Haemodynamic assessment and support in sepsis and septic shock in resource-limited settings

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Background: Recommendations for haemodynamic assessment and support in sepsis and septic shock in resource-limited settings are largely lacking.

Methods: A task force of six international experts in critical care medicine, all of them members of the Global Intensive Care Working Group of the European Society of Intensive Care Medicine and with extensive bedside experience in resource-limited intensive care units, reviewed the literature and provided recommendations regarding haemodynamic assessment and support, keeping aspects of efficacy and effectiveness, availability and feasibility and affordability and safety in mind.

Results: We suggest using capillary refill time, skin mottling scores and skin temperature gradients; suggest a passive leg raise test to guide fluid resuscitation; recommend crystalloid solutions as the initial fluid of choice; recommend initial fluid resuscitation with 30 ml/kg in the first 3 h, but with extreme caution in settings where there is a lack of mechanical ventilation; recommend against an early start of vasopressors; suggest starting a vasopressor in patients with persistent hypotension after initial fluid resuscitation with at least 30 ml/kg, but earlier when there is lack of vasopressors and mechanical ventilation; recommend using norepinephrine (noradrenaline) as a first-line vasopressor; suggest starting an inotrope with persistence of plasma lactate >2 mmol/L or persistence of skin mottling or prolonged capillary refill time when plasma lactate cannot be measured, and only after initial fluid resuscitation; suggest the use of dobutamine as a first-line inotrope; recommend administering vasopressors through a central venous line and suggest administering vasopressors and inotropes via a central venous line using a syringe or infusion pump when available.

Conclusion: Recommendations for haemodynamic assessment and support in sepsis and septic shock in resource-limited settings have been developed by a task force of six international experts in critical care medicine with extensive practical experience in resource-limited settings.

Keywords: Circulation, Fluid resuscitation, Inotrope, Sepsis, Septic shock, Vasopressor

Introduction

Recommendations for care in patients with sepsis or septic shock are largely based on evidence originating from resource-rich settings.\textsuperscript{1} It is increasingly appreciated that these recommendations cannot be directly generalized to resource-limited settings for several reasons, including restrictions in human and material resources, but also concerns regarding costs and safety.\textsuperscript{2,3} It is
even possible that the efficacy and effectiveness of certain strategies differ between resource-rich and resource-limited settings. Indeed, efficacy and effectiveness could depend on the type of sepsis, and it is well known that non-bacterial sepsis is much more common in resource-limited than in resource-rich settings.2

A task force of the Global Intensive Care Working Group of the European Society of Intensive Care Medicine (ESICM) wished to answer five practical questions regarding haemodynamic assessment and support in sepsis and septic shock in resource-limited settings. As recognition of hypoperfusion and return to normal perfusion, as well as detection of fluid responsiveness, could avoid under- or overresuscitation or under- or overuse of vasoactive agents, there is need for affordable bedside tools for tissue perfusion monitoring as well as a better understanding of practicalities of passive leg raise tests in these settings. As costs and the availability of, but also indications for, intravenous fluids can be different in resource-limited settings, certain types and amounts of intravenous fluid should be used during fluid resuscitation, and the proper timing of intravenous fluid treatment for sepsis and septic shock in resource-limited intensive care units (ICUs) is essential. Finally, because of the limited availability of vasopressors and inotropes, and the risks associated with their use, recommendations on their indications, titrations and ways of administration in settings with limited resources are necessary.

Therefore, six international experts in critical care medicine reviewed current guidelines and the existing literature. For this they used the recently updated guidelines of the Surviving Sepsis Campaign3 and searched for additional evidence originating from resource-limited settings. They reformulated the existing recommendations for haemodynamic assessment and support, focusing on efficacy and effectiveness and aspects such as availability, feasibility, affordability and safety.

Methods

Full methods are provided in the supplementary material. The methods followed a similar approach as used previously by other task forces of the Global Intensive Care Working Group of the ESICM.4–9 External peer review was provided through the complete panel of the Global Intensive Care Working Group.3

Task force team members

The process for selection of task force members involved in this review and the key issues in haemodynamic assessment and support to be discussed are described in the supplementary material.

Search strategy

The search strategy for relevant studies was as described for the development of the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016 guidelines.1 The search terms included PubMed, MEDLINE, Embase and the Cochrane Libraries, with a focus on investigations originating from resource-limited settings.

Recommendations

The generated list of recommendations was graded for the level of evidence and strength of each recommendation, using Grading of Recommendations Assessment, Development and Evaluation (GRADE) tools,10 details of which are provided in the supplementary material. The primary source of evidence was studies performed in resource-limited settings, and grading of evidence included efficacy and effectiveness, availability and feasibility and affordability and safety in resource-limited settings (detailed in Table 1 in the supplementary material). Recommendations concern adult as well as paediatric populations; where the recommendations were different, these were separated.

Using the principles of GRADE, task force members classified the quality of evidence as high (grade A), moderate (grade B), low (grade C) or very low (grade D) and recommendations as strong (grade 1) or weak (grade 2). The term ‘recommend’ was used for strong recommendations, whereas ‘suggest’ was used in case of lower-level evidence. In case a recommendation was based on expert opinion from the group, it was classified as ‘ungraded’ (UG) (detailed in Table 2 in the supplementary material).

Recommendations for simple bedside tools

(1) Which simple bedside tools for assessing tissue perfusion could be useful in sepsis and septic shock in resource-limited settings?

Recommendation: We suggest using capillary refill time, skin mottling scores and, if affordable, skin temperature gradients to assess the adequacy of tissue perfusion in paediatric and adult sepsis and septic shock, either alone or in combination (UG). It remains uncertain whether these tools are effective in malaria. These tools are non-invasive and safe and come at no additional or low cost, although the cost of temperature probes could still be too high for certain resource-limited settings. This recommendation remains weak, mainly because of the absence of evidence that these bedside tools can adequately guide important decisions in haemodynamic support.

Rationale Timely detection of tissue hypoperfusion is one crucial aspect of haemodynamic assessment in patients with sepsis or septic shock. The Surviving Sepsis Campaign does not recommend simple and affordable bedside tools for assessing tissue perfusion.1 A search of the literature combining various search terms such as ‘skin perfusion’, ‘skin colour’, and ‘skin temperature gradients’, alone and in combination with diverse search terms covering ‘sepsis and septic shock’ and ‘resource-limited settings’ resulted in 12 articles, the majority still from resource-rich settings.11–22

Several studies showed that capillary refill times >5 s following initial haemodynamic optimization are associated with worsening organ failure.11–13 Normalization of capillary refill time was prognostic of survival in septic shock patients.14 During early septic shock, capillary refill time was found to be a good predictor of short-term mortality15 and related to perfusion of the liver, spleen, kidneys and intestines in adults.16 There was noticeable variation though in how capillary refill times were checked, at least in investigations involving children (Table 1), and several factors may affect the accuracy of capillary refill time, including ambient temperature and light, the site of measurement and the amount of pressure applied to the capillary bed.23 There was debate about whether capillary refill time is subject to interobserver variability.23,24 One study in India
suggests capillary refill time is insensitive to detect tissue hypoperfusion in patients with malaria.25

Mottling, patchy skin discolorations due to heterogenic small vessel vasoconstriction that usually start around the knees and elbows in patients with shock could also reflect abnormal skin perfusion. A score that is simple to apply at the bedside, using a scale from 0 (‘no mottling’) to 5 (‘grave mottling’) (Table 2 and Figure 1), related well to plasma lactate levels, urine output, degree of organ dysfunction and even mortality in patients with septic shock.17 Patients whose mottling score decreased during the resuscitation period had a better prognosis.17 The prognostic value of this score was confirmed in other cohorts of critically ill patients.18,19 The mottling score had good reproducibility and did not suffer from interobserver variability.17

Skin temperature gradients, the difference between two different measurement points, such as between the forearm and fingertip or central core to the toe, can be useful in detecting changes in skin perfusions in sepsis and septic shock.20,21 The advantage of using skin temperature gradients between, for example, the forearm and fingertip, instead of a single skin temperature, is that both spots are similarly affected by ambient temperature. The normal skin temperature gradient between the forearm and fingertip is 0°C. Skin temperature gradients between the forearm and fingertip >4°C were associated with severe vasoconstriction. Increased skin temperature gradient was related to the outcome of sepsis.22

(2) Is the passive leg raise test feasible in resource-limited settings and can simple tools replace frequently lacking direct measurements of cardiac output?

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**Table 1. Different methods of measuring and interpreting capillary refill time in children**

| Method | Interpretation |
|--------|----------------|
| Apply pressure to the nail bed or other area with visible circulation; measure the length of time it takes for blanching to disappear | A capillary refill time <2 s is normal and >4 s is abnormal. A capillary refill time between 2 and 4 s should prompt further consideration of the presence of shock |
| The preferred location to test capillary refill time is the sternum. If the finger or toe is used, the leg or arm must be elevated. Press firmly for 5 s. After fingertip pressure to a distal extremity, blood should refill the area in <2 s after release | A capillary refill time >5 s indicates an inadequate cardiac output |
| Press on the sternum or digit at the level of the heart for 5 s | A capillary refill time >2 s in the setting of other signs of shock indicates a compensated shock state |
| Cutaneous pressure on the sternum or on a digit for 5 s | A capillary refill time >2 s is a clinical feature of shock |
| Grasp the child’s thumb or big toe between finger and thumb and look at the pink of the nail bed. Apply minimal pressure necessary for 3 s to produce blanching of the nail bed. The time to capillary refill is from the moment of release until a total return of the pink colour | Capillary refill time should be <3 s. If >3 s the child may have a problem with shock |

Adapted and modified from Pandey and John.44

**Table 2. Skin mottling score after initial fluid resuscitation**

| Score | Description |
|-------|-------------|
| 0     | No no mottling |
| 1     | Modest Coin size, localized to the centre of the knee |
| 2     | Moderate Mottling does not exceed the superior edge of the kneecap |
| 3     | Mild Mottling does not exceed the middle thigh |
| 4     | Severe Mottling does not exceed beyond the fold of the groin |
| 5     | Grave Mottling exceeds beyond the fold of the groin |

Adapted from Ait-Oufella et al.17

**Figure 1. Skin mottling score. Adapted from Ait-Oufella et al.17**
The study A search for evidence originating from resource-limited set-
tings. The test needs to be executed so that it
fundamentally affects its haemodynamic
parameters.

Figure 2. For maximum reliability, a passive leg raise test should be per-
formed following some rules. One possible variation of the test starts
from a semi-recumbent position. The second step is to raise the legs,
maintaining the angle between them using the automatic motion of the
bed to avoid artefacts. The third step returns the patient to the semi-
recumbent position to ensure that the patient recovers the previous
haemodynamic parameters.

Recommendation: We suggest using the passive leg raise
test to guide fluid resuscitation in sepsis or septic shock in
resource-limited settings (2A). It is uncertain whether the pas-
septic shock, like in severe malaria or severe dengue. We sug-
severe falciparum malaria (1B). We also recom-
and not colloids for initial fluid resuscit-
tive leg raise test has predictive values in all types of sepsis and
ical setting. The use of dynamic
pulse pressure when performing a passive leg
raise test (1C) and suggest using changes in pulse pressure if
malaria. The latter could be a challenge in resource-limited settings
where beds are usually not easily adjustable. While it is best to use a
direct measure of cardiac output or stroke volume, this is fre-
quently impossible in settings in low-resource settings. A less
accurate but still acceptable approach is to detect changes in
pulse pressure. The test starts with an initial (non-invasive) blood
pressure measurement and after 60–90 s of passively raising the
legs the blood pressure measurement is repeated. A change in
the difference between the systolic and diastolic pressure >15% could indicate that the patient is fluid responsive.27

It remains uncertain whether the passive leg raise test has
comparable predictive values in various types of sepsis and sep-
tic shock, e.g., in severe malaria or severe dengue, as literature
is lacking. This could actually be seen as one major objection
against widespread use of the passive leg raise test in resource-
limited settings. This is also true for young children. So far only
one preliminary study suggests that a passive leg raise test is
helpful in predicting fluid responsiveness in children, but not in
those younger than 5 y of age.28

Rationale If it is decided that a patient is hypovolemic, it should
also be determined whether that patient is fluid responsive. The
Surviving Sepsis Campaign weakly recommends the use of dynamic
vs static variables like the passive leg raise test.4 A search of the li-
terature combining various search terms for ‘passive leg raise’ alone
and in combination with diverse search terms covering ‘sepsis or
septic shock’ and ‘resource-limited settings’ failed to identify any
investigation originating from resource-limited settings.

The method for performing the passive leg raise test is
important because it fundamentally affects its haemodynamic
effects and reliability.26 The test needs to be executed so that it
does not result in pain and anxiety, as this may influence the
results. Furthermore, a proper passive leg raise test consists of
lifting the bed at the foot end, not lifting the legs (Figure 2). The
latter could be a challenge in resource-limited settings where
The Fluid Expansion As Supportive Therapy (FEAST) trial in
children in sub-Saharan Africa with compensated septic shock,
of which 57% had severe falciparum malaria, showed a detri-
mental effect of saline bolus as well as albumin bolus therapy
compared with a more conservative fluid therapy.29 The study
supersedes earlier small studies suggesting a survival benefit of
albumin infusion over crystalloids in children with severe falcip-
arum malaria and severe sepsis.30,31

Three randomized trials in patients with dengue shock syn-
drome did not show better outcome parameters with (more
expensive) colloids vs crystalloid fluids.32–34 A quasi-randomized
study from the Philippines alternating the allocation of colloids
with crystalloids also did not show an additional benefit of
colloids.35

From the task force members’ experience, it is important
that in wards caring for critically ill patients, intravenous fluids
should be stockpiled so that they are immediately available for
emergency treatment, to save time and to prevent incurring
additional costs for the patient’s family.

Recommendations: We recommend that fluid resuscitation
should be initiated in patients with sepsis and suspected hypo-
1. universal goals
2. maximum reliability
3. which intravenous fluids
4. how much and how fast

Recommendations for fluid strategies

(3) Which intravenous fluids should be used for fluid resuscita-
tion in sepsis and septic shock in resource-limited ICUs?

Recommendation: We recommend crystalloid solutions as
the initial fluid of choice in patients with severe bacterial sepsis
or septic shock (1B) and recommend against the use of syn-
thetic colloid solutions (1B). We recommend the same for
patients with severe falciparum malaria (1B). We also recom-
end using crystalloids and not colloids for initial fluid resuscit-
tion (1B) in severe dengue with compensated shock, but there
is insufficient evidence to recommend fluid choices in severe
dengue with hypotensive shock. In order to avoid delays in initial
resuscitation, it is advisable that wards caring with
sepsis or septic shock stockpile crystalloid solutions for their
immediate availability to avoid delaying initial fluid resuscitation (UG).

Rationale There is a large body of literature from resource-
rich settings on the choice of fluids in severe sepsis and septic shock,
with a strong focus on sepsis caused by bacterial patho-
gen. The theoretical benefits of colloid solutions over crystal-
loids, with better retention in the intravascular compartment,
has not translated to better outcomes with colloids for the
treatment of severe sepsis or septic shock in randomized clinical
trials performed in resource-rich settings. In addition, synthetic
colloid solutions have shown important adverse effects, in particu-
ar nephrotoxicity with the use of starch solutions. Consequently
the Surviving Sepsis Campaign makes a strong recommendation
for the use of crystalloid solutions over colloids for fluid resuscita-
tion.1 A search for evidence originating from resource-limited set-
tings and for specific causes of sepsis or septic shock in these
settings, like malaria and dengue, resulted in seven additional arti-
cles.29–35
Early goal-directed therapy has since been shown to be effective in treating sepsis-induced hypoperfusion. This trial showed an alarming increase in mortality with bolus intravenous infusion in critically ill patients. The Surviving Sepsis Campaign recommends that in the resuscitation from sepsis-induced hypoperfusion, at least 30 ml/kg of intravenous crystalloid fluid be given within the first 3 h. A systematic search of the literature was performed combining the search terms ‘goal-directed therapy’ with ‘sepsis’ or ‘infection’ and ‘resource-limited settings’, yielding five additional articles originating from resource-limited settings.

The largest fluid trial performed in resource-limited settings is the above-cited FEAST trial in children. This trial showed an alarming increase in mortality with bolus intravenous infusion in critically ill children. There is an ongoing debate about whether mortality increased because of the development of pulmonary fluid overload that could not be compensated for by mechanical ventilation. A secondary analysis of FEAST exploring whether boluses may contribute most to excess deaths with rapid fluid resuscitation, at least as assessed by means of plasma lactate levels, yielded only two relevant articles originating from resource-limited settings. We largely follow the recommendations of the Surviving Sepsis Campaign, but provide additional recommendations mainly based on task force members’ experiences.

Vasopressors and inotropes have a narrow therapeutic window, necessitating accurate dosing. Continuous administration at exact doses is safeguarded preferably by automatic infusion with a syringe or infusion pump. Although less accurate, when syringe pumps are not available, these drugs can be diluted in normal saline and administered using a mechanical drop counter. Vasopressors are not generally available in hospitals with limited resources. Dopamine is more widely available, but reported best access in resource-limited settings is to epinephrine. We prefer dopamine to epinephrine, as epinephrine may cause lactate acidosis. In resource-limited settings, dobutamine is only available in selected regions, and stock outages of the drug are very common.

Titration of inotropes in resource-limited ICUs is a challenge, as assessed by means of plasma lactate levels is expensive, and is frequently not possible. Capillary refill time (<3 s) and the skin mottling score can be used to evaluate the effect of infusion of vasopressors and inotropes, but there is no documented evidence regarding efficacy or safety. And it should be noted that vasopressors can affect capillary refill time and skin mottling scores.
Conclusions

An international team of six physicians from resource-rich and -limited settings reported on a set of pragmatic recommendations for haemodynamic assessment and support in patients with sepsis and septic shock in resource-limited settings. The paucity of evidence from resource-limited settings and in specific types of sepsis and septic shock underscores the urgent need for rigorous trials, since efficacy and effectiveness of commonly used interventions in resource-rich settings can differ greatly in resource-limited settings.

Supplementary data

Supplementary data are available at Transactions online (http://trstmh.oxfordjournals.org/).

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References

1 Rhodes A, Evans LE, Alhazzani W et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45(3):486–552
2 Arabi YM, Schultz MJ, Salluh JIF. Intensive care medicine in 2050: global perspectives. Intensive Care Med 2017;43(11):1695–99.
3 Schultz MJ, Dunser MW, Dondorp AM et al. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med 2017;43(5):612–24.
4 Papali A, Schultz MJ, Dunser MW. Recommendations on infrastructure and organization of adult ICUs in resource-limited settings. Intensive Care Med 2017 Nov 20. doi:10.1007/s00134-017-4972-0. [Epub ahead of print]
5 Mer M, Schultz MJ, Adhikari NK. Core elements of general supportive care for patients with sepsis and septic shock in resource-limited settings. Intensive Care Med 2017;43(11):1690–4.
6 Dondorp AM, Hoang MNT, Mer M. Recommendations for the management of severe malaria and severe dengue in resource-limited settings. Intensive Care Med 2017;43(11):1683–5.
7 Thwaites CL, Lundeg G, Dondorp AM. Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings. Intensive Care Med 2016;42(12):2040–2.
8 Serpa Neto A, Schultz MJ, Festic E. Ventilatory support of patients with sepsis or septic shock in resource-limited settings. Intensive Care Med 2016;42(1):100–3.
9 Musa N, Murthy S, Kisson N. Pediatric sepsis and septic shock management in resource-limited settings. Intensive Care Med 2016;42(12):2037–9.
10 Schünemann H, Brozek J, Guyatt G, Oxman A eds. GRADE handbook. Handbook for grading quality of evidence and strength of recommendations using the GRADE approach. Updated October 2013. Available from: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html.
11 Hernandez G, Pedreros C, Veas E et al. Evolution of peripheral vs metabolic perfusion parameters during septic shock resuscitation. A clinical-physiologic study. J Crit Care 2012;27(3):283–8.
12 Limo A, Jansen TC, van Bommel J et al. The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. Crit Care Med 2009;37(3):934–8.
13 van Genderen ME, Lima A, Akkerhuis M et al. Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. Crit Care Med 2012;40(8):2287–94.
14 Hernandez G, Luengo C, Bruhn A et al. When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring. Ann Intensive Care 2014;4:30.
15 Ait-Oufella H, Bige N, Boelle PY et al. Capillary refill time exploration during septic shock. Intensive Care Med 2014;40(7):958–64.
16 Brunauer A, Kokofer A, Bataar O et al. Changes in peripheral perfusion rate to visceral organ perfusion in early septic shock: a pilot study. J Crit Care 2016;35:105–9.
17 Ait-Oufella H, Lemoine S, Boelle PY et al. Mottling score predicts survival in septic shock. Intensive Care Med 2011;37(5):801–7.
18 Ait-Oufella H, Joffre J, Boelle PY et al. Knee area tissue oxygen saturation is predictive of 14-day mortality in septic shock. Intensive Care Med 2012;38(6):976–83.
19 Coudray R, Jamet A, Frat JP et al. Incidence and impact of skin mottling over the knee and its duration on outcome in critically ill patients. Intensive Care Med 2015;41(3):542–9.
20 Akata T, Kanna T, Yoshino J et al. Reliability of fingertip skin-surface temperature and its related thermal measures as indices of peripheral perfusion in the clinical setting of the operating theatre. Anaesth Intensive Care 2004;32(4):519–29.
21 Rubinstein EH, Sessler DI. Skin-surface temperature gradients correlate with fingertip blood flow in humans. Anesthesiology 1990;73(3):541–5.
22 Thompson MJ, Ninis N, Perera R et al. Clinical recognition of meningococcal disease in children and adolescents. Lancet 2006;367(9508):397–403.
23 King D, Morton R, Bevan C. How to use capillary refill time. Arch Dis Child Educ Pract Ed 2014;99(3):111–6.
24 Postelnicu R, Evans L. Monitoring of the physical exam in sepsis. Curr Opin Crit Care 2017;23(3):232–6.
25 Hanson J, Lam SW, Alam S et al. The reliability of the physical examination to guide fluid therapy in adults with severe falciparum malaria: an observational study. Malar J 2013;12(1):348.
26 Monnet X, Teboul JL. Passive leg raising: a systematic review and meta-analysis of fluid responsive rules, not a drop of fluid! Crit Care 2015;19(1):18.
27 Cherpanath TG, Hirsch A, Geerts BF et al. Predicting fluid responsiveness by passive leg raising: a systematic review and meta-analysis of 23 clinical trials. Crit Care Med 2016;44(5):981–91.
28 Lu GP, Yan G, Chen Y et al. The passive leg raise test to predict fluid responsiveness in children—preliminary observations. Indian J Pediatr 2015;82(1):5–12.
29 Maitland K, Kiguli S, Opoka RO et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364(26):2483–95.
30 Maitland K, Pamba A, English M et al. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. Clin Infect Dis 2005;40(4):538–45.
31 Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. BMJ 2010;341:c4416.

32 Wills BA, Nguyen MD, Ha TL et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med 2005;353 (9):877–89.

33 Dung NM, Day NP, Tam DT et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis 1999;29(4):787–94.

34 Ngo NT, Cao XT, Kneen R et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis 2001;32(2):204–13.

35 Cifra HL, Velasco JN. A comparative study of the efficacy of 6% Haes-Steril and Ringer’s lactate in the management of dengue shock syndrome. Crit Care Shock 2003;6:95–100.

36 Rivers E, Nguyen B, Havstad S et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345(19):1368–77.

37 Andrews B, Muchemwa L, Kelly P et al. Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. Crit Care Med 2014;42(11):2315–24.

38 Baker T, Schell CO, Lugazia E et al. Vital signs directed therapy: improving care in an intensive care unit in a low-income country. PLoS One 2015;10(12):e0144801.

39 Jacob ST, Banura P, Baeten JM et al. The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study. Crit Care Med 2012;40(7):2050–8.

40 Andrews B, Semler MW, Muchemwa L et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial. JAMA 2017;318(13):1233–40.

41 Maitland K, George EC, Evans JA et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. BMC Med 2013;11:68.

42 Day NP, Phu NH, Bethell DP et al. The effects of dopamine and adrenaline infusions on acid-base balance and systemic hemodynamics in severe infection. Lancet 1996;348(8922):219–23.

43 Mahmoud KM, Ammar AS. Norepinephrine supplemented with dobutamine or epinephrine for the cardiovascular support of patients with septic shock. Indian J Crit Care Med 2012;16(2):75–80.

44 Pandey A, John BM. Capillary refill time. Is it time to fill the gaps? Med J Armed Forces India 2013;69(1):97–8.