Executive Summary Table 1: Summary of Guidelines

A. RECOGNITION AND MANAGEMENT
1. In children who present as acutely unwell, we *suggest* implementing systematic screening for timely recognition of septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence). Remarks: Systematic screening needs to be tailored to the type of patients, resources, and procedures within each institution. Evaluation for the effectiveness and sustainability of screening should be incorporated as part of this process.
2. We were unable to issue a recommendation about using blood lactate values to stratify children with suspected septic shock or other sepsis-associated organ dysfunction into low-versus high-risk of having septic shock or sepsis.
3. We *recommend* implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction (BPS).
4. We *recommend* obtaining blood cultures before initiating antimicrobial therapy in situations where this does not substantially delay antimicrobial administration (BPS).
5. In children with septic shock, we *recommend* starting antimicrobial therapy as soon as possible, within 1 hour of recognition (strong recommendation, very low quality of evidence). 6. In children with sepsis-associated organ dysfunction but without shock, we *suggest* starting antimicrobial therapy *as soon as possible* after appropriate evaluation, within 3 hours of recognition (weak recommendation, very low quality of evidence).
7. We *recommend* empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (BPS). 8. Once the pathogen(s) and sensitivities are available, we *recommend* narrowing empiric antimicrobial therapy coverage (BPS). 9. If no pathogen is identified, we *recommend* narrowing or stopping empiric antimicrobial therapy according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice (BPS).
10. In children without immune compromise and without high risk for multidrug-resistant pathogens, we *suggest* against the routine use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy (weak recommendation, very low quality of evidence). Remarks: In certain situations, such as confirmed or strongly suspected group B streptococcal sepsis, use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy may be indicated. 11. In children with immune compromise and/or at high risk for multidrug-resistant pathogens, we *suggest* using empiric multi-drug therapy when septic shock or other sepsis-associated organ dysfunction is present/suspected (weak recommendation, very low quality of evidence).
12. We *recommend* using antimicrobial dosing strategies that have been optimized based on published pharmacokinetic/pharmacodynamic principles and with consideration of specific drug properties (BPS).
13. We *recommend* that emergent source control intervention be implemented as soon possible after a diagnosis of an infection amenable to a source control procedure is made (BPS).

Remarks: Appropriate diagnostic testing to identify the site of infection and microbial etiology should be performed, and advice from specialist teams (e.g., infectious diseases, surgery) should be sought, as appropriate, in order to prioritize interventions needed to achieve source control.

14. We *recommend* removal of intravascular access devices that are confirmed to be the source of sepsis or septic shock after other vascular access has been established and depending on the pathogen and the risks/benefits of a surgical procedure (strong recommendation, low quality of evidence).

15. In children with septic shock or sepsis-associated organ dysfunction who are receiving antimicrobials, we *recommend* daily assessment (e.g., clinical, laboratory assessment) for de-escalation of antimicrobial therapy (BPS).

    Remarks: This assessment should include a review of the ongoing indication for empiric antimicrobial therapy after the first 48 hours that is guided by microbiologic results and in response to clinical improvement and/or evidence of infection resolution. This recommendation applies to patients being treated with empiric, targeted, and combination therapy.

16. We *recommen*d determining the duration of antimicrobial therapy according to the site of infection, microbial etiology, response to treatment, and ability to achieve source control (BPS).

B. HEMODYNAMICS AND RESUSCITATION

17. In healthcare systems with availability of intensive care, we *suggest* administering up to 40-60 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

18. In healthcare systems with no availability of intensive care, we *suggest* administering up to 20 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).

    Remarks: Clinical markers of cardiac output may include heart rate, blood pressure, capillary refill time, level of consciousness, and urine output. The need for bolus fluid administration should be guided by frequent reassessment of clinical markers of cardiac output, serial blood lactate measurement and advanced monitoring, when available. Even in low-resource settings, the subset of children with septic shock *and hypotension* should receive cautious fluid bolus therapy. Signs of fluid overload may include clinical signs of pulmonary edema or new or worsening hepatomegaly.

19. We were unable to issue a recommendation about whether to target mean arterial blood pressure (MAP) at the 5^{th} or 50^{th} percentile for age in children with septic shock and other sepsis-associated organ dysfunction

20. We *suggest* not using bedside clinical signs in isolation to categorize septic shock in children as "warm" or "cold" (weak recommendation, very low quality of evidence).

21. We *suggest* using advanced hemodynamic variables, when available, in addition to bedside clinical variables to guide the resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

Remarks: Advanced hemodynamic monitoring may include cardiac output/cardiac index, systemic vascular resistance, or central venous oxygen saturation ($ScvO_2$).

22. We *suggest* using trends in blood lactate levels, in addition to clinical assessment, to guide resuscitation of children with septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

23. We *suggest* using crystalloids, rather than albumin, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).

    Remarks: Although there is no difference in outcomes, this recommendation takes into consideration cost and other barriers of administering albumin compared to crystalloids.

24. We *suggest* using balanced crystalloids, rather than 0.9% saline, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

25. We *recommend* against using starches in the acute resuscitation of children with septic shock or other sepsis-associated organ dysfunction (strong recommendation, moderate quality of evidence).

26. We *suggest* against using gelatin in the resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

27. We *suggest* using epinephrine, rather than dopamine, in children with septic shock (weak recommendation, low quality of evidence).

28. We *suggest* using norepinephrine, rather than dopamine, in children with septic shock (weak recommendation, very low quality of evidence).

29. We were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock.

30. We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock.

    Remarks: It is reasonable to begin vasoactive infusions after 40-60 mL/kg of fluid resuscitation if the patient continues to have evidence of abnormal perfusion. Either epinephrine or norepinephrine may be administered through a peripheral vein (or intraosseous, if in place) if central venous access is not readily accessible. Dopamine may be substituted as the first-line vasoactive infusion, administered either peripherally or centrally, if epinephrine or norepinephrine is not readily available.

31. We *suggest* either adding vasopressin or further titrating catecholamines in children with septic shock who require high-dose catecholamines (weak recommendation, low quality of evidence).

    Remarks: No consensus was achieved on the optimal threshold for initiating vasopressin. Therefore, this decision should be made according to individual clinician preference.

32. We were unable to issue a recommendation about adding an inodilator in children with septic shock and cardiac dysfunction despite other vasoactive agents.

33. We *suggest* using veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) as a rescue therapy in children with septic shock only if refractory to all other treatments (weak recommendation, very low quality of evidence).

C. VENTILATION

34. We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock.

35. We *suggest* not to use etomidate when intubating children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

36. We *suggest* a trial of non-invasive mechanical ventilation (over invasive mechanical ventilation) in children with sepsis-induced pediatric ARDS (PARDS) without a clear indication for intubation and who are responding to initial resuscitation (weak recommendation, very low quality of evidence)

    Remarks: When non-invasive mechanical ventilation is initiated, clinicians should carefully and frequently re-evaluate the patient's condition.

37. We *suggest* using high positive end-expiratory pressure (PEEP) in children with sepsis-induced PARDS (weak recommendation, very low quality of evidence)

    Remarks: The exact level of high PEEP has not been tested or determined in PARDS patients. Some RCTs and observational studies in PARDS have used and advocated for use of the ARDS-network PEEP to fractional inspired oxygen (FiO_2) grid though adverse hemodynamic effects of high PEEP may be more prominent in children with septic shock.

38. We cannot *suggest* for or against the use of recruitment maneuvers in children with sepsis-induced PARDS and refractory hypoxemia.

    Remarks: If a recruitment maneuver is considered, the use of a stepwise, incremental and decremental PEEP titration maneuver is preferred over sustained inflation techniques that have not been optimized through direct testing in PARDS patients. All PARDS patients must be carefully monitored for tolerance of the maneuver.

39. We *suggest* a trial of prone positioning in children with sepsis and severe PARDS (weak recommendation, low quality of evidence)

    Remarks: Research trials in adults with ARDS and children with PARDS have emphasized prone positioning for at least 12 hours per day, as tolerated.

40. We *recommend* against the routine use of inhaled nitric oxide (iNO) in all children with sepsis-induced PARDS (strong recommendation, low quality of evidence).

41. We *suggest* using iNO as a rescue therapy in children with sepsis-induced PARDS and refractory hypoxemia after other oxygenation strategies have been optimized (weak recommendation, moderate quality of evidence)

42. We were unable to issue a recommendation to use high-frequency oscillatory ventilation (HFOV) versus conventional ventilation in children with sepsis-induced PARDS.

43. We *suggest* using neuromuscular blockade in children with sepsis and severe PARDS (weak recommendation, very low quality of evidence)

    Remarks: The exact duration of neuromuscular blockade use in severe PARDS patients has not been determined to date. Most of the adult RCT data and pediatric observational data support treatment for 24-48 hours after ARDS onset.

44. We *suggest* using veno-venous ECMO in children with sepsis-induced PARDS and refractory hypoxia (weak recommendation, very low quality of evidence)

D. ENDOCRINE AND METABOLIC THERAPIES
45. We *suggest* against using intravenous hydrocortisone to treat children with septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (weak recommendation, low quality of evidence).
46. We *suggest* that either intravenous hydrocortisone or no hydrocortisone may be used if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability (weak recommendation, low quality of evidence).
47. We were unable to issue a recommendation regarding early hypocaloric/trophic enteral feeding followed by slow increase to full enteral feeding versus early full enteral feeding in children with septic shock or sepsis-associated organ dysfunction without contraindications to enteral feeding.
48. We *suggest* not withholding enteral feeding solely on the basis of vasoactive-inotropic medication administration (weak recommendation, low quality of evidence). Remarks: Enteral feeding is not contraindicated in children with septic shock after adequate hemodynamic resuscitation who no longer require escalating doses of vasoactive agents or in whom weaning of vasoactive agents has started.
49. We *suggest* enteral nutrition as the preferred method of feeding and that parenteral nutrition may be withheld in the first 7 days of PICU admission in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).
50. We *suggest* against supplementation with specialized lipid emulsions in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).
51. We *suggest* against the routine measurements of gastric residual volumes (GRV) in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).
52. We *suggest* administering enteral feeds through a gastric tube, rather than a post-pyloric feeding tube, to children with septic shock or other sepsis-associated organ dysfunction who have no contraindications to enteral feeding (weak recommendation, low quality of evidence)
53. We *suggest* against the routine use of prokinetic agents for the treatment of feeding intolerance in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).
54. We *recommend* against insulin therapy to maintain glucose target at or below 140 mg/dL (7.8 mmol/L) (strong recommendation, moderate quality of evidence).
55. We were unable to issue a recommendation regarding what blood glucose range to target for children with septic shock and other sepsis-associated organ dysfunction.
56. We *suggest* against the use of selenium in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).
57. We *suggest* against the use of glutamine supplementation in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).
58. We *suggest* against the use of arginine in the treatment of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

59. We *suggest* against using zinc supplementation in children with septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

60. We were unable to issue a recommendation as to whether to target normal blood calcium levels in children with septic shock or sepsis-associated organ dysfunction

61. We *suggest* against the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid state (weak recommendation, low quality of evidence).

62. We *suggest* either antipyretic therapy or a permissive approach to fever in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).

63. We *suggest* against the use of ascorbic acid (vitamin C) in the treatment of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

64. We *suggest* against the use of thiamine to treat children with sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

65. We *suggest* against the acute repletion of vitamin D deficiency (VDD) for treatment of septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

E. ADJUNCTIVE THERAPIES

66. We *suggest* against transfusion of red blood cells if the blood hemoglobin concentration is ≥7 g/dL in hemodynamically stabilized children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).

    Remarks: According to the 2018 Transfusion and Anemia Expertise Initiative (TAXI) guidelines, for the purposes of red blood cell transfusion, "hemodynamically stabilized" is defined as a mean arterial blood pressure higher than 2 standard deviations below normal for age and no increase in vasoactive medications for at least 2 hours.

67. We cannot make a recommendation regarding hemoglobin transfusion thresholds for critically ill children with unstable septic shock.

68. We *suggest* against prophylactic platelet transfusion based solely on platelet levels in non-bleeding children with septic shock or other sepsis-associated organ dysfunction and thrombocytopenia (weak recommendation, very low quality of evidence).

69. We *suggest* against prophylactic plasma transfusion in non-bleeding children with septic shock or other sepsis-associated organ dysfunction and coagulation abnormalities (weak recommendation, very low quality of evidence).

    Remarks: Prophylactic plasma transfusion refers to situations in which there is an abnormality in laboratory coagulation testing but no active bleeding.

70. We *suggest* against using plasma exchange in children with septic shock or other sepsis-associated organ dysfunction without thrombocytopenia-associated multiple organ failure (TAMOF) (weak recommendation, very low quality of evidence).
71. We cannot suggest for or against the use of plasma exchange in children with septic shock or other-sepsis-associated organ dysfunction with TAMOF.

72. We *suggest* using renal replacement therapy to prevent or treat fluid overload in children with septic shock or other sepsis-associated organ dysfunction who are unresponsive to fluid restriction and diuretic therapy (weak recommendation, very low quality of evidence).
73. We *suggest* against high-volume hemofiltration over standard hemofiltration in children with septic shock or other sepsis-associated organ dysfunction who are treated with renal replacement therapy (weak recommendation, low quality of evidence).
74. We *suggest* against the routine use of intravenous immune globulin (IVIG) in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). Remarks: Although routine use of IVIG is not recommended, select patients may benefit from such treatment.
75. We *suggest* against the routine use of stress ulcer prophylaxis in critically ill children with septic shock or other sepsis-associated organ dysfunction, except for high-risk patients (weak recommendation, very low quality of evidence). Remarks: Although *routine* stress-ulcer prophylaxis is not recommended, some high-risk patients may benefit from stress ulcer prophylaxis. Studies have supported benefit of stress ulcer prophylaxis when baseline rate of clinically important bleeding is approximately 13%.
76. We *suggest* against routine deep vein thrombosis (DVT) prophylaxis (mechanical or pharmacologic) in critically ill children with septic shock or other sepsis-associated organ dysfunction, but potential benefits may outweigh risks and costs in specific populations (weak recommendation, low quality of evidence).