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REVIEW

Management of adult sepsis in resource-limited settings: global expert consensus statements using a Delphi method

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Abstract

Purpose: To generate consensus and provide expert clinical practice statements for the management of adult sepsis in resource-limited settings.

Methods: An international multidisciplinary Steering Committee with expertise in sepsis management and including a Delphi methodologist was convened by the Asia Pacific Sepsis Alliance (APSA). The committee selected an international panel of clinicians and researchers with expertise in sepsis management. A Delphi process based on an iterative approach was used to obtain the final consensus statements.

Results: A stable consensus was achieved for 30 (94%) of the statements by 41 experts after four survey rounds. These include consensus on managing patients with sepsis outside a designated critical care area, triggers for escalating clinical management and criteria for safe transfer to another facility. The experts agreed on the following: in the absence of serum lactate, clinical parameters such as altered mental status, capillary refill time and urine output may be used to guide resuscitation; special considerations regarding the volume of fluid used for resuscitation, especially in tropical infections, including the use of simple tests to assess fluid responsiveness when facilities for advanced hemodynamic monitoring are limited; use of Ringer's lactate or Hartmann's solution as balanced salt solutions; epinephrine when norepinephrine or vasopressin are unavailable; and the administration of vasopressors via a peripheral vein if central venous access is unavailable or not feasible. Similarly, where facilities for investigation are unavailable,

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there was consensus for empirical antimicrobial administration without delay when sepsis was strongly suspected, as was the empirical use of antiparasitic agents in patients with suspicion of parasitic infections.

Conclusion: Using a Delphi method, international experts reached consensus to generate expert clinical practice statements providing guidance to clinicians worldwide on the management of sepsis in resource-limited settings. These statements complement existing guidelines where evidence is lacking and add relevant aspects of sepsis management that are not addressed by current international guidelines. Future studies are needed to assess the effects of these practice statements and address remaining uncertainties.

Keywords: Sepsis, Resource-limited settings, Delphi methodology, Anti-infective agents, Hemodynamic monitoring, Vasoactive agents

Introduction

In 2017, sepsis was estimated to be responsible for 49 million cases with 11 million associated deaths globally. [1] Eighty-five percent of sepsis cases and resultant deaths occur in low- and middle-income countries (LMICs) particularly in Africa, Asia and South America. Many cases occur in vulnerable and underserved populations. Improving detection and appropriate management of sepsis in such settings are high priorities to reduce the global burden of sepsis.

The World Health Assembly Resolution (70.7) on 'Improving the Diagnosis and Management of Sepsis' specifically recommends that Member States should establish guidelines and capability for effective sepsis diagnosis and management [2]. The most widely used guidelines globally are focussed primarily on high-income settings. A 2019 survey in the Asia Pacific Region showed over 80% of middle-income countries in the region used the Surviving Sepsis Campaign (SSC) Guidelines [3]. However, multiple studies highlight the difficulties in implementing non-contextualised guidelines in resource-limited settings [4–6].

Limited resources may be a significant factor impeding the implementation of sepsis guidelines in LMICs, but there may also be other important contextual factors that restrict applicability of international guidelines. For example, there are differences in disease aetiology, comorbidities and case-mix of sepsis populations, necessitating different management strategies. [7–13] Additionally, international guidelines do not address the safe management of critically ill patients with sepsis in the absence of an intensives care unit (ICU) beds, when factors such as the location for management, minimum monitoring, triggers for escalation of care and safe transport are important.

The World Health Organization (WHO) is aiming to use the best available evidence to generate recommendations for management of sepsis which can support national programs around the world. [5] However, high quality research on sepsis management in resource-limited settings is lacking. Therefore, to complement existing guidelines, we conducted a Delphi study among global experts in sepsis management representing diverse geographical and income settings, with the aim of generating consensus on strategies for management of sepsis in resource-limited settings where barriers to the effective implementation of current international guidelines exist or where guidance for specific sepsis management issues relevant in these settings is lacking.

Methods

Delphi process

A multidisciplinary Steering Committee (SNM, LT, BA, PN, VQD, SF, AK, LL, SL and RS) from different geographical settings and professional expertise in sepsis management, including a Delphi methodologist (PN), was convened by the Asia Pacific Sepsis Alliance (APSA). The study protocol was registered on ClinicalTrials.gov [NCT05909384]. Oxford Tropical Research Ethics Committee (OxTREC) confirmed that the study was exempt from ethics review in March 2023.

We used Delphi survey methodology to generate expert consensus and draft statements on the management of sepsis in resource-limited settings. For the purpose of this survey, the term 'resource-limited settings' was used to describe settings with lack or limited availability of trained healthcare professionals, infrastructure, laboratory diagnostic facilities and equipment for the management of sepsis and is not restricted to any geographical area or world bank definition of economic development. "Sepsis" was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. [7] Survey rounds were conducted based on previously published Delphi survey studies and reported based on Accurate Consensus Reporting Document (ACCORD) guidelines [14]. The ACCORD Checklist is provided in Appendix 1: Table 1, Pages 1–2.

A multidisciplinary international panel of experts including doctors and nurses was convened based on predefined selection criteria: clinical expertise in adult sepsis management and demonstrated involvement with sepsis–related research, education, policy/protocols or

professional activities. The complexity of understanding technical terminology, associated with the diagnosis and management of sepsis used in the Delphi process, prevented engaging other healthcare workers. Potential experts were identified through purposive sampling among professional connections of the APSA, Global Sepsis Alliance, Surviving Sepsis Campaign, and network recommendations. A concerted effort was made to select a diverse group of experts from a wide geographical distribution with at least 70% from LMICs.

An email invitation to participate in the Delphi study was sent to 48 potential experts. Upon acceptance, the experts were recruited in the Delphi process and the Delphi survey questionnaire was disseminated to the panel by email. The identity of the experts was concealed until the end of the Delphi process. Delphi questionnaires were prepared in the form of surveys using Google™ Forms.

The scope of the project was developed through qualitative evidence synthesis from a focused search of the published literature on sepsis management in resource-limited settings and published sepsis guidelines [15]. The literature revealed a lack of high-quality evidence for the management of sepsis in resource-limited settings, and our aim was to provide alternative solutions where there may be barriers to evidence-based practice, therefore the GRADE methodology was not used. The literature search strategy and subsequent PRISMA flowchart describing the studies included for qualitative evidence synthesis is provided in Appendix 1.

Domains were decided following detailed discussion among the Steering Committee members after identifying barriers to the effective implementation of current international guidelines for sepsis management and gaps identified in the literature for sepsis management in resource-limited settings.

The first open round of the Delphi survey included five domains: 1. need for additional clinical guidance; 2. need for additional clinical guidance on differences in population characteristics and disease type; 3. timing and locations for managing adult patients with sepsis; 4. diagnostic considerations for sepsis in adults with suspected or proven infection; and 5. clinical management of adults with sepsis.

Experts provided guidance on the domains and statements and advised changes or inclusion of other interventions for sepsis management in resource-limited settings. Experts responded to iterative rounds to prioritise consensus on topics for inclusion [16]. Feedback obtained in each round refined the questions and this was then presented back to the experts in the subsequent round as a consolidated report. The survey questionnaire included multiple-choice questions and 7–point Likert scale statements. A question was continued in the Delphi process until stability of the responses was attained.

Consensus and stability

Consensus was considered achieved if 80% or more of experts voted for a particular option in multiple-choice questions. For an ordinal 7–point Likert scale, consensus was achieved when 70% or more of experts voted for agreement (score of 5–7) or 'disagreement' (score of 1–3). Median and interquartile range (IQR) were used to describe the central tendency and dispersion of responses in Likert–scale statements. The stability of the responses was assessed between two consecutive rounds, starting from round two onwards, using the non-parametric Chi-square ($\chi 2$) test or Kruskal–Wallis test with $p < 0{\cdot}05$ considered a significant variation or unstable.

Expert clinical practice statements

The Steering Committee drafted expert clinical practice statements from the statements that generated consensus and stability during the Delphi process. Final results of the Delphi process, expert clinical practice statements and the draft manuscript were circulated among the experts for comments and approval prior to submission for publication.

Research priorities in this field were identified based on the feedback provided by the experts during the Delphi process and the gaps identified in the literature.

Results and discussion

Of the 48 experts invited, 41 (85%) accepted the invitation and participated in round one. Of these 38 (93%) completed all rounds of the Delphi process (Appendix 1: Fig. 2). The participating experts were from 29 countries and six continents, and 29 (71%) were from low and middle-income countries (Fig. 1).

The median age of the experts was 56 (IQR 47–65) years, and 15 (37%) were female. Most worked in university–affiliated hospitals (69%) or public hospitals (12%), and 49% did not have national–level guidelines on sepsis management in their country. The demographic profile of the individual experts including their primary specialty is provided in Appendix 1: Table 3 and 4.

Four Delphi rounds were conducted between 18 May and 23 August 2023 with 30 (94%) of questions achieving consensus and stability. Two questions did not achieve consensus despite multiple modifications and testing in iterative Delphi rounds. The final results are provided in Tables 1 and 2 with consolidated report of the Delphi rounds as an online supplement (Online Resource

Table 1 Delphi-survey results on the need for and type of clinical guidance required for resource-limited settings

Need for additional clinical guidance for managing adult sepsis in resource–limited settings	Agree (%)	Neutral (%)	Disagree (%)	Median (IQR)	χ^2 *p*–value
1. Clinical guidelines for the management of sepsis in high–income countries may not be applicable to resource–limited settings. It is important to have specific guidelines for managing adults with sepsis in resource–limited settings	90	5	5	7(1)	0.24
2. Guidelines for managing adults with sepsis in resource–limited settings should ideally be?*					1.0
International best practice guidelines adapted for resource–limited settings	65.8				
International best practice guidelines with a section on resource–limited settings	34.2				
Other	0				
3. What elements should be included in guidelines for managing adults with sepsis in resource–limited settings?	Imp. (%)	Neutral (%)	Not–imp. (%)		
Suitable alternative clinical locations to manage adults with sepsis if critical care not available or at capacity	88	5	7	6.5(2)	0.39
Alternative diagnostic methods if recommended pathology tests/equipment not available	90	3	7	7(1)	0.29
Alternative clinical management if methods (e.g., medications, fluids, equipment, etc.) are not available	88	3	10	7(1)	0.99
Alternative strategies if appropriate staff and/or staff expertise are not available	80	7	13	6(2)	0.84
Locally tailored strategies to support recovery	87	10	3	6(0.5)	0.13
Triage strategies to facilitate optimal use of resources for adults with sepsis when ICU beds are limited	93	7	0	6(1)	0.05
Need for additional clinical guidance on differences in population characteristics and disease type for managing adult sepsis in resource–limited settings	Agree (%)	Neutral (%)	Disagree (%)	Median (IQR)	χ^2 *p* value
1. Clinical guidance for managing adult sepsis should address different population characteristics relevant to resource–limited settings	100	0	0	7 (1)	0.89
2. What population characteristics may be different from high–income settings and should be considered in managing adult sepsis in resource–limited settings?					0.96
Different age of population and patients (e.g., young adults vs elderly)	87.5				
Different comorbidities (e.g., HIV, diabetes)	95				
Malnutrition	95				
Obesity	27.5				
Pregnant or postpartum	52.5				
3. What social and environmental characteristics may be different from high–income settings and should be considered in managing adult sepsis in resource–limited settings?					0.85
Socio–economic status	82.5				
Education level	60				
Access to care	100				
Alternative/traditional therapies	62.5				
Environmental pollution	27.5				
4. Clinical guidance should address different etiologies of sepsis in adults related to resource–limited settings	98	2	0	7(1)	0.64
5. What different etiologies of sepsis should be considered in managing adult sepsis in resource–limited settings?					0.93
Different bacterial infections	90				
Different viral infections	75				
Fungal infections	57.5				
Parasitic infections	97.5				
Different infection source (e.g., injury, influenza, gastroenteritis, pyelonephritis, etc.)	50				
None of the above	0				

ICU, Intensive Care Unit HIV, Human Immunodeficiency Virus

*statements which did not achieve consensus

$p < 0.05$ is unstable

1). Expert clinical practice statements on the timing and location of sepsis management, and diagnostic interventions are provided in Fig. 2. Expert clinical practice statements on haemodynamic, antimicrobial and respiratory therapies are provided in Fig. 3.

The Delphi process resulted in consensus on 30/32 (94%) items regarding sepsis management in adult patients in resource-limited settings across five domains, from which 23 clinical practice statements were derived. To the best of our knowledge, this is the first global Delphi convened among international experts to achieve expert consensus on the management of sepsis in resource limited settings.

There was consensus that clinical guidance for managing adult patients with sepsis in resource-limited settings should consider differences in population characteristics, socioeconomic factors and aetiologies of sepsis. Agreement could not be reached on the exact format of these guidelines, though a recent Delphi study on the management of sepsis by the Indian Society of Critical Care Medicine (ISCCM) reached consensus on there being a discrete section for the management of sepsis in resource-limited settings incorporated into international guidelines. [17] However, the paucity of evidence on sepsis management from resource-limited settings is a significant impediment to the development of dedicated guidance in any format.

When considering what elements guidelines should provide, experts agreed that guidance should cover alternative clinical locations for management of adults with sepsis if an ICU bed is not available, alternative diagnostic and management methods, as well as alternative strategies if appropriate staff and/or expertise are not available. Experts also agreed that triage strategies to facilitate optimal use of resources when ICU beds are limited and locally tailored strategies to support recovery should be provided. The research priorities identified are summarised in Appendix 1: Table 5.

To optimise the timing, transfer and setting for the clinical management of *sepsis* in resource-limited settings, clinical guidance should consider:

- Clinical and operational triggers (e.g., staff availability) for escalating the level of care.
- Factors to be considered prior to transferring patients to another facility including the availability of staff with appropriate clinical expertise, access to diagnostic and therapeutic interventions, and the clinical support needed for safe transportation.
- As a minimum prior to transfer, the patient should undergo a clinical assessment and receive appropriate airway maintenance, respiratory support and oxy-

Fig. 1 Choropleth depicting the geographical distribution of expert panellists for the Delphi study on sepsis management in resource-limited settings

Table 2 Delphi survey results on the clinical management of sepsis in resource-limited settings

Timing and locations for managing adult sepsis in resource–limited settings	Agree (%)	Neutral (%)	Disagree (%)	Median (IQR)	χ^2 *p*-value
1. Guidelines should consider the clinical and operational triggers for escalation of the clinical management of adults with sepsis in resource–limited settings	95	2.5	2.5	7(1)	0.05
2. Important considerations for transfer (to another facility) of adults with sepsis in resource–limited settings include:					0.96
Staff availability and skill mix	95				
Unavailability of a senior clinician supervision	50				
Diagnostics unavailability	92.5				
Therapeutics unavailability	100				
Stability of patient	72.5				
Transportation type	57.5				
Care during transportation	87.5				
3. What do you consider to be the minimum standard of care required before transferring adults with sepsis in resource–limited settings for a higher level of care (such as to ICU/HDU in another facility)?					0.64
Airway management	95				
Supplemental oxygen and adequate respiration	95				
Haemodynamic stability	67.5				
IV access	97.5				
Blood cultures obtained	15				
Biochemistry samples taken including lactate	12.5				
IV fluid administration commenced	85				
Antibiotics administered	80				
Transfer is prompt and not delayed	60				
4. For adult patient with acute sepsis (non–ventilated) managed outside a designated critical care area in a resource–limited setting which of the following physiological monitoring, treatment and resources in your opinion is required as minimum standard of care to ensure safe and effective care?					
Continuous ECG monitoring	55	7	38	5(4)	0.38
Intermittent manual pulse rate (palpation)	77	3	20	7(2)	0.19
Continuous pulse oximetry	65	7	28	7(3)	0.42
Intermittent pulse oximetry	85	0	15	6(2)	0.32
Continuous invasive blood pressure monitoring	12	10	78	2(2)	0.07
Intermittent blood pressure monitoring (either non–invasive electronic or manual device)	95	5	0	7(0.5)	1.0
Continuous central venous pressure monitoring	15	5	85	1(1)	0.75
Intermittent central venous pressure monitoring (using a fluid column)	7	10	83	1.5(2)	0.53
Intermittent observed respiratory rate	90	3	7	7(1)	0.74
Intermittent capillary refill time (manually assessed)	90	3	7	7(1)	0.91
Continuous urine monitoring (indwelling catheter with hourly measures)	62	3	35	5(4)	0.63
Intermittent urine monitoring (patient voids with urinal)	58	12	30	5(3)	0.26
Neurological assessment (e.g., AVPU, GCS scales)	92	3	5	7(1)	0.74
White blood cell count	80	10	10	6(2)	0.37
C-reactive protein	43	7	50	3.5(4)	0.94
Blood sugar level	85	5	10	6(2)	0.45
Blood lactate	63	7	30	5(3.5)	0.98
Arterial blood gases	47	10	43	4.5(3)	0.56

Table 2 (continued)

Timing and locations for managing adult sepsis in resource–limited settings	Agree (%)	Neutral (%)	Disagree (%)	Median (IQR)	χ^2 *p*-value
Access to basic medical imaging (X–ray or ultrasound)	83	10	7	6(1.5)	0.56
Staff experience/trained in acute care	83	12	5	6(2)	0.58
Documented process/tool to escalate care due to the risk of, or actual, clinical deterioration	85	5	10	6(2)	0.77
Clinical supervision by appropriately experienced staff on site or immediately available	80	10	10	6(2)	0.92
Access to source control/surgery	80	5	15	6.5(2)	0.87
Access to clinical support by phone or telemedicine when onsite expertise advice is not available	90	7	3	6(2)	0.76
5. Guidance on when to transfer an adult patient recovering from sepsis from critical care to intermediate or acute care (i.e., ICU discharge) should be included in guidelines for adults in resource–limited settings	93	5	2	7(1)	0.55
6. Remote monitoring (or tele–monitoring) may be considered to guide management of patients with sepsis in the resource–limited settings	95	2.5	2.5	7(1.5)	0.9
Diagnostic considerations for sepsis in adults with suspected or proven infection in resource–limited settings	**Agree (%)**	**Neutral (%)**	**Disagree (%)**	**Median (IQR)**	**χ^2 *p* value**
1. In your experience, which of the following scores are doable in resource–limited settings?					0.94
SOFA	15.8				
qSOFA	97.4				
SIRS	65.8				
NEWS	52.6				
MEWS	44.7				
2. In the absence of serum lactate, which of the following clinical parameters alone or in combination are just as useful as lactate in assessing tissue hypoperfusion?					0.62
Distal limb temperature	22.5				
Mottling	55				
Capillary refill time	100				
Altered mental status	80				
Decreased urine output	75				
3. Urine output should be monitored in all adult patients with sepsis in resource–limited settings	98	2	0	7(1)	0.1
4. Urine output should be monitored in all adult patients with sepsis in resource–limited settings using an indwelling urinary catheter*	55	12.5	32.5	5(3)	0.85
5. Urine output should be monitored in all adult patients with septic shock in resource–limited settings using an indwelling urinary catheter	95	5	0	7(1)	0.2
Clinical management of adults with sepsis in resource–limited settings	**Agree (%)**	**Neutral (%)**	**Disagree (%)**	**Median (IQR)**	**χ^2 p value**
1. Clinical parameters such as capillary refill time and urine output may be used in to guide resuscitation, if lactate is not available	100	0	0	7(0)	0.89
2. For adults with possible sepsis without shock, where investigations (such as laboratory or imaging) to exclude a non–infectious cause of acute illness are not readily available and if concern for infection persists, antimicrobials should be administered without delay	98	2	0	7(1)	0.89

Table 2 (continued)

Clinical management of adults with sepsis in resource–limited settings	Agree (%)	Neutral (%)	Disagree (%)	Median (IQR)	χ^2 p value
3. In the resource–limited settings, for adults with a high likelihood for sepsis or with septic shock, antimicrobials should be administered immediately, ideally within one hour of recognition of sepsis	100	0	0	7(0)	0.7
4. In areas of high risk for parasitic infection, an empirical anti–parasitic agent (e.g., anti–malarial) should be administered without delay to patients with suspected sepsis of parasitic origin	90	2.5	7.5	7(1)	0.08
5. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of antibiotic therapy is unclear, the following indicators, if available, are acceptable to guide cessation of antibiotic therapy by:					
Clinical improvement alone	75	5	20	6(2.5)	0.06
Clinical improvement plus trend in C–reactive protein	75	15	10	6(2)	0.08
Clinical improvement plus trend in white blood cell count	80	15	5	6(2)	0.08
Clinical improvement plus trend in procalcitonin	70		22	6(3)	0.39
6. When the facilities for hemodynamic monitoring are limited, the following may be used to guide fluid therapy?					
Fluid challenge	92	0	8	7(1)	0.05
Central venous pressure	35	10	55	3(3)	0.25
Plethysmographic indices for fluid responsiveness	53	20	27	5(3)	0.68
Pulse pressure variation (PPV and tidal volume challenge (both require an invasive arterial line)	65	5	30	6(1.5)	–
Passive leg raising (used with pulse pressure or PPV)	80	8	12	6(2)	0.72
Ultrasonography	85	3		6.5(2)	0.74
7. When facilities for advanced hemodynamic monitoring are unavailable, tests using an arterial line (e.g., PPV and tidal–volume challenge) may be used to guide fluid therapy	87	8	5	7(1)	0.22
8. For adults with sepsis or septic shock, when a balanced salt solution is indicated in resource–limited settings, a non-proprietary balanced salt solution (e.g., Ringer's lactate, Hartmann's solution, etc.) may be used	100	0	0	7(0)	1.0
9. Special consideration may be required regarding the volume of fluid for resuscitation in sepsis or septic shock due to tropical infections	100	0	0	7(0)	0.34
10. Epinephrine is an acceptable alternative to vasopressin (if vasopressin not available) in patients with septic shock and an inadequate mean arterial pressure response to norepinephrine	95	2.5	2.5	7(1)	0.07
11. Epinephrine is acceptable alternative to norepinephrine (if norepinephrine not available) in patients with septic shock and inadequate mean arterial pressure	98	2	0	7(1)	0.41
12. Vasopressors can be initiated and continued peripherally if central venous access is not available or feasible	98	2	0	7(0)	0.44
13. Non–Invasive ventilation is an acceptable alternative to HFNO, if HFNO is not available for the management of acute hypoxic respiratory failure	100	0	0	7(1)	0.06

HDU High Dependency Unit, *ICU* Intensive Care Unit, *ECG* Electrocardiogram; *IV* Intravenous; *AVPU* Alert, verbal, pain, unresponsive; *GCS* Glasgow coma scale; *SIRS* Systemic inflammatory response syndrome; *SOFA* Sequential organ failure assessment; qSOFA, quick SOFA; *NEWS* National early warning score; *MEWS* Modified early warning score; *PPV* Pulse pressure variation; *HFNO* High flow nasal oxygen

*statements which did not achieve consensus

$p < 0.05$ is unstable

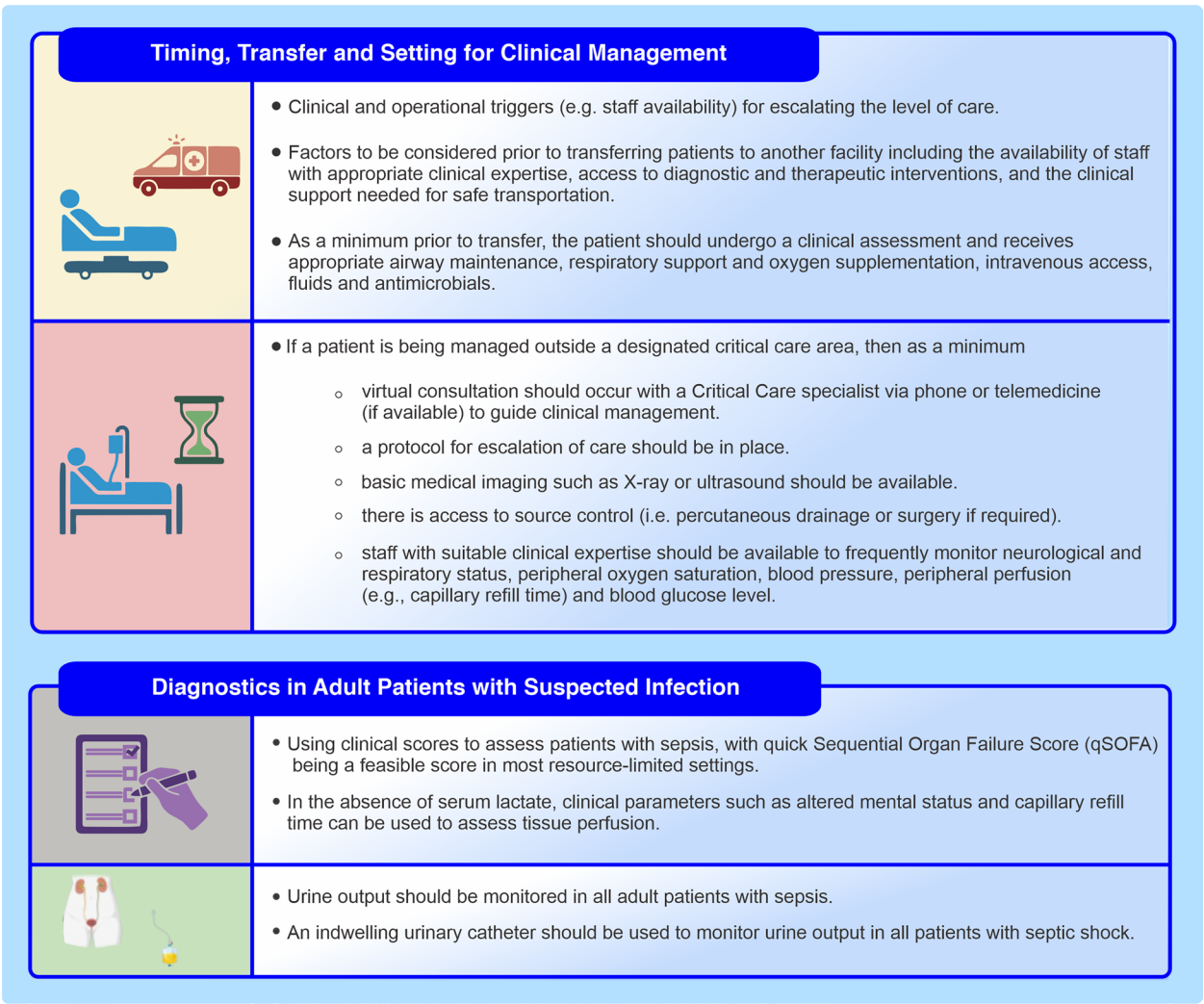

Fig. 2 Clinical practice statements on timing, location and diagnostic interventions for sepsis management in resource-limited settings

gen supplementation, intravenous access, fluids and antimicrobials.

- If a patient is being managed outside a designated critical care area, then as a minimum:
- Virtual consultation should occur with a Critical Care specialist via phone or telemedicine (if available) to guide clinical management.
- A protocol for escalation of care should be in place.
- Basic medical imaging such as X-ray or ultrasound should be available.
- There is access to source control (i.e., percutaneous drainage or surgery if required).
- Staff with suitable clinical expertise should be available to frequently monitor neurological and respiratory status, peripheral oxygen saturation, blood pressure, peripheral perfusion (e.g., capillary refill time) and blood glucose level.

Most guidelines recommend treating critically ill patients with sepsis in an ICU. However, resource limited health services are constrained by insufficient capacity, infrastructure, equipment, diagnostic testing, medications, clinical support modalities and adequate numbers of appropriately skilled staff. [18] In LMICs, many patients with sepsis receive treatment outside of a designated and appropriately equipped and staffed critical care facility and may be located a considerable distance from such a facility. [19] While the theoretical knowledge of clinical staff is often comprehensive, translating this into high-quality clinical practice may not be feasible. Experts considered that guidance on sepsis management in resource-limited settings should consider both the available expertise and interventions but also minimum requirements for safe patient transport. They also considered that alternative options such as telephone

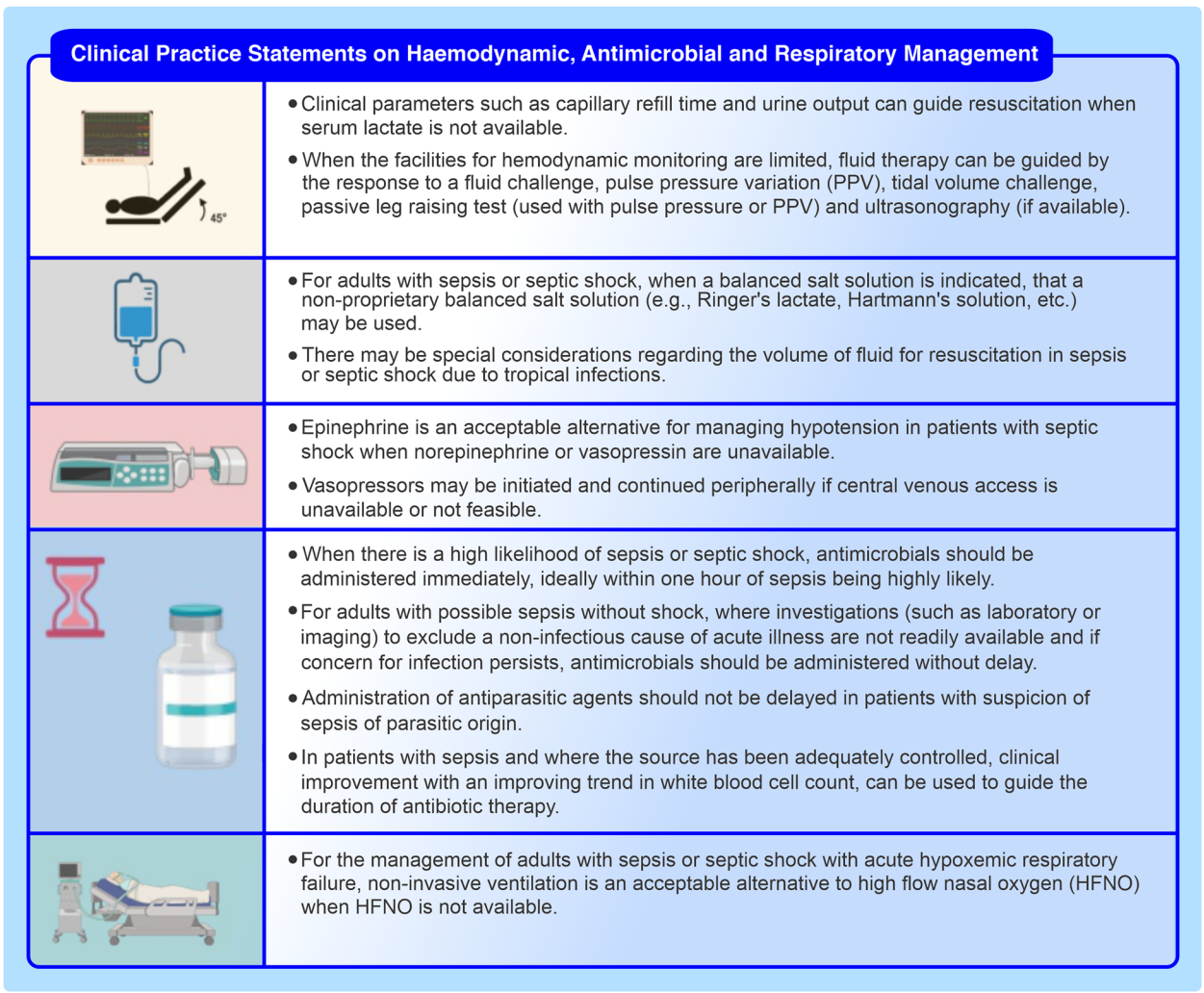

Fig. 3 Clinical practice statements on haemodynamic, antimicrobial and respiratory management for sepsis management in resource-limited settings

or telemedicine access to expertise could be used to support bedside expertise.

Appropriate diagnostics in adults with suspected infection in resource-limited settings, require clinical guidance that considers:

- Using clinical scores to assess patients with sepsis, with quick Sequential Organ Failure Assessment (qSOFA) score being a feasible score in most resource–limited settings.
- In the absence of serum lactate, clinical parameters such as altered mental status and capillary refill time can be used to assess tissue perfusion.
- Urine output should be monitored in all adult patients with sepsis.
- An indwelling urinary catheter should be used to monitor urine output in all patients with septic shock.

Currently, there is no widely applicable standard sepsis score to prompt a presumptive diagnosis of sepsis or a tool to confirm the diagnosis across primary and acute healthcare settings [20]. A variety of scores are used for sepsis screening, including systemic inflammatory response syndrome (SIRS) criteria, qSOFA score, National Early Warning Score (NEWS), or the Modified Early Warning Score (MEWS), but there is considerable variation between them in terms of sensitivity, specificity and ease of implementation [15, 20]. Use of qSOFA to screen for or diagnose sepsis is controversial with a body

of evidence and guidelines questioning its specificity, sensitivity and utility in the early recognition of sepsis. The 2021 SSC Guidelines recommend using SIRS, NEWS, or MEWS in preference to qSOFA when screening for sepsis or septic shock [15]. Feasibility of implementation is particularly relevant to resource-limited settings [21, 22], and may have prompted the experts to select qSOFA [21, 23].

Clinical parameters such as altered mental status, capillary refill time (CRT) and measurement of urine output can be performed in any setting and are acceptable indicators of tissue perfusion [24–30]. The ISSCM position statement, and the World Federation of Societies of Intensive and Critical Care Medicine Task Force report on the management of sepsis in resource-limited settings, reinforce the value of clinical parameters including urine output and CRT for the initial assessment of shock. [17, 19]. Though none of these indices is sensitive or specific when used alone, a combination of two or more physiological variables increases the sensitivity and specificity of the diagnosis of shock. [31] Additionally, prolonged CRT during the early phase of shock may be a predictor of increased risk of death [32]. Coupled with this finding, close monitoring of urine output is also a valuable surrogate of organ perfusion. However, recommending the use of an indwelling catheter for urine output measurement to guide management in all patients with sepsis did not achieve consensus among the sepsis experts in this Delphi study. Besides the resource constraint, this may reflect concern around catheter–acquired urinary tract infections [33, 34]. Other tissue perfusion parameters such as the *mottling score*, [35, 36] which has been shown to correlate well with tissue perfusion during resuscitation of septic shock, with a high prognostic value for mortality and *distal limb temperature,* did not achieve the desired consensus. Perhaps the experts felt that the feasibility and the interpretation of the other parameters mentioned above, were easier to assess and more objective in comparison. In addition, the difficulty of using mottling score in dark-skinned patients is a limitation [37]

Clinical guidance on haemodynamic management of *sepsis* in resource-limited settings, should recognize that

- Clinical parameters such as CRT and urine output can guide resuscitation when serum lactate is not available.
- When the facilities for hemodynamic monitoring are limited, fluid therapy can be guided by the response to a fluid challenge, pulse pressure variation (PPV), tidal volume challenge, passive leg raising test (used with pulse pressure or PPV) and ultrasonography (if available).
- For adults with sepsis or septic shock, when a balanced salt solution is indicated, a non-proprietary balanced salt solution (e.g., Ringer's lactate, Hartmann's solution, etc.) may be used.
- There may be special considerations regarding the volume of fluid for resuscitation in sepsis or septic shock due to tropical infections.
- Epinephrine is an acceptable alternative for managing hypotension in patients with septic shock when norepinephrine or vasopressin are unavailable.
- Vasopressors may be initiated and continued peripherally if central venous access is unavailable or not feasible.

Clinical examination including the assessment of the three windows of tissue perfusion, that is, altered mentation, skin perfusion and oliguria can be used to detect acute circulatory failure. [38] CRT rapidly changes in response to hemodynamic interventions, making it a valuable tool for bedside monitoring and guiding therapy in patients with septic shock. [39, 40] The ANDROMEDA-SHOCK trial showed no reduction in 28-day mortality when a resuscitation strategy targeting normalization of CRT was compared with targeting serum lactate level [31]; a post hoc Bayesian analysis, however, suggested that peripheral perfusion-guided resuscitation could reduce all-cause mortality at 28-days [41]. In addition to being a zero cost intervention, CRT is a universally available and is recommended by the SSC 2021 guidelines for use when lactate measurement is not available, making it an attractive indicator for use in resource-limited settings [15].

Fluid overload results in tissue edema increasing the risk of receiving invasive mechanical ventilation, impeding weaning from mechanical ventilation, and is an independent predictor of mortality in patients with sepsis. [42–44] These findings are especially relevant in resource-limited settings where mechanical ventilation may not be available. Studies have shown that only about 50% of unstable critically ill patients will actually respond positively to a fluid challenge. [45] Fluid bolus therapy was associated with worse outcome in children with severe febrile illness, due primarily to malaria, in Africa. [46] A trial from Zambia reported that early, protocolized fluid resuscitation and vasopressor use in adult patients increased in-hospital mortality compared with usual care. [47] It should be noted that in this trial, fluid administration was not titrated to usual hemodynamic targets, the amount of fluid was higher than 20–30 mL/kg and all patients received 4 L of fluids regardless of hemodynamic improvement. Nevertheless, these studies indicate

potential risks of fluid therapy in resource-limited settings with limited hemodynamic monitoring capacity. While assessing fluid responsiveness may pose additional workload for the staff, it has been shown to decrease the volume of fluid administered [48], which may be vital in resource-limited settings where there may be limited availability of respiratory support. Considering the high prevalence of tropical infections in resource-limited settings, the experts suggested special considerations regarding the volume of fluid used for resuscitation and the importance of identifying fluid responsiveness in patients who might benefit from fluids and avoiding fluid overload.

A fluid challenge is performed by the rapid administration of relatively low fluid volumes to assess the cardiac preload reserve of the patient. [49] This is usually interpreted using CVP and arterial pressure in resource-limited settings. However, the fluid challenge requires the administration of a fluid bolus to the patient. Therefore, the use of dynamic tests that predict fluid responsiveness, and help prevent fluid overload, can be vital in these settings. However, most of these tests require continuous cardiac output measurement and invasive mechanical ventilation to accurately predict fluid responsiveness, which poses a challenge in resource-limited settings [50, 51].

Pulse pressure variation (PPV) reliably predicts fluid responsiveness in mechanically ventilated patients with septic shock [52]. The test has a few limitations, the most common being the use of low tidal volume ventilation, where false negative values may occur [53]. The tidal volume challenge (TVC) is a novel test that can overcome this limitation [54]. Since PPV and TVC require only an invasive arterial line, they can be used in mechanically ventilated patients when cardiac output monitoring is unavailable, making them particularly useful in resource-limited settings to predict fluid responsiveness. Alternatively, fluid responsiveness can be predicted with ultrasound using respiratory variations in inferior vena cava diameter. Though they may be expensive, ultrasound devices are increasingly available in LMIC's and acquiring the device is a one-time cost. It is important to note that these indices are more reliable in mechanically ventilated patients.

Passive leg raising (PLR) test can reliably predict fluid responsiveness in both ventilated and non-ventilated patients. While it requires cardiac output monitoring to be accurate, PLR can be measured with ultrasound, if available. Alternatively, PPV can be used as demonstrated by a recent study showing that a reduction in PPV by > 3.5% after performing PLR can reliably predict fluid responsiveness [55].

The effect of balanced crystalloids, including both Ringer's lactate and acetate solutions such as Plasmalyte, compared with 0.9% saline in the critically ill remains unclear. A recent systematic review and individual patient data meta-analysis (BEST-Living) involving 34,685 patients from six trials, concluded that there is a high probability that use of balanced solutions in the ICU reduces in-hospital mortality [56]. However, the certainty of the evidence was moderate, the absolute risk reduction was small, and in patients with traumatic brain injury, the use of balanced solutions was associated with increased in-hospital mortality [56]. Administration of 0.9% saline may be considered, provided the serum electrolyte, especially chloride levels are monitored.

The SSC and European Society of Intensive Care Medicine clinical practice guidelines recommend the use of balanced crystalloids instead of 0.9% Saline for resuscitation. [15, 57]. A small randomized controlled trial comparing Ringer's lactate with acetate solutions in adult critically ill patients showed no difference in time to correction of metabolic acidosis, though the higher cost of acetate solutions would limit routine use in resource-limited settings [58]. The experts suggested that when a balanced salt solution is indicated, a non-proprietary balanced salt solution, such as Ringer's lactate or Hartmann's solution, may be used.

Many guidelines strongly recommend the use of norepinephrine over other vasopressors as a first line agent when managing septic shock and suggest adding vasopressin instead of increasing the dose of norepinephrine when the mean arterial pressure (MAP) remains inadequate. The SSC Guidelines committee and the Delphi experts agree that epinephrine can be used as an alternative when norepinephrine or vasopressin is unavailable [15]. A randomized trial in patients with shock, comparing norepinephrine with epinephrine, has shown no difference in 90-day mortality and vasopressor-free days [59]. Phenylephrine as an alternative to adrenaline or noradrenaline was not explored in the Delphi process. Increased hospital mortality was noted in a study assessing patient outcomes during the 2011 norepinephrine shortage in the United States of America, when phenylephrine was the most commonly administered alternative vasopressor for septic shock [60].

Vasopressors are usually administered through a central venous catheter (CVC) due to concerns about extravasation which may lead to local tissue ischemia when administered through a peripheral venous catheter. However, special equipment and the expertise required for central venous access may not be available in resource-limited settings. Given the possibility of restoring blood pressure faster and the low incidence of complications with peripheral vasopressor use, the experts

agreed that vasopressors may be initiated and continued peripherally, if central venous access is unavailable or not feasible. A recent systematic review of peripheral administration of vasopressors found 3.4% extravasation events with no reports of tissue necrosis or limb ischemia, with the need for active treatment of the extravasation not reported in a majority of studies [61]. These findings were supported by another systematic review which found that most patients who have an extravasation event, do not experience long-term sequelae [62]. While the administration of vasopressors through a peripheral venous catheter appears to be safe, close monitoring for early detection of extravasation should be practiced.

Antimicrobial clinical guidance for managing *sepsis* in resource-limited settings should recognize that

- When there is a high likelihood of sepsis or septic shock, antimicrobials should be administered immediately, ideally within one hour.
- For adults with possible sepsis without shock, where investigations (such as laboratory or imaging) to exclude a non–infectious cause of acute illness are not readily available and if concern for infection persists, antimicrobials should be administered without delay.
- Administration of antiparasitic agents should not be delayed in patients with suspicion of sepsis of parasitic origin.
- In patients with sepsis and where the source has been adequately controlled, clinical improvement with an improving trend in white blood cell count can be used to guide the duration of antibiotic therapy.

Providing appropriate and timely antimicrobial therapy in sepsis is central to improving outcomes. However, in resource-limited settings, achieving this goal must be balanced against providing other aspects of care, especially to the sickest patients. Providing timely antimicrobial therapy should also be balanced with concerns regarding antimicrobial resistance where infections are commonly caused by resistant organisms and empiric therapy is likely to include broad-spectrum antibiotics [63]. While the World Health Assembly recognises the need to promote 'judicious use of antimicrobials' in sepsis management [64], how best to do this in patients with sepsis is unclear and likely will need significant improvements in both diagnostics and antimicrobial stewardship programmes. The WHO's global research agenda for antimicrobial resistance includes research priorities of context-specific optimization of antimicrobial stewardship and empiric antimicrobial regimens and new rapid point-of-care diagnostics which would be of great value in addressing this complex issue [65].

In many resource-limited settings, the underlying infectious agents are different to high-income countries [66]. Sepsis of parasitic origin, for example malaria, is a significant burden in many low resource settings. Severe malaria requires rapid parasitological diagnosis by microscopy or rapid diagnostic test and prompt initiation of appropriate treatment. Coinfection between malaria and bacteria is frequently reported, although rates significantly vary with endemicity and age-group [67, 68]. Dengue, whilst mild in the majority of cases, can be associated with significant capillary leak, multiorgan failure and shock in some. Massive outbreaks in South and Southeast Asia in 2022 and 2023 [69], placed the regions ICUs under considerable strain and highlighted the need for further research into treating severe forms of the disease.

Limited diagnostics in resource-limited settings further compound difficulties in decision-making around empirical antimicrobial agents. Tuberculosis is a common comorbidity in many LMICs but is also independently associated with sepsis syndromes in people with and without underlying immunological deficiency [70]. Early and appropriate treatment of tuberculosis in adults presenting with sepsis is important for both patients and healthcare systems and delaying anti-tuberculosis therapy in patients is associated with worse outcomes. HIV/AIDS is a common comorbidity and is associated with its own spectrum of pathogens which may require specific consideration in terms of antimicrobial therapy. Viral diseases such as dengue and chikungunya are common causes of sepsis syndromes in some regions, often occurring in large outbreaks and putting further strain on stretched resources.

Rapid point-of-care diagnostics which can differentiate bacterial and viral causes of sepsis are part of WHO's antimicrobial resistance research agenda and could significantly improve antimicrobial stewardship [66], however further research and education are likely needed to optimise their use. For example, 26% of patients hospitalised with dengue in Taiwan (2008–2015) continued to receive antibiotics after the diagnosis of dengue was confirmed [71].

The overuse of antibiotics is a significant problem globally, and evidence suggests that antibiotic duration may be longer and is combined with higher rates of resistance in resource-limited settings [72, 73]. De-escalation of antibiotics and early cessation are particularly important in these settings. In addition to driving antimicrobial resistance, antibiotics are also a major driver of costs and catastrophic healthcare expenditure in many LMICs. [74] Unnecessary antibiotics also increase the risk of adverse reactions in critically-ill populations [75, 76]. While fixed shorter treatment regimens (typically seven days or less)

are safe in critically ill patients with infections that often lead to sepsis, the optimal treatment duration of antimicrobials for patients with sepsis and septic shock remains uncertain, particularly for patients in LMICs with community acquired infections [77]. A meta-analysis including randomized clinical trials to investigate methods to minimize antibiotic duration in patients with infections or sepsis in ICU showed a reduced duration of antibiotic therapy with procalcitonin-guided therapy or prespecified limited duration compared to clinical algorithms, however there was no difference in mortality [78]. As CRP and PCT may be unavailable or expensive in resource-limited settings, we sought expert consensus on alternative approaches to support optimal antibiotic use. Our expert panel recognised clinical improvement and white blood cell count as useful indicators to guide antibiotic de-escalation in patients with sepsis and adequate source control.

Nevertheless, a recent recommendation from experts in Southeast Asia and India strongly supported the inclusion of PCT in the region's antibiotic stewardship programs [79]. Furthermore, PCT-guided initiation of antibiotic and de-escalation was associated with reduced antibiotic prescription, shortened duration of antibiotics and increased antibiotic-free days, which could offset costs associated with procalcitonin tests in a randomised controlled trial in two Malaysian ICUs [80].

For the management of adults with sepsis or septic shock with acute hypoxaemic respiratory failure, non-invasive ventilation (NIV) is an acceptable alternative to high flow nasal oxygen (HFNO) when HFNO is not available

Guidelines from the European Society of Intensive Care Medicine on acute respiratory distress syndrome and the European Respiratory Society on acute respiratory failure (ARF) recommended the use of HFNO over conventional oxygen therapy to reduce the risk of tracheal intubation in patients with acute hypoxaemic respiratory failure. However, recommendations are unclear on how to choose between NIV and HFNO due to low certainty of evidence [81]. The WHO Clinical Management of COVID-19 Living Guideline [82], chose not to make a recommendation between CPAP, HFNO and NIV for acute hypoxaemic respiratory failure not requiring intubation due to uncertainty of data. Serpa Neto et al. recommended the use of NIV in select cases of ARF with relatively stable haemodynamics under close monitoring, among the pragmatic recommendations provided for ventilatory support in the management of sepsis and septic shock in resource-limited settings [83]. Higher oxygen consumption with HFNO, as well as the setup and availability of equipment, may be a limitation to its use in resource-limited settings [84, 85].

Strengths and limitations

Our study has several strengths. First, a diverse international panel representing six continents and 29 countries, with over 70% of the experts from LMIC's. The expert panel included many who serve on various other sepsis guideline groups. Second, the position statements addressed the knowledge gaps in ICU admission and timing of therapeutic interventions, considering population, socio-environmental and etiological characteristics. Third, we followed a robust Delphi process, with anonymity of experts and their individual responses maintained until the end of the Delphi process to prevent any bias, dominance or group pressure.

Our study has some limitations. Although a concerted effort was made to select experts from a wide geographical distribution, we could not achieve a homogenous distribution of experts from different regions. Only 25% of the experts were from sub-Saharan Africa or South America. Nevertheless, as per our methodology, 70% of the experts were from LMICs. Another limitation is that we excluded non-English articles in the literature search. However, we did not exclude non-English speakers from our expert panel, a majority of whom were from LMICs (70%), that drafted the statements based on consensus. In addition the experts were encouraged to comment on the domains and statements and provide suggestions for changes or inclusion of other interventions for sepsis management in resource-limited settings not addressed in the literature.The non-availability of infrastructure and/or inadequate experience with certain interventions representing different health care systems/populations, may have influenced the opinion of some experts. While these differences were not captured, the controlled feedback, received during the iterative Delphi rounds and inclusion of the statements only after the predefined consensus was achieved by the entire group of experts, may have reduced this bias and ensured face-validity of the position statements. Nevertheless, the clinical practice statements may need to be adapted for adoption in relation to these differences.

The clinical practice statements focus largely on management strategies for patients with sepsis in resource-limited settings. Apart from safe transport of these patients, triaging, requirements for managing a patient outside the ICU including virtual consultation and triggers for escalation of care, other organizational issues have not been addressed. In addition, there may be interventions superior to the ones proposed by the experts. However, our study did not attempt to address the science related to best practices. The objective of the study was to obtain guidance on how clinicians in resource limited settings could fulfil the requirements to meet best

practice within their constraints. Finally, the feasibility, acceptability and adoption of clinical practice statements were not formally assessed, and future epidemiologic and prospective multicentre studies may change the guidance as the evidence evolves.

Conclusion

Using a Delphi method, experts reached consensus for 30 statements from which 23 expert clinical practice statements were derived for the management of sepsis in resource-limited settings. These addressed important clinical decisions for patient management worldwide, in areas where evidence is lacking. These clinical practice statements complement current global guidelines by providing additional guidance for management of a critically ill patient with sepsis while awaiting an ICU bed, safe patient transfer and specific considerations related to the type of infection seen in some resource-limited settings. Future research is needed to assess the feasibility, adoption and effects of these practice statements and address the remaining uncertainties.

Supplementary Information

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Author contributions

The Steering Committee (SC) included SNM, LT, BA, PN, VQD, SF, AK, LL, SML and RS. The SC drafted the survey questionnaires for each round, analyzed the results and drafted the expert clinical practice statements from the statements that generated consensus and stability during the Delphi process. SNM, LT, PN and BA contributed to the conceptualization, design of the work, data curation, project administration, verification of the underlying data, and drafting of the manuscript. PN served as the Delphi methodology expert, conducting the literature search and formal analysis. The experts (DA, MA, YMA, AA, LA, EB, AC, KDA, JDW, JVD, EE, LE, AF, NEH, MH, MSH, STJ, JJ, YJ, KK, LKC, ML, GL, FRM, YM, MM, DNS, GAOT, MO, CP, HCP, KR, GRV, HSK, GSS, WS, TLT, ST, ST, BV, JLV) completed the survey questionnaires in the various rounds of the Delphi process, the results of which were used to draft the expert clinical practice statements. All authors contributed to reviewing and editing of the manuscript for intellectual content and are responsible for the content of this review.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest

Massimo Antonelli: Grants from GE and Fisher & Paykel; Lecture fees from Menarini, Shionogi, Fisher & Paykel, Dimar. Jan De Waele: Consulted for Biomerieux, Menarini, MSD, Pfizer, Roche Diagnostics, ThermoFisher and Viatris (fees and honoraria paid to institution). Supported by a Sr Clinical Research Grant from the Research Foundation Flanders (FWO, Ref.1881020N). Jigeeshu Divatia: Lecture fees from Edwards India paid to my institution. Simon Finfer: Supported by an NHMRC Investigator Fellowship (Leadership Level 3 App

2017580), has received consulting fees paid to his employer from RevImmune Inc. and owns options in Sepsis Scout. Naomi E Hammond: Supported by an NHMRC Investigator Fellowship (Emerging Leader Level 1 App 1196320), has received consulting fees paid to her employer from RevImmune Inc. Arthur Kwizera: Grants from the Wellcome Trust; NIHR; Fisher & Paykel Ltd; Gradian Health Systems; Vygon Ltd; Speaker support from the ESICM; Makerere University Research and Innovation Fund. Marlies Ostermann: Institution received research funding from Baxter and Biomerieux.

Ethical approval and consent

The study protocol was registered on clinicaltrials.gov [NCT05909384]. Oxford Tropical Research Ethics Committee (OxTREC) confirmed that the study was exempt from ethics review in March 2023.

Consent to participate and publish

All authors and collaborators consented to participate in and publish this study.

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