Challenges and Solutions in translating sepsis guidelines into practice in resource-limited settings

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Abstract: Sepsis and septic shock are major contributors to the global burden of disease, with a large proportion of patients and deaths with sepsis estimated to occur in low- and middle-income countries (LMICs). There are numerous barriers to reducing the large global burden of sepsis including challenges in quantifying attributable morbidity and mortality, poverty, inadequate awareness, health inequity, under-resourced public health, and low-resilient acute health care delivery systems. Context-specific approaches to this significant problem are necessary on account of important differences in populations at-risk, the nature of infecting pathogens, and the healthcare capacity to manage sepsis in LMIC. We review these challenges and propose an outline of some solutions to tackle them which include strengthening the healthcare systems, accurate and early identification of sepsis the need for inclusive research and context-specific treatment guidelines, and advocacy. Specifically, strengthening pediatric intensive care units (PICU) services can effectively treat the life-threatening complications of common diseases, such as diarrhoea, respiratory infections, severe malaria, and dengue, thereby improving the quality of pediatric care overall without the need for expensive interventions. A thoughtful approach to developing paediatric intensive care services in LMICs begins with basic fundamentals: training healthcare providers in knowledge and skills, selecting effective equipment that is resource-appropriate, and having an enabling leadership to provide location-appropriate care. These basics, if built in sustainable manner, have the potential to permit an efficient pediatric critical care service to be established that can significantly improve sepsis and other critical care outcomes.

Keywords: Low- and middle-income countries (LMIC); sepsis; shock; antibiotics; fluids

Introduction

The burden of infectious diseases disproportionately affects populations in low- and middle-income countries (LMIC) with a corresponding prevalence of sepsis. In these settings delivery of health care is generally suboptimal resulting in high death rates (1,2).

Regardless of the underlying etiology, the 'sepsis syndrome', defined by the presence of severe infection with organ-dysfunction, is a common pathway contributing to this mortality. In patients with sepsis, multi-organ dysfunction

leading to persistent end organ damage and refractory hypotension is associated with increasing deaths (3,4).

The global burden of sepsis is undoubtedly massive (accounting for 20% of all deaths) with 90% of the annual 48.9 million cases and 11 million deaths in 2017 occurring in LMIC, where the barriers to improving outcomes are numerous (1).

Available data on sepsis management of patients across all age-groups in resource-limited settings (RLS) suggest that the high death rates is associated with sub-optimal management including delayed and inappropriate empiric antimicrobial therapy as well as ineffective initial resuscitation. Thus, in order to reduce sepsis mortality, a focus on improved management in these settings is urgently needed (2).

Worldwide, although >90 percent of the pediatric sepsis burden lies in LMIC and sepsis is a leading cause of maternal and childhood mortality (1,5); sepsis remains a neglected killer without adequate recognition of its overarching contribution to childhood mortality (6,7).

Moreover, the real burden of sepsis is very difficult to ascertain when clinicians rarely document it in their daily practice. For instance, although malaria, pneumonia and diarrheal diseases share sepsis as their final pathway to death, there has been very little emphasis on programs that specifically address sepsis. Patients are often classified based on the primary infective source, such as urinary tract infection or pneumonia, but sepsis is rarely included or considered in the diagnosis, and the use of nonspecific terms such as "septicemia" remains unfortunately pervasive (8).

The World Health Organization (WHO) has ,recognized sepsis as a global health priority which accounts for many millions of preventable deaths every year, and in 2017 adopted a resolution targeting the prevention, diagnosis, and treatment of sepsis, especially in LMIC (9).

This article aims to briefly outline the obstacles to optimal sepsis care in resource-limited settings (RLS), identify the knowledge gaps and inherent limitations in international definitions and treatment guidelines, and suggest broad avenues for improvement while acknowledging the fallacy of overgeneralizing across massively diverse geographies.

We provide suggestions how critical care resources can be made more accessible to a larger LMIC population, describe a suggested pragmatic approach to manage sepsis, and highlight key issues and research agenda that must be addressed to further refine best practice for the management of sepsis in these challenging settings.

We conclude with a brief outline of possible future application of creative, rapidly-evolving modern low-cost technological innovations that hold potential to advance LMIC closer to equity in the global healthcare arena.

Barriers and deficiencies in LMIC that contribute to preventable sepsis deaths (*Table 1*) (8,10,11)

The enormous burden of childhood mortality in LMIC is tragic considering that many deaths could be prevented by timely, simple resuscitative measures despite austere environments that lack critical care services (6,7,12-14).

The challenges and difficulties in LMICs includes severely limited government spending on public health, inadequate coverage with vaccines, poor sanitation and water, inadequate primary education which results in higher prevalence of diseases and poorer outcomes including that for sepsis (8,15).

Even when care for sepsis is sought, further obstacles to appropriate care are numerous, and include poorly-equipped transport to an appropriate medical facility, rudimentary or no triage and non-availability of an organized screening for sepsis or institution of critical care support. Major contributors are also lack of trained medical and nursing personnel and equipment for emergency care including the administration of timely antibiotics and resuscitation, which poses a greater challenge in resource-limited settings in LMICs than wealthier regions (16).

Challenges in provision of quality treatment might also include counterfeit antimicrobials, limited surgical and obstetrical interventions, and intensive care that might or might not have life support interventions or protocols for managing patients with physiologic derangements (16,17).

Limited understanding of epidemiology and pathogenesis of sepsis in developing countries

Limited understanding of the epidemiology and pathogenesis in LMICs stems from the fact that the majority of published experience are from large, often academic urban centres, rather than rural or district level healthcare facilities where most patients present. Furthermore, there is a major lack of meaningful data about the risk factors for developing sepsis and how they should be managed especially from the lowest income countries where sepsis is most common and associated with the poorest outcomes (6,18). It is difficult also to extrapolate data and generalize information reported from a few resource-limited areas as being representative to all LMIC since the

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Table 1 Pediatric sepsis-summary of challenges and proposed solutions in resource limited regions (8,10,11)

(I) Overarching challenges	(II) Cause/consequence	(III) Possible solutions
Low-resilience public health systems that are often under-resourced	Poverty, political corruption, health inequity	Advocacy: Recognize sepsis as a major public health threat
		Global and national-level economic policies to improve funding to LMIC
Inadequate acute and urgent healthcare delivery systems		Sustained efforts to fortify public health services and also acute health care delivery
		Enhanced focus on infection prevention, including maternal education, nutrition, vaccination, improved living environments including sanitation and clean drinking water
Limited human resources	Inadequate healthcare personnel, major knowledge gaps in healthcare providers' training that delay timely identification and management of sepsis	Adequately staffed and well-supplied referral centres accessible to all.
		Ongoing training programmes
Rampant anti-microbial resistance	Limited microbiological laboratory services.	Improved microbiological lab capacity, which can improve implementation of antimicrobial stewardship
	Increased ESBL rates leading to greater high-end antibiotic use and further resistance	Focus on prevention of hospital-acquired infection
Inadequate quantification of sepsis burden in LMIC	Wide variations in case definitions developed in HIC with uncertain utility in LMIC	Locally relevant operationalization of sepsis definitions, including greater emphasis on clinical criteria and simple vital signs rather than laboratory criteria to define sepsis
Lack of relevance in translating high-resource sepsis treatment guidelines in LMIC	Different genetic features of immune response	Local testing of international treatment guidelines using available resources.
	Different comorbidities such as HIV, malnutrition	
	Different invading pathogens: parasitic, viral, mycobacteria	
	Highly variable acute healthcare services	
Lack of locally relevant research and innovations to guide therapy	Suggested solutions: large high-quality prospective sepsis studies in LMICs and austere environments; focus on safe cost-effective and readily available interventions; promote creative frugal innovations to enable large scale diagnostics in order to tackle antimicrobial resistance; promote low-cost mobile technology including wearables for patient monitoring, even after hospital discharge	

LMIC, low- and middle-income countries; HIC, high income countries; ESBL, extended spectrum beta lactamase; HIV, human immunodeficiency virus.

host characteristics, sepsis etiology and pathogenesis are likely to vary a great deal across the enormous range of regions classified in the LMIC category (19).

Varying spectrum of causative agents and pathophysiology

The etiology of sepsis in LMICs is diverse and poses difficulties because of unique causative pathogens in these mostly tropical countries, limited epidemiological data because of inadequate capacity of microbiological services, leading to poor antibiotic stewardship and a higher degree of AMR.

There is a wide-range of pathogens in LMIC, and while gram-negative and gram-positive bacterial etilogies are fairly common, other bacteria that that are infrequently encountered in HIC but commonly result in the sepsis syndrome in Asia include *Burkholderia pseudomalle*, *Rickettsiosis* and salmonella infections which may be responsible for melioiododis, scrub typhus and enteric fever respectively (16,20,21).

Further, acute non-bacterial diseases may be often be responsible for sepsis including protozoal diseases such as malaria, and viral diseases such as measles, dengue, or viral hemorrhagic fevers (17). Non-bacterial causes are understudied and under-represented, and the

pathophysiology and treatment of bacterial sepsis may not be generalizable to these other causes of sepsis

While non-bacterial etiology may also result in a dysregulated host response and organ failure, other mechanisms of organ failure include 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, both micro- and macrovascular dysfunction may be contributory factors and it has been well established that an infected and sequestered red blood cell biomass can obstruct the microcirculation and directly cause of vital organ failure (22,23). Similarly, in severe dengue, the viral proteins may directly cause endothelial glycocalyx damage leading to plasma leakage and shock, and organ failure can also occur due to direct virus invasion (24).

Widespread anti-microbial resistance

Although the bacterial pathogens that cause sepsis in LMICs are similar to those reported in high-income countries (HIC), antimicrobial resistance (AMR) patterns can be very different. Increasing reports of the high prevalence of multidrug-resistant bacteria, including extended spectrum beta-lactamase (ESBL)- producing bacteria, methicillin-resistant Staphylococcus aureus, resistant Mycobacterium tuberculosis, and Enterobacteriaceae producing carbapenamase are of concern and may contribute to the high mortality observed in LMICs particularly among infants (8,17).

Levels of Gram-negative bacterial resistance in LMIC are alarmingly high, particularly in Asia, where hospital-acquired ESBL rates above 60 and 80% in India and China respectively have been reported (25). The high-ESBL rates leads to increased carbapenem use in these regions with selection pressures resulting in the appearance of carbapenem resistance (26). Five countries with the highest burden of under-five deaths (Nigeria, India, China, Pakistan, and the Democratic Republic of the Congo) also have the greatest rates of neonatal deaths from AMR (27). The costs and quality of the medication are important factors guiding antibiotic choice and, although generic products are cheaper; the quality may be sub-standard or even counterfeit (28).

Challenges in the application of pediatric sepsis definition and recognition in LMICs

Sepsis is a complex heterogenous syndrome, the variable

manifestations of which are determined by multiple factors including genetic, background chronic illness, nutritional status, pathology and invading organism, time for initiating therapy among others (3,29). Despite the huge burden that sepsis imposes on the health of children, there remains a dynamic conflict between various iterations of the consensus criteria of sepsis and the criteria that clinicians use at the bedside to diagnosis sepsis or septic shock (12,30).

On account of the non-specific physiologic abnormalities, there is discordance between the sepsis definitions and physician-diagnosed sepsis, both in wealthier and lesser-resourced countries (31). We all agree on the definition which is a philosophical and physiological construct of presumed or suspected infection and end organ dysfunction. What is uncertain is how it is operationalized at the bedside because of varying levels of resources to confirm organ dysfunction (15,32).

The recognition children at risk for sepsis or septic shock, even before advanced organ dysfunction is established and timely initiation of therapy may improve morbidity and/or mortality and assumes greater importance in LMIC regions where advanced organ support is limited or unavailable. However, the primary healthcare workers in LMIC who cater to all-comers including infants, older children and adults may not be educated or trained to recognize pediatric sepsis in the early stages when the clinical signs are subtle.

Even experienced pediatric providers in high-income countries may have difficulties in pediatric sepsis diagnosis and recognition. A study in a tertiary care children's hospital in US reported prevalent sepsis knowledge deficits, provider discomfort, and diagnostic delays among all provider groups (33).

The 2005 pediatric sepsis definition is outdated, has low specificity and sensitivity and is now being updated.

Challenges in therapy of sepsis in LMIC

Similar to the challenges in defining sepsis in LMIC, extrapolation of international treatment recommendations in LMIC is fraught with challenges.

Antimicrobial therapy: the need to cover a broad range of etiological agents vs. practicing antibiotic stewardship in regions with major antimicrobial resistance

There is a high degree of variation in the microbiological etiology of sepsis between and within resource-limited settings and the empiric antibiotic regimen for a patient

who presents with suspected sepsis in LMIC must cater to local epidemiology and resistance patterns, including bacterial and or non-bacterial etiologies such as TB and malaria, and viral diseases such as dengue or measles.

Further, the limited microbiological laboratory capacity in many LMICs leads to difficulty in practicing antibiotic stewardship by de-escalation of the empiric broad antibiotic regimen based on exact etiology, further compounding the problem of antimicrobial resistance.

Timing of antibiotics

The Peds SSC recommendation aims to optimize antibiotic stewardship by attempting a balance between timely antibiotic therapy to optimize outcomes while simultaneously attempting to minimize antibiotic use in non-bacterial conditions. Accordingly, the recommendation is to provide antimicrobial therapy within 1 hour of recognition in the presence of septic shock, while in children without shock but with sepsis-associated organ-dysfunction, the suggestion is to start antimicrobial within 3 hours of recognition. This period will permit appropriate and expeditious diagnostic investigation for patients with an uncertain diagnosis in order to discriminate those with actual sepsis and those with suspected infection, and this approach is appropriate even in LMIC (3).

Early resuscitatio: HIC model may not be relevant

The overarching premise that governs early sepsis resuscitation protocols was that a time-based sepsis pathway that promotes aggressive use fluid resuscitation and vasoactive agents would improve both the quality of resuscitation thereby sepsis outcomes, whereas patients who received (slower) usual care were at higher risk of under-resuscitation, with consequent poorer survival rates. The protocolized rapid resuscitation was in stark contrast to the pervasive practice of slow correction of deranged vital parameters that underpins usual care practices in many LMICs (34). However, and in contrast to expectation, the 3 African fluid studies in adults and children demonstrate that caution may in fact be warranted, and that the quest to rapidly normalize deranged parameters for patients with severe sepsis in resource-limited settings may be counter-productive (35-37).

An improved focus on identifying the priority interventions for sepsis management in RLS is a major challenge. While there is evidence in LMIC for the benefit

of timely and appropriate antimicrobials, the utility of other interventions commonly practiced in HIC is difficult (8). For example, what are the risks *vs.* benefits of fluid resuscitation in the absence of vigilant patient monitoring and timely respiratory support? Similarly, are invasive central venous lines beneficial for guiding fluid resuscitation in a RLS considering the greater risks of infection and mechanical complications? Finally, given global efforts to improve oxygen therapy practices, what is the optimal level of oxygen saturation in septic patients? Clearly some interventions such oxygen in hypoxemic respiratory failure are universally useful while others such as fluids may have conflict.

Fluid resuscitation: changing paradigms

Since its introduction during the cholera epidemics of the nineteenth century, intravenous fluid resuscitation has served as a mainstay of supportive sepsis care (38). Today, there is increasing concern that intravenous fluids may unexpectedly augment septic endothelial dysfunction, potentially negating the beneficial hemodynamic effects of fluid resuscitation (38,39).

All aspects initial fluid resuscitation in septic shock are extensively debated, and there is controversy regarding the volumes, rates, and type of fluid to be administered, and even whether the initial fluid bolus is required at all in every patient with septic shock. Fluid boluses can cause undesirable effects, and while pulmonary edema and fluid overload are best known, adverse effects can occur due to its vasodilating properties (40) and effects on the endothelial glycocalyx promoting worse capillary leak and increased lung fluid even without fluid overload (39). Fluid can cause respiratory deterioration and cardiovascular collapse in the presence of abnormal cardiac function (which may be present in 40–60% of patients) (3), which may lead to death if rescue ventilation is not immediately available. Large volume resuscitation may be harmful in children with underlying chronic illness such as TB, malaria, malnutrition and anemia.

Studies in even well-resourced countries demonstrate that the desired response to the fluid bolus in terms of improved cardiac output may be transient, with reports of 2/3rds of children with septic shock who received FB demonstrating an increased CI >10% at 5 minutes, of whom only 14% remained fluid-responsive at 60 minutes, suggesting that in the remaining patients the administered fluid might have leaked out into the interstitial compartment, causing short-

lived benefit and unintended harm (41).

There may not be a single ideal rate and volume of fluids to be administered to all children presenting with septic shock in resource-limited regions

It is clear that there is no single best volume or rate of fluid resuscitation that will suit all patients presenting with septic shock in any area of the world, least of all in LMIC. While many children with septic shock may have decreased intake and increased losses, absolute volume deficits may not be large. Plasma leak may also occur to some degree in sepsis, but not to the extent seen in established capillary leak conditions such as dengue shock. Even in patients with severe dengue shock with clear evidence of capillary leak-induced hemo-concentration, pleural and ascitic collections and narrow pulse volume, fluid replacement comprising 20–25 mL/kg over the initial 2 hours, with an ongoing decreasing regimen depending on response is sufficient in most children (42).

In septic shock also, fluids deficits may not be large in the absence of clear fluid-losing state. Hypovolemia is more relative (from re-distribution in vasodilatory shock) with a minor degree of absolute hypovolemia (43). We have demonstrated that a more physiologic approach to improve preload in vasodilatory septic shock includes an initial small volume followed by agents such as low-dose pressors which improve the venous return (rather than large volume fluid boluses) (44).

Respiratory/ventilatory support for patients with septic shock: challenges in LMIC

Many patients with septic shock require oxygen and respiratory support either from their primary illness such as pneumonia or during the period of rapid fluid resuscitation.

There are many barriers to delivering high-quality support to patients with acute respiratory failure in RLS, chief among which include inadequate equipment that are poorly maintained, and understaffed health personnel who are inadequately trained (17).

The practice of intubation and mechanical ventilation is limited in LMIC and carries high crude mortality, with reported ICU death rates of between 36–72% (45). The risk of ventilator-associated pneumonia (VAP) and other complications are also greater in LMICs than in HIC with greater costs, length of stay and mortality (45).

Looking ahead: WHAT are the ways to improve outcomes of critically ill septic children in LMIC

Advocacy required at many levels

The UN sustainable development goals (SDG) have set ambitious targets to reduce neonatal and under-5 mortality to less than 12 and 25 per 1,000 live births respectively, and universal access to vaccines and affordable medications (8,17,46).

Advocacy is also required at the global, national, and regional levels to raise awareness in order to prevent infections, to increase access to medications and life-support equipment, and to ultimately build strong and resilient healthcare systems that will be able to provide sustained healthcare services even when infectious outbreaks occur (47). These global efforts will bring nations closer to reaching the SDG of attaining lower neonatal and under-5 mortality rates (48,49).

The Global Sepsis Alliance is raising awareness at the international level on strategies to prevent sepsis as well as monitor, manage, and reduce morbidity and mortality, while simultaneously advocating for inclusion of sepsis as a separate cause of death in the Global Burden of Disease framework.

Preventative measures

Advocacy at national and regional levels requires national health policy makers to focus on not just poverty alleviation, but also prevention of the risk factors for high infant and under-5 mortality such as low-birth-weight, undernutrition, indoor air pollution, incomplete immunization at one year, HIV, lack of exclusive breast-feeding for the first 6 months, over-crowding and lack of hygiene, the lack of clean water and sanitation, maternal illiteracy, and challenges in accessing healthcare due to longer travel times (46,50,51).

Effective communication with government health managers and policy makers on a consistent basis is crucial in order to improve funding and support of the critically ill child, emphasizing that may diagnoses that contribute to the high burden of disease in LMIC, such as sepsis, dengue, poisoning, and diarrhoea are acute fully curable critical illnesses, and can be managed through prompt, simple low-cost treatments despite limited pediatric intensive care resources compared with HIC (52,53).

Considering these key differences, there is a compelling public-health argument for basic intensive care services even in LIC given that even a short period of critical care is a cost-effective and essential part of the treatment of the

acute life-threatening conditions that affect the lives of millions of young people worldwide. In a Malawi hospital, emergency department triage and treatment for children costs just US$1.75 per patient and has greatly reduced hospital mortality and the cost of providing oxygen just 1-6 US dollars per day (54).

Continuous public education to seek better health care

To reduce U5M, basic education regarding early signs and symptoms of common infectious diseases should be repeatedly provided to caregivers so that they are able to easily recognize these and seek care promptly. In LMICs, the ability of caregivers to recognise common diseases such as diarrhea, pneumonia or malaria and their danger signs, and to seek health care promptly is very low. These issues are even more prominent in rural regions, where delays due to the use of traditional care practices is also of concern. Other factors influencing appropriate healthcare seeking include socioeconomic status and cost of care; severity of illness, and in some regions even the gender of the child with girls less likely to receive appropriate care (55).

Prompt antimicrobials and oxygen

Timely antimicrobials have repeatedly shown to improve sepsis outcomes in both HIC and LMIC. An analysis in 101 countries has shown that with an estimated 590,000 cases of pneumonia in under-5 children, universal access to antimicrobials can prevent 445,000 deaths (14). However, many LMICs have limited access to even basic life-saving medications, which adds to the burden of preventable sepsis-associated deaths. Strong and sustained advocacy to increase universal access to life-saving medications can greatly reduce the massive burden of sepsis (56).

Supplemental oxygen has been shown to decrease death rates in childhood pneumonia by up to 35% and is listed on the WHO's essential medications (57). However a survey conducted among 97 physicians from 19 countries across Asia, Africa, and South America reported that less than a third of respondents reported working with uninterrupted oxygen supplies in their healthcare facilities (58).

Universal vaccinations

Vaccinations remain amongst the most cost-effective interventions to reduce sepsis mortality and their access in LMICs should be greatly improved. Further, antibiotic use may be greatly reduced with widespread vaccinations, and a recent analysis of 75 countries showed that with adequate access to vaccines for children under-5 years of age, an estimated 11.4 million antibiotic days can be averted each year with improvement in death rates (27,59). Gavi, the international alliance that actively advocates and promotes improved immunisation, has partnered with LMIC governments to vaccinate 580 million children, thereby averting greater than 8 million deaths over the previous 15 years (60) (http://www.gavi.org/progress-report/#section2).

Unfortunately, a growing section of the society has become vaccine-hesitant because of the risk-benefit concerns that are often inappropriately raised related to political motives and social media (61). Because of its negative influence on vaccination confidence, the availability of misinformation on social media should be identified as a threat to the public's health.

In a vaccine-hesitant atmosphere, sustained health education that supporting the government campaigns against vaccine refusal are essential in changing attitudes (62). This requires a climate of respect and mutual trust between science and society to be promoted, where scientific knowledge is not only taught but also cultivated and sustained coupled with an ongoing emphatic understanding of citizens worries, needs of reassurance and health expectations (62).

Critical care is expensive! Can an inexpensive model be developed?

The annual healthcare expenditure per capita across LMIC is only around 5% that of HIC, and provision of critical care is rarely considered to be a priority in LMIC. Furthermore, in LMICs, critical care costs are only seldom covered by the health insurance and high out-of-pocket expenses may be incurred with each ICU admission (8,16), leading to restricted access to ICU care for the socioeconomically disadvantaged and uninsured. Therefore, an urgent need to develop an alternative inexpensive yet effective critical care model for LMIC is required.

It is becoming increasingly obvious that high quality critical care in LMIC is unlikely to be achieved by efforts to replicate the HIC model based on resource-intensive ICUs with technologically advanced equipment and vast numbers of highly-trained staff. Rather, efforts to develop of context-appropriate solutions that are devised and championed by local healthcare professionals based on locally relevant

evidence may be lead to far more successful outcomes (52,63).

The WHO has published a pocketbook for the management of common pediatric illnesses (64) which provides clinical guidelines for hospitalized children in regions with limited resources. These guidelines have led to improvements in staff training and have clearly demonstrated that significant gains can be achieved in caring for critically ill children in LMICs by appropriate triage and rapid supportive treatment using inexpensive therapeutic modalities, including fluids, oxygen, and antimicrobial therapy. However, rapid recognition, triage and the ability to provide rapid supportive interventions still remains mostly inadequate in many LMIC settings leading to unabated high mortality even in common treatable infections such as pneumonia and malaria, further 90% of deaths from childhood trauma also occur in LMICs (65).

Thoughtful approaches are urgently required to develop Emergency and Critical Care Services in LMIC (66) and can impact outcomes if combined with a focus on caregiver recognition of serious illness, prompt access to care, safe and expedited transport and efficient triage (67).

Even when hospitals have facilities to deliver emergency care, often a lack of co-ordination, prioritisation, timely identification and institution of basic life-saving treatments can result in millions of salvageable lives lost (67). Baker *et al.* have proposed a new focus on Essential Emergency and Critical Care (EECC)-care that critically ill patients should receive in all healthcare facilities including LMIC (66). EECC-care should be part of universal health coverage, is appropriate for all countries in the world, and is intended for patients irrespective of age, gender, underlying diagnosis, medical specialty, or location in the hospital.

Well-organized EECC-care is pragmatic and low-cost and does not need to be excessively reliant on sophisticated technology, and can be developed to have a primary focus on simple, effective actions that have large potential impact on the population.

Locally relevant and user-friendly treatment protocols should be developed and implemented with WHO's leadership and through local authorities. The forefront role of oxygen therapy should be emphasised, uninterrupted oxygen supplies and delivery systems ensured along with guidelines for appropriate use. Other essential care includes a patient in head-up position, functioning suction, and basic chest physiotherapy, and these elements of care can easily be implemented by health workers with basic training (67).

Setting up EECC-care in a LMIC setting requires careful planning, region-specific resources, and most crucially, investment in the permanent healthcare providers, both nursing and medical (53,65), and starts with the fundamentals: continuous training healthcare professionals in skills and knowledge, selecting resource-appropriate equipment, and having an enabling leadership to provide a supportive environment for appropriate care. If these fundamentals building blocks can be built in a sustainable manner, an resource-appropriate critical care service can be establish that has the potential to significantly reduce childhood mortality thus enabling LMIC to reach toward the sustainable development goals (SDG) (68).

Good quality essential critical care can have a large positive impact on mortality even without formal ICUs. Moreover, timely provision of essential supportive care can prevent progression to multi-organ dysfunction, thereby reducing the burden on limited ICU capacity (67).

Critical care is a limited resource all over the world, and more so in LMIC, and allocating these resources for the sickest patients who are most likely to benefit must be emphasized. Patients who have milder illnesses as well as those who are moribund must not be admitted to scarce ICU beds and should be cared for in general hospital wards or palliative-care units, respectively.

Further, it is essential to promote staff wellness so that the few and "precious" trained personnel are not over-worked, emotionally ravaged and compelled to leave, further worsening a limited resource. Witnessing a high ICU mortality rate even in treatable conditions leads to personal and professional frustrations that could risk fatalism and staff burnout , leading to inappropriate therapy of even potentially salvageable patients (69). Attention to improved hospital functioning coupled with investment in clinician education, emotional support and counseling may improve the retention of trained healthcare providers and educators (69).

How can critical care practitioners practice locally relevant intensive Care?

Critical care practitioners must make pragmatic modifications so that the care is locally relevant

Given the paucity of good quality evidence regarding various interventions from LMIC for sepsis, there is a natural tendency to 'force-fit' existing time-based treatment protocols in vastly different LMIC environments. However, there is growing realization that recommended international intensive care interventions for the management of patients

with sepsis may be impractical, unaffordable, and possibly even harmful when implemented in middle- and low-income countries (68), and local critical care leadership in various regions must tailor pragmatic diagnostic and therapeutic approaches catering to a wide range of settings. We have outlined a few suggestions below.

Striking a balance in sepsis screening, recognition, and definition in LMIC

Screening tools and severity scores must enable effective triage and early sepsis recognition in LMIC, these will facilitate earlier treatment that is more likely to be successful with lesser resource utilization. However, there may be difficulties in implementing screening modalities developed by HIC and these may be impractical in resource-poor settings where laboratory diagnostic capacity is limited and most healthcare workers have minimal training.

In settings with high mortality rates, particularly in LMIC, the challenges in sepsis screening stem from the need for a shift from specificity toward sensitivity, whilst de-emphasizing the requirement for laboratory testing and with a therapeutic response graded according to severity of illness to permit earlier recognition. Front-line clinicians need robust screening tools rather than just risk-stratification tools. Further, a separate treatment pathway must be offered for patients who are unwell but not yet sick enough to satisfy standard scoring criteria (70).

Although the initial support of a patient with sepsis can proceed even without identification of the pathogen but includes the administration of broad-spectrum antibiotics along with source control where appropriate, laboratory information and expensive-technology is not relevant in the early stages (8).This strategy highlights the need for sensitive criteria allowing early recognition of and intervention for sepsis, with an emphasis on a clinician-defined spectrum of disease that relies on easily available data.

Screening tools based on available resources: Using simple vital signs and deranged physiology

The mainstay of critical care is monitoring vital signs (temperature, pulse rate, blood pressure, respiratory rate, mental status, oxygen saturation) and these can be implemented in hospitals without advanced monitoring facilities, and once identified, treating deranged physiology emergently may be lifesaving (71).

Deranged physiology indicates that the patient is at risk of acute deterioration, and are also termed as "Danger Signs" to emphasize the need for immediate intervention. The Danger Signs must be included in a simple to follow checklist in order to standardize the triage and streamline the initiation of early life saving therapies. For example, a checklist in Africa specifies that a patient with even a single Danger Sign (e.g., 'reduced conscious level') is classified as an emergency, and also indicates the investigations or treatments that should be initiated (14).

The most effective screening tools in LMIC emphasize clinical criteria rather than laboratory investigations, and among children, a study from Africa reported that largely clinical criteria and simple vital signs can be useful for screening patients where the admission burden is very high, to indicate those children at greatest risk of poor outcome, in order to prioritize intravenous antimicrobials and prompt supportive therapies. Severe forms of sepsis, pneumonia, or malaria were the most common causes of death in Africa (72), yet the differentiation of the specific diagnosis or pathogen is not clear at time of admission since they had similar clinical characteristics at presentation, furthermore, most of the deaths occurred within the first hospital day (73).

The authors have proposed a bedside clinical risk score, the FEAST-PET [FEAST Pediatric Emergency Triage (PET) score] for severely ill children presenting to emergency care wards in resource-limited settings in Africa, based on data collected during the Fluid as Expansive Supportive Therapy (FEAST) trial (72), and this score has been externally validated. The FEAST-PET score aims to identify patients at highest risk of death within 48 hours of admission based solely on bedside clinical parameters that can be rapidly identified by busy healthcare workers at admission, and does not need a specific disease/ infection to be identified, and that adequately discriminates between children at different mortality risk.

Recent studies in LMIC suggest that syndromic identification represents a crucial method to triage sick children appropriately, and a practical triage tool for children is in the process of validation by Fung *et al.* that can rapidly and reliably be used by low-skilled frontline healthcare workers to identify children at risk of sepsis without the need for extensive memorization or training (74).

Advantages of SIRS in LMIC

Although the systemic inflammatory response syndrome (SIRS) criteria have a poor discriminant validity, in LMIC,

SIRS could still have a role in identifying patients with infections who may benefit from antibiotics, fluids and screening for organ dysfunction. Many quality improvement (QI programmes) have used this approach and have reported a positive impact on mortality reduction (15), and in the presence of a documented infection, the presence of 2 or more SIRS criteria may help to identify patients who need additional screening for organ dysfunction (8).

Adapting sepsis- associated organ failure definitions to the existing health care system

With respect to sepsis induced pediatric acute respiratory distress syndrome (PARDS), the definition is made when a child with hypoxemic respiratory failure requires invasive or non-invasive ventilation and is based on oxygenation indices and acute onset chest X-ray changes (75). However, when facilities to perform blood gases or provide positive end-expiratory pressure (PEEP) are not present, it may be difficult to even identify PARDS which may consequently be under-diagnosed, and appropriate management delayed.

Alternate diagnostic modalities may permit ARDS recognition in resource-limited settings, and a study from Rwanda reported the Kigali modification of the Berlin definition of adult ARDS that aimed to overcome the local diagnostic challenges by modifying the ARDS definition to the existing healthcare facility. The Kigali modification permits ARDS definition even without PEEP values, and hypoxia was defined with SpO_2/FIO (SF ratio) less than or equal to 315 along with the presence of bilateral opacities at chest X-Ray or bedside lung ultrasound (76,77).

While a disease definition aims to facilitate case recognition and match treatment options to severity and has the same clinical importance world over. The Kigali modification of the ARDS definition emphasizes the pragmatic adjustments that can facilitate critical care medicine even in resource-limited regions.

Pediatric septic shock resuscitation: fluid bolus decision depends on resources available

The most recent pediatric SSC has a differentiated approach to initial fluid resuscitation depending on the resources available at the health-care facility where the patient presents. In resource-poor settings without adequate critical care services, the Pediatric SSC recommend a careful, personalized approach to fluid bolus administration and for those without evidence of severely impaired circulation

without access to ICU resources, only maintenance fluids administration is recommended. For patients with evidence of hypotensive shock suggesting a severely impaired circulation, a carefully monitored fluid bolus of 10–20 mL/kg over 30 minutes is suggested (3).

The WHO regimen is also similarly cautious and suggests that the initial bolus of 10-20 mL/kg of isotonic crystalloid (balanced crystalloid preferred, if unavailable normal saline) may be infused over 30–60 minutes depending on the severity of shock/dehydration (78).

The effectiveness of oral rehydration therapy in severe diarrhoeal dehydration shows that the gastrointestinal tract is a potentially useful route of fluid resuscitation, even in extreme intravascular depletion, and merits evaluation in sepsis (12).

A monitored and individualized septic shock resuscitation pathway in LMIC (Figure 1) (80)

Patients presenting with sepsis and septic shock to austere health care settings require an individualized and guarded approach regarding fluids and vasoactive agents with frequent re-assessment. However, regarding infection workup and antimicrobial administration, a protocolized approach is still likely to be extremely useful. The pathway (*Figure 1*) attempts to provide instruction on pediatric sepsis treatment in RLS with emphasis on the initial 2 hours (resuscitation), 2–6 hours, and 6–24 hours (post-resuscitation), taking into consideration the wide microbial spectrum, potential resource constraints, the presence of a fluid-losing state, possible underlying chronic co-morbidity.

This physiologically-driven pathway is modified from the WHO algorithm for management of shock in areas with limited resources, with elements based on the authors' own work demonstrating a fluid-sparing effect of early norepinephrine use in pediatric septic shock (44,81,82). However, this treatment pathway is untested in large trials, and we urge caution in its use.

Key points emphasized through the pathway stress early recognition, appropriate antimicrobial use while simultaneously addressing source control and reversing physiologic aberrations by restoring circulation with carefully-monitored fluids and/or vasoactives and oxygen. Frequent monitoring of the response to treatment is emphasized. Judiciously timed blood transfusion should be considered in unresolved shock depending on the patient condition and local cut-offs for transfusion.

Regarding the initial fluid bolus, where patients with

A

First TWO hours: *Resuscitation*

Recognize Septic shock

Suspected infection + (any TWO)
- Tachycardia*
- Poor perfusion: cold extremities, capillary refill time > 3 secs, weak peripheral pulses
- Tachypnoea/respiratory distress
- Mental status change
- BP normal (compensated shock)/ low (hypotensive shock)**

Check and correct low glucose, calcium, hypothermia
Check for co-morbidities# (HIV, TB, anemia, malnutrition)
Check pulse oximetry and respiratory status

Treat infection

Urgent empirical antimicrobials depending on local microbiology patterns
Antibiotics
Antimalarials
Influenza -specific antiviral (if suspect influenza)

Identify source of infection
Use signs or symptoms to consider source
Complete blood count, CRP
Send blood cultures.
Malaria tests, dengue test
Where available & indicated, molecular testing for TB or AFB smear of sputum
Chest X-ray
Gram-stain sputum
Urine analysis and culture if indicated

Fix the physiology Initial support

Oxygen: Titrate to SpO2 > 92%
2 options for initial hemodynamic support

Fluid bolus of Ringers Lactate (RL) 10-20 ml/kg over 30-60 min (preferred if history of fluid loss, such as diarrhoea vomiting), consider oral rehydration.

OR

Start low dose vasoactive-inotropes at a dilute strength via a peripheral line (epinephrine OR norepinephrine OR dopamine), may be preferred 1st option if no history of fluid loss and chronic co-morbidity. (# above)

Observe cardio-respiratory status
Monitor vitals and clinical markers of cardiac output: HR, BP, mental status (AVPU), respiratory rate, respiratory distress, SpO2

If equipment and expertise available, perform Point-of-Care ultrasound (POCUS) heart lung and inferior vena cava (IVC) to fine-tune fluid boluses ± inotropic support

Fluid Intolerance:
Cardio- respiratory worsening: Increasing tachycardia ± tachypnoea, gallop, fall in saturation, worsening perfusion, fall in BP, OR increase in liver span-> cease fluids

⬇

If still in shock, consider low dose epinephrine OR dopamine at a dilute strength via a wide-bore peripheral line.

Shock not improved, no fluid intolerance:
Consider repeat fluid bolus OR provide first fluid bolus (10-20 ml/kg RL over 30-60 mins) for patients started on initial vasoactives,

⬇

Fine-tune vasoactives
Wide pulse pressure: Add norepinephrine OR dopamine
Narrow pulse pressure + clinical markers of low cardiac output: Add epinephrine

Shock and perfusion better
Continue fluids OR vasoactives, titrate to lowest dose/ fluid rate as per desired end-points

⬇

Consider enteral oral rehydration solutions (ORS) (oral or nasogastric tube)

Monitor and record

Every 30 minutes until stable then every 1 hour
SBP, heart rate
Respiratory rate
SpO2
Mental status (AVPU)
Auscultate for gallop, new lung signs
Check for increasing liver span

Check results of emergency laboratory
If haemoglobin (Hb) < 7 g/dL, and shock not reversed, consider transfusion
Consider stress dose steroids if recent steroid exposure, vasopressor dependency

B

2 -6 hours: *Monitor and fine-tune*

Recognize
- Establish infection source
- Re-consider diagnosis or consider alternative diagnosis if shock unresolved

- If poor response, reconsider pneumothorax, pleural effusion/empyema, heart failure, poisoning, TB, and PCP associated with HIV. Consider abscess drainage
- Check for ongoing fluid loss

Treat infection Source control
- Drain surgical infection if required.

- Consider source of infection.
- Consider alternate diagnosis
- Review results of investigations

Fix the physiology

Oxygen: Titrate to SpO2 > 92%
Hemodynamic support
- If no worsening of cardiorespiratory status, continue RL at 5-10ml/kg/hr until better. Consider electrolyte solution per oral or via nasogastric tube.
- Titrate minimal dose inotropes to achieve SBP and clinical markers of perfusion
- If features of fluid intolerance is present, discontinue fluids, initiate inotrope/vasoactive
- Match ongoing losses if present

- Drain pneumothorax, pleural effusion
- If respiratory markers worsening consider non-invasive ventilation: high flow nasal cannula oxygen (HFNC) or mask CPAP or BiPAP. Consider intubation.
- Repeat POCUS to decide on further fluids and fine-tune inotropic support if equipment and expertise available.
- Repeat glucose, Hb & calcium if initial values abnormal.

Monitor and record

Every 30 minutes until stable, then every 1 hour
- SBP, heart rate
- Respiratory rate
- SpO2
- Mental status (AVPU)
- Auscultate for gallop, new lung signs
- Check for increasing liver span

Every 6 hours
- Temperature
- Urine output
- Repeat glucose and Hb if initial values abnormal.

Respond

If respiratory function declining (increasing breathlessness, increasing RR, or SpO2 <90%)
Stop IV fluids, give furosemide 0.5 mg IV, and raise head of bed.
Consider NIV (HFNC/CPAP)
If clinical markers of low cardiac output present: Add epinephrine

6 - 24 hours: *Post-resuscitation*

Recognize

Perform full re-assessment.
- Review available diagnostic data and treat underlying diagnosis.
- Evidence of a primary cardiac or surgical process?
- Switch to specific management.

If poor response, reconsider pneumothorax, pleural effusion, heart failure, poisoning, TB, and PCP associated with HIV.

Check for ongoing fluid loss

Treat infection Source control

Continue antimicrobials
Antibiotics
Antimalarials (give IV anti-malarials for at least 24 hours total before switching to oral)
Antiviral if suspect influenza
Consider imaging for source control depending on available resource (ultrasound/CXR)

Fix the physiology

Oxygen: Titrate to SpO2~90-92% and discontinue when 90% on room air.
Fluids: When perfusion improved, reduce fluids to maintenance rates, encourage enteral feeds.
Reduce rates of vasopressor-inotrope infusion with careful monitoring.

Respond

If respiratory function declining (increasing breathlessness, increasing RR, or SpO2 <90%)
Stop IV fluids, give furosemide 0.5 mg IV, and raise head of bed,
Consider NIV (HFNC/CPAP)

Nutrition

After patient has stabilized, initiate enteral feeds by mouth or nasogastric tube.
Due to risk of aspiration, do not give food orally if patient cannot safely swallow, (due to, e.g. altered mental status, severe shortness of breath, or severely ill with ongoing vomiting). Increase rate of feeding as tolerated.

Figure 1 A suggested pediatric septic shock pathway in resource-limited settings. (A) (I) Definition of shock and hypotension: WHO (78). Triad of cold hands and/or feet (temperature gradient), CRT >3 s and weak and fast pulse (note: BP measurement de-emphasized, "fast" pulse is subjective). PALS: tachycardia, cold extremities, capillary refill time >3 secs, BP normal (compensated shock) or low (hypotensive shock) (79). (II) Criteria for hypotension by age based on systolic BP (PALS). Term neonates (0 to 28 days) <60 mmHg; infants (1–12 months) <70 mmHg; children 1–10 years <70+ (age in years ×2); children >10 years <90 mmHg. (III) Criteria for Hypotension by Age based on FEAST trial (80). History of fever and impaired consciousness and/or respiratory distress; with tachycardia heart rate (HR) >180 (<12 months), >160 (12 months to 5 years), >140 (age >5 years); poor extremity perfusion CRT >2 s; core-peripheral temperature gradient; feeble extremity pulse; severe hypotension with systolic blood pressure (SBP) <50 mmHg (<2 months), <60 mmHg (1–5 years), <70 mmHg (age >5 years). *, tachycardia: suggested limits: (HR) >180 (<12 months), >160 (12 months–5 years), >140 (age >5 years) (80). **, the definition/criteria for shock for hypotension are variable (80), and caregivers are advised to apply the definition they are familiar with. #, chronic co-morbidity. Permission granted by the World Health Organization for reproducing the contents of this figure from the IMAI District Clinician Manual (81). The pathway takes into consideration potential resource limitations, recognizing that many some parts of the world do not have access to ICU support. Modified from Jacob *et al.* (2) and Ranjit *et al.* (44) and IMAI District Clinician Manual: WHO 2011 (81). TB, tuberculosis; HIV, human immunodeficiency virus; SpO2, oxygen saturation; AVPU, mental status score (awake; response to voice; response to pain; unresponsive); PCP, pneumocystis pneumonia. NIV, non-invasive ventilation; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure.
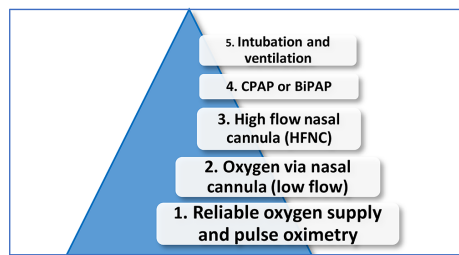
Figure 2 A suggested priority order for oxygen and respiratory support in LMIC. Modified from Inglis *et al*. (45).

clear history of fluid losses (diarrhoea, vomiting) or decreased intake must be prioritized for titrated modest volume fluid resuscitation. It is important to check and correct low levels of glucose depending on available facilities. If point-of-care monitoring of blood gases lactate and/or metabolic parameters such as calcium are present, these should be expeditiously performed.

In light of the risk of fluid-overload especially in patients with co-morbidities including anemia and malnutrition, a suggested option is to avoid the initial fluid bolus in the absence of a fluid-losing state, and, if the patient perfusion is impaired, initiate low dose vasoactive infusion depending on availability.

Regarding initial vasoactive-inotrope, studies conducted in India and Brazil comparing dopamine *vs.* epinephrine indicated that epinephrine may be associated with lower risk of mortality and more organ failure-free days among survivors, and norepinephrine or epinephrine are now considered as first choice of vasoactive support in pediatric sepsis (3). However, the initial choice depends on availability and familiarity, and in many parts of the world dopamine and epinephrine are the usual first-line agents since they are cheap and readily available (83).

A dilute concentration of the vasoactive medication may be infused via a secure peripheral or intraosseous line if central access is unavailable.

Clinical identification of fluid-overload (FO) is especially challenging in young children, in whom crackles may be absent even when gross pulmonary edema is present (3). Worsening respiratory mechanics, particularly increasing tachypnoea, chest X-Ray features of pulmonary edema, or increasing liver span may be the only evidence of progressive fluid overload. Even in low-income countries, some health-care facilities may have access and expertise for rapid bedside point-of-care ultrasound, which can be very useful to tailor fluid and vasoactive inotrope infusions.

Bedside echocardiography and ultrasound may be very helpful to assess early FO, as there is increasing evidence that a "full" inferior vena cava (IVC) with minimal respiratory variation indicates adequate intravascular volume (84). A "wet" lung profile may also confirm that further fluid bolus administration may be harmful.

In the event that a patient presents with septic shock without a history of fluid loss, alternatives to initial small fluid bolus include early initiation of an inotrope-vasoactive agent ± small volume fluid bolus especially in regions without access to mechanical ventilation, where the ability to provide respiratory support in the event that the patient worsens may be not be available.

Abnormal electrolyte values, especially low glucose, and calcium levels as well as hypothermia and hypoxemia should be corrected during the initial resuscitation.

Monitoring of cardiorespiratory response and titration of hemodynamic support

Whether fluids or vasoactive infusions are the first approach to the treatment of septic shock, the caregiver must carefully assess the response by monitoring serial trends in the heart rate, systolic mean and diastolic arterial blood pressure, oxygen requirement and respiratory mechanics, as well as clinical markers of cardiac output, all of which are reasonably straightforward to monitor even in LMICs.

Respiratory/ventilatory support for patients with septic shock in LMIC: pragmatic solutions (*Figure 2*)

Oxygen

Supplemental oxygen is the most important support for patients with acute respiratory failure and pulse oximetry is mandatory to monitor this therapy (85). Nasal cannulae (NC) are useful options in many hospital wards in environments with limited personnel since lower nursing skills are required to use this device safely (45).

Continuous positive airway pressure (CPAP)

Three trials from LMICs have recently demonstrated that CPAP can improve survival in children <5 years, compared with oxygen delivered via standard nasal cannula, further CPAP can also minimize the requirement for invasive mechanical ventilation (86-88).

High flow nasal cannula (HFNC) oxygen therapy is a very effective and promising respiratory support modality in LMIC among patients with moderately severe hypoxaemia, and can decrease the need for invasive mechanical ventilation since it can provide low-levels of CPAP as well as minimize dead-space, thereby eliminating carbon dioxide (89). Moreover, HFNC requires less training for safe use and is generally well tolerated without VAP risks.

The disadvantage of HFNC is the requirement for very high oxygen requirements which may be a heavy draw on a hospital's limited oxygen supplies, however, HFNC is an important target for exploration in LMIC (45).

Consideration should be given to a trial of high-flow nasal oxygen or mark noninvasive ventilation (NIV) for patients with moderately severe hypoxaemia before considering endotracheal intubation. While the WHO guidelines continue to support the use of HFNC oxygen, they emphasize close monitoring to recognize clinical deterioration that may require emergent intubation (90).

Non-invasive ventilation (NIV)

A 2018 systematic review and meta-analysis outlined a comprehensive review of noninvasive ventilation (NIV) in LMICs, including bubble CPAP and ventilator-delivered NIV in both children and adults (90).

NIV was reported to be a safe support in ICUs in Africa and South Asia. However, the greatest risk of NIV is the potential to for intubation to be delayed, leading to higher mortality, further, NIV requires significant training and close patient monitoring to deliver effectively. However NIV is feasible and safe in many LMICs, and warrants further investigation to use safely in these areas (90).

Intubation and controlled mechanical ventilation must be considered in those with decreased conscious level, or decreased airway protection, or those with significant cardio-respiratory decompensation.

Sedative and analgesic drugs along with positive pressure ventilation (PPV) may cause significantly found reduced preload resulting in worse hemodynamic instability in the peri-intubation period. Isotonic fluids and dilute solutions of vasoactive infusions should be readily available. Ketamine should be the preferred induction agent since it can maintain relative cardiovascular stability (3). However, low titrated doses should be used, since patients who are "catecholamine-depleted" are at risk for cardiovascular collapse. Induction with agents such as benzodiazepines and propofol can result in profound hypotension and should be avoided (16).

If intubation and ventilation are unavoidable, iatrogenic harm must be avoided by minimizing secondary infections, and efforts to expedite weaning and liberate the patient from the ventilator at the earliest opportunity. Moreover, discussions with the family must emphasize expectations that are realistic with regards to duration of ventilation, prognosis and costs and, in order to minimize risks of continuing support to the point of futility at an ongoing escalating cost that is usually borne by the family (45). This strategy has important implications in contexts where the provision of PPV even for a single day can result in catastrophic expenditure (91).

Training and quality improvement programmes

Championing low-cost high-impact quality improvement (QI) programmes

It is essential that the critical care leadership in LMIC relentlessly champion the meticulous implementation of simple QI measures that have large impact e.g., those that can greatly improve outcomes at minimal resources and cost. Two examples in an Indian pediatric cardiac-surgical ICU include establishment of a strong infection prevention programme in the ICU and implementation of a surgical safety checklist (92,93). While some obstacles may have to be initially overcome to engage all concerned stakeholders successfully, once improvements become evident, implementation becomes easier.

Education, training and mentorship of health professionals at many levels

This is a invaluable investment because it empowers personnel, especially nurses. Nurse empowerment leads to improved outcomes through higher-quality care, ongoing education, improved infection control and a far greater motivation (68,94).

International Collaboration-developing partnerships

Despite great differences in environments, a lot may be learnt from the established health care facilities in HIC.

The LMIC- HIC collaboration can successfully improve many aspects of patient care, and provide career growth opportunities for local researchers (95). However, care should be taken that such collaborative efforts are well-grounded with realistic goals within the LMIC hospital systems.

The future is closer than you thought! Harnessing progress in innovative digital health technology in LMIC

Although the challenges to scaling up to high-quality intensive care services are numerous, the opportunities to creatively improvise in this field are even more and hold promise to move LMIC closer to HIC equity in global healthcare (96). Emerging digital health and innovative technology may offer a large part of the solution paving the way for the development of an inexpensive, scalable, and sustainable model of critical care in LMICs.

At the global level, collaborative efforts towards a less-siloed approach to scaling and integrating digital health may provide the necessary leadership to enable innovative solutions to reach healthcare practitioners and patients in LMICs (97).

Wide-spread penetration of mobile technology

Ubiquitous tools and technologies such as smart phones, cloud computing, three-dimensional printers, crowdfunding and social media have given rise to frugal grassroots innovation and entrepreneurship (98). For example, India used its Information-technology (IT)-ability to leapfrog poor medical infrastructure. "*India leapfrogged twice earlier, and went from no phone to smartphone, and from no books to the internet. Technology can make quality healthcare accessible at affordable prices to all our citizens even in the remotest corners of countries.*" (99).

The problem of limited clinical availability can be overcome using smart technology especially when identifying of the child at risk. A novel digital triage tool is being developed and clinically evaluated in Africa that aims to identify high-risk patients and reduce treatment times. This mobile health platform, will provide an individualized risk prediction in real-time to facilitate the rapid triage patients and institution of life-saving therapies for children in LMIC, where the concerned specialists may not always be available and sepsis deaths are common (100).

Telemedicine

Telemedicine as applied to critical care also referred to as tele-critical care (TCC) accommodates the concept that TCC services can be provided to locations beyond the physical confines of an ICU, or a hospital (101).

Digital health in the Philippines pioneered open-source telemedicine and mobile Health projects that connected remote patients with specialists in the Philippine General Hospital (PGH). This community-based approach delivering eHealth solutions has gathered momentum in recent years, as the lack of doctors, nurses and other allied health workers in underserved areas became more severe (102).

Wearable technology

Inexpensive wearable devices offer an affordable approach to monitoring of vital signs in LMICs, and when combined with artificial intelligence (AI), may potentially also improve patient care, not only within the hospital but also to provide monitoring after discharge of high-risk patients with sepsis and ARDS (103).

Wireless wearable smart patches continuously and automatically track a patient's vital signs and is able to flag any changes in patient's condition and alert caregivers to early-onset sepsis far sooner than may be done by traditional monitoring. Further, these "smart patches" also performs real-time monitoring of the patient's response to treatment. Developments in this technology may be useful for clinicians and nurses in LMIC, since it have the potential for providing earlier alerts of patient clinical deterioration than with manual monitoring alone, especially for clinicians and nurses who are battling overwhelming workloads (104).

Artificial intelligence (AI) and machine learning models may improve early detection and complex decision making in sepsis

In order to reduce the great clinical variability in sepsis treatment with less than optimal decisions often leading to poorer outcomes, a reinforcement learning agent, the Artificial Intelligence (AI) clinician was developed, which extracted knowledge from many patients' data that exceeds by many-fold the life-time experience of human caregivers and was able to learn optimal therapeutic approach by analyzing multiple treatment decisions. The authors reported that the "AI clinician model" was able to provide individualized treatment decisions for sepsis that could improve survival from sepsis (105).

Frugal innovation: doing more with less for more

Frugal innovation is the idea that more can be done for less for many more people globally. i.e., to create significantly

more value while minimizing the use of resources (102).

The healthcare sector stands to benefit most from the concept of 'frugal medical technologies that are poised to disrupt the healthcare economy and will hopefully meet the unmet clinical needs of the world' (106,107).

A brief outline of types of frugal innovation in medicine with examples include the following.

Lean tools refer to techniques that simplify and adapt existing technologies and provide healthcare innovations to many more at greatly reduced costs. For example, a low-cost toaster-sized ventilator (AGVA) costing ~2,000 USD was developed in India by a neurosurgeon and robotic scientist and has been shown to provide safe ventilator support even in non-ICU environments. It is small (~3.5 kg), portable, robust, compatible with temperature fluctuations, unstable power sources and can function even with oxygen from a cylinder and has a built-in air-compressor. The device is highly functional, hardy, and user-friendly (by intensivists, nurses, and even family members during home-use if required), and is especially relevant during the current COVID-19 pandemic. While not optimal for infants and smaller children, it's consumables are re-usable.

General Electric's MACi ECG (108) and Rice University's bubble CPAP (88) are prime examples of equipment stripped of superfluous functions enabling the costs to be reduced to 1/2–1/15th that of the original counterparts. Beyond being simply low-cost these devices have many advantages: they are portable, easy to maintain, able to function in austere environments with inexpensive and accessible spare parts. Lean tools developed for LMIC are sometimes so cost-effective and efficient that they are even better than the original solutions used in HIC. For example, Chinese engineers at Siemens company have removed infrequently used settings and developed an inexpensive CT scanner. The resulting machine has cut the cost by a third and the technology has "reversely" spread in the United States (109).

Opportunistic solutions refer to the clever use of inexpensive widely available technologies to overcome "old problems". Evolving mobile phone technology and the internet can have radical possibilities, from improved adherence to antiretroviral therapy via a mobile-phone text messages (110) to identifying drugs that are counterfeit (111). 3D printers may improve accessibility to medical devices ranging from low-cost prosthetics (112) to equipment spare-parts.

Contextualized adaptations refer to the re-purposing existing materials tools or techniques, for example, urine

reagent strips used to evaluate cerebrospinal fluid (113) or synovial fluid (114) were found to be reasonably good diagnostic tests, that are cheap and usable in poorly-resourced environments.

Ready for prime-time: rapid identification of infectious diseases, sepsis identification and antibiotic susceptibility testing

While rapid sepsis diagnosis is ideal for targeted therapy and infection control, conventional laboratory approaches are expensive, labour-intensive, and associated with unacceptable time-delays. Recent advances in micro-nanotechnologies have facilitated the development of low-cost micro-fluidic point-of-care (POC) devices for the rapid diagnosis of malaria, sepsis, and HIV infections, and the authors discuss the challenges to practical implementation and future perspectives (115).

Antimicrobial resistance (AMR) is at the forefront of global importance and concern, with increasing mortality rates and rising economic burden. Inadequate antimicrobial stewardship has resulted in an increasingly diverse scale and range of AMR mechanisms, and tackling this effectively requires ongoing education and improved diagnostics. A study that employed inexpensive, commercially available screen-printed electrodes that were modified with an agarose-based hydrogel deposit that show rapid growth, with potential time to antibiotic susceptibility results that were <45 minutes, demonstrating a significant improvement on the current gold standard of 24–48 hours, potentially allowing doctors to be able to prescribe the correct antibiotic to a patient for an infection more quickly (116).

Pediatric critical care and pediatric sepsis research gaps in LMIC

In the last 2 decades intensive care medicine research has picked up the pace and countless randomised controlled trials have been performed, supplying clinical care with the much needed scientific foundation, discarding obsolete treatments, and saving lives (117). Unfortunately only 10% of global health-care research expenditure addresses conditions that affect the poorest 90% of the world's population, often referred to as the Research "10–90 gap" (118). Worldwide conformity in sepsis care is an elusive pipe dream; thus, we should accept that differences exist but foster research to improve systems and tailor best practices to local context.

Lessons from the pandemic

In LMICs, the COVID-19 pandemic has drawn stark attention to the scarcity of vitally-important critical care resources; it has also emphasized the ongoing need for training of health-care workers, the need for establishing management approaches that match local resources, and research that is focused on the unique clinical practice in LMICs.

Conclusions

In LMIC settings, the burden of childhood mortality from preventable deaths remains unacceptably high and a large undocumented burden of sepsis and critical illness continues to exist.

The great heterogeneity of common critical care syndromes such as sepsis and ARDS has slowed down progress in identifying treatment targets and consequently the needs of critically ill patients in LMIC are often unmet, with some patients exposed to interventions that can even harm. Given the wide variation in resources, it may be unrealistic to expect similar targets and global consensus on all aspects of management, and local critical care leadership in various regions must tailor a pragmatic diagnostic and therapeutic approaches to a range of conditions in their settings (117). This approach will engage many more clinicians and benefit children afflicted with sepsis in both resource poor and rich environments.

The Millennium Developmental Goals era has witnessed great progress in child health which has been due to collaborations among the public, governments, as well as the private sectors. Avoiding preventable deaths will not only greatly reduce the disease burden and mortality but will also help improve life expectancy and thereby decrease birth rates, increase household productivity, and even have a favourable impact on the gross domestic product. Investments in critical care should be appropriate and effective rather than cost- or technology- intensive. Such investments, can have large dividends across many clinical specialties as well as have a favourable impact on the health outcomes of populations (119).

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