**CRITERIA FOR PEDIATRIC SEPSIS – A SYSTEMATIC REVIEW AND META-ANALYSIS BY THE PEDIATRIC SEPSIS DEFINITION TASKFORCE**

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**Abstract:**

**Objective:**  To determine the associations of demographic, clinical, laboratory and illness severity variable values on admission in children with infection with 1) development of sepsis, severe sepsis or septic shock in children with infection and 2) multi-organ dysfunction or death.

**Data Sources:** MEDLINE, Embase and the Cochrane Central Register of Controlled Trials from January 1, 2004 and November 16, 2020.

**Study Selection:** Case-control, cohort studies and randomized controlled trials in children 37 weeks to 18 years of age with suspected or confirmed infection which included the terms sepsis, septicemia or septic shock in the title or abstract.

**Data Extraction: S**tudy characteristics, patient demographics, clinical signs, laboratory values and organ dysfunction and illness severity scores were extracted. All analyses were performed using random-effects meta-analysis.

**Data Synthesis:** One hundred and six studies representing 35 countries met the eligibility criteria and 81 studies enrolling 154,474 patients were included in the meta-analysis. In children with infections, level of consciousness and Pediatric Risk of Mortality (PRISM) score were associated with severe sepsis and sepsis respectively. The pooled mortality rates varied between high, upper middle and lower middle-income countries for patients with sepsis, severe sepsis and septic shock (P < 0.0001). Mortality in patients with sepsis, severe sepsis or septic shock was statistically associated with 28 of the 54 variables tested. Chronic conditions, oncologic diagnosis, use of vasoactive/inotropic agents, mechanical ventilation, serum lactate, platelet count, fibrinogen, procalcitonin, multi-organ dysfunction syndrome, Pediatric logistic organ dysfunction score, Pediatric Index of Mortality-3 and PRISM score all demonstrated significant and consistent associations with mortality in greater than four studies.

**Conclusions:** Numerous variables were identified that showed consistent and significant associations with mortality in children with sepsis despite marked heterogeneity in clinical settings and study populations.

1. **BACKGROUND**

Infections account for 26.5% of the global burden of disease (1) and 25% of deaths in children worldwide (2). However, the clinical manifestations of these infections vary from minimal or absent symptoms to multiorgan failure and death. The concepts of sepsis, severe sepsis and septic shock were developed and refined using different criteria to help identify, treat and study those infections who are at higher risk of significant morbidity and mortality (3,4). However, specific variables identifying children with sepsis and their resulting outcomes have never been rigorously evaluated in a systematic review.

The 2016 sepsis definition update in adult patients (Sepsis-3) included a systematic review of reported criteria used to identify adults with septic shock (5). This review only assessed hemodynamic criteria and specifically excluded pediatric studies, in addition specific patient populations (such as oncology patients) were excluded. Furthermore, results of adult trials cannot be automatically generalized to children because of differences in epidemiology (6), mortality rates (7), underlying diseases (8), disease-specific outcomes (9,10) and differing responses to therapy (11,12).

Therefore, the Society of Critical Care Medicine (SCCM) convened the Pediatric Sepsis Definition Taskforce to evaluate, develop and validate criteria for the identification of sepsis in children. As part of this process, the Taskforce conducted a systematic review with explicit goals to determine demographic, clinical and laboratory variables and organ dysfunction/illness severity scores in children with suspected or confirmed infection associated with 1) development of sepsis, severe sepsis or septic shock in children with suspected or confirmed infection; and 2) new or progressive multi-organ dysfunction (NPMODS) or mortality in children with sepsis, severe sepsis or septic shock.

1. **METHODS**

The protocol has been previously published (13) and is summarized below.

**Eligibility criteria**

Inclusion criteria for studies were: 1) the word “sepsis”, “septic shock” or “septicemia” was present in the title or abstract; 2) publication date between January 1, 2004 and November 16, 2020; 3) NPMODS or mortality was reported as an outcome; 4) case-control study, cohort study (prospective or retrospective), randomized or quasi-randomized trial design and 5) a study population of children ≥ 37 weeks post-gestational age to < 18 years. Studies meeting the following criteria were excluded: 1) less than 50 children with sepsis, septicemia, severe sepsis or septic shock; 2) abstract only publications, case studies, narrative reviews, surveys or study protocols; 3) reported exclusively on adult patients; 4) ineligible medical conditions (e.g. septic arthritis); 5) no comparator group for variable in question; 6) sepsis criteria not specified; 7) article not available; or 8) focused on criteria only available for research (e.g. gene-expression data). Only 17 non-English language articles (0.23%, 17/7502) were identified by the search. As such, the decision was made to exclude non-English language studies.

**Data Sources**

We identified eligible studies by searching the following databases: MEDLINE (including Epub Ahead of Print), Embase and the Cochrane Central Register of Controlled Trials.

**Study screening and selection**

The titles, abstracts and full-texts were screened using a previously validated crowdsourcing platform Insight Scope (14). Each title and full-text article was screened by two reviewers for inclusion in the final set of articles for data extraction. At each screening level and for data extraction, conflicts were resolved by a third reviewer.

**Data extraction and management**

Data from included full-text articles was extracted by two reviewers per citation using a REDcap platform (15) hosted at the Children’s Hospital of Eastern Ontario Clinical Research Unit. Corresponding authors were contacted twice to obtain missing data on identified variables or mortality. The quality of selected articles was assessed using the first four domains of the QUIPS (Quality in Prognostics Studies) tool for assessment of risk of bias in observational studies (16). The overall risk of bias was determined as the highest risk of bias attributed to any criterion. Only unadjusted data were extracted since many studies did not report adjusted data and others did not specify the variables they adjusted for or adjusted for different variables (17). Articles containing variables that were assessed in two or more studies were included in the meta-analysis. The remaining eligible studies are described in the narrative review. Sensitivity and specificity analyses were performed if two studies or more studies used the same threshold for any given variable.

**Definition of variables**

We aimed to identify variables on admission to hospital or PICU for potential use in future pediatric sepsis criteria, as part of the Pediatric Sepsis Definition Taskforce project. The purpose of this systematic review was to assess in a meta-analysis whether a given variable, such as for example arterial hypotension, was associated with outcomes rather than comparing specific definitions of hypotension. Therefore, we collated original data from different studies on variables such as “hypotension” even if they applied different definitions. The same principle applied to all variables investigated. Countries were categorized as low-(LIC), low-middle-(LMIC), upper-middle-(UMIC) and high-income countries (HIC) according to the World Bank classification of 2019-2020 (18).

**Outcomes**

The primary outcome for the meta-analysis of articles describing children with infection was the development of sepsis, severe sepsis or septic shock. The primary outcome for the meta-analysis of articles describing children with sepsis, severe sepsis or septic shock (henceforth collectively referred to as sepsis) was the development of NPMODS and/or death.

**Data synthesis and analysis**

Frequencies and descriptive statistics are reported for study demographics and patient characteristics in included studies. Random effects meta-analyses with inverse described in Cochrane Handbook (19).The mean and standard deviation were imputed from the median, interquartile range or range (minimum and maximum) and sample size (20). Statistical heterogeneity was assessed using I2 statistic and visual inspection of the forest plots. DerSimonian-Laird random-effects models were employed for all comparisons and Stata (StataCorp, Release 16.1. College Station, TX) for data analyses (21). All laboratory values were converted to conventional units. Baseline sepsis, severe sepsis and septic shock rates between HIC, UMIC and LMIC were compared using Kruskal-Wallis tests weighted for study sample sizes.

**3. RESULTS**

*Overview of included studies*

The search yielded 12,343 articles of which 969 underwent full-text review for eligibility. Of these, 863 were excluded (see Figure 1). One hundred and six articles were retained for the systematic review, and 81 articles were used in the meta-analysis. Study characteristics are summarized in Table 1. The majority of studies were conducted at a single site (80/106, 75.5%) and studies included patients from 35 countries. These countries represented all seven regions from the World Bank list of economies with 46.2% (49/106) being from HICs, 30.2% (32/106) from UMICs, 22.6% (24/106) from LMICs, and one study from a LIC. The majority of studies were conducted in the PICU setting (89/106, 84.0%). The patient characteristics for included studies are shown in Table 2. More than half the patients were male (pooled estimate 55.7%, 95% CI: 54.8, 56.6). The majority of studies were of PICU patients (70.8%, 75/106) followed by those from the Emergency Department (10.4%, 11/106).

The most commonly used definition of sepsis was the Goldstein criteria (69.8%, 74/106) (3). The mortality endpoint in included studies was unspecified (n=17 studies) or reported at 72-hours (n=1), PICU discharge (n=14), 28 or 30-days (n=31) or hospital discharge (n=20). In the 107 included studies, the pooled mortality rate using a random-effects model for patients with sepsis was 10.9% (n = 47 studies; 95% CI, 8.9-13.2), for severe sepsis patients was 23.0% (n = 26 studies; 95% CI, 19.6-26.9) and for septic shock patients was 36.8% (n = 28 studies; 95% CI, 29.4-44.9). The pooled mortality rates varied between HIC, UMIC and LMIC locations for sepsis, severe sepsis and septic shock patients (P < 0.0001, see Figure 2).

The studies included in the meta-analysis, their overall risk of bias and the narrative review are detailed in Supplementary Tables 1 and 2 respectively. The variables assessed in the meta-analysis are listed in Supplementary Table 1 and those discussed in the narrative review are summarized in Supplementary Table 2. Forest plots for variables with significant findings are shown in Supplementary Figures 1-8 and associations of these variables with the outcomes of sepsis and mortality are summarized in Table 3.

*Variables associated with sepsis, severe sepsis, septic shock*

Sixteen studies on 9,732 patients provided data for the meta-analysis of the association of 16 variables with the primary outcome of sepsis, severe sepsis, septic shock. Our meta-analysis did not demonstrate an association between age, age groups, gender or malnutrition (22-26) and sepsis, severe sepsis or septic shock. Sepsis among infected children was not associated with pooled estimates of hemoglobin (27-29), C-reactive protein (30,31) or procalcitonin (32,33). Severe sepsis and sepsis among infected children were associated with decreased level of consciousness in (30,31,34,35) and higher PRISM scores (36,37) respectively (Supplementary Figures 3 and 8).

*Variables associated with NPMODS and mortality*

Seventy-one studies (146,182 patients) provided data for the meta-analysis of the association of 52 variables with the primary outcome of mortality. One study reported separately on two populations which were therefore reported as two studies in the meta-analysis (38). Only one study reported NPMODS as an outcome and two reported a composite outcome of NPMODS and death. Meta-analysis with NPMODS as the outcome was not possible as none of these studies assessed the same variables.

The evidence does not support an association between age, age groups or gender with mortality. In addition, no association was noted with race (38,39), obesity (40-42) or malnutrition (22-26) and mortality but only a small number of studies assessed these variables. Pooled estimates supported an increased odds of mortality in patients with severe acute malnutrition (23,43,44), chronic conditions (23,25,45-53), and oncologic conditions (23,38,50,54-57) (Supplementary Figure 1).

*Clinical variables*

Among children with sepsis, pooled estimates provide strong evidence for increased mortality in patients with hypotension (49,50,58,59), use of vasoactive agents/inotropes (23-25,35,43,44,47,52,53,58,60-69), increased vasoactive inotropic score (54,56,68,70-72), decreased level of consciousness (58,59,67), decreased Glasgow Coma Scale (56,70,73) and mechanical ventilation (23,24,35,36,43-47,49,52-54,56,58-62,65-69,71-78) (Supplementary Figure 3). There were no mortality difference in mean heart rate (50,56,58,71,74,79), median mean blood pressure (56,71) and systolic blood pressure (50,58,67,74,79), but the reported values did not account for the ages of included patients. Additionally, non-survivors and survivors had similar central venous pressures (54,56,71) and arterial oxygen saturations (50,58).

*Laboratory variables*

Pooled estimates provided strong support for a difference in the following laboratory measures between non-survivors and survivors: serum pH (56,58,72,73), lactate (46,53,54,56,60-62,65,68,71-74,79-82), serum base deficit (62,71,73,74,83,84), urea (58,74,80,85), creatinine (56,58,71,74,80,82,84,85), platelets (44,46,53,56,58,62,71,75,80,82-84,86,87) and fibrinogen (62,80,83,84,86) potassium (62,71,74), albumin (56,74,82), procalcitonin (27,35,46,74,82,84,88-90) and alanine aminotransferase (58,74,80) (Supplementary Figures 2, 4, 5 and 6). Pooled estimates did not support a difference in mean glucose (53,68,71,72,74), total bilirubin (56,58,74,80,84,85), WBC (35,46,53,56,58,62,71,73-75,80,82,84,86,88), hemoglobin (35,46,53,71,82,84), INR (62,80), PT(56,71,74,80,91,91), aPTT (62,71,80,91,91) and BNP (54,66,74) between non-survivors and survivors.

*Illness severity and organ dysfunction scores*

Our meta-analysis provided strong support for greater organ dysfunction in non-survivors compared to survivors as shown by the pooled estimates for renal dysfunction (53,64,67,70), MODS (25,38,44,53,69,70,92,93), number of organ dysfunctions (36,43,64,82), PELOD (36,38,40,43,47,53,56,60,65,72,84), PELOD-2 (84,85,94), pSOFA (53,58,70,94), SOFA (84,85,94), PRISM (24,40,46,54,56,60-62,64,68,70-73,75,80,83,84,87), PIM-2 (77,84) and PIM-3 (38,61,65,84) (Supplementary Figures 7 and 8).

*Narrative review*

In patients with septic shock, those with hematopoetic cell transplants had increased odds of mortality (OR 4.74; 95% CI, 2.56, 8.77) (95) and those with progressively higher LODS and AVPU scores demonstrated increasing positive predictive values for early mortality from 40% to 60% and 39.3% to 50% respectively (96). In one study, the Tp-e interval/QT on an ECG was an independent predictor of mortality in patients with septic shock (97). Laboratory values that showed an association with mortality in single studies included red cell distribution width elevation (98), anti-thrombin III levels below 41.5% (< 1 year) and 67.5% (≥ 1 year) (91), 25-hydroxy vitamin < 50 nmol/L (99), baseline cortisol cut-off of 20 µg/dL and post ACTH stimulation level of ≤ 9 µg/dL (100), lower serum zinc levels (101), lower HDL, LDL and cholesterol levels (102) and lower total T3 and T4, and free T3 and T4 hormone levels (103).

Several studies assessed the association of serum troponin and mortality in sepsis. Two studies provided incomplete data (66,74), another reported an association with a cut-off of > 1 ng/dL (104) and one study found higher levels of troponin in non-survivors compared to survivors (71). Two studies provided differing thresholds of CRP and procalcitonin levels (81.9 nmol/dL and 43 ng/mL) and (154.3 nmol/dL and 19.1 ng/mL) for developing septic shock in patients with meningococcemia (105) and sepsis (106) respectively. Serum lactate levels were studied using three criteria. Serum lactate to albumin ratio > 1.17 was associated with increased mortality (107), a level of > 3 mmol/L with increased risk of sepsis (108) and lack of lactate clearance (decrease of ≤10%) or normalization (< 2 mmol/L) was associated with persistent MODS (109). Finally, several studies assessed thresholds for hemodynamic variables. A VIS of > 20 was associated with increased mortality (110), another suggested time dependant cut-offs for shock index values from 0 to 6 hours post admission (111) and two studies each found an association of a decreased LVEF (45% and 55%) with mortality (112,113).

**4. DISCUSSION**

Our systematic review and meta-analysis evaluated over 50 variables for their association with sepsis in children with infection and with mortality in children who already had sepsis. We found evidence of increased odds of mortality for septic patients with severe acute malnutrition, chronic conditions, oncologic disorders, hypotension, use of inotropes, mechanical ventilation, decreased level of consciousness and lower GCS. In addition, we found a significant difference in vasoactive-inotropic scores, serum base excess, pH, lactate, platelets, fibrinogen, urea, creatinine, albumin, potassium, ALT, and procalcitonin between non-survivors and survivors. All measures of organ dysfunction and illness severity in sepsis showed significant differences between those who survived and those who died.

Our study evaluated data from 35 countries in seven geographic regions and all income levels of World Bank Income Classification (18). This is an important consideration given that up to 85% of all sepsis cases and sepsis related deaths occur in lower- and middle-income countries (2). However, although 18 studies were included from LIC and LMIC countries, these represented only 1.8% (2,784/154,474) of the patients analyzed. The potential biases that may be introduced include distinct causes of sepsis (114), limited access to and availability of treatments (115) and higher mortality rates (2) in patients with sepsis from LMIC/LIC versus UMIC/HIC locations. It is possible that a sub-group analysis of the assessed variables in LMIC/LIC countries may have yielded differential results which will need to be accounted for in the data validation phase of the Pediatric Sepsis Definition Taskforce.

For continuous variables such as vasoactive-inotropic scores and laboratory values, we were not able to determine thresholds for the development of sepsis or for mortality due to lack of data. However, we determined overall means for survivors and non-survivors for variables with a significant mean difference which may provide initial thresholds to be explored in the data analysis phase of the Pediatric Sepsis Definition Taskforce project.

It could be argued that determination of the association of certain variables with mortality in septic children using pre-established definitions of sepsis may appear to be a self-confirming exercise. However, even though variables such as serum lactate were included in the 2001 Consensus Conference definition (116) and Bone criteria (117), their inclusion was the result of a consensus process and was never formally validated. Furthermore, several of the variables assessed including serum lactate are not included in the Goldstein criteria or ICD-9 codes which were collectively used in 78% of studies and 92.3% of patients.

This review had several limitations. The first is that several variables in the meta-analysis demonstrated significant heterogeneity. However, since the purpose of this review was to identify potential variables for use in an updated definition of pediatric sepsis rather than draw conclusions regarding a treatment effect, the actual effect size and its associated I2 value may be less relevant. Secondly, our pragmatic approach resulted in the inclusion of studies with different definitions of sepsis. Although this may have limited our ability to find associations of some variables with our outcomes of interest, it may also have contributed to the robustness of the associations for other variables. Thirdly, all included studies were observational and therefore subject to confounding with regards to the outcomes of interest.

This systematic review is the first study to rigorously assess the association of individual variables with development of sepsis in children with infections and the odds of mortality in children with sepsis, severe sepsis and septic shock. The included studies were from economically diverse regions of the world, populations with diverse underlying conditions and varying definitions of sepsis. Despite the clinical heterogeneity and limited number of studies for some variables, strong associations with the outcomes of interest were seen for many of the variables assessed, supporting the value of including these variables in the database validation phase of the Pediatric Sepsis Definition Taskforce.

**List of Abbreviations:**

ESCIM European Society of Intensive Care Medicine

ESPNIC European Society of Pediatric and Neonatal Intensive Care

MODS Multi-Organ Dysfunction Syndrome

OR Odds ratio

PELOD Pediatric Logistic Organ Dysfunction score

PICU Pediatric Intensive Care Unit

PIM Pediatric Index of Mortality

PRISM Pediatric Risk of Mortality

SOFA Sequential (Sepsis-related) Organ Failure Assessment

pSOFA pediatric Sequential (Sepsis-related) Organ Failure Assessment

SSC Surviving Sepsis Campaign

SCCM Society of Critical Care Medicine

SIRS Systemic Inflammatory Response Syndrome

SOFA Sequential (Sepsis-related) Organ Failure Assessment

VIS Vasopressor Inotrope Score

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