

Neglected Diseases

Strategies to Reduce Mortality from Bacterial Sepsis in Adults in Developing Countries

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Sepsis is a progressive injurious process resulting from a systemic inflammatory response to infection [1]. In developed countries, sepsis is an important cause of mortality: in the United States alone, up to 750,000 people annually suffer from severe sepsis—mostly bacterial in aetiology—of whom 29% may die [2,3]. Unfortunately, data on bacterial sepsis in developing countries are notably lacking, particularly in adults. Estimates of the burden of lower respiratory tract infections, meningitis, and “other infections”, of which a significant proportion are associated with severe sepsis, show that the majority of deaths and disability-adjusted life years lost occur in low-income countries (Figure 1) [4]. Additionally, severe sepsis is likely to complicate a varying proportion of cases of malaria, HIV/AIDS, diabetes, maternal conditions, and cancer deaths globally.

The standard of care varies significantly across lower- and middle-income developing countries, but published reports suggest that outcomes are poor even at major hospitals [5–10]. Melioidosis, a serious tropical infection caused by *Burkholderia pseudomallei* that often presents with sepsis, is endemic in a region containing both high- and low-income countries [11]. Outcomes vary significantly: the case fatality rate for melioidosis is higher in Thailand (40%–50%) than in Australia (10%–20%) [11–13], and the case-fatality rate for melioidosis with severe sepsis is approximately 50% in Singapore compared with 90% in a Thai clinical trial [14,15]. The burden of disease and case fatality of patients with melioidosis in less developed countries such as Cambodia and Myanmar are unknown. Although melioidosis is not common outside of southeast Asia, extrapolating this experience suggests that the outcomes from all-cause bacterial sepsis in underdeveloped regions are likely to be poor.

The recently updated “Surviving Sepsis Campaign” guidelines have been widely disseminated in the developed world as a model of optimal sepsis management [16]. Although there has been some controversy regarding the recommendations and the development of the guidelines [17–19], most interventions based on improving early management of septic patients are less controversial. Crucially, most of the studies on which these recommendations are based were undertaken in the developed world and may not be applicable to the majority of the world’s population who live in poorer regions. The purpose of this paper is to highlight the paucity of epidemiological or management data on bacterial sepsis in the developing world, discuss current management approaches to sepsis in adults, and examine how clinical

The Neglected Diseases section focuses attention either on a specific disease or describes a novel strategy for approaching neglected health issues in general.

Summary Points

- The burden of sepsis is understudied but likely to be high in developing countries.
- Most previous studies have been disease-specific rather than syndrome-focused.
- The recently updated “Surviving Sepsis” guidelines have defined the standard of care for patients with severe sepsis in the developed world but do not incorporate the realities of health care in resource-constrained settings.
- A focus on early management of severe sepsis, including fluid management, blood pressure control, timely administration of antibiotics, and source control, is likely to be the most cost-effective intervention for critically ill, septic patients in resource-constrained settings. The efficacy of particular strategies of care needs to be evaluated in clinical studies.
- An integrated programme of management for adults, which includes training for health care workers on the prevention, recognition, and management of severe sepsis, is required.

sepsis management guidelines could be best adapted to provide improved care at low cost in under-resourced regions. We use the term “developing country” to refer to lower- or middle-income countries as defined by the World Bank [20].

Identification of Sepsis

Interventions performed soon after diagnosis of sepsis in developed regions have been shown to improve survival [21,22], and in developing countries, interventions to identify

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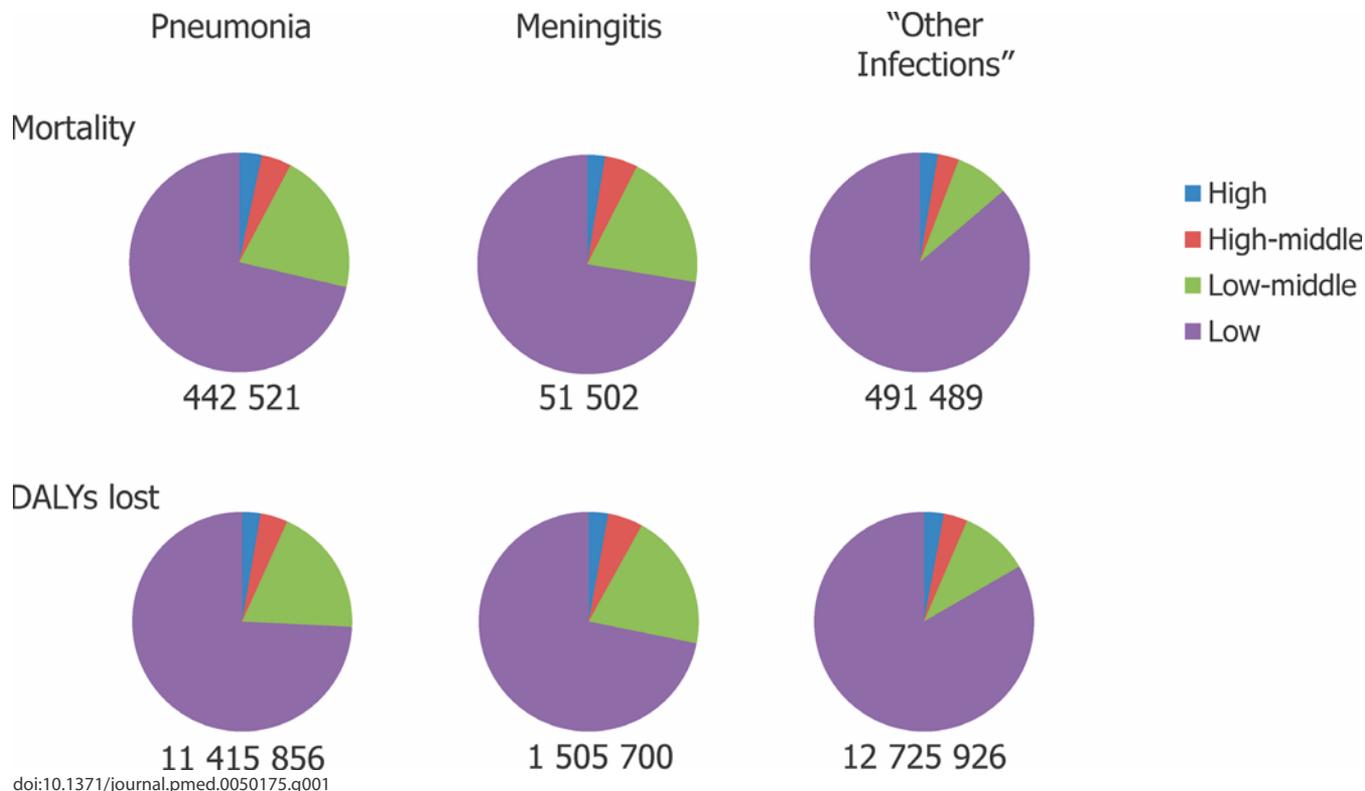
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Figure 1. Mortality and Disability-Adjusted Life Years (DALYs) Lost in Adults 15–60 Years Old in 2002 for Three Selected Indicator Diseases, by World Bank Income Level [4]

and treat pneumonia in children reduce mortality [23]. Thus, prompt identification of sepsis in developing countries is an essential component of any management strategy. Most studies of infection have focused on specific diseases, but sepsis itself is a clinically recognisable syndrome despite its heterogeneous causes. From a practical standpoint, sepsis is largely a clinical diagnosis [24], and implementation of strategies to promote recognition of sepsis as a clinical syndrome should be feasible even in the most resource-challenged areas where supportive radiographic imaging or laboratory measurements are not available. Education of health care providers about sepsis is critical to enhance the early identification of sick patients and may help facilitate transfer to available health care facilities. Simple algorithms tailored to local medical capacities that comprise the basic components of sepsis, such as diagnosed or suspected infection and the systemic manifestations of infection, may be useful.

Initial Treatment of Sepsis

Volume resuscitation is a well-established initial therapy of sepsis. Many studies have demonstrated that tissue perfusion in sepsis is partly impaired by hypovolaemia [25,26], and patients may have substantial fluid deficits requiring 6–10 l within the first 24 hours [21,27]. Guidelines suggest that hypotensive patients should receive an initial challenge of 20 ml/kg or boluses of 500–1000 ml of crystalloid with ongoing monitoring of volume status [16,28,29]. Observational evidence suggests that aggressive fluid resuscitation was associated with decreased early mortality from typhoid with ileal perforation in a rural African hospital [30].

Although albumin is at least as effective as crystalloids for volume resuscitation in sepsis, the latter is cheaper and more

widely available [31]. Judicious enteral fluid loading with standard oral rehydration solution has been used in other forms of hypovolaemia, but is as yet untested as a strategy in sepsis [32,33]. In severely compromised patients, oral fluids may be associated with a risk of pulmonary aspiration and are less likely to be effective with severe intravascular hypovolaemia. Invasively measured endpoints of fluid resuscitation have been defined [28], but clinical endpoints such as blood pressure and heart rate measurements, skin colour and capillary refill, mental status, or urinary output are the most feasible measures for monitoring in underdeveloped regions. Central venous access, where available, may be helpful for monitoring of central venous pressure and administration of vasopressors. Simpler non-invasive devices such as tissue perfusion monitors may be more practical but are not yet used widely [33].

Because septic shock is often characterised by inappropriate peripheral vasodilation, initiation of vasopressor therapies is indicated for persistent hypotension following fluid loading [16,34]. Although norepinephrine and (supra-renal dose) dopamine are accepted first-line agents [16,28], both may be associated with extravasation-related tissue necrosis if infused into a peripheral vein when central venous access is not possible. Accurate titration of intravenous vasopressors is also problematic in the absence of infusion pumps. Finally, non-invasive monitoring of blood pressure may be less accurate than intra-arterial blood pressure monitoring [16]. We have identified very few studies of non-intravenous vasopressor agents, such as oral midodrine [35], yet conceivably such therapies may play a role in sepsis management when intravenous medications are not feasible.

Haemodynamic optimisation measures in the resuscitation of ill septic patients often require extensive nursing and medical resources. An invasive goal-directed haemodynamic optimisation therapy approach to early sepsis management, while effective, has proven challenging to implement even in large hospitals in the United States, and is not practical to consider in this form for health care facilities in most developing settings [21,36]. Nonetheless, in regions where basic sepsis therapies exist yet early management is suboptimal, enhanced care could be achieved with simple, clearly defined fluid resuscitation and blood pressure management protocols, incorporating clinical endpoints and non-invasive tools if available. In areas where paramedical staff are available, simply engaging an assistant to observe patient status may be a cost-effective substitute for electronic monitoring. In better staffed facilities, designation of a dedicated nurse for at least the initial resuscitation period may be beneficial. However, more studies are required to determine optimal fluid resuscitation strategies where invasive haemodynamic monitoring and fall-back therapies (such as mechanical ventilation and dialysis) may not be available.

Antibiotic Regimens

The timely and appropriate use of antibiotics in the early management period is associated with survival from sepsis and pneumonia [22,37]. A potential barrier to the formulation of an effective empiric antimicrobial regimen is that the spectrum of bacterial pathogens in the tropics is often diverse. In one study in Kenyan children, 16 individual pathogens, each of which accounted for less than 10% of cases, accounted for over a third of bacteraemias [38]. Similarly, in a study of adults in Nepal, no single pathogen accounted for more than 13% of patients where a pathogen was identified [39].

Many regions do not have access to diagnostic microbiology laboratories, so the causes of sepsis and their susceptibility profiles may not be known. The list of common bacterial pathogens may also show significant variation, even between neighbouring countries. An example of this is between the adjacent countries of Thailand and Laos. In northeast Thailand, common causes of community-acquired sepsis include *Staphylococcus aureus*, pneumococci and other streptococci, *Escherichia coli* and other Enterobacteriaceae, *Pseudomonas* spp., and *B. pseudomallei* [40], as well as leptospirosis, scrub typhus, and dengue [41]. In adjacent Vientiane, Laos, the commonest cause of community-acquired bacteraemia in one study was *Salmonella enterica* serovar typhi (50.9%), followed by *S. aureus* and *E. coli* [42]. Causes of hospital-acquired sepsis are also poorly characterised in resource-constrained settings where culture facilities are limited or absent, but lack of infection control infrastructure is likely to be associated with a significant burden of nosocomial sepsis. Because improved outcomes in sepsis management depend on early and appropriate antibiotic administration, it is critical that these issues be addressed in future epidemiological studies.

The role of the clinical microbiology laboratory in developing countries has been discussed extensively elsewhere, and issues relating to problems with clinical misdiagnosis, poor use of existing resources, and quality assurance are well documented [43,44]. Possible solutions include the development of low-cost laboratories, or the

intermittent use of mobile diagnostic “clinics” that can define the range of pathogens and their susceptibility patterns in a given area to inform a rational empiric prescribing policy. These data should be widely disseminated to clinicians within the region. Evidence for the impact on mortality of accurate diagnosis can be seen from mortality rates from melioidosis in northeast Thailand over time. The burden of melioidosis became apparent after diagnostic laboratories were introduced into this area in the early 1970s [45]. This led to the first clinical treatment trial that reported a reduction in mortality from 74% to 37% for patients with acute melioidosis treated with ceftazidime compared with the previous combination antibiotic therapy [46]. Similarly, recent clinical trials have been prompted by the recognition of emerging resistance in *Salmonella typhi* [47].

There are a number of concerns with respect to antibiotic therapy in developing regions. In many developing countries, antibiotics are not regulated and are freely available, particularly in urban areas. It is becoming widely appreciated that a significant proportion of patients in rural Asia will have taken antibiotics prior to presentation to hospital [48,49]. This has major implications both for antibiotic resistance and the sensitivity of diagnostic culture when the patient presents to hospital. The quality of antibiotics is a further consideration. Fake drugs are widespread in the tropics [50] and have been implicated in deaths from malaria. Furthermore, many antibiotics are stored at room temperature, but ambient temperatures may reach 40° C in the tropics.

Supportive and Adjunctive Therapeutic Agents

Prophylaxis for deep venous thrombosis and for peptic “stress” ulcers can be readily implemented in many developing countries. Histamine blockers such as ranitidine are inexpensive and can be administered via nasogastric

Five Key Papers in the Field

Dellinger et al., 2008 [16] These international guidelines detail the current standard of care for patients with severe sepsis in developed countries.

Cheng et al., 2007 [15] This trial demonstrated poor outcomes from septic shock due to suspected melioidosis despite hospital care in Thailand, with in-hospital mortality exceeding 80%. Granulocyte colony stimulating factor, as an adjuvant to antibiotics, was not associated with a mortality benefit.

Phu et al., 2002 [63] This trial in Vietnam demonstrated that haemodialysis was more effective than peritoneal dialysis in patients with infection-related acute renal failure predominantly due to malaria. Despite the increased cost, the mortality benefit was large, suggesting that haemodialysis was more cost-effective.

Rivers et al., 2001 [21] This single-centre randomised controlled trial demonstrated a 16% absolute decrease in in-hospital mortality associated with early goal-directed management compared with standard management.

Gove S, 1997 [73] This paper describes the development and evaluation of the integrated management of childhood illness guidelines and training course for health workers in developing countries.

tube to intubated patients. Although some have argued that the incidence of venous thromboembolism is lower in populations of non-European origin [51–53], more recent evidence suggests that this may not be the case in post-operative and medical patients [54,55]. In the absence of studies in critically unwell patients with prolonged immobilisation, the use of subcutaneous unfractionated heparin seems warranted.

Other interventions often used in the developed setting for patients with severe sepsis are renal replacement therapy and mechanical ventilation. Respiratory failure is a frequent complication of severe sepsis, and progression to acute lung injury is most commonly caused by sepsis [56,57]. In a trial of granulocyte colony stimulating factor in severe sepsis due to melioidosis in Thailand [15], 70% of patients required intubation and ventilation. Where available, mechanical ventilation of septic patients in developing countries is associated with extremely high mortality rates [6], and in some countries, patients with respiratory failure are ventilated by hand by relatives (A. C. Cheng, personal experience). Many ventilators in developing countries are simple devices that do not have minute ventilation alarms or allow for adjunct ventilator functions such as positive end-expiratory pressure. Sub-optimal ventilator care may lead to ventilator-associated pneumonia [58,59], and the lack of low-volume “lung-protective” strategies may be associated with poor outcomes from acute lung injury [60]. The reliance on non-invasive monitoring using peripheral oxygen saturation may reduce the ability to monitor the adequacy of ventilation. Although non-invasive positive-pressure ventilation is mainly used for respiratory failure in non-septic patients, it has been used successfully in developing countries [61,62], and strategies incorporating non-invasive positive-pressure ventilation should be evaluated further where invasive mechanical ventilation cannot be managed adequately.

The cost of equipment and trained staff largely prohibits the use of renal replacement therapies in low-income settings, although they are used to a variable extent in rural regions of middle-income countries. In Vietnam, haemofiltration was more cost-effective than peritoneal dialysis in infection-related renal failure despite its significant cost [63]. This study primarily included patients with malaria, but such a study would be of significant interest in patients with sepsis in resource-constrained settings where haemofiltration is possible. In a study of severe sepsis in melioidosis, acute renal failure and acidosis were prominent on admission, suggesting that aggressive fluid resuscitation and/or renal replacement therapy would be potentially beneficial in this group [15]. There has been increasing awareness of the importance of acidosis and fluid and electrolyte imbalances in severe malaria, and despite differences in pathophysiology, such research may be relevant to severe bacterial sepsis [64,65].

There have been few trials of adjuvant therapies in developing countries, and results of studies may not be generalisable to this setting. For example, granulocyte colony stimulating factor appeared to be associated with significant benefit in treating melioidosis in Australia [13], but was not associated with a significant mortality benefit in Thailand in a clinical trial [15]. Conversely, high-dose steroids are not thought to be useful in severe sepsis generally, but may possibly have a specific application in severe typhoid [66–68]. Interventions that are of marginal benefit in developed

countries, such as physiological dose steroid replacement [19,69] or intensive insulin therapy, are unlikely to be effective in developing countries in the absence of other standard intensive care interventions. The risk of adverse events, such as hypoglycaemia, associated with intensive insulin regimens are likely to be greater in resource-poor settings, and the setting of less strict blood glucose targets may be warranted [16,18,70]. However, the safety and efficacy of such strategies require study. The effectiveness of activated protein C (drotrecogin alfa) has also been subject to intensive debate, but the cost of this therapy is prohibitive for most health care systems in developing countries [71,72].

Training

Implicit in this discussion is the need for appropriately trained health care providers at the local level. Ideally, sepsis identification and management training should be integrated into general adult health care. Such a strategy is analogous to the World Health Organization’s Integrated Management of Childhood Illness training course, which included severe infection, chronic diseases, and preventative measures for all levels of health workers including doctors, nurses, medical assistants, and literate paramedical workers at both a primary, and more recently, hospital level [73,74]. This course was integrated into a comprehensive strategy that also included measures to improve drug supply, health care infrastructure, and family behaviour in relation to sick children.

Cost-Effectiveness

The development of critical care services has significant resource implications for developing countries. We propose a stepwise approach based on income level, from extremely limited services in Africa and parts of southeast Asia, to more extended services in lower-middle-income countries such as Thailand and some South American countries (Table 1). Some evidence suggests that critical care services may be cost-effective even in poor countries, but such a decision needs to be made on a case-by-case basis [75]. We feel that with the current paucity of evidence regarding the effectiveness of potential interventions for severe sepsis, such decisions cannot currently be made. We further note that factors other than cost-effectiveness must be considered in priority setting in health care resource allocation, including equity, ethical, and political considerations [76]. However, where such services already exist, the challenge is to integrate these into the broader health care system to ensure access and to provide a cost-effective and sustainable staffing model [77]. Further research is required to define the most effective interventions for sepsis in developing countries, as well as evaluation and quality control programmes for existing services.

Prevention

Few vaccines are available against most of the common causes of severe sepsis in the tropics, and many vaccines with known substantial efficacy against common diseases such as typhoid and pneumococcal disease are not generally available to developing countries because of cost. Other preventative measures may be useful for specific diseases. In a case-control study in northeast Thailand, the use of protective clothing reduced the incidence of leptospirosis [78], and protective footwear may also help prevent

Table 1. Possible Interventions for the Management of Sepsis in Resource-Constrained Settings

Issue	Management Where Few Resources Are Available	Management Where Some Resources Are Available	Considerable Resources Available, But Less Than in Developed Countries	Standard of Care in Developed Countries
Example of setting	• Community health station	• Community hospital	• Provincial hospital, middle-income countries	• Referral centre, developed countries
Strategy	• Early recognition and treatment of sepsis • Referral to centre with basic supportive care where possible	• Early recognition and treatment of sepsis • Referral to centre with basic supportive care where possible	• Early recognition and management of sepsis and treatment of disease • Referral to centre with more advanced supportive care where required	• Early recognition and management of sepsis and treatment of disease • Rapid diagnosis with advanced supportive care
Initial assessment	• Recognition of sepsis syndrome	• Recognition of sepsis and severe sepsis syndromes, basic assessment of organ dysfunction	• Recognition of sepsis and severe sepsis syndromes, comprehensive assessment of organ dysfunction	• Recognition of sepsis and severe sepsis syndromes, comprehensive assessment of organ dysfunction
Antibiotic therapy	• Prompt oral (+/- parenteral) antibiotic management to cover common causes of sepsis	• Prompt empiric antibiotic treatment to cover common causes of sepsis • Gram stain to guide antibiotic management	• Prompt empiric antibiotic treatment to cover common causes of sepsis • Specimen culture (+/- advanced diagnostics at regional reference laboratories)	• Prompt (within <1 hour) empiric antibiotic treatment to cover common causes of sepsis • Diagnostics (including invasive specimen sampling, use of rapid tests) to guide antibiotic management
Source control	• Clinical assessment and referral as appropriate	• Clinical assessment of deep foci of infection +/- drainage	• Clinical assessment and imaging, with surgical or radiologically guided drainage	• Clinical assessment and imaging for deep foci of infection with drainage
Fluid therapy	• Oral fluid administration	• Fluid challenge (>20 ml/kg) if hypotensive • Fluid management guided by clinical assessment of volume status • Electrolyte monitoring and replacement where possible	• Fluid challenge if hypotensive • Fluid management guided by central venous monitoring • Electrolyte monitoring and replacement	• Fluid challenge if hypotensive • Fluid management guided by central venous monitoring • Electrolyte monitoring and replacement • Later conservative fluid strategy if ARDS present
Vasopressors and inotropes	• Refer if required, where possible	• Dopamine to maintain MAP >65 mmHg after fluid challenge	• Continuous arterial pressure monitoring • Norepinephrine or dopamine (+/- inotropes) if central venous infusions can be administered	• Continuous arterial pressure monitoring • Norepinephrine or dopamine (+/- inotropes) via central venous catheter
Ventilatory support	• Supplemental oxygen where available	• Support guided by clinical assessment and SpO ₂ • Mechanical ventilation	• Arterial blood gas monitoring • More complex ventilation strategies (PEEP, low-volume lung-protective ventilation if indicated) • Non-invasive ventilation	• Arterial blood gas monitoring • PEEP • Low-volume lung-protective ventilation if indicated • Weaning protocol • Non-invasive ventilation
Sedation	• Analgesia where available	• For ventilated patients, regular administration of sedatives with dosing according to protocol based on sedation scale	• For ventilated patients, intermittent or continuous dosing of sedatives according to protocol based on sedation scale	• For ventilated patients, intermittent or continuous dosing of sedatives according to protocol based on sedation scale
Renal replacement therapy	• Refer if required, where possible	• Peritoneal dialysis	• Intermittent haemodialysis or CVVHF	• Intermittent haemodialysis or CVVHF if unstable
Other management recommendations		• Stress ulcer prophylaxis • DVT prophylaxis • Basic glycaemic control (<200 mg/l)	• Stress ulcer prophylaxis • DVT prophylaxis • Glycaemic control (180–200 mg/l)	• Stress ulcer prophylaxis • DVT prophylaxis • Glycaemic control (~150 mg/l) using insulin infusion • Use of activated protein C for patients at high risk of death • Use of physiological dose steroids for refractory shock
Other issues	• Public awareness and prevention • Staffing and training	• Integration of critical care services into health system • Basic staffing and training • Public awareness and prevention • Research and evaluation	• Medical/specialist supervision (+/- "closed" intensive care model) • Specialist nursing training	• "Closed" intensive care model • High staff-patient ratio • Specialist medical and nursing training

ARDS, acute respiratory distress syndrome; CVVHF, continuous veno-venous haemofiltration; DVT, deep venous thrombosis; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; SpO₂ saturation of oxygen in arterial blood flow.
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melioidosis, scrub typhus, snake bite, and physical injury. Although anecdotal reports suggested that farmers found protective footwear uncomfortable, particularly during the ploughing and planting seasons (V. Wuthiekanun, personal communication), it is possible that this obstacle could be overcome through a combination of education and the development of comfortable and practical clothing. Predictive modelling has proven to be a useful tool in malaria control [79], and similar techniques have been developed for a variety of other diseases such as cholera [80] and arboviruses [81]. Such tools might allow for targeting of public health interventions that may reduce exposure or disease transmission in specific populations.

Conclusion

The burden of sepsis is greatest in developing countries, and there is a need to translate modern management strategies for adults with severe sepsis to this context. The majority of studies of infectious diseases to date have been pathogen-specific, but efforts are required to define the epidemiology of all-cause sepsis in developing countries and to define the most cost-effective interventions that are sustainable in these countries. Principles of management may be adapted from current guidelines, particularly low-cost interventions targeted at early sepsis. Critical care services need to be considered in the context of competing priorities for resource allocation, but where they currently exist, standardised protocols need to be developed and evaluated to make the best use of available resources.

Access to diagnostic facilities is fundamental to the care of the individual and to the development of logical and effective empiric prescribing regimens. Low-income countries rarely have access to diagnostic laboratories, and this is a major impediment to the improvement of care. Primary prevention is theoretically possible for a range of serious tropical infections, and studies are required to define acceptable measures and to validate their effectiveness. ■

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