



Current Challenges in the Management of Sepsis in ICUs in Resource-Poor Settings and Suggestions for the Future

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Marcus J. Schultz, Martin W. Dünser, Arjen M. Dondorp, Neill K. J. Adhikari, Shivakumar Iyer, Arthur Kwizera, Yoel Lubell, Alfred Papali, Luigi Pisani, Elisabeth D. Riviello, Derek C. Angus, Luciano C. Azevedo, Timothy Baker, Janet V. Diaz, Emir Festic, Rashaan Haniffa, Randeep Jawa, Shevin T. Jacob, Niranjana Kisson, Rakesh Lodha, Ignacio Martin-Loeches, Ganbold Lundeg, David Misango, Mervyn Mer, Sanjib Mohanty, Srinivas Murthy, Ndidiamaka Musa, Jane Nakibuuka, Ary Serpa Neto, NT Hoang Mai, Binh Nguyen Thien, Rajyabardhan Pattnaik, Jason Phua, Jacobus Preller, Pedro Pova, Suchitra Ranjit, Daniel Talmor, Jonarthan Thevanayagam, and C. Louise Thwaites

M. J. Schultz (✉) · A. M. Dondorp · L. Pisani
Mahidol University, Bangkok, Thailand

Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

M. W. Dünser
Kepler University Hospital, Johannes Kepler University, Linz, Austria

N. K. J. Adhikari
Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

S. Iyer
Bharati Vidyapeeth Deemed University Medical College, Pune, India

A. Kwizera · J. Nakibuuka
Mulago National Referral Hospital, Kampala, Uganda

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- Y. Lubell
Department of Intensive Care, Academic Medical Center, University of Amsterdam,
Amsterdam, The Netherlands
- A. Papali
University of Maryland School of Medicine, Baltimore, MD, USA
Division of Pulmonary and Critical Care Medicine, Atrium Health, Charlotte, NC, USA
- E. D. Riviello · D. Talmor
Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
- D. C. Angus
University of Pittsburgh, Pittsburgh, PA, USA
- L. C. Azevedo
Hospital Sirio-Libanes, São Paulo, Brazil
- T. Baker
Karolinska Institute, Stockholm, Sweden
- J. V. Diaz
California Pacific Medical Center, San Francisco, CA, USA
- E. Festic
Mayo Clinic, Jacksonville, FL, USA
- R. Haniffa
Mahidol University, Bangkok, Thailand
- R. Jawa
Stony Brook University Medical Center, Stony Brook, NY, USA
- S. T. Jacob
Liverpool School of Tropical Medicine, Liverpool, UK
- N. Kissoon · S. Murthy
British Columbia Children's Hospital, Vancouver, BC, Canada
- R. Lodha
All India Institute of Medical Science, Delhi, India
- I. Martin-Loeches
St. James's University Hospital, Dublin, Ireland
- G. Lundeg
Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia
- D. Misango
Aga Khan University Hospital, Nairobi, Kenya
- M. Mer
Johannesburg Hospital, University of the Witwatersrand, Johannesburg, South Africa
- S. Mohanty · R. Pattnaik
Ispat General Hospital, Rourkela, Odisha, India
- N. Musa
Seattle Children's Hospital, University of Washington, Washington, WA, USA
- A. Serpa Neto
Department of Intensive Care, Academic Medical Center, University of Amsterdam,
Amsterdam, The Netherlands
Medical Intensive Care Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil

NT Hoang Mai

Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam

B. N. Thien

Trung Vuong Hospital, Ho Chi Minh City, Vietnam

J. Phua

National University Hospital, Singapore, Singapore

J. Preller

Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

P. Pova

Nova Medical School, CEDOC, New University of Lisbon, Lisbon, Portugal

Hospital de Sao Francisco Xavier, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal

S. Ranjit

Appolo Hospitals, Chennai, India

J. Thevanayagam

Mzuzu Central Hospital, Mzuzu, Malawi

C. L. Thwaites

Nuffield Department of Medicine, Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK

1.1 Introduction

In many low- and middle-income countries (LMICs), with improved public health services like sanitation and immunization, the relative importance of curative care to improve health becomes more important. This includes care for sepsis, a major reason for intensive care unit (ICU) admission in LMIC. These patients will currently often be treated in general wards, but basic intensive care facilities are becoming increasingly available. The scope of the current review is limited to the ICU setting. ICUs in resource-restricted settings have to function with important limitations, including both infrastructure and materials and human resources. It is important to address economic aspects around the provision of relatively expensive intensive care in low-income countries. Most LMICs have tropical or subtropical climates, and causes of sepsis will often be different from high-income countries (HICs), where most sepsis guidelines have been developed. Because of the different settings and the different causes of sepsis, existing guidelines will need prudent interpretation. There is a broad research agenda around this, which is currently still hardly addressed. Finally, expansion of setting-adapted training will be important to improve ICU performance in LMICs.

In this review, written by a group of physicians from resource-poor and resource-rich ICUs in LMICs and high-income countries, respectively, who were involved in the development of a series of sets of recommendations for sepsis management in resource-poor settings as recently published [1–4], the estimated burden, pathogens,

and pathophysiology of sepsis are compared between resource-poor and resource-rich settings. The availability of critical care and guidelines and costs of critical care in LMICs are compared to that in high-income countries. Suggestions for future directions are provided.

1.2 Burden and Causes of Sepsis and Its Management

1.2.1 Disease Burden

While detailed information has been reported on the epidemiology and outcome of sepsis in HICs [5, 6], only scant systematically collected epidemiological data exist from LMICs [7, 8], despite that these countries carry about 80% of the global mortality caused by infections [9]. At present, the epidemiology of sepsis in LMICs can only be loosely estimated from the epidemiology of acute infectious diseases with a potential to cause sepsis captured in the “Global Burden of Disease” database [10–12]. This database reported important regional differences in the epidemiology of such acute infectious diseases (Fig. 1.1). For instance, while the majority of acute infections in resource-limited settings are acquired in the community [9], the incidence of nosocomial infections such as catheter-related bloodstream infections or ventilator-associated pneumonia is several fold higher in LMICs than in high-income countries like the United States [13]. Similarly, only few data on sepsis mortality in LMICs have so far been published. These suggest that sepsis-related mortality greatly varies among regions and countries according to their income level. The case fatality attributable to sepsis in HICs has been decreasing over the last decades to 30–40% [5, 6], whereas case fatality rates of up to 80% continue to be reported from resource-poor regions of the world [14–17].

1.2.2 Causative Pathogens and Pathogenesis

Although many bacterial pathogens causing sepsis in LMICs are similar to those in high-income countries, resistance patterns to antimicrobial drugs can be very different. It has been suggested that the high prevalence of multidrug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus*, extended spectrum beta-lactamase-producing bacteria, carbapenamase-producing *Enterobacteriaceae*, and *Mycobacterium tuberculosis*, contributes to the excess deaths observed in LMICs caused by invasive infections with these bacteria, particularly among infants [13, 18]. Five countries with the highest burden of under five deaths (China, Nigeria, Pakistan, India, and the Democratic Republic of the Congo) also have the highest neonatal deaths from antimicrobial resistance [19]. The problems with antimicrobial resistance and its implications for the treatment of sepsis in LMICs have been described before [4].

Whereas the majority of severe sepsis in HICs is caused by bacterial infections, in LMICs, many of which are located in the tropics, causes of sepsis also include

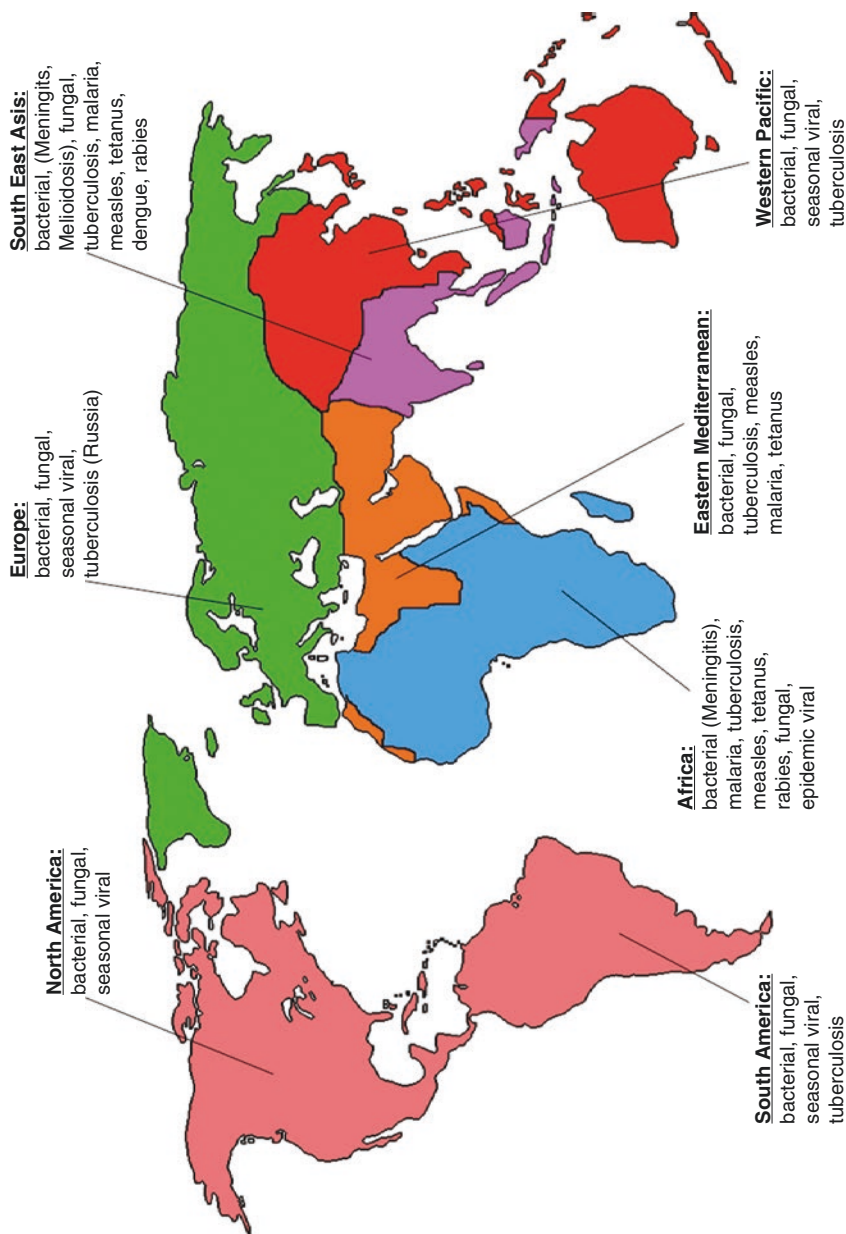


Fig. 1.1 Most relevant infectious diseases as reported by the Global Burden of Disease study stratified by the six World Health Organization regions. From [10, 11]

acute non-bacterial diseases, including protozoal diseases such as malaria, and viral diseases such as measles, dengue, or viral hemorrhagic fevers. The international literature mainly focuses on sepsis caused by invasive bacterial infections and the associated systemic inflammatory response [20, 21]. Therefore, non-bacterial causes are understudied, and the acquired knowledge on the pathophysiology and treatment of sepsis may not be generalizable to these other causes of sepsis [22].

Previous sepsis definitions put a large emphasis on the “dysregulated response of the host’s immune system” as the key element of the pathogenesis of sepsis [23, 24]. Although this will be generally correct, it ignores potential direct damaging effects of certain pathogens or pathogen products, which can in particular play a role in tropical diseases. For instance, in severe falciparum malaria, a blocked microcirculation resulting from the sequestered infected red blood cell biomass is a direct cause of vital organ failure [25]; and in dengue shock syndrome, virus proteins are thought to directly damage the glycocalyx lining the endothelium [26, 27]. Intervening in these pathophysiological pathways will obviously require therapeutic approaches different from those in bacterial sepsis.

1.2.3 Poor Availability of Critical Care

There is persisting substantial heterogeneity in ICU capacity around the world. In Europe and Northern America, the ICU capacity is between 5 and 30 beds per 100,000 inhabitants. In LMICs, the scarce data available show ICU capacities that are much lower, albeit quite variable [28]. For instance, in Asia the reported ICU capacity is only 0.3 beds per 100,000 inhabitants in Bangladesh, 2.4 per 100,000 inhabitants in Malaysia, 2.5 per 100,000 inhabitants in Sri Lanka, and 3.9 per 100,000 inhabitants in China [29], but in contrast 11.7 adult and pediatric ICU beds per 100,000 inhabitants in Mongolia [30]. Studies from several countries in sub-Saharan Africa reported as few as 0.1–0.2 ICU beds per 100,000 inhabitants [31, 32]. With the exception of Mongolia [30] and Latin-American countries [33], almost no data on the availability of dedicated pediatric ICU capacities have been published for resource-limited settings [34].

We tend to look at LMICs as if they are “uniform,” but this is a too simplistic if not naive approach. Within and between LMICs, there is an important heterogeneity in the availability of intensive care, resourcing of ICUs, quality of services, and case mix [35]. The rapidly expanding urban population in many LMICs will provide a challenge for the current urban ICU capacity because of the associated increase in case load [36].

Another problem in reporting ICU capacity is the lack of a commonly agreed definition of an ICU or ICU bed [37, 38]. The spectrum of how ICUs are staffed and equipped differs vastly between countries and regions. Table 1.1 summarizes published evidence and personal experience of the authors in an attempt to categorize different ICU structures worldwide. As surveys from various countries suggest, the availability of ICU-related material resources directly correlates with the countries’ income level and healthcare spendings [7, 31, 32, 39–43]. The shortage of medical

Table 1.1 Proposal for a categorization of intensive care units^a

Proposed categories	Category I—unrestricted	Category II—moderate restrictions	Category III—severe restrictions	Category IV—no formal ICU structure
Typical setting (not including private settings)	High-income countries	Higher-middle-income countries	Lower-middle and low-income (major cities) countries	Rural areas of low-income countries
Formal ICU structure/service	Yes	Yes	Partly	No
Availability of specifically trained physicians and nurses	Widespread	Irregular	Rare	Unavailable
Availability of ICU equipment (i.e., patient monitor, mechanical ventilator, renal replacement therapy)	Unrestricted	Moderate restrictions (i.e., irregular maintenance of equipment, limited availability of advanced treatment modalities such as RRT)	Severe restrictions (i.e., basic monitoring typically available, limited number of mechanical ventilators, widespread unavailability of advanced treatment modalities such as RRT)	Unavailable
Availability of ICU drugs and disposable materials	Unrestricted	Mild restrictions	Moderate restrictions	Severe restrictions

Abbreviations: ICU intensive care unit, RRT renal replacement therapy

^aThe categories proposed here should not be seen as definite, but merely should serve as a starting point of future thinking

professionals specifically trained in the care of acutely and critically ill patients is another widespread and serious challenge for ICU services in many LMICs [31, 32, 39–42]. A notable exception to this is well-staffed and well-equipped ICUs in private healthcare facilities. Such services can typically be found in some HICs and LMICs, but these usually remain only accessible for those who can afford it.

The increasing but still low ICU capacity in poorer regions [44] implies that access to ICU services for critically ill patients is usually severely limited. This results in frequent triage decisions [32], which likely increases preventable mortality [45]. Even though costs of care in ICUs of resource-limited settings are only a fraction of those encountered in HICs [46], expenses for ICU care are usually to a large extent covered by the patient's family and relatives in LMICs. Unwanted consequences can be denial or refusal of ICU admission of poor patients, but also the premature withdrawal of lifesaving interventions [47, 48]. In other instances, costs

of care for a critically ill patient, who may eventually die, can exceed the limited budget of many families leaving them with high debts or even causing private bankruptcy.

1.2.4 Incomplete and Unadjusted Guidelines

The principle of “evidence-based medicine” is equally important in resource-limited as in resource-rich settings. Development of local evidence is important, since case mix and causes of sepsis, but also available infrastructure and facilities, are essentially different from those in HICs. Resource-limited ICUs are frequently limited in the availability of equipment, laboratory support, and skilled physician and nursing staff. As a result, recommendations on sepsis management in resource-poor settings, such as those developed by the *Global Intensive Care Working Group* of the European Society of Intensive Care Medicine (ESICM) [49], differ in several aspects from the Surviving Sepsis Campaign guidelines, which were developed in high-income settings [50]. Obvious examples include targeting strict blood glucose levels with insulin, which can be safe with frequent and reliable blood glucose monitoring, while it is a dangerous strategy when the effects of insulin titrations are determined infrequently or not at all. Other modifications in recommendations for sepsis management could result from differences in the availability of and indications for fluids in sepsis patients between resource-rich and resource-poor settings, but also the cause of sepsis (see also Box 1.1).

Box 1.1: Availability of and Indications for Fluids in Sepsis Patients Differ Between High-Income Countries and Low- and Middle-Income Countries

Intravenous infusion of fluids is a key intervention in patients with sepsis as this syndrome frequently leads to intravascular hypovolemia from extravasation due to capillary leaking.

RESOURCE-RICH SETTINGS: physicians and nurses, independent from each other, have free and unlimited excess to fluids for intravenous infusion, which may facilitate a “too liberal” fluid approach leading to “overzealous” fluid resuscitation known to be associated with worse outcome of sepsis patients.

RESOURCE-POOR SETTINGS: usually there is a shortage of fluids for intravenous fluids, decision on the amounts of fluids to be given is restricted to attending physicians and not nurses, and the type of fluid chosen may depend on its price (e.g., dextrose-containing fluids, such as 5% dextrose or 10% dextrose, are cheap and thus readily available, opposite to crystalloid solutions); inadequate resuscitation, either because of too low or too late given or wrong fluids infused, may worsen outcome of sepsis patients.

FLUID THERAPY IN BACTERIAL SEPSIS: the recommendations on fluid therapy in sepsis patients are largely built on evidence coming from randomized controlled trials in patients in *RESOURCE-RICH SETTINGS*, where most patients do have *BACTERIAL SEPSIS*.

FLUID THERAPY IN NON-BACTERIAL SEPSIS: interestingly, randomized controlled trials including patients with severe falciparum malaria or dengue shock syndrome suggest more restricted fluid therapy than recommended for bacterial sepsis to be better. One major difference between *BACTERIAL SEPSIS* and *NON-BACTERIAL SEPSIS* is that fluid bolus resuscitation is not recommended in hyperlactatemic patients with severe falciparum malaria who are not hypotensive. Also, in dengue shock syndrome, proper fluid management is pivotal to ensure a good outcome; fluid therapy in dengue shock syndrome should ensure adequate circulating volume to support tissue perfusion, but avoid overfilling, which will cause interstitial edema, which is in particular harmful in the lung.

Despite the importance of building “local” evidence, many aspects of existing guidelines and basic principles of good critical care are universal. Access to adequate information has improved massively in this cyber age, and several courses (such as the *BASIC for Developing Healthcare Systems* courses developed by the Chinese University of Hong Kong, Hong Kong, China, and *Médecins Sans Frontières*) are available. Theoretical knowledge of specialist doctors in developing countries is often impressive, but translating this into practical implementation can lag behind, which is an important scope for training. Training should not only be for ICU physicians but also for nurses and other clinical personnel. It will be important that education on sepsis management does not focus only on ICU staff but includes medical schools, nursing schools, and training of other health workers, as many sepsis patients in LMICs receive treatment outside an ICU. “Train-the-trainer” models and fostering local champions for positive change are important to sustain improvements of care.

1.3 Costs of Care in Sepsis

1.3.1 Expensive but Likely Cost-Effective Critical Care

The vast resources consumed by ICUs, up to a staggering 1% of total gross domestic product in the United States [51], demand their subjection to explicit economic cost-benefit considerations [52]. The literature from high-income settings has indeed expanded over the past decade, demonstrating that many critical care interventions offer significant health returns with costs per quality-adjusted life year (QALY) gained well below a threshold of US \$50,000, indicative of a cost-effective intervention in this context.

For countries in which more basic services are still relatively undeveloped, it might be questioned whether investment in ICUs should take priority over the strengthening of lower tiers of the healthcare system [53]. Irrespective of these considerations, the reality is that in many growing economies, ICUs are increasing in number [44], with virtually no evidence regarding the cost-effectiveness of their services.

1.3.2 Costs of Critical Care Among Regions

One approach is to consider the evidence from HICs, with a much lower willingness to pay the abovementioned threshold. Applying a threshold of US \$4000 per QALY gained [54] suggests that numerous ICU interventions and those for sepsis in particular [55–61] are likely to be cost-effective in ICUs in LMICs (Table 1.2). For several reasons these cost-effectiveness ratios might be conservative in the context of LMICs. First, the cost of ICUs in these countries is much lower than in HICs. The two largest standardized multicountry reviews of critical care costs in high-income settings estimated the cost per ICU day ranging from US \$850 to US \$3400 in 2015 [63, 64], with labor being the dominant cost driver (61% and 67%, respectively). The proportional difference in labor costs between high-income countries and LMICs will be similar to or higher than that of their respective gross domestic product per capita [65]. This alone implies that the critical care costs in LMICs will be less than a third that in HICs. Other costs, such as laboratory services (10% of total critical care cost [64]), are also likely to be far lower for similar reasons, as well as drug costs and cost-saving practices such as recycling of consumables [66]. In one of the few costing analyses of an ICU from a LMIC, the total cost per ICU admission day in India was estimated at just over US \$200 [67], between approximately 5 and 20% that for HICs.

However, also the absolute financial outlay per intervention multiplied by the number of interventions is important to consider, in particular in LMICs. Even in a wealthy country with a high threshold, its tolerance depends exquisitely on the number of times it must spend the money, especially if up-front costs are high. In other words, an intervention might appear cost-effective, but if it would have to be applied to a massive portion of the public, the costs would still be perceived as financially impossible. This also requires there is an effective system of triage in place to see that these interventions are offered to patients who are most likely to benefit, at times a challenge in LMICs.

Finally, we are uncertain whether applying a threshold of US \$4000 per QALY gained is one that could be promoted or generalized, as there is a large intra- and inter-region variation in resources. Country- and ideally region-specific currency conversions/purchase power parity comparisons should be made.

Table 1.2 The cost-effectiveness of interventions for the management of severe sepsis

Author, year [Reference]	Cohorts (country)	Intervention	Conventional	Cost/QALY (in 2015 US \$)
Huang et al. 2007 [57]	Monte Carlo simulation of patients with sepsis undergoing EGDT beginning either in the ED or ICU (USA)	EGDT in ED or ICU	Standard care	\$3506–8953
Talmor et al. 2008 [61]	Prospective cohort study of patients treated with an integrated sepsis protocol compared to controls (USA)	Integrated sepsis protocol	Standard care	\$20,265 (2015)
Lehmann et al. 2010 [60]	Monte Carlo simulation of sepsis episodes in ICU patients with use of PCR with cultures to identify the causative organism and initiate tailored antibiotic therapy (EU)	PCR and cultures	Traditional cultures only	\$3798
Karlsson et al. 2009 [59]	Prospective cohort study of sepsis patients admitted to the ICU who were followed for 2 years (Finland)	ICU care for severe sepsis	Standard care	\$2664
Jones et al. 2011 [58]	Prospective before-after clinical trial to establish the initiation of EGDT in the ED prior to transfer to ICU for newly admitted sepsis patients (USA)	EGDT for sepsis in ED	Standard ED care for sepsis	\$6283 (2015)
Suarez et al. 2011 [62]	Prospective before-after clinical trial to assess the impact of an educational program on adherence to “Surviving Sepsis Campaign Guidelines” (Spain)	Surviving sepsis protocol for severe sepsis	Standard care	\$7810 (2015)
Assuncao et al. 2014 [55]	Prospective case-control analysis of patients treated with EGDT vs. standard care (Brazil)	EGDT	Standard care	Dominant
Harrison and Collins 2015 [56]	Markov model assessing cost-effectiveness of PCT as a diagnostic tool for bacterial infection in ICU patients (USA)	PCT	Standard diagnostic techniques	Dominant

Abbreviations: EGDT early goal-directed therapy, ED emergency department, ICU intensive care unit, PCR polymerase chain reaction, PCT procalcitonin

1.3.3 Benefit of Critical Care Among Regions

The mean age of adult patients admitted to ICUs in HICs is consistently higher than those reported in LMICs. For example, in European ICUs, the mean age of adult admissions is typically 55–66 years, much higher than the median age of 34 years in a Rwandan ICU [68], the mean age of 32 years in one of the few ICUs in Uganda [1], and the median age of 37, 51, and 49 years in ICUs in Bangladesh, Nepal, and India [69]. Although not specified for admission diagnoses, it likely also reflects the younger age of sepsis patients. This can be taken as an argument to invest in better intensive care to save these young lives from an in principle treatable disease. Also, in LMICs where social security networks are usually lacking, the loss of an individual's economic activity has far more extensive economic consequences for the families involved.

By generalizing the evidence from HICs and considering the lower costs and higher potential gains, there are strong indications that a wide range of critical care services are likely to be cost-effective in LMICs. Unfortunately, there is a dearth of evidence directly from these settings to confirm this. The only economic evaluation of an ICU in Bosnia and Herzegovina concluded that critical care was highly cost-effective in their setting [46]. A study from Brazil showed that the implementation of a sepsis management protocol was associated with an absolute reduction of 18% in mortality and with cost savings [55].

1.3.4 Impact of Certain Interventions Among Regions

Despite these suggestions that a broad range of ICU services could be cost-effective in LMICs, there is also reason for caution. First, some interventions are likely to have a much lower impact in poorly functioning environments than they might have in resource-rich settings. For example, invasive monitoring in an ICU with poor basic infection control could result in more harm than benefit. For this reason it is imperative that basic standards of care are in place prior to introduction of costly interventions whose effect might otherwise be compromised. Training programs to improve the general quality of care that require no costly interventions have been shown to have beneficial effects [69]. Second, while hypothetically cost-effectiveness should correspond with affordability, in LMICs where health systems are often fragmented and divided between the private and public sector and an abundance of vertically funded health programs, this is often not the case. It is imperative therefore that only interventions with modest budgetary impacts are shortlisted for consideration and those that have the greatest beneficial effects, with the lowest incremental costs, are selected for implementation. Some such low-cost approaches have been identified and should be prioritized for evaluation. Better surveillance systems for local etiologies of sepsis and antimicrobial susceptibility patterns have been recognized as a key requirement for improving the management of sepsis and critical care [4], and a modeling-based economic evaluation supported the notion that this is likely to be highly cost-effective [70].

Likewise, the development and adaptation of LMIC-specific risk prediction models have been shown to potentially outperform models widely used in high-income settings like the frequently used Acute Physiology and Chronic Health Evaluation Score and the Simplified Acute Physiology Score [68], which might not even be feasible in many ICUs in LMICs. The same is true for scoring systems in children, and scoring systems that are context relevant should also be explored because the Predicted Risk of Mortality may underpredict mortality [71].

Critical care in general and a subset of specific interventions can be an efficient use of scarce resources in LMICs. But despite the aforementioned lower costs, an ICU admission, e.g., in India, would most likely represent a catastrophic expenditure consuming over half the mean annual household income [44, 67] (see also: Box 1.2). As such facilities expand in LMICs and inevitably consume increasing resources, it is imperative for health authorities to ensure these offer affordable and cost-effective services while monitoring and continuing to seek opportunities to improve the quality of critical care and their efficiency at low cost. This was exemplified by the United Kingdom in the late 1990s, where a countrywide initiative to transform and modernize critical care was associated with a 10% reduction in mortality at lower cost increases than would otherwise be expected [72].

Box 1.2: Critical Care Expenditure in Indian Hospitals

In India critical care services are offered in four broad types of hospitals, with variable reimbursements. Variable reimbursements potentially lead to a great diversity in care of the critically ill, especially those who tend to have an extended ICU stay (i.e., longer than just a view days).

GOVERNMENTAL hospitals: the ICU bed, ventilation, and basic medications may be free of costs, but patient will need to spend out of pocket for expensive medications like certain antibiotics and disposables and for the family to stay in a distinct place (far) away from their homes. Often in a few days, they will exhaust their meager finances after which their care will be compromised.

PUBLIC CHARITY TRUST hospitals, including hospitals of private medical colleges: these hospitals have a mandate to provide free treatment to patients below the poverty line. In addition, these hospitals also offer concessional treatment under various governmental insurance schemes for poor patients that, however, are mainly utilized for surgical patients and short-stay patients like myocardial infarction and stroke. The insurance offered for sepsis is very meager and cannot cover more than the first few days in ICU. Patients thus will need to spend out of pocket for expensive medications like certain antibiotics and disposables and for the family to stay in a distinct place (far) away from their homes.

PRIVATE CORPORATE hospitals: these will treat affording patients either paying out of pocket or through some form of insurance. Except for

the rich and very rich, in a week or two, such patient will exhaust their finances and will then either be transferred to *GOVERNMENTAL* hospitals or *PUBLIC CHARITY TRUST* hospitals. These transfers however are not easy given scarcity of beds. Public charitable hospitals will generally have an admission policy that will discourage patients that are deemed unsalvageable or may require some form of limitation of therapy. *GOVERNMENTAL* hospitals have to accept such patients, but here the bed crunch is often more severe. This leaves patient and caregivers in a very difficult position and may lead to withdrawal of care or discharge against medical advice.

Smaller *PRIVATE NURSING HOMES*: these may offer critical services for selected patients, but this too follows a similar trajectory as that of the *PRIVATE CORPORATE* hospitals, i.e., once patients' finances are exhausted, they need to be transferred.

1.4 Sepsis Research in Resource-Limited Settings

1.4.1 A Yet Largely Untouched Research Agenda

With only 1.7% of all biomedical research publications originating in LMICs [73], and a likely even greater disparity in critical care [44], both the needs and the opportunities for critical care research are vast. Recent rigorous attempts to quantify the global burdens of sepsis, infection, and respiratory failure confirm a profound lack of epidemiologic critical illness data from LMICs, with the only reliable data limited to single-center descriptions [68, 74–77]. The *International Severe Acute Respiratory and Emerging Infection Consortium* (ISARIC), the *Global Intensive Care Working Group* of the ESICM, and the Mahidol Oxford Research Unit in Bangkok, Thailand, are three examples of groups working to create the infrastructure for global epidemiologic data on critical illness, for use both as baseline data at regular intervals and in preparation for disease outbreaks [78].

Research on infectious diseases that lead to critical illness are perhaps the most successful areas of investigation thus far, with impressive scientific advancements in diseases such as malaria, tuberculosis, and melioidosis [79–81]. Defining and testing quality metrics are an area prioritized in both critical care and global public health [82], but quality improvement in resource-limited ICUs remains largely unexplored [44, 83]. The latter requires some ability to benchmark ICUs with severity of illness scores, also a nascent area of study [68]. Research into medical education models like the *Human Resources for Health* program in Rwanda [84], decision support tools like the *Checklist for Early Recognition and Treatment of Acute Illness* (CERTAIN) [85], and *Vital Signs Directed Therapy* [86] could help in better defining how to optimize knowledge acquisition and application for providers in resource-limited settings.

1.4.2 Challenges with Research in Resource-Restricted Settings

The realities of restriction in resources interact to create complex challenges to producing quality critical care research. Many short-term multisite epidemiologic studies depend on individual sites to participate without funding for the perceived minimal data collection burden. However, staff at resource-constrained sites often cannot spare even the short-term investment required to participate, and “standard” clinical data such as arterial blood gas analyses and chest radiographs are often not available at these sites [76, 78]. Likewise, multicenter clinical trials are significantly more expensive to perform in resource-limited settings since baseline clinical or analytic infrastructure of any sort cannot be assumed. Efforts to build resource capacity in research and to ensure fair authorship opportunities also mean that research has two resource-intensive and sometimes competing goals: that of developing local researchers without prior training and that of producing high-quality research. An unintended consequence of (appropriate) increasing involvement by local institutional review boards is that lack of staffing and experience may lead to unnecessary delays in research approvals. These resource barriers to collecting epidemiologic data are exacerbated by the fact that “critical illness” is not a laboratory-defined condition but rather one that is often defined by the expensive resources used to treat it [28, 87].

Ethical considerations are complex as well. All participants in resource-limited settings must be considered potentially “vulnerable” populations due to extreme need and lack of health or research literacy. Deciding where equipoise exists for interventions proven to work in high-resource settings in settings of low resources is difficult. Asking the question, “How do we do this better given limited resources?” uncomfortably raises the question “How do we increase resources and to what extent are we obligated to do so?” Ethical considerations also include relationships between local and foreign researchers, the latter who often bring financial and experiential resources leading to unequal power dynamics and potential for abuse [88]. Allowing lower standards for publication for research originating in low-resource settings has been considered in order to decrease some of the publication bias toward resource-rich settings; however, it is not at all clear that publishing poor-quality research that could impact clinical care is ethical or advisable.

1.5 Suggestions for the Future

1.5.1 Better Definition of Sepsis

The latest sepsis definition [89], which refers to sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, better reflects the fact that sepsis can complicate any serious acute infection. As pointed out earlier, direct damaging effects of the pathogen itself or its products can sometimes be the main process. Consequently, research on sepsis treatment should not focus only on immunomodulating strategies in bacterial sepsis but also on faster illumination of

the pathogen and its products, which could be in particular relevant in certain non-bacterial causes of sepsis like falciparum malaria, cryptococcal, and various viral infections.

Another unmet need is to validate the various definitions for sepsis in more varied populations, like children in LMICs, adults in LMICs, and areas where the causative pathogens of sepsis differ from Western countries where the present definitions have been developed.

1.5.2 Better Research Infrastructures and Planning

Experience, resources, and human power are critical for building evidence, which are not routinely available in resource-poor settings. The global critical care community should help building local clinical research capacities and contribute to obtaining adequate funding. Engagement of a variety of stakeholders, including local intensive care societies, healthcare authorities (e.g., ministries of health), and universities, will be crucial in this respect [90]. There are large funding bodies, such as the Wellcome Trust, that support several efforts, but additional funds are clearly needed. Teaming up of researchers from established groups in HICs with local groups in resource-limited settings has proven a good model, provided equal and reciprocal relationships are guaranteed. Formulating essential topics for research will be important and could benefit from increased networking between critical care physicians from developing countries. This would also foster research networks needed to perform adequately powered clinical trials. Requirements for quality clinical research are not necessarily available in many LMICs, with often little research infrastructure or human resources for research available. Hospitals and their doctors can be overburdened by their service delivery tasks, leaving little room for research. Offering a career path to clinical research physicians could free up manpower for this important aspect of improving evidence-based critical care. Priority settings and governance regarding financial resources for research and implementation projects will become extremely important. Also, local institutions, including ethical review boards, should help create an enabling environment for research benefiting the local population, and not promote unnecessary barriers, which is now at times the case.

1.5.3 Obtaining Relevant Evidence and Adapting Guidelines

Obtaining local intelligence on the most important causes of sepsis and the resistance patterns of the infecting microorganisms is crucial to guide local empirical antimicrobial treatment. Since microbiological capacity is often lacking in hospitals in LMICs, research collaborations could help obtaining this evidence from strategically located sentinel study sites.

We need additional recommendations for those interventions not yet covered in the published guidelines. Multicenter trials assessing clinical efficacy and

effectiveness of new interventions and interventions known to be effective in resource-rich settings are sorely needed, given differences in epidemiologic and treatment contexts [44]. The Fluid Expansion As Supportive Therapy (FEAST) trial on fluid resuscitation in febrile African children with shock demonstrates that these trials are feasible and may yield unexpected results [91]. Networks of critical care researchers are increasingly established in more resource-limited areas of the world, which could lead to additional studies of this kind [44]. Beyond these broad areas of research, specific subtypes deserve special attention in resource-limited settings. Social determinants of disease and barriers to care are of particular relevance to all research in resource-limited settings including intensive care [82]. While cost-effectiveness analyses are arguably important in all environments without infinite resources, their need is more acute in places with fewer resources to allocate [92]. Locally adapted prediction models can help ensure that interventions are targeted in a cost-effective manner.

Another important area for critical care research is on developing templates for expanding urban ICU capacity in fast-growing cities [36]. Setting-specific guidance, instead of country-specific guidance on how to build and equip an ICU probably, is an additional and substantial area of research.

Finally, research on the process whereby scientific knowledge is translated into improved quality of care, “global health delivery science,” gets at the immediate challenge in patient care in resource-poor settings, the fact that so much of what is known is not implemented effectively [82].

1.5.4 Opportunities

While the challenges are daunting, the opportunities are similarly impressive. Outbreaks like Ebola have increased the drive for intensive care research in resource-limited settings both by demonstrating how critical illness in these settings impacts people in resource-rich settings and by highlighting the need for improved critical care capacity in all areas of the world [93]. Interest in and funding for global health have increased steadily over the last few decades, such that career path and funding opportunities for HIC researchers are better than ever before. Researchers from resource-limited settings now also have opportunities for high-quality training and mentorship through programs, for example, through the Wellcome Trust or the UK “Medical Research Council” schemes and the American Thoracic Society’s “Methods in Epidemiologic, Clinical, and Operations Research” (MECOR) program [94].

An example of building a research structure is one from India, where the Indian Society of Critical Care Medicine initiated a “cloud-based database” called “Customized, Health in Intensive care, Trainable Research, and Analysis (CHITRA)” (<http://www.isccm.org/chitra.aspx>).

Finally, LMICs and HICs could mutually benefit from their research agendas; HICs also gain from more LMIC research. For example, LMIC considerations about direct pathogen effects could, in turn, generate better critical thinking about

sepsis, from which both HICs and LMICs gain. Similarly, technologic innovation under resource constraints can yield gains for all. Critical care could be ripe for this at times called “frugal innovation” or “reverse innovation” concept [95]. Also, in our personal experience [69], nurses from HICs who have worked in LMICs, and even for a short time, are more cost-conscious than their colleagues.

1.6 Conclusions

Strategies to improve the quality of sepsis management in resource-poor settings require consideration of disease-specific and setting-specific factors and meticulous evaluation of the best way to adapt and deploy quality improvement initiatives. Critical care, including sepsis management, is expensive but likely cost-effective in LMICs, but we need to better understand what the true financial impact of critical care is, both at a macro- and micro-economy level. Sepsis management in resource-limited settings is a largely unexplored frontier with a clear mandate and exciting opportunities for impact.

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