World Federation of Pediatric Intensive Care and Critical Care Societies: Global Sepsis Initiative*

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Background: **According to World Health Organization estimates, sepsis accounts for 60%–80% of lost lives per year in childhood. Measures appropriate for resource-scarce and resource-abundant settings alike can reduce sepsis deaths. In this regard, the World Federation of Pediatric Intensive Care and Critical Care Societies Board of Directors announces the Global Pediatric Sepsis Initiative, a quality improvement program designed to improve quality of care for children with sepsis.**

Objectives: **To announce the global sepsis initiative; to justify some of the bundles that are included; and to show some preliminary data and encourage participation.**

Methods: **The Global Pediatric Sepsis Initiative is developed as a Web-based education, demonstration, and pyramid bundles/checklist tool (http://www.pediatricsepsis.org or http://www.wfpiccs.org). Four health resource categories are included. Category A involves a nonindustrialized setting with mortality rate <5 yrs and >30 of 1,000 children. Category B involves a nonindustrialized setting with mortality rate <5 yrs and <30 of 1,000 children. Category C involves a developing industrialized nation. In category D, developed industrialized nation are determined and separate accompanying administrative and clinical parameters bundles or checklist quality improvement recommendations are provided, requiring greater resources and tasks as resource allocation increased from groups A to D, respectively.**

Results: **In the vanguard phase, data for 361 children (category A, n = 34; category B, n = 12; category C, n = 84; category D, n = 231) were successfully entered, and quality-assurance reports were sent to the 23 participating international centers. Analysis of bundles for categories C and D showed that reduction in mortality was associated with compliance with the resuscitation (odds ratio, 0.369; 95% confidence interval, 0.188–0.724; $p < .0004$) and intensive care unit management (odds ratio, 0.277; 95% confidence interval, 0.096–0.80) bundles.**

Conclusions: **The World Federation of Pediatric Intensive Care and Critical Care Societies Global Pediatric Sepsis Initiative is online. Success in reducing pediatric mortality and morbidity, evaluated yearly as a measure of global child health care quality improvement, requires ongoing active recruitment of international participant centers. Please join us at http://www.pediatricsepsis.org or http://www.wfpiccs.org. (Pediatr Crit Care Med 2011; 12: 494–503)**

KEY WORDS: children; critical illness; infection; outcomes; quality assurance; sepsis; shock

In 2005, the World Health Organization (WHO) announced that 80% of global child deaths were related to five severe infections, namely pneumonia, malaria, measles, neonatal sepsis, and diarrhea (1, 2). According to WHO–Integrated Management of Childhood Illnesses guidelines, sepsis is defined as infection with tachypnea and tachycardia; severe sepsis is defined by sepsis with acidosis or other organ failure; and septic shock is defined as stage III shock with tachycardia and poor perfusion and stage IV shock with hypotension (2). Mortality increases as disease progresses from sepsis, to severe sepsis, and to septic shock. Remarkably, trials demonstrate that simple interventions including immunization, vitamin and mineral supplements, antibiotics, fluid resuscitation, and inotropic support reduce mortality from these conditions 10- to 100-fold in a cost-effective manner (Fig. 1).

The World Federation of Pediatric Intensive Care and Critical Care Societies (WFPICCS) announced at the World Congress in Geneva Switzerland in 2007 that it intended to launch its first global health initiative, a quality improvement program with the goal of realization of these simple interventions for children. The Global Pediatric Sepsis Initiative has now begun at http://www.wfpiccs.org/sepsis and http://www.pediatricsepsis.org. Here, educational materials, protocols, evidence-based clinical practice parameters, interactive education sepsis videos, Web site sepsis bundle/checklist registration, and Web site clinical research registration are present. Three sets of published evidence-based guidelines for the management of sepsis (Integrated Management of Childhood Illnesses–World Health Organization) (2, 3), severe sepsis (Sur-

*See also p. 589.

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On behalf of the WFPICCS and Contributors, see Appendix.

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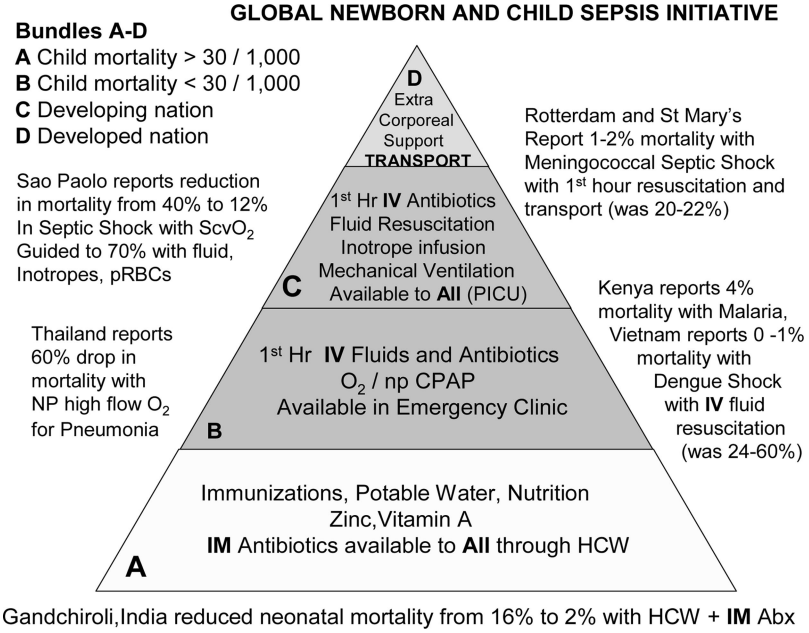

Figure 1. The sepsis initiative administrative bundles pyramid. This pyramid demonstrates the administrative recommendations according to levels of health resources from the health resource-scarce (level A) to health resource-abundant (level D). The foundation of care is level A. It is expected to be provided to populations with <5-yr child mortality and >30 of 1,000 children. Level B is distinguished from level A by the ability to deliver oxygen and intravenous therapies. It is expected to be provided to populations with <5-yr child mortality and <30 of 1,000 children. Category A indicates nonindustrialized setting with child mortality rate >30 of 1,000 children; category B indicates nonindustrialized setting with child mortality rate <30 of 1,000 children; category C indicates industrialized developing nation; and category D indicates industrialized developed nation. Level C is distinguished from level B by the ability to deliver machine-driven therapy to all. It is expected to be provided in the developing industrialized setting. Level D is distinguished from level C by the presence of an organized transport system and the ability to deliver extracorporeal therapies to all. It is expected to be provided in the developed industrialized setting. Categories A and B are in the nonindustrialized setting. Categories C and D are in the industrialized setting. In category A Bang et al, demonstrated an eight-fold reduction in neonatal mortality when intramuscular (*IM*) gentamicin and oral cotrimoxazole were administered by rural healthcare workers. In category B, investigators in Thailand, Vietnam, and Kenya demonstrated that administering high-flow oxygen (O_2) and isotonic intravenous fluid boluses reduced mortality from pneumonia, dengue shock, and severe malaria. In category C, de Oliveira et al demonstrated a four-fold reduction from septic shock with American College of Critical Care Medicine/Pediatric Advanced Life Support goal-directed therapy. In Rotterdam and London, investigators demonstrated a ten-fold reduction in mortality from purpura and meningococcemia with a transport team and tertiary center care. *IV,* intravenous; *PICU,* pediatric intensive care unit; *npCPAP,* nasopharyngeal continuous positive airway pressure; *HCW,* healthcare worker; $ScvO_2$, superior vena cava oxygen saturation; *pRBC,* packed red blood cells; *NP,* nasopharyngeal.

viving Sepsis Campaign) (4, 5), and septic shock (American College of Critical Care Medicine [ACCM]/Pediatric Advanced Life Support [PALS]/American Heart Association [AHA]) (6–8) are available at the Web site. The sepsis bundles/checklists were developed based on the recommendations of these three sets of internationally sanctioned guidelines. Implementation of these guideline-derived bundles/checklists and subsequent evaluation of their effectiveness require worldwide documentation of clinician practice and patient outcome, which is the ultimate goal of the Global Pediatric Sepsis Initiative.

Although the success of this initiative depends entirely on voluntary participation by the world's pediatric critical care professionals, most deaths from sepsis occur globally in locations without intensive care units. Many of these deaths can be prevented when using less sophisticated measures recommended, in part, in WHO–Integrated Management of Childhood Illnesses guidelines. Participation of colleagues in the developed and developing countries in the initiative will enable a better understanding of regional resource limitations and potentially improve outcomes with implementation of resource-appropriate quality improvement programs. Recognizing the importance of resource disparities, the Global Sepsis Initiative incorporates separate quality improvement recommendations or bundle/checklists according to the resource settings recognized by WHO. First, participants log into the initiative at http://www.pediatricsepsis.org or at http://www.wfpicccs.org. Here, they can click on educational, guideline, research, or quality-assurance icons. Participants who wish to join in the quality-assurance initiative first register and answer prompts that result in their placement into categories depending on the information they provide regarding resources that are available. Based on this information, they are directed to guideline based recommendations that are condensed into bundles of tasks or "checklists" that have been created for use according to these regional child mortality rates and economic parameters. These four resource-specific categories based on WHO recommendations are: 1) category A: nonindustrialized setting with <5-yr mortality >30 of 1,000 children; 2) category B: nonindustrialized setting with <5-yr mortality and <30 of 1,000 children; 3) category C: industrialized developing nation; and 4) category D: industrialized developed nation.

Each category has separate administrative and clinical care bundles, with recommendations for more technologies and interventions as child mortality rates decreases and wealth increases. Because institutions may not fit well into one category or another, participants are given the opportunity to choose the category that they feel best fits their needs.

Depending on the category assigned, the participant is then directed to enter the individual patient data aided by a series of prompts. Before entering data, participants are asked to review the guidelines available on the site and to determine whether a given intervention was needed. For each recommendation, the participant enters "yes" if it was performed, "no" if it was not performed, and "not applicable" if it was not performed but was not applicable to this particular patient. For example, if a patient needed a mechanical ventilator and it was not provided, then the participant enters "no." If the participant did not receive a ventilator because it was not needed, then the participant enters "not applicable." If a ventilator is provided, then the participant enters "yes." A quarterly report is generated and sent back to the partici-

pant for comparison with the previous performance and with the other anonymous institutions in the same category to allow for tracking of administrative and clinical practice progress in quality improvement initiatives. The intention of tracking these bundles is to evaluate outcomes over time in each participating center and, most importantly, globally. This initiative is an attempt to provide a global progress report on international child health care for sepsis and to spur initiatives to improve outcomes. The anonymous results will be reported every 4 yrs at the WFPICCS World Congress and submitted for publication to *Pediatric Critical Care Medicine*. This is the first such report to our knowledge on the vanguard phase of the initiative.

QUALITY ASSURANCE PROGRAM

The sepsis bundles/checklists provided according to each WHO resource-specific category were derived from clinical recommendations in the WHO–Integrated Management of Childhood Illnesses handbook, the ACCM/PALS hemodynamic support guidelines, and the Pediatric subcommittee of the Surviving Sepsis Campaign. These source documents are also available on the Web site. These recommendations present evidence when available and the experience and consensus of experts when it is not.

Category A: Nonindustrialized Setting With Child Mortality Rate >30 of 1,000 Children

Table 1 shows the resource-specific category A bundle/checklist. There is strong evidence that the following preventive interventions reduce mortality from the common causes of sepsis in developing countries where child and neonatal mortality is high: breast feeding, immunizations, clean water, sanitation and hygiene, clean birthing process, antibiotics for premature rupture of membranes, and vitamin A and zinc supplementation (9). Level 1 evidence also exists for antibiotic treatment for pneumonia, antibiotics for sepsis and dysentery, the use of zinc in the treatment of diarrhea, and vitamin A in the treatment of measles. Bang et al (10, 11) reported an eight-fold reduction in all neonatal mortality in rural India when rural health workers provided a 5-day course of intramuscular gentamicin and oral sulfamethoxazole to neonates who had diarrhea, tachypnea, or poor feeding (16% to 2%). Brooks et al (12) reported a dramatic decrease in death from pneumonia (10 of 1000 to 0 of 1000) when infants in Bangladesh were administered daily or weekly oral zinc supplementation.

Table 1. Administrative bundle

Clean water provided	Yes☐ No☐
Rural/urban health workers provided	Yes☐ No☐
Immunizations provided	Yes☐ No☐
Zinc/vitamin A supplementation provided	Yes☐ No☐
Clinical practice parameter bundle	
Parent education provided on signs to call for health worker	Yes☐No☐
Tachypnea, poor feeding, diarrhea	Yes☐No☐
Five days of intramuscular gentamicin and oral cotrimoxazole (or trimethoprim-sulphamethoxizole)	Yes☐No☐NA☐
Oral World Health Organization hydration	Yes☐No☐NA☐
Oral antimalarials in malaria belts	Yes☐No☐NA☐

NA, not applicable.

Table 2. Administrative bundle

Clean water provided	Yes☐ No☐
Rural/urban health workers provided	Yes☐ No☐
Immunizations provided	Yes☐ No☐
Zinc/vitamin A supplementation provided	Yes☐ No☐
Provide hospital emergency room/clinic stocked with IV fluids (D10, normal saline, lactated Ringers)	Yes☐ No☐ NA☐
Albumin (malaria belt)	Yes☐ No☐
IV catheters	Yes☐ No☐
IV antibiotics/antimalarials	Yes☐ No☐
Oxygen with high-flow capabilities (pneumonia)	Yes☐ No☐
Clinical parameter bundle	
Parent education provided on signs to call for health worker	Yes☐No☐
Tachypnea, poor feeding, diarrhea	Yes☐No☐
Five days of intramuscular gentamicin and oral clotrimaxazole and oral World Health Organization hydration	Yes☐No☐NA☐
Oral antimalarials in malaria belts	Yes☐No☐NA☐
Capillary refill restored to <2 secs and blood pressure restored to normal in ED/first hour	Yes☐No☐
Administer IV fluids in ED/first half-hour for stage III/IV shock	Yes☐No☐NA☐
Administer IV antibiotics/antimalarials if appropriate in ED/first hour	Yes☐No☐NA☐
Administer high-flow oxygen/nasal continuous positive airway pressure in ED/first hour for tachypnea/pneumonia	Yes☐No☐NA☐
D10 with sodium administered at maintenance to prevent hypoglycemia	Yes☐No☐

IV, intravenous; ED, emergency department; NA, not applicable.

Category B: Nonindustrialized Setting With Child Mortality Rate <30 of 1,000 Children

Table 2 shows the resource-specific category B bundle/checklist. Four randomized controlled studies have shown that isotonic fluid resuscitation in the emergency department attains nearly 100% survival in children with WHO classification stage III and stage IV shock (13–16). A series of studies show that intravenous fluid resuscitation of severe malaria (malaria plus acidosis or hypotension) with 5% albumin reduces mortality from 18% to 4% compared to fluid resuscitation with isotonic crystalloid (17–19). A 10% dextrose-containing solution at maintenance fluid rate (with sodium added to prevent hyponatremia) provides needed glucose requirements. In adults, every hour that goes by without administering antibiotics increases mortality by 7%. Because microbes grow just as quickly in children as in adults, antibiotics and antimalarials should be administered early (20). High-flow nasal cannula O_2 or nasal continuous positive airway pressure

Table 3. Administrative bundle

ED/intensive care unit available for patients	Yes☐ No☐
High-flow oxygen/nasopharyngeal continuous positive airway pressure available to all patients	Yes☐ No☐
Ventilator available for all patients	Yes☐ No☐
Peripheral and central IV catheters available to all patients	Yes☐ No☐
Inotropes available for all patients	Yes☐ No☐
Intravascular pressure monitoring available for all patients	Yes☐ No☐
Superior vena cava or inferior vena cava/RA pressure, oxygen saturation monitoring available for all patients	Yes☐ No☐
Dialysis available for patients	Yes☐ No☐
Infusion pumps available	Yes☐ No☐
Clinical parameter bundle	
Capillary refill restored to <2 secs in ED/first hour	Yes☐No☐
Blood pressure restored to normal in ED/first hour	Yes☐No☐
Administer IV fluids in ED/first half-hour for stage III/IV shock	Yes☐No☐NA☐
Administer IV antibiotics/antimalarials if appropriate in ED/first hour	Yes☐No☐NA☐
Administer high-flow oxygen/nasopharyngeal continuous positive airway pressure in ED/first hour for tachypnea/pneumonia	Yes☐No☐NA☐
D10 with sodium administered at maintenance to prevent hypoglycemia	Yes☐No☐
Fluid resuscitation >20 mL/kg up to 60 mL/kg administered in first hour if appropriate	Yes☐No☐NA☐
Peripheral epinephrine administered in first hour if appropriate	Yes☐No☐NA☐
Central epinephrine for cold shock/norepinephrine for warm shock in first hour if appropriate	Yes☐No☐NA☐
Normal mean arterial pressure–central venous pressure and superior vena cava or inferior vena cava/RA oxygen saturation >70% targeted in intensive care unit	Yes☐No☐NA☐
Absolute adrenal insufficiency treated with steroids	Yes☐No☐NA☐
Ketamine used as sedation agent for intubation/central line placement	Yes☐No☐NA☐
Ventilator provided for respiratory failure	Yes☐No☐NA☐
Tidal volume maintained at 6-8 mL/kg	Yes☐No☐NA☐
Appropriate (sensitive) antibiotic administered in first 2 hrs	Yes☐No☐NA☐
Immunosuppressants held if using immune suppressive therapy	Yes☐No☐NA☐
Hyperglycemia controlled by insulin	Yes☐No☐NA☐
Intravenous immunoglobulin/clindamycin administered for toxic shock (group A Streptococcus or Staphylococcus)	Yes☐No☐NA☐
Surgical nidus removed if appropriate	Yes☐No☐NA☐

ED, emergency department; IV, intravenous; NA, not applicable; RA, right atrium.

can be adequate for up to 40% of patients with respiratory distress and pneumonia (21), and the systematic detection of hypoxemia and administration of oxygen substantially reduces mortality from pneumonia in rural hospitals (22).

Category C: Industrialized Developing Nation

Table 3 shows the resource-specific category C bundle/checklist. Mortality from meningococcal septic shock was reduced from 22% to 2% when community physicians administered aggressive 4% albumin resuscitation and inotropic support, intubated with ketamine, and transported children to a tertiary center (number needed to treat = 5) (23–25). Newborns and children with all-comer septic shock also have decreased mortality, 6% vs. 38% (number needed to treat = 3), when stepwise emergency access, fluid resuscitation, and inotropic therapy are started in the community hospital setting (26). Mortality increases two-fold for every hour without restoration of capillary refill <2 secs and normal blood pressure. Although these data are obtained from industrialized developed countries, they are equally applicable to this setting. This is evidenced by the improved outcomes seen in dengue shock syndromes when aggressive treatment is administered (a decrease in mortality from 16.5% to 6.3%) even in a resource-limited setting (15). Titration of therapies to maintain normal mean arterial and central venous pressure differences (mean arterial pressure − central venous pressure) and mixed venous O_2 saturation >70% reduced mortality from 39% to 12% (number needed to treat = 3.8) (27). Three factors that can help survival from septic shock are: 1) adherence to ACCM/PALS guidelines for hemodynamic support; 2) timely administration of the proper antibiotic with removal of any surgical nidus of infection; and 3) withdrawal of immune suppressants in patients receiving immunosuppressant therapy that prevents their ability to kill infection. Use of insulin for hyperglycemia, intravenous immunoglobulin, and clindamycin for toxic shock, lung protection strategy, and diuretics/dialysis are recommended for severe sepsis by the Surviving Sepsis Campaign (5).

Category D: Industrialized Developed Nation

Table 4 shows the resource-specific category D bundle/checklist. Developed countries have increased resources that can be used to further reduce mortality and morbidity during the emergency department, transport, and pediatric intensive care unit interface, and in the pediatric intensive care unit. Organized coordinated specialty transport systems in the developed world settings reduce mortality substantially by reducing the severity of illness of patients at the time of transport (23–25). Monitoring of cardiac output can be attained noninvasively using ultrasound, or invasively using pulmonary artery, peripherally inserted continuous cardiac output, or femoral artery thermodilution catheterization. Multiple organ system extracorporeal support therapies are used to support cardiopulmonary function (extracorporeal membrane oxygenation) and renal function (continuous renal replacement therapy), and to reverse thrombocytopenia-associated multiple organ failure (plasma exchange for thrombotic microangiopathy) (28, 29). High-frequency oscillatory ventilation and inhaled nitric oxide may reduce the need for extracorporeal membrane oxygenation for cardiopulmonary failure in acute respiratory distress syndrome and persistent pulmonary hypertension of the newborn (6, 7).

Statistical Analysis of Bundle Compliance and Relationship to Outcome

Analysis of the associative effect of bundle compliance was performed for the "resuscitation" phase (high-flow ox-

Table 4. Administrative bundle

ED/intensive care unit available for patients	Yes☐ No☐
High-flow oxygen/nasopharyngeal continuous positive airway pressure available to all patients	Yes☐ No☐
Ventilator available for all patients	Yes☐ No☐
Peripheral and central IV catheters available to all patients	Yes☐ No☐
Infusion pumps available	Yes☐ No☐
Inotropes available for all patients	Yes☐ No☐
Intravascular pressure monitoring available for all patients	Yes☐ No☐
Superior vena cava or inferior vena cava/RA pressure/oxygen saturation monitoring available for all patients	Yes☐ No☐
Cardiac output monitoring available for all patients	Yes☐ No☐
Continuous renal replacement therapy available for all patients	Yes☐ No☐
Plasma exchange available for all patients	Yes☐ No☐
Extracorporeal membrane oxygenation available for all patients	Yes☐ No☐
High-flow oxygen ventilation available for all patients	Yes☐ No☐
Inhalable nitric oxide available for all patients for persistent pulmonary hypertension of the newborn	Yes☐ No☐
Clinical parameter bundle	
Capillary refill restored to <2 secs in ED/first hour	Yes☐ No☐
Blood pressure restored to normal in ED/first hour	Yes☐ No☐
Administer IV fluids in ED/first half-hour for stage III/IV shock	Yes☐ No☐ NA☐
Administer IV antibiotics/antimalarials if appropriate in ED/first hour	Yes☐ No☐ NA☐
Administer high flow oxygen in ED/first hour for tachypnea or pneumonia	Yes☐ No☐ NA☐
D10 with sodium administered at maintenance to prevent hypoglycemia	Yes☐ No☐
Fluid resuscitation >20 mL/kg up to 60 mL/kg administered in first hour if appropriate	Yes☐ No☐ NA☐
Peripheral epinephrine administered in first hour if appropriate	Yes☐ No☐ NA☐
Central epinephrine for cold shock/norepinephrine for warm shock in first hour if appropriate	Yes☐ No☐ NA☐
Normal mean arterial pressure–central venous pressure and superior vena cava or inferior vena cava/RA oxygen saturation >70% targeted in intensive care unit	Yes☐ No☐ NA☐ Yes☐ No☐ NA☐
Absolute adrenal insufficiency treated with steroids	Yes☐ No☐ NA☐
Ketamine used as sedation agent for intubation/central line placement	Yes☐ No☐ NA☐
Ventilator provided for respiratory failure	Yes☐ No☐ NA☐
Effective tidal volume maintained at 6-8 mL/kg	Yes☐ No☐ NA☐
Appropriate (sensitive) antibiotic administered in first 2 hrs	Yes☐ No☐ NA☐
Immunosuppressants held if using immune suppressive therapy	Yes☐ No☐ NA☐
Hyperglycemia controlled by insulin	Yes☐ No☐ NA☐
Intravenous immunoglobulin/clindamycin administered for toxic shock (group A Streptococcus or Staphylococcus)	Yes☐ No☐ NA☐
Surgical nidus removed if appropriate	Yes☐ No☐ NA☐
Cardiac index maintained between 3.3 and 6.0 using American College of Critical Care Medicine guidelines	Yes☐ No☐ NA☐
Continuous renal replacement therapy used for fluid overload and multiorgan failure before 3 days if appropriate	Yes☐ No☐ NA☐
Plasma exchange used to treat thrombocytopenia-induced multiorgan failure until resolution of thrombocytopenia	Yes☐ No☐ NA☐
High-flow oxygen ventilation used if peak inspiratory pressure >35 cmH_2O	Yes☐ No☐ NA☐
Inhalable nitric oxide used for persistent pulmonary hypertension of the newborn	Yes☐ No☐ NA☐
Extracorporeal membrane oxygenation used for refractory cardiopulmonary failure	Yes☐ No☐ NA☐

ED, emergency department; IV, intravenous; NA, not applicable; RA, right atrium.

ygen, appropriate sensitive antibiotic, restoration of normal blood pressure and capillary refill, fluid resuscitation, peripheral inotrope, mechanical ventilator) and ongoing intensive care unit management phase (all other subsequent checklist tasks). Compliance was considered complete if all "applicable" tasks were accomplished. Categories were included for analysis in this vanguard phase only if they had data for >50 patients entered. Hence, statistical analysis was performed only for resource-specific categories C and D. Treatment effects were evaluated using odds ratios, including 95% confidence intervals, and using logistic regression models. Six logistic regression models were built to encompass all possible combinations of treatments (resuscitation, subsequent management) and outcomes (alive, neurologic morbidity, other morbidity). Cases of death were discarded from morbidity outcomes. Logistic models fit was assessed using chi-square test for dispersion and Wald test was used for the proportion of log-likelihood accounted for by the model. Information was extracted from the Web database and analyzed using SPSS 17.0 (SPSS, Chicago, IL).

RESULTS

The Vanguard of the WFPICCS Global Sepsis Initiative

The initiative was conceived and ambassadors were assembled through volunteerism at the WFPICCS World Congress in Geneva, 2007. The Web site was developed and brought to full operation in 2009. Data for 361 children were entered from 23 international participating centers. The greatest enrollment was in level D (n = 231), followed by level C (n = 84), level A (n = 34), and level B (n = 12). Figures 2 through 5 show the quality-assurance reports sent according to resource-specific category to the participating centers. The participants also received their own performance analysis (not shown) as well the anonymous group performance analysis (Figs. 2–5), which they were then able to use for ongoing quality-assurance improvement at their respective institutions.

As the categories progressed from A to D, the mortality rates decreased (A = 30%; B = 16.7%; C = 29.8%; and D = 11.3%), the neurologic morbidity rates decreased (A = 16%; B = 10%; C = 11.9%; D = 2.0%), and the non-neurologic morbidity rates decreased (A = 5.9%; B = 8.3%; C = 6.8%; D = 1.0%). There were 35 virus infections, 70 Gram-negative infections, 120 Gram-positive infections, eight fungal infections, and 32 mixed infections. The most common were respiratory syncytial virus, *Escherichia coli*, *Enterobacter* and *Klebsiella* species, Streptococcus pneumonia, Meningococcus, *Staphylococcus aureus*, and *Candida* species, respectively.

Only categories C and D had >50 patients, so the relationship between compliance and outcome was only evaluated in this sample. There were no differences in gender in categories C (50% female) and D (41.6% female) or in age in categories C (51.12 ± 51.94) and D (74.68 ± 77.91). There was less bundle compliance in category C vs. category D (resuscitation bundle 23.8% vs. 51.9% and subsequent management bundle 9.5% vs. 25.1%). There was more death and disability in category C vs. category D. The odds ratio of mortality for a patient was reduced when considering compliance with the resuscitation bundle/checklist

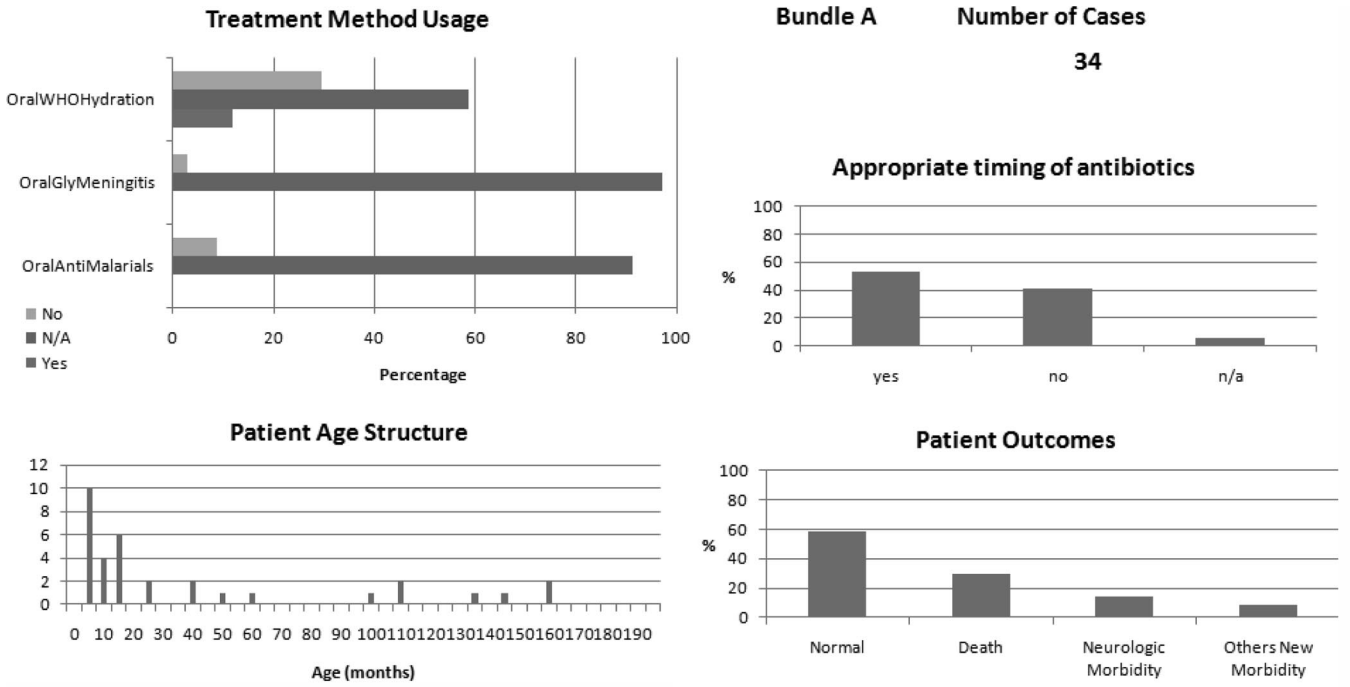

Figure 2. The Global Sepsis Initiative category A bundle report. The participants enter their own administrative data and then are assigned their respective health resource level. Members in the A level received this report of all participants as well as their own anonymous single-center report for use in quality assurance and process improvement. Yes indicates that the treatment was warranted and was administered. No indicates the treatment was not administered even though it was warranted. Not applicable or not appropriate (*n/a*) indicates the treatment was not warranted and therefore it was not administered. Three treatments are recommended in category A. Antibiotics were administered in a timely manner to <60%. Mortality was 30%. *OralGlyMeningitis*, oral glycerol for meningitis; *WHO*, World Health Organization.

(odds ratio, 0.369; 95% confidence interval, 0.188–0.724; $p < .004$) or the subsequent intensive care unit management bundle/checklist (odds ratio, 0.277; 95% confidence interval, 0.096–0.800; $p < .018$). The models have an acceptable fit (Omnibus chi-square test, 9.282, degrees of freedom = 1, $p < .002$ and Wald test = 8.392, degrees of freedom = 1, $p < .004$ for resuscitation bundle; and Omibus chi-square test, 7.556, degrees of freedom = 1, $p < .006$ and Wald test = 5.628, degrees of freedom = 1, $p < .018$ for subsequent management bundle).

DISCUSSION

The Pediatric Global Sepsis Initiative has begun. There are functioning video links with lectures and interactive cases, source guideline documents, and the quality-assurance bundle/checklist program. Thus far in the vanguard phase, 23 centers have participated and received quality-assurance reports to inform local quality improvement programs. In a participating center (Joseph A. Carcillo), the reports were found to be helpful. The participants congratulated themselves when they found they were administered antibiotics and fluid resuscitation in the emergency department at a rate commensurate with our resource-specific category group but were surprised to find that our emergency department was not starting peripheral inotropes. They were performing below our resource-specific category in this part of the checklist and are now embarking on a root cause analysis to determine what barriers exist to this recommended practice in our local setting.

The initiative now needs continued participation by the 23 centers and, more importantly, recruitment of other centers. The numbers of patients admitted in centers with administrative bundles A and B who participated were few and entered few patient data in the database despite many centers completing the initial registration. This may be because of a variety of reasons, including limited resources to enter patient data and overwhelming workloads, as are already recognized in many of these areas. However, it is in these very areas where large numbers of patients present with sepsis and many die with these infections even before arriving to definitive therapy within institutions (30). It is therefore imperative that these centers not be ignored and that more effort be placed on determining the reasons and in facilitating their participation in this project. At the upcoming WFPICCS World Congress, new approaches will need to be developed to outreach these centers.

Centers with high resources (categories C and D) were able to enter data. However, most of the data were contributed by five centers, with most of the patients in category D. Individuals in these centers indicated that all consecutive patients with sepsis were enrolled and, hence, this represents the likely treatment that would be obtained in centers C and D. Our data indicate that most patients whose data were entered were younger than 6 yrs and that the management bundle and resuscitation bundles were not applied rigorously. These data are in keeping with the experience from the adult Surviving Sepsis Campaign Web-based bundles/checklist quality-assurance initiative that, although being a more mature project (165 sites and 15,022 subjects), demonstrated that compliance with the entire resuscitation bundle was only 31% and compliance with the entire subsequent management bun-

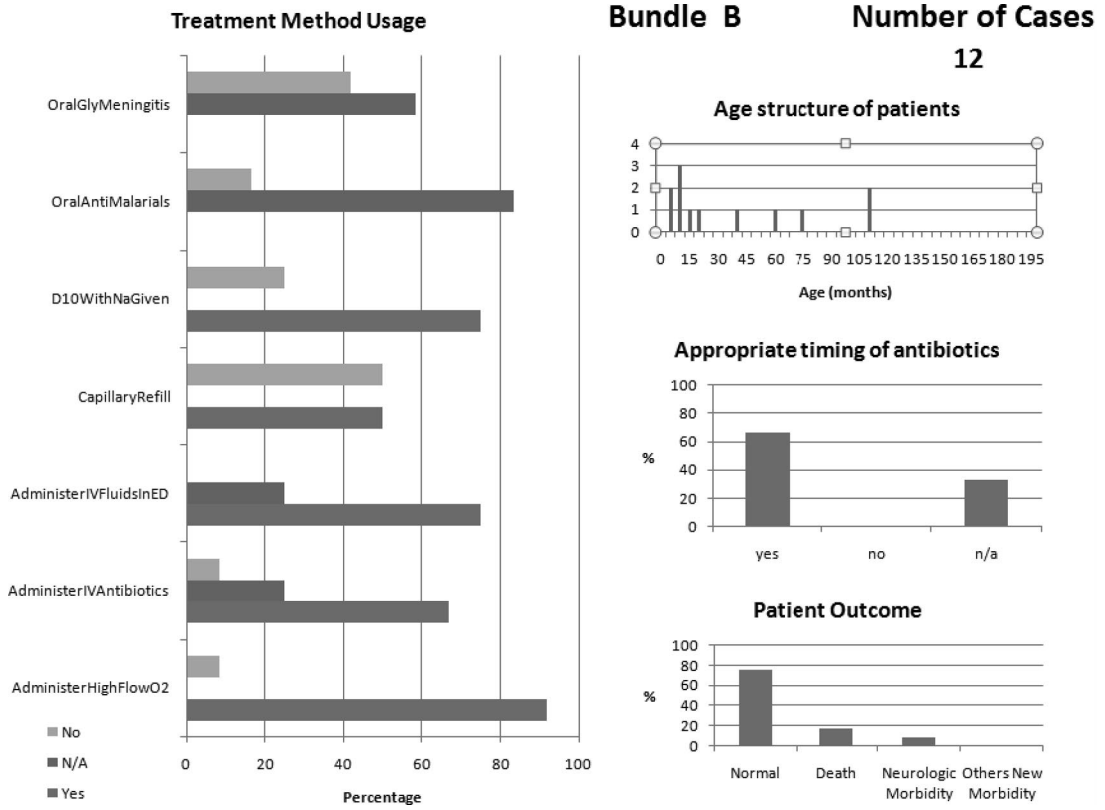

Figure 3. The Global Sepsis Initiative category B bundle report. The participants enter their own administrative data and then are assigned their respective health resource level. Members in the B level received this report of all participants as well as their own anonymous single-center report for use in quality assurance and process improvement. Yes indicates the treatment was warranted and was administered. No indicates the treatment was not administered even though it was warranted. Not applicable or not appropriate (*n/a*) indicates the treatment was not warranted and therefore it was not administered. Seven interventions are recommended on the checklist for category B. More than 60% received antibiotics in a timely manner, 90% received high-flow oxygen (O_2), and all received intravenous (*IV*) fluids. Mortality was 18%. *OralGlyMeningitis*, oral glycerol for meningitis; *ED*, emergency department; *Na*, sodium.

dle was only 36% by the end of the second year (31).

Studies involving adults have shown that improvement in survival is related to the number of bundle interventions completed. For instance, Castellanos-Ortega et al (32) using a quasi-experimental design with a historical comparison group in a single center described the effectiveness of the campaign bundles with regard to implementation and outcome in patients with septic shock and determined the contribution of the various bundle elements to outcome. They found that in-hospital mortality was reduced from 57% in the historical group to 38% in the interventional group ($p = .001$). Furthermore, improvements in survival were related to the number of bundle interventions completed (32). In support of this finding, we also observed that improved survival was associated with increased bundle compliance in our vanguard phase. It is expected that individual centers will review their data regarding compliance with therapies relevant to their environment and determine oversight or deficiencies in care that need to be addressed. With this approach, we expect to see a decrease in mortality from sepsis as adherence to comprehensive bundles is increased. This is the overall goal of the initiative. To achieve this, centers can expect to see their scorecard of adherence to individual recommendations and a summary of their outcomes, as well as comparison to other centers with similar resources. Although the denominator of this activity (the total number of sepsis admissions) cannot be verified without on-site audits, individuals have committed to submit data from all patients. This will be reinforced by periodic reminders but cannot be guaranteed.

Our low compliance rate is similar to that observed in the concurrent audit of the U.K. pediatric intensive care study group. Inwald et al (33), in an observational study of pre-intensive care unit care in the United Kingdom involving 17 pediatric intensive care units, reported that the ACCM/PALS guidelines were not followed in 62% of cases. Furthermore, the odds ratio for death if shock was present on intensive care unit admission was 3.8 (95% confidence interval, 1.4–10.2; $p = .008$). In the U.K. study, failure to recognize shock and inadequate fluid and inotropic support in the first crucial hours contributed to unresolved shock (33). The ACCM/PALS guidelines were only followed in 36% of instances in those patients in whom shock was not resolved when entering the intensive care unit. There is also the issue of perception vs. practice gap, as outlined by Brunkhorst et al (34), which may present barriers to adoption of sepsis bundles. This is an important finding because failure to provide aggressive treatment was associated with poor outcomes in our international sample as well. The odds for survival for a given patient was reduced more than three-fold if the subsequent management procedures were not undertaken, and it was reduced almost threefold when resuscitation procedures were not undertaken. This mirrors the U.K.

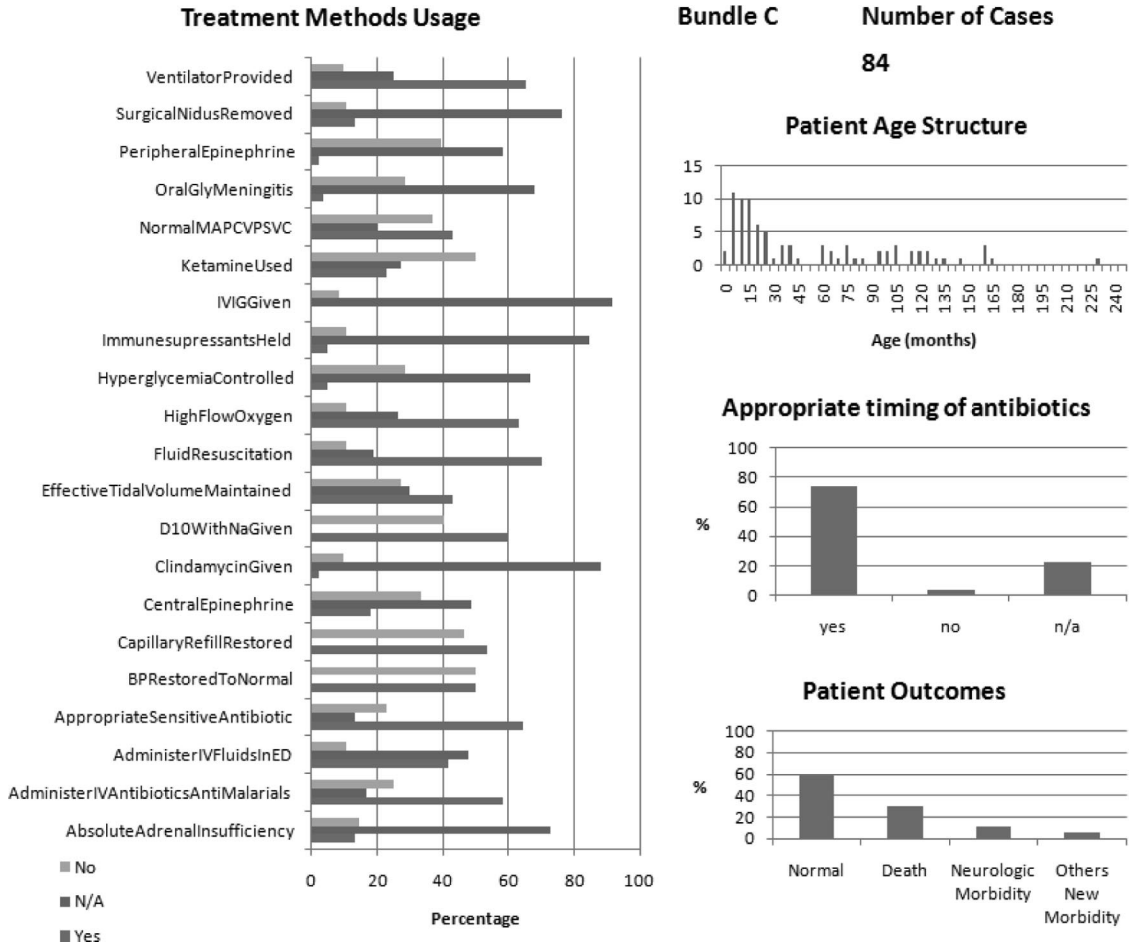

Figure 4. The Global Sepsis Initiative category C bundle report. The participants enter their own administrative data and then are assigned their respective health resource level. Members in the C level received this report of all participants as well as their own anonymous single-center report for use in quality assurance and process improvement Yes indicates the treatment was warranted and was administered. No indicates the treatment was not administered even though it was warranted. Not applicable or not appropriate (*n/a*) indicates the treatment was not warranted and therefore it was not administered. Twenty-one interventions are recommended for category C. Appropriate timing of antibiotics occurred in 70%, 80% received fluids in the emergency department (*ED*), 85% received mechanical ventilation, and peripheral epinephrine was administered to 10%. Mortality was 29.8%. *OralGlyMeningtis*, oral glycerol for meningitis; *MAP*, mean arterial pressure; *CVP*, central venous pressure; *SVC*, superior vena cava; *IVIG*, intravenous immunoglobulin; *Na*, sodium; *BP*, blood pressure; *IV*, intravenous.

audit result. At the upcoming WFPICCS World Congress, we will discuss better ways to learn about and overcome barriers to implementation.

The initiative is a nascent work in progress. We hope to have spirited discussion on many topics related to the Pediatric Global Sepsis Initiative at the WFPICCS international meeting in Sydney, Australia, in 2011. How many localities in category B have emergency clinics? How many hospitals in developing countries have the capacity to ventilate more than a few patients? Who should enter the data in the initiative? Should the data be quality-controlled? How does one decide if an intervention is applicable? How will data be analyzed? Should severity of illness data be included? How should one address difficulties in allocation to category? Presently, if a participant is in a developing country but cannot provide a mechanical ventilator to all children in the unit, then the program defaults to category B, not category C as the participant may wish. Also, participants in the developed world may not have a transport team or extracorporeal support available. The program will default this participant to category C, not category D as the participant may wish. The participants can override the decision and pick the category of their choice. Is this acceptable? What human subjects protection thinking relates to global quality-assurance programs such as the WHO hospital infection surveillance programs? What are the barriers to bundle compliance? Is it lack of available equipment? Is it lack of agreement with WHO–Integrated Management of Childhood Illnesses, ACCM-PALS, and Surviving Sepsis recommendations? Is it lack of agreement that the checklist represents these recommendations? Is it lack of organization or human effort? This article is intended to highlight the launching of the initiative, to outline its potential benefits, and to raise the issue that we need input from member organizations and individuals to resolve to improve the deliverables from this initiative. It is hoped that discussions of these questions will lead to understanding systems in various parts of the world to further inform what needs to be accomplished to improve international participation and attainment of the child health goals of the initiative. In addition, further understanding of

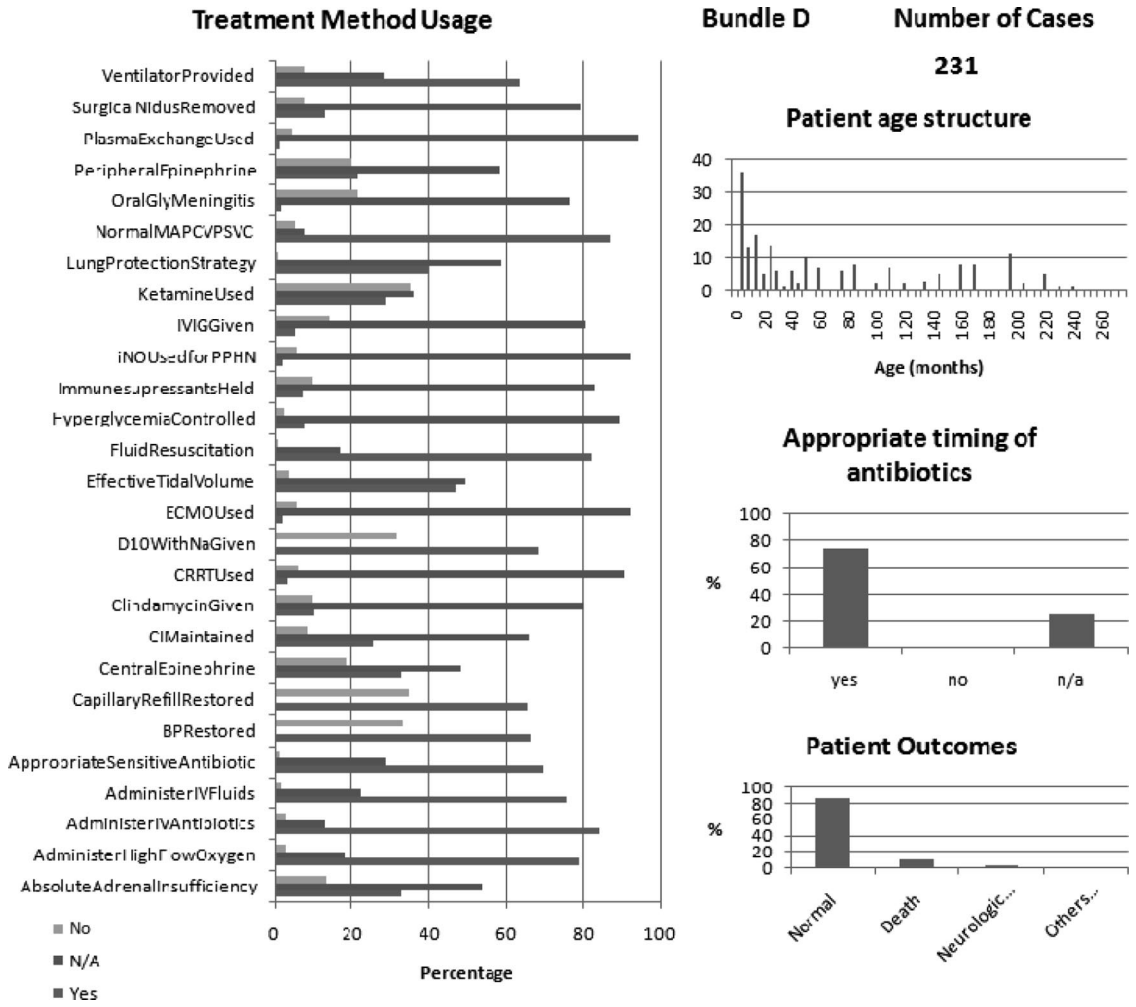

Figure 5. The Global Sepsis Initiative category D bundle report. The participants enter their own administrative data and then are assigned their respective health resource level. Members in the D level received this report of all participants as well as their own anonymous single-center report for use in quality assurance and process improvement Yes indicates the treatment was warranted and was administered. No indicates the treatment was not administered even though it was warranted. Not applicable or not appropriate (*n/a*) indicates the treatment was not warranted and therefore it was not administered. Twenty seven interventions are recommended in Category D. Appropriately timed antibiotics were delivered in over 70%, early fluid resuscitation occurred in 99%, mechanical ventilation was given to 90%, and peripheral epinephrine to >50%. Mortality was 11.3%.OralGlyMeningitis = Oral glycerol for meningitis; *MAP*, mean arterial pressure; *CVP*, central venous pressure; *SVC*, superior vena cava; *IVIG*, intravenous immunoglobulin; *Na*, sodium; *BP*, blood pressure; *IV*, intravenous *iNO*, inhaled nitric oxide; *ECMO*, extracorporeal membrane oxygenation; *PPHN*, persistent pulmonary hypertension of the newborn; *CRRT*, continuous renal replacement therapy; *CI*, confidence interval.

the contribution of various components of the bundle to outcome also needs to be undertaken. This can be accomplished with ongoing enrollment and maturation of this child health program.

The bundle/checklist component of the Surviving Sepsis Campaign for adult severe sepsis has been considered successful in decreasing sepsis adverse outcomes globally. The Federation is confident that the same can be attained for our children. Please become ambassadors for the Pediatric Global Sepsis Initiative and join the initiative by contacting us online or meeting us at the Pediatric Critical Care World Congress in Sydney, Australia, March 13–17, 2011. Please join us at http://www.pediatricsepsis.org or http://www.wfpiccs.org.

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