Pediatric Sepsis and Septic Shock Management in Resource-Limited Settings

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10.1 Introduction

Infectious diseases leading to septic shock remain a major cause of childhood mortality around the globe [1, 2]. Recommendations in the Surviving Sepsis Campaign (SSC) guidelines for pediatric patients rely on evidence from resource-rich settings [3]. However, recommendations are context dependent, and published guidelines deriving evidence primarily from resource-rich settings may be less relevant in areas where resources are minimal and the epidemiology is very different, given the differences in infection-related mortality between regions. Thus, recommendations for the treatment of septic shock in children in intensive care units (ICUs) in resource-limited settings are sorely needed.

There is no standardized definition of an ICU, but for the purposes of these recommendations, we are focusing on referral hospitals with the capability to intensively monitor critically ill children, ideally with the availability of some form of mechanical ventilation [4]. These ICUs may not exclusively care for children and are likely staffed by a variety of care providers, within a context of a resource-limited health system. The need for these recommendations is underlined by the surprising results from one large randomized controlled trial on fluid therapy in

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African children [5], at least suggesting that not all evidence for benefit from certain interventions in resource-rich settings guarantees equal benefit in resource-limited settings. The World Health Organization (WHO) issues guidelines on emergency triage and treatment, which these recommendations aim to supplement by addressing ICU-specific contexts.

We provide a set of simple, readily available, and affordable recommendations based on management of pediatric patients with severe sepsis and septic shock in resource-limited settings. Recommendations and suggestions are summarized in Table 10.1.

Table 10.1 Recommendations and suggestions on pediatric sepsis or septic shock management in resource-limited settings (with grading)

1	Identification	Observe for a combination of danger signs of end-organ dysfunction and including lactic acid levels if affordable and available (1C)
2	Intraosseous access	Placement of an intraosseous line must be considered for vascular access after 3–5 min of intravenous access attempts (2B)
3	Resuscitation of malnourished children	Children with severe acute malnutrition without signs of severe shock should not receive rapid intravenous fluids as bolus therapy (2C); children with severe acute malnutrition and signs of septic shock have high levels of mortality, and we suggest that they should be given intravenous rehydration with either half-strength Darrow's solution with 5% dextrose or Ringer's lactate solution with 5% dextrose at a rate of 10–15 ml/kg/hour with avoidance of rapid bolus therapy (2C)
4	Bolus fluid resuscitation	Use a careful but foremost individualized approach to fluid administration in children with sepsis in resource-poor settings (1B); for those who do not have evidence for severely impaired circulation, administer maintenance fluids only (1B)—for those who do have evidence of severely impaired circulation, very carefully administer 10–20 mL/kg of crystalloids over 30 minutes, which may be repeated if there are no signs of improvement and no signs of fluid overload (2C)
5	Goal-directed fluid resuscitation	No recommendation can be made regarding incorporating early goal-directed therapy for children with septic shock in resource-limited ICUs, specifically pertaining to using central venous oxygen saturation, lactate, or central venous pressure to guide resuscitation (UG); incorporate quality assurance protocols for timely antibiotic administration, oxygen and respiratory support, and fluid management protocols into resource-limited settings for the management of pediatric sepsis (1D)
6	Transfusion in severe malaria and sepsis	Transfuse children with severe anemia and malaria only if there are signs of severe sepsis such as respiratory distress or shock (1C); transfuse children with severe anemia (hemoglobin level < 4 g/dL) (1D); there is no evidence to support a specific transfusion threshold for children with anemia and sepsis in resource-limited settings
7	Noninvasive ventilation	Children with severe respiratory distress and hypoxemia from sepsis related to pneumonia benefit from bubble CPAP (1B)
8	Low tidal volume ventilation	Use a tidal volume of 5 to 8 mL/kg predicted body weight in all mechanically ventilated children with sepsis-induced acute lung injury in resource-limited settings (1D)

10.2 Identification of Septic Shock in Children

The burden of septic shock in children admitted to ICUs in resource-limited settings is undoubtedly large, though difficult to define. The International Consensus Conference on Pediatric Sepsis [3] defines sepsis as the systemic inflammatory response syndrome (SIRS) plus suspected or proven infection, while septic shock incorporates cardiovascular dysfunction leading to hypotension. New adult definitions have yet to be validated in children or in low-resource settings [4]. From a clinician's viewpoint, a diagnosis of septic shock recognizes that children who die from infections, regardless of their source, develop various combinations of cardiac failure, acute respiratory distress syndrome, or other organ dysfunction. Indeed, the largest clinical trial of children with severe febrile illness and impaired perfusion in sub-Saharan Africa supports this contention, where the major cause of death in this population is cardiovascular collapse [5, 6]. It may be possible to identify children with septic shock, regardless of underlying etiology, relatively early in ICUs, where intensive monitoring is available and mechanical ventilation possible. Recognizing this complex syndrome (septic shock) rather than focusing on a single disease entity, i.e., pneumonia or diarrhea may be important, given that interventions must often be performed before a definitive diagnosis is available [7–11]. The WHO uses this approach by highlighting danger signs and therapies rather than individual diseases through their emergency triage and treatment (ETAT) [12]. Emergency signs of shock or severely impaired circulation, as outlined by ETAT, include cold extremities, weak pulse volume, and prolonged capillary refill, with a definition of shock constituting having *all* three of the above. These recommendations are supplemental to existing guidelines such as ETAT on the identification of severely ill children and are restricted to the context of intensive care units, where advanced monitoring is feasible.

A large number of studies examined various clinical tools in various settings in determining outcomes of children with severe infections in low-resource settings. The accuracy of International Consensus Conference definitions or other alternate definitions has not been prospectively validated in ICUs in resource-limited settings. A systematic review of sepsis definitions focusing upon low-resource settings in children was identified. Using data from the FEAST trial [13], the presence of a weak pulse, prolonged capillary refill time, a temperature gradient, and coma were all significantly associated with a higher rate of mortality in this large population with sepsis. Prolonged capillary refill time has been shown to be a predictor of outcomes in severely ill children with infection in other high- and low-resource settings, [13, 16–18], although poor inter-rater variability and reproducibility render its clinical utility by inexperienced clinicians suspect [19–22]. Weak pulse volume, declining mental status, and hypothermia are also all associated with worse outcomes in children with severe infections [13, 23–26]. Hypoxemia, as measured by pulse oximetry, is a consistent predictor of outcome in severely ill children with infections, though not consistently associated with elevated mortality [14, 15, 27, 28]. Also, consistent across the studies in low-middle-income countries is the role of lactate in predicting likelihood of mortality in children with severe infections

[16, 29–32]. The recent creation of a bedside clinical risk score, FEAST PET, for triage and identification of severely ill children in resource-limited settings shows great promise [13]. The role of the WHO criteria in defining shock, as outlined above, is unclear, given a relatively low incidence among studied cohorts in emergency room populations [5, 33, 34], and likely bears little relevance within any ICU context where more intensive monitoring is available.

The systematic review of definitions documented accuracy of modified definitions of SIRS and international consensus criteria, which deserves further validation in larger cohorts and vital sign changes with age [35–37]. An observational study of children in resource-limited ICUs to develop a score for early identification of children with nosocomial infections shows great promise [38]. Sepsis screening tools for inpatients using chart abstraction or electronic health record data have been used successfully in resource-rich contexts but are likely not feasible in resource-limited settings [39, 40].

The use of clinical skills, incorporating historical findings of poor feeding and declining mental status and physical findings of weak pulse volume, prolonged capillary refill time, and temperature abnormalities, can identify most patients with septic shock and can be easily taught in any context. Pulse oximetry is becoming more available and feasible, with low-cost devices being disseminated; given the prevalence of pneumonia, this could hold great use for further management and research, limiting the need for expensive blood-gas analysis. Point-of-care lactic acid determination is becoming more prevalent in all health settings and should be further studied as a management guide for severe sepsis in resource-limited settings. Emergency triage and treatment protocols from the World Health Organization have been disseminated widely in low-income settings for the identification of shock.

We recommend that severely ill children with signs of infection be identified by observing for a combination of danger signs of end-organ dysfunction, including lactic acid levels (1C). More studies are urgently required to determine accuracy of definitions and scoring systems for septic shock identification and mortality prediction in ICUs in resource-limited settings.

10.3 Intraosseous Access as Initial Vascular Access in Septic Children

Rapid vascular access is critical and usually a rate-limiting step in the resuscitation of children in shock. The International Liaison Committee on Resuscitation has recommended the placement of an intraosseous access if vascular access cannot be achieved in a timely manner [41]. Vascular access facilitates intravascular volume replacement as well as early antimicrobial administration, with a delay in rapid administration of antibiotics associated with higher mortality in critically ill adults as well as children [42, 43]. Intraosseous access is a rapid and safe alternative to peripheral and central venous access when time is of the essence [44]. Children in

resource-limited settings sometimes present late in shock when peripheral veins may not be visible due to vascular collapse, thus making intravenous access challenging and time-consuming. In these settings, a rapidly placed intraosseous line can be lifesaving.

A search of the medical literature resulted in one clinical trial from India, a case series from Northern Iraq, and two systematic reviews. The clinical trial compared intraosseous and intravenous access in severely dehydrated children with hypovolemic shock from gastroenteritis [45]. Sixty children with severe dehydration according to WHO classification received 30 mL/kg of normal saline by either intravenous or intraosseous routes assigned alternately, followed by identical protocols regarding the reintroduction of oral fluids. The primary end point was time to placement, with secondary end points including stabilization of vital signs, correction of dehydration, and complications. There was no difference in efficacy of rehydration or correction of laboratory abnormalities between groups. Intraosseous placement was significantly faster (67 vs 129 s) and more reliable, with a 33% failure rate in intravenous placement and no failures in intraosseous placement at 5 min. There were no short-term complications, but long-term follow-up was not included. The study was not specific to sepsis, but it was context specific addressing intraosseous use in shock in LMICs.

The case series documented experiences with alternate modes of vascular access in dehydrated children at a military hospital in Iraq [46]. Intraosseous access was effective and timely in this context.

A systematic review addressed intraosseous access as an alternative route for rehydration in resource-limited settings by reviewing 16 articles: 1 clinical trial (described above), 12 case reports, and 3 case series [47]. Conclusions from this systematic review indicated that intraosseous access was easy to obtain and effective in rehydration and medication administration. A Cochrane review included the study from India as discussed above [45, 48]. This review looked at the comparison of routes for achieving parenteral access, with a focus on the management of patients with Ebola virus disease. The authors concluded that quality of the evidence based on GRADE criteria is limited because of lack of adequately powered trials [48]. All of these studies are downgraded for indirectness to children with septic shock and for bias.

All of the studies described above reported that the use of the intraosseous route was safe and associated with no major adverse events. Successful use of the intraosseous route relies on an initial outlay of resources for the device and training for placement. Intraosseous needles are inexpensive and can be readily available in appropriate settings. Non-disposable needles are available and can be sterilized and reused and hence further reduce their costs.

We suggest that in severely ill children with sepsis in resource-limited settings, the placement of an intraosseous line can be considered for vascular access after 3–5 min of intravenous access attempts (2B). Further studies are required to document its role in resource-limited settings, including maintaining training of practitioners.

10.4 Bolus Fluids or Blood to Malnourished Children with Signs of Severe Sepsis

Undernutrition is a major contributor to childhood mortality worldwide and renders children more vulnerable to contract infections as well as more commonly to suffer from severe sepsis and septic shock. The risk of overhydration in malnourished children leading to interstitial, pulmonary, and cerebral edema has resulted in recommendations of cautious fluid administration in modest amounts. Additionally, recommendations have favored hypotonic fluid administration and limiting sodium intake because of the concern of precipitating heart failure, under the premise that malnourished children, especially those with pitting edema, are sodium overloaded. The most recent guidelines from the WHO state that children with severe acute malnutrition should receive slow infusions of intravenous fluids at 15 mL/kg/h only in the setting of shock with one of half-strength Darrow's, Ringer's lactate, or half-normal saline, with 5% dextrose added to each [49]. WHO guidelines state that blood should be administered with similar indications for anemia due to malaria or if there is a failure to improve after 1 h of intravenous therapy [12].

Nine observational studies [26, 50–57], one randomized controlled trial [58], and a systematic review [59] were included in the final review. There were no randomized trials examining transfusion or fluids versus none in severely malnourished children with septic shock. Observational studies were of moderate quality and described clinical practice with transfusions and fluid administration. The one randomized trial that was identified compared half-strength Darrow's to Ringer's lactate solution in malnourished children with shock. The observational studies and the systematic review are consistent in describing that malnourished children who do not have signs of shock (of varying definitions) or do not have severe anemia should not receive intravenous fluids or blood which is associated with increased mortality in this group. This approach, however, must be tempered by the large risk of substantial selection bias in these studies. The randomized trial comparing half-strength Darrow's with 5% dextrose versus Ringer's lactate was stopped due to high levels of baseline mortality (51%) and inadequate correction of shock in all study arms, revealing no significant harm from isotonic fluid administration, compared to hypotonic fluids. A randomized trial looking at composition of an oral rehydration solution in children with severe malnourishment, severe dehydration, and cholera documented no adverse events from 100 mL/kg of intravenous fluid over 4–6 h [56]. There are no comparative data for blood transfusion thresholds or indications for this population.

Intravenous fluids are typically available in resource-limited settings; however, half-strength Darrow's is often unavailable in many regions. Blood is often unavailable or not readily accessible in many of these settings.

Based upon the available evidence, we suggest that children with severe acute malnutrition without signs of impaired circulation not receive rapid intravenous fluids as bolus therapy (2C). Children with severe acute malnutrition and signs of septic shock have high levels of mortality, and we suggest that they should be given intravenous rehydration with either half-strength Darrow's solution with 5%

dextrose or Ringer's lactate solution with 5% dextrose at a rate of 15 mL/kg/h, as per the WHO recommendations (2C). There is no evidence to support a specific blood transfusion threshold in this population, with consensus guidelines suggesting transfusion if the hemoglobin level is <4 g/dL or <6 g/dL in patients with signs of shock.

10.5 Bolus Fluid Resuscitation with 5% Albumin or Normal Saline, Compared to No Bolus Fluids, in Pediatric Sepsis

The major physiological abnormality in shock is hypovolemia, either due to fluid loss as in dehydration and hemorrhage (absolute hypovolemia) or due to redistribution of fluids as seen with capillary leaks in severe sepsis and septic shock (relative hypovolemia). This results in impaired cardiac filling, tissue perfusion, and oxygen delivery to the vital organs. Early intravascular fluid infusion to correct hypovolemia should improve this physiologic state, in principle. Fluid boluses include rapid administration of isotonic or colloid solutions; however, there is no clear consensus on whether to use crystalloids or colloids in early fluid resuscitation. In critically ill adults in high-income settings, outcome is largely dependent on the quantity rather than type of fluids used in the first hour [60]. The approach that is widely endorsed in pediatric life support training programs is to administer bolus resuscitation preferably within the first 15 min of diagnosing shock [61, 62]. As per these guidelines, rapid fluid boluses of 10–20 mL/kg should be administered, observing for improvement in perfusion as well as for markers of fluid overload—the development of rales, hepatomegaly, and increased work of breathing. Up to 60 mL/kg may be administered in the first hour, with a 2C recommendation per the Surviving Sepsis Campaign guidelines; however, no clear agreement exists supporting the present practice. The WHO advocates exercising caution in aggressive fluid administration, especially in children with shock in resource-limited conditions [12, 63].

We could identify only two randomized controlled trials that compared different rates of fluid administration in the first hour in children presenting with impaired circulation and were potentially relevant to these recommendations. After further screening, one trial had to be excluded as there was no comparator arm receiving maintenance fluid only or maintenance fluids plus a small bolus [64]. There were two recently published systematic reviews, which have data mostly derived from the one large randomized controlled trial [65, 66].

Only one study—the Fluid Expansion as Supportive Therapy (FEAST Trial)—compared bolus with maintenance fluid alone [5]. We also identified articles reporting the subgroup analysis of the data from this trial [6, 67]. In this randomized controlled trial performed in Uganda, Kenya, and Tanzania (n = 3141), children with severe febrile illness *and* clinical evidence of impaired perfusion (one or more of the following—capillary refill >2 s, lower limb temperature gradient, weak pulse volume, severe tachycardia) were randomized to fluid bolus therapy or maintenance fluids only. Major exclusion criteria were children with malnutrition and/or dehydration. The majority of children had malaria, and a third had a hemoglobin

level of <5 g/dL. The 48-h mortality was 10.6%, 10.5%, and 7.3% in the albumin bolus, saline bolus, and control groups, respectively (relative risk for saline bolus vs. control, 1.44; 95% confidence interval [CI] 1.09 to 1.90; $p = 0.01$; relative risk for albumin bolus vs. saline bolus, 1.01; 95% CI 0.78 to 1.29; $p = 0.96$; and relative risk for any bolus vs. control, 1.45; 95% CI 1.13 to 1.86; $p = 0.003$). There was no difference in neurologic sequelae, pulmonary edema, or increased intracranial pressure between groups.

Interestingly, at 1 h, shock had resolved (responders) more frequently in the bolus versus the control groups (43% vs. 32%, $p < 0.001$), but excess mortality with boluses was reported in both responders (relative risk 1.98, 95% confidence interval 0.94 to 4.17, $p = 0.06$) and non-responders (relative risk 1.67, 95% confidence interval 1.23 to 2.28, $p = 0.001$). Only 65 children met the WHO criteria for shock, for which the children receiving boluses had a higher mortality than the no bolus arm [RR: 2.4; 95% CI 0.84, 6.88]. The systematic reviews largely support these findings, with the data for children with severely impaired circulation being less convincing and the data being driven primarily by the large FEAST study. Definitions for shock were variable, and determining fluid responsiveness by severity of illness was not performed.

Patients enrolled in the FEAST trial had no access to intensive care including respiratory support and ventilators. Saline is safe, inexpensive, and readily available as compared to 5% albumin, which may not be affordable in resource-poor areas. The availability of monitoring of shock with blood lactate levels, central venous pressure, central venous oxygen saturation levels, and other invasive monitoring is unavailable in the included studies.

Based upon the available evidence, we recommend a careful, individualized approach to fluid administration in children with sepsis in ICUs in resource-limited settings (1B). For those without evidence of severely impaired circulation in a resource-limited ICU, we recommend administration of maintenance fluids only (1B). For those with evidence of severely impaired circulation, we suggest very careful administration of 10–20 mL/kg of crystalloids over 30 min. This may be repeated if there are no signs of improvement and no signs of fluid overload (2C). Further studies incorporating goal-directed resuscitation in resource-limited settings are urgently required (See Sect. 10.6), as is standardization of the definitions of shock for clinical and research purposes.

10.6 Should Sepsis Management Be Guided by Goal-Directed Protocols of Care for Children in Resource-Limited Settings?

The implementation of "sepsis bundles" to enable rapid diagnosis and time-sensitive management based on protocols upon presentation has been adopted in numerous healthcare settings [68]. Diagnosis is facilitated through rapid triage and deployment of diagnostic tests, while management is ideally guided by a protocol based on local context and resources. Given the wide variability of available resources in

low- and middle-income settings, there is a great need for contextual-based protocols for sepsis management for children in these settings. However evidence for generating these protocols is lacking because large randomized trials addressing the role of goal-directed protocols for sepsis management have only been studied in adults in high-income countries.

The search criteria identified a number of studies examining goal-directed sepsis protocols in children, six of which were conducted outside of high-income regions. There were two randomized controlled trials in low- and middle-income countries: one from Brazil examining early goal-directed therapy in children using central venous oxygen saturation-guided resuscitation versus usual care in children with septic shock [69] and the other from India examining different fluid protocols with early initiation of inotropic support [64]. There were three observational studies with significant bias, examining central venous oxygen saturation-guided resuscitation in children in India [70], a before-after study examining implementation of Surviving Sepsis Campaign guidelines, in India [71], and a retrospective study from Brazil examining time-to-fluid administration as it relates to clinical outcome [72]. There was also a before-after study for patient flow optimization in a Malawi hospital that included a number of children with presumed severe sepsis [73]. A worldwide quality assurance program assessed compliance with sepsis bundles in various pediatric settings [68]. There are four observational and retrospective studies examining sepsis protocols in children in high-income regions that were deemed relevant [74–77]. There are three major adult randomized trials recently published examining goal-directed therapy in adults in high-income countries, with an associated meta-analysis [78–81], one randomized study in adults in Zambia [82], and a before-after study in adults in Uganda [83]. There are no randomized studies examining goal-directed resuscitation or protocol-based sepsis care in children in high-income countries.

The randomized studies in adults with septic shock in high-income countries are consistent in showing no benefit from specific early goal-directed resuscitation protocols, when compared with usual care guided by current standards of care, but the evidence is downgraded for indirectness to our question. The randomized adult study performed in Zambia documented no difference in mortality in a management protocol guided by jugular venous pressure assessment, compared with usual care. The adult study performed in Uganda documented a 12% absolute risk reduction in mortality with early sepsis management guided by a dedicated study officer through a before-after design. Both are downgraded for indirectness to our population of interest.

The observational studies in children in high-income countries document improvement in the outcomes of duration of hospitalization, survival, and time to interventions but were downgraded for poor quality. The randomized study in Brazil revealed significant mortality benefits with early goal-directed therapy. The trial in India was downgraded for indirectness related to the question at hand. The observational studies document a mortality benefit for instituting a protocol for sepsis care for children in LMICs but were downgraded for bias. The quality assurance program documented improved survival with sepsis bundle compliance, but numbers from resource-limited settings were small.

Relevant resources including personnel, equipment, and supplies are less readily available for children in resource-limited settings as compared to adults, and hence protocols for children should be more modest in their scope and are less likely to be followed. Intuitively, it seems reasonable that early goal-directed protocols would be of benefit in guiding care in those who are unfamiliar in treating children with sepsis and septic shock. However, the availability of many of the tools for currently recommended early goal-directed protocols is poor in many LMICs [84], including monitoring capabilities such as frequent lactate monitoring and central venous oxygen saturation monitoring and management such as transfusions and inotrope administration.

Based upon the available evidence and resources, we can make no recommendation regarding incorporating early goal-directed therapy for children with septic shock in resource-limited settings, specifically pertaining to using central venous oxygen saturation, lactate, or central venous pressure to guide resuscitation. Further studies are required to determine the major differences between adults and children with regard to goal-directed resuscitation in septic shock.

We recommend incorporation of quality assurance protocols for timely antibiotic administration, oxygen and respiratory support, and fluid management protocols into resource-limited settings for the management of pediatric sepsis (1D). Resource capabilities for fluid resuscitation and monitoring should be expanded to allow for further study and implementation of resuscitation research in critically ill children admitted to resource-limited ICUs.

10.7 Is Transfusion Recommended for Children with Anemia and Sepsis Due to Severe Malaria in Resource-Limited Settings?

Severe anemia is a major contributor to child mortality worldwide. Administration of blood to children with severe anemia, malaria, and signs of severe illness such as respiratory distress or shock is essential. The balance of benefits and risks of blood transfusions is particularly important in settings where blood supply is limited. Given the risks associated with transfusion, transfusion practices must be evidence-based and associated with benefit in any setting. The current WHO recommendations suggest limiting transfusions to those with hemoglobin levels less than 4 g/dL or less than 6 g/dL with signs of severe disease [63]. However, clinical evidence for these thresholds is lacking.

The systematic search resulted in two randomized controlled trials from sub-Saharan Africa, one meta-analysis of the published randomized controlled trials, a subgroup analysis of another randomized controlled trial, and a number of observational and retrospective publications that directly or indirectly address the question.

The two randomized trials [85, 86] and the meta-analysis [87] report that there is insufficient evidence to routinely recommend giving blood to children with severe anemia due to malaria. The subgroup analysis of a large fluid resuscitation trial in

children with signs of sepsis in sub-Saharan Africa documented a large burden of anemia and a significant delay in blood transfusions leading to an increased risk of associated mortality [88]. Nine observational or retrospective studies [50–52, 89–94] suggest a benefit to transfusing children with severe malaria and anemia, especially if accompanied by signs of severe sepsis such as shock and/or respiratory distress. A randomized trial of 20 mL/kg versus 30 mL/kg of blood transfused in children with severe anemia, including malaria, showed higher rates of anemia correction in the larger blood volume group [95].

We have the opinion that blood transfusions should be made more readily available for those in need. Observational and other data suggest that mortality is high in patients who meet the current WHO recommendations for receiving blood during the waiting period after recognition of the need for blood transfusion [88]. Ensuring safe and rapidly accessible blood supplies is an area of active investigation, as well as optimizing initial transfusion strategies in critically ill children in low-resource settings.

Based upon the available evidence, we recommend transfusing children with severe anemia and malaria only if there are signs of severity such as respiratory distress or shock (1C). We recommend that children with severe anemia (hemoglobin levels <4 g/dL) be transfused (1D). There is no evidence to support a specific transfusion threshold for children with severe anemia and sepsis in ICUs in resource-limited settings. Further evidence is needed to make a recommendation for children with severe anemia and malaria (hemoglobin levels <4–6 g/dL) without respiratory distress or shock.

10.8 Noninvasive Ventilation for Children with Acute Respiratory Distress from Sepsis in Resource-Limited Settings

Pneumonia is the leading cause of death in the under-five age group in resource-limited settings [96]. Reed and colleagues demonstrated that in children hospitalized with pneumonia, hypoxia and malnutrition were the strongest predictors of mortality [97]. The management of hypoxia continues to be a major challenge for clinicians in developing countries [98]. While about 10–20% of sick children will be referred to a hospital, the delay in recognition, late presentation, lack of resources, and illness severity make the first 24 h of hospitalization the most vulnerable period, with a third of patient deaths occurring during this time [73]. Improving oxygen therapy has been shown to reduce mortality from severe pneumonia in resource-limited settings [99]. However, observational studies from these settings have demonstrated that despite the provision of oxygen, antibiotics, and supportive care, case fatality rates for severe pneumonia and hypoxemia remain unacceptably high (5–15%) [100–108].

While mechanical ventilation may be of benefit in decreasing mortality, it is an expensive and complex respiratory support method that requires a high level of technical skill and maintenance for optimal benefit. Many countries do not have the

funds, infrastructure, or expertise to provide such technology to all patients [109]. Therefore, noninvasive respiratory support technologies could be lifesaving in resource-limited settings.

Two randomized controlled trials were identified in children looking at the use of continuous positive airway pressure (CPAP) in children in resource-limited settings [110, 111]. There were three observational studies [112–114] and a systematic review primarily looking at neonates [109].

A randomized controlled trial in Bangladesh examined the role of bubble CPAP for children with severe pneumonia and hypoxemia. This open-label trial enrolled children under 5 years with severe pneumonia and hypoxemia to receive oxygen therapy by either bubble CPAP (5 L/min starting at a CPAP level of 5 cm H_2O), standard low-flow nasal cannula (2 L/min), or high-flow nasal cannula (2 L/kg per min up to the maximum of 12 L/min). The trial was stopped early for higher mortality in the low-flow oxygen group. For the composite primary outcome of treatment failure, the study concluded that bubble CPAP improved outcomes when compared with the low-flow group (RR 0.27, 99.7% CI 0.07–0.99: $p = 0.026$). There was no statistically significant difference between the bubble CPAP and high-flow nasal cannula group for the primary outcome (RR 0.50, 99.7% CI 0.11–2.29, $p = 0.175$). A randomized controlled trial in Ghana compared early CPAP for children with respiratory distress to delayed CPAP, documenting an improvement in the primary outcome of improved respiratory rate [111]. Two observational study in Malawi reported both improved respiratory physiology with the use of bubble CPAP in children up to age 14 years and a 70% survival in all children treated with bubble CPAP, with a strong ease of use reported [112, 114]. An observational study in India reported a decreased rate of need for intubation, compared with children started on nasal prong oxygen [113].

The systematic review study examining the efficacy and safety of bubble CPAP primarily in premature infants in LMICs included 19 studies. The three randomized controlled trials revealed a reduced need of mechanical ventilation of 30–50% for bubble CPAP compared with oxygen therapy, which was downgraded for indirectness to population.

Bubble CPAP is a relatively low-cost device, especially when compared with invasive mechanical ventilation. Its availability is increasing, with novel devices and strategies in place in various regions of the world. Training and device management are minimal for its dissemination, with minimal ICU staffing present in the documented studies. No significant safety issues from bubble CPAP are documented. Upper limits for age of bubble CPAP are unclear, with the previously mentioned study from Malawi documenting decreasing mask tolerance as age increases. Ventilator CPAP is available in certain ICUs in resource-limited settings and can be used as an alternative, where available. High-flow nasal cannulas are an increasingly used option in resource-rich settings, with limited studies in resource-limited settings currently available. The oxygen requirement for high-flow nasal cannula is often greater than with bubble CPAP, which may be a limitation in some settings. The recent ETAT guidelines review the full evidence for high-flow nasal cannula in resource-limited settings [12].

Based on the available evidence, we recommend that children with severe respiratory distress and hypoxemia from sepsis related to pneumonia benefit from bubble CPAP in resource-limited settings (1B). Further research needs to clarify upper age limits for effectiveness of bubble CPAP and the role of humidified high-flow nasal cannula.

10.9 Should Low Tidal Volume Ventilation Be Recommended for Children with Acute Lung Injury from Sepsis in Resource-Limited ICUs?

The data for the use of low tidal volumes (4–6 mL/kg) in children with acute lung injury have been extrapolated from adult data and adapted to children in resource-rich settings. There are no randomized controlled trials in children to date comparing low tidal volumes (4–6 mL/kg) to high tidal volumes (12 mL/kg). The Pediatric Acute Lung Injury Mechanical Ventilation (PALIVE) study demonstrated that children were generally ventilated with a mean tidal volume of 8 mL/kg in resource-rich settings [115]. Current guidelines in resource-rich settings recommend using tidal volumes of 5–8 mL/kg for any mechanically ventilated pediatric patient and using patient-specific tidal volumes according to disease severity [116]. The definitions of acute lung injury and the pediatric acute respiratory distress syndrome have recently incorporated pulse oximetry for contexts where blood-gas analysis is unavailable.

There was one observational study from a resource-limited setting, comparing historical controls in an era of high tidal volume to a group ventilated with low tidal volumes [117]. We identified a systematic review and meta-analysis that examined observational studies in children [118].

The meta-analysis demonstrated no association between tidal volume and mortality in ventilated children, with significant heterogeneity in the pooled analysis. This review included the one observational study from a resource-limited setting that demonstrated a mortality benefit to low tidal volume strategy [117]. This review is downgraded for quality and indirectness.

The availability of mechanical ventilation is limited in many resource-limited ICUs. Low tidal volume ventilation, where available, is likely to be safe, as documented in the adult studies. The diagnosis of the acute respiratory distress syndrome is often difficult in resource-limited settings, and specific criteria should be developed and implemented where the appropriate diagnostics are unavailable, including pulse oximetry [119]. Monitoring ventilated patients with blood-gas analysis to follow permissive hypercapnia is a challenge in resource-limited settings without access to blood-gas analyzers.

We recommend using a tidal volume of 5–8 mL/kg in all mechanically ventilated children with sepsis-induced acute lung injury in resource-limited settings (1D). Further research to better define and manage the acute respiratory distress syndrome in children in ICUs in resource-limited settings is urgently needed.

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