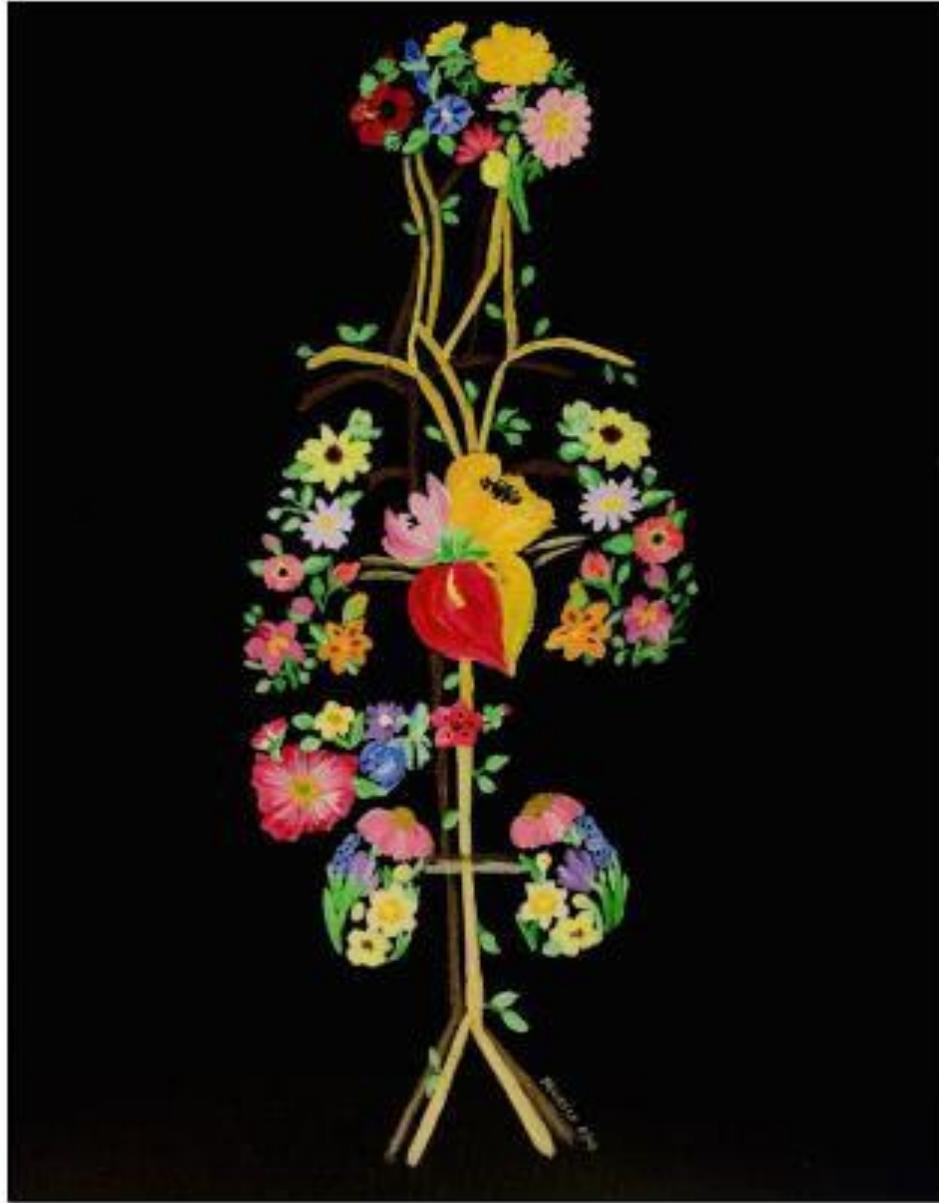




SOCIETY OF PEDIATRIC CRITICAL CARE MEDICINE PHILIPPINES



FORWORD

Sepsis is a leading cause of death among all ages worldwide, with a mortality rate of 20% within the first hour, increasing by 8% for each hour of delayed treatment.

Healthcare measures to prevent sepsis are of prime importance with early recognition and immediate management keys to improving mortality rates.

As pediatricians, we need to do our part by being timely in our clinical updates, because our knowledge, skills and emphatic care can save lives. In saving lives, we will be able to save people's futures.

May we benefit from these Consensus Statements on Sepsis & Septic Shock in Children. SPCCMP dedicates this to the Filipino children, so that more of them and future generations may live longer and have a brighter tomorrow.


Elizabeth B. Villano, M.D
President

Society of Pediatric Critical Care Medicine Philippines 2022-2024

About the Cover

This is an acrylic painting on canvas that depicts the major organ systems that can be affected by severe sepsis and septic shock. The artist, Dr. Mayleen Jennifer L. Laico, is a nephrologist whose works have made it to the cover of several national and international journals and other medical publications.

Society of Pediatric Critical Care Medicine of the Philippines
**CONSENSUS STATEMENTS ON SEPSIS AND
SEPTIC SHOCK IN CHILDREN**

March 2023

Technical Working Group

Chair: Ronald V. Limchiu, MD, FPPS, FSPCCMP
Assistant Chair: Ramon V. Najarro, MD, FPPS, FSPCCMP

Panelists:

Wilfredo Tente E. Dublin Jr., MD, DPPS, FSPCCMP
Audrey Anne Najarro-Diaz, MD, FPPS, FSPCCMP
Tyronne V. Lariago, MD, DPPS, DSPCCMP
Lorelie C. Ramos, MD, DPPS, DSPCCMP
Rudy A. Amatong, MD, FPPS, FSPC
Belle M. Ranile, MD, FPPS, FPIDSP
Arnold Nicholas T. Lim, FPPS, FPAPP

Associates:

Jethro V. Solite, MD, DPPS
Neil John D. Wahing, MD, DPPS

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Disclosure

This project is solely funded by the Society of Pediatric Critical Care Medicine of the Philippines.

Objective

To formulate consensus statements on controversial issues and new modalities of diagnosis and treatment of pediatric sepsis

Introduction

Sepsis is the leading cause of Pediatric Intensive Care Unit (PICU) admissions and mortality in infants and young children worldwide (1, 2, 3, 4, 5). Estimated mortality rates range between 1-5% for sepsis and 9-20% for severe sepsis. The risk for mortality is greater in the younger age group, the unimmunized or incompletely immunized, in healthcare-associated infections, those with underlying comorbidities (immunocompromised and malnourished), and non-adherence to the sepsis bundles (1, 2, 3). The World Health Organization (WHO) Global Report on the Epidemiology and Burden of Sepsis states that almost half of all estimated sepsis cases (20.3 million) worldwide in 2017 occurred in children under 5 years of age with 2.9 million deaths (26.4%) related to pediatric sepsis (4). Alternatively, other sources report the burden of sepsis in children to be approximately 1.2 million cases globally every year (1, 2).

Significant disparities exist between high-income versus low and middle-income countries. Eighty-five percent of sepsis cases and 84.8% of sepsis-related deaths occurred in countries with low, low to middle or middle socio-demographic indices particularly in Sub-Saharan Africa and Southeast Asia (4). Moreover, sepsis increases the burden on PICUs in terms of deaths, complications, costs, and allocation of resources (1). Furthermore, about a third of pediatric sepsis survivors show a decline in cognitive skills 28 days after hospital discharge.

Locally, as reported in the Philippine Pediatric Society (PPS) registry for January 1, 2012, to December 10, 2022, the total number of sepsis cases is 210,101, with total deaths of 29,343 (14%) vis-à-vis total all-cause mortality of 372,291 (7.3%) (5, 1). This may be an underestimation as the data only includes cases reported by PPS-accredited hospitals.

Methodology

Upon the request of the Society of Pediatric Critical Care Medicine of the Philippines (SPCCMP) Board, a group of pediatric critical care specialists convened to review and discuss critical clinical questions regarding sepsis and septic shock in pediatrics. The group formulated ten (10) questions, including early recognition and diagnosis issues, fluid management, vasoactive agents, corticosteroid use, non-invasive and invasive respiratory support, and glycemic control. We did not do any de novo research. Instead, we conducted a literature search for each question to determine the best available evidence. We used Pubmed, NEMJ, EMBASE, Cochrane Library and OVID. The keywords commonly used were "sepsis", "septic shock", "septicemia", "pediatric", "children", and "neonates" as per the literature search. We excluded articles that were not in the English language. The group identified recent meta-analysis, systematic reviews and randomized control trials (RCTs) to answer the specific questions based on its Population, Intervention, Comparators, and Outcomes (PICO). To assess the validity of each study, we utilized the Critical Appraisal Skills Program (CASP) checklist, an appraisal tool licensed by the Creative Commons Attribution for systematic reviews, meta-analysis, and randomized control trials. We then tabulated the strengths and weaknesses (biases) of the collected and reviewed articles and identified their validity, methodological soundness, results, and applicability to the local setting.

The group also invited external panelists to review and comment on the group's output. We invited a pediatric infectious disease specialist to comment on the questions about early recognition and diagnosis of sepsis. We also invited a pediatric cardiologist to comment on fluid management, vasoactive agents, and glycemic control. And lastly, we asked a pediatric pulmonologist to review the non-invasive and invasive ventilatory support of Pediatric Acute Respiratory Distress Syndrome (PARDS) in Sepsis.

Based on the strength of the evidence given in Table 1, we categorized our recommendations as either "strong" or "weak" (6). For strong recommendations, we used the phrase "we recommend," whereas for weak recommendations, we used the phrase "we suggest." We determined that an intervention with a Strong Recommendation (SR) will significantly have more positive effects on adherence than negative ones. We determined that a Weak Recommendation (WR) in favor of an intervention would likely have more positive effects than negative ones if it were followed. However,

confidence is weakened either because the evidence was of low quality or because the advantages and disadvantages were fairly evenly distributed. Table 2 illustrates the effects of classifying a recommendation as either strong or weak (6). Strong recommendations do not always indicate a standard of treatment, and there may be instances in which they cannot or ought not to be followed for a specific patient. We allowed strong recommendations "for" an intervention where it could increase survival and there was little chance of immediate damage based on weak or very weak evidence. When there was an uncertain benefit but extremely likely or certain damage, including substantial costs, we allowed strong recommendations "against" an intervention based on poor or very low quality of evidence.

TABLE 1. Determination of the Quality of Evidence

Underlying methodology

High: Systematic reviews, Randomized Control Trials (RCTs)

Moderate: Downgraded RCTs or upgraded observational studies

Low: Well-conducted prospective observational studies

Very low: Downgraded observational cohort studies, case control studies, case series or expert opinion or other evidence

Factors that may decrease the strength of evidence

Methodologic features of available RCTs suggesting high likelihood of bias

Inconsistency of results, including problems with subgroup analysis

Indirectness of evidence (differing population, intervention, control outcomes, comparison)

Imprecisions of results

High likelihood of reporting bias

Factors that may increase the strength of evidence

Large magnitude of effect (direct evidence, relative risk > 2 with no plausible confounders)

Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels)

Dose-response gradient

TABLE 2. Implications of the Strength of Recommendation					
Category	Strength	Quality of evidence	Implication to Patients	Implication to Clinicians	Implication to Policymakers
Strong recommendation	Strong	Usually high or moderate	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preference.	Can be adapted as policy in most situations, including for use as performance indicators
Weak recommendation	Weak	Any	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstance, such as the patient's or family's values and preference.	Policies will likely be variable

How a consensus was made:

After a statement to answer the critical clinical question was made, each panelist voted individually on whether to agree or disagree on the merits of the statement. A consensus was made when 80 % of the panelists agreed with the statement. All areas of disagreement were discussed, and if necessary, a second or third vote was cast to arrive at a consensus. If no consensus was made after a thorough discussion with the internal panel of pediatric intensivists, an external panelists' (pediatric cardiologist, infectious disease specialist, or pediatric pulmonologist) opinion was sought to contribute to the discussion of the issue. All ten consensus statements formulated in this manuscript have been approved by 90% or more of the panelists. No Best Practice Statements (BPS) were issued.

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Clinical question #1

Will implementing a Pediatric Tracking and Trigger Tool (PTTT), particularly the Pediatric Early Warning Score (PEWS), help in the early recognition of severe sepsis and septic shock?

Consensus statement #1

We suggest that a PTTT such as PEWS be implemented in all hospital levels of care to increase early recognition of sepsis and septic shock. (WR)

Supporting statements

Although there was evidence that healthcare systems (both in resource-limited and resource-adequate settings) which implemented PEWS showed a trend towards a decrease in mortality and code rates, the panel, however, could not find strong evidence that PTTT decreases clinical deterioration (1).

Because of the studies' heterogeneity, the panel would suggest further research to investigate the effectiveness of PEWS and other PTTT in preventing clinical deterioration (1, 2).

Context

Early recognition of sepsis in an acutely ill child leads to subsequent administration of timely appropriate management and, therefore, can improve outcomes among these patients. Pediatric early warning systems have been developed as part of rapid response systems to detect deterioration among hospitalized patients and trigger the rapid response protocol (3).

Pediatric healthcare uses this as a tool for early recognition of sepsis to prevent poor outcomes or mortality. The validity of PEWS in detecting clinical deterioration and its effectiveness in improving patient outcomes have been a focus of clinical research showing varied results. To date, further high-quality studies on PEWS still need to be undertaken (4, 5).

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
<p>Trubey et al</p> <p>“Validity and effectiveness of pediatric early warning systems and track and trigger tools for identifying and reducing clinical deterioration in hospitalized children: a systematic review”</p> <p>(Systematic review)</p>	2018	<p>Population – inpatients aged 0-18 years</p> <p>Intervention – pediatric early warning systems and track and trigger tools</p> <p>Comparison – PEWS vs No PEWS</p> <p>Outcome – mortality and critical events (unplanned admission to a higher level of care, cardiac arrest, respiratory arrest, medical emergencies requiring immediate assistance, children reviewed by PICU in the ward or reviewed by external PICU staff, acuity at PICU admission and PICU outcomes)</p> <p><u>Conclusion:</u> There are several fundamental methodological limitations in the PTTT literature, and the predominance of single-site studies carried out in specialist centers greatly limits generalizability. With limited evidence of effectiveness, calls to make PTTT mandatory across all pediatric units are not supported by the evidence.</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>Comprehensive search - appropriate type of papers reviewed</p> <p>Timely review of evidence</p> <p>Biases:</p> <p>Methodological weaknesses</p> <p>Heterogeneity in study populations, study designs and outcomes</p>

<p>Chong SL et al</p> <p>“Do pediatric early warning systems reduce mortality and critical deterioration events among children? A systematic review and meta-analysis”</p> <p>(Systematic review, Meta-analysis)</p>	<p>2022</p>	<p>Population – children < 18 years old in inpatient units and emergency departments</p> <p>Intervention – pediatric early warning systems</p> <p>Comparison – group without pediatric early warning systems</p> <p>Outcome – mortality, cardiopulmonary arrests, unplanned codes and critical deterioration events (unplanned/crash tracheal intubation, unanticipated fluid resuscitation and inotropic/vasopressor use, CPR or ECMO, death in patients without DNR order and unplanned or emergency admission to PICU</p> <p><u>Conclusion:</u> Healthcare systems that implemented PEWS were associated with reduced mortality and code rates. We recognise that these gains vary depending on resource availability and efferent response systems.</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>Appropriate type of papers reviewed</p> <p>Due diligence in assessing quality of included studies</p> <p>Reasonably combined studies</p> <p>Results applicable to local population</p> <p>Biases:</p> <p>Variation in patient population</p> <p>Most study designs employed fraught by confounding factors</p>
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Clinical question #2

Which of the biomarkers correlates best with the diagnosis of pediatric sepsis?

Consensus statement #2

We recommend the combined use of Procalcitonin (PCT) and C-Reactive Protein (CRP) in the early detection of pediatric sepsis, as doing so has demonstrated to be superior to just PCT or CRP alone. Presepsin (P-SEP), if available, is also an option as it is comparable to the PCT and CRP combination. (SR)

Supporting statements

In a meta-analysis done by Pontrelli et al. (2017), PCT showed a moderate accuracy for the diagnosis of sepsis in neonates at the cut-off of 2-2.5 ng/ml with a sensitivity of 0.85 (95% CI 0.76; 0.90) and specificity of 0.54 (95% CI 0.38; 0.70). However, in older children, a cut-off of <2.0 ng/ml showed lower sensitivity of 0.78 (95% CI 0.66; 0.87) and a specificity of 0.57 (95% CI 0.40; 0.73) (1). Even though it showed suboptimal results, the findings were still significant, given the high mortality of the condition.

Another biomarker that is gaining popularity is Presepsin. Although P-SEP is not yet readily available locally, the use of Presepsin as a biomarker for sepsis is helpful in the early detection and prompt decision to start antibiotics. In a study by Niccolò Parri, and Giulia Trippella (2019), P-SEP showed high diagnostic accuracy for neonatal sepsis (2). Even though the study cannot recommend P-SEP as a single diagnostic biomarker for sepsis, P-SEP could be a helpful and valuable biomarker in neonates with suspected sepsis.

In another meta-analysis done by Ruan et al. (2018), there was a comparison between CRP and PCT alone vs. CRP plus PCT vs. P-SEP alone in patients with neonatal sepsis. The results showed that the single use of PCT is more sensitive than CRP alone (0.85 vs 0.71, 95% CI) in the detection of neonatal sepsis. However, CRP plus PCT showed higher sensitivity than the single use of PCT or CRP (0.91 vs 0.85 vs 0.71, 95% CI). Furthermore, the single use of P-SEP had comparable results with the use of CRP plus PCT in the early detection of sepsis (0.94 vs 0.91, 95% CI) (3). Results also showed good predictions with an area under the curve (AUC) for presepsin (0.99 (95% CI 0.98, 1.00)) was more significant than PCT plus CRP (0.96 (95% CI 0.93, 0.97)), CRP (0.85 (95% CI 0.82, 0.88)) and PCT (0.91 (95% CI 0.89, 0.94)) (3). This finding was also comparable to another meta-analysis done by Yoon et al. (2019), which showed that the pooled sensitivity of P-SEP was

higher than those of CRP and PCT [P-SEP: 0.94 (95% CI: 0.74-0.99); CRP: 0.51 (95% CI: 0.24–0.78); PCT: 0.76 (95% CI: 0.59–0.88)], yet CRP and PCT were more specific than presepsin in the diagnosis of sepsis in neonates and children [P-SEP: 0.71 (95% CI: 0.35–0.92); CRP: 0.81 (95% CI: 0.53–0.94); PCT: 0.76 (95% CI: 0.67–0.83)] (4).

Context

Blood culture is the gold standard in diagnosing bacterial septicemia. Given its importance in managing sepsis, it has significant limitations, such as long turn-around time, a high percentage of false negatives, and the effect of previous antimicrobial therapy (5). In children with protracted compensation to infection, any delay in the management may significantly increase morbidity and mortality.

The role of biomarkers in providing a timely diagnosis and making guided interventions is an essential aspect of sepsis management. The most commonly utilized biomarkers in the pediatric population are C-reactive protein (CRP) and procalcitonin (PCT). CRP is a pentameric protein (pCRP) synthesized by the liver. It irreversibly dissociates into five monomeric components (mCRP) at sites of inflammation and infection. It is a non-specific acute phase reactant whose levels rise in response to IL-6 (6). Its value increases within 24-72 hours with tissue damage such as trauma or progressive cancer (7). Compared to the erythrocyte sedimentation rate, CRP levels rise and fall rapidly with the onset and removal of the inflammatory stimulus. Thus, its value can be used in acute and chronic inflammation (6). CRP has been shown to be beneficial in resource-limited areas by improving the rational use of antibiotics; however, due to its low positive predictive value, it is not advised to be used alone (8).

Procalcitonin, another promising biomarker, is a 116-amino acid residue derived as a precursor of the hormone calcitonin produced by C cells in the thyroid gland and in some other neuroendocrine cells. PCT has been used to differentiate bacteria from viral infections (9). PCT levels have been shown to increase steadily in 4-6 hours following the onset of bacterial sepsis. Its half-life is 20 to 24 hours; thus, once antibiotics have been started in a patient with an intact immune system, its levels decrease by 50% (9). These characteristics make procalcitonin a valuable tool in the early diagnosis, initiation, and response to antibiotics in patients with bacterial sepsis.

Among the recent biomarkers being studied today, presepsin, formed from soluble CD14 subtype (sCD14-ST), is cleaved by cathepsin D and other proteases in the plasma after stimulation by bacterial endotoxins such as LPS of gram-negative bacteria (10). Compared to procalcitonin, presepsin levels increase abruptly within 2 hours and reach their peak within 3 hours (11). This makes presepsin a reliable diagnostic and prognostic marker for sepsis.

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
<p>Pontrelli et. al.</p> <p>Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis"</p> <p>(Meta-analysis)</p>	2017	<p>Population – Neonates and children with systemic inflammatory response syndrome (SIRS) or suspected sepsis (microbiologically confirmed or evaluated as probable sepsis by chart review)</p> <p>Intervention – Accuracy of procalcitonin in the diagnosis of sepsis</p> <p>Comparison – none</p> <p>Outcome –</p> <p>Primary outcome: assess the diagnostic accuracy of procalcitonin at the cut-off of 2-2.5 ng/ml</p> <p>Secondary outcome: analyze procalcitonin cut-offs <2ng/ml and >2.5ng/ml</p>	<p>Strengths:</p> <p>Clearly focused research question</p> <p>Does not show heterogeneity among results</p> <p>Can be applied to local settings</p> <p>Biases:</p> <p>The need for larger, high quality studies</p> <p>Study designs used were prospective and cross-sectional studies</p>

		<p>"Procalcitonin shows a moderate accuracy for the diagnosis of sepsis in neonates with suspected sepsis at the cut off of 2-2.5ng/ml."</p> <p>Procalcitonin cut-off could be higher for neonates with early onset sepsis (EOS) than for neonates with late onset sepsis (LOS).</p> <p>Studies on neonates with EOS and LOS were grouped together. In the neonatal group, we calculated a sensitivity of 0.85, confidence interval (CI) (0.76; 0.90) and specificity of 0.54, CI (0.38; 0.70) at the PCT cut-off of 2.0-2.5 ng/ml.</p> <p>In the pediatric group it was not possible to undertake a pooled analysis at the PCT cut-off of 2.0-2.5 ng/ml, due to the paucity of the studies.</p>	
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<p>Ruan et. al.</p> <p>“The combination of procalcitonin and C-reactive protein of presepsin alone improves the accuracy of diagnosis of neonatal sepsis: a meta-analysis and systematic review.”</p> <p>(Meta-analysis and Systematic review)</p>	<p>2018</p>	<p>Population – Neonatal patients with sepsis</p> <p>Intervention – Test the sensitivity and specificity of PCT and CRP or presepsin with neonatal patients with sepsis.</p> <p>Comparison – Patients with non-sepsis (the patient is suspected of having sepsis but has no sepsis).</p> <p>Outcome –</p> <p>Primary outcome: the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOC), AUC and corresponding 95% CI.</p> <p>Secondary outcome: sensitivity and specificity in multiple subgroup analysis.</p> <p>The pooled sensitivity of CRP (0.71 (0.63, 0.78)) was weaker than that of PCT (0.85 (0.79, 0.89)), PCT plus CRP (0.91 (0.84, 0.95)) and presepsin (0.94 (0.80, 0.99)).</p> <p>The pooled NLR of presepsin (0.06 (0.02, 0.23)) and PCT plus</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>Results applicable to local population (60.7% of trials from Asia)</p> <p>Majority of the studies have low risk of biases</p> <p>No significant publication bias.</p> <p>Biases:</p> <p>Studies include case-control, prospective cohort and cross-sectional studies.</p> <p>Significant heterogeneity in some of the studies.</p>
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	<p>CRP (0.10 (0.05, 0.19)) were less than CRP (0.33 (0.26, 0.42)).</p> <p>The AUC for presepsin (0.99 (0.98, 1.00)) was greater than PCT plus CRP (0.96 (0.93, 0.97)), CRP (0.85 (0.82, 0.88)) and PCT (0.91 (0.89, 0.94)).</p> <p>The results of the subgroup analysis showed that 0.5–2 ng/mL may be the appropriate cutoff interval for PCT.</p> <p>A cut-off value > 10 mg/L for CRP had high sensitivity and specificity.</p>	
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<p>Yoon et. al.</p> <p>"Presepsin as a diagnostic marker of sepsis in children and adolescents: a systematic review and meta-analysis"</p> <p>(Systematic review, Meta-analysis)</p>	<p>2019</p>	<p>Population – Pediatric age range was defined as >4 weeks and < 18 y diagnosed with sepsis</p> <p>Intervention – Studies evaluating the accuracy of presepsin in the diagnosis of pediatric sepsis</p> <p>Comparison – CRP and PCT</p> <p>Outcome –</p> <p>Primary outcome: The pooled sensitivity and pooled specificity, PLR, PNR, DOR and AUC</p> <p>The pooled sensitivity of presepsin was higher than those of CRP and PCT [P-SEP: 0.94 (95% CI: 0.74-0.99); CRP: 0.51 (95% CI: 0.24–0.78); PCT: 0.76 (95% CI: 0.59–0.88)].</p> <p>In contrast, the pooled specificity of presepsin was lower than that of CRP and PCT [P-SEP: 0.71 (95% CI: 0.35–0.92); CRP: 0.81 (95% CI: 0.53–0.94); PCT: 0.76 (95% CI: 0.67–0.83)]. The AUC of presepsin (0.925) was higher than that of CRP (0.715) and PCT (0.830).</p>	<p>Strengths: Clearly focused question</p> <p>Risk of bias was low in most studies as they clearly defined their exclusion criteria. The studies including CRP and PCT indicated no publication bias</p> <p>Biases: Limited studies included</p> <p>Significant heterogeneity among the studies.</p> <p>Can't be applied to local population due to limited availability of Presepsin</p>
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		<p>Presepsin has higher sensitivity and diagnostic accuracy, but lower specificity, than PCT or CRP in detecting sepsis in children.</p>	
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<p>Niccolò Parri, Giulia Trippella,</p> <p>“Accuracy of presepsin in neonatal sepsis: systematic review and meta-analysis”</p> <p>(Systematic review, Meta-analysis)</p>	<p>2019</p>	<p>Population – Preterm or term neonates with neonatal sepsis. For these patients, P-SEP was taken as a biomarker for sepsis.</p> <p>Intervention – blood culture, clinical, and laboratory signs</p> <p>Comparison – None</p> <p>Outcome – Primary outcome: Estimates of sensitivity, specificity and diagnostic odds ratio (DOR) for P-SEP.</p> <p>The reported sensitivity in detecting sepsis ranged between 0.67 and 1.00, while specificity ranged between 0.75 and 1.00</p> <p>The pooled sensitivity 0.90 (95% confidence interval [CI] 0.86-0.93) and specificity 0.90 (95% CI 0.86-0.93).</p> <p>The pooled DOR was 120.94 (95% CI 40.11-364.69) while the AUC was 0.968</p> <p><u>Conclusion:</u> Our data showed a high diagnostic accuracy of P-SEP for neonatal sepsis. Even though it cannot be</p>	<p>Strengths: Studies extensively reviewed to meet the eligible criteria</p> <p>Research questions are specific and clear</p> <p>Biases: Small number of studies included and the high heterogeneity among them.</p> <p>Further analysis with high quality data and evidence from multicenter studies are necessary.</p>
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		recommended as a single diagnostic test, P-SEP could be a helpful and valuable biomarker in neonates with suspected sepsis	
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Clinical question #3

Will the use of Multiplex Polymerase Chain Reaction (PCR) Assays help in the early detection of etiologic pathogens in pediatric sepsis?

Consensus statement #3

We cannot suggest using Multiplex PCR Assays for the early detection of pathogens in pediatric sepsis. (WR)

Supporting statements

The reviewed studies, mainly on Early Onset Neonatal Sepsis (EONS) and Late Onset Neonatal Sepsis (LONS), showed a positive correlation between PCR studies and blood culture. However, the PCR study results came in much earlier (8 to 12 hours) than the blood culture results (2 to 3 days) (1, 2).

Rapid diagnosis and the early and accurate detection of the etiologic agent in pediatric sepsis are essential because of the association of high morbidity and mortality with delayed diagnosis and inaccurate antibiotic use. The PCR Assay Test is promising as a tool in rapidly diagnosing bacterial, viral, and fungal sepsis and narrowing down the spectrum of antibiotic coverage (1).

However, the present recommendation of the manufacturer of the locally available Multiplex PCR Assay Test is that a blood specimen to be tested by PCR assay should also come from a blood culture positive sample makes the PCR Assay redundant and would not outweigh the benefit (early detection) versus the harm (cost).

Context

Early identification of the etiologic agent in sepsis facilitates timely and appropriate management, including targeted antimicrobial coverage leading to a positive outcome. Blood culture remains the gold standard in the diagnosis of sepsis. However, it is limited by its low diagnostic yield, low sensitivity in patients previously treated with antimicrobials, and long turnaround time, with results available at least 48 to 72 hours after specimen collection.

The advent of Multiplex polymerase chain reaction (PCR) assay as a diagnostic tool in sepsis allows for early identification of the causative agent, cutting the time of identification down to 6 to 12 hours. Multiplex PCR is a

molecular diagnostic technique in which as little as 0.2 milliliter blood sample PCR is used to amplify several different DNA sequences simultaneously (3). In addition, some multiplex PCR assays can also identify the antibiotic resistance profile of certain microorganisms and further aid in choosing the most appropriate antimicrobial for the patient. Unfortunately, the widespread use of PCR-based microbiologic identification is curtailed by its cost and availability.

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
Oeser C, et al “PCR for the detection of pathogens in neonatal early onset sepsis” (Prospective Observational study)	2019	<p>Population – inborn neonates in neonatal and maternity ward less than 72 hours of age with suspected early onset sepsis (compatible clinical or laboratory signs or perceived risk factors in an otherwise asymptomatic neonate)</p> <p>Intervention – Multiplex bacterial, candida PCR and 16S rRNA gene broad-range PCR</p> <p>Comparison – Blood culture</p> <p>Outcome – Pathogen detection</p> <p><u>Conclusion:</u> Real-time PCR has the potential to be a valuable additional tool for the diagnosis of neonatal sepsis.</p>	<p>Strengths: Clearly focused question</p> <p>Biases: Sample collection (extraction) limitation</p> <p>Type of study</p>

<p>Van den Brand M et al</p> <p>“Evaluation of a real-time PCR assay for detection and quantification of bacterial DNA directly in blood or preterm neonates with suspected late-onset sepsis”</p> <p>(Prospective Observational study)</p>	<p>2018</p>	<p>Population – Preterm (AOG <32 weeks) as well as VLBW (<1500g) infants suspected of having a nosocomial (age at onset >72 hours and hospitalized) bloodstream infection</p> <p>Intervention – Multiplex PCR assay</p> <p>Comparison – Blood culture</p> <p>Outcome – Pathogen detection, bacterial DNA load (BDL)</p> <p><u>Conclusions:</u> Multiplex PCR provides a powerful assay to enhance rapid identification of the causative pathogen in late-onset sepsis. BDL measurement may be a useful indicator of severity of infection.</p>	<p>Strengths: Clearly focused question</p> <p>Biases: Limited sample size, sample collection (extraction) and technical limitation</p> <p>Type of study</p>
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Clinical question #4

Are balanced crystalloids better intravenous fluid compared to normal saline solution (NSS) for use with septic shock patients at risk for hyperchloremia and metabolic acidosis?

Consensus statement #4

We suggest that balanced crystalloids be the initial resuscitation fluid of choice for patients with septic shock at risk for hyperchloremia and metabolic acidosis. (WR)

Supporting statements

In one RCT study, there was no difference in mortality between a balanced salt solution and a normal saline solution, but the use of NSS had a trend toward more frequent hyperchloremic metabolic acidosis in children with septic shock (1).

In an observational cohort review, the use of balanced crystalloids (BCS) was shown to decrease hospital length of stay (HLOS), PICU length of stay (PLOS) and reduce mortality as compared with normal saline solution in pediatric sepsis. Furthermore, using BCS at 72 hours showed lower mortality, lower prevalence of acute kidney injury (AKI), and fewer vasoactive infusion days compared to NSS.

Context

Even today, severe sepsis significantly contributes to the morbidity and mortality that occur in children. In treating severe sepsis, resuscitation with fluids is still essential, and crystalloids are the types of fluids that are administered most commonly. Crystalloids can be classified into two categories based on their composition: balanced and unbalanced. Isotonic solutions with an electrolyte composition that is more similar to plasma make-up balanced fluids (BFs). An unbalanced fluid (UF) produces a drop in the plasma strong ion difference (SID), which in turn leads to metabolic acidosis (1, 2).

When it comes to the early treatment of severe sepsis, the standard treatment guidelines that are now in place do not provide any specific recommendations for either BFs or UFs. On the other hand, findings from recent research on adults imply that utilizing BFs may offer outcome benefits (3). To this day, further studies have yet to be conducted that look at how the

composition of crystalloids affects the outcomes for children with severe sepsis. When compared with the use of UFs, it was found that the sole use of BF for initial fluid resuscitation in pediatric septic shock was related to enhanced survival [4]. This was seen in some of the research that was conducted. The use of balanced crystalloids was observed to lower hospital length of stay (HLOS), PICU length of stay (PLOS), and mortality rates in pediatric sepsis when compared with the use of normal saline solution (4). This was discovered through the use of observational cohort studies. Compared to NSS, the use of BCS at 72H was linked with a reduced mortality rate, a lower prevalence of AKI, and fewer days of vasoactive infusion treatment (4). In addition, there was a lower prevalence of AKI when using BCS at 72 hours.

Comparing the clinical results of NSS and BCS in pediatric shock is difficult because there needs to be more research in this area. A recent study that was matched retrospectively indicated no difference in the mortality rate between the BCS and NSS groups in pediatric sepsis (5). No study has compared the effects of different initial isotonic crystalloid fluid boluses on pediatric patients experiencing septic shock that has been randomized, blinded, and controlled.

Although there was no difference in mortality between balanced salt solution and a normal saline solution in one RCT, there was a trend toward more frequent hyperchloremic metabolic acidosis in children diagnosed with septic shock when NSS was used (6).

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
Anantasit N., et al “Balanced salt solution versus normal saline solution as initial fluid resuscitation in pediatric septic shock: A randomized, double-blind controlled trial.”	2020	<p>Population – children 1 month to 18 years old in-patients diagnosed with septic shock</p> <p>Intervention – Balanced salt solution initial fluid resuscitation</p> <p>Comparison – Normal saline solution initial fluid resuscitation</p> <p>Outcome – Primary outcome: in-hospital mortality</p> <p>Secondary outcome: presence of hyperchloremic metabolic acidosis</p>	<p>Strengths: First double-blind RCT of different types of initial fluid resuscitation in children with septic shock</p> <p>Biases: Done in a single center with a relatively small population</p> <p>Sample size was calculated for the primary outcome, thus the outcome may be low powered</p>

<p>Emrath E., et al.</p> <p>“Resuscitation with balanced fluids is associated with improved survival in pediatric severe sepsis”</p>	<p>2022</p>	<p>Population - PICU in-patients aged 0-18 years old</p> <p>Intervention - Data review from January 2004 to December 2012</p> <p>Comparison - Balanced fluid (MES) versus unbalanced fluid (NSS) therapy</p> <p>Outcome -</p> <p>Primary outcome: in-hospital mortality</p> <p>Secondary outcome: presence of AKI, HLOS, PLOS, and vasoactive infusion days</p>	<p>Strength: Propensity-matched analysis (AUC)</p> <p>Biases: Use of administrative database is retrospective and lacks clinical detail</p> <p>PHIS database does not differentiate sepsis on admission from hospital-acquired sepsis</p>
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Clinical question #5

In a resource-limited setting, should we follow restrictive fluid administration or fluid bolus therapy?

Consensus statement #5

We suggest that restrictive fluid therapy be used for fluid resuscitation of children with sepsis or septic shock in institutions with limited resources. (WR)

Supporting statements

A meta-analysis showed a high quality of evidence to support that fluid bolus is harmful compared to no bolus.

A systematic review has reported low- to high-quality evidence indicating that it is uncertain whether there is any difference in adverse events between liberal and conservative fluid therapy.

Context

Both adults and children can be affected by the potentially fatal consequences of infection, known as sepsis and septic shock. Both of these conditions are linked to high rates of morbidity and mortality. Fluid therapy is considered an extremely important intervention when it comes to the initial management of sepsis. It is currently unknown whether or not fluid therapy that is either conservative or liberal can enhance clinical outcomes in individuals who are suffering from sepsis and septic shock.

Li et al. (2018) included three pediatric RCTs (N = 3402) but only extracted data from two (n = 3288). India (two studies) and Africa conducted these trials. Children 1 month -12 years old sepsis or septic shock patients were included. All three trials compared liberal versus conservative fluid therapy, but definitions varied. Liberal fluid therapy may increase in-hospital mortality by 38% (2 studies; N = 3288; RR 1.38, 95% CI 1.07 to 1.77; NNTH = 34; moderate quality evidence) and follow-up mortality by 39% (1 study; N = 3141; RR 1.39, 95% CI 1.11 to 1.74; NNTH = 29; high-quality evidence). The third study's findings regarding in-hospital mortality were unclear, indicating that the quality of the evidence was relatively low (1).

A randomized trial, a quasi-randomized trial, or a controlled before-and-after study assessing children with septic shock in which at least one group was

treated with bolus fluids was sought out by Ford et al. (2012) for their investigation. The researchers searched three databases for such studies. The death rate at 48 hours was the key measure of success.

When compared to giving any bolus, the researchers found that giving no bolus resulted in significantly better mortality outcomes at 48 hours for children with general septic shock (relative risk 0.69; 95% confidence interval (CI) 0.54–0.89) and children with malaria (relative risk 0.64; 95% CI 0.45–0.91). This outcome is mainly attributable to a single study that was of very high quality (the Fluid Expansion as Supportive Therapy or FEAST trial). In children suffering from acute malnutrition or Dengue fever, there is no research comparing the administration of boluses to the elimination of boluses. It was discovered that colloid and crystalloid boluses have the same impact on death rates across all subgroups (general septic shock, malaria, Dengue fever, and severe malnutrition).

The FEAST trial, which demonstrated that fluid boluses were harmful compared to receiving no bolus at all, accounts for the vast bulk of all randomized evidence that has been gathered (2). Healthcare practitioners should assess who will benefit from and be harmed by bolus fluids.

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
<p>Li D., et al</p> <p>“Liberal versus conservative fluid therapy in adults and children with sepsis or septic shock”</p> <p>(Systematic Review)</p>	2018	<p>Population – adults and children with initial sepsis and septic shock</p> <p>Intervention – Liberal initial fluid therapy</p> <p>Comparison – Conservative fluid therapy</p> <p>Outcome – data on mortality, pulmonary edema, and organ dysfunction</p>	<p>Strengths:</p> <p>All three studies showed appropriate study design and reliable conduct</p> <p>Randomization and allocation concealment were generally well conducted and described</p> <p>Minimal potential bias as the authors strictly complied with the Cochrane Handbook for Systematic Reviews of Interventions</p> <p>Biases:</p> <p>Authors had to downgrade the quality of evidence for study limitations due to high risk of attrition bias</p>

<p>Ford N., et al</p> <p>“Mortality after fluid bolus in children with shock due to sepsis or severe infection: a systematic review and meta-analysis”</p> <p>(Systematic review and meta-analysis)</p>	<p>2018</p>	<p>Population – Children with shock in resource-limited settings</p> <p>Intervention – Fluid bolus therapy</p> <p>Comparison – No bolus therapy</p> <p>Outcome –</p> <p>Primary outcome: mortality at 48 hours</p> <p>Secondary outcome: mortality at 4 weeks (FEAST trial)</p>	<p>Strength:</p> <p>Three databases searched for randomized trials, quasi-randomized trials, and controlled before-after studies assessing children with septic shock</p> <p>Biases:</p> <p>Majority of all randomized evidence comes from the FEAST trial</p> <p>Small sample sizes resulted in poor precision and did not achieve adequate power</p>
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Clinical question #6

What is the recommended first line vasoactive agent of choice for pediatric patients with fluid-refractory septic shock?

Consensus statement #6

We suggest the use of epinephrine as the first line vasoactive agent of choice in pediatric patients with fluid-refractory septic shock. (WR)

Supporting statements

In two randomized control trials, epinephrine showed better reversal of shock for pediatric patients with fluid-refractory septic shock compared with dopamine. In another randomized control trial comparing dopamine with epinephrine in the neonatal population, both have comparable results. This was also observed in a meta-analysis in pediatric and neonatal populations.

Based on a study done by Ramaswamy et al. (2016), resolution of shock within the first hour was achieved in a more significant proportion of children receiving epinephrine (n = 12; 41%) than dopamine (n = 4; 13%) (OR, 4.8; 95% CI, 1.3–17.2; p = 0.019) and persisted even at 6 hours (48.3% vs. 29%; p = 0.184) (1). In another study done by Baske et al. comparing the use of dopamine vs. epinephrine in the neonatal population, there was no significant difference in the proportion of neonates achieving 'reversal of shock' by 45 minutes RR 0.83 (95% CI 0.30, 2.29) (2). Similarly, in a meta-analysis consisting of three randomized control trials including pediatric or neonatal patients with septic shock (Wen and Xu 2020), dopamine and epinephrine reveal comparable shock reversal within 1 hour (risk ratios (RR) = 0.61; 95% CI = 0.16 to 2.31; P =0.47) (3).

In a randomized control trial done by Ventura et al. (2015), dopamine was associated with an increased risk of death (OR 6.5; 95% CI, 1.1-37.8; p=0.037) compared with epinephrine (4). However, in Ramaswamy's study, no significant difference in mortality was observed between the two groups. A similar result was also observed in the same meta-analysis by Wen and Xu.

Secondary outcomes of children given epinephrine had lower Sequential Organ Function Assessment scores on day 3 (8 vs. 12; p = 0.05) and more organ failure-free days (24 vs. 20 d; p = 0.022). However, epinephrine showed elevated serum lactate and impaired gut perfusion. On the other hand, dopamine was associated with more healthcare-associated infection

(OR, 67.7; 95% CI, 5.0–910.8; $p = 0.001$) (1). Other outcomes noted in the article reviewed showed no significant difference in the heart rate, systolic blood pressure, mean arterial pressure, and adverse events.

Context

Patients in shock unresponsive to 40-60ml/kg of IV crystalloids are highly susceptible to increased morbidity and mortality. Vasoactive agents are vital in the reversal of fluid-resistant shock. Although phenylephrine, epinephrine, norepinephrine, vasopressin, and dopamine are all vasoactive agents, epinephrine and dopamine are commonly regarded as the first line drugs (5). The updated Surviving Sepsis Campaign International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children suggest the use of epinephrine or norepinephrine as the first-line vasoactive agent for fluid-refractory septic shock. Although this is a weak recommendation, supporting studies show that epinephrine had better outcomes in mortality and end-organ damage after 28 days compared with dopamine (6).

Norepinephrine has been used as the first-line vasoactive agent of choice for septic shock in adults. In two meta-analyses, norepinephrine was comparable to other vasopressors in terms of mortality and achievement of the target MAP outcomes (7,8). However, these studies were done in the adult population, and the investigators failed to find studies in the pediatric population.

Dopamine effectively reduces mean arterial pressure in patients with fluid refractory shock. It is also useful in patients with a concomitant cardiac function reduction owing to its dose-dependent inotropic effect. However, dopamine is associated with adverse events. In a systematic review by Xu and Peter comparing dopamine and norepinephrine, there was no significant difference in mortality at 28 days, but dopamine was associated with more episodes of arrhythmia (9). In another study, dopamine showed increased splanchnic oxygen requirement in adult patients with septic shock (10). Dopamine may be detrimental as it inhibits inflammation-induced upregulation of cytokines, chemokines, and adhesion molecules and induces the production of anti-inflammatory mediators, increasing the risk for hospital acquired infections (HAI) (11). In the Surviving Sepsis Guidelines, although not preferred as the first-line vasoactive drug, it can be used as an alternative if epinephrine or norepinephrine is not available.

The two mostly studied vasoactive agents in the pediatric population were epinephrine and dopamine. The proponents of this consensus statement would like to verify further the recommendations made previously.

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
<p>Ventura et al</p> <p>"Double-Blind Prospective Randomized Control Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock"</p> <p>(Randomized Control Trial)</p>	2015	<p>Population – Children aged 1 month to 15 years old who met the clinical criteria for fluid-resistant refractory shock</p> <p>Intervention – giving vasopressors for patients who did not improve after 40 ml/kg of crystalloids.</p> <p>Comparison – dopamine vs epinephrine</p> <p>Outcome –</p> <p>Primary outcome: death from any cause by 28 days after inclusion</p> <p>Secondary outcome: HAI, the need for other vasoactive drugs and multiorgan dysfunction score</p> <p><u>Conclusion:</u> "The use of dopamine was associated with increased death and HAI odds ratios. Early administration of peripheral or intraosseous epinephrine was safe and</p>	<p>Strengths:</p> <p>Clearly focused research question</p> <p>Randomization done</p> <p>Participants who entered the study were accounted for</p> <p>Methodologically sound</p> <p>Can be applied to local population</p> <p>Biases:</p> <p>Single-center nature limits its external validity</p>

		associated with increased survival rates compared with dopamine."	
Ramaswamy et al "Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock." (Randomized Control Trial)	2016	<p>Population – children 3 months to 12 years old, with fluid-refractory hypotensive septic shock.</p> <p>Intervention – giving vasopressors</p> <p>Comparison – Dopamine and placebo vs Epinephrine and placebo</p> <p>Outcome – Primary outcome: resolution of shock within the first hour of resuscitation.</p> <p>Secondary outcomes: resolution of shock within 6 hours of resuscitation, day-28 all cause mortality, length of PICU stay, length of mechanical ventilation, time to achieve central venous saturation greater than 70% and lactate below 2 mmol/L, requirement of other vasoactive agents, improvement of SOFA at 72 hours, organ failure-free days and occurrence of nosocomial infection and adverse events</p> <p><u>Conclusion:</u> Epinephrine was three times more likely to achieve resolution of shock within</p>	<p>Strengths: Clearly focused question</p> <p>Randomization done</p> <p>Participants who entered the study were accounted for</p> <p>Methodologically sound</p> <p>Results applicable to local population</p> <p>Biases: Limited sample size</p>

		the first hour of resuscitation as compared to dopamine.	
<p>Baske et al</p> <p>"Epinephrine Versus Dopamine in Neonatal Septic Shock: A Double-Blind Randomized Control Trial."</p> <p>(Randomized Control Trial)</p>	2018	<p>Population – neonates (enrolled in two gestational age strata $\leq 306/7$ and $\geq 310/7$ weeks) with fluid-refractory septic shock.</p> <p>Intervention – giving vasopressor</p> <p>Comparison – Epinephrine vs Dopamine</p> <p>Outcome – Primary outcome was reversal of shock during the first 45 mins of vasoactive drug infusion</p> <p>Secondary outcome: hemodynamic stability, requirement of additional vasoactive drugs, physiologic variables, lactate clearance as marker of microcirculation, all-cause mortality by 28 days of life, incidence of medium term complications</p>	<p>Strengths: Clearly focused question</p> <p>Can be applied to local population</p> <p>Biases: Limited sample size</p>

		<p><u>Conclusion:</u> Among neonates with septic shock, the reversal of shock in the first 45 minutes of vasoactive drug therapy was comparable between epinephrine and dopamine groups.</p>	
<p>Wen and Xu</p> <p>“The efficacy of dopamine versus epinephrine for pediatric or neonatal septic shock: a meta-analysis of randomized controlled studies</p> <p>(Meta analysis)</p>	2020	<p>Population – pediatric and neonatal patients with septic shock</p> <p>Intervention – Vasopressors in pediatric and neonatal septic shock</p> <p>Comparison – Epinephrine vs Dopamine</p> <p>Outcome – shock reversal within 1 hour and mortality</p> <p><u>Conclusion:</u> The results find that dopamine and epinephrine intervention demonstrate comparable shock reversal within 1 h (RR =0.61; 95% CI=0.16 to 2.31; P= 0.47) with significant heterogeneity among the studies (I2 =71%, heterogeneity P=0.06.</p>	<p>Strengths: Clearly focused question</p> <p>Appropriate type of papers reviewed</p> <p>Can be applied in local setting</p> <p>Biases: There is significant heterogeneity</p>

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Clinical question #7

Will the use of steroids in pediatric cases with fluid and vasoactive refractory septic shock yield better results than not using them at all?

Consensus statement #7

The panel cannot recommend for or against the use of steroids in fluid and vasoactive refractory pediatric septic shock. (WR)

Supporting statements

In a recent network meta-analysis used in a Cochrane review on the use of steroids in fluid and vasoactive agent refractory septic shock, hydrocortisone was shown to result in faster reversal of shock, but the primary outcome of 28-day mortality rate did not show any difference between those that were given steroids and those that were not given steroids (1).

Furthermore, in 2 meta-analyses on the use of steroids in pediatric sepsis, steroids increased the risk for complications (increased infections, decreased immune response, increased GI bleeding) and increased the mortality rate (2).

Context

The hallmark of sepsis is the dysregulated systemic inflammation that mainly contributes to the progression from organ dysfunction to death. Adrenal insufficiency may develop during this hyperinflammatory state as elevated levels of proinflammatory cytokines have an inhibitory effect on the hypothalamic, pituitary, adrenal, and target tissue levels, alter cortisol metabolism, and cause ACTH and glucocorticoid resistance (3).

Corticosteroids can reduce organ dysfunction by reducing tissue inflammation and fostering tissue repair by improving tissue perfusion. It also induces sodium retention through actions on mineralocorticoid and glucocorticoid receptors and, thus, contributes to correcting the hypovolemia that characterizes the early phase of sepsis (4).

Corticosteroid administration in patients with fluid and vasoactive refractory shock remains controversial, with adult studies showing conflicting results.

Even though the use of highly potent glucocorticoids was noted to cause increased mortality in adults with sepsis, some experts recommend consideration of the use of low-dose hydrocortisone, a steroid with less glucocorticoid effect and more mineralocorticoid effect, for empiric treatment of adrenal insufficiency in fluid and vasoactive refractory septic shock as it has been associated with improved mortality and more rapid shock reversal in adult severe sepsis and septic shock in some studies (3).

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
Ben Gibbison et al “Corticosteroids in septic shock: a systematic review and network meta-analysis” (Systematic review, Meta analysis)	2017	<p>Population - children and adults with sepsis Intervention – treatment with any type of corticosteroid preparation Comparison – standard therapy or placebo Outcome – 28-day mortality, hospital mortality, ICU LOS, ICU mortality, shock reversal, incidence of GI bleeding and superinfection</p> <p><u>Conclusion:</u> There was no clear evidence that any one corticosteroid drug or treatment regimen is more likely to be effective in reducing mortality or reducing the incidence of gastrointestinal bleeding</p>	<p>Strengths: Structured approach of Cochrane review, applies different statistical approach to data</p> <p>Biases: Few direct comparisons of treatment regimens</p> <p>Data used was in the last 50 years</p> <p>Did not compare the effect of the dose of corticosteroids</p>

		<p>or superinfection in septic shock.</p> <p>Hydrocortisone delivered as a bolus or as an infusion was more likely than placebo and methylprednisolone to result in shock reversal.</p>	
<p>Sarah J. Atkinson et al</p> <p>“Corticosteroids and Pediatric Septic Shock Outcomes: A Risk Stratified Analysis“</p> <p>(Retrospective, Cohort Study)</p>	<p>2014</p>	<p>Population – full term neonates and children admitted to the PICU meeting pediatric-specific criteria for septic shock</p> <p>Intervention – corticosteroid during the first 7 days of meeting criteria for septic shock</p> <p>Comparison –no corticosteroid</p> <p>Outcome –</p> <p>Primary outcome: 28-day mortality, organ failure defined using pediatric-specific criteria</p> <p>Secondary outcome: stratified based on PRISM score (1st tertile: PRISM score \leq 10, 2nd tertile: PRISM score 11-17, 3rd tertile: PRISM</p>	<p>Strengths:</p> <p>Type of study</p> <p>Risk stratification</p> <p>Biases:</p> <p>– Indication for and timing of corticosteroids and general care for sepsis was not standardized across subjects</p> <p>Cannot determine diagnosis of relative adrenal insufficiency</p> <p>Retrospective design of study</p>

		<p>score >17</p> <p><u>Conclusion:</u> Risk stratified analysis failed to demonstrate any benefit from corticosteroids in this pediatric septic shock cohort.</p>	
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Clinical question #8

Before escalating to non-invasive positive pressure ventilation (NIPPV), what is an effective alternative mode of respiratory support for pediatric septic patients with respiratory distress unresponsive to standard flow oxygen?

Consensus statement #8

We recommend using Continuous Positive Airway Pressure (CPAP) as a form of non-invasive respiratory support in pediatric septic patients with respiratory distress unresponsive to standard flow oxygen. (SR)

Supporting statements

In a meta-analysis done by Xueqin Zao et al. comparing the outcomes of nasal CPAP versus High Flow Nasal Cannula (HFNC) in pediatric patients with acute respiratory disease, nasal CPAP is associated with lower rates of treatment failure and reintubation rates but higher adverse event rates than HFNC in children with respiratory distress that required escalation of respiratory support (1).

A prospective study by Jayashree et al examined the use of nasal bubble CPAP in children 1 month to 12 years old with hypoxemic clinical pneumonia in a resource-limited setting and has shown that nasal bubble CPAP (bCPAP) is a safe and effective method of providing non-invasive respiratory support to children with clinical pneumonia with few failure rate and complications (2). While a study in China by Chih-Ching Chang et al. showed high flow nasal cannula can also be initiated as first-line respiratory support in pediatric patients with various etiologies of respiratory distress in the PICU, this was only a retrospective cohort study (3).

Context

There are different modalities of oxygen supplementation in pediatric patients presenting with respiratory distress due to a variety of etiology. The standard flow oxygen therapy (through a standard nasal cannula) provides oxygen without the need for humidification when the oxygen flow is either low (i.e., 1–2 L/min) or the room air has high humidity (4). On the other hand, high flow rates usually require humidification due to the drying effect of non-humidified cold oxygen on nasal secretions and the respiratory mucosa (5). HFNC oxygen therapy delivers warm and humidified oxygen at a higher flow than the normal inspiratory flow and studies have suggested its usefulness for improving oxygenation and alleviating the requirement for mechanical ventilation in children with respiratory distress (6).

Another respiratory management modality is using continuous positive airway pressure (CPAP) with a positive end expiratory pressure (7) which has been shown to reduce the ventilation need duration and the overall hospitalization length in children presenting with respiratory distress. Nasal bubble continuous positive airway pressure was also found to be useful in hypoxemic patients in resource-limited settings (8).

Studies, both observational and randomized controlled trials (RCTs), have been published previously that compared outcomes among children receiving HFNC and CPAP (9).

In a single center study, high flow nasal cannula (HFNC) was utilized as first line therapy for PICU patients with acute respiratory distress of various etiologies across the pediatric age groups (10). While majority of the panel members consider this strategy as safe, an important consideration in the local setting is the availability of the equipment in our local intensive care units.

Nasal CPAP, when compared with HFNC, was found to be associated with lower rates of treatment failure and reintubation in patients with respiratory distress. However, HFNC had lower adverse event rates. CPAP was also associated with effective lowering of the respiratory rate in patients with severe pneumonia, although there is still a lack of evidence supporting its definite significance in other clinical parameters (11).

The panel members recommend the use of CPAP as a form of non-invasive respiratory support when escalating oxygen therapy in patients with respiratory distress. HFNC remains a safe alternative in settings where CPAP is unavailable.

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
<p>Xueqin Zhao</p> <p>“Outcomes of High-Flow Nasal Cannula Vs. Nasal Continuous Positive Airway Pressure in Young Children with Respiratory Distress: A Systematic Review and Analysis”</p> <p>(Systematic Review and Meta Analysis)</p>	<p>Nov. 2021</p>	<p>Population – RCTs on infants and children with Acute Respiratory Distress (1 months to 7 months) that compared outcomes of interest after treatments with either CPAP or HFNC</p> <p>Intervention– HFNC and CPAP on patients with Acute respiratory distress</p> <p>Comparison– HFNC vs CPAP</p> <p>Outcome – Primary outcomes: Treatment failure, intubation need, mortality, and any adverse events</p> <p>Secondary outcomes: Treatment duration, respiratory distress severity, hospitalization length, time to treatment failure, respiratory rate (RR) and Arterial Blood Gas (ABG) parameters.</p> <p><u>Conclusion</u>: Nasal CPAP is associated with lower rates of treatment failure and reintubation rates but higher adverse event</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>Well reviewed titles and abstracts that fulfilled the inclusion criteria</p> <p>Applicable in our local setting</p> <p>Biases:</p> <p>Number of included studies is relatively low (N = 6)</p> <p>Lack of homogeneity in the primary clinical diagnosis among included infants</p> <p>Secondary outcomes showed a high degree of heterogeneity among included studies.</p>

		<p>rates than HFNC in children with respiratory distress that required escalation of respiratory support.</p>	
<p>Chih-Ching Chang, Yi-Chen Lin et al</p> <p>“High-Flow Nasal Cannula Therapy in Children with Acute respiratory distress with Hypoxia in PICU – A single Center Experience”</p> <p>(Retrospective Cohort Study)</p>	<p>May 2021</p>	<p>Population – Children from 1 month to 18 years of age with acute respiratory distress with hypoxia admitted in PICU</p> <p>Intervention – High Flow Nasal Cannula</p> <p>Comparison- None</p> <p>Outcome – Improvement or worsening in the following parameters: RR, FiO₂, heart rate, SpO₂/FiO₂ratio, comfort, escalation to non-invasive ventilation (NIV) or intubation</p> <p>Conclusion:HFNC could be initiated as the first line therapy in all age groups of children with</p>	<p>Strengths: Clearly focused question</p> <p>Results applicable to local population</p> <p>Biases: Retrospective study with limited cohort of children with acute respiratory distress receiving HFNC therapy at a single center Not clearly defined criteria for escalating therapy to CPAP or intubation</p>

		various etiologies of acute respiratory distress in PICU.	
<p>Muralidharan Jayashree, et al</p> <p>“Use of Nasal Bubble CPAP in Children with Hypoxemic Clinical Pneumonia – Report from a Resource Limited Set-Up”</p> <p>(Prospective Study)</p>	Sept 2015	<p>Population – 1 month to 12 years old with clinical pneumonia enrolled prospectively over 1 year</p> <p>Intervention– bCPAP as a non-invasive respiratory support</p> <p>Comparison– None</p> <p>Outcome –</p> <p>Primary outcome: Proportion of patients on bCPAP requiring intubation</p> <p>Secondary outcome: Duration of bCPAP, Occurrence of hypercarbia (defined as $PCO_2 > 50$ mmHg anytime during delivery of bCPAP)</p> <p>Incidence of nasal trauma, gastric</p>	<p>Strengths: Prospective study done from a developing country in the post neonatal age group</p> <p>Applicability in our local setting</p> <p>Biases: Technical difficulties in improving the circuit to deliver a fixed oxygen concentrations</p>

		<p>distension, shock and air leaks Length of emergency stay</p> <p><u>Conclusion:</u> Nasal bCPAP is a safe and effective method of providing non-invasive respiratory support to children with clinical pneumonia. The failure rate and clinically significant complications were few.</p>	
<p>Zhi-Li Wang, Yu-He</p> <p>“Continuous positive airway pressure in children with severe pneumonia: a meta analysis” (Meta Analysis)</p>	<p>May 2020</p>	<p>Population – RCTs and cross over studies; having a comparison group (standard therapy or low flow oxygen) and involving inpatients with severe pneumonia defined by WHO younger than 18 yrs old Intervention– CPAP in children with severe pneumonia Comparison – Low flow oxygen Outcome – Primary outcomes: Intubation rate and mortality Secondary outcomes: Change in RR, HR, duration of hospital stay and adverse events</p> <p><u>Conclusion:</u></p>	<p>Strengths: Clearly defined question Reviewed articles met the inclusion criteria Applicability in our local setting</p> <p>Biases: Only four studies were reviewed Results were heterogeneous</p>

		<p>Limited evidence suggests CPAP may reduce respiratory rate. Still, there is a lack of evidence to show significant benefit for the use of CPAP for other outcomes.</p>	
<p>J. Walk et al</p> <p>“Non-invasive ventilation with Bubble CPAP is feasible and improves respiratory physiology in hospitalized Malawian children with acute respiratory failure”</p> <p>(Prospective Observational Study)</p>	<p>Feb 2016</p>	<p>Population – A prospective observational study of bCPAP aged 1 week to 14 years with progressive acute respiratory failure despite oxygen and antimicrobial therapy</p> <p>Intervention– bCPAP</p> <p>Comparison– None</p> <p>Outcome – Treatment failure defined as a patient who either died receiving bCPAP or required intubation</p> <p><u>Conclusion:</u> A low cost bCPAP device can be used effectively in a resource-constrained setting.</p>	<p>Strengths: Clearly focused question</p> <p>Applicability in our local setting</p> <p>Biases: Non-randomized and uncontrolled</p> <p>Small sample size</p> <p>Busy and understaffed institution</p>

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Clinical question #9

Will the use of initial ventilatory settings with high positive end-expiratory pressure (PEEP) in pediatric cases with sepsis-induced pediatric acute respiratory distress syndrome (PARDS) reduce in-hospital mortality?

Consensus statement #9

Yes. We suggest the judicious use of high PEEP of ≥ 10 cmH₂O as an initial ventilatory setting in patients with sepsis-induced PARDS to reduce in-hospital mortality, accompanied by vigilant monitoring of potential effects on hemodynamics from increased intrathoracic pressure. (WR)

Supporting statements

Observational analysis by Khemani et al. (2018) showed that the use of lower PEEP relative to FIO₂ than what was recommended by the ARDSNet model was associated with increased mortality compared to patients managed with a higher PEEP level.

It was known that higher PEEP will contribute to elevations in intrathoracic pressure, which will cause harmful effects on hemodynamics, such as a decrease in cardiac output. But in a single center, prospective study by Ingaramo et al. (2013) on hemodynamically stable mechanically ventilated pediatric patients, decreased cardiac output as PEEP was increased from 0 – 12 cmH₂O (although statistically significant), the mean change was only 10%, which was relatively not clinically significant. For hemodynamically unstable mechanically ventilated patients, as in septic shock, further studies need to be conducted as the group was unable to find studies in this subset of patients.

Context

Sepsis-induced PARDS is one of the entities under sepsis-associated organ dysfunction. PARDS prevalence among sepsis in children is unknown, and it has been associated with poor outcomes (1). Globally, mortality accounted for an average of 20-30% (2).

The primary goal in managing PARDS is optimizing oxygenation and ventilation to meet the metabolic demands of the disease with careful assessment of the risk and benefits of ventilatory support.

PEEP prevents alveolar collapse at the end-expiration, limiting atelectrauma

(3). In the lack of conclusive pediatric data, PALICC advised that patients with severe PARDS should have relatively increased levels of PEEP (10–15 cm H₂O) titrated to the observed oxygenation and hemodynamic response. For severe PARDS, PEEP values > 15 cm H₂O may be necessary, with special attention paid to keeping the peak airway pressure within reasonable limits (3).

The panel was able to review one literature on the relationship between PEEP and mortality as their primary outcome. Observational analysis by Khemani et al. (2018) showed that the use of lower PEEP relative to FIO₂ than what was recommended by the ARDSNet model was associated with increased mortality compared to patients managed with a higher PEEP level (4).

It was known that higher PEEP will contribute to elevations in intrathoracic pressure, which will cause harmful effects on hemodynamics, such as a decrease in cardiac output. But in a single center, prospective study by Ingaramo et al. (2013) on hemodynamically stable mechanically ventilated pediatric patients, decreased cardiac output as PEEP was increased from 0 – 12 cmH₂O (although statistically significant), the mean change was only 10%, which was relatively not clinically significant. For hemodynamically unstable mechanically ventilated patients, as in septic shock, further studies need to be conducted as the panel was unable to find studies in this subset of patients (5). Although outcomes for PARDS have improved over the past decade, mortality and morbidity remain significant.

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
<p>Khemani RG, et al</p> <p>“Positive end-expiratory pressure lower than the ARDS network protocol is associated with higher pediatric acute respiratory distress</p> <p>(Multicenter, retrospective analysis)</p>	2018	<p>Population – Four previously published datasets of invasively mechanically ventilated children with PARDS</p> <p>Intervention – Low and High PEEP on patient with PARDS</p> <p>Comparison – Low PEEP vs High PEEP</p> <p>Outcome – Primary outcome: ICU mortality</p> <p><u>Conclusion:</u> Patient with PARDS managed with lower PEEP relative to FIO₂, than recommended by ARDSNet model had higher mortality.</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>Results applicable to local population</p> <p>Good number of study subjects</p> <p>Biases:</p> <p>Retrospective Study</p>
<p>Ingaramo OA, et al.</p> <p>“Impact of Positive End-</p>	2013	<p>Population – Fifty mechanically ventilated, hemodynamically stable children</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>Results</p>

<p>Expiratory Pressure on Cardiac Index Measured by Ultrasound Cardiac Output Monitor”</p> <p>(Prospective, single center, interventional)</p>		<p>between 1 month and 20 years old</p> <p>Intervention – alteration of PEEP levels in mechanically ventilated patients</p> <p>Comparison – different levels of PEEP</p> <p>Outcome – Cardiac index (cardiac output)</p> <p><u>Conclusion:</u> In hemodynamically stable mechanically ventilated children, although there is a statistically significant decrease in cardiac output as positive end-expiratory pressure is increased between 0 and 12cm H₂O, the mean change is less than 10%, and this is likely not clinically significant.</p>	<p>applicable to local population</p> <p>Biases:</p> <p>Single center</p> <p>Small number of study subjects</p>
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Clinical question #10

Will tight glyceamic control improve outcome in pediatric patients with sepsis?

Consensus statement #10

We cannot recommend tight glyceamic control in pediatric patients with sepsis. (SR)

In two meta-analyses, tight glyceamic control (the use of insulin to maintain the blood glucose level between 80 to 110 mg/dl) has been found to increase the risk of severe hypoglycemia.

Supporting statements

In a randomized control trial done by M.S.D. Agus et al among critically ill pediatric patients receiving vasoactive support and mechanical ventilation who had elevated blood glucose levels, continuous IV insulin was given to maintain a target range with the group randomized into either maintaining blood sugar levels between 80 - 110mg/dl versus 150 - 180mg/dl. Results showed an enriched population of critically ill children with hyperglycemia and those with blood glucose target of 150 - 180 mg/dl was associated with clinical outcomes that were similar to outcomes with a target of 80 - 110 mg/dl, but with a lower risk of hypoglycemia (1).

In a systematic review and meta-analysis done by Lylin Chen et al, they found that Tight Glycemic Control (TGC) was not associated with a significant reduction in hospital mortality, seizures, or sepsis, but appears to be associated with a reduction in new need for dialysis. However, TGC was associated with a markedly increased risk of hypoglycemia (2).

Context

Hyperglycemia is a prevalent occurrence in critically ill pediatric patients with more than 80% having blood glucose levels more than 110 mg/dl, more than 60% a concentration greater than 150 mg/dl, and more than 30% a concentration exceeding 200 mg/dl (1). If left untreated, hyperglycemia can have adverse outcomes such as organ failure, sepsis, prolonged hospitalization, and mortality (2). The practice of tight glyceamic control (TGC) especially in adults became a feasible strategy to ameliorate the adverse outcomes of hyperglycemia (3).

Several investigations have examined the benefits and risks of using TGC in critically ill children. In 2009, Vlasselaers et al. published a single-center,

randomized controlled trial (RCT) of critically ill children showing that TGC of 80–110 mg/dl reduced hospital mortality by half, and reduced the infection rate and length of stay, but also presented extremely high rates of severe hypoglycemia (4). However, subsequent multicenter large RCTs of TGC have failed to replicate this mortality benefit. Thus an updated systematic review and meta-analysis was done by Lylin Chen et al in 2018 examining the risks and benefits of tight glycemic control as compared to usual glycemic control among critically ill pediatric patients (5). In this meta-analysis of six randomized control trials of TGC versus usual control, there was no significant difference in the risk of hospital death, sepsis, or seizures though TGC was associated with lower need of new dialysis. On the other hand, TGC was associated with a 4-fold increase of hypoglycemia (6).

Given the above studies, the panel found clear evidence of the main harm of TGC. Furthermore, there were no significant differences in other parameters being studied when TGC was compared with usual glycemic control. Although no definite target glucose level has been established in critically ill pediatric patients, the panel could not recommend tight glycemic control.

Summary of Evidence

Main Author	Year	PICO	Strengths and Biases
<p>M.S.D. Agus, D. Wypij, E.L. Hirshberg et al</p> <p>“Tight Glycemic Control in Critically Ill Children: A Multicenter Randomized Control Trial”</p> <p>(Randomized Control Trial)</p>	<p>Aug 23 2017</p>	<p>Population – Critically Ill children aged 2 weeks to 17 years old who were receiving vasoactive support for hypotension and mechanical ventilation</p> <p>Intervention – Continuous intravenous insulin to maintain blood glucose in a target range</p> <p>Comparison – 80-110 mg/dl vs 150-180 mg/dl</p> <p>Outcome –</p> <p>Primary outcome: number of ICU-free days to day 28.</p> <p>Secondary outcomes: 90-day mortality, severity of organ dysfunction (according to the Pediatric Logistic Organ Dysfunction [PELOD] score), number of ventilator-free days to day 28, incidence of healthcare-associated infection according to current published definitions from the Centers for Disease Control and Prevention (CDC) and incidence of hypoglycemia</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>There was Randomization</p> <p>Study is easy to replicate</p> <p>Explicit methods to control glucose and limit hypoglycemia</p> <p>Extensive training of clinicians</p> <p>Applicable in our local setting</p> <p>Biases:</p> <p>Blinding was not done</p> <p>Informed consent was obtained only after hyperglycemia was confirmed, which created a delay between the onset and treatment of hyperglycemia</p>

		<p><u>Conclusion:</u> We conclude that in an enriched population of critically ill children with hyperglycemia, a blood glucose target of 150 to 180 mg per deciliter was associated with clinical outcomes that were similar to outcomes with a target of 80 to 110 mg per deciliter, with a lower risk of hypoglycemia.</p>	<p>In order to compare two tight glucose-control targets within the range of usual care, we did not include a third group in which hyperglycemia was not treated</p>
<p>Lvlin Chen, Tiangui Li, Fang Fang, Yu Zhang et al</p> <p>“Tight glycemic control in critically ill pediatric patients: a systematic review and meta-analysis”</p> <p>(Systematic Review and Meta Analysis)</p>	<p>2018</p>	<p>Population – RCTs that met each of the following criteria: the setting was a PICU, and the patient was child (age < 16 years); the intervention group received TGC (glucose goal < 140 mg/dl obtained using insulin treatment during part or all of the PICU stay); the comparison group received usual care (method of insulin administration and glucose goal could vary between trials)</p> <p>Intervention – insulin treatment</p> <p>Comparison – Very tight control (upper limit of glucose goal < 110 mg/dl); and moderately tight control (upper limit</p>	<p>Strengths:</p> <p>Clearly focused question</p> <p>Articles were all RCTs</p> <p>Trials were conducted in different countries</p> <p>Independently assessed risk for bias</p> <p>Appropriate type of papers reviewed</p> <p>Results applicable to local population</p>

	<p>of glucose goal 110–140 mg/dl). vs Usual Control (140–180 mg/dl)</p> <p>Outcome – Primary outcome: hospital mortality (reduction in hospital mortality considered to be the most important potential benefit of TGC)</p> <p>Secondary outcome: included hospital mortality, hypoglycemia (any, severe), new need for dialysis, sepsis, or seizures.</p> <p><u>Conclusion:</u> We found that TGC was not associated with a significant reduction in hospital mortality, seizures, or sepsis, but appears to be associated with a reduction in new need for dialysis. However, TGC was associated with a markedly increased risk of hypoglycemia.</p>	<p>Biases: Treating clinicians were not blinded, however investigators were blinded</p> <p>Small numbers of studies and those in individual subgroup analyses limited power in our conclusions</p> <p>All included studies were conducted in developed countries. Thus, our findings are applicable only to developed countries</p>
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Summary

In summary, ten consensus statements were formulated to answer ten critical clinical questions on sepsis and septic shock in children. The consensus statements were issued after a thorough literature search and critical appraisal of the available research articles. The consensus statements were graded as either a strong recommendation (SR) or weak recommendation (WR) according to the level of evidence, the expected benefit or harm vis a vis the other, and the applicability of the recommendation in the local setting.

This set of recommendations were issued only as a guide to help clinicians in the management of pediatric sepsis and septic shock. The clinician will have to consider the patient's clinical condition, the estimated benefit versus harm it can impose on the patient, and the applicability of these recommendations in their institution.

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Lastly, the group would like to thank the SPCCMP Board for entrusting this project to the Cebu group. We hope that your confidence and trust in us will be rewarded by the publication of our own SPCCMP CONSENSUS STATEMENT ON PEDIATRIC SEPSIS AND SEPTIC SHOCK.

**Technical Working Group
The Panelists**



**Ronald Limchiu, MD, Ramon Najarro, MD (seated)
Tyronne Lariago, MD, Lorelie Ramos, MD,
Audrey Anne Diaz, MD, Wilfredo Dublin Jr., MD**

The Panelists



Rudy Amatong, MD



Belle Ranile, MD



Arnold Nicholas Lim, MD

The Associates



**Jethro Solite, MD, Neil John Wahing, MD
with the panelists**

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