32.