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## Recommendations for sepsis management in resource-limited settings

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**Abstract Purpose:** To provide clinicians practicing in resource-limited settings with a framework to improve the diagnosis and treatment of pediatric and adult patients with sepsis. **Methods:** The medical literature on sepsis management was reviewed. Specific attention was paid to identify clinical evidence on sepsis management from resource-limited settings. **Results:** Recommendations

are grouped into acute and post-acute interventions. Acute interventions include liberal fluid resuscitation to achieve adequate tissue perfusion, normal heart rate and arterial blood pressure, use of epinephrine or dopamine for inadequate tissue perfusion despite fluid resuscitation, frequent measurement of arterial blood pressure in hemodynamically unstable patients, administration of hydrocortisone or prednisolone to patients requiring catecholamines, oxygen administration to achieve an oxygen saturation >90%, semi-recumbent and/or lateral position, non-invasive ventilation for increased work of breathing or hypoxemia despite oxygen therapy, timely administration of adequate antimicrobials, thorough clinical investigation for infectious source identification, fluid/tissue sampling and microbiological work-up, removal, drainage or debridement of the infectious source. Post-acute interventions include regular reassessment of antimicrobial therapy, administration of antimicrobials for an adequate but not prolonged duration, avoidance of hypoglycemia, pharmacological or mechanical deep vein thrombosis prophylaxis, resumption of oral food intake after resuscitation and regaining of consciousness, careful use of opioids and sedatives, early mobilization, and active weaning of invasive support. Specific considerations for malaria,

puerperal sepsis and HIV/AIDS patients with sepsis are included. *Conclusion:* Only scarce evidence exists for the management of pediatric and adult sepsis in resource-limited settings. The presented

recommendations may help to improve sepsis management in middle- and low-income countries.

**Keywords** Sepsis · Intensive care · Resource-limited settings ·

Middle-income countries · Low-income countries · Recommendations · Management

## Introduction

Infection and sepsis are among the leading causes of death worldwide. The annual burden of sepsis in high-income countries is estimated to approach 2.8 million cases with a mortality of ~40% [1]. Despite these figures from industrialized countries, the largest part of the global sepsis burden occurs in middle- and low-income countries. Ninety percent of the worldwide deaths from pneumonia, meningitis or other infections occur in less developed countries [2]. Around 70% of the 9 million global deaths in neonates and infants are attributable to sepsis, with the majority of cases occurring in Asia and sub-Saharan Africa [3]. A high incidence of bacterial, parasitic and HIV infection combined with low hygienic standards and vaccination rates, widespread malnutrition and lack of resources, explain the disproportionately high morbidity and mortality from sepsis in these countries [4, 5].

In 2004 and 2008, the Surviving Sepsis Campaign released guidelines for severe sepsis and septic shock management [6, 7]. Implementation of these guidelines together with timely administration of essential therapies (e.g., fluid resuscitation, antibiotics, source control measures) improved management and outcome [8, 9]. Similar initiatives have been undertaken in children resulting in comparable improvements in outcome [10, 11]. Despite their benefits, the Surviving Sepsis Campaign and the American College of Critical Care Medicine pediatric guidelines cannot be implemented in most middle- or low-income countries due to lacking resources [12–15]. This leaves those clinicians caring for the majority of sepsis patients worldwide without standardized and adoptable guidance for sepsis care.

The purpose of these recommendations is to provide clinicians practicing in resource-limited settings with a framework to improve the management of pediatric and adult septic patients. The recommendations are specifically based on resources affordable and commonly available in middle- and low-income countries and systematically weigh the available scientific evidence for its applicability in resource-limited settings. They are not meant to replace the Surviving Sepsis Campaign [6, 7] or American College of Critical Care Medicine pediatric guidelines [10, 11] but can be considered if the latter are impossible to implement due to resource constraints.

## Methods

These recommendations were developed by the Global Intensive Care working group of the European Society of Intensive Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. The working group consists of critical care physicians and nurses from high-, middle- and low-income countries aiming to improve intensive care in resource-limited areas. Their members have extensive experience in caring for critically ill patients in resource-limited settings. No external funding was used. None of the authors had a financial conflict of interest in regards to drugs or techniques discussed in the manuscript or received honoraria for any role while establishing the recommendations.

Plans and methods to develop the recommendations were conceptualized in summer 2010. The group met at the 23rd ESICM Congress in Barcelona/Spain, and the 31st ISICEM in Brussels/Belgium. In between, face-to-face meetings, teleconferences and electronic-based discussions among group members were held to improve the recommendations. Any disagreement was resolved by further discussion and consensus, whenever possible. Voting results of the expert panel on individual recommendations are presented in the Electronic Supplementary Material.

To identify the contemporary scientific evidence for sepsis management, a structured literature review was conducted using pre-defined terms (see Electronic Supplementary Material for further details on the search process). Furthermore, reference lists of identified articles, the latest sepsis guidelines, textbooks and personal libraries were reviewed. Specific attention was paid to identify clinical evidence on sepsis management originating from resource-limited settings. Based on survey data on the availability of resources to implement the Surviving Sepsis Campaign guidelines and American College of Critical Care Medicine pediatric guidelines in middle- and low-income countries [12–15], scientific evidence was adjusted to resource-limited settings. In addition, expert opinion and clinical experience of the authors in providing sepsis care in middle- and low-income countries was considered. The level of scientific evidence (LoE) of each recommendation was classified as high (LoE: A; supported by the results of randomized, controlled trials or meta-analyses), moderate (LoE: B; supported by the results of low-quality randomized

controlled trials or high-quality observational studies), low (LoE: C; supported by the results of observational studies) or very low (LoE: D; supported by the results of case series or the opinion of experts). Since extrapolation of evidence from well-resourced to resource-limited countries is problematic given fundamental differences in sepsis epidemiology [2, 4], the educational level of health care providers [15, 16], health care facilities and resources [12–15], the level of evidence attributed to some recommendations differs from recommendations published by others [6, 7, 10].

### Recognizing the septic patient

Recognizing the patient with sepsis is an essential step for effective treatment. Given the widespread lack of facilities to diagnose sepsis according to international definitions in resource-limited settings, modified definitions of sepsis, severe sepsis and septic shock, which can be applied also with limited resources, are summarized in Table 1. More details on how to recognize the patient with sepsis in resource-limited settings are given in the Electronic Supplementary Material.

### Treating the septic patient

#### General considerations

General considerations regarding the treatment of patients with sepsis are summarized in Table 2. More details are presented in the Electronic Supplementary Material.

#### Acute interventions

Acute interventions (Table 3) refer to treatments recommended to be administered without delay. Although acute interventions are presented and suggested in this manuscript in a certain order (Fig. 1), some interventions could and should be performed simultaneously, depending on the condition of the patient.

#### Circulation

1. Use adequate tissue perfusion as the principal endpoint of resuscitation (LoE: A). In addition, target a systolic arterial blood pressure  $>90$  mmHg in adults, as well as normal heart rate and arterial blood pressure in children (LoE: D).

*Background* Given that tissue hypoperfusion is a key factor contributing to sepsis-associated organ failure [17],

one principal goal of resuscitation is to promptly restore tissue perfusion [6, 7]. Although adequate tissue perfusion is often associated with a systolic arterial blood pressure  $>90$  mmHg, some patients may restore tissue perfusion with lower arterial pressures. On the other hand, achievement of a normal arterial blood pressure is not necessarily associated with adequate tissue perfusion [18]. Therefore, arterial blood pressure alone is not a reliable endpoint for assessing adequacy of tissue perfusion. Although no clinical parameter exists to directly assess adequacy of tissue perfusion, clinical variables presented in Table 4 may be used [19]. Clinical signs of dehydration (e.g., dry mucous membranes, skin tenting) are rare in acute sepsis and should make the clinician consider a sub-acute or chronic disease process with superimposed infection.

2. In patients with tissue hypoperfusion, infuse fluids aggressively and continue liberal infusions for 24–48 h (LoE: C). More than 4 L during the first 24 h may be required to adequately resuscitate the adult septic patient.

*Background* Despite the development of interstitial edema, hypovolemia arising from true fluid loss or capillary leakage with interstitial edema formation is a main cause of tissue hypoperfusion in sepsis [20]. Fluid therapy increases systemic blood flow and oxygen delivery [21]. Aggressive fluid resuscitation reduced mortality in patients with typhoid ileal perforation in rural Africa [22]. In Ugandan patients with Gram negative bacteremia, mortality was decreased in patients receiving  $>1$  L of fluid compared to those receiving less or no fluids [23]. Children with septic shock receiving  $<20$  mL/kg of fluids had twice as high mortality compared to children receiving  $>40$  mL/kg of fluids during the first hour [24]. Fluid resuscitation is of particular importance in children with the Dengue shock syndrome, a clinical scenario characterized by vascular leakage and hypovolemia [25, 26].

A recent study by Maitland et al. [27] reported increased mortality in African children (median age 24 months) with sepsis who received fluid boluses in addition to maintenance fluids (2.5–4 mL/kg/h). Harmful effects of fluid boluses were mainly observed in children with compensated shock and profound anemia. More than half of the children had malaria, a state where microcirculatory dysfunction is common due to sequestration of parasitized erythrocytes rather than frank hypovolemia. Widespread lack of intensive care facilities among study centers may have contributed to harmful effects of aggressive fluid loading.

Based on these data, patients with sepsis and tissue hypoperfusion appear to benefit from a rapid bolus of intravenous crystalloid solution of at least 20 mL/kg. Further fluid resuscitation should be guided by the

**Table 1** Definition of infection and sepsis syndromes

	Suggested sepsis diagnosis with limited resources	Sepsis diagnosis according to international consensus (22, 23)
Sepsis	Proven or highly suspected infection plus presence of $\geq 2$ of the following conditions: Heart rate $>90$ bpm Respiratory rate $>20$ bpm Temperature $<36$ or $>38^{\circ}\text{C}$ Malaise and/or apathy	Proven or highly suspected infection plus presence of $\geq 2$ of the following conditions: Heart rate $>90$ bpm Respiratory rate $>20$ bpm or $\text{PaCO}_2 <32$ mmHg Temperature $<36$ or $>38^{\circ}\text{C}$ WBC $<4$ or $12$ g/L or $>10\%$ immature forms
Severe sepsis	Sepsis-induced tissue hypoperfusion or organ dysfunction Tissue hypoperfusion Decreased capillary refill or skin mottling Peripheral cyanosis Arterial hypotension Systolic arterial blood pressure $<90$ mmHg or a systolic arterial blood pressure decrease $>40$ mmHg  Pulmonary dysfunction SpO <sub>2</sub> $<90\%$ with or without oxygen Central cyanosis Signs of respiratory distress (e.g., dyspnea, wheezing, crepitations, inability to talk sentences) Renal dysfunction Acute oliguria (urine output $<0.5$ mL/kg/h or $45$ mL/h for at least 2 h despite adequate fluid resuscitation)  Hepatic dysfunction Jaundice  Coagulation dysfunction Petechiae or ecchymoses Bleeding/oozing from puncture sites Gastrointestinal dysfunction Ileus (absent bowel sounds)	Sepsis-induced tissue hypoperfusion or organ dysfunction Tissue hypoperfusion Decreased capillary refill or skin mottling Hyperlactatemia ( $>1$ mmol/L) Arterial hypotension Systolic arterial blood pressure $<90$ mmHg; mean arterial blood pressure $<70$ mmHg; or a systolic arterial blood pressure decrease $>40$ mmHg Pulmonary dysfunction PaO <sub>2</sub> /FiO <sub>2</sub> $<300$  Renal dysfunction Acute oliguria (urine output $<0.5$ mL/kg/h or $45$ mL/h for at least 2 h despite adequate fluid resuscitation) Creatinine increase $>0.5$ mg/dL or $44.2$ $\mu\text{mol/L}$ Hepatic dysfunction Hyperbilirubinemia (plasma total bilirubin $>4$ mg/dL or $70$ $\mu\text{mol/L}$ ) Coagulation dysfunction Thrombocytopenia (platelet count, $<100,000/\mu\text{L}$ ) Coagulation abnormalities (INR $>1.5$ or a PTT $>60$ s) Gastrointestinal dysfunction Ileus (absent bowel sounds)
Septic shock	Sepsis-induced arterial hypotension despite adequate fluid resuscitation (note that patients on inotropics or vasopressors may not be hypotensive despite of presence of shock) and signs of tissue hypoperfusion	Sepsis-induced arterial hypotension despite adequate fluid resuscitation (note that patients on inotropics or vasopressors may not be hypotensive despite of presence of shock) and signs of tissue hypoperfusion

PaCO<sub>2</sub> partial arterial carbon dioxide tension, WBC white blood cell count, SpO<sub>2</sub> plethysmographic oxygen saturation, PaO<sub>2</sub>/FiO<sub>2</sub> partial arterial oxygen tension/fractional inspiratory oxygen

concentration quotient, INR international normalized ratio, PTT partial thromboplastin time

response to fluid loading. A positive response to fluid loading can be considered as one of the following:  $>10\%$  increase of systolic/mean arterial blood pressure,  $>10\%$  reduction of heart rate, and/or improvement of mental state, peripheral perfusion and/or urine output. Some adult patients may require several liters of fluids during the first 24–48 h to achieve this goal. Likewise, fluid amounts as high as 110 mL/kg may be required in children with septic shock during early resuscitation [28]. In children with profound anemia and severe sepsis, particularly due to malaria, fluid boluses must only be administered cautiously, and blood transfusion should be considered instead [27].

Fluid resuscitation should be stopped or interrupted when no improvement of tissue perfusion occurs in response to volume loading. Development of crepitations

in adults plus hepatomegaly in children indicate fluid overload or impaired cardiac function. Since aggressive fluid resuscitation can lead to respiratory impairment, additional fluid resuscitation following the initial fluid boluses should be performed carefully if no mechanical ventilator is available. In such a scenario, it may be necessary to balance adequate pulmonary gas exchange against optimum intravascular filling. However, this is an infrequent conundrum within the first 6 h.

Fluid administration in septic patients should occur intravenously even if access needs to be attained by surgical cut-down or central venous cannulation. Alternatively, an intra-osseous access may be used. An intra-osseous cannula should only be used if running freely and for  $<24$  h. Although oral rehydration is efficient to treat dehydration [29], no data on the efficacy and safety of oral

**Table 2** General considerations for sepsis care

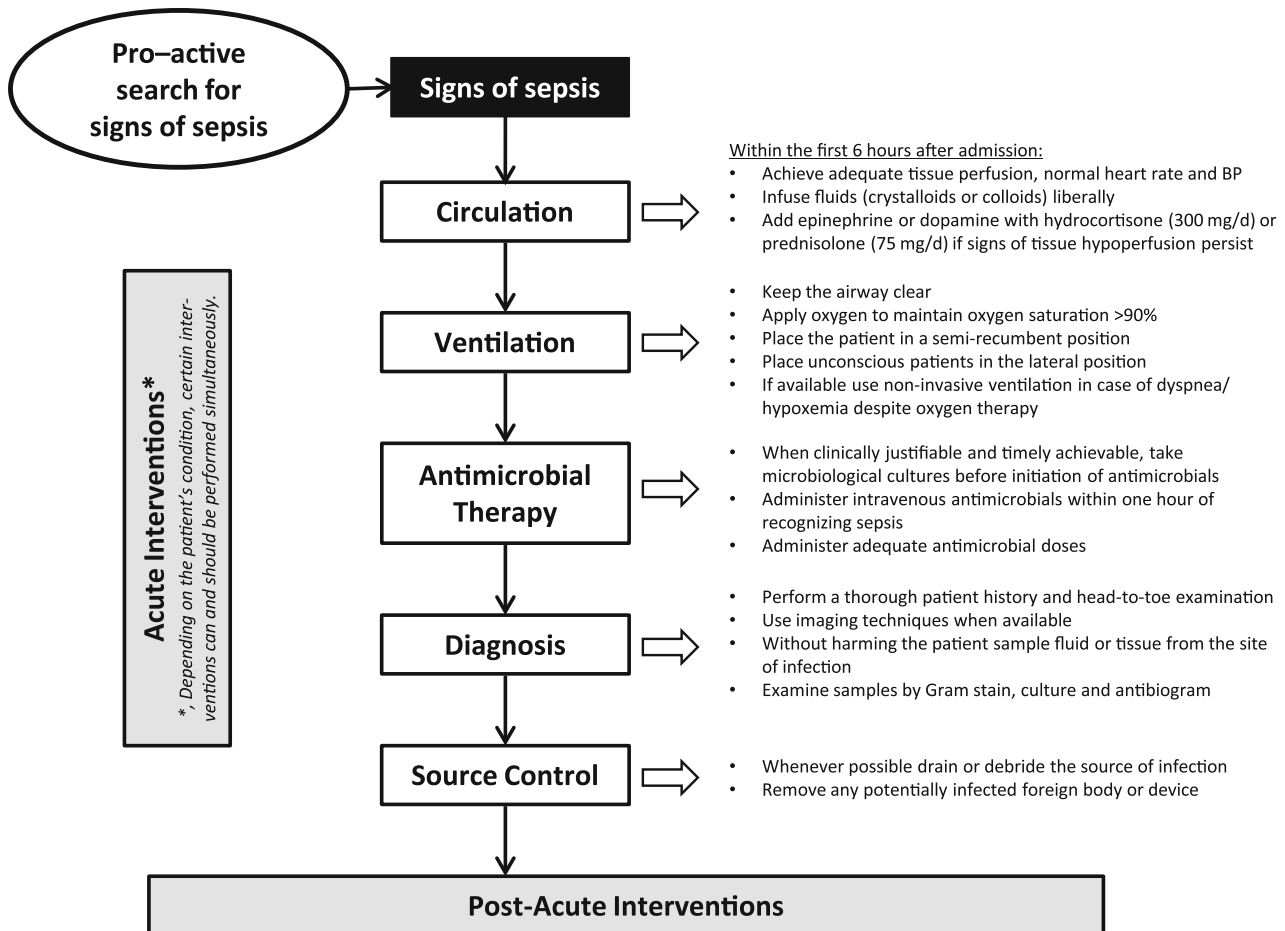
Timing	Diagnose sepsis as early as possible (LoE: D) Initiate sepsis treatment as early as possible (LoE: B). Antimicrobials should be given within 1 h of recognizing sepsis (LoE: C). Hemodynamic endpoints should be achieved within 6 h of recognizing sepsis (LoE: C)
Hygienic precautions	Wash hands before and after each patient contact and whenever contaminated (LoE: B). Prefer alcohol rubs, otherwise use running water and soap
Patient monitoring	Use sterile barrier precautions when performing invasive procedures or surgical interventions (LoE: A) Never leave the septic patient alone. Ensure continuous observation (LoE: D) Perform clinical examinations several times per day (LoE: D) Whenever available use a continuous patient monitor and set meaningful alarm limits (1D). Alarms for children should be set at age appropriate ranges (LoE: D)
Multidisciplinary care	Whenever applicable, seek consultation from experienced health care workers of other medical specialties (LoE: D)
Data documentation	Keep a patient record and document vital signs at meaningful intervals (LoE: D) If the patient deteriorates or fails to improve look for the cause and seek medical review (LoE: D) Convey essential information to all team members involved in the care of the septic patient (LoE: C)
Emergency drugs and equipment	Keep an emergency supply of drugs and equipment on the ward that is available 24 h/day and is checked and replenished daily (LoE: D)
Patient transfer	Transfer of septic patients to hospitals with more resources and/or medical expertise may save lives. However, the risks must always be critically weighed against benefits (LoE: D) Whenever possible transfer should be attended by a physician or other experienced medical personnel (LoE: D)
Estimating prognosis and Treatment limitation	For each patient, critically assess the prognosis and extent of treatment (LoE: D) Limit treatment in adult patients with grave prognosis (LoE: D). Whenever possible make decisions together with other colleagues and compassionately communicate it to the patient and family
Quality control	Whenever possible and compatible with local culture, perform autopsies in patients who died from sepsis. Communicate autopsy results to all team members and critically discuss points that could have been done better (LoE: D) Identify local strengths and weaknesses in sepsis management by documenting key aspects of sepsis care and outcome (LoE: D)

*LoE* level of evidence

**Table 3** Acute interventions to treat septic patients with limited resources

Circulation	Use adequate tissue perfusion as the principal endpoint of resuscitation (LoE: A). In addition, target a systolic arterial blood pressure >90 mmHg in adults, as well as normal heart rate and arterial blood pressure in children (LoE: 2D) In patients with tissue hypoperfusion, infuse fluids aggressively and continue liberal infusions for 24–48 h (LoE: C). More than 4 L during the first 24 h may be required to adequately resuscitate the adult septic patient Use crystalloids and/or colloids for fluid resuscitation (LoE: B). When available, use colloid solutions for fluid resuscitation in children with severe Dengue shock syndrome (LoE: B) Use dopamine or epinephrine (adrenaline) in patients with persistent tissue hypoperfusion despite liberal fluid resuscitation (LoE: C) In patients requiring dopamine or epinephrine (adrenaline) measure arterial blood pressure and heart rate frequently (LoE: D) Administer intravenous hydrocortisone (up to 300 mg/day) or prednisolone (up to 75 mg/day) to adult patients requiring escalating dosages of epinephrine (adrenaline) or dopamine (LoE: B). Consider the use of equivalent hydrocortisone or prednisolone doses in children with severe shock (LoE: C)
Ventilation	Apply oxygen to achieve an oxygen saturation >90% (LoE: B). If no pulse oximeter is available administer oxygen empirically in patients with severe sepsis or septic shock (LoE: C) Place patients in a semi-recumbent position (head of the bed raised to 30–45°) (LoE: C) Unconscious patients should be placed in the lateral position. The patient's airway should be kept clear (LoE: D) If available and medical staff is adequately trained, use non-invasive ventilation in patients with dyspnea and/or persistent hypoxemia despite oxygen therapy (LoE: C)
Antimicrobial therapy	Initiate sepsis treatment as early as possible (LoE: B). Antimicrobials should be given within 1 h of recognizing sepsis (LoE: C) Administer intravenous antimicrobials at adequate dosages and with a high likelihood to be active against the suspected bacterial pathogens (LoE: C)
Diagnosis	Perform a detailed patient history and thorough clinical examination to identify the source of infection (LoE: D). Use imaging techniques when available (LoE: D) Whenever possible and without harm to the patient, sample fluid or tissue from the site of infection (LoE: C) Examine the sampled fluid or tissue by Gram stain, culture and whenever possible by antibiogram (LoE: C)
Source control	Whenever possible drain or debride the source of infection (LoE: C) Remove any foreign body or device that may potentially be the source of infection (LoE: C)

*LoE* level of evidence

**Antimicrobial Therapy:**

- Reassess the effectiveness of antimicrobial therapy regularly
- Administer antimicrobials for an adequate but not prolonged time

**Glucose Control:**

- Whenever possible check blood glucose levels
- Maintain blood glucose >70 mg/dL (4 mmol/L)

**Deep Vein Thrombosis:**

- Use prophylactic heparin or apply elastic bandages on both legs
- No deep vein thrombosis prophylaxis in pre-pubertal children

**Enteral Nutrition and Stress Ulcer Prophylaxis:**

- Allow the patient to eat and drink small amounts once she/he is fully resuscitated and awake

**Sedation and Pain Relief:**

- Use opioids to relieve pain but be cautious in unstable patients
- Only sedate the agitated and uncooperative patient
- Encourage mobilization as soon as the patient is stable

**Wean Invasive Support:**

- Remember that every therapy and intervention has the potential to harm the patient
- As soon as the patient is improving, try to actively wean the extent of invasive support

DO NOT use hypotonic fluids for fluid resuscitation; DO NOT use fluid balance as a guide for fluid therapy; DO NOT use high dose steroids; DO NOT use muscle relaxants (except for endotracheal intubation); DO NOT use succinylcholine in immobilized patients; DO NOT use furosemide unless hypervolemia, hyperkalemia and/or acidosis are present; DO NOT use dopamine for renal indications; DO NOT use sodium bicarbonate; DO NOT use non-steroidal anti-inflammatory drugs; DO NOT use sodium bicarbonate; DO NOT restrict oxygen; DO NOT diagnose „fever of unknown origin“; DO NOT use insulin if blood glucose cannot be measured regularly.

**Fig. 1** Flowchart and summary of recommendations



**Table 4** Clinical indicators of adequate tissue hypoperfusion

Normal capillary refill time <sup>a</sup>
Absence of skin mottling
Warm and dry extremities
Well felt peripheral pulses (e.g., radial or dorsalis pedis pulses)
Return to baseline mental status before sepsis onset
Urine output >0.5 (adults) or 1 (children) mL/kg/hour <sup>b</sup>

<sup>a</sup> Age dependent: children and adults (<65 years), <2–3 s; elderly patients (>65 years) <4.5 s

<sup>b</sup> Unless elevated creatinine plasma levels or sign of established renal failure

rehydration in septic patients with tissue hypoperfusion exist. Considering a relevant aspiration risk, oral rehydration should be avoided in septic shock patients.

3. Use crystalloids and/or colloids for fluid resuscitation (LoE: B). When available, use colloid solutions in children with severe Dengue shock syndrome (LoE: B).

*Background* There are no data supporting the superiority of colloid over crystalloid solutions for resuscitation of adults or children with bacterial sepsis [28, 30, 31]. In most situations, adequacy of fluid resuscitation is more relevant than the type of fluid infused. Considering high costs [32], the risk of allergies [33] and potential renal and coagulatory side effects [34] of colloids, crystalloid solutions appear more suitable in resource-limited settings. However, colloids may bear potential benefits in children with severe Dengue shock syndrome (pulse pressure  $\leq 10$  mmHg) [25]. In moderate Dengue shock syndrome (pulse pressure  $>10$  and  $\leq 20$  mmHg) colloid and crystalloid solutions lead to similar outcomes. Since moderate Dengue shock syndrome is more common than severe, crystalloids remain the first-line fluid in the majority of cases [25, 31].

4. Use dopamine or epinephrine (adrenaline) in patients with persistent tissue hypoperfusion despite liberal fluid resuscitation (LoE: C).

*Background* If fluid resuscitation cannot restore tissue perfusion, the use of dopamine or epinephrine (adrenaline) should be considered. While cool extremities, extended neck veins, crepitations or crackles, a third or fourth heart sound, and/or a positive hepato-jugular reflux characterize the patient with impaired heart function, patients with excessive peripheral vasodilation typically present with warm extremities, oliguria and impaired mental state. In many cases, however, it is difficult to differentiate between the two states without measuring cardiac output. Arrhythmogenic and obstructive causes of fluid-resistant tissue hypoperfusion (e.g., pneumothorax, pericardial tamponade, abdominal compartment syndrome) must be excluded.

Studies suggest that neither dopamine nor epinephrine is inferior to a balanced infusion of norepinephrine (noradrenaline) and dobutamine with respect to septic shock outcome [35–37]. Considering frequent aggravation of lactic acidosis during epinephrine infusion [38], norepinephrine should, whenever available, be preferred over epinephrine. Since all catecholamines typically exert dose-dependent adverse side effects, doses should be kept at a minimum. Although dopamine-refractory shock may be reversed with epinephrine or norepinephrine infusion in children [39], combined use of dopamine and epinephrine is discouraged.

Preferentially, dopamine or epinephrine is infused through a central venous catheter. If central venous catheters are unavailable or the medical staff has insufficient experience handling them [40], a peripheral venous cannula, placed in a large bore vein, or an intra-osseous cannula can be used. It is important to frequently check the site of infusion for signs of drug extravasation, since substantial skin necrosis may occur [41]. Dopamine and epinephrine should be administered continuously. When pumps are unavailable or power cuts frequently occur, dopamine (e.g., 250 mg) or epinephrine (e.g., 5–10 mg) can be diluted in 500 mL of crystalloid solution and infused using a drop regulator or micro-infusion set. Dosing should occur based on the clinical response.

5. In patients requiring dopamine or epinephrine (adrenaline) measure arterial blood pressure and heart rate frequently (LoE: D).

*Background* In children and adults requiring dopamine or epinephrine (adrenaline), blood pressure should be measured frequently [6, 7, 11]. The invasive technique is rarely available in resource-limited settings and requires specific training. Alternatively, blood pressure can be measured non-invasively. Specifically in children, adequately sized cuffs must be used to ensure accurate readings. Intervals for non-invasive blood pressure measurements should be set at 5–15 min as long as epinephrine or dopamine is infused.

6. Administer intravenous hydrocortisone (up to 300 mg/day) or prednisolone (up to 75 mg/day) to adult patients requiring escalating dosages of epinephrine (adrenaline) or dopamine (LoE: B). Consider the use of equivalent hydrocortisone or prednisolone doses in children with severe shock (LoE: C).

*Background* Relative adrenal insufficiency with inadequately low plasma cortisol levels is frequent in septic shock [42]. If hydrocortisone is administered to adults requiring escalating catecholamine doses in high-income settings, shock duration and mortality are reduced [42, 43]. An Indian randomized pilot study suggested a trend towards earlier shock reversal and less inotrope use when

hydrocortisone (5 mg/kg/day in four divided doses followed by half the dose for a total of 7 days) was administered to children with septic shock [44]. Until more data are available, use of hydrocortisone must be considered a rescue therapy in pediatric septic shock. Daily corticosteroid dosages must not exceed equivalent doses of 300 mg hydrocortisone or 75 mg prednisolone, since higher doses may predispose for infections [45]. Corticosteroids should not be administered to patients not requiring catecholamines unless they are on chronic corticosteroid therapy. When epinephrine or dopamine can be withdrawn, corticosteroids should be tapered off (over days) to avoid rebound hypotension [42].

### Ventilation

1. Apply oxygen to achieve an oxygen saturation >90% (LoE: B). If no pulse oximeter is available administer oxygen empirically in patients with severe sepsis or septic shock (LoE: D).

*Background* Apart from tissue hypoperfusion, organ dysfunction associated with sepsis arises from hypoxemia [46], which is highly prevalent in resource-limited settings [47]. Clinical signs (e.g., cyanosis) are not reliable, particularly in patients with dark complexion. Clinical signs of respiratory distress (dyspnea, increased work of breathing) reflect changes in respiratory mechanics and may not be reliable gauges of hypoxemia. Therefore, it is essential to monitor septic patients with a pulse oximeter [48, 49]. Patients presenting with hypoxemia should receive oxygen to achieve an oxygen saturation >90%. In Papua New Guinea, installation of hospital wide oxygen systems facilitated oxygen therapy for hypoxemic children with pneumonia and reduced the risk of death [50]. If no pulse oximeter is available, oxygen should empirically be administered to all septic patients (see Electronic Supplementary Material for technical details).

2. Place patients in a semi-recumbent position (head of the bed raised to 30–45°) (LoE: C).

*Background* Unless hemodynamically unstable, septic patients should be placed in a semi-recumbent position (head of the bed raised to 30–45°). Semi-recumbency reduces the risk of tracheal aspiration and hospital-acquired pneumonia, particularly when mental state is impaired or enteral nutrition administered [51, 52].

3. Unconscious patients should be placed in the lateral position. The patient's airway should be kept clear (LoE: C).

*Background* Unconscious patients and subjects who cannot keep their airway open for other reasons should be placed in the lateral position. In addition, an oro-

nasopharyngeal airway can be inserted if the lateral position alone cannot maintain airway patency. Inability to clear the airway is associated with a high risk for aspiration of saliva or regurgitated gastric contents. Oral hygiene (tooth brushing and cleansing with an oral antiseptic at least twice daily), repetitive suctioning of oropharyngeal secretions and placement in the semi-recumbent position (also the lateral position) can prevent pneumonia [53].

4. If available and medical staff is adequately trained, use non-invasive ventilation in patients with dyspnea and/or persistent hypoxemia despite oxygen therapy (LoE: C).

*Background* Sepsis may lead to deterioration of lung function. In severe cases, respiratory insufficiency may not be sufficiently treated by oxygen alone, even when administered at high flow rates. Wherever available and when medical staff is adequately trained, mechanical ventilation should be instituted early in patients with increased work of breathing and/or persistent hypoxemia despite oxygen therapy. In many resource-limited settings, non-invasive mechanical ventilation (administration of ventilatory support through a mask instead of an endotracheal tube or tracheostoma) appears to be the ventilation technique of choice [54]. Non-invasive ventilation has been applied with good success in patients with acute respiratory failure in Pakistan [55]. Data from India reported that non-invasive intermittent positive pressure ventilation decreased the need for endotracheal intubation in acute respiratory failure of diverse origin [56]. Nasal continuous positive airway pressure improved the management of respiratory insufficient children with Dengue hemorrhagic fever in Southeast Asia [57]. Despite these positive reports, studies performed in high-income settings demonstrate that not all patients can successfully be managed with non-invasive ventilation [54]. This is specifically true for septic patients with impaired consciousness, severe respiratory or cardiovascular failure. Particularly young children may not tolerate non-invasive ventilation. Furthermore, airway anatomy (large tongue, short neck) combined with the need for lower tidal volumes makes non-invasive ventilation in children difficult [58].

If equipment is available and medical staff adequately trained, mechanical ventilation may be delivered via an endotracheal tube. When doing so an adequate level of positive end-expiratory pressure with tidal volumes of 6 mL/kg ideal body weight should be set [59, 60]. Furthermore, peak (pressure control ventilation mode) or plateau (volume control ventilation mode) pressures should not exceed 30 cmH<sub>2</sub>O [61]. Spontaneous breathing modes are equally preferred in intubated patients [62]. If mechanical ventilators are unavailable, anesthetic circuits or machines may be used to ventilate a patient with respiratory distress or during the postoperative period.



### Antimicrobial therapy

1. Initiate sepsis treatment as early as possible (LoE: B). Antimicrobials should be given within 1 h of recognizing sepsis (LoE: C).

*Background* Robust evidence indicates that timely diagnosis of sepsis and rapid initiation of treatment reduces morbidity and mortality both in children and adults [63–68]. In a high-income country, each hour of delay in antibiotic administration was associated with an average 7.6% decrease in survival of septic shock [66]. Similarly, in a predominantly HIV-infected septic patient population in Uganda, any delay in the administration of adequate antibiotics increased all cause and attributable mortality [23]. Likewise, pre-referral administration of rectal artesunate reduced death in severe malaria in rural Asia and Africa [69].

2. Administer intravenous antimicrobials at adequate dosages and with a high likelihood to be active against the suspected bacterial pathogens (LoE: C).

*Background* Intravenous antimicrobial therapy is one of the key treatments in septic patients. If intravenous access cannot be promptly attained in children, first antimicrobial dosages may be administered intra-muscularly or by the oral or rectal route. Two factors critically determine the benefit of antimicrobial therapy both in resource-rich [66–68] and resource-limited settings [22]: timing and adequacy. Since the causative pathogen cannot be identified immediately, antimicrobial therapy must be started empirically. To ensure that empirical antimicrobial therapy is active against the causative microorganisms, it is vital to account for the likely pathogen spectrum. In middle- and low-income settings, this is particularly challenging since the range of infectious diseases and causative microorganisms is broad, including bacterial, viral, fungal and parasitic pathogens [23]. Further difficulties arise from frequent antimicrobial resistance [70], common preceding self-medication with over-the-counter antibiotics [71, 72] and the limited availability of potent intravenous antimicrobials [12–15]. Considerable regional heterogeneities in these aspects make recommendation of empirical antimicrobial strategies difficult. In a multicenter study performed in middle- and low-income countries, chloramphenicol was superior to injectable ampicillin plus gentamicin in the treatment of community-acquired severe pneumonia in children aged 2–59 months [73]. To optimize chances of appropriate empirical antimicrobial therapy, empiric antimicrobial therapy should be adjusted to local infectious disease patterns including HIV/AIDS prevalence, pathogen spectrum and antimicrobial resistance.

Adequate dosing is another important aspect of antimicrobial therapy. Considering the high risk of death associated with sepsis, antimicrobial drugs need to be

administered at maximum recommended dosages during the initial phase [74]. This is of particular importance if antimicrobials of unclear quality (e.g., counterfeit or expired drugs) are used. Following the acute phase, many antibiotics require dose adjustments to renal or hepatic function. To achieve optimum bioavailability, the intravenous route is preferred. When the patient improves, antimicrobials may be administered orally provided that intestinal absorption is maintained.

### Diagnosis

1. Perform a detailed patient history and thorough clinical examination to identify the source of infection (LoE: D). Use imaging techniques when available (LoE: D).

*Background* Following first resuscitation steps and initiation of empirical antimicrobial therapy, it is critical to identify the source of infection. A thorough patient history and clinical investigation are essential to do so. Although imaging techniques (e.g., X-ray, ultrasound) may be used to answer specific diagnostic questions, nothing can replace a thorough medical history and systematic head-to-toe examination.

2. Whenever possible and without harm to the patient, sample fluid or tissue from the site of infection (LoE: C).

*Background* Microbiological identification of the causative microorganism of sepsis is useful to confirm presence the diagnosis and allows for targeted antimicrobial therapy. For microbiological cultures, blood, fluid or tissue from the suspected site of infection needs to be sampled in a sterile fashion [75]. Whenever clinically justifiable and timely achievable this should be done before initiation of empirical antimicrobial therapy to maximize the sensitivity of microbiological cultures. If microbiological cultures are unavailable, it may still be rational to collect samples for visual or microscopic analysis.

3. Examine the sampled fluid or tissue by Gram stain, culture and whenever possible for antibiotic susceptibility (LoE: C).

*Background* After samples have been obtained, transport to the microbiological laboratory should take place as fast as possible. Gram staining and microscopic examination should be performed whenever applicable. Also in resource-limited areas, microbiological cultures remain the gold standard to cultivate microbes. When microorganisms grow, susceptibility to locally available antibiotics should be assessed allowing for targeted antimicrobial therapy. Where parasitic infections are endemic

or suspected specific laboratory tests should be used (e.g., thick smear analysis for diagnosis of malaria). Rapid communication of positive microbiological test results to the clinician in charge is imperative.

### Source control

1. Whenever possible drain or debride the source of infection (LoE: C).

**Background** Along with timely and adequate antimicrobial therapy, source control is the only causative therapy of sepsis. As soon as basic resuscitation measures and empiric anti-infective therapy have been instituted, source control measures must be prioritized. Source control measures should be timed depending on several factors such as the patient's condition, surgical expertise and resource availability. In invasive *Staphylococcus aureus* infection, source control reduced mortality in a provincial hospital in northeast Thailand [76]. Typical infectious sources requiring emergent source control measures are abscesses (except for pulmonary abscesses), necrotizing soft tissue and wound infections, gastrointestinal perforation, cholangitis, obstructive urinary tract infection, and any deep space infection such as pleural empyema or septic arthritis. Depending on local availability of experts and resources, the least invasive technique should be chosen (e.g., percutaneous/endoscopic instead of surgical abscess drainage). Not all infectious sources are amenable to surgical source control (e.g., pneumonia, meningitis). In these patients, timing and adequacy of antimicrobial therapy remain the key component of sepsis care.

2. Remove any foreign body or device that may potentially be the source of infection (LoE: C).

**Background** Device-related infections are particularly frequent in intensive care units of middle- and low-income countries [77, 78]. Any artificial device (e.g.,

venous catheter) should carefully be checked for signs of infection. When signs of infection are present, removal of the device represents the key treatment. Infectious signs are frequently insensitive to diagnose infections arising from artificial devices, since infection of internal parts of the device may not cause cutaneous reactions. Therefore, removal of artificial devices should be considered if device-related infection is suspected. Before explanting permanent intravascular (e.g., implanted central venous access) or surgically introduced devices (e.g., hip or knee prosthesis, cardiac pacemaker), other sources of infection need to be safely excluded.

### Post-acute interventions

Post-acute interventions (Table 5) may be postponed until the patient has been resuscitated but should be instituted within 24 h of recognizing sepsis.

### Antimicrobial therapy

1. Reassess the effectiveness of the antimicrobial regimen regularly (LoE: C).

**Background** Regular assessment of the patient's response to source control and antimicrobial therapy is essential to promptly recognize inadequate source control. Although no clear time limit has been defined, worsening or ongoing organ dysfunction and persistence of infectious signs (e.g., fever) for more than 48 to 72 h following initiation of treatment should question the adequacy of sepsis therapy. Common causes of treatment failure are summarized in Table 6. Aside from situations when the patient's condition worsens or fails to improve, empirical antimicrobial therapy should be re-assessed after microbiological results are available. Antimicrobial therapy needs adjustment to pathogen susceptibility. De-escalation of antimicrobial therapy reduces the likelihood of bacterial selection and induction of resistance [79]. If

**Table 5** Post-acute interventions to treat septic patients with limited resources

Antimicrobial therapy	Reassess the effectiveness of the antimicrobial regimen regularly (LoE: C) Administer antimicrobials for an adequate but not prolonged time (LoE: D)
Glucose control	Whenever possible check blood sugar levels in every septic patient (LoE: D) Aim to keep blood glucose >70 mg/dL (>4 mmol/L) by providing a glucose calorie source (LoE: B). Do not target upper blood glucose levels <150 mg/dL (<8.3 mmol/L) (LoE: D)
DVT prophylaxis	Use prophylactic heparin and/or apply elastic bandages on both legs in post-pubertal children and adults (LoE: A). No deep vein thrombosis prophylaxis is required in pre-pubertal children
Enteral nutrition	Allow the patient to eat and drink small amounts once she/he is fully resuscitated and awake (LoE: C)
Sedation and pain relief	Use opioids to relieve pain. Titrate opioids cautiously in unstable patients (LoE: D) Only sedate the agitated and uncooperative patient (LoE: D) As soon as the patient is stable encourage mobilization (LoE: A)
Wean invasive support	As soon as the patient is improving, try to actively wean the extent of invasive support (LoE: D)

LoE level of evidence, DVT deep venous thrombosis

**Table 6** Common causes for treatment failure in sepsis in resource-poor settings

Inadequate empirical anti-infective therapy <sup>a</sup>
Missed or insufficient control of the infectious focus
Insufficient supportive therapy (suboptimal fluid resuscitation)
Development of new antimicrobial resistance
Occurrence of a new, hospital-acquired infection
Clinical symptoms are due to other diseases than sepsis

<sup>a</sup> Common reasons for inadequate empirical anti-infective therapy are: wrong group of pathogen targeted (e.g., bacterial instead of protozoic pathogen), administration of antimicrobial with a too narrow spectrum, primary resistance of the pathogen against antimicrobial therapy, use of counterfeit or expired drugs

microbiological cultures remain negative, it is critical to discern whether infection is present but pathogens were not cultivated or a non-infectious disease is present. The sensitivity of microbiological cultures depends on the sampled specimen and is far from 100%, even in high-income countries [75]. Sensitivities of microbiological cultures in resource-limited settings must be assumed to be even lower due to a widespread lack of appropriate inoculation and culture media [80].

2. Administer antimicrobials for an adequate but not prolonged time (LoE: D).

*Background* The aim of antimicrobial therapy is to administer an adequate anti-infective agent long enough to eradicate causative microbes and short enough to prevent super-infection with microorganisms selected during antimicrobial therapy. Unnecessary antimicrobial therapy, administered for presumed safety reasons, poses a significant threat [81]. The length of antimicrobial treatment must individually be determined based on the type of pathogen cultivated, site of infection, adequacy of source control, treatment response, presence of artificial devices and immune status.

#### Glucose control

1. Whenever possible check blood sugar levels in every septic patient (LoE: D).

*Background* Disturbances of glucose homeostasis often occur in sepsis [82, 83]. Hypoglycemia was observed in 16.3% of Ugandan patients with sepsis on hospital admission. Hypoglycemia was independently associated with in-hospital mortality. Altered mental state at admission revealed a specificity of 86% to predict hypoglycemia in septic patients [83]. Certain infectious diseases (e.g., malaria) are associated with an increased risk of hypoglycemia, particularly in children and patients with limited glycogen stores (e.g., malnourished patients or subjects with liver disease) [84]. Considering detrimental

effects of even short periods of hypoglycemia [85], blood sugar levels should be measured as early as possible, especially in patients with impaired mental state. If it is not possible to check blood sugar in a patient with impaired mental state at hospital admission, a presumptive diagnosis of hypoglycemia should be made and intravenous glucose administered.

2. Aim to keep blood glucose >70 mg/dL (>4 mmol/L) by providing a glucose calorie source (LoE: B). Do not target upper blood glucose levels <150 mg/dL (<8.3 mmol/L) (LoE: D).

*Background* Given the harmful effects of hypoglycemia [85], patients without hyperglycemia should receive an oral/enteral or intravenous glucose calorie source to prevent hypoglycemia. In patients presenting with low blood sugar, 30–50 g of glucose must urgently be administered.

Tight glucose control [targeting an upper glucose limit <150 mg/dL (<8.3 mmol/L)] is associated with an increased risk of hypoglycemic events, morbidity and mortality in sepsis and critical illness [34, 85]. In resource-limited settings, further aspects (e.g., limited availability of resources to measure blood glucose) increase the risk of hypoglycemia when targeting a tight glucose level range. Based on this, we discourage from targeting upper blood glucose levels <150 mg/dL (<8.3 mmol/L).

#### Deep vein thrombosis prophylaxis

1. Use prophylactic heparin and/or apply elastic bandages on both legs in adults and post-pubertal children (LoE: A). No deep vein thrombosis prophylaxis is required in pre-pubertal children (LoE: A).

*Background* Although in many resource-limited settings the prevalence of deep venous thrombosis has been assumed to be too low to justify widespread antithrombotic prophylaxis [86], more recent data point at relevant morbidity and mortality associated with deep venous thrombosis also in middle- and low-income countries [87, 88]. In a post mortem analysis of 989 Nigerian patients, sepsis and immobility >4 days were predisposing factors for venous thromboembolism [89]. Routine thromboembolism prophylaxis should be administered to all post-pubertal septic patients who have no increased bleeding risk or ongoing hemorrhage [90]. In settings where no heparin is available, either antithrombotic stockings or elastic bandages can be applied [91].

#### Enteral nutrition

1. Allow the patient to eat and drink small amounts once she/he is fully resuscitated and awake (LoE: C).

**Background** Sepsis disrupts the integrity of the gastrointestinal mucosal barrier and exposes the patient to an increased risk of gastric ulcer formation, particularly when shock, hypoxemia, coagulopathy and corticosteroid therapy are present [92]. Breakdown of the intestinal mucosal barrier can lead to persistent stimulation of the immune system and translocation of bacteria or bacterial components into the bloodstream [93]. Early administration of small amounts of fluids or enteral nutrition through a nasogastric tube improves gastrointestinal mucosal integrity and outcome in high-income settings [94]. At the same time, early enteral nutrition decreases the risk of gastric ulcer formation and upper gastrointestinal hemorrhage [94]. However,

early enteral nutrition is not without risks and may cause gastrointestinal ischemia when administered to patients in shock [95]. Particularly in middle- and low-income countries where patients rarely have their airway protected, early enteral nutrition may predispose to gastric regurgitation and pulmonary aspiration [unpublished data, Arjen Dondorp]. Therefore, enteral nutrition should be administered as early as possible, but only after the patient has adequately been resuscitated and is fully awake. In intubated patients, enteral nutrition (e.g., milk supplemented by cooking oil, salt, sugar, soya and a multivitamin tablet) through a nasogastric tube should be initiated after hemodynamic function has stabilized.

**Table 7** Suggested therapies to be avoided in the septic patient (level of evidence: D)

	Background
DO NOT use hypotonic fluids (e.g., glucose solutions) for fluid resuscitation	Hypotonic fluids only have a little effect on intravascular volume status but carry a high risk of tissue edema, brain edema and dyselectrolytemia
DO NOT use fluid balance as a guide to administer or withhold further volume loading	Fluid resuscitation should always be indicated by the patient's condition and the individual response to fluid loading. Significant under-resuscitation may occur
DO NOT use high dose steroids (e.g., hydrocortisone >300 mg/day or prednisolone >75 mg/day)	High dose steroids do not change mortality but relevantly increase the risk of hospital-acquired infection, hyperglycemia, gastrointestinal bleeding and/or delirium. Note relevant exceptions <sup>a</sup>
DO NOT use muscle relaxants except for endotracheal intubation and in mechanically ventilated patients with severe respiratory distress	Muscle relaxants increase the risk of neuromuscular weakness and prolonged paralysis from sepsis
DO NOT use succinylcholine in patients immobilized >3 days or with neuromuscular diseases	Succinylcholine may cause hyperkalemia resistant to treatment when administered to patients immobilized >3 days or with neuromuscular diseases
DO NOT use furosemide unless hypervolemia, hyperkalemia and/or renal acidosis are/is present	Furosemide cannot improve kidney function but may even be harmful to the kidney. Treat the patient and not the urine output!
DO NOT use dopamine in an attempt to improve renal function	Dopamine cannot prevent renal failure in sepsis but may even cause adverse side effects
DO NOT use sodium bicarbonate to treat metabolic acidosis arising from tissue hypoperfusion	Effectiveness of sodium bicarbonate to correct metabolic acidosis is unsure. Although a marker of disease severity, acidosis may have protective effects
DO NOT use non-steroidal anti-inflammatory analgesics	Non-steroidal anti-inflammatory analgesics cannot improve sepsis outcome but may impair renal and coagulation function as well as increase the risk of stress ulcer formation
DO NOT restrict oxygen because of considerations to reduce respiratory drive	Only few patients with chronic obstructive pulmonary disease have their respiratory drive suppressed by oxygen. The risk of accepting hypoxia in the majority of patients is unacceptably higher than the risk of inducing hypoventilation in a few
DO NOT diagnose "fever of unknown origin"	"Fever of unknown origin" is a diagnosis by exclusion. Resource limitations usually do not allow for full work-up of patients to make this diagnosis. Always assume and treat infection in the patient in whom fever cannot be explained by other pathologies
DO NOT use insulin if blood sugar cannot be measured regularly	If blood sugar is not measured regularly liberal insulin use may result in hypoglycemia with devastating neurological results. Depending on the availability of blood sugar tests adjust the upper glucose limit. If blood sugar can be measured several times a day the optimum blood sugar range would be 70–180 mg/dL (4–10 mmol/L)

<sup>a</sup>Indications for steroids in infectious diseases (Lit mervyn CC 2006): meningitis (dexamethasone 4 × 10 mg/day for 48 h, optimally commence before first antibiotic dose, does not seem to be effective in Asian patients), severe pneumocystis jiroveci pneumonia with hypoxemia (prednisolone 2 × 40 mg/day for 5 days + 1 × 40 mg/day

for 5 days + 1 × 20 mg for 10 days), tuberculous meningitis (dexamethasone 0.3–0.4 mg/kg/d tapered over 4 weeks), tuberculous pericarditis (prednisolone 60 mg tapered over 11 weeks), and onchocerciasis (prednisolone 60 mg for 3 days)



### Sedation and pain relief

1. Use opioids to relieve pain. Titrate opioids cautiously in unstable patients (LoE: D).

*Background* Opioids are potent analgesics and useful in patients suffering pain. Particularly in unstable patients, they may cause adverse effects (respiratory depression, hypotension, bradycardia, alteration of mental state) and must be used cautiously. This is of particular importance when facilities to secure the airway and provide mechanical ventilation are limited. Opioids should only be administered at diluted concentrations by the intravenous route. Intramuscular injections of large depot dosages may result in unpredictable effects. Septic shock patients typically require lower opioid dosages than hemodynamically stable patients [96]. If opioids are administered a ventilation bag and opioid antagonist should readily be available to treat unexpected respiratory depression.

2. Only sedate the agitated and uncooperative patient (LoE: D).

*Background* Similar to opioids, sedatives can reduce ventilatory drive, increase the risk of pulmonary aspiration, impair hemodynamic function and alter mental state. Therefore, sedatives should only be administered to agitated and uncooperative patients who cannot be managed by other means. In cases where symptoms of acute delirium prevail, neuroleptic drugs (e.g., haloperidol) are preferred over benzodiazepines [97]. Like opioids, all

sedative agents need to be titrated to the patient's response, and emergency equipment be held available. Encourage family members to participate in care to calm the patient.

3. As soon as the patient is stable encourage mobilization (LoE: A).

*Background* Prolonged bed rest causes numerous unwanted effects, including muscular atrophy, prolonged weakness, respiratory compromise, autonomic dysfunction, hypovolemia, gastrointestinal paralysis, deep venous thrombosis, and delirium [98]. Early mobilization may prevent or counteract these effects and hasten recovery [99].

### Wean invasive support

1. As soon as the patient is improving, try to actively wean invasive support (LoE: D).

*Background* Every therapy carries risk of adverse effects and may potentially harm. Therapies that are commonly administered and are associated with a high risk of adverse events are invasive procedures [77, 78], use of catecholamines [100], steroids [101] and sedative/opioid agents [102]. Therapies whose risks outweigh their assumed benefits and should be avoided based on the authors' expert opinion are listed in Table 7. Therefore, it is crucial to actively reduce invasive support as soon as the patient has stabilized. Active but careful reduction of

**Table 8** Management of sepsis due to specific causes

Malaria	Prompt start of parenteral artesunate in adults and children (2.4 mg/kg STAT followed by the same dose at 12 h, 24 h, and then daily until oral medication can be taken) (LoE: A) If injectable artesunate is unavailable intramuscular artemether (3.2 mg/kg on admission followed by 1.6 mg/kg daily), artesunate by suppositories (8–16 mg/kg at 0 and 12 h and then daily) or intravenous quinine (20 mg/kg loading dose over 4 h followed by 10 mg/kg over 4 h 8 hourly until oral medication is possible) can be used (LoE: A) In children, parenteral antibiotics should be given in addition to antimalarial treatment (LoE: A) Parenteral antibiotics should be given to adults with slide proven malaria and who present with a clinical syndrome requiring parenteral antibiotics (meningitis/encephalopathy, malnutrition, very severe or severe pneumonia) (LoE: A) Seizures should be treated with rectal or intravenous diazepam, intravenous lorazepam, paraldehyde or other standard anticonvulsants (LoE: B) In the absence of shock, fluid management should be performed judiciously and more restrictively than in patients with bacterial sepsis (LoE: B) In case of severe anemia (e.g., hemoglobin level <6 g/dL), blood transfusion should be considered (LoE: A) Empirical antibiotic therapy needs to cover Gram-positive, Gram-negative and anaerobic bacteria (LoE: B)
Puerperal sepsis	Treatment of tuberculosis infection in resource-limited settings is best performed by timely initiation of the combination of isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampicin alone for another 4 months (LoE: A)
Septic patients with HIV/AIDS	Patients with open mycobacterial infections require isolation/cohorting (LoE: A) In Pneumocystis jiroveci pneumonia, the therapy of choice is trimethoprim/sulfamethoxazole administered for 3 weeks. In patients with hypoxemia, prednisolone (40 mg bid for 5 days followed by 40 mg/day for 5 days and then 20 mg/day for 11 days) should be added (LoE: B) In malnourished patients, energy supply should be re-started slowly with a stepwise increase of daily caloric intake and avoidance of large amounts of carbohydrates to prevent the re-feeding syndrome (LoE: B)

LoE level of evidence



therapeutic intensity can reduce length of hospital stay and prevent complications. A prospective study from Thailand revealed that reminding physicians to remove unnecessary urinary catheters reduced the rate of catheter-associated urinary infections [103].

### Specific considerations for sepsis management

Specific considerations for the management of septic patients with malaria, puerperal sepsis or HIV/AIDS are summarized in Table 8 and detailed in the Electronic Supplementary Material.

### Implementing current recommendations into clinical practice

Effective implementation of guidelines into clinical practice is challenging. Summarizing different recommendations in care bundles has been shown to facilitate implementation of the Surviving Sepsis Campaign guidelines [8, 9]. Accordingly, we suggest two care bundles in order to implement the presented recommendations on sepsis management in resource-poor settings (Table 9). Although it is yet unclear which guideline implementation strategy is most likely to be efficient [104], several approaches have been successfully applied. Common single interventions include reminders, dissemination of educational materials, audits and feedback. Multifaceted approaches typically involve daily application of checklists, educational outreach, a multidisciplinary approach, as well

**Table 9** Suggested care bundles for sepsis management in resource-poor settings

Acute care bundle	Oxygen therapy Fluid resuscitation Early and adequate antimicrobial therapy Surgical source control
Post-acute care bundle	Re-evaluation of antimicrobial therapy Deep venous thrombosis prophylaxis Glucose control Weaning of invasive support

as a conceptual framework [104]. Dissemination of mobile phone text message reminders to health care workers in Kenya resulted in a sustained improvement of adherence to pediatric malaria guidelines [105].

### Endorsements

The present recommendations for sepsis management in resource-limited settings have been endorsed by the European Society of Intensive Care Medicine, the World Federation of the Pediatric Intensive and Critical Care Societies, the Global Sepsis Alliance, the Federation of Austrian Societies of Intensive Care Medicine, the Ugandan Society of Intensive Care Medicine and the Mongolian Society of Anesthesiology and Intensive Care Medicine.

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