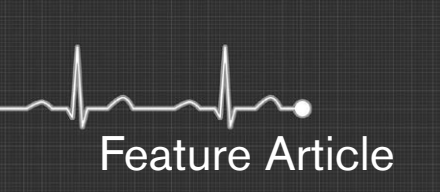


# Admission Hyperoxia Is a Risk Factor for Mortality in Pediatric Intensive Care*

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**Objectives:** To determine whether the association between hyperoxia and increased risk-adjusted mortality in adult intensive care patients is also observed in a pediatric intensive care population.

**Design:** Single-center retrospective analysis of admissions to ICU over a 5-year period commencing January 1, 2012, examining the relationship between $Pao_2$ measured within the first hour of admission and risk-adjusted mortality. Standardized mortality rates were calculated using the Pediatric Index of Mortality-3, and patients were grouped into 50 mm Hg (6.67 kPa) $Pao_2$ bands to assess the relationship between initial $Pao_2$ and risk-adjusted mortality.

**Setting:** Tertiary PICU with 17 beds and 1,100 annual admissions located in metropolitan Sydney, Australia.

**Patients:** A total of 1,447 patients 0–18 years old with $Pao_2$ recorded at admission to the ICU.

**Interventions:** None.

**Measurements and Main Results:** There were 5,176 patients admitted to the ICU during the study period and 1,447 (28%) with $Pao_2$ recorded at admission. A *U*-shaped relationship between raw mortality and admission $Pao_2$ was observed, with lowest mortality (2.3% and 2.6%, respectively) observed in the 101–150 (13.5–20.0 kPa) and 151–200 mm Hg (20.1–26.7 kPa) bands and the highest mortality observed in patients with $Pao_2$ less than 50 mm Hg (6.67 kPa) with mortality of 5.3%, or greater than 350 mm Hg (46.7 kPa) with mortality of 18.2%. Hyperoxia at admission was associated with an increase in risk-adjusted mortality, with polynomial regression indicating a strong correlation between $Pao_2$ band and risk-adjusted outcome ($r^2 = 0.845$). When included in a multivariate model that included the Pediatric Index of Mortality-3 variables, the odds ratio for hyperoxia (defined as $Pao_2 > 250$ mm Hg [33.3 kPa]) predicting death was 2.66 ($p = 0.047$).

**Conclusions:** In this single-center study, hyperoxia at admission to the PICU was highly correlated with increased risk-adjusted mortality. Further investigation of these observations in a large multicenter cohort is warranted. (*Pediatr Crit Care Med* 2018; 19:699–704)

**Key Words:** hyperoxia; hypoxia; mortality; outcome; pediatrics; risk-adjusted mortality

The use of oxygen as a therapy for respiratory disorders was first proposed by Priestly (1) in the late 18th century, and increasingly applied following Haldane's landmark paper published in 1917 (2). Haldane (2) recognized the potential for harm from this newly described therapy and went so far as to define a median lethal dose ($LD_{50}$) of 12 weeks exposure to 70% inspired oxygen in laboratory mice. Despite the prescient warnings by Haldane (2), oxygen began to be used liberally for a wide variety of respiratory and nonrespiratory disorders. Concerns regarding toxicity began to emerge in the latter half of the 20th century. Prolonged exposure to high concentrations of oxygen was recognized as a causative factor for retinopathy of prematurity in 1952 (3), and in 1967, Nash et al (4) were the first to describe "respirator lung" in adults, which was postulated to be related to high inspired oxygen concentrations (although was probably a combination of oxygen and pressure-/volume-related injury). Bronchopulmonary dysplasia in neonates was reported contemporaneously (5).

Risks associated with the administration of supplemental oxygen have more recently been recognized in specific patient populations. Hyperoxia has been associated with increased mortality following cardiac arrest (6–10) and increased early myocardial injury and infarct size following acute myocardial infarction (11) although several other large trials failed to demonstrate any deleterious effects (12, 13). Laboratory studies indicate proinflammatory and cytotoxic effects of hyperoxia on human cardiac myocytes (14). Hyperoxia has also

***See also p. 775.**

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been linked to either worse outcomes or increased mortality risk in retrospective studies of adult patients with trauma (15), traumatic brain injury (16, 17), and stroke (18). In pediatric subjects, a number of studies have indicated worse outcomes following cardiac arrest (10, 19) and in patients requiring extracorporeal support after cardiac surgery (20).

A number of recent studies in adult populations have demonstrated an association between hyperoxia and mortality in general intensive care populations. In a large retrospective study of 36,307 ventilated patients in 50 Dutch ICUs, de Jonge et al (21) demonstrated a *U*-shaped relationship between $Pa_{O_2}$ in the first 24 hours (defined as the $Pa_{O_2}$ from the blood gas with the worst $Pa_{O_2}/Fi_{O_2}$ in that period) and mortality, an association that remained significant after correction for illness severity (Simplified Acute Physiology Score [SAPS] II) and demographic variables. The lowest standardized mortality rate (SMR) was observed in patients with a $Pa_{O_2}$ in the range of 8.9–10.6 kPa (65–80 mm Hg), with values below and above this range associated with higher SMRs. de Jonge et al (21) also demonstrated a linear relationship between $Fi_{O_2}$ and hospital mortality—with higher $Fi_{O_2}$ in the first 24 hours of admission associated with increased mortality (after adjustment for $Pa_{O_2}/Fi_{O_2}$ and SAPS II score)—thus suggesting a relationship between mortality and both the concentration of oxygen administered to the patient and the $Pa_{O_2}$. A similar study performed in Australasian ICUs (22) failed to demonstrate any relationship between $Pa_{O_2}$ and Acute Physiology and Chronic Health Evaluation (APACHE) III risk-adjusted mortality (although a *U*-shaped curve was observed in both unadjusted data and SAPS II risk-adjusted data). An interesting observation from this study was the high prevalence of hyperoxia, with 49.8% of patients having at least one $Pa_{O_2}$ greater than 120 mm Hg (16.0 kPa) in the first 24 hours of ICU care. Both Eastwood et al (22) and de Jonge et al (21) focussed largely on a single measurement of $Pa_{O_2}$ in the first 24 hours of ICU admission (at the time of the worst $Pa_{O_2}/Fi_{O_2}$ result). Cumulative exposure to oxygen over the course of an ICU admission has also been examined. Helmerhorst et al (23) analyzed 295,079 arterial blood gases in 14,441 ICU patients in three tertiary ICUs in the Netherlands, using interpolation to calculate an area under the curve representing total exposure to hyperoxia over the first 24 and 96 hours of ICU stay as well as the total duration of the ICU admission. Both duration of exposure to mild hyperoxia (defined as $Pa_{O_2}$ 120–200 mm Hg [16.0–26.7 kPa]) and severe hyperoxia ($Pa_{O_2}$ > 200 mm Hg [26.7 kPa]) demonstrated a linear relationship with APACHE IV risk-adjusted mortality. Helmerhorst et al (23) also examined the relationship between first recorded $Pa_{O_2}$ and risk-adjusted mortality in this cohort, demonstrating a *U*-shaped relationship similar to the findings by de Jonge et al (21).

Although an increasing body of evidence points to deleterious effects of hyperoxia in specific diagnostic subgroups in both adults and children, as well as general adult ICU populations, no studies in mixed PICU patients have been reported. This study was undertaken to investigate the relationship between initial $Pa_{O_2}$ and standardized mortality risk in patients admitted to PICU.

## MATERIALS AND METHODS

The study was undertaken in the ICU at Sydney Children's Hospital, a 17-bed tertiary referral mixed medical and surgical ICU located in metropolitan Sydney admitting approximately 1,100 patients per annum. Approval to conduct the study was obtained from the local research ethics committee.

All admissions between January 1, 2012, and December 31, 2017, were eligible for inclusion and complete admission, and outcome data were available for all patients. $Pa_{O_2}$ obtained within 1 hour of admission is routinely recorded for the Pediatric Index of Mortality (PIM) calculation. For the purposes of this study, "admission $Pa_{O_2}$" was defined as the first value recorded within the first 60 minutes of admission to the ICU. All patients with an admission $Pa_{O_2}$ value recorded were included in the study. The commencement date of January 1, 2012, was chosen as data recording for the most recent version of PIM (version 3 [24]) commenced at this time, allowing examination of initial $Pa_{O_2}$ as a potential PIM variable. Patients were a priori assigned to groups delineated by 50 mm Hg (6.67 kPa) $Pa_{O_2}$ increments (i.e., 1–50 mm Hg, 51–100 mm Hg, 101–150 mm Hg, and so on). Mortality was defined as death occurring in the ICU or within 24 hours of discharge as per PIM-3.

The relationship between $Pa_{O_2}$ and mortality was examined using polynomial regression, and the impact of hyperoxia as a potential PIM variable was analyzed using multiple logistic regression and receiver operating characteristic (ROC) curves. Data were analyzed using Wizard Statistics (version 1.9.13, Evan Miller) and GraphPad Prism (version 7.0; GraphPad Software, La Jolla, CA). Binomial proportions were compared by chi-square testing, and standardized mortality was analyzed using a Poisson distribution (25). Nonparametric data were compared using the Mann-Whitney test.

## RESULTS

There were 5,176 patients admitted to the ICU during the study period, with an observed mortality of 126 (2.4%) and a PIM-3–predicted mortality of 141.54 (SMR, 0.890; $p = 0.10$). Median age was 1.7 years (interquartile range [IQR], 0.3–7.1 yr). A total of 1,447 patients (28% of all patients) had $Pa_{O_2}$ recorded at admission to the ICU. Observed mortality in this group was 58 (4.0%) with a predicted mortality of 72.08 (SMR, 0.805; $p = 0.05$). Admission $Pa_{O_2}$ ranged from 14 to 613 mm Hg (1.87–81.7 kPa) with a median of 144 mm Hg (19.2 kPa) (IQR, 99–202 mm Hg [13.2–26.9 kPa]). Admission $Fi_{O_2}$ was recorded in 1,290 patients and ranged from 0.21 to 1.00 (median, 0.40; IQR, 0.30–0.51). A total of 1,021 patients (70.5%) received invasive or noninvasive mechanical ventilatory support within the first hour of admission. When compared with patients who did not have $Pa_{O_2}$ recorded at admission, patients in whom admission $Pa_{O_2}$ was measured had significantly higher mortality (4.0% vs 1.8%; $p < 0.001$) were significantly older (median [IQR], 3.2 yr [0.7–10.2 yr] vs 1.3 yr [0.3–6.1 yr]; $p < 0.001$) and were more likely to receive invasive or noninvasive mechanical ventilatory support within the first hour of admission (70.5% vs 41.2%; $p < 0.001$).

The most common admission diagnoses were broadly similar in the subgroup with $Pa_{O_2}$ measured at admission compared with the entire cohort of intensive care patients. For

**TABLE 1. Raw Mortality and Pediatric Index of Mortality-3 Standardized Mortality Rate by Admission $Pao_2$ in 50 mm Hg Bands**

| $Pao_2$ (mm Hg) | *n* | Deaths | % Mortality | Standardized Mortality Rate |
|---|---|---|---|---|
| 1–50 | 38 | 2 | 5.26 | 0.58 |
| 51–100 | 336 | 15 | 4.46 | 0.73 |
| 101–150 | 385 | 9 | 2.34 | 0.69 |
| 151–200 | 312 | 8 | 2.56 | 0.67 |
| 201–250 | 206 | 6 | 2.91 | 0.60 |
| 251–300 | 89 | 6 | 6.74 | 1.00 |
| 301–350 | 37 | 4 | 10.81 | 1.18 |
| >350 | 44 | 8 | 18.18 | 1.22 |

the entire ICU cohort, the top five diagnoses were bronchiolitis ($n = 839$), postoperative anterior or posterior craniotomy ($n = 270$), postoperative cardiac surgery ($n = 256$), asthma ($n = 214$), and seizure disorder ($n = 211$). Four of the top five most common diagnoses for the entire cohort were also among the top five diagnoses for the subgroup with $Pao_2$ measured. In this subgroup, the top five diagnoses were as follows: postoperative cardiac surgery ($n = 245$), postoperative anterior or posterior craniotomy ($n = 158$), bronchiolitis ($n = 67$), postoperative spinal instrumentation ($n = 66$), and seizure disorder ($n = 51$).

A significant proportion of patients were hyperoxic at admission using commonly accepted definitions (22, 23). Mild hyperoxia ($Pao_2$, 121–200 mm Hg [16.1–26.7 kPa]) was recorded in 512 of 1,447 patients (35.6%), and a further 401 (27.9%) had severe hyperoxia ($Pao_2$, > 200 mm Hg [26.7 kPa]).

Mortality was calculated for patients in $Pao_2$ bands of 50 mm Hg (6.67 kPa) (i.e., 1–50 mm Hg, 51–100 mm Hg, 101–151 mm Hg, and so on). Patients with $Pao_2$ greater than 350 mm Hg (46.7 kPa) were grouped together because of small number of patients in each 50 mm Hg band above this value. A *U*-shaped relationship between raw mortality and admission $Pao_2$ was observed, with lowest mortality (2.30% and 2.56%, respectively) observed in the 101–150 and 151–200 mm Hg (13.5–20.0 and 20.1–26.7 kPa) bands (**Table 1**). Although mortality was increased in patients with both low and high $Pao_2$, the highest mortality was observed in hyperoxic rather than hypoxic patients. Mortality in the lowest band, $Pao_2$ 1–50 mm Hg (0.1–6.67 kPa), was 5.3% (2/38), compared with 18.2% (8/44) in the group with $Pao_2$ greater than 350 mm Hg (46.7 kPa). Polynomial regression with 2 *df* revealed a close correlation between admission $Pao_2$ and ICU mortality ($r^2 = 0.981$) (**Fig. 1**).

Adjusting mortality using PIM-3–generated similar results in that hyperoxia (although not hypoxia) was associated with an increased risk of mortality. Risk-adjusted mortality was relatively constant up to a $Pao_2$ of 250 mm Hg (33.3 kPa) with SMR ranging from 0.58 to 0.69, but increased sharply at higher $Pao_2$ values with SMR of 1.0, 1.18, and 1.22 in the next three $Pao_2$ bands (Table 1). Once again, polynomial regression indicated a strong correlation between $Pao_2$ band and risk-adjusted outcome ($r^2 = 0.845$) for a second-order function (**Fig. 2**).

The single largest diagnostic group was patients admitted to the ICU following cardiac surgery. Hyperoxia at admission to the ICU is likely to be commonly observed in this group given that they are all transferred from the operating theater, almost invariably with high $Fio_2$. Although the predicted mortality in most postoperative cardiac patients is not substantially different to that of a general ICU cohort, the causes of mortality may well be different, and a recent publication identified hyperoxia as an independent risk for death in postoperative cardiac surgical patients requiring extracorporeal support (20). Removing this subgroup from the analysis did not materially change the results of the polynomial regression. In the cohort of patients who were not admitted following cardiac surgery ($n = 1,202$), both raw mortality and SMR were strongly associated with $Pao_2$ band ($r^2 = 0.988$ and 0.925, respectively). There was only one death in the cardiac subgroup, making analysis by $Pao_2$ band uninformative.

To determine if admission $Pao_2$ has potential to improve the accuracy of PIM, the effect of including $Pao_2$ either as a continuous or categorical variable in a PIM model was explored. The polynomial regression curve for standardized mortality suggested a value of $Pao_2$ of 250 (33.3 kPa) as a suitable category discriminator. Both initial $Pao_2$ (as a continuous variable) and $Pao_2$ category as defined above demonstrated significant associations with mortality in univariate analysis ($p < 0.001$), but the odds ratio (OR) for $Pao_2$ category indicated a more robust association (8.47 for the dichotomous category compared with 1.02 for $Pao_2$ as a continuous variable). Adding a hyperoxia categorical variable into the existing PIM-3 score in multivariate analysis marginally improved the performance of the score (area under ROC curve 0.956 compared with 0.951 without the hyperoxia variable; $p$ = not significant). In this multivariate model, the OR for hyperoxia (defined as $Pao_2$ > 250 mm Hg [33.3 kPa]) predicting death was 2.66 ($p = 0.047$).

Diagnoses in nonsurvivors were observed to vary with $Pao_2$ category. Shock was more common in patients with high initial $Pao_2$, being present in five of 18 patients (27.8%) with $Pao_2$ greater than 250 mm Hg (33.3 kPa) compared with three of 40 patients (7.5%) with $Pao_2$ less than or equal to 250 mm Hg (33.3 kPa) ($p = 0.04$). Respiratory disorders trended toward being less common in the hyperoxia category, being noted in 10/40 of patients (25.0%) with $Pao_2$ less than or equal to 250 mm Hg (33.3 kPa) compared with only one of 18 (5.6%) in patients with $Pao_2$ greater than 250 mm Hg (33.3 kPa) ($p = 0.08$).

## DISCUSSION

An increasing body of evidence suggests that hyperoxia is associated with increased risk-adjusted mortality in adult intensive care patients. Reports to date have largely focussed on either a single-point measurement of $Pao_2$ in the first 24 hours (obtained at the time of the worst $Pao_2/Fio_2$ result [21–23])

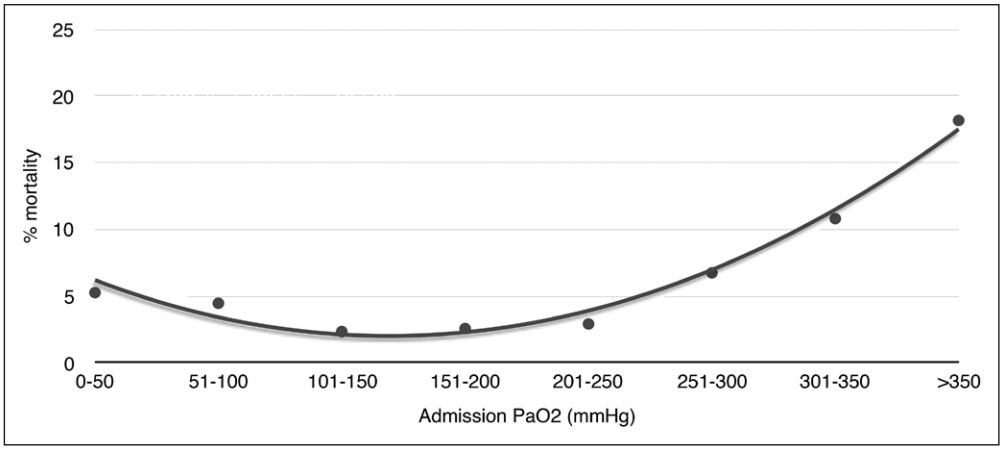


**Figure 1.** Polynomial regression for raw mortality versus $Pao_2$ band.

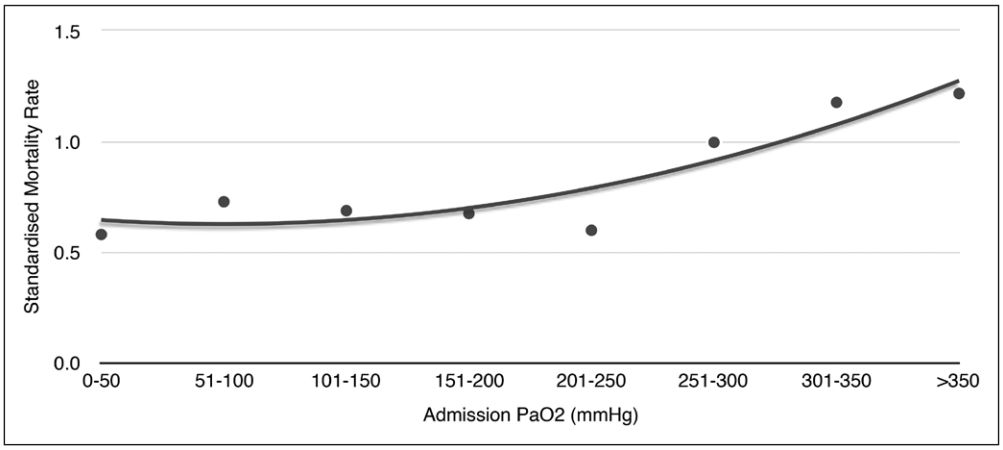


**Figure 2.** Polynomial regression for Pediatric Index of Mortality-3 standardized mortality versus $Pao_2$ band.

or attempted to gauge cumulative exposure to hyperoxia by interpolating sequential blood gas results (23). As with most biological insults, it is more likely that toxicity will be related to an "area under curve" parameter reflecting total exposure rather than a single-point measurement. Helmerhorst et al (23) demonstrated a linear correlation between risk-adjusted in-hospital mortality and hours of hyperoxia, with a weaker correlation between first-recorded $Pao_2$ (obtained at a median of 26 min after ICU admission) and ICU outcome in 14,441 adult ICU patients. Helmerhorst et al (23) also demonstrated a correlation between oxygen parameters measured in the first 24 hours of admission and cumulative exposure estimated from interpolation of all arterial blood gases, suggesting that early point measurements of $Pao_2$ may have some value as an estimate of cumulative exposure.

Although there is no reason to necessarily expect that $Pao_2$ measured at admission to the ICU will correlate with cumulative exposure to hyperoxia throughout the ICU stay, it remains a worthwhile parameter to explore on the basis that it may reflect a period of some hours antecedent hyperoxia (e.g., during surgery, emergency department resuscitation, or retrieval before ICU admission). Because $Pao_2$ is collected as part of the PIM dataset in PICU, existing data are readily available for large number of patients, facilitating studies of association. Furthermore, if $Pao_2$ at admission does impact on mortality risk, it can reasonably be proposed as a new variable that may improve the performance of predictive indices. PIM already includes an "oxygenation" variable, $Fio_2$:$Pao_2$ ratio (24), but this parameter reflects severity of lung disease and will trend in the opposite direction to $Pao_2$ alone (i.e., if $Fio_2$:$Pao_2$ is high, $Pao_2$ is likely to be low). The plot of raw mortality against $Pao_2$ demonstrates a *U*-shaped relationship with higher mortality observed at both low and high $Pao_2$ values. Using SMR (rather than raw mortality) flattens this curve at the lower $Pao_2$ range but standardized mortality increases in the upper $Pao_2$ bands, particularly above 250 mm Hg (33.3 kPa), indicating a failure of the PIM algorithm to correct for the effect of high $Pao_2$. Multivariate logistic regression using the PIM-3 variables (including $Fio_2$:$Pao_2$ ratio) suggests that high $Pao_2$ is independently associated with increased mortality risk. The Pediatric Risk of Mortality score also includes $Pao_2$, with points allocated for two ranges of hypoxia (< 42.0 mm Hg [5.6 kPa] and 42.0–49.9 mm Hg [5.6–6.7 kPa]) but no weighting for higher (hyperoxic) $Pao_2$ values (26, 27).

Our data demonstrate a strong correlation between admission hyperoxia and risk-adjusted mortality ($r^2$ = 0.845). Inclusion of hyperoxia as a categorical variable in PIM was statistically significant with OR equals to 2.66 ($p$ = 0.047) but failed to significantly improve the area under the ROC curve, suggesting only marginal utility as an outcome predictor. Additionally, only a minority of patients have $Pao_2$ measured at admission (28% of all ICU patients in this study), which potentially limits the usefulness of this parameter as a predictive variable for mortality, although this criticism can be applied to several PIM variables including systolic blood pressure, base excess, and $Fio_2$:$Pao_2$ ratio.

The results of this study suggest that further exploration of the potentially toxic effects of hyperoxia in critically ill patients is warranted. Studies in both general adult ICU populations (21, 23) and specific diagnostic groups (6–10, 16–18) have indicated that hyperoxia may pose a mortality risk that (if validated) can be

easily avoided. Correlation does not necessarily imply causation, and other explanations can be proposed. Potentially confounding variables including the use of vasoactive and ventilatory support, fluid resuscitation, and surgical and other procedural interventions were not examined but could impact on the relationships observed in this study. The inherent selection bias of including only patients who had $Pa_{O_2}$ measured within an hour of admission to the ICU suggests that our findings should not necessarily be generalized to all pediatric intensive care patients. It has been suggested that cumulative exposure to hyperoxia during the course of an ICU stay may simply be a marker for a lack of responsive care rather than a causative factor for bad outcomes of itself (23), and our data suggest that there may be associations between hyperoxia and particular diagnostic categories (e.g., sepsis) that carry high mortality risk. In this setting, hyperoxia at admission to the ICU may simply be a marker for severity of critical illness rather than a causative factor for poor outcomes. Nevertheless, there is biological plausibility for hyperoxia to be injurious, particularly in critical illness (14, 28, 29).

An important finding in this study was the high incidence of hyperoxia in patients admitted to ICU. This underscores a widespread acceptance of high arterial oxygen saturation and $Pa_{O_2}$ values among medical staff, which may not be appropriate given the emerging data. Given the prevalence of hyperoxia in our patients, identification of any deleterious effect is of considerable importance, particularly as there is some evidence to suggest that limiting exposure to hyperoxia can reduce intensive care and hospital mortality. A randomized controlled trial comparing a conservative oxygen regimen (targeting $Pa_{O_2}$ 70–100 mm Hg [9.3–13.3 kPa]) compared with a more liberal oxygen regimen (allowing $Pa_{O_2}$ up to 150 mm Hg [20 kPa]) was recently reported from a single adult ICU in Italy (30), with a substantial reduction in ICU mortality observed in conservative oxygen group—11.6% compared with 20.2% in the more liberal oxygen group. A reduction in hospital (but not ICU) mortality was associated with the introduction of a conservative oxygen regimen targeting $Pa_{O_2}$ 55–86 mm Hg (7.3–11.5 kPa) in 15,045 adult ICU patients (31). Targeting moderately low $Pa_{O_2}$ or saturation values (e.g., saturations of 88–92% in one recent study [32]) appears to be safe and feasible in adult ICU populations, but there are no data in pediatric populations. Hypoxia is, obviously, potentially deleterious, and any consideration of lower $Pa_{O_2}$ or oxygen saturation targets must be approached with considerable caution.

## CONCLUSIONS

In this single-center study, hyperoxia at admission to the PICU was common and was highly correlated with increased risk-adjusted mortality, although it is not clear whether this represents true causation. Further investigation of these observations in a large multicenter cohort is warranted.

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