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Latin American Consensus on the Management of Sepsis in Children: Sociedad Latinoamericana de Cuidados Intensivos Pediátricos [Latin American Pediatric Intensive Care Society] (SLACIP) Task Force: Executive Summary

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Introduction

Sepsis is one of the main causes of morbidity and mortality worldwide.[1] In the US, for example, sepsis is the most important cause of inpatient mortality and consumes more than 24 billion dollars per year.[2] A large study published in 2017 estimated 48.9 million sepsis cases around the world, of which 20.3 million were in children under five years old. Eleven million people died of sepsis, representing 19.7% of global deaths. Of these deaths, 2.9 million were in children under five years old and 454,000 were in children between five and 19 years old. Sepsis incidence and mortality vary widely between the different regions of the world, with a greater burden in Sub-Saharan Africa, Oceania, South Asia, East Asia and Southeast Asia.[3]

Recent studies have shown that fatal sepsis cases are higher in middle and low-income countries than in high-income countries (31.7% vs. 19.3%).[4] There is a greater risk of death in continents with middle and low-income countries (Africa 7.89, 95% CI 6.02-10.32; Asia 3.81, 95% CI 3.60-4.03; South America 2.91, 95% CI 2.71-3.12) compared with North America, especially in the youngest children. Among children under five years old, the most common causes of sepsis in 2017 were diarrheal disease (5.9 million cases of sepsis), neonatal disorders (5.1 million cases of sepsis) and lower respiratory tract infections (3.3 million cases of sepsis).[3,4] All of these problems are frequent causes of death in countries with limited resources and health care inequality.[5,6]

The objective of a recent publication by the Surviving Sepsis Campaign (SSC) in children carried out by the Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM) and the International Sepsis Forum[5] was to develop evidence-based guidelines and recommendations for the resuscitation and management of sepsis patients. Seventy-seven recommendations were issued without taking available resources into account, except one related to fluid resuscitation. These guidelines are mostly based on studies in high-income countries and issue recommendations which seek to guide "*best practice*" more than to establish treatment algorithms or determine different standards of care.

Given that healthcare access limitations, the burden of non-communicable chronic diseases and the availability of resources, among others, are determining factors for the outcomes of children with sepsis in low and middle-income countries, the SSC guidelines are not completely applicable in the healthcare context of countries with limited resources.[6] Therefore, the *Sociedad Latinoamericana de Cuidados Intensivos Pediátricos* (SLACIP) decided to carry out this first consensus in order to produce recommendations for the recognition and management of sepsis in children living in countries with limited resource availability, particularly in Latin America.

These guidelines seek to generate recommendations based on the best available evidence, including local and regional studies in countries with limited resources, which do not replace individual clinical judgement in the care of children with sepsis. The intention is not to replace the SSC or other existing guidelines; on the contrary, the purpose is to contribute through experts who live in, and are familiar with the reality of, these low and middle-income countries, providing recommendations using the best available evidence to improve clinical practice and health care in children with sepsis in countries with limited resources.

Methods

A formal consensus was designed using the modified Delphi method, combining the opinions of nominal groups of experts with the interpretation of the available scientific evidence in a systematic process of consolidation of a body of recommendations. The protocol is registered on the Open Science Framework (https://osf.io/ezxmr).

Consensus planning began with the establishment by the SLACIP Sepsis Committee of the 10 topical domains. Ten questions (some with sub-questions) were generated using the PICO format which describes the Population (P), Intervention (I), Control (C) and Outcomes (O). A systematic review of the literature was conducted for each domain, using the Johanna Briggs Institute guidelines.[9] The systematic search was performed by an expert librarian and included specific algorithms for the Cochrane, PubMed, Lilacs and Scopus specialized registry databases and the OpenGrey database for grey literature. The search results were imported to the Rayyan tool which was used for screening. Special emphasis was placed on search engines which included original studies performed in LMICs. Studies in English, Spanish and Portuguese were included. The GRADEpro GDT guide was used for grading each of the selected articles. This grading was organized in a book of evidence which was submitted to the experts as a complement for emitting the recommendations.

Expert Selection

For this consensus, the topical (FSJ, DSD) and methodological (MA, NV) coordinating groups defined "experts" to be those who met at least two of the three criteria described below and who agreed to participate in this consensus: membership in

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the SLACIP Sepsis Committee from 2019 to 2021 or 2017 to 2019; principal author or corresponding author of at least one original study on sepsis in children in LMICs within the last five years, published in a Q1, Q2 or Q3 indexed journal; and at least 10 continuous years of work experience in a middle or low-income country in intensive care, emergency or pediatric infectious disease. The Sociedad Latinoamericana de Infectología [Latin American Society of Infectious Disease] was invited to participate (specifically on the topic of antibiotics in sepsis), along with the Sociedad Latinoamericana de Emergencias [Latin American Society of Emergency Care] and the Instituto Latinoamericano de Sepsis [Latin American Sepsis Institute] (ILAS), who selected their participants according to the expert requirements suggested by the topical and methodological coordinating groups.

The experts' participation in this study was voluntary and did not garner any type of compensation. A consent to participate and a declaration of conflict of interest were requested, which were signed and approved by the participants. The experts' affiliations did not affect their participation in the consensus. The experts were organized in 10 nominal groups coordinated by a spokesperson. Each group developed a proposal of recommendations based on the working questions; subsequently, the recommendations were voted on using the Delphi method and a virtual conference discussion consensus.

First consultation, returns and defining consensus: An initial exploratory consultation was performed using the Delphi method individually and asynchronously. The experts were given a packet of referenced evidence which had been previously assessed for quality. They determined their degree of agreement using a Likert scale from 1 to 9: 1 to 3 against; 4 to 6 neither in favor nor against; and 7 to 9 in favor. Consensus was defined as a greater than 75% agglutination. The strength of the recommendation was determined by the percentage vote of the experts, considered to be weak if the agreement was between 75% and 79%, and strong if it was over 80%. The final recommendation was drafted stating the direction, strength and certainty of the accompanying evidence.

Consensus conference: Through virtual meetings carried out from February 2020 to February 2021, the topical and methodological coordinating groups, group spokespersons and the entire group of experts reviewed the recommendations and suggestions. In order for a recommendation to be accepted it had to have a vote consensus of more than 75%. A vote under 75% showed that there was no consensus. If the final vote was between 75% and 79%, a *suggestion* was made (discretional or weak) in favor of or against the intervention. If the vote was equal to or greater than 80%, it was *recommended* (strongly in favor of or against the intervention). This was the task force's criterion regarding the strength of the recommendation. These recommendations are summarized in *Supplement 1*.

Results

The Consensus provided 62 recommendations for the diagnosis and treatment of pediatric sepsis in LMICs. Overall, 60 were strong recommendations, although 56 of these had a low level of evidence (*supplementary file 1*). Figure 1 summarizes the recommendations for hemodynamic management and fluid resuscitation made by the expert panel for these countries.

Recommendations

1. DEFINITION

1.1 The definition of sepsis and its clinical (operational) criteria should be considered as two different concepts (*Strong recommendation in favor, low level of evidence.*)

1.2 Sepsis is a clinical syndrome characterized by a potentially fatal organ dysfunction caused by an dysregulated host response to the infection. (*Strong recommendation in favor, low level of evidence.*)

1.3 Septic shock is sepsis with especially profound circulatory, cellular and metabolic abnormalities associated with a greater risk of mortality than sepsis alone. (*Strong recommendation in favor, low level of evidence.*)

2. Sepsis Epidemiology and Prevalence in Latin America

Infections, especially respiratory tract and gastrointestinal infections hold first and third place among the causes of death in children under the age of five, and seventh and sixth place in children from 5 to 14 years old, respectively;[6,10] the highest proportion of these deaths are attributed to sepsis and septic shock. There is no unified system of regional notification of morbidity and mortality in Latin America. Epidemiological data on the burden of sepsis are extracted from private research initiatives and from mathematical models based on vital statistics. Thus, the actual incidence cannot be estimated.[11]

In 19 PICUs in Colombia, Jaramillo-Bustamante et al. found an overall mortality of 18% and a pulmonary focus in 54% of 1051 patients. The groups with the highest risk of mortality were patients with septic shock, those under two years of age, those with organ failure, or those with a low socioeconomic status.[14] De Souza et al. in a study of patients from 21 regional hospitals (Brazil, Argentina, Chile, Paraguay and Ecuador), report frequencies of 42.4% for sepsis, 25.9% for severe sepsis and 19.8% for septic shock among patients hospitalized in the PICU between June and September 2011.[15] Mortality in the different studies ranged from 13 to 33.7%[16] in Latin American countries.

3. Bundles and Initial Care in Countries with Limited Resources

3.1 We suggest that, once sepsis has been diagnosed, interventions be carried out at the times recommended for each; interventions which should be reinforced and universally used. (*Strong recommendation in favor, low level of evidence.*)

3.2 We recommend requesting advice promptly from the referral center, whether from the pediatrician, emergency physician or intensivist, for treatment suggestions. The appropriate

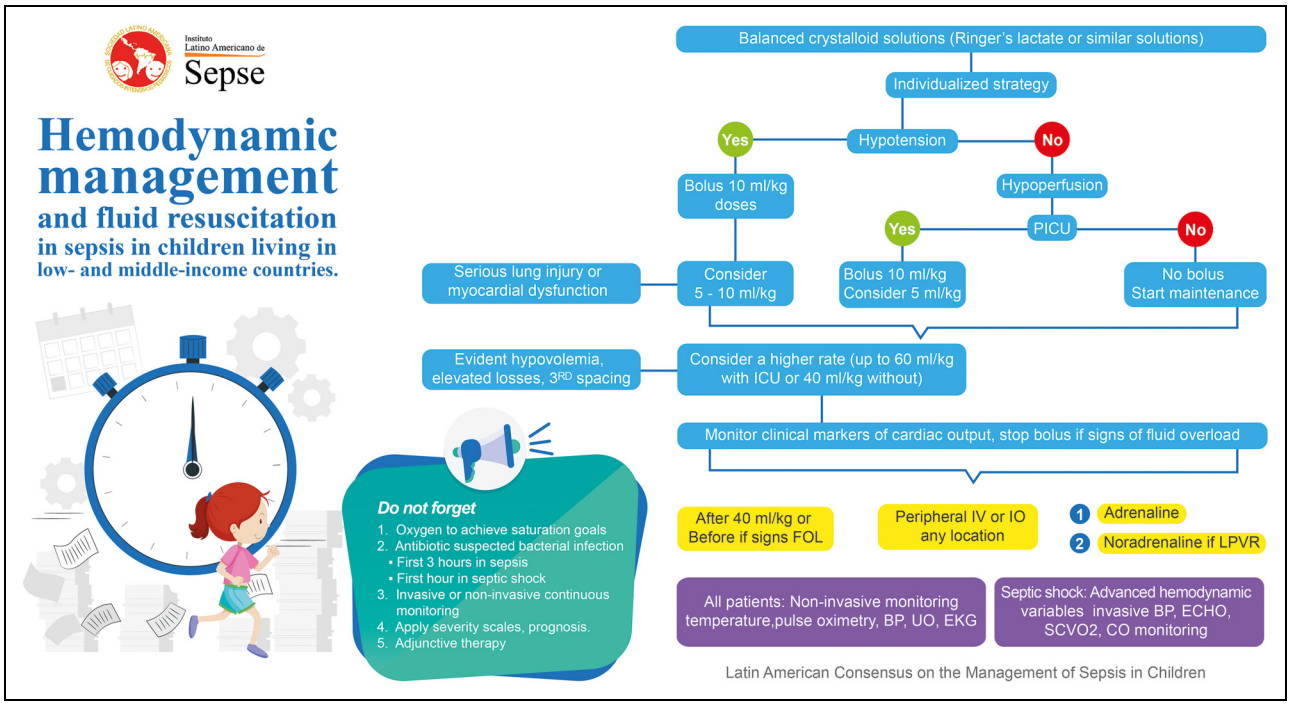

Figure 1. Hemodynamic management and fluid resuscitation in sepsis in children living in low- and middle-income countries.
PICU: Pediatric Intensive Care Unit, FOL: fluid overload, LPVR: low peripheral vascular resistance, BP: Blood pressure, UO: urine output, EKG: electrocardiogram, SCVO2: Central venous oxygen saturation, CO: cardiac output.

time for transfer, clinical conditions prior to transfer (stabilization), transfer team and means of transport should be decided together with the referral center. (*Strong recommendation, low level of evidence.*)

3.3 We recommend systematically using the *Pediatric Assessment Triangle (PAT)* for the initial assessment of children with sepsis. It is recommended that treatment be initiated without waiting for lab exam results. (*Strong recommendation, low level of evidence.*)

3.4 We suggest understanding the context of children with sepsis (clinical history, healthcare system) to determine the risk of some viral and parasitic infections prevalent in each country which may require special interventions and precautions. (*Weak recommendation, low level of evidence.*)

3.5 We suggest considering the simultaneous application of the septic shock bundle within the first hour of care. This package of actions should include the recognition, resuscitation, stabilization and process control bundles. The first interventions should include obtaining peripheral venous access (ideally within the first five minutes), administering oxygen (when there is hypoxemia), beginning antibiotics within the first hour along with vasoactive medications (through the peripheral vein, if central access is not available), and applying the fluid resuscitation strategy suggested in this consensus (*Strong recommendation, low level of evidence.*)

4. Early Recognition and Severity Scales

4.1 For early recognition of sepsis in children, we recommend taking into account the clinical criteria described in the text, the medical team and parents' perception of the severity of the illness, and the presence of comorbidities. (*Strong recommendation, low level of evidence.*)

4.2 We suggest using procalcitonin either together with or as an alternative to C-reactive protein as a complement to clinical assessment, according to the availability at each healthcare facility, to guide a possible bacterial sepsis diagnosis. (*Strong recommendation in favor, low level of evidence.*)

4.3 The use of ferritin as a priority biomarker in the initial assessment cannot be recommended, as the cut-off point has not been determined, it is nonspecific and it is not widely available. (*Strong recommendation against, low level of evidence.*)

4.4 The use of serum lactate for patient stratification is not recommended. Its serial measurement and assessment of change over time may be useful for follow up and as a guide for resuscitation. (*Strong recommendation in favor, low level of evidence.*)

4.5 We suggest considering the use of an organ dysfunction score (e.g., pSOFA or PELOD-2) as a predictor of mortality in the initial assessment and follow up of patients with sepsis. (*Strong recommendation in favor, low level of evidence.*)

4.6 We recommend the Pediatric Index of Mortality (PIM3) as a predictor of mortality on admission to the PICU. (*Strong recommendation in favor, low level of evidence.*)

4.7 We recommend using the Functional Status Scale (FSS) to evaluate morbidity in patients with sepsis, measured at PICU and hospital discharge. (*Strong recommendation in favor, low level of evidence.*)

5. Oxygen Administration Systems and Ventilatory Management

5.1 We recommend administering oxygen via bubble CPAP or noninvasive ventilation in children with sepsis with respiratory failure, in countries with limited resources, when invasive mechanical ventilation is not possible or safe. (*Strong recommendation, low level of evidence.*)

5.2 We do not recommend immediate initial intubation in children with septic shock. It is indicated in cases of apnea and coma, or lack of response to the initial treatment. (*Strong recommendation, low level of evidence.*)

5.3 We recommend performing endotracheal intubation and invasive respiratory support when there is deterioration of the respiratory or cardiovascular function, or it does not improve with the initial support measures in children with septic shock. A good fluid resuscitation and infusion of vasoactive medications, if needed, should be ensured prior to intubation. (*Strong recommendation, low level of evidence.*)

5.4 The following goals are recommended for children with sepsis receiving invasive mechanical ventilation: normoxemia ($paO2 \geq 60$ mm Hg or $SaO2 \geq 90\%$), and 90 to 94% saturation in patients with mild pARDS with a PEEP <10 cm/H20. For patients with serious pulmonary disease, and to avoid iatrogenic (nonprotective) ventilatory parameters, saturations may be kept $\geq 88\%$ (88-92%). (*Strong recommendation, low level of evidence.*)

5.5 For children with sepsis receiving mechanical ventilation, we recommend using plateau pressures lower than or equal to 30 cm H_2O with tidal volumes between 5 to 8 mL/kg in patients with low pulmonary compliance or elevated elastance. In patients with low pulmonary elastance, higher tidal volumes may be used to reach saturations between 88% −92%, keeping the plateau pressure lower than or equal to 30 cm H_2O. (*Strong recommendation, low level of evidence.*)

5.6 In children with sepsis on mechanical ventilation, we recommend using the necessary PEEP to obtain the best possible compliance and an arterial saturation equal to or greater than 90% or PaO2 of 60 mm Hg, with an FiO2 less than or equal to .6. (*Strong recommendation, moderate quality evidence.*)

5.7 We recommend considering the use of high-frequency oscillatory ventilation (HFOV) in respiratory failure refractory to other conventional methods, when oxygenation or ventilation goals are not reached, or when non-protective conventional MV parameters must be used to achieve these goals, such as: plateau pressure greater than 30 cm H_2O, driving pressure > 15 cm H_20 and FiO_2 greater than .6. (*Strong recommendation, low level of evidence.*)

6. Fluid Resuscitation

6.1 For healthcare systems with limited availability of intensive care, we recommend not administering bolus fluids for patients without hypotension, and starting maintenance fluids (*Strong recommendation, high quality evidence.*)

6.2 For healthcare systems with ICU availability or limited availability, during initial resuscitation, when hypotension is present, we recommend administering a 10 mL/kg bolus (up to 40 mL/kg) during the first hour. Clinical markers of cardiac output should be monitored, and the bolus should be discontinued if signs of fluid overload develop (*Strong recommendation, low level of evidence.*)

6.3 For healthcare systems with ICU availability, when hypotension or signs of serious hypovolemia are absent, or when there is serious lung injury or myocardial dysfunction, we recommend considering a lower rate of fluid resuscitation (5-10 mL/kg boluses). (*Strong recommendation, low level of evidence.*)

6.4 We recommend individualizing the fluid administration strategy for each patient. A higher rate (up to 60 mL/kg with ICU availability or 40 mL/kg without) should be considered in cases of evident hypovolemia, elevated losses or third spacing when accompanied by hypotension. (*Strong recommendation, high quality evidence.*)

6.5 We recommend using balanced crystalloid solutions (Ringeŕs lactate or similar solutions) for fluid resuscitation in children with sepsis. (*Strong recommendation, low level of evidence.*). *Figure 1*.

7. VASOACTIVE MANAGEMENT

7.1 We recommend beginning vasoactive medication administration after 40 mL/kg of fluid resuscitation, if the patient still has clinical or monitoring signs of hypoperfusion. It may even be started before 40 mL/kg of volume expanders have been administered, if the child shows signs of volume overload or other limitations to fluid administration. (*Strong recommendation, low level of evidence.*)

7.2 We recommend using adrenaline as the drug of choice, reserving noradrenaline for cases with clinical or monitoring evidence of low peripheral vascular resistance. (*Strong recommendation, low level of evidence.*)

7.3 We recommend that vasoactive drug administration be initiated regardless of the area of the hospital in which the patient is located, using peripheral (diluted vasoactive drugs) or intraosseous access, and as soon as possible after it is considered to be required. (*Strong recommendation, low level of evidence.*)

8. MONITORING

8.1 We recommend noninvasive monitoring for all patients in septic shock, including temperature, pulse oximetry, arterial pressure, urine output and continuous electrocardiogram readings. (*Strong recommendation, low level of evidence.*)

8.2 For children with septic shock, we recommend using advanced hemodynamic variables such as invasive arterial pressure, echocardiograms, central venous oxygen saturation (ScvO2) and, if available, cardiac output monitoring, to guide resuscitation and treatment changes. (*Strong recommendation, low level of evidence.*)

9. Antibiotics

9.1 We recommend starting empirical broad spectrum antibiotic treatment within the first hour after diagnosis in all cases of septic shock, basing the choice of antibiotic and dose on the local antimicrobial resistance patterns (*Strong recommendation, low level of evidence.*)

9.2 We recommend starting antibiotic treatment as soon as possible, within the first three hours after diagnosis, in pediatric patients with sepsis with organ dysfunction, but without shock data (*Strong recommendation, low level of evidence.*)

9.3 We recommend obtaining peripheral blood cultures (volume according to age and weight), along with samples from other sites according to the clinical suspicion of the infectious source, prior to beginning antibiotic treatment. If microbiological samples are taken after administering antibiotics, the time elapsed since the beginning of antibiotic treatment should be taken into account when interpreting the results. (*Strong recommendation, low level of evidence.*)

9.4 Empirical antibiotic treatment should be broad spectrum and achieve adequate blood and tissue concentrations in order to provide adequate coverage for all possible microorganisms causing sepsis or septic shock. (*Strong recommendation, low level of evidence.*)

9.5 The choice of empirical antibiotic treatment should be based on local epidemiological data, age, type of host (underlying diseases), invasive procedures, site of the infection, history of prior antibiotic treatment, and infection or colonization with multidrug-resistant microorganisms (*Strong recommendation, low level of evidence.*)

9.6 In patients over one month old with community-acquired septic shock without a clinically apparent source of infection, coverage should be considered for *S. pneumoniae, N. meningitidis, Haemophilus spp* and methicillin-resistant *Staphylococcus aureus* (MRSA). In areas with a high prevalence of MRSA, empirical treatment may include a third-generation cephalosporin along with an antibiotic with specific MRSA coverage. (*Strong recommendation in favor, low level of evidence.*)

9.7 In children with septic shock, coverage of Gram-negative bacilli should be considered when the initial clinical source of infection is genitourinary or gastrointestinal. In immunosuppressed individuals, initial empirical coverage should be provided for extended spectrum beta lactamase (ESBL)-producing enterobacteria (*Pseudomonas* and methicillin-resistant *Staphylococcus aureus*, among others). (*Strong recommendation, low level of evidence.*)

9.8 For patients with septic shock and a history of fungal colonization or possible infection, the addition of lipid or liposomal amphotericin B or echinocandins, as applicable, will be considered. (*Strong recommendation, low level of evidence.*)

9.9 Once the etiological agent has been confirmed, the definitive treatment will be adjusted to the narrowest spectrum and lowest toxicity possible, according to the confirmed type of infection, microorganism and sensitivity. If the cultures are negative, the clinical source of infection will be evaluated along with the patient's clinical situation to determine, together with Infectious Disease (if available), the antibiotic regimen with the narrowest possible spectrum, according to the source and type of infection. (*Strong recommendation, low level of evidence.*)

9.10 If an intravascular device-related infection is suspected (long-term catheters), we recommend obtaining a blood culture through this device, in addition to the peripheral blood cultures. If the infection is confirmed, the intravascular device should be removed. (*Strong recommendation, moderate quality evidence.*)

10. Adjuvant Therapy

10.1 We recommend considering hydrocortisone administration in children with septic shock refractory to fluids, inotropes and vasoactive drugs. (*Strong recommendation, low level of evidence.*)

10.2 We recommend monitoring sodium and glucose levels and assessing muscle weakness in children with septic shock treated with hydrocortisone. (*Strong recommendation, low level of evidence.*)

10.3 We recommend discontinuing hydrocortisone treatment once inotropes or vasoactive medications are no longer necessary or have been reduced to low doses. We recommend tapering the hydrocortisone treatment when it has been used for extended periods of time. (*Strong recommendation, low level of evidence.*)

10.4 We recommend not routinely measuring thyroid hormone levels in children with sepsis or septic shock. (*Strong recommendation, low level of evidence.*)

10.5 We cannot recommend in favor of or against routine administration of vitamin C or thiamine in children with sepsis or septic shock. (*Strong recommendation, low level of evidence.*)

10.6 We recommend conducting a nutritional assessment on admission and periodically thereafter in all children with sepsis; if possible, with the participation of nutrition specialists. (*Strong recommendation, low level of evidence.*)

10.7 We recommend starting enteral nutritional support within 48 h of admission in children with sepsis who are hemodynamically stable and have an intact gastrointestinal tract. (*Strong recommendation, low level of evidence.*)

10.8 We recommend not postponing enteral nutrition solely based on the administration of inotropes or vasoactive medications. (*Strong recommendation, low level of evidence.*)

10.9 We recommend beginning enteral feeding through the gastric route in children with sepsis, reserving transpyloric feeding for patients who do not tolerate the gastric route or in whom it is contraindicated. (*Strong recommendation, low level of evidence.*)

10.10 We recommend not using hydrolyzed formulas for initial enteral feeding in children with sepsis, and not supplementing enteral nutrition with omega-3 fatty acids. (*Strong recommendation against, low level of evidence.*)

10.11 We recommend not using gastric residual volume as an indicator for reducing or stopping nutrition in children with sepsis. We do not recommend the routine use of prokinetic

agents for treating feeding intolerance in children with sepsis. (*Strong recommendation against, low level of evidence.*)

10.12 We recommend using parenteral nutrition in children with sepsis who do not tolerate enteral nutrition or when it is contraindicated. (*Strong recommendation, low level of evidence.*)

10.13 We recommend not making nutritional modifications, such as changes in glucose, amino acids or the administration of insulin, to stimulate albumin synthesis in children with sepsis. (*Strong recommendation against, low level of evidence.*)

10.14 We recommend not using special lipid emulsions in the parenteral nutrition of children with sepsis or septic shock. (*Strong recommendation against, low level of evidence.*)

10.15 We recommend not routinely supplementing the nutrition of children with sepsis with glutamine, arginine, selenium, zinc or vitamin D. We recommend only supplementing if there is a proven deficit of these elements. (*Strong recommendation against, low level of evidence.*)

10.16 We recommend not using a liberal strategy of red blood cell transfusion in children with sepsis. (*Strong recommendation against, high level of evidence.*)

10.17 We recommend using a hemoglobin (Hgb) count of less than 7 g/dL to indicate the need for packed red blood cell transfusion in hemodynamically stabilized children with sepsis, while also evaluating the rest of the organ dysfunctions. We recommend transfusing red blood cells which, preferably, have been stored for fewer than 21 days. (*Strong recommendation, high level of evidence.*)

10.18 We cannot make recommendations regarding hemoglobin thresholds in critically ill children with septic shock without hemodynamic stability. (*Strong recommendation, low level of evidence.*)

10.19 We recommend not prophylactically transfusing platelets in children with septic shock or with sepsis-related organ dysfunction who do not have bleeding or coagulation disorders, unless they have counts under 10 000 cells/mm3 and a risk of central nervous system bleeding. (*Strong recommendation against, low level of evidence.*)

10.20 We recommend not transfusing fresh plasma prophylactically or as an expander in children with septic shock or sepsis-related organ dysfunction. Its use is only recommended when there are abnormal coagulation tests and a risk of or clinical bleeding. (*Strong recommendation against, low level of evidence.*)

Discussion

This paper presents the first consensus of recommendations for the management of sepsis in children living in LMICs. After conforming to the methodological structure suggested by the modified Delphi method, 62 recommendations were emitted by 29 experts (topical and methodological) with extensive experience and a long track record in managing children with sepsis in these countries. Given the importance of the context in the care of children with sepsis, the heterogeneity of healthcare services, the burden of chronic noncommunicable diseases and the availability of resources in LMICs, we believe these guidelines will contribute significantly to the improved care and survival of many children living in these countries.

In this regard, our recommendations have some points in common and some differences with those published recently by the SSC in children.[5] Our consensus always had as its working principle to make recommendations considering the context and their applicability for LMICs, as well as the importance of including high quality research studies carried out in these countries, with no language restriction. We believe that the reality of sepsis is very different for high-income countries compared with LMICs, and the differential epidemiological data on morbidity and mortality support this.[4,5] However, the main aspects in common with the SSC guidelines are related to ventilatory management, use of vasoactive medications and fluid resuscitation. In fact, this last recommendation is the only one in which the SSC takes the available resources into account.

The main differences between our recommendations and those of the SSC are related to other very important aspects of sepsis for LMICs. This consensus, following the recommendation of the SLACIP sepsis committee, worked with 10 domains, while the SSC worked with six. For LMICs, we believe it is very important to emphasize the definition, sepsis bundle (highlighting the importance of early recognition) and relevant epidemiological data from these countries.

Thus, one of the most important aspects mentioned in this consensus is the adjustment and adaptation of the new definition of sepsis which has been used in adults and which is being updated in pediatrics.[19] A problem which has arisen since 2016 is the differentiation between the "definition" and the "clinical operationalization" of this concept, that is, the clinical criteria to identify it. The indiscriminate use of these has led to confusion. The Sepsis-3 authors indicated the difference between these two points. They understood "definition" to be the "*description of a concept of disease*;" thus, a definition of sepsis should describe what sepsis "*is*," a matter which allows discussion regarding biological concepts which are not completely understood today, such as genetic influence and cellular anomalies.[19,20] When the pediatric Sepsis-3 was evaluated in a PICU in India, which included a smaller population but with a much higher sepsis mortality (40%), high specificity was found (identifying the most serious cases of sepsis), but with little sensitivity, because it was unable to identify 18% of the sepsis episodes diagnosed by the 2005 Consensus Conference.[24]

We also differ from the recommendations made by the SSC[5] in that, in LMICs, we believe it is important to continue using bundles for a comprehensive approach to children with sepsis. In the context of pediatric intensive care, the implementation of packages of care interventions has been successful in controlling ventilator-associated pneumonia as well as other healthcare-associated infections.[25] Infectious diseases and sepsis are frequent causes of mortality in the pediatric population of low and middle-income countries,[26] exceeded only by perinatal complications.[27] This is particularly true in Latin America, a diverse region in terms of geopolitics and economic

and human development, which has a direct impact on the structure of healthcare systems and their accessibility. According to the World Health Organization (WHO), the number of physicians per 100 000 inhabitants may vary up to almost four times among Latin American countries, and more than 30 times if the Latin America and Caribbean macroregion is considered.[31] This explains why most seriously ill children in Latin America are initially seen by general practitioners or nonmedical healthcare professionals in urban and suburban zones. In rural zones, initial care is often provided by nonprofessional technical personnel. In light of these reasons, the establishment of comprehensive strategies like sepsis bundles allows a comprehensive approach to children with sepsis living in LMICs.

Likewise, important aspects such as early recognition, initial laboratory tests, and follow up are mentioned, as well as the use of severity scales in countries with limited resources.[32] The use of pSOFa or PELOD-2 as predictors of mortality is recommended.[37] The importance of using the FSS for evaluating residual mortality in patients with sepsis is particularly highlighted, a practice which is not very common in these countries.[42] Given the frequency of chronic noncommunicable diseases in the region, an analysis of this topic was considered to be important.[6]

Recommendations are also provided regarding oxygen administration systems, the parameters for initiating mechanical ventilation and subsequent adjustments.[43] We share some aspects with the SSC guidelines, but also have some differences. Although high quality health care is provided in the PICUs of many capital cities in Latin America, with similar outcomes to those described by high-income countries, we have a limited number of critical care beds in our territories. In Latin America, the mortality rate in townships less than 5 km apart may be up to four times higher, due to difficulties in accessing high complexity healthcare services.[47] In these countries, patients often spend hours in the emergency room awaiting transfer to the PICU, due to a lack of immediate availability of this resource.[27,32] Thus, we believe it is important to begin oxygen support systems early in patients who require them and reserve advanced airway management only for patients who do not respond to the initial treatment, always ensuring the availability of resources and personnel trained in advanced airway management.

Fluid resuscitation and vasoactive management are essential in the treatment of children with septic shock and sepsis-associated organ dysfunction. A high percentage of children admitted to the PICU are not yet adequately resuscitated,[48%] and 35% die in the early stage of the disease (< 3 days) due to refractory shock,[49] a situation which is more pronounced in LMICs.[14,15,27] Factors such as comorbidities, access to first aid, knowledge of healthcare professionals and the level of education caregivers may be extremely relevant when determining fluid resuscitation strategies and should always be evaluated. This consensus, as well as the SCCM in children, made recommendations for hemodynamic resuscitation targeted at resource-limited regions, particularly for Latin America and for children with the most frequent pathologies in these regions. The recommendations were based on studies that demonstrated that an indiscriminate administration of fluids without considering the context and comorbidities may result in increased complications, morbidity and mortality.[50,51] In pediatrics, the main study is undoubtedly the one carried out by Maitland et al. in which the administration of fluid boluses significantly increased mortality in septic children in Africa.[50] However, in hypotensive patients in order to avoid cardiopulmonary collapse, we strongly recommend that fluids should be administered urgently (10 mL/Kg bolus to 40 mL/Kg) without using any predictor of fluid responsiveness. Unlike the SSC in children, in which most experts did not have personal experience with caring for children with sepsis in LMICs, and whose hemodynamic resuscitation recommendations were mostly weak; in this Consensus, the experts have lived the reality of inadequate knowledge of sepsis and difficult care, and their hemodynamic resuscitation recommendations are strong, despite the low level of evidence.

In addition to the important considerations of crystalloid doses and time of administration in children with sepsis and septic shock in LMICs, it is very important to consider their composition. In a cohort of Latin American children with sepsis and septic shock who required fluid resuscitation with crystalloids, it was found that the group receiving balanced solutions had less acute kidney injury (aOR 0.75: 95% CI 0.65-0.64: $p = 0.006$), less need for renal replacement therapy (aOR 0.48: 95% CI 0.36-0.64) and a shorter PICU stay.[52] Thus, according to SSC recommendations for children, and with the current evidence in adults and studies in high-income countries[53] as well as in LMICs, it seems reasonable to prefer the use of balanced solutions in the fluid resuscitation of children with sepsis.

We recommend adrenaline be used as the first line vasoactive and reserve noradrenaline for cases with clinical or monitoring evidence of low peripheral vascular resistance. We recognize that the SSC in children did not issue a recommendation for a specific first-line vasoactive infusion for children with septic shock as there are no available studies directly against adrenaline with noradrenaline. However, we believe this is supported by a double-blind prospective randomized controlled trial conducted in Latin America that demonstrated that early administration of peripheral or intraosseous epinephrine in children with fluid-refractory septic shock was associated with longer survival (OR 6.49), when compared to dopamine.[54]

Antimicrobial therapy is an important component in the treatment of sepsis as it directly targets the underlying cause of sepsis. The guideline of antibiotic administration within the first hour after the onset of shock is mainly derived from observational studies in which delayed administration is associated with greater mortality.[55] Therefore, based on the available evidence from observational studies in pediatric tertiary care centers and recommendations from the experts participating in this consensus, we consider that antibiotics should be administered at the latest within the first hour after recognizing septic shock. Furthermore, early administration within the first hour has been related to decreased hospital stay and slower progression of multiple organ failure in children. The group of patients in whom the "*the diagnosis of sepsis is not certain*" or who have

sepsis without cardiovascular involvement should be differentiated in countries with limited resources. In these cases, without shock, beginning antibiotic treatment within three hours after diagnosis could be adequate, according to studies performed in high-income countries.

Given the difficulty of treating children with septic shock refractory to catecholamines due to the difficulty of advanced hemodynamic monitoring in most services and the difficulty of performing ECMO in children in Latin America, the current sepsis guidelines in children recommend considering hydrocortisone administration in children with septic shock refractory to fluids, inotropes and vasoactive drugs. However, there are insufficient data to compare the efficacy of the various types of corticosteroids in pediatric septic shock.[56] Likewise, the optimal dose of hydrocortisone for refractory septic shock in children is unknown. Other important points in the treatment of critically ill children with sepsis, such as nutritional therapy, endocrine and metabolic therapies and blood products, were recommended in this Consensus in accordance with the SSC recommendations for children, due to the lack of strong evidence in LMICs.

We believe this consensus may have a few limitations. First, the participating researchers did not represent absolutely all of the Latin American countries. However, we sought to have a group of participating experts who met the criteria described in the materials and methods section, with special importance given to work experience in the region and publication of original research on sepsis in LMICs. Second, the recommendations issued are only applicable for children living in LMICs, as is the case in the vast majority of Latin American countries. We believe that the context and available resources are essential components of the care of critically ill children with sepsis and should always be considered. Ultimately, although we have some topics and recommendations in common with the SCCM consensus, there are differential factors that we believe are very important for the care of children living in LMICs and which are supported by studies performed in these limited resource contexts.

Conclusions

These are the first consensus recommendations for the diagnosis and management of pediatric sepsis focused on LMICs, more specifically, Latin American countries. The Consensus shows that, in these regions, where the burden of pediatric sepsis is greater than in high-income countries, there is little high-level evidence. The Consensus points to numerous perspectives to be studied in the diagnosis and treatment of pediatric sepsis in Latin America. Despite the limitations, this Consensus is an important step forward for the diagnosis and treatment of pediatric sepsis in Latin America.

Authors' Note

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Author Contributions

Drs. JF, DCS, and RJ conceived the idea for the manuscript. Drs. JF, DCS, AM, VN, JL, VSL, MPAL, WB, CFO, JCJ, FD, AY, SR, MM, PV,RI, MPM, GG, MY, CT, PC, GP, CG, MS, SC, SG, NS, PG and RJ participated in the writing and voting process with modified delphi methodology as described. All the authors drafted the manuscript and contributed significantly to the article revision. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. None of the researchers have conflicts of interest to declare.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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Supplemental Material

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