Review Article

Sepsis and septic shock

A global perspective and initiative

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ABSTRACT

الالتهاب الإنتاني (تعفن الدم) والصدمة التعفنية من العوامل الكبير المؤدية لوفاة الأطفال على مستوى العالم. هناك عدة عوامل تؤدي إلى نتائج سيئة في حالة حدوث الصدمة التعفنية، وتعتبر محدودية المصادر في الدول النامية أحد أهم هذه العوامل. قد يؤدي الكشف المبكر والمعالجة اللازمة باستخدام الطرق البسيطة إلى وقف هذا التدهور والشفاء من حالة الصدمة في معظم حالات الأطفال. ومن المعروف، وعلى الرغم من محدودية المصادر إلى انه قد تم إحراز نجاح كبير في بعض مناطق العالم. نستعرض في هذه التقرير الإنجازات المميزة خلال السنوات الماضية، كما قمنا بمناقشة وإصدار أنظمة منهجية لتؤخذ بعين الاعتبار في بيئة محدودة المصادر. بالإضافة إلى الدعوة لتوسيع المشاركة في المبادرة العالمية للالتهاب.

Sepsis and septic shock are major contributors to mortality in children worldwide. While many factors may contribute to poor outcomes, resource limitations play a role in developing countries. However, early recognition and aggressive therapy using simple measures can reverse shock in most children. Indeed, great gains have been realized in some areas with limited resources. In this manuscript, the significant gains over the last few years are outlined, and issues to consider in resource limited environments are discussed. In addition, an invitation is extended to participate in a global sepsis initiative.

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Sepsis and septic shock are the major contributors to death in children worldwide with severe pneumonia, diarrhea, malaria, and measles leading the way. Indeed 80% of deaths in children can be classified as sepsis deaths.[1,2] Most of these deaths and the under 5-year-old age group occurs in Africa and the Asian subcontinent (**Figure 1**). While many factors may contribute to the deaths, there seems to be an inverse relationship between the Gross Domestic Product (GDP) of a country (a reasonable surrogate marker of its wealth) and mortality in the under 5-age group (**Figure 2**). However, GDP cannot be the only contributing factor to deaths as evidenced by marked decrease in mortality in pediatric septic shock from 1963-2005.[3] Indeed, some of the major gains in the outcomes from malaria and dengue shock have been made in areas with limited resources. Overall, while initial gains in sepsis outcomes were heralded by the emergence of intensive care medicine as a discipline in the late 1970s, later gains can be attributed to the WHO's recommendation of aggressive fluid resuscitation and in the 1990s by dedicated teams with training and expertise in treatment of shock.[3] Intensive care therapies are important in the treatment of septic shock, however, appropriate treatment and good outcomes for most patients do not depend on sophisticated critical care and can be achieved with limited resources in most parts of the world. Indeed, the approach to the management of septic shock as outlined in the American College of Critical Care Guidelines highlight simple effective measures that are useful in any circumstance.[4]

The management of shock can be thought of as an occurring in various phases as outlined in **Table 1**. Prevention is ideal, but it is not always possible. Early and aggressive treatment of shock at any stage may later halt the progression to stages and may negate the need for complex, expensive therapies that are not available for many children in the developing world. In this manuscript, the author outline the gains in sepsis outcomes that have been achieved worldwide;

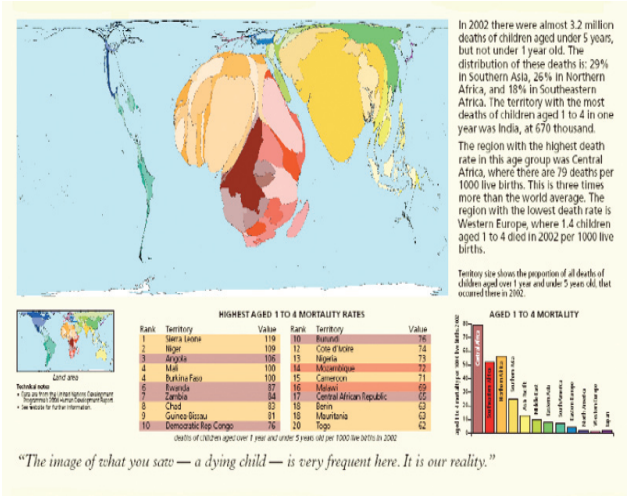

Figure 1 - Distribution of mortality of 1-4 year old worldwide represented by landmass. Copyright 2006 SASI Group (University of Sheffield) and Mark Newman (University of Michigan) (http://www.worldmapper.org/).

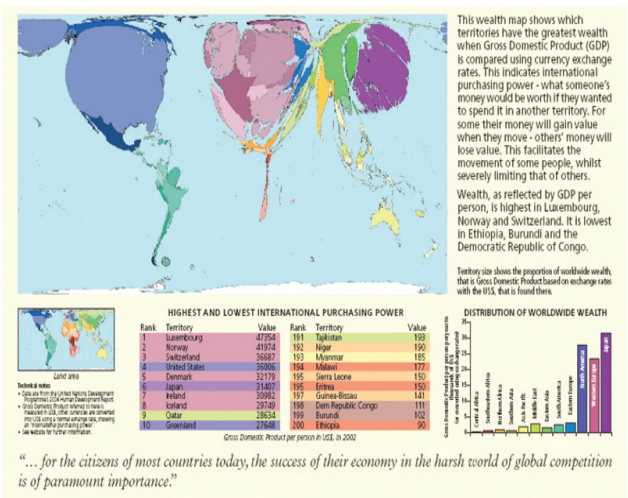

Figure 2 - Distribution of wealth worldwide represented by landmass. Copyright 2006 SASI Group (University of Sheffield) and Mark Newman (University of Michigan) (http://www.worldmapper.org/).

Table 1 - The continuum of care for the child with shock of various stages.

Shock of various stages and continuum care
Pre-shock
Prevention
Adequate nutrition
Micronutrients
Portable water
Immunizations
Early shock
Preservation
Airway, breathing
Circulation
Oxygen
Fluid boluses
Antibiotics
Late shock
Resuscitation
As for preservation
Assisted ventilation
Vasopressor
Inotropes
Post shock stabilization
Organ support
As for resuscitation
Complex ventilation
Vital organ support, such as renal replacement therapy and ECLS

ECLS - extracorporeal life support

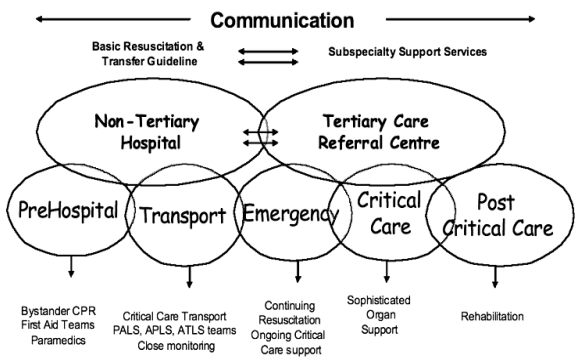

Figure 3 - Optimal outcome for the critically ill children. CPR - cardiopulmonary resuscitation, PALS - Pediatric advanced life support, APLS - advanced pediatric life support, ATLS - advanced trauma life support.

issues to consider in resource limited environments and highlight a global initiative to treat sepsis based on available resources. This is not intended as an exhaustive systematic review of sepsis, however, it includes up-to-date relevant studies, consensus opinions and items from discussions and meetings of experts on the subject at the World Federation of Pediatric Intensive and Critical Care meeting in Geneva in 2007.[5]

Improvement in sepsis outcomes. Sepsis is a dynamic process in which early interruption of insults can prevent organ damage.[6] Sepsis is associated with an early transient activity of pro-inflammatory cytokines corresponding to the clinical designation of systemic inflammatory response syndrome (SIRS) and the onset of damage. Shortly after this phase, endogenous anti-inflammatory pathways become activated, the compensatory anti-inflammatory response syndrome (CARS), which includes anti-inflammatory cytokine release and the development of a refractory state characterized by a decreased capacity of mononuclear cells to produce pro-inflammatory cytokines on stimulation ex-vivo. Recovery occurs if homeostasis

is reestablished.[5] Early interruption of the cycle and homeostasis should therefore be the goal of treatment in all cases. This contention is also supported by Kumar et al[6] who reported a mortality risk increase with delay in initiation of effective anti-microbial therapy (hospital mortality-adjusted odd ratio 1.12 per hour of delay, 95% confidence interval: 1.101 to 1.36, $p<0.0001$).[7] If one considers the critically ill septic child, it is well recognized that early fluid resuscitation antibiotics and inotrope therapy directed to goals of threshold heart rate, normal mental status normal perfusion pressure, urine output of >1 ml/kg/hr and capillary refill less than 2 seconds improves outcome.[4] Indeed, repeated use of the 2002 Guidelines revealed useful and effective without evidence of harm.[8-13] Wills et al[14] reported that there was nearly 100% survival when fluid resuscitation was performed in children with dengue shock. The success in treating meningococcal sepsis is evidenced by a reduction in mortality to approximately 2% with early goal-directed resuscitation (a reduction not predicted by the Pediatric Risk of Mortality [PRISM] score).[15] Conversely, there was an association between delay in inotrope resuscitation and a 22.64 fold increased adjusted mortality odd ratios in meningococcal septic shock.[15]

Resource limitations and outcomes. It is important to realize that while the gains in meningococcal sepsis have occurred in the developed world (well resourced environment),[14] gains in malaria, dengue and bacterial sepsis outcomes have been achieved in the developing world with limited resources.[6,14,16,17] However, the lack of resources including mechanical ventilation puts children in the developing world at a disadvantage.[17] In order to frame the issue of vulnerability in children in developing countries, it is instructive to compare the medical response and outcome for a child with a similar affliction in the developed and developing world. Using severe meningococcal shock as an example, the best outcome (mortality rate of 2%) is afforded when there is seamless deliveries of protocolized care from the pre-hospital setting, during transport, and the availability of tertiary pediatric emergency and critical care facilities.[14] However, the ability to provide this level of care is sorely lacking in many developing countries.[17-20] Management failure in the treatment of meningococcemia on the other hand has been attributed to the absence of pediatric care, failure in supervision by consultant, failure in assessment of patients and failure to recognize severity factors all too common in the developing world.[10] These factors may result in the administration of too little fluid or inadequate inotropes.[10] However, these oversights do not tell the full story. Even in situations where shock is recognized, essential medications, supplemental oxygen, appropriate fluids, and adequate staff are under-resourced in many referral centers.[18] Besides lack of resources, poor use of IV fluids and poor airway management skills, lack of resuscitation protocols also hampers the care of children when they arrive to the hospitals.[21] It is therefore not surprising that outcomes are worse in these environments. Another issue that may contribute to increased mortality and morbidity from sepsis and septic shock in developing countries is the fact that nearly three-fourth of the world's underweight children live in just 10 countries including India, Bangladesh, Pakistan, China, Ethiopia, Indonesia, Democratic Republic of Congo, Philippines, and Vietnam. The importance of being underweight or malnourished is highlighted by the fact that nearly half of neonatal deaths are deaths due to diarrhea, pneumonia, and malaria, and are often children who are underweight.[19] Moreover, being malnourished also complicates the management of shock.[22] Treatment of the child in septic shock or other critical illness is also hampered by the lack of resources to provide the full continuum of care from pre-hospital care through emergency and critical care and post care rehabilitation (**Figure 3**). That the full spectrum of services is required that was highlighted by a report from Andhra Pradesh, India wherein patients were transported using rickshaw, cars, and buses without oxygen or airway support to get patients to a well-equipped modern pediatric intensive care unit. Under these circumstances, mortality due to respiratory disease was 52% and 71% in those under one year of age who were ventilated.[20] In addition, 40% of children died within 12 hours highlighting the severity of their condition on arrival to the hospital.[20] Even when optimal aggressive care is provided in the emergency department, children may die due to lack of ready availability of mechanical ventilators for those in respiratory failure.[17] Another example was provided by a multi-center trial of 3 PICU(s) in Malaysia comparing non-specialized transport (n=827) versus in hospital transfers (n=877); there was no difference in the standardized mortality rate adjusted for PRISM scores, length of stay or age[23] again highlighting the need for optimal pre-hospital as well as hospital services. However, recognition and acceptance of the need for the full spectrum of services still beg the question of whether this goal is achievable or whether other models of care need to be explored.

Ethics of care in resource limited environment. If those in the developing world attempt to provide access to intensive care units at the standard of care in the developed world, one would not have the resources. Any attempt to do so will seriously distort health care budgets. Engelhardt have argued persuasively that the inegalitarian health care promised to American's (the best of care, equal care, physician/patient choice without

runaway costs) and others in the developed world is impossible to achieve and suggests that an egalitarian health care policy should be adopted in which there are numerous standards with some critical care.[24] For instance, standards may be as follows: excellent basic care with access to excellent critical care; basic general care with access to basic critical care; basic care without access to critical care; and curtailed basic care. Based on the principles of equity, all countries should ensure that highly cost-effective health interventions that will reduce mortality are available to all before funding intensive care services. Others have argued that defining a minimum level of care based upon the nation's resources that must be available for all children should be guided by the principle of distributive justice.[25] For example, in South Africa the HIV epidemic has placed large burden on pediatric intensive care[26,27] and raised complex ethical issues. Some have suggested a utilitarian approach whereby it is ethically defensible to refuse to ventilate children with severe HIV-associated pneumonia if such resources were redirected towards program aims at preventing mother-to-child transmission.[28] Such decisions can never be made on an individual case, but rather can only be decided after consideration of distributive justice and broader health policies. This debate is at the core of the treatment of sepsis and septic shock because they contribute the most to mortality in childhood in developing countries.[1,2] Adequate resources are a pipe dream for most of the developing world, and hence we must look at the alternative methods of care delivery.

Alternative models of care. Provision of care for children with sepsis in developing countries needs not be guided by high tech interventions such as complicated monitoring of cardiovascular function. If shock is recognized early and the ACCM guidelines are followed, most children will respond to the initial therapy (fluids, antibiotics, and supplemental oxygen), some will require mechanical ventilation, very few will require complex ventilation, renal replacement therapy, or extracorporeal life support. However, in situations in which the resources are available to monitor central venous oxygen saturation continuously, it has proven of benefit in decreasing morbidity and mortality.[29] Indeed, monitoring of central venous saturation may prevent target organ dysfunction and obviate the need for high tech therapy such as renal replacement and extra corporeal life support.[30] However, in some areas of the world the scarcity of physicians and even nurses may necessitate that other models of care and a different type of care provider are used. For instance, care can be modeled after the neonatal care delivery model that has been highly successful in Bangladesh, India, and Pakistan with a decrease of 60% in neonatal mortality in the Gadchiroli district.[31] The cost per life saved was US$95.40 (NNT = 18) in Maharastra.[32] The WHO handbook provides useful resource for training such teams and implementing prevention and treatment programs.[22] Its use should be encouraged in all countries with limited resources. Recognition of the resource limitations has also led to the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS) global initiative as an educational, interactive, and participative program to assist in treating sepsis and septic shock. World Federation of Pediatric Intensive and Critical Care Societies sepsis initiative (www.wfpiccs.org).[5] This global health initiative was launched because of the recognition that simple interventions including immunization, vitamin and mineral supplements, antibiotics, fluid resuscitation and inotrope support can reduce mortality from sepsis and septic shock in a remarkably cost effective manner. The evidence-based recommendations are condensed into a bundle of tasks. There are 4 potential categories to choose from based on regional child mortality rate and national economy. These are: 1) non-industrialized setting with child mortality >30/1,000, 2) non-industrialized setting with child mortality <30/1,000, 3) industrialized developing nation, and 4) industrialized developed nation. Each category has both administrative and clinical care bundles, with recommendations for more technologies and interventions as child mortality rates decrease and wealth increases. To participate, one must register your institution and then enter patient data anonymously into the appropriate bundles. In order for participating institutions to keep track of progress from an administrative and clinical practice standpoint, a regular report will be generated and sent back to all participants. The intention of tracking these bundles is to demonstrate the improving outcomes as a bundle compliance improvement over time in each participating center. Moreover, comparisons can be made within centers with similar resources to look for best practice. The initiative is anchored at the www.wfpiccs.org/sepsis website. In this website, the sepsis bundle registry are available for all practitioners such as education materials, protocols, interactive forum and education videos. Implementation of guidelines and subsequent evaluation of the effectiveness of it will be achieved by using the bundle registry strategy. In addition, by encouraging and involving worldwide documentation of clinical practice and patient outcomes, we will be better able to understand factors responsible for regional differences in outcomes. Therefore, all clinicians are urged to participate in this endeavor.

In conclusion, we recognize that treatment of the critically ill child with sepsis and septic shock mostly does not require sophisticated and expensive resources.

However, even these resources are non-existent or deficient in many parts of the world. Where resources are limited western models of provision of care including the inegalitarian approach are not relevant and hence a change with a different strategy is necessary. It is also recognized that the developed world can learn lessons from the developing world to decrease the inefficiency in our systems. Relationships between the developed, and developing world should therefore be symbiotic.

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