Respiratory Dysfunction Criteria in Critically Ill Children: The PODIUM Consensus Conference

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abstract

CONTEXT: Respiratory dysfunction is a component of every organ failure scoring system developed, reflecting the significance of the lung in multiple organ dysfunction syndrome. However, existing systems do not reflect current practice and are not consistently evidence based.

OBJECTIVE: We aimed to review the literature to identify the components of respiratory failure associated with outcomes in children, with the purpose of developing an operational and evidence-based definition of respiratory dysfunction.

DATA SOURCES: Electronic searches of PubMed and Embase were conducted from 1992 to January 2020 by using a combination of medical subject heading terms and text words to define respiratory dysfunction, critical illness, and outcomes.

STUDY SELECTION: We included studies of critically ill children with respiratory dysfunction that evaluated the performance of metrics of respiratory dysfunction and their association with patient-centered outcomes. Studies in adults, studies in premature infants (≤36 weeks' gestational age), animal studies, reviews and commentaries, case series with sample sizes ≤10, and studies not published in English in which we were unable to determine eligibility criteria were excluded.

DATA EXTRACTION: Data were abstracted into a standard data extraction form.

RESULTS: We provided binary (no or yes) and graded (no, nonsevere, or severe) definitions of respiratory dysfunction, prioritizing oxygenation and respiratory support. The proposed criteria were approved by 82% of members in the first round, with a score of 8 of 9 (interquartile range 7–8).

LIMITATIONS: Exclusion of non-English publications, heterogeneity across the pediatric age range, small sample sizes, and incomplete handling of confounders are limitations.

CONCLUSIONS: We propose definitions for respiratory dysfunction in critically ill children after an exhaustive literature review.

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Dr Yehya oversaw the design of the systematic review and wrote the first draft; Dr Thomas oversaw the design of the systematic review; Drs Khemani, Erickson, Smith, Rowan, and Ward focused on identification of future research priorities; and all authors performed abstract screening and full-text reviews and edited and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Respiratory dysfunction is a component of every organ failure scoring system developed,[1–4] reflecting the significance of the lung in multiple organ dysfunction syndrome (MODS). In existing scoring systems, pulmonary dysfunction is scored by using metrics of oxygenation and respiratory support,[1–4] with most systems also considering hypercapnia.[1–3] Respiratory dysfunction in the setting of sepsis and MODS shares terminology and an overall conceptual model with acute respiratory distress syndrome (ARDS),[5,6] itself defined as acute noncardiogenic pulmonary edema causing severe hypoxemia. Although detailed imaging criteria, respiratory system compliance, and dead space have been considered in adult ARDS definitions, both the 1994 American-European Consensus Conference[5] and the 2012 Berlin definitions of ARDS[6] retained only hypoxemia and bilateral infiltrates. A major advance of the Berlin definition was clarifying a minimum level of respiratory support. Thus, modern definitions of adult ARDS prioritize hypoxemia, with minimum respiratory support requirements.

However, neither the American-European Consensus Conference definition nor the Berlin definition of ARDS addressed pediatric considerations, despite recognition that the syndrome occurs in children. To address these shortcomings, in 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) developed the first pediatric-specific definitions for pediatric acute respiratory distress syndrome (PARDS),[7] with a subsequent multinational study of PARDS epidemiology validating the PALICC definition.[8] The PALICC definition differed from the Berlin definition in use of more permissive imaging criteria; use of the oxygenation index (OI) instead of the P_{AO_2}/fraction of inspired oxygen (F_{IO_2}) ratio to risk stratify severity of hypoxemia in intubated patients; and explicit use of oxygenation metrics, such as pulse oxygen saturation (S_{PO_2}), given the decreasing prevalence of arterial blood gases (oxygen saturation index [OSI]). Other differences included separate criteria for patients on noninvasive ventilation (NIV), in patients with cyanotic congenital heart disease, and in children with baseline ventilator dependence.

However, although the adult Berlin and pediatric PALICC definitions are accepted for identifying and defining ARDS and PARDS, respectively, they do not capture the more subtle levels of respiratory dysfunction associated with MODS. Moreover, existing definitions of pediatric respiratory dysfunction and PARDS do not address whether the support provided by humidified high-flow nasal cannula (HHFNC), an increasingly commonly used modality, constitute respiratory dysfunction. It is important that definitions of pediatric respiratory dysfunction reflect current practice and, when possible, are evidence based.

Therefore, under the auspices of the Pediatric Organ Dysfunction Information Update Mandate (PODIUM), we aimed to perform a systematic review of the existing literature to identify the components of respiratory failure associated with clinically relevant outcomes in children. On the basis of this review, we propose an operational and evidence-based definition of respiratory dysfunction.

METHODS

The PODIUM collaborative sought to develop evidence-based criteria for organ dysfunction in critically ill children. In the present article, we report on the systematic review on respiratory dysfunction scoring tools performed as part of PODIUM, provide a critical evaluation of the available literature and propose evidence-based criteria for respiratory dysfunction in critically ill children as well as recommendations for future research. The PODIUM executive summary details Population, Interventions, Comparators, and Outcomes questions, search strategies, study inclusion and exclusion criteria, and processes for risk of bias assessment, for data abstraction and synthesis, and for drafting and developing agreement for criteria indicating respiratory dysfunction.[9]

RESULTS

Criteria

Of 4992 unique citations published between 1992 and 2020, 203 studies were eligible for inclusion, as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig 1). Data tables (Supplemental Tables 1 and 2) and risk of bias assessment summaries (Supplemental Fig 1) are detailed in the Supplemental Information, as are proposed research priorities. Criteria for respiratory dysfunction in critically ill children informed by the evaluated evidence are listed in Table 1. We provided both binary (no or yes) and graded (no, nonsevere, or severe) criteria. The definitions prioritized oxygenation and respiratory support, and although there were no specific metrics of ventilation or hypercapnia, respiratory dysfunction from predominantly ventilatory failure was addressed. The proposed criteria were approved by 47 of 56 (82%) voting PODIUM members in the first round, with a score of 8 (interquartile range 7–8, range 3–9), thereby passing the criteria for acceptance.

We propose that as a binary definition, respiratory dysfunction

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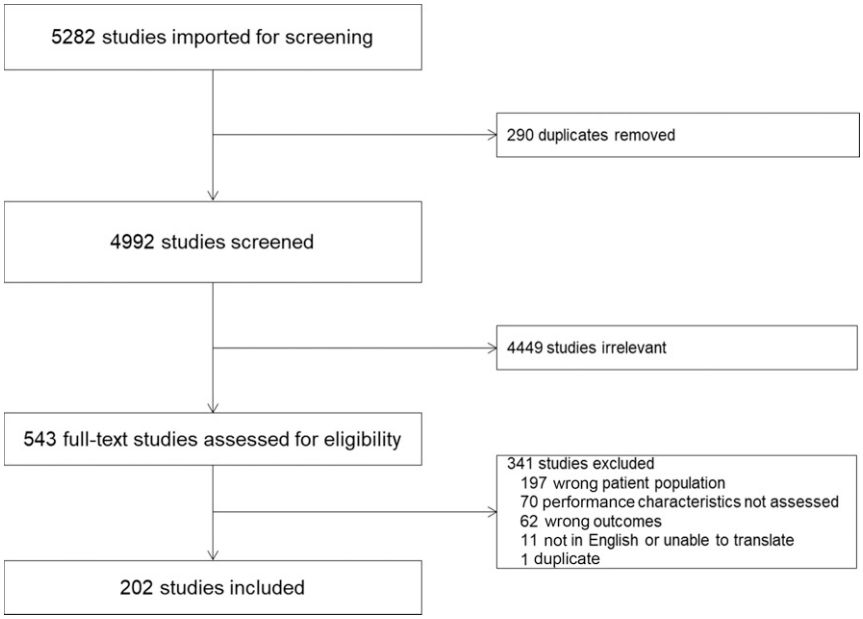

FIGURE 1
Study flow diagram according to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols recommendations.

be separately defined by whether a patient is invasively ventilated. For noninvasively supported patients, minimum respiratory support required to define dysfunction is an HHFNC output of ≥1.5 L/kg per minute (or ≥30 L/minute), NIV, use of a nonrebreather, or use of a venturi mask, with an F_{IO_2} ≥0.4 for all modes. Respiratory dysfunction is defined as a P_{AO_2}/F_{IO_2} ratio of ≤300 or a S_{PO_2}/F_{IO_2} ratio of ≤264 (when 80% ≤ S_{PO_2} ≤ 97%) or NIV for predominantly ventilatory failure (obstructive lung disease without concurrent oxygenation failure). For invasively ventilated patients, respiratory dysfunction is defined as an OI ≥4 or an OSI ≥5 or invasive ventilation for predominantly ventilatory failure or extracorporeal life support (ECLS) for any respiratory failure.

We propose that as a graded definition, respiratory dysfunction be separately defined by whether a patient is invasively ventilated, with severe respiratory dysfunction requiring invasive ventilation. We propose 2 categories for the grading: nonsevere and severe. We propose defining nonsevere respiratory dysfunction for all patients supported with NIV, defined as above, and all invasively ventilated patients with an OI ≥4 to <16 or an OSI ≥5 to <12.3 (when 80% ≤ S_{PO_2} ≤ 97%) or invasive ventilation for predominantly ventilatory failure. We propose defining severe respiratory dysfunction for invasively ventilated patients with an OI ≥16 or an OSI ≥12.3 or ECLS for any respiratory failure.

Rationale for Inclusion

The definition of respiratory dysfunction prioritizes the degree of

TABLE 1 Binary and Graded Criteria for Respiratory Dysfunction in Critically Ill Children

	Respiratory Support	Dysfunction Defined by Hypoxemia	Dysfunction Defined by Support
Binary definition			
Noninvasive (F_{IO_2} ≥ 0.4 in all modes)	HFNC ≥ 1.5 L/kg per min or ≥30 L/min, NIV, nonrebreather, venturi face mask	P_{AO_2}/F_{IO_2} ratio ≤ 300, S_{PO_2}/F_{IO_2} ratio ≤ 264 (when 80% ≤ S_{PO_2} ≤ 97%)	NIV for ventilatory failure
Invasive	Invasive ventilation	OI ≥ 4, OSI ≥ 5 (when 80% ≤ S_{PO_2} ≤ 97%)	Invasively ventilated for ventilatory failure, ECLS for any respiratory failure
Graded definition			
Nonsevere			
Noninvasive (F_{IO_2} ≥ 0.4 in all modes)	HHFNC ≥ 1.5 L/kg per min or HHFNC ≥ 30 L/min, NIV, nonrebreather, venturi face mask	P_{AO_2}/F_{IO_2} ratio ≤ 300, S_{PO_2}/F_{IO_2} ratio ≤ 264 (when 80% ≤ S_{PO_2} ≤ 97%)	NIV for ventilatory failure
Invasive	Invasive ventilation	OI ≥ 4–<16, OSI ≥ 5–<12.3 (when 80% ≤ S_{PO_2} ≤ 97%)	Invasively ventilated for ventilatory failure
Severe			
Invasive	Invasive ventilation	OI ≥ 16, OSI ≥ 12.3 (when 80% ≤ S_{PO_2} ≤ 97%)	ECLS for any respiratory failure

OI = (F_{IO_2} × M_{PAW} × 100)/P_{AO_2}. OSI = (F_{IO_2} × M_{PAW} × 100)/ S_{PO_2}. ECLS, extracorporeal life support; HFNC, high-flow nasal cannula; M_{PAW}, mean airway pressure.

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respiratory support and hypoxemia. We established separate criteria based on whether a subject was invasively ventilated or not, with separate cutoffs for hypoxemia in the definition. Our rationale was predicated on the current state of existing literature, with predictors of outcome defined according to whether a patient was supported with HHFNC, NIV, or invasive ventilation.

The inclusion of NIV for ventilation failure was included as an acknowledgment that respiratory dysfunction can occur from primarily obstructive disease processes affecting carbon dioxide exchange, rather than oxygenation, which do not escalate to invasive ventilation. Conditions such as critical asthma, critical bronchiolitis, bronchopulmonary dysplasia, cystic fibrosis, and bronchiolitis obliterans syndrome can therefore meet criteria for respiratory dysfunction while the patient is on NIV. Although some of these patients will have concurrent hypoxemia sufficient to meet criteria for respiratory dysfunction without this specific category, the entity of primarily obstructive disease causing significant respiratory embarrassment requiring high levels of respiratory support was felt to be inadequately addressed by any definition lacking this specific component. Given the current state of trial evidence revealing NIV to be a higher level of support,[9] we operationalized respiratory dysfunction from ventilation failure to require NIV or invasive ventilation, rather than HHFNC or other modalities. Respiratory dysfunction from ventilation failure should be differentiated from requiring NIV or invasive ventilation for upper airway obstruction or tracheal anomalies.

We propose the use of oxygenation cutoffs provided by PALICC to define PARDS in the definitions of respiratory dysfunction. Multiple studies implicated oxygenation as predictive for outcome in all forms of respiratory failure (Supplemental Table 1). However, specific cutoffs varied substantially. The area under the receiver operating characteristic curve for discriminating mortality ranged between 0.55 and 0.75, depending on the populations being studied and the mortality rate of that cohort. Oxygenation measurements are also simple and reproducible and, with the use of S_{PO_2}, do not require specialized equipment or invasive testing beyond pulse oximetry, making them feasible for all settings. The heterogeneity of these studies precluded a complete synthesis to identify optimal cut points for the P_{AO_2}/F_{IO_2} ratio, S_{PO_2}/F_{IO_2} ratio, OI, or OSI. Thus, to promote concordance with existing and widely accepted consensus criteria, we used the P_{AO_2}/F_{IO_2} ratio and S_{PO_2}/F_{IO_2} ratio cutoffs for HHFNC, NIV, nonrebreathers, and venturi masks and the OI and OSI criteria for invasively ventilated patients established for PALICC PARDS. Thus, all patients with PARDS will meet criteria for respiratory dysfunction. However, we acknowledge that an overreliance on existing PALICC oxygenation cutoffs risks limiting generalizability of our proposed respiratory dysfunction definitions.

We provide both binary and graded definitions. The rationale for the graded definitions was the relatively larger association between initial severe hypoxemia and poor outcome in children by using both adult[11,12] and pediatric definitions[8,12] of ARDS. The inclusion of ECLS for any respiratory failure as a qualifying criterion, without any comment regarding level of respiratory support (invasive or noninvasive) or hypoxemia, is predicated on the use of ECLS for either severe hypoxemic or hypercapnic respiratory failure.[13–15] Importantly, we do not differentiate between venovenous or venoarterial ECMO because other considerations impact precise mode of support.

CONCLUSIONS

We propose consensus criteria for respiratory dysfunction for PODIUM after a structured literature review. We provide both binary and graded definitions, based primarily on level of respiratory support and degree of hypoxemia, with allowance for pure ventilatory failure requiring NIV. For consistency, we attempt to make these proposed definitions congruent with existing PALICC definitions for PARDS.

ABBREVIATIONS

ARDS: acute respiratory distress syndrome
ECLS: extracorporeal life support
F_{IO_2}: fraction of inspired oxygen
HHFNC: humidified high-flow nasal cannula
MODS: multiple organ dysfunction syndrome
NIV: noninvasive ventilation
OI: oxygenation index
OSI: oxygen saturation index
PALICC: Pediatric Acute Lung Injury Consensus Conference
PARDS: pediatric acute respiratory distress syndrome
PODIUM: Pediatric Organ Dysfunction Information Update Mandate
S_{PO_2}: pulse oxygen saturation

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REFERENCES

1. Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2–8
2. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med.* 2013;41(7):1761–1773
3. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest.* 1996;109(4):1033–1037
4. Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a Pediatric Sequential Organ Failure Assessment score and evaluation of the Sepsis-3 definitions in critically ill children. *JAMA Pediatr.* 2017; 171(10):e172352
5. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149(3 pt 1):818–824
6. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307(23):2526–2533
7. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med.* 2015;16(5):428–439
8. Khemani RG, Smith L, Lopez-Fernandez YM, et al; Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) Investigators; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. *Lancet Respir Med.* 2019; 7(2):115–128
9. Bembea MM, Agus M, Akcan-Arikan A, et al. Pediatric organ dysfunction information update mandate (PODIUM) contemporary organ dysfunction criteria: executive summary. *Pediatrics.* 2022;149(suppl 1):e2021052888B
10. Milési C, Essouri S, Pouyau R, et al; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Med.* 2017;43(2):209–216
11. De Luca D, Piastra M, Chidini G, et al; Respiratory Section of the European Society for Pediatric Neonatal Intensive Care (ESPNIC). The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: multicenter evaluation and expert consensus. *Intensive Care Med.* 2013;39(12):2083–2091
12. Yehya N, Servaes S, Thomas NJ. Characterizing degree of lung injury in pediatric acute respiratory distress syndrome. *Crit Care Med.* 2015;43(5):937–946
13. Zabrocki LA, Brogan TV, Statler KD, Poss WB, Rollins MD, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: survival and predictors of mortality. *Crit Care Med.* 2011;39(2):364–370
14. Minneci PC, Kilbaugh TJ, Chandler HK, Behar BJ, Localio AR, Deans KJ. Factors associated with mortality in pediatric patients requiring extracorporeal life support for severe pneumonia. *Pediatr Crit Care Med.* 2013;14(1):e26–e33
15. Rowan CM, Klein MJ, Hsing DD, et al. Early use of adjunctive therapies for pediatric acute respiratory distress syndrome: a PARDIE study. *Am J Respir Crit Care Med.* 2020;201(11):1389–1397

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