Admission Pao_2 and Mortality in Critically Ill Children: A Cohort Study and Systematic Review

Sainath Raman, MBBS, MRCPCH[1]; Nicholas J. Prince, MBBChir, MA, MRCPCH, MSc[2]; Aparna Hoskote, MBBS, DCH, MD, MRCP[3]; Samiran Ray, MBBChir, MA, MRCPCH[1]; Mark J. Peters, FRCPCH, MRCP, PhD[1]

Objective: To describe the relationship between Pao_2 at intensive care admission and mortality in critically ill children and to review systematically the literature describing this relationship.

Design: Cohort study: A review of consecutive tertiary pediatric intensive care admissions (January 2004 to December 2014) in a single center. The relationship between admission Pao2 and crude and standardized mortality was explored using nonlinear regression. Systematic review: A search of MEDLINE (1950 to January 2015), EMBASE (1980 to January 2015), Cochrane and Database of Abstracts of Reviews of Effects databases was undertaken using the following terms: "hyperoxia," "hypoxia," "critically ill children," "pediatric intensive care," "mortality," and/or "survival."

Setting: Tertiary PICU.

Patients: Patients younger than 18 years of age.

Interventions: The association of hyperoxia (Pao_2, > 300 torr [40 kPa]) and hypoxia (Pao_2, < 60 torr [8 kPa] or peripheral oxygen saturations, < 90%) to mortality in critically ill children was explored.

Measurements and Main Results: Cohort study: Of 14,321 admissions, 7,410 children had recorded Pao_2 and Fio_2 at admission. Crude mortality was 7.4% (555/7,410). This varied with admission Pao_2 from 15.4% (204/1,324) in the hypoxia group (< 8 kPa) to 5.3% (287/5,385) with normoxia and 9.1% (64/701) in the hyperoxic group (> 40 kPa). Nonlinear regression displayed a "*U*-shaped" relationship between Pao_2 and crude and case-mix adjusted mortality. Systematic review: Fourteen studies and one conference abstract were eligible for inclusion. Eleven studies ($n = 5,280$) relate to hypoxia with combined odds ratio for death, of 3.13 (95% CI, 1.79–5.48; $p < 0.001$) compared to normoxia. Six studies ($n = 2,012$) relate to hyperoxia and suggest no effect on mortality compared to normoxia (odds ratio, 1.15; 95% CI, 0.42–3.17; $p = 0.77$).

Conclusions: Hypoxia at admission is associated with increased mortality in critically ill children, whereas the association with hyperoxia is less clear. The cohort study demonstrated a *U*-shaped association between admission Pao_2 and mortality. Further examination is needed to explore the effect of hyperoxia upon mortality prediction accuracy. (*Pediatr Crit Care Med* 2016; 17:e444–e450)

Key Words: hyperoxia; hypoxia; intensive care; mortality; pediatric

Associations between hypoxia and poor outcome are well known (1, 2). However, the risks of hypoxia vary widely with context and time-frame (3, 4). "Hyperoxia" is associated with increased mortality following stroke, cardiac arrest (CA), and traumatic brain injury (TBI) in critically ill adults (5–7).

The true distribution of risk associated with levels of oxygenation during critical illness is likely to be complex. De Jonge et al (8) reported a "*U*-shaped" relationship between early Pao_2 and mortality in adult ICUs. Martin and Grocott (9) proposed "precise control of arterial oxygenation" and "permissive hypoxemia" for optimizing risk and benefit of oxygen therapy during critical illness. Avoidance of hyperoxia was safe in a randomized pilot trial of mechanical ventilated adults comparing conservative (88–92%) and liberal (> 96%) oxygen saturation targets (10). In infants with bronchiolitis, oxygen saturation targets of greater than 90% were as safe as greater than 94%, and required shorter durations of support (11).

There is no consensus on the ideal Pao_2 in critically ill children. Here, we examine the hypothesis that the Pao_2 at admission does not influence risk-adjusted mortality in critically ill children in a large cohort and through systematic review of the literature.

[1]Respiratory, Critical Care and Anesthesia Group, Infection, Immunity, Inflammation Programme, Institute of Child Health–University College London and Great Ormond Street Hospital, London, United Kingdom.

[2]Pediatric Intensive Care Unit, Great Ormond Street Hospital, London, United Kingdom.

[3]Cardiac Intensive Care Unit, Great Ormond Street Hospital, London, United Kingdom.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Dr. Raman is a holder of an HCA fellowship. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: sainath.raman@ucl.ac.uk

DOI: 10.1097/PCC.0000000000000905

METHODS

Cohort Study

We reviewed prospectively collected data for all admissions to the pediatric, neonatal, and cardiac critical care units at Great Ormond Street Hospital over an 11-year period (January 2004 to December 2014).

Patients were included if they had a documented Pao_2 and Fio_2 at admission. The definitions of normoxia, hypoxia, hyperoxia, and admission Pao_2 reflect those used by Kilgannon et al (12) and De Jonge et al (8).

The Pediatric index of Mortality (PIM) 2 score was recorded and a modified PIM (mPIM) score was calculated for each patient by excluding the coefficient of Fio_2/Pao_2 (F-to-P ratio) from the logit equation. Patients were empirically categorized into six groups according to their admission Pao_2 (< 8, 8.1–10, 10.1–13, 13.1–25, 25.1–40, and > 40 kPa). Standardized mortality ratio (SMR), modified SMR (mSMR, calculated using mPIM) and 95% CIs were calculated and plotted for each group using PIM2 and mPIM.

Regression curve estimation (SPSS: IBM Software v21.0; IBM Corp, Armonk, NY) was used to determine best-fit model for the Pao_2-mortality relationship. Nonlinear regression analysis with mortality as the outcome and admission Pao_2, age, ethnicity, weight, and mPIM2 as covariates was performed to assess the relationship between oxygenation and crude and case-mix adjusted mortality.

Systematic Review

The systematic review was performed following the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" guidelines (13). The inclusion criteria were as follows:

1) Age: 4 weeks to 18 years.
2) For the observation cohort, hyperoxia defined as Pao2 greater than 300 torr (40 kPa) or hypoxia defined as peripheral oxygen saturations less than 90% or Pao2 less than 60 torr (8 kPa).
3) For the comparison cohort, normoxia defined as Pao2 between 60 and 300 torr (8.1–40 kPa) or peripheral oxygen saturations greater than 90%. Alternative thresholds were analyzed separately (**Supplemental Digital Content 1**, http://links.lww.com/PCC/A288).
4) Randomized control trials (RCTs) or cohort studies.
5) Outcome measure: Mortality at hospital discharge.

Search Strategy

The terms "hyperoxia," "hypoxia," "survival," and "critically ill children" or "pediatric intensive care" and "mortality" (**Supplemental Digital Content 2**, http://links.lww.com/PCC/A289; **Supplemental Digital Content 3**, http://links.lww.com/PCC/A290; and **Supplemental Digital Content 4**, http://links.lww.com/PCC/A291) were used to identify RCTs and cohort studies in MEDLINE (1950 to January 2015), EMBASE (1980 to January 2015), Cochrane and Database of Abstracts of Reviews of Effects databases. The search was conducted in April 2015.

Primary Summary Measure and Meta-Analysis

A meta-analysis was performed with OpenMeta[Analyst] software (14). I^2 was used as the measure of consistency for heterogeneity analysis. For subgroup analysis, the studies were divided into patients admitted with lower respiratory tract infection (LRTI) or CA or TBI.

RESULTS

Cohort Study

Over the 11-year period, 7,410 of 14,321 admissions had a recorded Pao_2 in the first hour. Of these, 1,324 (17.8%) were hypoxic, 5,385 (72.6%) were normoxic, and 701 (9.4%) were hyperoxic at admission. The crude mortality was 204 (15.4%), 287 (5.3%), and 64 (9.1%), respectively. Pao_2 and crude mortality was found to have a quadratic (*U*-shaped) relationship using nonlinear regression analysis with Pao_2, age, gender, and mPIM as covariates. (**Fig. 1**) The timing of death was described in Kaplan-Meier curves (**Supplemental Digital Content 5**, http://links.lww.com/PCC/A292).

On the basis of the primary diagnosis at admission, the patients with cyanotic congenital heart disease were identified and separately analyzed. The *U*-shaped relationship between Pao_2 and crude mortality was preserved even in this subgroup of children with cyanotic cardiac disorders (**Supplemental Digital Content 6**, http://links.lww.com/PCC/A293).

The SMR and mSMR were 0.93 and 1.34 for the hypoxic group (Pao_2 <8 kPa), 0.75 and 0.83 for the normoxic group (8–40 kPa), and 0.82 and 0.85 the hyperoxic group (> 40 kPa), respectively. (**Fig. 2**)

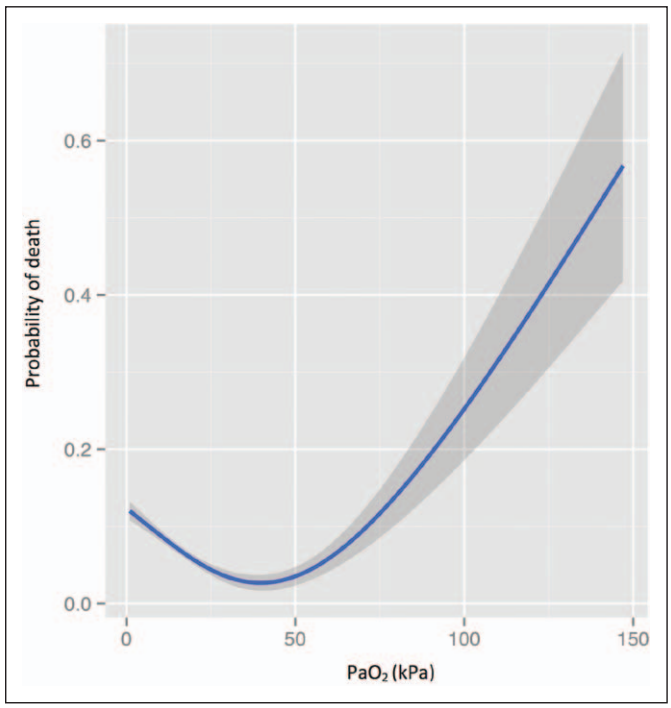

Figure 1. Pao_2-mortality. Relationship between Pao_2 at admission and unadjusted mortality in 7,410 critically ill children admitted to Great Ormond St Hospital Intensive Care 2004–2014. The regression curve estimation shows that Pao_2-mortality relationship is a quadratic function (*U-shaped curve*).

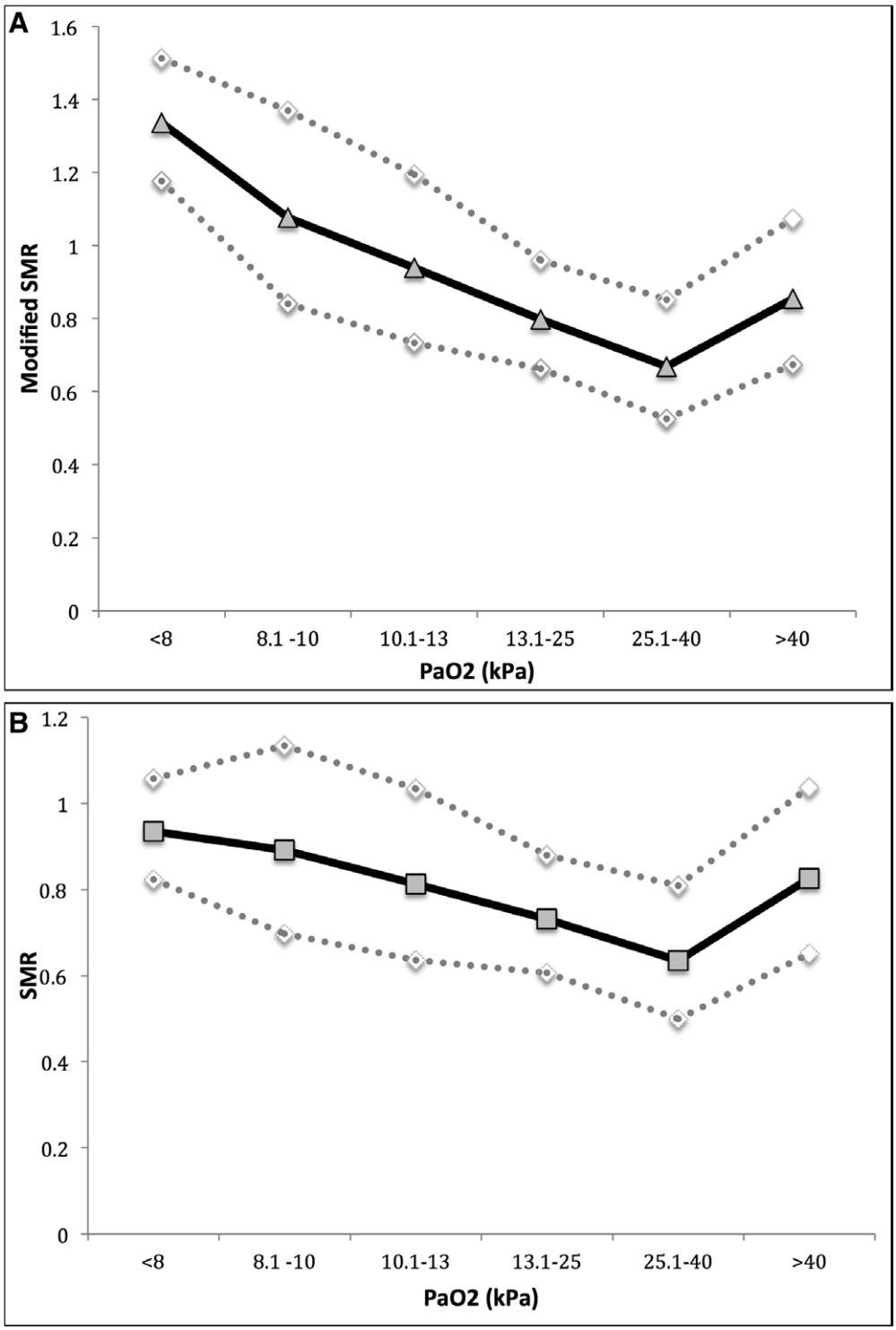

Figure 2. Pao_2-standardized mortality ratio (SMR). **A** and **B**, The relationship between Pao_2 and the modified SMR and SMR. The modified SMR was calculated by excluding the FIo_2/Pao_2 coefficient from the Pediatric Index of Mortality (PIM) 2 calculation. SMR was calculated using the PIM2 score. The *grey dashed lines* represent upper and lower CIs.

Systematic Review

Study Selection and Characteristics. A single reviewer performed the search resulting in 1,749 articles. Duplicate publications (155) were discarded. From the remaining 1,594 articles, 1,513 were excluded after abstract review. Eighty-one articles were reviewed as full text, of which 66 were excluded as being of unsuitable study design (**Fig. 3**). No study investigated cyanotic congenital heart disease group.

The hypoxia studies analyzed were: four CA cohort studies, three LRTI, two post TBI, and one each of children with malaria and diarrhoea. The hyperoxia studies analyzed were: five CA cohort studies and one TBI study.

Hypoxia. The crude mortality in the hypoxic patients was 26.2% compared to 19.9% in the normoxia group.

Eleven studies of 5,280 children revealed a higher odds ratio (OR) of deaths with hypoxia compared to normoxia (OR, 3.13; 95% CI, 1.79–5.48; $p < 0.001$). Heterogeneity was high ($I^2 = 86\%$). (**Fig. 4**)

Hyperoxia. The crude mortality from all the hyperoxia studies was 38.5% for the hyperoxia group and 38.4% in the normoxia group.

Six studies of 2,012 children revealed no effect on mortality. The combined OR risk of death with hyperoxia compared to normoxia was 1.15 (95% CI, 0.42–3.17; $p = 0.77$). Heterogeneity was high ($I^2 = 82\%$). (Fig. 4)

Subgroup Analysis. The odds of death with hypoxia were higher in CA, LRTI, and TBI subgroups. There was no association between hyperoxia and mortality in the CA subgroup. (**Supplemental Digital Content 7**, http://links.lww.com/PCC/A294)

Tables 1 and **2** and **Supplemental Digital Content 8** (http://links.lww.com/PCC/A295) and **Supplemental Digital Content 9** (http://links.lww.com/PCC/A296) give a summary of the characteristics recorded from the studies including the odds ratio and the outcome measures.

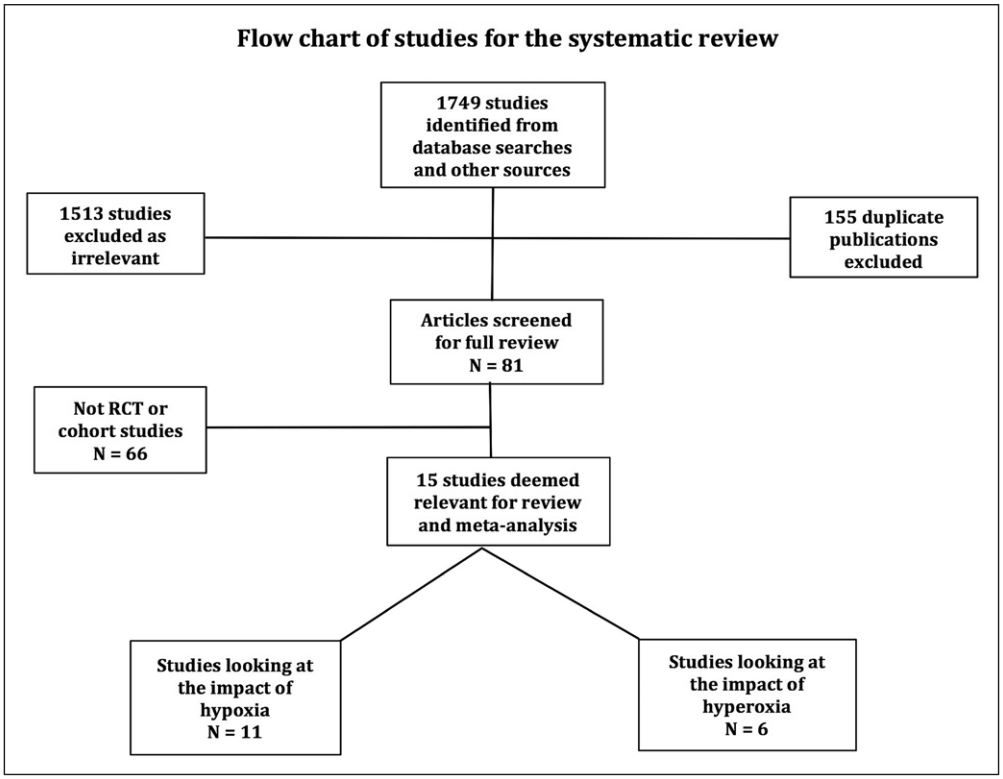

Figure 3. Flowchart systematic review. Flowchart showing the selection of hypoxia and hyperoxia studies. RCT = randomised control trial.

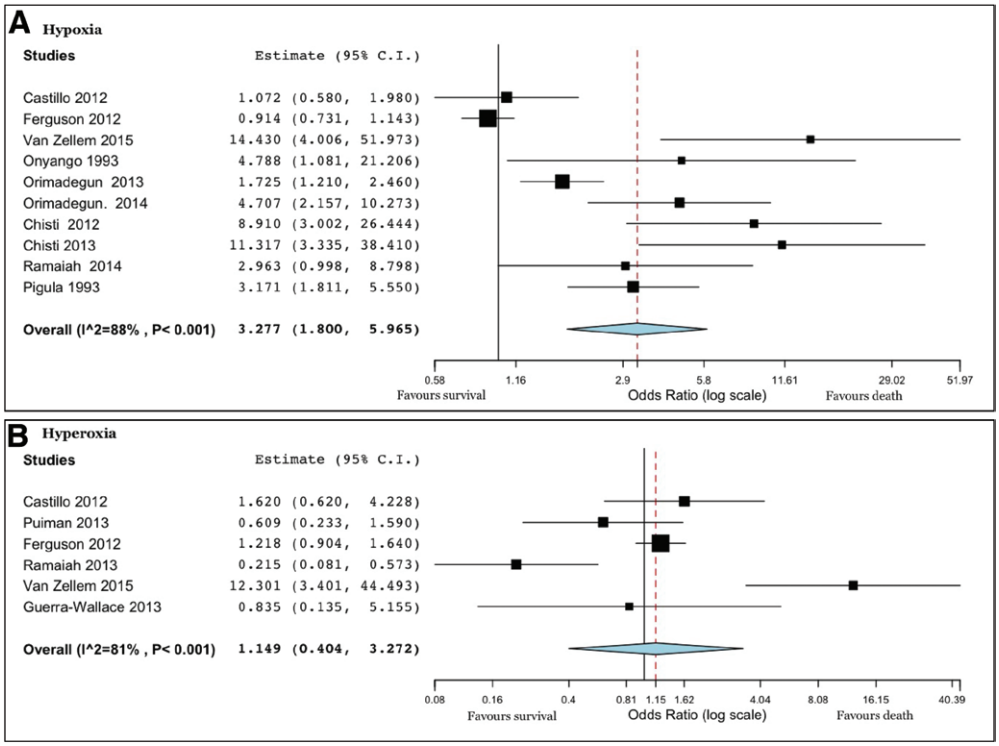

Figure 4. Forrest plots. Forrest plots of hypoxia (**A**) and hyperoxia (**B**) studies. The estimate assessed is the odds ratio of death with hypoxia/hyperoxia. I^2 is the measure of heterogeneity. The width of the horizontal line for each study represents 95% CI. The *red vertical dashed line* represents the overall odds of death. The *blue rhomboid* represents the 95% CI of the overall odds ratio. Ctrl = control, Ev = event, Trt = treatment.

Risk of Bias Across Studies

The funnel plots of both hypoxia and hyperoxia studies suggest a publication bias. (**Supplemental Digital Content 10**, http://links.lww.com/PCC/A297)

DISCUSSION

Our cohort study demonstrates a quadratic (*U*-shaped) relationship between admission PaO_2 and mortality in critically ill children. As the PaO_2 increased the difference between SMR and mSMR ceased to exist. Thus, the influence of PaO_2 on PIM2 predicted risk of death is higher in the hypoxic range than the hyperoxic range. The systematic review indicates worse outcome with hypoxia compared to normoxia.

Hypoxia has a detrimental effect in critically ill children. This effect has been best described in the context of TBI (30, 31). Our findings support international recommendations on the management of TBI in children (32).

The effect of hyperoxia on the outcome in various critically ill patient subgroups was recently reported (7, 33). However, this relationship lacks widespread agreement (34). There was no evidence of the increased mortality with hyperoxia in the overall population of critically ill children in our study. Of note, the odds of death with hyperoxia increased insignificantly in children admitted following CA. This is consistent with the adult reports (12).

The *U*-shaped relationship between admission PaO_2 and mortality from our study differs from the inverse relationship between PaO_2 and mortality in the PIM2 model. There may be two explanations

TABLE 1. List of Hyperoxia Studies Included in the Systematic Review (Type of Study, Age Group of Patients, Thresholds Employed for the Intervention and Control Group, Sample Size, and Outcome are Described)

References	Design	Threshold for Hyperoxia, Pao_2	Threshold for Hypoxia, Pao_2	Control	Age	Sample Size	Outcome
Postcardiac arrest patients							
Del Castillo et al (15)	Prospective cohort study	> 300 mm Hg (40 kPa)	< 60 mm Hg (8 kPa)	Normoxia	1 mo to 18 yr	223	In-hospital mortality
Ferguson et al (16)	Retrospective cohort study	> 300 mm Hg (40 kPa)	< 60 mm Hg (8 kPa)	Normoxia	< 16 yr	1,875	In-PICU mortality
Guerra-Wallace et al (17)	Retrospective cohort study	> 300 mm Hg (40 kPa)	< 60 mm Hg (8 kPa)	Normoxia	< 18 yr	74	Mortality at 6 mo
Puiman et al (18)	Retrospective cohort study	> 300 mm Hg (40 kPa)	None	Normoxia	Unclear	67	In-hospital mortality
Bennett et al (19)	Retrospective cohort study	> 200 mm Hg (26.7 kPa)	< 50 mm Hg (4 kPa)	Normoxia	24 hr to 18 yr	195	In-hospital mortality
Van Zellem et al (20)	Retrospective cohort study	> 300 mm Hg (40 kPa)	< 60 mm Hg (8 kPa)	Normoxia	> 28 d to 18 yr	200	In-hospital mortality
Traumatic brain injury patients							
Michaud et al (21)	Retrospective cohort study	> 350 mm Hg (46 kPa)	< 105 mm Hg (13.8 kPa)	Normoxia	< 16 yr	75	In-hospital mortality
Ramaiah et al (22)	Retrospective cohort study	> 300 mm Hg (40 kPa)	< 60 mm Hg (8 kPa)	Normoxia	< 14 yr	194	In-hospital mortality

TABLE 2. List of Hypoxia Studies Included in the Systematic Review (Type of Study, Age Group, Etiology, Thresholds Employed for the Intervention and Control Group, Sample Size, and Outcome are Described)

References	Design	Threshold for Hypoxia Peripheral O_2 Saturations or Pao_2	Control	Age, yr	Etiology	Sample Size	Outcome
Smyth et al (23)	Prospective observational cohort study	< 92%	≥ 92%	< 5	LRTI	158	Survival to hospital discharge
Onyango et al (24)	Prospective observational cohort study	< 90%	≥ 90%	< 3	LRTI	256	Survival on day 5
Orimadegun et al (25)	Prospective cohort study	≤ 90%	> 90%	< 15	LRTI	1,726	Survival to hospital discharge
Orimadegun et al (26)	Prospective cohort study	< 90%	≥ 90%	< 5	Malaria	369	Survival to hospital discharge
Chisti et al (27)	Prospective cohort study	< 90%	≥ 90%	< 5	Diarrhoea	258	Survival to hospital discharge
Chisti et al (28)	Prospective unmatched case-control study	< 90%	≥ 90%	< 5	LRTI	148	Survival to hospital discharge
Pigula et al (29)	Prospective cohort study	Pao_2 < 60 mm Hg	> 60 mm Hg	< 17	Traumatic brain injury	451	Survival to hospital discharge

LRTI = lower respiratory tract infection.

to this apparent dissimilarity. Although hyperoxic children seem to have a higher crude mortality, the relationship may not be causal. They are hyperoxic because clinicians recognize them as being sick and are reluctant to wean oxygen. Alternatively, PIM2 may need to have a modified coefficient for hypoxia and hyperoxia.

LIMITATIONS

The retrospective design and heterogeneous patient population with different mechanisms for hypoxia or hyperoxia make interpretation of the results difficult. We focused on the relationship between Pa_{O_2} and mortality. While Pa_{O_2} is a marker of alveolar gas exchange, tissue oxygen delivery is influenced by various factors, including hematocrit, macro and microcirculatory variables. The effect of ventilatory strategy on Pa_{O_2} was not explored. We did not seek to investigate association between Pa_{O_2} and attributed cause of death. We felt this analysis would be confounded by wide variability in practice in the recorded cause of death.

A more detailed analysis of the distribution and severity of organ failures with Pa_{O_2} would be of interest and will be the subject of future work. However, we would hypothesize that multiple organ failure would be present at both extremes—since organ dysfunction can be secondary to hypoxia or increased reactive oxygen species during hyperoxia. The picture is further complicated by the contribution from any iatrogenic injury from more aggressive treatments.

Finally, we accept that the mode of death and withdrawal of care due to ongoing hypoxia may introduce bias to our association. In the systematic review, the possibility of selection bias within each study is high. The funnel plots suggest some reporting bias.

Nearly all the studies explore the relationship of Pa_{O_2} either less than 60 torr (8 kPa) or greater than 300 torr (40 kPa) on mortality suggesting an inherent bias in the setting up of Pa_{O_2} thresholds for the cohorts. Most of the studies included in this review have small sample sizes (< 200 patients). This further limits the generalizability of the results. However, despite these limitations, our study would inform future studies in this area.

CONCLUSIONS

Our systematic review suggests that avoiding hypoxia is beneficial in all critically ill children, particularly in the TBI subgroup. Whether hyperoxia has an association with mortality is not clear. Thresholds for hyperoxia may have to differ depending on age, pre-ICU condition, and the disease process among other factors. Adequate oxygenation based on objective end organ perfusion indices may be more important than a single Pa_{O_2} value at admission to ICU. The cohort study displays a *U*-shaped admission Pa_{O_2}-mortality relationship that warrants further scrutiny.

ACKNOWLEDGMENTS

We thank Dr. Erika Fink for providing patient level data from their study (17).

REFERENCES

1. Eastwood G, Bellomo R, Bailey M, et al: Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med* 2012; 38:91–98
2. Choi WI, Shehu E, Lim SY, et al; Korean Study group on Respiratory Failure (KOSREF): Markers of poor outcome in patients with acute hypoxemic respiratory failure. *J Crit Care* 2014; 29:797–802
3. Gray FD Jr, Horner GJ: Survival following extreme hypoxemia. *JAMA* 1970; 211:1815–1817
4. Grocott MP, Martin DS, Levett DZ, et al; Caudwell Xtreme Everest Research Group: Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; 360:140–149
5. Damiani E, Adrario E, Girardis M, et al: Arterial hyperoxia and mortality in critically ill patients: A systematic review and meta-analysis. *Crit Care* 2014; 18:711
6. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, et al: Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. *Crit Care* 2015; 19:348
7. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, et al: Association between arterial hyperoxia and outcome in subsets of critical illness: A systematic review, meta-analysis, and meta-regression of cohort studies. *Crit Care Med* 2015; 43:1508–1519
8. de Jonge E, Peelen L, Keijzers PJ, et al: Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008; 12:R156
9. Martin DS, Grocott MP: Oxygen therapy in critical illness: Precise control of arterial oxygenation and permissive hypoxemia. *Crit Care Med* 2013; 41:423–432
10. Panwar R, Hardie M, Bellomo R, et al; CLOSE Study Investigators; ANZICS Clinical Trials Group: Conservative versus liberal oxygenation targets for mechanically ventilated patients. A Pilot Multicenter Randomized Controlled Trial. *Am J Respir Crit Care Med* 2016; 193:1–51
11. Cunningham S, Rodriguez A, Adams T, et al; Bronchiolitis of Infancy Discharge Study (BIDS) group: Oxygen saturation targets in infants with bronchiolitis (BIDS): A double-blind, randomised, equivalence trial. *Lancet* 2015; 386:1041–1048
12. Kilgannon JH, Jones AE, Shapiro NI, et al; Emergency Medicine Shock Research Network (EMShockNet) Investigators: Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010; 303:2165–2171
13. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009; 6:e1000097
14. Wallace, Byron C., Issa J. et al: Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Software* 2012; 49:5
15. Del Castillo J, López-Herce J, Matamoros M, et al; Iberoamerican Pediatric Cardiac Arrest Study Network RIBEPCI: Hyperoxia, hypocapnia and hypercapnia as outcome factors after cardiac arrest in children. *Resuscitation* 2012; 83:1456–1461
16. Ferguson LP, Durward A, Tibby SM: Relationship between arterial partial oxygen pressure after resuscitation from cardiac arrest and mortality in children. *Circulation* 2012; 126:335–342
17. Guerra-Wallace MM, Casey FL 3rd, Bell MJ, et al: Hyperoxia and hypoxia in children resuscitated from cardiac arrest. *Pediatr Crit Care Med* 2013; 14:e143–e148
18. Puiman P, Van Zellem L, De Jager E, et al: Hyperoxia in children treated with therapeutic hypothermia after cardiac arrest: Does it increase mortality? *Intensive Care Med* 2013; 39(Suppl 1):1–200
19. Bennett KS, Clark AE, Meert KL, et al; Pediatric Emergency Care Medicine Applied Research Network: Early oxygenation and ventilation measurements after pediatric cardiac arrest: Lack of association with outcome. *Crit Care Med* 2013; 41:1534–1542
20. van Zellem L, de Jonge R, van Rosmalen J, et al: High cumulative oxygen levels are associated with improved survival of children treated with mild therapeutic hypothermia after cardiac arrest. *Resuscitation* 2015; 90:150–157

21. Michaud LJ, Rivara FP, Grady MS, et al: Predictors of survival and severity of disability after severe brain injury in children. *Neurosurgery* 1992; 31:254–264
22. Ramaiah VK, Sharma D, Ma L, et al: Admission oxygenation and ventilation parameters associated with discharge survival in severe pediatric traumatic brain injury. *Childs Nerv Syst* 2013; 29:629–634
23. Smyth A, Carty H, Hart CA: Clinical predictors of hypoxaemia in children with pneumonia. *Ann Trop Paediatr* 1998; 18:31–40
24. Onyango FE, Steinhoff MC, Wafula EM, et al: Hypoxaemia in young Kenyan children with acute lower respiratory infection. *BMJ* 1993; 306:612–615
25. Orimadegun AE, Ogunbosi BO, Carson SS: Prevalence and predictors of hypoxaemia in respiratory and non-respiratory primary diagnoses among emergently ill children at a tertiary hospital in south western Nigeria. *Trans R Soc Trop Med Hyg* 2013; 107:699–705
26. Orimadegun AE, Babatunde O, Bose O, et al: Hypoxemia predicts death from severe falciparum malaria among children under 5 years of age in Nigeria: The need for pulse oximetry in case management. *Afr Health Sci* 2014; 14:397–407
27. Chisti MJ, Duke T, Robertson CF, et al: Clinical predictors and outcome of hypoxaemia among under-five diarrhoeal children with or without pneumonia in an urban hospital, Dhaka, Bangladesh. *Trop Med Int Health* 2012; 17:106–111
28. Chisti MJ, Salam MA, Ashraf H, et al: Clinical risk factors of death from pneumonia in children with severe acute malnutrition in an urban critical care ward of Bangladesh. *PLoS One* 2013; 8:e73728
29. Pigula FA, Wald SL, Shackford SR, et al: The effect of hypotension and hypoxia on children with severe head injuries. *J Pediatr Surg* 1993; 28:310–314; discussion 315
30. Mayer TA, Walker ML: Pediatric head injury: The critical role of the emergency physician. *Ann Emerg Med* 1985; 14:1178–1184
31. Ong L, Selladurai BM, Dhillon MK, et al: The prognostic value of the Glasgow Coma Scale, hypoxia and computerised tomography in outcome prediction of pediatric head injury. *Pediatr Neurosurg* 1996; 24:285–291
32. Adelson PD, Bratton SL, Carney NA, et al; American Association for Surgery of Trauma; Child Neurology Society; International Society for Pediatric Neurosurgery; International Trauma Anesthesia and Critical Care Society; Society of Critical Care Medicine; World Federation of Pediatric Intensive and Critical Care Societies: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 4. Resuscitation of blood pressure and oxygenation and prehospital brain-specific therapies for the severe pediatric traumatic brain injury patient. *Pediatr Crit Care Med* 2003; 4:S12–S18
33. Asfar P, Singer M, Radermacher P: Understanding the benefits and harms of oxygen therapy. *Intensive Care Med* 2015; 41:1118–1121
34. Akca O: Hyperoxia: Is it a biomarker for mortality? *Intensive Care Med* 2015; 41:1873–1874