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

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abstract

CONTEXT: Renal dysfunction is associated with poor outcomes in critically ill children.

OBJECTIVE: To evaluate the current evidence for criteria defining renal dysfunction in critically ill children and association with adverse outcomes. To develop contemporary consensus criteria for renal dysfunction in critically ill children.

DATA SOURCES: PubMed and Embase were searched from January 1992 to January 2020.

STUDY SELECTION: Included studies evaluated critically ill children with renal dysfunction, performance characteristics of assessment tools for renal dysfunction, and outcomes related to mortality, functional status, or organ-specific or other patient-centered outcomes. Studies with adults or premature infants (≤36 weeks' gestational age), animal studies, reviews, case series, and studies not published in English with inability to determine eligibility criteria were excluded.

DATA EXTRACTION: Data were extracted from included studies into a standard data extraction form by task force members.

RESULTS: The systematic review supported the following criteria for renal dysfunction: (1) urine output <0.5 mL/kg per hour for ≥6 hours and serum creatinine increase of 1.5 to 1.9 times baseline or ≥0.3 mg/dL, or (2) urine output <0.5 mL/kg per hour for ≥12 hours, or (3) serum creatinine increase ≥2 times baseline, or (4) estimated glomerular filtration rate <35 mL/minute/1.73 m^2, or (5) initiation of renal replacement therapy, or (6) fluid overload ≥20%. Data also support criteria for persistent renal dysfunction and for high risk of renal dysfunction.

LIMITATIONS: All included studies were observational and many were retrospective.

CONCLUSIONS: We present consensus criteria for renal dysfunction in critically ill children.

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DOI: https://doi.org/10.1542/peds.2021-052888J

Accepted for publication Sep 24, 2021

Renal dysfunction occurs commonly in critically ill children admitted to the PICU with an incidence of 25%.[1–3] The hallmark of renal dysfunction is a reduced ability to clear waste, regulate electrolytes, and maintain fluid homeostasis. Traditionally, renal dysfunction has been defined on the basis of increased serum creatinine (SCr), oliguria, and the receipt of renal replacement therapy (RRT). Currently, consensus criteria for acute kidney injury (AKI) developed by the Kidney Diseases: Improving Global Outcomes (KDIGO) group represents the gold standard to define AKI.[4]

Renal dysfunction is common in the setting of the multiple organ dysfunction syndrome (MODS) and is independently associated with poorer short- and long-term outcomes.[2,5–7] As a result, accurately characterizing renal dysfunction in children with MODS is critical. To this end, after completing a systematic review of the literature, the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Renal Organ Dysfunction task force created a set of definitional criteria. These criteria are built on the KDIGO AKI criteria, underscoring the importance of SCr and oliguria in identifying renal dysfunction.[4] The PODIUM definition adds to KDIGO by incorporating total body fluid overload (FO); FO may occur in the absence of overt AKI, and substantial literature supports the association of FO and poor outcomes.[8–12] Additionally, FO has a dilutional effect on SCr that may mask a SCr rise, so inclusion of FO captures silent episodes of renal injury. Although the definition proposed herein is operationally dichotomous, we offer recommendations regarding criteria for renal organ dysfunction persistence and risk, and tools for defining baseline SCr.

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 renal dysfunction scoring tools performed as part of PODIUM, provide a critical evaluation of the available literature, and propose evidence-based criteria for renal dysfunction in critically ill children, as well as recommendations for future research listed in the Supplemental Information. 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, data abstraction and synthesis, and for drafting and developing agreement for criteria indicating renal dysfunction.[13]

RESULTS

Systematic Review

Of 6007 unique citations published between 1992 and 2020 identified, 192 met the inclusion and exclusion criteria, as shown in the PRISMA flowchart (Fig 1), data tables (Supplemental Tables 1 and 2), and risk of bias assessment summary (Supplemental Fig 1). Seventy-seven studies were performed in a pediatric cardiac ICU population, whereas 103 were performed in noncardiac, mixed cardiac and noncardiac, or PICU populations of unknown composition. The remaining 12 studies were performed in newborn units or mixed inpatient settings that included PICU patients.

Researchers in 38 studies evaluated existing AKI scoring systems (KDIGO, Risk Injury Failure Loss of kidney function End-stage kidney disease [RIFLE], pediatric-modified RIFLE [pRIFLE], Acute Kidney Injury Network [AKIN]). Researchers in 24 studies evaluated FO. In 11 studies, researchers reported on scoring systems to predict renal dysfunction. Those in a variety of studies used clinical tests, such as furosemide responsiveness, hemodynamic measures, or other novel scores predicting renal dysfunction or outcomes. Researchers in 77 studies reported on biomarkers that may measure or predict renal dysfunction.

Criteria for Renal Organ Dysfunction and Rationale

MODS-associated renal dysfunction is defined when a critically ill child meets any 1 of the criteria listed in Table 1.

Rationale: SCr, urine output (UOP), and RRT. Following the derivation of the RIFLE criteria,[14] there have been 3 iterations of consensus criteria used to define AKI: the AKIN criteria,[15] the pRIFLE criteria,[16] and the KDIGO criteria.[4] All use a combination of changes in SCr or creatinine clearance and UOP to describe AKI thresholds ranging from "risk" or stage I to "failure" or stage 3. We reviewed 8 studies (n = 19 382 children) in which researchers assessed the association between AKIN-defined stage 2/3 AKI and mortality, length of stay (LOS), and duration of mechanical ventilation in mixed, cardiac, and noncardiac ICU populations (Supplemental Table 3). Researchers in all but 1 consistently reported increased odds of poorer outcomes in children with AKI with greater risk in higher AKI severity. Of the 20 studies (n = 31 754) in which researchers used pRIFLE to define AKI, all found increased odds of mortality, LOS, and/or duration of mechanical ventilation; this association was strongest with "injury" or "failure" staged disease (Supplemental Table 3). Finally,

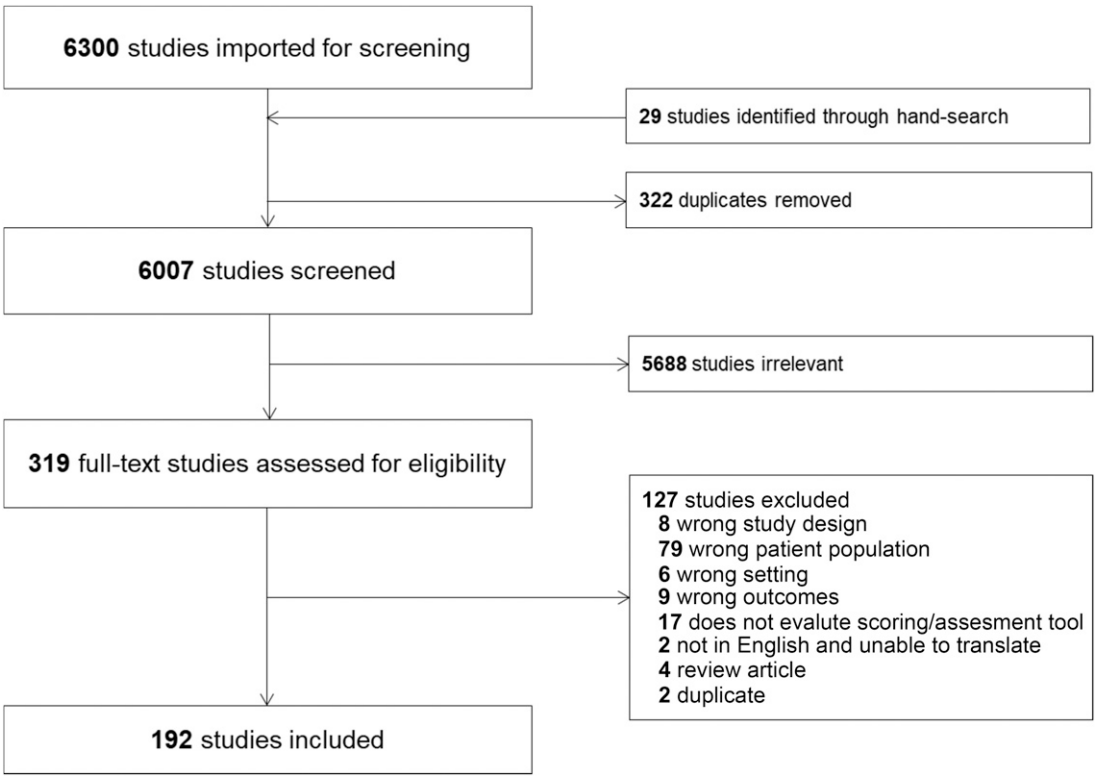

FIGURE 1
Study flow diagram according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols recommendations.

there were 15 pediatric studies (n = 37 837) investigating KDIGO-defined AKI with similar findings (Supplemental Table 3). Researchers in the largest study, who examined 14 795 children from a single center over 5 years, assessed the association between mortality and AKI across all 3 sets of criteria. Regardless of the criteria used, incremental increases in the likelihood ratios for mortality at each stage were similar,[3] supporting the consistency and validity of all 3 definitions. Because KDIGO incorporates all previous definitions, is the most recent iteration, and is applicable to adults and children, we used these criteria as the basis of our renal dysfunction definition.[4]

It is important to note that data are inconsistent regarding the association between stage 1 AKI and poorer outcomes. Thus, we believe that MODS-associated renal dysfunction should primarily be defined as meeting either the SCr or UOP criteria for KDIGO stage 2 AKI. However, researchers have found prognostically worse outcomes in children who met both SCr and UOP stage 1 criteria rather than meeting either in isolation.[5] As a result, we believe those who meet both stage 1 SCr and UOP thresholds should be considered to have MODS-associated renal dysfunction.

Rationale: FO. Data strongly support the physiologic relationship between FO and impaired renal function. Preservation of euvolemia is a primary renal function, and an inability to maintain fluid homeostasis indicates renal dysfunction. Epidemiological data has shown that the development of significant FO can predate meeting diagnostic criteria for AKI and delay the timely diagnosis of AKI, suggesting that FO may be an early biomarker of renal dysfunction. The interplay between FO and renal dysfunction is complex and most likely bidirectional, because both can lead to and exacerbate the other. Development of significant FO can further impair renal function by inhibiting renal perfusion (high venous pressure, interstitial edema, intraabdominal hypertension). Although the complex relationship between FO and AKI warrants further study, mounting evidence exists on the independent association of FO with clinical outcomes.

We reviewed 24 pediatric studies (n = 3632, Supplemental Table 4) that found consistent associations between positive net fluid balance and poor outcomes (oxygenation indices, duration of mechanical ventilation, LOS, mortality). FO, even in the absence of AKI, has been independently associated with morbidity and mortality in

TABLE 1 PODIUM: Criteria for Renal Organ Dysfunction in Pediatric Critical Illness

Organ System	Criterion for Organ Dysfunction	Suggested Thresholds	Conditions	Severity
Renal	UOP[a]	<0.5 mL/kg per h for ≥6 h	Concomitant SCr increase 1.5–1.9 times baseline[b] or ≥0.3mg/dL (≥26.5 μmol/L) increase	Not graded
		<0.5 mL/kg per h for ≥12 h	None	Not graded
Renal	SCr	Increase 1.5–1.9 times baseline or ≥0.3mg/dL (≥26.5 μmol/L) increase	Concomitant UOP[a] <0.5 mL/kg per h for ≥6 h	Not graded
		Increase ≥2 times baseline[b]	None	Not graded
Renal	eGFR	Decrease to <35mL/min/1.73m^2	Excludes neonates <30 d of age	Not graded
Renal	Initiation of RRT	Not applicable	Initiation of RRT for any reason other than toxic ingestion or hyperammonemia	Not graded
Renal	FO[c]	20%	Measured starting 48 h after ICU admission	Not graded

[a] Consider ruling out obstructive uropathy in the setting of low UOP.

[b] Use the lowest SCr value available in the 3 mo before admission as the baseline SCr. If a previous SCr is unavailable, baseline creatinine should be extrapolated from a normal eGFR for age and an appropriate estimating equation. In many critically ill children, heights are unavailable, making a height-independent equation preferential. Table 2 provides estimated baseline creatinine values based on a height-independent equation and normal reference eGFR for age. These creatinine values are derived from a healthy pediatric population[29] and have been validated in critically ill children.[28]

[c] FO can be calculated using intake and output or wt. For wt-based determination, $\mathrm{FO} = \frac{\textit{Current weight (kg)} - \textit{ICU admission weight (kg)}}{\text{ICU Admission weight } (kg)} \times 100\%$. For ins/outs based determination, $\mathrm{FO} = \frac{\textit{Cumulative fluid balance NET (fluid IN - fluid out)}}{\text{ICU Admission weight } (kg)} \times 100\%$. Use of wt-based formula for FO is preferential if wt data are available.

children.[9,17–20] The incorporation of FO into renal scoring systems further supports its inclusion.[21]

Despite the strength of the aforementioned associations, the threshold for defining pathologic FO and the timing of assessment continue to be debated. Studies have found that even 5% FO (equivalent to 50 mL/kg) is associated with poorer outcomes[9,22] and that each 1% increase in fluid balance increases the odds of death incrementally by 3% to 8%.[11,13,17,23] We recommend a conservative threshold of 20% FO as a criterion for renal dysfunction with the caveat that future data may support lower thresholds. We suggest that the reference weight for determining percent FO (Supplemental Table 4) should be the ICU admission weight as preadmission weights are unavailable in many patients.

Rationale: Timing. To ensure complete and comparable data, the above criteria are to be evaluated every 24 hours beginning at ICU admission, with the exception of FO. FO should be measured as the cumulative fluid balance from admission to 48 hours after ICU admission and for every 24-hour period after that. Adjudication of the impact of cumulative FO should begin 48 hours after ICU admission given that positive net fluid balance is to be expected during resuscitation, but inability to start toward diuresis beyond the initial resuscitative phase should be considered pathologic. The adjudication of timing and threshold of FO, proper delineation of epochs of fluid balance,[24] and the impact on the ICU course are important areas of future research.

Determination of Baseline Creatinine

Determination of baseline SCr is imperative when defining renal function. Previous researchers have found variation in AKI incidence depending on the baseline determination method used, emphasizing the importance of standardization.[25]

The ideal baseline SCr would be one measured before critical illness. In practice, SCr measurements are frequently unavailable in pediatric patients.[26,27] When such measurements are available, the most common practice is to use the lowest value from the 3 months before admission as a baseline.[16,26] As a general principle, the first SCr obtained during critical illness should not be used as the baseline because renal dysfunction is often present on admission.[24,27]

When a preadmission SCr is not available, one must be estimated. An approach often used is to back-calculate a baseline SCr by using the Schwartz formula assuming a "normal" estimated glomerular filtration rate (eGFR) of 120 mL per minute per 1.73 m^2.[25,28] This approach presents 2 potential issues: (1) the heights required for the Schwartz equation are commonly not available,[27] and (2) the "normal" pediatric GFR has age-dependent variation, especially in the first 2 years of life.[29] Another approach, which addresses these

issues, is the use of height independent, age- and sex-based norms.[29,30] Normal age- and sex-based SCr values are provided in Table 2[30]; we recommend using these values as a proxy baseline SCr when previous measurements are not available as the standard approach.

Persistent Renal Dysfunction

The best available data reveal that nontransient renal dysfunction carries additional outcome risk. Thus, we propose a subcategory of MODS-associated renal dysfunction: persistent renal dysfunction. Persistent renal dysfunction should be defined in patients meeting any one of 5 criteria for >48 hours:

1. UOP <0.5 mL/kg per hour,
2. Increase in SCr of ≥2 times baseline,
3. Decrease in eGFR to <35 mL per minute per 1.73m^2 (eGFR criterion excludes neonates <30 days of age),
4. Use of RRT for any reason other than toxic ingestion or hyperammonemia, and
5. 20% FO.

Rationale

Renal dysfunction criteria are inherently time-dependent, with stratified severity phenotypes that are associated with outcomes. In addition to severity strata, renal dysfunction can be broken down into time courses: transient, in which a patient regains baseline renal function within 48 hours, and persistent, in which a patient demonstrates renal dysfunction past 48 hours.[31]

In an effort to harmonize these concepts, the Acute Disease Quality Initiative 16 Workgroup defined persistent renal dysfunction lasting >48 hours. In our literature review, persistent renal dysfunction carries higher risk for poorer outcomes, including increased RRT, LOS, and mortality, when compared with transient dysfunction.[16,21,33–39]

Classifying a separate phenotype of persistent renal dysfunction allows evaluation of a distinct cohort of patients whose renal dysfunction does not respond to initial resuscitation alone. Early identification of persistent renal dysfunction may allow for tailored therapeutic strategies for potential intervention, both in clinical trials and quality improvement efforts. Defining this cohort of patients signals to practicing clinicians the importance of reassessing the patients' risk factors for additional organ dysfunction and ongoing kidney disease. Finally, given the multifactorial pathophysiology of renal dysfunction, it also allows the clinician to reevaluate the consequences of renal dysfunction and the therapies being used to treat the systemic disease as renal function changes.

TABLE 2 Determination of Baseline SCr

Age	Reference eGFR	Baseline SCr Boys	Baseline SCr Girls
<1 mo	45	0.57	0.62
1–2 mo	55	0.43	0.46
3–5 mo	70	0.35	0.37
6–11 mo	85	0.31	0.32
12–17 mo	90	0.32	0.32
18–23 mo	100	0.31	0.31
2–4 y	120	0.31	0.30
5–7 y	120	0.37	0.37
8–11 y	120	0.46	0.46
12–18 y	120	0.65	0.58

If preadmission SCr measurements are available for a patient, use the lowest SCr in the 3 mo before admission as baseline. If a previous SCr is unavailable, a baseline SCr based on age and sex norms may be used. The SCr values in the table were derived from healthy children and have been validated in critically ill pediatric patients.[28,29]

Determining Risk for Renal Dysfunction

Some patients are at higher risk for developing renal dysfunction. At the present time, widely available diagnostic tests continue to lack sensitivity for early stage or subtle injury, making the determination of "risk" crucial for clinicians adjudicating multiorgan injury. Systematic and objective criteria are required for the assessment of patients at risk for renal dysfunction. Although not part of the consensus criteria for renal organ dysfunction, 3 discrete metrics can be used to identify the at-risk patient, and patients meeting any 1 of these should be considered at risk for developing renal dysfunction:

1. UOP <0.5mL/kg per hour for ≥6 hours in a single ICU day,
2. increase in SCr of 1.5 to 1.99 times baseline (or an absolute increase of ≥0.3mg/dL (26.5 μmol/L),
3. 15% FO.

Although the first 2 of these metrics fulfill the KDIGO definition of stage 1 AKI, there are few data in any population demonstrating adverse outcomes associated with this stage. However, incipient AKI can be progressive, and evidence suggests even subtle changes may represent a separate risk tier. As a result, these patients should be categorized as at risk for developing MODS-associated renal dysfunction. The third metric for identifying patients "at-risk" is drawn from the renal angina index (RAI), which uses an FO of 15% to define higher AKI risk. The RAI is a score measured 12 hours into the ICU course and has been used to

identify patients at highest risk for developing severe AKI after 3 ICU days.[21] Once at-risk patients are identified, a systematic daily evaluation of kidney function is recommended. A multimodal approach, combining markers of filtration, tubular function (UOP or response to diuresis), assessment of FO, and exposure to nephrotoxins, may be useful for associative predictions with patient outcome.[40]

CONCLUSIONS

Renal dysfunction is common in critically ill children and negatively impacts ICU outcomes. After a systematic review of 192 published articles via a modified Delphi process, we present criteria for MODS-associated renal dysfunction in critically ill children that include measures of SCr, UOP, RRT, and FO and provide criteria for persistence of and risk for renal dysfunction.

ACKNOWLEDGMENTS

We are grateful for the contributions to the early portion of the project, including formulation of literature search terms, title and abstract review, and full text data extraction, by Dr Michael Zappitelli.

ABBREVIATION

AKI: acute kidney injury
AKIN: Acute Kidney Injury Networke
GFR: estimated glomerular filtration rate
FO: fluid overload
KDIGO: Kidney Diseases: Improving Global Outcomes
LOS: length of stay
MODS: multiple organ dysfunction syndrome
PODIUM: Pediatric Organ Dysfunction Information Update Mandatep
RIFLE: pediatric-modified Risk Injury Failure Loss End-stage
RAI: renal angina index
RIFLE: Risk Injury Failure Loss End-stage
RRT: renal replacement therapy
SCr: serum creatinine
UOP: urine output

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Department of Pediatrics at the Medical University of South Carolina, Department of Pediatrics at the Emory School of Medicine, and Division of Critical Care at the Children's Hospital of Philadelphia contributing to funding for publication costs for this article. Dr Fitzgerald is supported by NIH NIDDK K23DK119463. Dr Fuhrman is supported by NIH K23DK116973. The guidelines/recommendations in this article are not American Academy of Pediatrics policy, and publication herein does not imply endorsement. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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