Inadequate Oxygen Delivery Dose and Major Adverse Events in Critically Ill Children With Sepsis

By Katie L. Roy, DNP, Anna Fisk, PhD, Peter Forbes, MA, Conor C. Holland, BEng, Sara R. Schenkel, MPH, Sally Vitali, MD, and Michele DeGrazia, PhD

Background The inadequate oxygen delivery (IDo_2) index is used to estimate the probability that a patient is experiencing inadequate systemic delivery of oxygen. Its utility in the care of critically ill children with sepsis is unknown.
Objective To evaluate the relationship between IDo_2 dose and major adverse events, illness severity metrics, and outcomes among critically ill children with sepsis.
Methods Clinical and IDo_2 data were retrospectively collected from the records of 102 critically ill children with sepsis, weighing >2 kg, without preexisting cardiac dysfunction. Descriptive, nonparametric, odds ratio, and correlational statistics were used for data analysis.
Results Inadequate oxygen delivery doses were significantly higher in patients who experienced major adverse events (n=13) than in those who did not (n=89) during the time intervals of 0 to 12 hours ($P<.001$), 12 to 24 hours ($P=.01$), 0 to 24 hours ($P<.001$), 0 to 36 hours ($P<.001$), and 0 to 48 hours ($P<.001$). Patients with an IDo_2 dose at 0 to 12 hours at or above the 80th percentile had the highest odds of a major adverse event (odds ratio, 23.6; 95% CI, 5.6-99.4). Significant correlations were observed between IDo_2 dose at 0 to 12 hours and day 2 maximum vasoactive inotropic score ($\rho=0.27$, $P=.006$), day 1 Pediatric Logistic Organ Dysfunction (PELOD-2) score ($\rho=0.41$, $P<.001$), day 2 PELOD-2 score ($\rho=0.44$, $P<.001$), intensive care unit length of stay ($\rho=0.35$, $P<.001$), days receiving invasive ventilation ($\rho=0.42$, $P<.001$), and age ($\rho=-0.47$, $P<.001$).
Conclusions Routine IDo_2 monitoring may identify critically ill children with sepsis who are at the highest risk of adverse events and poor outcomes. (*American Journal of Critical Care.* 2022;31:220-228)

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Sepsis is a common cause of pediatric morbidity and mortality around the world, with an estimated 1.2 million cases of pediatric sepsis and 3 million cases of neonatal sepsis per year.[1,2] In the United States, sepsis-associated mortality may reach 30% among children with septic shock who require intensive care.[2,3] Morbidity is similarly substantial. Among a sample of critically ill children with community-acquired septic shock, 35% of survivors had not regained their baseline health-related quality of life after 1 year.[4]

Given such devastating effects, the World Health Organization has recognized reducing sepsis as a global health priority and has adopted a resolution urging the pursuit of technologically innovative research to support sepsis management.[5,6] An emerging and promising prospect in this regard is the arena of predictive analytics. The inadequate oxygen delivery (IDo_2) index is a predictive algorithm developed by Etiometry Inc that synthesizes physiological and laboratory measures to estimate the probability that a patient is experiencing inadequate systemic delivery of oxygen (Do_2).[7]

In shock states, such as septic shock, an imbalance between Do_2 and oxygen consumption portends tissue hypoxia and organ dysfunction.[8] Venous oxygen saturation (Svo_2) and central venous oxygen saturation ($Scvo_2$) serve as indicators of this balance.[8] Although guidelines for sepsis management in adults no longer recommend targeted $Scvo_2$ therapy in the context of early goal-directed therapy amid a lack of supportive evidence, some pediatric studies have demonstrated the value of targeted $Scvo_2$ therapy in reducing mortality.[9-11] Sankar et al[10] found that among children with septic shock and low $Scvo_2$ at admission, only those in whom this value normalized to greater than 70% within the first 6 hours survived. Tools that continuously reflect $Scvo_2$ or Svo_2, such as the IDo_2 index, may allow early and ongoing risk stratification of children with sepsis and septic shock.

The IDo_2 index has been approved as a medical device by the US Food and Drug Administration for use in postsurgical patients aged 0 to 12 years with weight greater than 2 kg.[7] The utility of the IDo_2 index in patients older than 12 years has yet to be determined but deserves examination. Investigation of its applicability to those with sepsis is also warranted, as insufficient Do_2 is a critical determinant of sepsis-associated tissue hypoperfusion. Minimum data required for the IDo_2 index are heart rate every 60 seconds, oxygen saturation via pulse oximetry every 10 minutes, and arterial blood pressure every 10 minutes. If data are available, the algorithm will also use arterial oxygen saturation, Svo_2, hemoglobin level, temperature, regional oxygenation, and filling pressures.[7]

> Sepsis-associated mortality can reach 30% in children with septic shock who require intensive care.

Patient data are collected by Etiometry's T3 Data Aggregation and Visualization software and then filtered through the IDo_2 algorithm (Figure 1). The algorithm uses a software model of human physiology and estimation theory to compute the likelihood that Svo_2 is below a particular level, typically 40%.[7] Values of the IDo_2 index range from 0 to 100, with higher values indicating greater risk that the patient's Svo_2 is below the selected level.[7] The IDo_2 index values are computed every 5 seconds and can be displayed in real time at the bedside, providing an advantage over intermittent $Scvo_2$ or Svo_2 levels, which require central venous access for collection. The IDo_2 dose is calculated retrospectively and is an average of all IDo_2 index values over a specified time interval.

To date, the IDo_2 index has been used primarily in pediatric cardiac surgery patients, who may have

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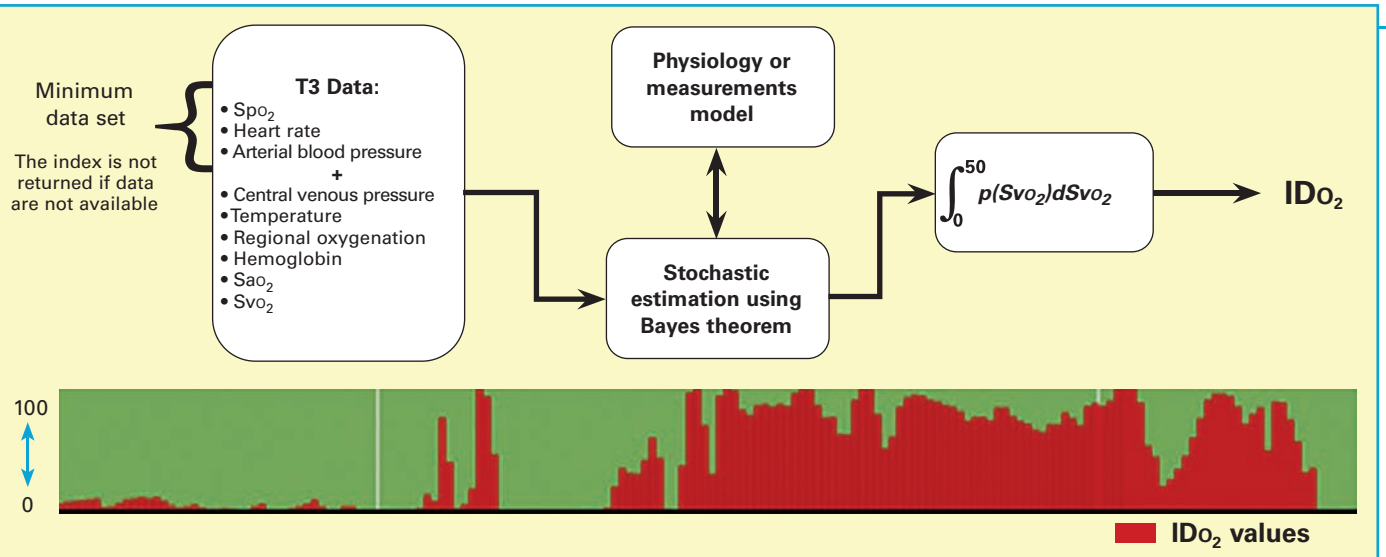

Figure 1 Flowchart of IDo_2 algorithm with graph of IDo_2 values. Red peaks indicate greater patient risk of Svo_2 below the selected level.

Abbreviations: IDo_2, inadequate oxygen delivery; Sao_2, arterial oxygen saturation; Spo_2, oxygen saturation as measured by pulse oximetry; Svo_2, venous oxygen saturation.

limited ability to increase cardiac output and systemic Do_2 in response to increased oxygen demand.[12] Single-ventricle and mixing lesions may similarly result in obligate arterial desaturation with reduced Do_2 and Svo_2.[12,13] A recent study by Dewan et al,[14] however, demonstrated good performance of the IDo_2 index in a general pediatric intensive care unit (PICU) sample in which the IDo_2 index indicated the probability that Svo_2 was below the level of 50%, instead of 40%. The 50% level may serve to enhance the sensitivity of the IDo_2 index among noncardiac populations.

The purpose of this retrospective study was to evaluate the relationship between IDo_2 dose during the first 48 hours of admission to the PICU and major adverse events (MAEs), illness severity metrics, and outcomes among critically ill children with sepsis, severe sepsis, or septic shock. In this study, IDo_2 dose indicated the probability that Svo_2 was below the level of 50%. We calculated IDo_2 doses for 4 discrete time intervals: 0 to less than 12 hours, 12 to less than 24 hours, 24 to less than 36 hours, and 36 to less than 48 hours (hereinafter referred to as 0-12, 12-24, 24-36, and 36-48 hours). We also calculated IDo_2 doses for 4 cumulative time intervals: 0 to less than 12 hours, 0 to less than 24 hours, 0 to less than 36 hours, and 0 to less than 48 hours (hereinafter referred to as 0-12, 0-24, 0-36, and 0-48 hours). Major adverse events were defined as cardiac arrest requiring chest compressions, extracorporeal membrane oxygenation (ECMO) cannulation, and all-cause 28-day mortality. Illness severity metrics included maximum vasoactive-inotropic score (VIS) and organ dysfunction as measured by the Pediatric Logistic Organ Dysfunction version 2 (PELOD-2) score.[15-18] Outcomes included PICU length of stay (LOS) and days receiving invasive ventilation.

Study patients were <18 years of age with an admission diagnosis of sepsis, severe sepsis, or septic shock.

Methods

This retrospective, observational study was granted exempt status from the hospital and university institutional review boards; procedures were implemented so that the identities of human participants could not be easily ascertained.

Setting and Sample

The study sample consisted of critical care patients aged 0 to less than 18 years admitted to a 30-bed medical-surgical ICU or a 22-bed medical ICU at a large quaternary academic children's hospital from January 1, 2017, to November 1, 2019, with an admission diagnosis of sepsis, severe sepsis, or septic shock. An additional inclusion criterion was the presence of an arterial catheter to obtain frequent blood pressure readings required for IDo_2 calculations. Exclusion criteria were preexisting cardiac dysfunction unrelated to sepsis and weight less than or equal to 2 kg.

Data Collection and Study Design

The medical-surgical ICU and medical ICU patient databases were searched to identify patients meeting study criteria. Those with an admission diagnosis of sepsis, severe sepsis, or septic shock were evaluated by a member of the research team

to confirm consistency with definitions established by the 2005 Pediatric Sepsis Consensus Conference.[19] Specifically, sepsis requires the presence of at least 2 of the age-specific systemic inflammatory response syndrome criteria, including either abnormal temperature or abnormal leukocyte count, in the context of infection. Severe sepsis requires the presence of sepsis with either cardiovascular organ dysfunction or acute respiratory distress syndrome, or 2 or more noncardiovascular organ system dysfunctions. Septic shock requires the presence of sepsis with cardiovascular organ dysfunction including hypotension, need for vasoactive medications, or objective signs of impaired perfusion.

Medical records were reviewed to obtain data on demographics, admission diagnoses, MAEs, PICU LOS, and days receiving invasive ventilation. Maximum VIS and PELOD-2 scores were calculated on days 1 (0-24 hours) and 2 (24-48 hours) of admission. Additional clinical indicators including peak lactate level, minimum hemoglobin level, and total volume of red blood cell transfusions and fluid boluses were also collected for the first 48 hours of PICU admission. Data were entered into Research Electronic Data Capture (REDCap) version 9.5 (Vanderbilt University) and exported into SAS software version 9.4 (SAS Institute). The IDo_2 doses of deidentified study patients were retrospectively calculated by Etiometry for the 4 discrete and 4 cumulative time intervals. The IDo_2 doses were exported into Excel (Microsoft) and then combined with demographic and clinical characteristics in SAS for analysis.

Statistical Analysis

Descriptive statistics were used to illustrate demographic and clinical characteristics. The Wilcoxon rank sum 2-sample test was used to compare the IDo_2 dose between groups with and without MAEs. The risk of MAEs for patients with an IDo_2 dose above versus below various percentile thresholds was quantified with odds ratios and 95% CIs. Spearman correlations were used to determine whether IDo_2 dose was related to illness severity metrics and outcomes, specifically maximum VIS, PELOD-2 scores, PICU LOS, and days receiving invasive ventilation. The threshold for statistical significance was set at P less than .05.

Results

A total of 102 patients were identified for study inclusion. Demographic and clinical characteristics are presented in Table 1. Thirteen patients experienced MAEs, and 3 of the 13 experienced more than 1 MAE. All cases of cardiac arrest requiring chest compressions and cannulation for ECMO occurred within the first 48 hours of admission. Comparing the groups with (n = 13) and without (n = 89) MAEs, the MAE group had a significantly lower mean hemoglobin level, a higher volume of red blood cell transfusions, a higher day 1 VIS, higher day 1 and day 2 PELOD-2 scores, a longer mean PICU stay, and a greater mean number of days receiving invasive ventilation. Of note, PICU LOS and invasive ventilator days were exclusive of those who required invasive ventilatory support at baseline, as those patients were ineligible for discontinuation of invasive ventilation and were required to remain in the PICU in accordance with the policy of the study institution.

The IDo_2 doses for the sample ranged from 0 to 79.81. The IDo_2 doses were significantly higher in patients with MAEs than in those without MAEs for the time intervals of 0 to 12 hours (mean, 17.91 vs 3.36; $P < .001$), 12 to 24 hours (mean, 9.08 vs 1.84; $P = .01$), 0 to 24 hours (mean, 12.65 vs 2.56, $P < .001$), 0 to 36 hours (mean, 9.26 vs 2.33; $P < .001$), and 0 to 48 hours (mean, 7.54 vs 2.20; $P < .001$) (Figure 2, Table 2). Figure 3 shows odds ratios for MAEs based on an IDo_2 dose above versus below various percentile thresholds for the 4 discrete time intervals. Odds of a MAE were greatest when the IDo_2 dose at 0 to 12 hours was at or above the 80th percentile dose for the sample population (odds ratio, 23.6; 95% CI, 5.6-99.4).

> IDo_2 doses were significantly higher in patients with major adverse events.

Spearman correlations were used to examine the time interval of 0 to 12 hours in more detail. Significant correlations were observed between the IDo_2 dose at 0 to 12 hours and each of the following: day 2 maximum VIS ($\rho = 0.27$, $P = .006$), day 1 PELOD-2 score ($\rho = 0.41$, $P < .001$), day 2 PELOD-2 score ($\rho = 0.44$, $P < .001$), PICU LOS ($\rho = 0.35$, $P < .001$), and days receiving invasive ventilation ($\rho = 0.42$, $P < .001$) (Table 3). The relationship between IDo_2 dose at 0 to 12 hours and day 1 maximum VIS ($\rho = 0.18$, $P = .07$) approached but did not reach statistical significance. A significant negative correlation was observed between IDo_2 dose at 0 to 12 hours and age ($\rho = -0.47$, $P < .001$). Additional assessment of the age effect revealed that the majority (62%) of those who experienced MAEs were less than 2 years of age, and the majority (62%) of those with IDo_2 dose at 0 to 12 hours at or above the 80th percentile were also less than 2 years of age.

Table 1
Demographic and clinical characteristics

Characteristic	All patients (N=102)	Patients with major adverse events (n=13)	Patients without major adverse events (n=89)	*P*
Sex, No. (%) of patients				.77
Male	56 (55)	8 (62)	48 (54)	
Female	46 (45)	5 (38)	41 (46)	
Race, No. (%) of patients				.83
White	41 (40)	7 (54)	34 (38)	
Hispanic/Latino	18 (17)	2 (15)	16 (18)	
Black	10 (10)	1 (8)	9 (10)	
Asian	10 (10)	0 (0)	10 (11)	
Other	7 (7)	0 (0)	7 (8)	
Unknown	16 (16)	3 (23)	13 (15)	
Age, mean (range), y	8.9 (0.0-17.9)	4.0 (0.0-15.3)	9.6 (0.0-17.9)	.001
Age in years, No. (%) of patients				.007
0 to <2	22 (22)	8 (62)	14 (16)	
2 to <6	13 (13)	1 (8)	12 (13)	
6 to <13	38 (37)	2 (15)	36 (40)	
13 to <18	29 (28)	2 (15)	27 (30)	
Sepsis diagnosis, No. (%) of patients				>.99
Sepsis/severe sepsis	18 (17.6)	2 (15)	16 (18)	
Septic shock	84 (82.4)	11 (85)	73 (82)	
Lowest hemoglobin level in first 48 h, mean (range), g/dL	8.6 (5.0-12.1)	7.9 (6.7-9.3)	8.8 (5.0-12.1)	.03
RBC transfusion volume in first 48 h, mean (range), mL/kg	6.1 (0.0-50.0)	22.3 (0.0-50.0)	3.7 (0.0-30.0)	<.001
Fluid bolus volume (not RBCs) in first 48 h, mean (range), mL/kg	25.8 (0.0-165.0)	35.3 (0.0-128.0)	24.4 (0.0-165.0)	.28
Peak lactate level in first 48 h, mean (range), mmol/L	4.4 (0.7-29.0)	7.9 (1.3-29.0)	3.9 (0.7-17.0)	.11
PICU LOS,[a] mean (range), d	10.9 (<1.0-63.0)	18.2 (2.0-46.0)	10.1 (<1.0-63.0)	.04
Invasive ventilator days,[a] mean (range)	5.9 (<1.0-62.0)	15.5 (2.0-42.0)	4.9 (<1.0-62.0)	<.001
Received fluid before PICU admission, No. (%) of patients	89 (87)	8 (62)	81 (91)	.01
Cardiac arrest,[b] No. (%) of patients	4 (4)	4 (31)	0 (0)	NA
ECMO cannulation, No. (%) of patients				NA
Venoarterial	6 (6)	6 (46)	0 (0)	
Venovenous	1 (1)	1 (8)	0 (0)	
28-day mortality, No. (%) of patients	5 (5)	5 (38)	0 (0)	NA
VIS day 1, mean (range)	24.6 (0.0-170.0)	43.6 (0.0-170.0)	21.3 (0.0-90.0)	.03
VIS day 2, mean (range)	9.1 (0.0-105.0)	7.0 (0.0-26.0)	9.4 (0.0-105.0)	.86
PELOD-2 score day 1, mean (range)	7.7 (0.0-29.0)	13.8 (9.0-29.0)	6.8 (0.0-21.0)	<.001
PELOD-2 score day 2, mean (range)	6.0 (0.0-23.0)	10.8 (5.0-23.0)	5.3 (0.0-12.0)	<.001

Abbreviations: ECMO, extracorporeal membrane oxygenation; LOS, length of stay; NA, not applicable; PICU, pediatric intensive care unit; PELOD-2, Pediatric Logistic Organ Dysfunction version 2; RBC, red blood cell; VIS, vasoactive-inotropic score.

[a] PICU LOS and invasive ventilator days excluded patients who were receiving invasive ventilation at baseline (9 excluded).
[b] Cardiac arrest required chest compressions.

Discussion

In this retrospective, observational study of critically ill children with sepsis, several statistically significant relationships were found between IDo_2 dose and MAEs, illness severity metrics, and outcomes. Specifically, patients with MAEs had higher IDo_2 doses over multiple time intervals, and an IDo_2 dose at 0 to 12 hours at or above the 80th percentile was associated with the greatest odds of experiencing a MAE. Additionally, there were significant correlations between IDo_2 dose at 0 to 12 hours and day 2 maximum VIS, organ dysfunction as measured by PELOD-2 score, PICU LOS, and days receiving invasive ventilation.

Although this is the first study to examine IDo_2 dose in critically ill children with sepsis,

investigators have reported similar encouraging findings in other pediatric populations. Futterman et al[20] found that among neonates with congenital heart disease who had undergone cardiopulmonary bypass surgery, higher IDo_2 dose was associated with increased risk of cardiac arrest during a 120-minute monitoring window that terminated 10, 20, or 30 minutes before the cardiac arrest. Although the current study did not examine IDo_2 dose just proximal to the MAE, it did identify the time interval of 0 to 12 hours to be particularly valuable. Sankar et al[10] similarly emphasized the importance of early $Scvo_2$ monitoring among children with septic shock, as they found that only those in whom $Scvo_2$ normalized within the first 6 hours of admission survived. In the future, IDo_2 monitoring at the bedside may be most critical early in the sepsis trajectory.

In contrast, Rogers et al[21] examined the IDo_2 index as a predictor of adverse events associated with low cardiac output syndrome in children with congenital heart defects after cardiac bypass and found that IDo_2 dose for the 12 hours following surgery did not have a significant relationship with adverse event occurrence within 72 hours of surgery. Although the small sample of 28 paired cases and controls may have precluded more significant findings, the authors also suggested that high variability of IDo_2 index values in a 12-hour interval can restrict the discriminative capability of the dose, or average value. The current study also used retrospectively

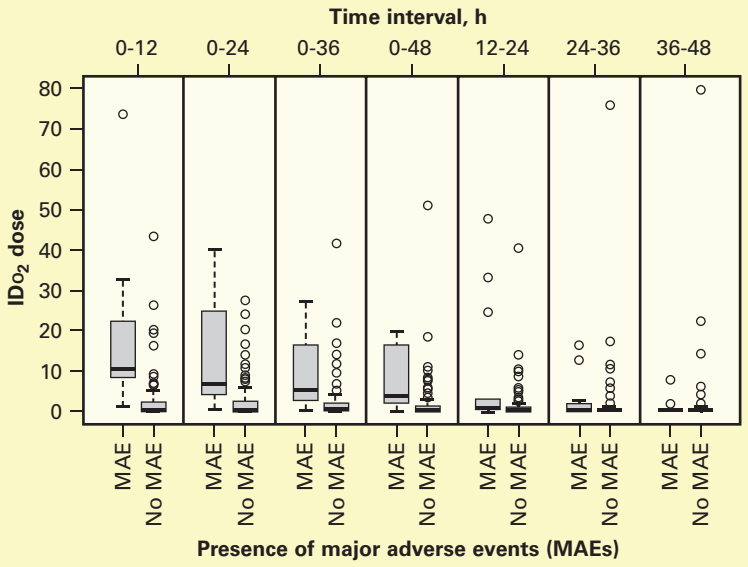

Figure 2 Comparison of inadequate oxygen delivery (IDo_2) dose by time interval between groups with and without major adverse events (MAEs). $P<.05$ for time intervals of 0-12 hours, 0-24 hours, 0-36 hours, 0-48 hours, and 12-24 hours.

calculated IDo_2 doses as a research tool for summarizing the index values, although it is likely that real-time bedside visualization of IDo_2 index values will more accurately reflect the patient's dynamic physiological state. In this way, the clinical team can be alerted to high-risk time periods and trends that prompt early interventions such as broadening antibiotics, administering fluid or inotropes, pursuing more aggressive source control, or electing early

Table 2
Inadequate oxygen delivery dose descriptive and rank sum statistics by time interval between groups with and without major adverse events

Time interval, h	Major adverse event	N	Mean dose	SD	Median	Minimum	Maximum	*P*
0-12	No	89	3.36	7.84	0.37	0.00	43.47	<.001
0-12	Yes	13	17.91	19.55	10.41	1.08	73.69	
0-24	No	89	2.56	5.20	0.29	0.00	27.42	<.001
0-24	Yes	13	12.65	12.56	6.81	0.45	40.19	
0-36	No	89	2.33	5.70	0.35	0.00	41.69	<.001
0-36	Yes	13	9.26	9.32	5.29	0.23	27.19	
0-48	No	89	2.20	6.28	0.30	0.00	50.94	<.001
0-48	Yes	13	7.54	7.66	3.85	0.16	19.72	
12-24	No	88[a]	1.84	5.08	0.18	0.00	40.44	.01
12-24	Yes	13	9.08	15.63	1.19	0.00	47.75	
24-36	No	89	1.88	8.42	0.07	0.00	75.88	.36
24-36	Yes	13	2.67	5.34	0.20	0.00	16.20	
36-48	No	88[a]	1.76	8.92	0.03	0.00	79.81	.52
36-48	Yes	13	1.43	2.86	0.13	0.00	7.90	

[a] No data available for a patient during this time interval.

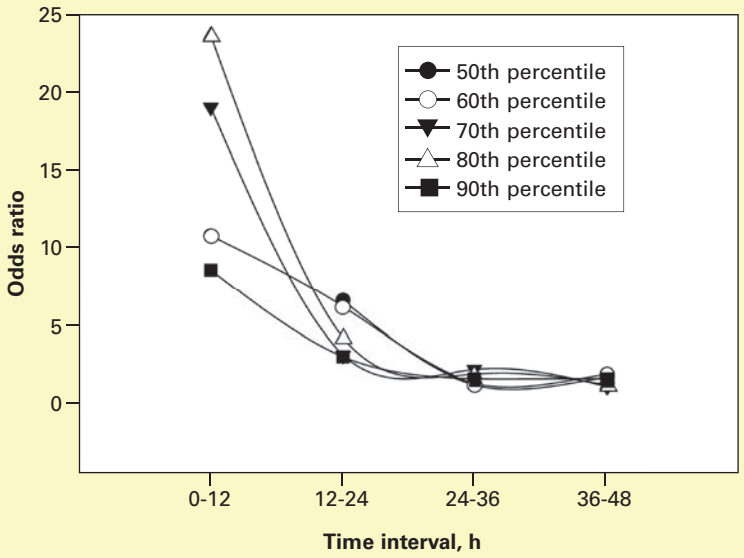

Figure 3 Odds ratios for major adverse events by inadequate oxygen delivery (IDo_2) dose above versus below percentile thresholds across discrete time intervals. (Odds ratio could not be computed for the 50th percentile threshold during the time interval of 0-12 hours because all major adverse events occurred in patients with IDo_2 doses above the 50th percentile during this time interval).

Table 3
Spearman correlations between inadequate oxygen delivery dose at 0 to 12 hours and age, illness severity metrics, and outcomes

Metric/outcome	Sample size (N)	Correlation coefficient (ρ)	*P*
Age	102	–0.47	<.001
VIS, day 1	102	+0.18	.07
VIS, day 2	102	+0.27	.006
PELOD-2 score, day 1	102	+0.41	<.001
PELOD-2 score, day 2	102	+0.44	<.001
PICU LOS[a]	93	+0.35	<.001
Ventilator days[a]	93	+0.42	<.001

Abbreviations: LOS, length of stay; PELOD-2, Pediatric Logistic Organ Dysfunction version 2; PICU, pediatric intensive care unit; VIS, vasoactive-inotropic score.

[a] Excluded patients receiving invasive ventilation at baseline.

advanced mechanical support. Demonstrating this benefit, Salvin et al[22] found that implementation of the IDo_2 index in clinical practice resulted in a significant relative reduction in LOS among neonates after cardiac surgery. Future studies are imperative for measuring interventions and outcomes associated with bedside IDo_2 monitoring of critically ill children with sepsis.

The correlational findings in the current study were also informative. The significant positive correlations between IDo_2 dose at 0 to 12 hours and the outcomes of PICU LOS and days receiving invasive ventilation suggest that IDo_2 dose may facilitate early recognition of patients at risk of extended LOS and ventilator-associated morbidity. In previous research, PELOD-2 score on PICU day 1 has been highly predictive of PICU mortality among children with suspected infection.[23] In the present study, the statistically significant relationship between IDo_2 dose and PELOD-2 scores suggests that IDo_2 dose may similarly identify those children with sepsis who are at highest risk of mortality. The near-continuous generation of IDo_2 index values may be advantageous over PELOD-2 scores, which are calculated manually and only intermittently.

Curiously, the correlation observed between IDo_2 dose at 0 to 12 hours and day 1 maximum VIS approached but did not reach statistical significance. It is possible that treatment strategies for impaired Do_2, including crystalloid resuscitation and colloid administration, preceded and attenuated the need for vasoactive-inotropic support. Additionally, current consensus guidelines lack recommendations for specific mean arterial pressure targets for children with sepsis and septic shock.[24] Ensuing differences in clinical practice could account for variations in VIS and lack of a statistically significant correlation with IDo_2 dose.

The significant negative correlation between IDo_2 dose and age was of particular interest. A possible physiological explanation is that younger children have a tendency toward cold shock,[25] which may yield a lower Svo_2 than warm shock. They may also have subtle, nonspecific symptoms that make it challenging to diagnose infection,[2] and delayed diagnosis may lead to worsening illness severity. Likewise, neonates carry unique physiological considerations including immunological immaturity, increased pulmonary vascular resistance, and immature mechanisms of thermogenesis.[26,27] Previous studies have found multiple organ dysfunction syndrome, often associated with sepsis, and subsequent PICU mortality to be highest in neonates and infants.[28,29] The Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study, however, cited no significant difference in PICU or hospital mortality rates by age among children with severe sepsis.[30] Collectively, these findings demonstrate an ongoing need to investigate the relationship between IDo_2 dose and age among children with sepsis.

Finally, the MAE group had a significantly lower mean hemoglobin level (7.9 g/dL vs 8.8 g/dL, $P = .03$) and higher mean volume of red cell transfusions

(22.3 mL/kg vs 3.7 mL/kg, $P < .001$) than the non-MAE group. The hemoglobin difference may not have been clinically meaningful, as the typical transfusion threshold at the study site is less than 7.0 g/dL. However, volume of red blood cell transfusions was explored as a potential contributor to the occurrence of MAEs, as red blood cell transfusion has been associated with morbidity and mortality in critically ill patients.[31] Further review demonstrated that all but 1 patient requiring 30 mL/kg or greater of red blood cell transfusions had undergone cannulation for ECMO. The other patient suffered acute hemorrhage. Thus, transfusion volume was likely a consequence of the MAE and not a contributor.

Limitations

This study had several limitations in addition to those inherent to a retrospective review of medical records. First, delayed placement or early removal of an arterial catheter, as well as early transfer from the PICU to an inpatient unit, occasionally resulted in less than 48 hours of IDo_2 data. Fortunately, data required to calculate the IDo_2 dose were available for most patients during at least 90% of the study period and no patients were excluded because of missing data. Also, each patient transferred to an inpatient unit within 48 hours of admission had an IDo_2 dose at 0 to 12 hours of less than 1 and experienced no MAEs, further supporting validation of the IDo_2 dose. Second, some study measures may have been influenced by concomitant diagnoses. For example, invasive ventilator days may have been attributable to an accompanying respiratory illness rather than the sepsis condition. Similarly, elevated PELOD-2 scores may have been related to comorbid conditions as opposed to sepsis pathophysiology. Finally, the 95% CI for the odds ratio statistic at the 80th percentile threshold was wide. A larger sample size may have produced a narrower CI, more precise results, and a stronger relationship between IDo_2 dose and VIS.

Conclusion

The results of this study suggest that routine IDo_2 monitoring of critically ill children with sepsis, particularly during the first 12 hours of PICU admission, may help identify those at highest risk so that interventions can be performed to optimize the clinical course. The ability of the IDo_2 index to continuously compile multiple data sources in an environment with a high cognitive workload, such as the PICU, may aid recognition of subtle patient changes that would otherwise go unnoticed. More research is needed to quantify the anticipated clinical benefits of real-time IDo_2 monitoring at the bedside. Future subgroup analysis of those with sepsis, severe sepsis, and septic shock may also offer guidance in the use of the IDo_2 index across the spectrum of sepsis diagnoses. Amid increasing availability of analytic tools to support clinicians in all realms of health care, it is essential to continue to explore how integration of these tools into practice can benefit patients and optimize outcomes.

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Mr Holland is a software engineer at Etiometry Inc. and a credentialed vendor at Boston Children's Hospital. Mr Holland assisted with data collection and manuscript development but was not directly involved in analysis of the data. The remaining authors have nothing to disclose.

SEE ALSO

For more about sepsis in children, visit the *Critical Care Nurse* website, **www.ccnonline.org**, and read the Practice Pointers, "New Sepsis Guidelines Specific to Pediatrics" (August 2020).

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