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

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abstract

CONTEXT: Studies of organ dysfunction in children are limited by a lack of consensus around organ dysfunction criteria.

OBJECTIVES: To derive evidence-informed, consensus-based criteria for hematologic dysfunction in critically ill children.


STUDY SELECTION: Studies were included if they evaluated assessment/scoring tools to screen for hematologic dysfunction and assessed outcomes of mortality, functional status, organ-specific outcomes, or other patient-centered outcomes. Studies of adults or premature infants, animal studies, reviews/commentaries, small case series, and non-English language studies with inability to determine eligibility were excluded.

DATA EXTRACTION: Data were abstracted from each eligible study into a standard data extraction form along with risk of bias assessment.

RESULTS: Twenty-nine studies were included. The systematic review supports the following criteria for hematologic dysfunction: thrombocytopenia (platelet count <100000 cells/µL in patients without hematologic or oncologic diagnosis, platelet count <30000 cells/µL in patients with hematologic or oncologic diagnoses, or platelet count decreased ≥50% from baseline; or leukocyte count <3000 cells/µL; or hemoglobin concentration between 5 and 7 g/dL (nonsevere) or <5 g/dL (severe).

LIMITATIONS: Most studies evaluated pre-specified thresholds of cytopenias. No studies addressed associations between the etiology or progression of cytopenias overtime with outcomes, and no studies evaluated cellular function.

CONCLUSIONS: Hematologic dysfunction, as defined by cytopenia, is a risk factor for poor outcome in critically ill children, although specific threshold values associated with increased mortality are poorly defined by the current literature.

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The guidelines/recommendations in this article are not American Academy of Pediatrics policy, and publication herein does not imply endorsement.

Drs Muszynski and Parker contributed to study design, reviewed all included studies, drafted and revised organ dysfunction criteria, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Cholette, Steiner, Tucci, and Doctor contributed to study design, reviewed all included studies, drafted and revised organ dysfunction criteria, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Organ dysfunction is consistently associated with increased mortality in pediatric critical illness. Although many scoring systems have been developed to assess organ dysfunction and to quantify risks of adverse outcomes, there is no universal agreement on which scoring system has the highest predictive power. This lack of consensus may in part result from differences in the criteria and/or methodologies used to define organ dysfunction. In the case of hematologic dysfunction, most scoring systems include cytopenias that have not been tested in a manner to validate specific thresholds or to consider different etiologies of cytopenia. Additionally, unlike other organ systems in which organ function is assessed using established functional markers, similar markers to assess the function of circulating hematologic cells have not been well studied. Each of these limitations affects the quality of data available to define hematologic dysfunction. Lastly, hematologic dysfunction has historically been defined by combinations of cytopenias and/or the presence of abnormal results on plasma-based coagulation assays. However, except for platelet count, hemostatic homeostasis is distinct from bone marrow function, and it was decided that the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) initiative would consider hematologic function and coagulation function as 2 separate entities.

To address the lack of consensus for current definitions of hematologic dysfunction, we describe here the results of a structured literature search to create evidence-informed, consensus-based definitions for hematologic dysfunction in critically ill children as part of the PODIUM consensus conference series.

METHODS
The PODIUM collaborative sought to develop evidence-based criteria for organ dysfunction in critically ill children. The present article reports the systematic literature review on elements of hematologic dysfunction performed as part of PODIUM, proposes evidence-based criteria for hematologic dysfunction in critically ill children, and provides a critical evaluation of the available literature. The PODIUM Executive Summary details Population, Interventions, Comparators, and Outcomes questions; search strategies; study inclusion and exclusion criteria; and methodologies for risk of bias assessment, data abstraction and synthesis, and establishing consensus. Search terms specific to hematologic dysfunction included anemia, hemoglobin, hematocrit, leukopenia, thrombocytopenia, terms addressing red blood cell (RBC) indices (mean corpuscular volume, red blood cell distribution width [RDW]), distribution of neutrophils (neutrophil index, δ neutrophil index), platelet indices (mean platelet volume, platelet distribution width), and circulating platelet mass (“plateletcrit”).

RESULTS
Of 10,681 unique citations published between 1992 and 2020, 29 studies were eligible for inclusion (Fig 1). Data tables (Supplemental Tables 1 and 2) and risk of bias assessment summaries (Supplemental Fig 1) are detailed in Supplemental Information. Criteria for hematologic dysfunction in critically ill children informed by the evaluated evidence are in Table 1. A cytopenia that meets the following definitions in any of 1 of the 3 cell-lines (platelets, leukocytes, or erythrocytes [RBCs]) is considered sufficient for the diagnosis of hematologic dysfunction.

Platelet Count
Hematologic dysfunction will be defined by a platelet count of <100,000 cells/μL for patients without underlying hematologic or oncologic diagnosis, <30,000 cells/μL for patients with underlying hematologic or oncologic diagnosis, or ≥50% decrease from baseline for patients with baseline platelet count <100,000 cells/μL. For the purposes of defining hematologic dysfunction, thrombocytopenia should exist in the absence of coagulation dysfunction as defined by PODIUM criteria.

Rationale
Thresholds for platelet count are based on Choi et al, the only included study that evaluated thresholds of platelet count predictive of clinical outcomes stratified by hematologic/oncologic diagnosis. Other studies evaluated scoring systems that include platelet counts (eg, the heme portion of the pediatric logistic organ dysfunction score, the pediatric risk of mortality score, disseminated intravascular coagulation scores, the Rotterdam score to predict mortality in meningococcal sepsis, and the base excess platelet count score) or identified lower platelet count as a risk factor for mortality.

Leukocyte Count
Hematologic dysfunction will be defined by a total leukocyte count <3,000 cells/μL.

Rationale
Low total white blood cell count was independently associated with adverse outcomes in several studies. A data-driven threshold was identified in only 1 study, which derived a threshold of <4,000 cells/μL in a small cohort of children with meningococcemia. Other studies evaluated WBC thresholds as part of existing scoring systems or did not derive thresholds predictive of outcomes.
such, no high-quality data are available to validate or refute thresholds used in existing scoring systems (ie, the pediatric risk of mortality score).\(^8\) As ingest study evaluated absolute neutrophil count (ANC) in oncology patients admitted to the PICU, and although ANC may be an important marker of marrow failure, applicability of ANC thresholds outside of the oncology population remains unclear.\(^24\) Two studies evaluated platelet neutrophil product in children with meningococcal disease.\(^25,26\) The platelet neutrophil product is a promising measure to assess marrow failure because it includes derangements in 2 cell lines, each of which are consistently associated with adverse outcomes in critical illness, though data to date are limited.

**Hemoglobin concentration**

Severe hematologic dysfunction will be defined by a hemoglobin concentration \(<5\, \text{g/dL}\). Mild hematologic dysfunction will be defined by a hemoglobin concentration of between 5 and 7 \(\text{g/dL}\).

**Rationale**

Hemoglobin \(<5\, \text{g/dL}\) was associated with higher risk of mortality in Kenyan children.\(^27\) There is a paucity of data describing relationships between anemia and outcomes in the general PICU population, and thresholds of anemia associated with outcomes are unknown. Although these data do not exist, the addition of anemia to the definition of hematologic dysfunction was felt to be important, and consensus-based thresholds are provided.

**DISCUSSION**

The basis for each of our recommendations is largely expert opinion, as none of our recommendations were supported by randomized clinical studies and only 2 assessed a cytopenia as a continuous variable to allow determination of a discriminative threshold for marrow failure.\(^10,23\) Consequently, most studies were not able to determine specific

**TABLE 1 PODIUM: Criteria for Hematologic Dysfunction in Pediatric Critical Illness**

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Criterion for organ dysfunction</th>
<th>Suggested thresholds</th>
<th>Conditions</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>Platelet count(^a)</td>
<td>(&lt;100,000, \text{cells/μL})</td>
<td>Patients without underlying hematologic or oncologic diagnoses</td>
<td>Not graded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;30,000, \text{cells/μL})</td>
<td>Patients with underlying hematologic or oncologic diagnoses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\geq50% \text{ decrease from baseline})</td>
<td>Patients with baseline thrombocytopenia regardless of etiology (ie, baseline platelet count (&lt;100,000, \text{cells/mm}^3))</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>Leukocyte count</td>
<td>(&lt;3000, \text{cells/μL})</td>
<td>None</td>
<td>Not graded</td>
</tr>
<tr>
<td>Hematology</td>
<td>Hemoglobin</td>
<td>(5 - \leq7, \text{g/dL})</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hematology</td>
<td>Hemoglobin</td>
<td>(&lt;5, \text{g/dL})</td>
<td>None</td>
<td>Severe</td>
</tr>
</tbody>
</table>

\(^a\)For the purposes of defining hematologic failure, thrombocytopenia should exist in the absence of coagulation dysfunction (ie, presence of at least 2 of the 4 PODIUM coagulation dysfunction criteria).

\(^b\)For patients with underlying hematologic or oncologic disease and baseline thrombocytopenia, both \(<3000\, \text{cells/μL}\) and \(50\% \text{ decrease from baseline} \) criteria must be met.
thresholds for each cell type with independent predictive value for hematologic dysfunction. Similarly, the relative importance of specific thresholds across different diagnoses and causes of multiple organ dysfunction remains unknown. It is also not known how the timing or duration of cytopenias may impact associations with outcomes and whether these factors should also be included in the definition of hematologic dysfunction. Lastly, none of our recommendations address the etiologies of cytopenias, although the lower thresholds for cytopenias in oncology patients recognize the presence of chemotherapy-induced myelosuppression when defining hematologic dysfunction in these patients.

Three of the included studies correlated increased RDW with adverse outcomes.28–30 RDW may serve as a marker of RBC destruction, altered RBC maturation or metabolism, and/or marrow activity. Although RDW was considered for the definition of hematologic dysfunction, it was noted that elevated RDW is not specific to critical illness, and mechanisms underlying these associations are unclear. Notably, RDW may also represent appropriate marrow response to anemia. Future studies are needed to determine why RDW is associated with adverse outcomes and how to measure these mechanisms in critically ill patients.

Lastly, in addition to cytopenias, critically ill patients may also experience hematologic cell dysfunction. Incorporation of cellular functional analyses would align how we define hematologic dysfunction with how we assess other organ systems. Development and validation of feasible assays to measure specific functions of RBCs, platelets, and leukocytes are needed.

CONCLUSIONS
Hematologic dysfunction in critically ill children, as defined by cytopenia, is a risk factor for poor outcome (ie, risk of mortality), although the explicit threshold values for any specific cytopenia (eg, platelets, leukocytes, RBCs) associated with increased mortality is poorly defined by the current literature. Additionally, current definitions that rely on cell number do not incorporate cellular function or the etiology of the cytopenias that may inform diagnostic and/or therapeutic options.

ABBREVIATION
ANC: absolute neutrophil count
PODIUM: Pediatric Organ Dysfunction Information Update Mandate
RBC: red blood cell
RDW: red blood cell distribution width

REFERENCES

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