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

E. Vincent S. Faustino, MD, MHS,[a] Oliver Karam, MD, PhD,[b] Robert I. Parker, MD,[c] Sheila J. Hanson, MD, MS,[d] Leonardo R. Brandão, MD, MSc,[e,f] Paul Monagle, MBBS, MD, MSc, FRACP, FRCPA, FCCP,[g,h,i,j] on behalf of the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Collaborative

abstract

CONTEXT: Previous criteria for coagulation dysfunction in critically ill children were based mainly on expert opinion.

OBJECTIVE: To evaluate current evidence regarding coagulation tests associated with adverse outcomes in children to inform criteria for coagulation dysfunction during critical illness.

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

STUDY SELECTION: Studies were included if critically ill children with coagulation dysfunction were evaluated, if performance characteristics of assessment and/or scoring tools to screen for coagulation dysfunction were evaluated, and if outcomes related to mortality or functional status, organ-specific outcomes, or other patient-centered outcomes were assessed.

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

RESULTS: The systematic review supports the presence of at least 2 of the following criteria reflecting coagulation dysfunction in the absence of liver dysfunction: platelet count $<100\,000$ cells per μL, international normalized ratio >1.5, fibrinogen level <150 mg/dL, and D-dimer value above 10 times the upper limit of normal, or above the assay's upper limit of detection if this limit is below 10 times the upper limit of normal.

LIMITATIONS: The proposed criteria for coagulation dysfunction are limited by the available evidence and will require future validation.

CONCLUSIONS: Validation of the proposed criteria and identified scientific priorities will enhance our understanding of coagulation dysfunction in critically ill children.

[a]*Section of Pediatric Critical Care Medicine, Department of Pediatrics, School of Medicine, Yale University, New Haven, Connecticut;* [b]*Division of Pediatric Critical Care Medicine, Children's Hospital of Richmond at Virginia Commonwealth University, Richmond, Virginia;* [c]*Hematology/Oncology, Department of Pediatrics (Emeritus), Renaissance School of Medicine, Stony Brook University, Stony Brook, New York;* [d]*Critical Care Section, Department of Pediatrics, Medical College of Wisconsin and Children's Wisconsin, Milwaukee, Wisconsin;* [e]*Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada;* [f]*Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada;* [g]*Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia;* [h]*Department of Clinical Haematology, The Royal Children's Hospital Melbourne, Parkville, Victoria, Australia;* [i]*Murdoch Children's Research Institute, Parkville, Victoria, Australia; and* [j]*Kids Cancer Centre, Sydney Children's Hospital, Randwick, New South Wales, Australia*

Drs Faustino, Karam, Parker, Hanson, Brandão, and Monagle conceptualized and designed the study, collected data, drafted the initial manuscript, critically reviewed the manuscript for important intellectual content, and revised the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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

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

Accepted for publication Sep 24, 2021

Coagulation is seldom viewed as an "organ" in the various definitions of organ dysfunction, although derangements in coagulation have long been recognized as a prognostic factor for survival in critically ill children.[1] In addition, coagulation tests have been included in the definitions of hematologic and liver dysfunction in many scoring systems of critical illness. Thrombocytopenia, defined as a platelet count <20 000 cells per μL, was one of the criteria for hematologic dysfunction in the definition by proposed by Wilkinson et al.[2] In 1996, Proulx et al[3] also included thrombocytopenia (still defined as a platelet count <20 000 cells per μL) in the criteria for hematologic dysfunction but also added disseminated intravascular coagulation (DIC), which they defined as prothrombin time (PT) >20 seconds or activated partial thromboplastin time (aPTT) >60 seconds or an international normalized ratio (INR) value >2 in the presence of a positive assay result for fibrin-split products or a D-dimer level >0.5 mg/mL. In 2005, Goldstein et al[4] defined hematologic dysfunction as a platelet count <80 000 cells per μL or, for patients with chronic hematologic or oncologic disease, a decline of 50% in the platelet count from the highest value recorded over the preceding 3 days, or an INR >2.

The threshold values for platelet count, PT, INR, and aPTT were largely arbitrary because none were determined by rigorous methodology. Consequently, each of these definitions were based on expert opinion and consensus conferences. In 1999, Leteurtre et al[5] derived the Pediatric Logistic Organ Dysfunction (PELOD) score, the first evidence-based definition of multiple organ dysfunction, using data from 594 critically ill children. Platelet count, D-dimer level, PT, and aPTT were analyzed, but only platelet count and PT were found to be independently associated with mortality and were included as components of the PELOD score. This score was subsequently validated in a larger cohort of 1806 critically ill children, and excellent discrimination was demonstrated, that is, an area under the receiver operator characteristic curve of 0.91.[6] In 2013, the same group published an updated score (PELOD-2).[7] In this updated score, only a platelet count <77 000 cells per μL was associated with mortality, whereas the fibrinogen level and PT were not. The PELOD-2 score revealed an even higher discrimination value, with an area under the receiver operator characteristic curve of 0.94. In parallel, diagnostic criteria and severity rating for the evaluation of adults with DIC were developed by international societies, but the experience with DIC scores in the case of critically ill children is limited.[8–11]

In this project, our objective was to evaluate the current evidence regarding coagulation tests that are associated with outcomes in critically ill children to revise how clinicians identify coagulation dysfunction during critical illness. On the basis of our review of available studies, we proposed criteria for coagulation dysfunction.

METHODS

The Pediatric Organ Dysfunction Information Update Mandate (PODIUM) collaborative sought to develop evidence-based criteria for organ dysfunction in critically ill children. In the present article, we reports on the systematic review of coagulation dysfunction scoring tools performed as part of PODIUM, provide a critical evaluation of the available literature, propose evidence-based criteria for coagulation dysfunction in critically ill children as well as research priorities 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, for data abstraction and synthesis, and for drafting and developing agreement for criteria indicating coagulation dysfunction.[12]

RESULTS

Criteria With Rationale

Of 4741 unique citations published between 1992 and 2020, 86 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. Criteria for coagulation dysfunction in critically ill children informed by the evaluated evidence are listed in Table 1.

We defined coagulation dysfunction as dysfunction caused by a clinical imbalance in the regulation of hemostasis and not merely that due to a decrease in synthesis of hemostasis-related factors. We recognized that normal hemostasis involves at least 3 separate organ systems (ie, hematology [balance between bone marrow production and peripheral destruction or consumption of platelets], hepatic [synthesis of procoagulant and anticoagulant proteins], and endothelium [interaction of endothelial cells with platelets and soluble clotting-related factors]). Consequently, defining coagulation dysfunction should be holistic and account for these other organ systems. Furthermore, when

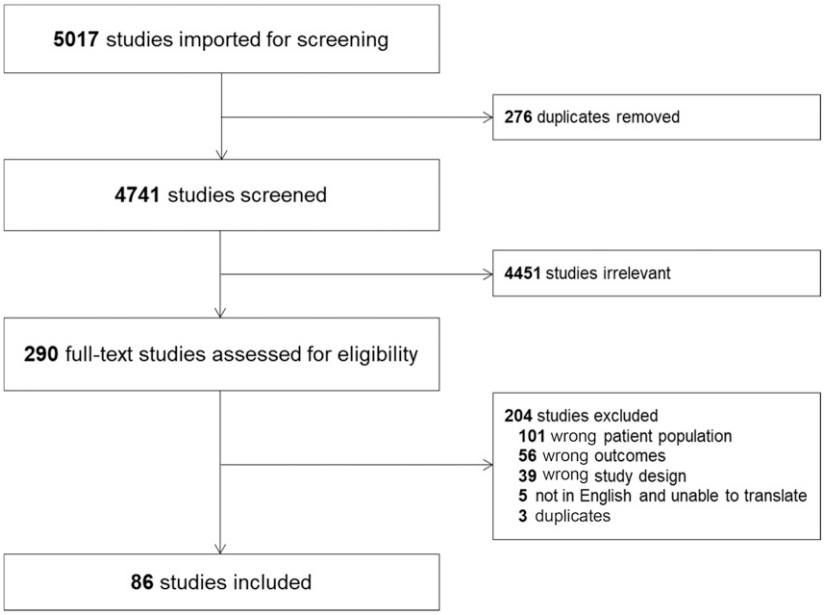

FIGURE 1
Study flow diagram according to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols recommendations.

assessing coagulation dysfunction, the outcome assessed should ideally be abnormal hemostasis (ie, hemorrhage or thrombosis) and not mortality unless death was directly due to hemorrhage or thrombosis.

We propose that in the absence of liver dysfunction, at least 2 of the following 4 criteria should be present to define coagulation dysfunction: platelet count <100 000 cells per μL, INR >1.5, fibrinogen level <150 mg/dL, and D-dimer value above 10 times the upper limit of normal, or above the assay's upper limit of detection if this limit is below 10 times the upper limit of normal (Table 1). In addition, the clinical context should be taken into account when applying these criteria. For instance, thrombocytopenia in a patient with malignancy may not reflect failure of the coagulation system but rather may reflect myelosuppression after chemotherapy. The proposed criteria have not been validated in children on mechanical circuits, such as extracorporeal membrane oxygenation, ventricular assist devices, and renal replacement therapy, and, as such, may not be valid in these populations.

Rationale for the Inclusion of Selected Criteria

Platelets

Our recommendation for a platelet count of <100 000 cells per μL to be included in the criteria was derived from data in 37 studies (section A of Supplemental Tables 1 and 2). Although thresholds of 10 000 to 150 000 cells per μL were derived in these studies, it was our expert opinion that a value of <100 000 cells per μL was a reasonable threshold to include in the criteria. Platelet count as a criterion for coagulation dysfunction is valid only in children without underlying hematologic or oncologic condition. This threshold is associated with an adjusted odds ratio of 7.86 for progressive hemorrhage in children with traumatic brain injury[13] and is identified as the optimal threshold for mortality among children with

TABLE 1 PODIUM: Criteria for Coagulation Dysfunction in Pediatric Critical Illness

Criterion for Organ Dysfunction	Suggested Thresholds	Conditions	Severity
Platelet count	<100 000 cells per μL	Absent liver dysfunction, presence of at least 1 additional coagulation dysfunction criterion	Not graded
INR	>1.5	Absent liver dysfunction, presence of at least 1 additional coagulation dysfunction criterion	Not graded
Fibrinogen	<150 mg/dL (<4.41 μmol/L)	Absent liver dysfunction, presence of at least 1 additional coagulation dysfunction criterion	Not graded
D-dimer	Above 10 times the upper limit of normal,[19] or above the assay's upper limit of detection if this limit is below 10 times the upper limit of normal	Absent liver dysfunction, presence of at least 1 additional coagulation dysfunction criterion	Not graded

We propose that in the absence of acute liver dysfunction, as defined by PODIUM, at least 2 of the 4 criteria should be present to define coagulation dysfunction. However, it should be noted that studies investigating combinations of these criteria are not available. The clinical context should be taken into account when applying these criteria in defining coagulation dysfunction. Furthermore, the proposed criteria have not been validated in children on mechanical circuits (extracorporeal life support, ventricular assist device, continuous renal replacement therapy, or cardiopulmonary bypass) and, as such, may not be useful in these populations because of the effects of the circuit and associated anticoagulation therapy.

sepsis but without a hematologic or oncologic condition.[14]

INR

A threshold of INR >1.5 was derived from data in 19 studies (section B of Supplemental Tables 1 and 2). Enrolled in most of these studies were children with either acute or chronic liver failure. Among those without liver failure, an INR >1.5 had a sensitivity of 57% and specificity of 92% for predicting mortality among children admitted for trauma.[15] Although a decrease in specific clotting factors (eg, factor VII) in liver disease will result in an increase of the INR, this increase has not definitively been shown to result in increased risk of bleeding.[16,17] Consequently, it was our expert opinion that INR as a criterion for coagulation dysfunction is valid only in children without underlying synthetic liver dysfunction or ongoing or recent warfarin treatment.

Fibrinogen

Our recommendation that a fibrinogen level <150 mg/dL be included was supported from data included in 13 studies (section C of Supplemental Tables 1 and 2). This is the most commonly reported threshold that links hypofibrinogenemia to mortality. Among neonates with sepsis, this threshold had a sensitivity of 92% and specificity of 81% for predicting mortality.[18] Among children post–cardiopulmonary bypass, this threshold had a sensitivity of 69% and specificity of 84% for predicting bleeding.[19] This recommendation reflects expert opinion.

D-Dimer

The role of D-dimer in predicting mortality was assessed in a total of 5 studies (section D of Supplemental Tables 1 and 2). A D-dimer value above 10 times the upper limit of normal, or above the assay's upper limit of detection if this limit is below 10 times the upper limit of normal, was deemed to be predictive of mortality. Among children admitted for trauma, a threshold of above 10 the upper limit of normal on day 1 had a sensitivity of 90% and specificity of 100% for predicting mortality.[20] Lower thresholds were identified during subsequent days.

aPTT was also considered as a criterion for coagulation dysfunction. However, available studies indicated that aPTT was neither sensitive nor specific to define coagulation dysfunction.[21–31] The presence of DIC was also considered. However, although current definitions of DIC vary, all are ultimately based on laboratory parameters that have been included in our proposed criteria for coagulation dysfunction.[8–11]

CONCLUSIONS

The current literature pertinent to coagulation dysfunction in critically ill children has significant limitations, with implications on the validity of our proposed criteria for coagulation dysfunction. Nevertheless, we propose that a combination of abnormal platelet count, INR, fibrinogen level, and D-dimer level be used to define coagulation dysfunction in critically ill children. Although the selected included criteria are supported by relevant literature, significant expert opinion was factored into the development of the proposed criteria for coagulation dysfunction to address the limitations of the available studies. Thus, the proposed criteria represent weak recommendations. We identified 4 scientific priorities (Supplemental Information) that will enhance our understanding of coagulation dysfunction and should result in a more valid criteria of this dysfunction in critically ill children.

ABBREVIATIONS

aPTT: activated partial thromboplastin time
DIC: disseminated intravascular coagulation
INR: international normalized ratio
PELOD: Pediatric Logistic Organ Dysfunction
PODIUM: Pediatric Organ Dysfunction Information Update Mandate
PT: prothrombin time

Address correspondence to E. Vincent S. Faustino, MD, MHS, Section of Pediatric Critical Care Medicine, Department of Pediatrics, School of Medicine, Yale University, 333 Cedar St, New Haven, CT 06520. E-mail: vince.faustino@yale.edu

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: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Faustino received grant funding from the National Institutes of Health and Grifols Shared Services North America, Inc; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Stiehm ER, Damrosch DS. Factors in the prognosis of meningococcal infection. Review of 63 cases with emphasis on recognition and management of the severely ill patient. *J Pediatr.* 1966;68(3):457–467
2. Wilkinson JD, Pollack MM, Ruttimann UE, Glass NL, Yeh TS. Outcome of pediatric patients with multiple organ system failure. *Crit Care Med.* 1986;14(4):271–274
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. 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
5. Leteurtre S, Martinot A, Duhamel A, et al. Development of a pediatric multiple organ dysfunction score: use of two strategies. *Med Decis Making.* 1999;19(4):399–410
6. Leteurtre S, Duhamel A, Grandbastien B, Lacroix J, Leclerc F. Paediatric logistic organ dysfunction (PELOD) score. *Lancet.* 2006;367(9514):897
7. 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
8. Gando S, Iba T, Eguchi Y, et al; Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med.* 2006;34(3):625–631
9. Kobayashi N, Maekawa T, Takada M, Tanaka H, Gonmori H. Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. *Bibl Haematol.* 1983;(49):265–275
10. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost.* 2001;86(5):1327–1330
11. Soundar EP, Jariwala P, Nguyen TC, Eldin KW, Teruya J. Evaluation of the International Society on Thrombosis and Haemostasis and institutional diagnostic criteria of disseminated intravascular coagulation in pediatric patients. *Am J Clin Pathol.* 2013;139(6):812–816
12. Bembea MM, Agus M, Akcan-Arikan A, et al. Pediatric organ dysfunction information update mandate (PODIUM) contemporary organ dysfunction criteria: executive summary Pediatrics. 2021: 149(suppl 1)e2021052888B
13. Hu GW, Lang HL, Guo H, et al. A risk score based on admission characteristics to predict progressive hemorrhagic injury from traumatic brain injury in children. *Eur J Pediatr.* 2017;176(6):689–696
14. Choi SJ, Ha EJ, Jhang WK, Jong Park S. Platelet indices as predictive markers of prognosis in pediatric septic shock patients. *Iran J Pediatr.* 2017;27(3):e7212
15. Leeper CM, Nasr I, McKenna C, Berger RP, Gaines BA. Elevated admission international normalized ratio strongly predicts mortality in victims of abusive head trauma. *J Trauma Acute Care Surg.* 2016;80(5):711–716
16. Segal JB, Dzik WH; Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion.* 2005;45(9):1413–1425
17. Nellis ME, Dalton H, Karam O; PediECMO Investigators. Quantifiable bleeding in children supported by extracorporeal membrane oxygenation and outcome. *Crit Care Med.* 2019;47(11):e886–e892
18. Ersoy B, Nehir H, Altinoz S, Yilmaz O, Dundar PE, Aydogan A. Prognostic value of initial antithrombin levels in neonatal sepsis. *Indian Pediatr.* 2007;44(8):581–584
19. Faraoni D, Willems A, Savan V, Demanet H, De Ville A, Van der Linden P. Plasma fibrinogen concentration is correlated with postoperative blood loss in children undergoing cardiac surgery. A retrospective review. *Eur J Anaesthesiol.* 2014;31(6):317–326
20. Foaud HM, Labib JR, Metwally HG, El-Twab KM. Plasma D-dimer as a prognostic marker in ICU admitted Egyptian children with traumatic brain injury. *J Clin Diagn Res.* 2014;8(9):PC01–PC06
21. McManus ML, Churchwell KB. Coagulopathy as a predictor of outcome in meningococcal sepsis and the systemic inflammatory response syndrome with purpura. *Crit Care Med.* 1993;21(5):706–711
22. Oren H, Cingöz I, Duman M, Yilmaz S, Irken G. Disseminated intravascular coagulation in pediatric patients: clinical and laboratory features and prognostic factors influencing the survival. *Pediatr Hematol Oncol.* 2005;22(8):679–688
23. Reed RC, Rutledge JC. Laboratory and clinical predictors of thrombosis and hemorrhage in 29 pediatric extracorporeal membrane oxygenation nonsurvivors. *Pediatr Dev Pathol.* 2010;13(5):385–392
24. Schöchl H, Solomon C, Traintinger S, et al. Thromboelastometric (ROTEM) findings in patients suffering from isolated severe traumatic brain injury. *J Neurotrauma.* 2011;28(10):2033–2041
25. Selladurai BM, Vickneswaran M, Duraisamy S, Atan M. Coagulopathy in acute head injury–a study of its role as a prognostic indicator. *Br J Neurosurg.* 1997;11(5):398–404
26. Podolsky-Gondim GG, Furlanetti LL, Viana DC, Ballestero MFM, de Oliveira RS. The role of coagulopathy on clinical outcome following traumatic brain injury in children: analysis of 66 consecutive cases in a single center institution. *Childs Nerv Syst.* 2018;34(12):2455–2461
27. Oladunjoye OO, Sleeper LA, Nair AG, et al. Partial thromboplastin time is more predictive of bleeding than anti-Xa levels in heparinized pediatric patients after cardiac surgery. *J Thorac Cardiovasc Surg.* 2018;156(1):332–340.e1
28. Algren JT, Lal S, Cutliff SA, Richman BJ. Predictors of outcome in acute meningococcal infection in children. *Crit Care Med.* 1993;21(3):447–452
29. Cheuk DK, Ha SY, Lee SL, Chan GC, Tsoi NS, Lau YL. Prognostic factors in children requiring admission to an intensive care unit after hematopoietic stem cell transplant. *Hematol Oncol.* 2004;22(1):1–9
30. Niederwanger C, Bachler M, Hell T, et al. Inflammatory and coagulatory parameters linked to survival in critically ill children with sepsis. *Ann Intensive Care.* 2018;8(1):111
31. Tude Melo JR, Rocco FD, Blanot S, et al. Mortality in children with severe head trauma: predictive factors and proposal for a new predictive scale. *Neurosurgery.* 2010;67(6):1542–1547