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Authors

Bembea, Melania
Agus, Michael
Akcan-Arikan, Ayse
et al.

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Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Contemporary Organ Dysfunction Criteria: Executive Summary

A full list of authors and affiliations appears at the end of the article.

Abstract

Prior criteria for organ dysfunction in critically ill children were based mainly on expert opinion. We convened the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) expert panel to summarize data characterizing single and multiple organ dysfunction and to derive contemporary criteria for pediatric organ dysfunction. The panel was composed of 88 members representing 47 institutions and 7 countries. We conducted systematic reviews of the literature to derive evidence-based criteria for single organ dysfunction for neurologic, cardiovascular, respiratory, gastrointestinal, acute liver, renal, hematologic, coagulation, endocrine, endothelial and immune system dysfunction. We searched the PubMed and EMBASE databases from January 1992 to January 2020. Study identification was accomplished using a combination of medical subject heading terms and text words related to concepts of pediatric organ dysfunction. Electronic searches were conducted by medical librarians. Studies were eligible for inclusion if they reported original data collected in critically ill children, evaluated performance characteristics of scoring tool(s) or clinical assessments for organ dysfunction, and assessed a patient-centered, clinically meaningful outcome. Data were abstracted from each included study into an electronic data extraction form. Risk of bias was assessed using the Quality in Prognosis Studies tool. Consensus was achieved for a final set of 43 criteria for pediatric organ dysfunction employing iterative voting and discussion. While the PODIUM criteria for organ dysfunction were limited by available evidence and will require validation, they provide a contemporary foundation for researchers to identify and study single and multiple organ dysfunction in critically ill children.

Table of Contents Summary:

We present evidence-informed, consensus criteria for organ dysfunction in critically-ill children, following systematic reviews of the literature on organ dysfunction clinical assessments and scoring tools.

Address correspondence to: Melania M. Bembea, MD, Johns Hopkins Hospital, 1800 Orleans Street, Bloomberg Suite 6321, Baltimore, MD 21287, Tel: 410-955-6412, mbembea1@jhmi.edu.

Contributors' Statement Page

Melania M. Bembea and Jerry J. Zimmerman conceptualized and designed the project, drafted the initial manuscript, and approved the final manuscript as submitted.

All authors carried out organ-specific systematic reviews on scoring tools and clinical assessments for organ dysfunction, contributed to the drafting of and consensus process for the final organ dysfunction criteria proposed herein, reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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

Keywords

organ dysfunction; critical illness; children

Introduction

Pediatric critical care largely focuses on preventing, stabilizing and hastening resolution of dysfunctional organ systems. Even in the best pediatric intensive care units (PICUs), recalcitrant multiple organ dysfunction syndrome (MODS) represents the most common antecedent for death.[1–3] Multiple investigations have ascertained that risk for mortality in the PICU is associated with number of dysfunctional organs in a dose-response fashion.[1,4–9] More recently, risks for short and long-term morbidity following pediatric critical illness, assessed as functional status or health-related quality of life, were strongly associated with intensity and duration of organ dysfunction.[4,9,10]

Although the history of pediatric MODS is rich with theory and controversy, confirmation of a unifying mechanism(s) for MODS as an underlying feature of critical illness pathophysiology remains elusive.[11–13] Clinical phenotypes, with individual treatment approaches, have been proposed for pediatric MODS[14,15] A recent survey of parents and care providers of critically ill children reported that following survival and functional status/health-related quality of life, duration of organ dysfunction was identified as the next most important outcome for a hypothetical interventional trial enrolling critically ill children.[16]

Despite its paramount importance in the practice of pediatric critical care, clinicians and researchers have relied on historical expert consensus definitions of organ dysfunctions that were derived in 2004 for the conduct of the RESOLVE trial of activated protein C (Xigris, Lily) for pediatric septic shock.[17] Results of this consensus conference were published in 2005 as a supplement to *Pediatric Critical Care Medicine* and represent the most frequently cited reference for this journal.[18] Accordingly, in March 26–27, 2015, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) convened a group of nearly 30 experts (clinicians, basic scientists, bioengineers, and others) in Rockville, Maryland, to discuss a research agenda for pediatric MODS with an ultimate goal of improving outcomes for children who experience this common syndrome. The workshop was sponsored by the Office of Science Policy, Analysis and Communication of the NICHD. A summary of this first Pediatric MODS Workshop was subsequently published as a supplement to *Pediatric Critical Care Medicine* in 2017.[19]

In addition to the development of new program announcements related to pediatric MODS (Research to Advance the Understanding and Management of MODS in Children, PAR-18–091, etc), the other immediate, clear directive that emerged during this workshop, was the organization of a grassroots, Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Collaborative. The PODIUM Collaborative focused on the notion that in order to advance knowledge related to pediatric MODS, the field required clearer, updated definitions and common data elements for MODS overall, as well as for individual organ dysfunction, particularly given the wealth of novel data that had been published on this subject over the preceding decade.

The PODIUM Collaborative addressed the key question, “What are the performance characteristics of currently used scoring tools and clinical assessments to screen for single and multiple organ dysfunction among critically ill children?” The long-term goal of the PODIUM Collaborative is to improve outcomes for children with MODS. The overall objectives of this work are to widely disseminate validated contemporary definitions of single and multiple pediatric organ dysfunction.

This executive summary describes the methodology and presents the final set of evidence-based pediatric organ dysfunction criteria. Additional details are provided in the accompanying manuscripts published as a Supplement in *Pediatrics*.*refPODIUMOrganSpecificSystematicReviews* The feasibility and the roadmap for the PODIUM project were established in 2016 in consultation with methodologists from the Johns Hopkins Evidence-based Practice Center (KAR) and informed by targeted evidence assessment by the Scientific Resource Center for Agency for Healthcare Research and Quality (AHRQ)’s Effective Health Care (EHC) Program. The methods for development of criteria characterizing organ dysfunction in critically ill children consisted of several predefined phases: 1) conduct twelve systematic reviews including identification, assessment, and synthesis of published literature on scoring tools and clinical assessments used for single and multiple organ dysfunction; 2) develop criteria indicating single organ dysfunction, including rationale and supporting evidence for each; and 3) undertake iterative voting for consensus building.

Definitions

Critically ill children were defined as admitted to an intensive care unit or cared for in an emergency department or hospital ward and at risk for admission to an intensive care unit. Pediatric age was defined as birth to <18 years, excluding critically ill premature babies (<37 weeks gestation) cared for in a neonatal intensive care unit. There are several available methods to identify organ dysfunction in critically ill children. We therefore did not require a specific definition for individual organ dysfunction, as we were interested in capturing a broad range of clinical, laboratory, physiological and imaging scoring and assessment tools utilized to screen for and identify organ dysfunction.

Selection and Organization of Panel Members

The selection of panel members was initiated by experts invited to participate in the aforementioned NICHD Pediatric MODS Workshop in 2015. Invitations were extended to experts based on their record of publication on organ dysfunction topics, and their leadership and participation in multicenter pediatric critical care clinical research studies during the prior five years. Two co-chairs were identified (MMB and JJZ) who were responsible for coordination of in-person meetings, conduct of educational webinars, overview of the systematic review and voting processes, and proofreading and editing of manuscripts for journal submission. Chair(s) for each subgroup were then identified and were charged with coordination of subgroup meetings and discussions, supervision of the subgroup’s progress in the conduct of their respective systematic review, evaluation of evidence for their subgroup’s topic, and oversight of the subgroup’s identification of criteria for organ dysfunction, accompanying rationales, any revisions needed based

on voting results, and manuscript drafting. Subgroups were formed by subtopic, as follows: MODS as a unifying diagnosis; individual organ dysfunction: neurologic, respiratory, cardiovascular, gastrointestinal, hepatic, renal, hematologic, coagulation, endocrine, immune, and endothelial; and data analysis and validation.

A total of 92 panelists were identified based on their record of peer reviewed publications on the subtopic of interest, with 4 eventually withdrawing due to time constraints. The final list of 88 panelists representing 47 institutions and 7 countries constituted the PODIUM Collaborative. Conflict of interest disclosures were sought from all panelists before the start of the systematic reviews, and again at the time of journal submission. All work was conducted voluntarily, without compensation.

Systematic Reviews and Data Synthesis

We set out to answer two key questions (KQ): “What are the performance characteristics of currently used scoring tools and clinical assessments to screen for 1) single and 2) multiple organ dysfunction in critically ill children?” We identified 11 subtopics for KQ1 and one topic for KQ2. The subtopics for KQ1 were specific to the following organ systems: neurologic, respiratory, cardiovascular, gastrointestinal, hepatic, renal, hematologic, coagulation, endocrine, immune, and endothelial. We developed Population, Intervention, Comparators, and Outcomes (PICO) questions specific to each of the 11 organ systems as well as for multiple organ dysfunction as listed in Table 1 of the Effective Health Care Pediatric MODS Topic Brief.[20] The 12 systematic reviews are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[21] The protocol for the 12 systematic reviews was registered on PROSPERO (CRD42018090500).

We searched the PubMed and Embase databases from 1992 to October 2017, with an update conducted in January 2020, using a combination of medical subject heading terms and text words for concepts of organ dysfunction specific to each subtopic, and outcomes.[20] Electronic searches were conducted by medical librarians at the William H. Welch Medical Library, Baltimore, MD. Search strategies, dates conducted, and number of resulting citations are detailed in Data Supplement, Supplemental Table 1.

Studies were eligible for inclusion if they reported original data collected from critically ill pediatric patients (<18 years), evaluated the performance characteristics of scoring tool(s) or clinical assessments for organ dysfunction, and assessed an included outcome: mortality (e.g., PICU mortality, 28-day mortality, hospital mortality, mortality post-discharge), functional outcomes/residual morbidity (e.g., neurofunctional, cognitive, adaptive behavioral, depression, post-traumatic stress disorder, or acute stress disorder), organ-specific outcomes/residual morbidity (e.g., tracheostomy, gastric tube insertion, renal replacement therapy at hospital discharge), outcomes related to MODS (e.g., duration of new or progressive MODS, composite time to complete resolution of organ dysfunction), cost of medical care, and other patient-centered outcomes (e.g., quality of life, symptom improvement, quality of dying, spillover effect of a patient’s health care on loved ones).[20]

Studies were excluded if the study population consisted of infants born preterm (<37 weeks gestation) or adults (all participants ≥18 years of age, or mixed pediatric and adult population with inability to separate data for patients <18 years). Other exclusion criteria included: animal-only studies, not original data (e.g., editorials, commentaries, meeting proceedings, etc.), case reports or case series with sample size ≤10 participants, abstract-only, and non-English language publications with inability to determine eligibility.

Two independent reviewers identified studies meeting criteria for inclusion, with differences resolved by a third reviewer. PRISMA flowcharts are presented for each PODIUM organ-specific systematic review.*refPODIUMOrganSpecificSystematicReviews*

Risk of Bias Assessment, Data Abstraction and Synthesis of Included Studies

Risk of bias for included studies was assessed using the Quality in Prognosis Studies (QUIPS) tool.[22] Key data elements were extracted from each study using an electronic form developed in REDCap[23] and exported into evidence tables. Graphical summaries of the risk of bias assessments and evidence tables for each subtopic are presented for each PODIUM organ-specific systematic review.*refPODIUMOrganSpecificSystematicReviews* Data synthesis was conducted by organ dysfunction assessment or scoring tool within each subtopic. Quantitative analysis was not pursued due to high heterogeneity among included studies.

Drafting and Developing Agreement for Criteria Indicating Organ Dysfunction

After completion of the systematic reviews, each subgroup proposed a set of criteria for organ dysfunction specific to their subtopic, accompanied by a rationale and supporting literature as identified through the review. In addition, suggested threshold(s), any conditions that would need to be met prior to applying a criterion in a clinical scenario, and severity grading were provided, as applicable. Proposed criteria, accompanying rationales and evidence tables were then disseminated to 60 PODIUM voting members (minimum of 3 from each subgroup), using an online tool that ensured anonymity of responses (Qualtrics, Provo, UT). Each set of criteria was scored using the Research and Development/UCLA Appropriateness scale, ranging from 1 (strongly disagree) to 9 (strongly agree).[24] Scores of 1–3 represented disagreement, 4–6 represented equipoise, and 7–9 represented agreement. A comment box was optional for scores in the agreement range, and mandatory for scores in the equipoise and disagreement ranges. The *a priori* level of agreement was set at ≥80% of PODIUM voters rating organ dysfunction criteria as 7–9. Criteria that did not reach at least 80% agreement were reviewed by the subgroup they originated from, along with comments justifying disagreement or equipoise. They were revised by the subgroup (with justification for revisions) over a period of two weeks. Revised criteria were resent to all PODIUM voters for a second round of voting. The same process was then followed in a third and final round of voting. The three rounds of voting took place between October 18, 2019 to October 31, 2019 (round 1), November 19, 2019 to December 3, 2019 (round 2), and December 18 to December 31, 2019 (round 3). Inter-voting periods were used for revision of criteria that did not meet at least 80% agreement. After review of additional evidence from the January 2020 literature review update, none of the subgroups required revision of already-proposed criteria, however risk of bias and evidence tables were updated accordingly.

In their evaluation of evidence supporting specific scoring tools or clinical assessments of organ dysfunction, each subgroup was instructed to discuss feasibility and usability of each proposed criterion (e.g., is a laboratory test routinely obtained in the intensive care unit, are there cost limitations, is the test/assessment tool invasive, resource intensive, or difficult to interpret).

Lastly, each PODIUM subgroup identified knowledge gaps during the process of the literature review and proposed priorities for future preclinical and clinical research. Research priorities were submitted to the full PODIUM membership for ranking on a five-tier priority scale.

PODIUM Organ Dysfunction Criteria

Based on evidence assessed through each organ-specific systematic review of currently used scoring tools and clinical assessments to screen for single organ dysfunction, organ dysfunction criteria were proposed for all individual organ systems, with the exception of endothelial dysfunction. Following the systematic review of the literature on endothelial dysfunction assessment tools, no published assessment tools or biomarkers were identified that adequately screened for or identified endothelial cell activation (i.e., acquisition of new cellular functions to restore homeostasis) or dysfunction (i.e., loss or inappropriate exaggeration of cellular functions worsening pathologic changes) in critically ill children.

A total of 40 criteria were proposed initially. Eight criteria were added and five were removed during voting rounds #2 and #3 based on feedback from PODIUM membership. There were 43 criteria remaining after the iterative voting process described above. Median agreement scores (IQR, range) and percent agreement for each of the three voting rounds are detailed in Data Supplement, Supplemental Table 2.

The organ dysfunction scoring tools and clinical assessments proposed by PODIUM are summarized in Table 1 of this executive summary. The evidence tables and rationale supporting each criterion are presented in each PODIUM organ-specific systematic review.*ref12PODIUMOrganSpecificSystematicReviews*

The top two priorities for future research identified by each PODIUM organ subgroup, and further prioritized through voting across the entire voting PODIUM membership, are summarized in Table 2 of this executive summary.

In summary, the PODIUM Collaborative was convened to review published literature on performance characteristics of multiple and single organ dysfunction scoring tools and clinical assessments, and to develop contemporary, evidence-based criteria for organ dysfunction in critically ill children. These goals were achieved by conducting systematic reviews of the literature for single and multiple organ dysfunction scoring tools and assessments, and by building consensus for the resulting criteria. The PODIUM criteria for organ dysfunction are meant to serve as a foundation to researchers to further validate, refine, and combine criteria to: accurately identify patients with single or multiple organ dysfunction; identify patterns of organ dysfunction combinations and temporal trends that constitute unique phenotypes associated with worse outcomes; and serve either as entry

criteria or as outcome measures for clinical trials, depending on the nature and scope of the intervention(s) tested.

The PODIUM project has several strengths and limitations. This is the first large-scale summary of existing evidence related to performance characteristics of scoring tools and assessments for organ dysfunction in critically ill children. Previously proposed criteria have been based on expert opinion, with potential bias inadvertently introduced by panel members. All systematic reviews conducted for PODIUM were rigorous, transparent and fully reproducible; the search strategy is published along with this executive summary, thus facilitating regular updates as new evidence and novel tests for organ dysfunction emerge. Special emphasis was placed on developing organ dysfunction criteria that are strongly supported by published studies, and not by expert opinion. In addition, whenever possible, we took into consideration issues of a) feasibility (i.e., tests or clinical assessments that can be conducted routinely in most critically ill children); b) safety (i.e., noninvasive or minimally-invasive tests preferable to invasive tests even if the latter have better performance characteristics); c) equity (i.e., tests or clinical assessments that can be conducted in intensive care units including those with limited resources); d) limitations for timing of assessment (i.e., generalizable to the entire intensive care unit or hospital stay vs studied only on specific days such as day of admission to the intensive care unit); e) barriers to accurate organ dysfunction assessments (i.e., difficult-to-interpret tests or tests requiring high level of training and specialization); f) operationalization (i.e., tests or clinical assessments routinely recorded in electronic medical records that will facilitate future development of clinical decision support tools).

Limitations are related to available data as well as the PODIUM process. There is extreme heterogeneity in categorization of various patient populations among pediatric critical care studies, and in definitions of common data elements (including “basic” data elements such as age categories). This rendered quantitative evaluation of performance characteristics of individual scoring and assessment tools in the form of meta-analyses inappropriate. While the PODIUM Collaborative emphasized diversity of institutions and diversity of age and gender among participating members, initial membership was dictated by participation in the 2015 NIH/NICHD symposium. We acknowledge that, while membership was broadened and included members from seven countries, it is still primarily representative of academic North American pediatric intensive care units.

Conclusions

The PODIUM criteria for organ dysfunction provide a foundation for clinicians and researchers to diagnose and study single and multiple organ dysfunction in critically ill children. These criteria will require further validation*NL S-P, et al PODIUM evaluation manuscript* and refinement followed by implementation in the clinical environment using bioinformatics tools. The PODIUM process is transparent and reproducible, and thus renders itself to serial updates as new evidence and novel criteria for organ dysfunction emerge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Melania M. Bembea, MD, MPH, PhD[1], Michael Agus, MD[2], Ayse Akcan-Arikan, MD[3], Peta Alexander, MD[4], Rajit Basu, MD, MS[5], Tellen D. Bennett, MD, MS[6], Desmond Bohn, MD[7], Leonardo R. Brandão, MD, MSc[8], Ann-Marie Brown, PhD, CPNP-AC/PC, CCRN, CNE, FCCM[9], Joseph A. Carcillo, MD[10], Paul Checchia, MD[11], Jill Cholette, MD[12], Ira M. Cheifetz, MD FCCM FAARC[13], Timothy Cornell, MD[14], Allan Doctor, MD[15], Michelle Eckerle, MD[16], Simon Erickson, MD[17], Reid W.D. Farris, MD, MS[18], E. Vincent S. Faustino, MD, MHS[19], Julie C. Fitzgerald, MD, PhD, MSCE[20], Dana Y. Fuhrman, DO, MS[10], John S. Giuliano Jr, MD[21], Kristin Guilliams, MD[22], Michael Gaies, MD[23], Stephen M. Gorga, MD[23], Mark Hall, MD[24], Sheila J. Hanson, MD, MS[25], Mary Hartman, MD[26], Amanda B. Hassinger, MD, MS[27], Sharon Y. Irving, PhD, MSN, CRNP[28], Howard Jeffries, MD[29], Philippe Jouvet, MD PhD MBA[30], Sujatha Kannan, MBBS[1], Oliver Karam, MD, PhD[31], Robinder G. Khemani, MD MsCI[32], Kissoon Niranjan, MD, FRCP(C), FAAP, FCCM, FACPE[33], Jacques Lacroix, MD[34], Peter Laussen, MD[35], Francis Leclerc, MD[36], Jan Hau Lee, MBBS, MRCPCH, MCI[37], Stephane Leteurtre, MD[36], Katie Lobner, MLIS[38], Patrick J. McKiernan, MD[39], Kusum Menon, MD, MSc[40], Paul Monagle, MBBS, MSc, MD, FRACP, FRCPA, FCCP[41], Jennifer A. Muszynski, MD, MPH[24], Folafoluwa Odetola, MB CHB, MPH, FAAP[23], Robert Parker, MD[42], Nazima Pathan, FRCPCH PhD[43], Richard W. Pierce, MD, MS[21], Jose Pineda, MD[32], Jose M. Prince, MD[44], Karen A. Robinson, MSc, PhD[45], Courtney M. Rowan, MD, MSCR[46], Lindsay M. Ryerson, MD, FRCPC[47], L. Nelson Sanchez-Pinto, MD, MBI[48], Luregn J Schlapbach, MD, PhD, FCICM[49], David T. Selewski, MD, MS[50], Lara S. Shekerdemian, MD[11], Dennis Simon, MD[10], Lincoln S. Smith, MD[18], James E. Squires, MD[39], Robert H. Squires, MD[39], Scott M. Sutherland, MD[51], Yves Ouellette, MD, PhD, FCCM[52], Michael C. Spaeder, MD, MS[53], Vijay Srinivasan, MBBS, MD, FCCM[20], Marie E. Steiner, MD, MS[54], Robert C. Tasker, MA, MD (Cantab), MBBS (Lond), DCH, FRCPCH, FRCP, FHEA (UK), AM (Harvard) MD (MA)[55], Ravi Thiagarajan, MD[4], Neal Thomas, MD[56], Pierre Tissieres, MD, DSc[57], Chani Traube, MD[58], Marisa Tucci, MD[34], Katri V. Typpo, MD, MPH[59], Mark S. Wainwright, MD, PhD, FAAN[60], Shan L. Ward, MD, MAS[61], R. Scott Watson, MD, MPH[18], Scott Weiss, MD, MSCE[20], Jane Whitney, MD, MSCE[2], Doug Willson, MD[31], James L. Wynn, MD, FAAP[62], Nadir Yeyha, MD, MSCE[20], Jerry J. Zimmerman, MD, PhD, FCCM[63]

Affiliations

[1]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Division of Medical Critical Care, Boston Children's Hospital, Harvard Medical School, Boston Children's Hospital, Boston, MA

[3]Department of Pediatrics, Sections of Critical Care and Nephrology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

[4]Department of Cardiology, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA

[5]Division of Pediatric Critical Care, Children's Healthcare of Atlanta, Emory University, Atlanta, GA

[6]Sections of Informatics and Data Science and Critical Care Medicine, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

[7]Department of Critical Care Medicine, The Hospital for Sick Children, Toronto

[8]Division of Hematology-Oncology, Department of Paediatrics, University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

[9]Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA

[10]Division of Pediatric Critical Care Medicine, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

[11]Section of Critical Care Medicine, Department of Pediatrics, Texas Children's Hospital and Baylor College of Medicine, Houston, TX

[12]Department of Pediatrics, University of Rochester Golisano Children's Hospital, Rochester, NY

[13]Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH

[14]Division of Pediatric Critical Care Medicine, Department of Pediatrics, Stanford University School of Medicine, Lucile Packard Children's Hospital Stanford, Palo Alto, CA

[15]University of Maryland School of Medicine, Center for Blood Oxygen Transport and Hemostasis

[16]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati OH USA and Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati OH

[17]Department of Paediatric Critical Care; Perth Children's Hospital and University of Western Australia; Perth, Western Australia, Australia

[18]Department of Pediatrics, University of Washington and Seattle Children's Hospital; Seattle, WA

[19]Department of Pediatrics, Section of Pediatric Critical Care Medicine, Yale School of Medicine, New Haven CT

[20]Department of Anesthesiology and Critical Care, The University of Pennsylvania Perelman School of Medicine and Children's Hospital of Philadelphia, Philadelphia, PA

[21]Section of Pediatric Critical Care Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, CT

[22]Department of Neurology, Division of Pediatric and Development Neurology, Department of Pediatrics, Division of Pediatric Critical Care Medicine, Washington University School of Medicine, St. Louis, MI

[23]Department of Pediatrics, University of Michigan, Ann Arbor, MI

[24]Division of Critical Care Medicine, Department of Pediatrics, The Ohio State University College of Medicine, Nationwide Children's Hospital, Columbus, OH

[25]Department of Pediatrics, Critical Care Section, Medical College of Wisconsin/ Children's Wisconsin, Milwaukee, WI

[26]Department of Pediatrics, Washington University, St. Louis, MO

[27]Department of Pediatrics, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, John R. Oishei Children's Hospital, Buffalo, NY

[28]Department of Family and Community Health, University of Pennsylvania School of Nursing, Philadelphia, PA

[29]Department of Pediatrics, University of Washington School of Medicine, Seattle WA

[30]Department of Paediatrics; Sainte-Justine Hospital and University of Montreal; Montreal, Québec, Canada

[31]Division of Pediatric Critical Care Medicine, Children's Hospital of Richmond at VCU, Richmond, VA

[32]Department of Anesthesiology and Critical Care Medicine; Children's Hospital Los Angeles and University of Southern California Keck School of Medicine; Los Angeles, CA

[33]Division of Critical Care, Department of Pediatrics, University of British Columbia and BC Children's Hospital

[34]Division of Pediatric Critical Care Medicine, Centre Hospitalier Universitaire de Sainte-Justine, Université de Montreal, Canada

[35]Department of Cardiology, Boston Children's Hospital and Department of Anesthesia, Harvard Medical School, Boston, MA

[36]Univ. Lille, CHU Lille, ULR 2694 - METRICS : Évaluation des technologies de santé et des pratiques médicales, F-59000 Lille, France

[37]Children's Intensive Care Unit, KK Women's and Children's Hospital, and, Duke-NUS Medical School, Singapore

[38]Welch Medical Library, The Johns Hopkins University School of Medicine, Baltimore, MD

[39]Division of Gastroenterology, Hepatology, and Nutrition, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA

[40]Division of Pediatric Critical Care, Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada

[41]Department of Clinical Haematology, Royal Children's Hospital, Victoria, Australia, and Haematology Research, Murdoch Children's Research Institute, Victoria, Australia

[42]Department of Pediatrics (Emeritus), Hematology/Oncology, Stony Brook University Renaissance School of Medicine, Stony Brook, NY

[43]Department of Paediatrics, University of Cambridge; Clinical Research Associate, Kings College, Cambridge, UK

[44]Department of Surgery and Pediatrics, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

[45]Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD

[46]Department of Pediatrics, Division of Pediatric Critical Care; Indiana University School of Medicine and Riley Hospital for Children; Indianapolis, IN

[47]Department of Pediatrics, University of Alberta, Edmonton, AB Canada

[48]Departments of Pediatrics (Critical Care) and Preventive Medicine (Health & Biomedical Informatics), Northwestern University Feinberg School of Medicine and Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

[49]Pediatric and Neonatal Intensive Care Unit, Children`s Research Center, University Children`s Hospital Zurich, Zurich, Switzerland

[50]Department of Pediatrics, Medical University of South Carolina, Charleston, SC

[51]Department of Pediatrics, Division of Nephrology, Stanford University School of Medicine, Stanford, CA

[52]Division of Critical Care Medicine, Department of Pediatrics, Mayo Clinic, Rochester, MN

[53]Department of Pediatrics, University of Virginia, Charlottesville, VA

[54]Department of Pediatrics, Critical Care Medicine & Hematology, University of Minnesota, Minneapolis, MN

[55]Department of Anesthesiology, Critical Care and Pain Medicine, Harvard Medical School, Boston MA

[56]Department of Pediatrics and Public Health Science, Division of Pediatric Critical Care Medicine; Penn State Hershey Children's Hospital; Hershey, PA

[57]Pediatric Intensive Care, AP-HP Paris Saclay University, Le Kremlin-Bicêtre, France

[58]Department of Pediatrics, Division of Critical Care Medicine, Weill Cornell Medical College, NY

[59]Department of Pediatrics and the Steele Children's Research Center, University of Arizona College of Medicine, Tucson, AZ

[60]Department of Neurology, Division of Pediatric Neurology, University of Washington, Seattle, WA

[61]Department of Pediatrics, Division of Critical Care, UCSF Benioff Children's Hospitals, San Francisco and Oakland, CA

[62]Department of Pediatrics and Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, Florida

[63]Department of Pediatrics, Seattle Children's Hospital, Seattle Children's Research Institute, University of Washington School of Medicine, Seattle, WA

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Abbreviations:

PODIUM	Pediatric Organ Dysfunction Information Update Mandate

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Table 1.

PODIUM: Criteria for organ dysfunction in pediatric critical illness

Organ system	Criterion for organ dysfunction	Suggested thresholds	Conditions	Severity
Neurologic	GCS	≤8	None	Not graded
	GCS-m	≤4	None	Not graded
	CAPD	≥9	None	Not graded
	EEG background attenuation and suppression; electrographic seizure activity	NA	Not applicable in patients with history of seizures or acute neurological injury on admission	Not graded
Respiratory	PaO_2/FiO_2	≤ 300	If on HFNC (≥ 1.5 L/kg/min or ≥ 30 LPM), NIV, non-rebreather, or venturi; FiO_2 ≥ 0.4 in all modes of support	Non-severe
	SpO_2/FiO_2	≤ 264	•⟶ If on HFNC (≥ 1.5 L/kg/min or ≥ 30 LPM), NIV, non-rebreather, or venturi; FiO_2 ≥ 0.4 in all modes of support •⟶ When 80% ≤ SpO_2 ≤ 97%	Non-severe
	Ventilatory failure (obstructive lung disease, e.g. asthma, without oxygenation failure)	NIV	If on HFNC (≥ 1.5 L/kg/min or ≥ 30 LPM), NIV, non-rebreather, or venturi; FiO_2 ≥ 0.4 in all modes of support	Non-severe
		Invasively ventilated	If invasively ventilated	Non-severe
	OI = (FiO_2 × M_{PAW} × 100)/PaO_2	≥ 4 to < 16	If invasively ventilated	Non-severe
		≥ 16	If invasively ventilated	Severe
	OSI = (FiO_2 × M_{PAW} × 100)/SpO_2	≥ 5 to < 12.3	•⟶ If invasively ventilated •⟶ When 80% ≤ SpO_2 ≤ 97%)	Non-severe
		≥ 12.3	•⟶ If invasively ventilated •⟶ When 80% ≤ SpO_2 ≤ 97%)	Severe
	ECLS for any respiratory failure	NA	If invasively ventilated	Severe
CV[a]	Venoarterial ECLS, temporary or durable LVAD or RVAD support	NA	None	Severe
	Cardiac Arrest	NA	None	Severe
	Heart rate (HR)	>2SD above normal for age •⟶ 0–7 days: HR>180 •⟶ >1 week – 1 m: HR>180 •⟶ >1 m – <1 y: HR>180 •⟶ >1 y – <6 y: HR>160 •⟶ 6 y – <13 y: HR>150 •⟶ 13 y – <18 y: HR>130	If present at the same time as any of the other criteria for CV organ dysfunction	Not graded
	Systolic blood pressure (SBP)	More than 2SD below normal for age •⟶ 0–7 days: SBP<50 •⟶ >1 week – 1 m: SBP<70 •⟶ >1 m – <1 y: SBP<75 •⟶ >1 y – <6 y: SBP<75 •⟶ 6 y – <13 y: SBP<80 •⟶ 13 y – <18 y: SBP<80	If present at the same time as any of the other criteria for CV organ dysfunction	Not graded
	Vasoactive-Inotropic Score[b]	≥5	If present at the same time as any of the other criteria for CV organ dysfunction	Not graded

Organ system	Criterion for organ dysfunction	Suggested thresholds	Conditions	Severity
	Serum lactate	≥3 – <5 mmol/L	If present at the same time as any of the other criteria for CV organ dysfunction	Non-severe
		≥5 mmol/L	If present at the same time as any of the other criteria for CV organ dysfunction	Severe
	Serum troponin I	0.6 – 2.0 ng/mL	If present at the same time as any of the other criteria for CV organ dysfunction	Non-severe
		>2.0 ng/mL	If present at the same time as any of the other criteria for CV organ dysfunction	Severe
	Central venous oxygen saturation	<70%	If present at the same time as any of the other criteria for CV organ dysfunction •→ In patients without cyanotic congenital heart disease •→ Ideally sampled from right atrium or pulmonary artery in a patient without intracardiac abnormalities, but proximal SVC and IVC acceptable. •→ Whole blood laboratory assay as standard, but consider validated continuous invasive monitoring	Not graded
	Echocardiographic estimation of left ventricular ejection fraction	30% – <50%	If present at the same time as any of the other criteria for CV organ dysfunction	Non-severe
		<30%	If present at the same time as any of the other criteria for CV organ dysfunction	Severe
Renal	Urine output[c]	<0.5 mL/kg/hr for ≥6 hours	Concomitant serum creatinine increase 1.5–1.9 times baseline[d] *OR* ≥0.3 mg/dL (≥26.5 μmol/L) increase	Not graded
		<0.5 mL/kg/hr for ≥12 hours	None	Not graded
	Serum creatinine	Increase 1.5–1.9 times baseline[d] *OR* ≥0.3 mg/dL (≥26.5 μmol/L) increase	Concomitant urine output[c] <0.5 mL/kg/h for ≥6 hours	Not graded
		Increase ≥2 times baseline[d]	None	Not graded
	eGFR	Decrease to <35 mL/min/1.73m^2	Excludes neonates <30 days of age	Not graded
	Initiation of RRT	NA	Initiation of RRT for any reason other than toxic ingestion or hyperammonemia	Not graded
	Fluid overload[e]	20%	Measured starting 48 hours after ICU admission	Not graded
GI	Bowel ischemia	Bowel perforation *OR* pneumatosis intestinalis *OR* ischemia present on gross inspection (surgical) or by plain abdominal film, CT, or MRI Sloughing of gut	None	Severe
Hepatic[f]	AST	>100 IU/L	Absent hemolysis or myopathy (Wilson disease is an exception as severe Coombs-negative hemolysis may be present) Presence of liver-based coagulopathy coupled with hepatic encephalopathy[g]	Not graded

Organ system	Criterion for organ dysfunction	Suggested thresholds	Conditions	Severity
	ALT	>100 IU/L	Absent hemolysis or myopathy (Wilson disease is an exception as severe Coombs-negative hemolysis may be present) Presence of liver-based coagulopathy coupled with hepatic encephalopathy[g]	Not graded
	GGT	>100 IU/L	Absent biliary obstruction Presence of liver-based coagulopathy coupled with hepatic encephalopathy[g]	Not graded
	Total bilirubin	>5 mg/dL (>85.5 μmol/L)	Absent suspected Gilbert's disease Presence of liver-based coagulopathy coupled with hepatic encephalopathy[g]	Not graded
	Direct or conjugated bilirubin	>2 mg/dL (>34.2 μmol/L)	Absent biliary obstruction Presence of liver-based coagulopathy coupled with hepatic encephalopathy[g]	Not graded
	Liver-based coagulopathy coupled with hepatic encephalopathy	PT ≥15 seconds or INR ≥1.5 accompanied by clinical hepatic encephalopathy For those with a PT ≥20 seconds or INR ≥2.0, HE is not required, but should be assessed. Hepatic encephalopathy is determined by age specific grading scales (Tables 2 and 3 in the PODIUM Online Supplement, Acute Liver Dysfunction Section) (*refPODIUMSupplement*)	Presence of: AST >100 IU/L *OR* ALT >100 IU/L *OR* GGT >100 IU/L *OR* Total bilirubin >5 mg/dL (>85.5 μmol/L) *OR* Direct or conjugated bilirubin >2 mg/dL (>34.2 μmol/L) To ensure vitamin K deficiency is not a principal component of the coagulopathy, a single dose of intravenous vitamin K (1 mg for infants up to 10 mg in adults) is administered with repeat PT/INR determined 6–8 hours later.	Not graded
Hematology	Platelet count[g]	<100,000 cells/μL	Patients without underlying hematologic or oncologic diagnoses	Not graded
		<30,000 cells/μL	Patients with underlying hematologic or oncologic diagnoses	Not graded
		50% decrease from baseline[h]	Patients with baseline thrombocytopenia regardless of etiology (i.e., baseline platelet count <100,000 cells/ μL)	Not graded
	Leukocyte count	<3,000 cells/μL	None	Not graded
	Hemoglobin	5 - <7 g/dL	None	Non-severe
		< 5 g/dL	None	Severe
Coagulation[i]	Platelet count	<100,000 cells/μL	•⟶ Absent liver dysfunction •⟶ Presence of at least one additional coagulation dysfunction criterion	Not graded
	International normalized ratio	>1.5	•⟶ Absent liver dysfunction •⟶ Presence of at least one additional coagulation dysfunction criterion	Not graded
	Fibrinogen	<150 mg/dL (<4.41 μmol/L)	•⟶ Absent liver dysfunction •⟶ Presence of at least one additional coagulation dysfunction criterion	Not graded
	D-dimer	>10x the upper limit of normal[j] or above the assay's upper limit of	•⟶ Absent liver dysfunction •⟶ Presence of at least one additional coagulation dysfunction criterion	Not graded

Organ system	Criterion for organ dysfunction	Suggested thresholds	Conditions	Severity
		detection if this limit is below 10x upper limit of normal		
Endocrine	Blood glucose	≥150 mg/dL (≥8.3 mmol/L)	None	Not graded
		<50 mg/dL (<2.8 mmol/L)	None	Not graded
	Serum total thyroxine (T4)	<4.2 mcg/dL (<54 nmol/L)	Not applicable for patients with pre-existing primary or central thyroid disease	Not graded
	Serum cortisol levels pre and post ACTH stimulation test	Peak <18 mcg/dL (500 nmol/L) and/or increment of <9 mcg/dL (250 nmol/L) post ACTH stimulation	Post stimulation cortisol level should be measured at 30 min following a low dose test and 1 hour following a high dose testing. Testing should only be considered in patients with clinical suspicion of primary adrenal insufficiency (e.g., unexplained hyponatremia, hyperkalemia, hypoglycemia and hemodynamic instability).	Not graded
Immune	Peripheral absolute neutrophil count	<500 cells/μL	None	Not graded
	Peripheral absolute lymphocyte count	<1,000 cells/μL	None	Not graded
	CD4+ T-lymphocyte count	<750 cells/μL	Age <1 y	Not graded
		<500 cells/μL	Age 1 y – 5 y	Not graded
		<200 cells/μL	Age ≥6 y	Not graded
	CD4+ T-lymphocyte percentage of total lymphocytes	<26%	Age <1 y	Not graded
		<22%	Age 1 y – 5 y	Not graded
		<14%	Age ≥6 y	Not graded
	Monocyte HLA-DR expression (where clinically available)[l]	< 30%	None	Not graded
	Ex vivo LPS-induced TNFα production capacity (where clinically available)[k]	Below manufacturer provided thresholds	None	Not graded

GCS, Glasgow Coma Score; GCS-m, Glasgow Coma Score motor response; CAPD, Cornell Assessment of Pediatric Delirium; EEG, electroencephalography; HFNC, high flow nasal cannula; LPM, liters per minute; NIV, non-invasive ventilation; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; OI, oxygenation index; OSI, oxygenation saturation index; M_{PAW}, mean airway pressure; PaO_2, partial pressure of oxygen in arterial blood; SpO_2, pulse oximetry oxygen saturation; ECLS, extracorporeal life support; CV, cardiovascular; SD, standard deviation; m, month; y, year; SVC, superior vena cava; IVC, inferior vena cava; LVAD, left ventricular assist device; RVAD, right ventricular assist device; CT, computed tomography; MRI, magnetic resonance imaging; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; PT, prothrombin time; INR, international normalized ratio; ACTH, adrenocorticotropic hormone; HLA-DR, Human Leukocyte Antigen – DR isotype; LPS, lipopolysaccharide; TNFα, tumor necrosis factor alpha

[a] Criteria for cardiovascular dysfunction in patients who have cardiovascular dysfunction in the setting of critical illness, excluding patients: 1) with underlying cyanotic congenital heart disease, and 2) those who underwent cardiopulmonary bypass (CPB) during the episode of care (i.e., the ICU admission). These criteria are not intended to assess or grade post-CPB impaired cardiac output or inflammatory state.

[b] Vasoactive Inotropic Score = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (units/kg/min) + 100 × norepinephrine dose (μg/kg/min)

[c] Consider ruling out obstructive uropathy in the setting of low urine output

[d] Use the lowest serum creatinine value available in the 3 months prior to admission as the baseline serum creatinine. If a prior serum creatinine 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. The table in supporting documents, providing 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[1] and have been validated in critically ill children[2].

[e] Fluid overload can be defined by input/output or weight-based calculations. For weight-based determination, FO = [(Current weight − ICU admission weight)/ICU admission weight] × 100. For input/output based determination, FO = {[Sum of daily (fluid in − fluid out)]/ICU admission weight} × 100. Use of weight-based formula for fluid overload is preferential if weight data are available.

[f] Condition that has to be met for all acute liver dysfunction criteria: no known evidence of chronic liver disease with duration of symptoms <8 weeks

[g] For the purposes of defining hematologic failure, thrombocytopenia should exist in the absence of coagulation dysfunction (i.e., presence of at least 2 of the 4 PODIUM Coagulation Dysfunction criteria).

[h] For patients with underlying hematologic or oncologic disease and baseline thrombocytopenia, both <30,000 and 50% decrease from baseline criteria must be met.

[i] 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/ cardiopulmonary bypass) and, as such, may not be useful in these populations due to the effects of the circuit and associated anticoagulation therapy.

[j] 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 Sep;8(9):PC01–6.

[k] These tests may be clinically available outside the U.S.

Table 2.

PODIUM: Research Priorities for the Study of Organ Dysfunction in Critically Ill Children[a]

PODIUM: Research Priorities
Develop and validate tools that use routine clinical data from the electronic health record that allow for automated and longitudinal calculation of scores to be made available for “real-time” clinical assessment
Develop scores to predict – rather than diagnose or describe – organ dysfunction
Identify trajectories or early warning signs of cardiovascular dysfunction in critical illness for prediction of clinical deterioration to cardiopulmonary arrest or institution of mechanical circulatory support. Can these be used to target early intervention in this high risk population?
Validate urinary biomarkers of AKI/renal dysfunction: a) appropriate thresholds in children, in particular non-cardiac populations, b) use of biomarkers to derive and target MODS-AKI phenotypes, c) development of a clinical renal function panel
Compare the epidemiology and outcomes of MODS as a syndrome versus co-existing, but pathobiologically distinct, multiple concurrent organ dysfunctions
Identify biomarkers (e.g. proteomic and/or transcriptomic signatures) of immune system dysregulation in critically ill children; to develop high-throughput, rapid-turnaround tests for these biomarkers; and to move them to clinical laboratory and/or the bedside for the diagnosis and management of immune system failure in critically ill children
Validate objective scoring systems for neurologic dysfunction in pediatric MODS that can be used longitudinally to detect a) patients at risk for neurologic injury, b) progression of injury, and c) resolution/repair of the injury
Ascertain impact of bundled care for AKI (e.g. use of balanced fluids, nephrotoxin avoidance, diuretics)
Identify and prognosticate according to existing and emerging technology (somatic and cerebral NIRS, analyses of cardiac index, echocardiographic parameters) in the assessment of cardiovascular dysfunction in critical illness. Can any be associated with improvement in clinical status with therapy?
Correlate biomarkers to physiological function and measured clinical parameters is also important. Unbiased, large scale analysis, so called “-omics" approaches, should be employed to monitor multiple variables simultaneously and provide novel insights into disease pathology
Evaluate host-microbial interactions in the gastrointestinal tract
Define coagulation dysfunction using different combinations of the laboratory tests included in the proposed criteria in children off and on mechanical circuits is a high research priority
Expand the definition of respiratory failure in MODS beyond gas exchange. Oxygenation and ventilation are nonspecific, affected by cardiac function, and do not address pathophysiology. Biomarkers of lung epithelial and endothelial disruption may provide additional structural and pathophysiologic information. Can biomarkers of pulmonary damage improve the definition of respiratory MODS?
Investigate the performance of von Willebrand factor, antithrombin, thrombomodulin, mean platelet volume, thromboelastography/ thromboelastometry to further define coagulation dysfunction
Explore correlation with critical illness outcomes and consider implications for clinical research for markers of adrenal axis function at the cellular level
Facilitate high-throughput, rapid-turnaround tests of leukocyte function (e.g. HLA-DR expression, cytokine production capacity) to the clinical laboratory and/or the bedside for clinical use for the diagnosis and management of immune system failure in critically ill children
Determine if effective minute ventilation via invasive or non-invasive measures improve the definition of respiratory MODS.
Consider if the definition of hematologic failure should include abnormal function in addition to abnormal quantity of cells/cellular components.
Identify mechanistic links between neurological dysfunction and other organ dysfunctions (e.g., exosomes released from liver triggering neurologic involvement, sepsis pathophysiology mechanisms and neurologic dysfunction, etc).
Develop a more fundamental understanding of how endothelial cells from various organs and vascular segments differentially respond to stimuli associated with critical illness, focused on human cell models with defined properties of specific vascular segments or organs
Develop reliable clinical score and/or biomarkers of feeding intolerance
Explore correlation of copeptin (an indirect measure of ADH/vasopressin concentrations) with critical illness outcomes
Characterize acute-on-chronic liver failure in children in order to provide a foundation to develop consensus guidelines
Determine if red cell distribution width is a clinically relevant biomarker of hematologic failure
Characterize disseminated intravascular coagulation in the setting of acute liver failure.

Abbreviations: PODIUM, Pediatric Organ Dysfunction Information Update Mandate; AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome; NIRS, near infrared spectroscopy; HLA-DR, Human Leukocyte Antigen – DR isotype; ADH, antidiuretic hormone

[a] In descending order of priority based on PODIUM membership ranking