Preface

The field of critical care medicine is in the midst of a dramatic change. Technological and scientific advances during the last decade have resulted in a fundamental change in the way we view disease processes, such as sepsis, shock, acute lung injury, and traumatic brain injury. Pediatric intensivists have been both witness to and active participants in bringing about these changes. As the understanding of the pathogenesis of these diseases reaches the cellular and molecular levels, the gap between critical care medicine and molecular biology will disappear. It is imperative that all physicians caring for critically ill children in this new era have a thorough understanding of the applicability of molecular biology to the care of these patients at the bedside in order to keep up with the rapidly evolving field of critical care medicine. To the same extent, the practice of critical care medicine is in the midst of fundamental change. In keeping with the Institute of Medicine's report "Crossing the Quality Chasm," the care of critically ill and injured children needs to be safe, evidence-based, equitable, efficient, timely, and family-centered [1,2]. In the following pages, these changes in our specialty are discussed in greater scope and detail, offering the reader fresh insight into not only *where we came from*, but also *where we are going* as a specialty. Once again, we would like to dedicate this textbook to our families and to the physicians and nurses who provide steadfast care every day in pediatric intensive care units across the globe.

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References

1. Institute of Medicine Committee on Quality of Health Care in America. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academy Press, 2001.
2. Slonim AD, Pollack MM. Integrating the Institute of Medicine's six quality aims into pediatric critical care: Relevance and applications. Pediatr Crit Care Med 2005;6:264–269.

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Epidemiology of Critical Illness

R. Scott Watson and Mary E. Hartman

Introduction

Since the first intensive care units (ICUs) were established in the United States in the 1960s, there has been a gradual growth in the appreciation of the importance and magnitude of critical illness. In the 1980s, Jacobs and Noseworthy [1] reported that ICU expenditures in the United States accounted for 1% of the gross domestic product, and similar findings were reported more recently [2]. The frequency of critical illness and the provision of critical care services have now reached what can be considered epidemic proportions. Of the 38 million annual U.S. hospital admissions of children and adults [3], nearly 6 million, or 2% of the U.S. population, are admitted to an ICU [4]. The disease burden of the myriad disorders and conditions that constitute critical illness is of sufficient scale that efforts to prevent and treat critical illness have implications for overall public health.

The clinical epidemiology of critical illness is vital to inform clinical care, meaningful patient-oriented research, and health policy in critical care. Describing the natural history of disease informs the development of treatments to improve outcomes and the care delivered at the bedside. Understanding the burden of disease influences the prioritization of research efforts and the allocation of health care resources. Knowledge of risk factors for disease aids in prevention of disease, timely intervention to treat it, and selection of study populations. However, there are a number of challenges in performing clinical epidemiologic research in critical care, not the least of which is related to a core principle of epidemiology. Delineating the epidemiology of a disease or condition starts with the ability to identify it, both reliably (different clinicians classify a patient in the same way as each other and over time) and validly (the classification distinguishes people with the disease from those without it). In critical care, this may be conceptually straightforward but is operationally challenging. In this chapter, we discuss several issues related to clinical epidemiology in critical care and summarize some of the large-scale work that has been done examining the epidemiology of critical illnesses in children.

Challenges of Defining a Population in Critical Care

Critical illness is made up of a heterogeneous group of conditions and disorders that share a risk of organ dysfunction, long-term morbidity, and mortality. However, definitions of the syndromes that most consider quintessential critical care *diseases* (sepsis, acute respiratory distress syndrome [ARDS] / acute lung injury [ALI], and even organ failure) lack gold standard tests by which to identify them. By necessity, then, definitions have been developed by consensus and expert opinion. Although these definitions represent a substantial improvement over the prior state of phenomenologic disarray, they still suffer from limitations in reliability and validity [5,6]. Even the minimum degree of organ dysfunction, or risk thereof, that suggests that a patient is *critically* ill is often debated.

Another challenge to identifying patients with critical illness is that critical illness is often defined by where care takes place (i.e., the ICU) and the interventions used to treat it (e.g., mechanical ventilation, infusions of medications to support hemodynamics, continuous renal replacement therapy). Although convenient, these definitions are significantly limited. The definition of an illness cannot rely on the availability of an ICU bed. Care that is provided in an ICU in one country or region may be provided on the ward in another (and even in a given hospital, the availability of ICU beds may change with hospital and ICU census). Critical illness often begins before ICU admission and can last beyond ICU discharge. The use of many interventions varies by provider, even when controlling for patient factors, such as severity of illness, so it is much easier to determine which patients received an intervention than it is to determine which patients actually needed it [7–11]. Nonetheless, with the increasing availability of large-scale databases and increasing numbers of large-scale epidemiologic studies of prospectively collected data, the size and scope of pediatric critical illness are beginning to be characterized.

Epidemiology of Children Receiving Critical Care Services

National estimates of the overall use of ICU services for children are limited. Extrapolating from a survey conducted in 2001 by Randolph and colleagues [12] for which pediatric ICU (PICU) directors were asked to report their annual number of PICU admissions, over 230,000 children are admitted to PICUs annually. In preliminary work, Garber et al. [13] estimated that 480,000 infants and children less than 20 years old received intensive care services in the United States in 2001 (in neonatal ICUs [NICUs], PICUs, and pediatric beds in adult ICUs). These patients represented 6.6% of pediatric hospitalizations. The population-based incidence of ICU care for infants was 10 to 25 times that for older children. Hospital mortality rate was 2.4% (or over 11,000 deaths nationally), was similar across age groups, and was consistent with that reported in Randolph and colleagues' survey (2.9%) [12]. Mean hospital costs were $19,000 per patient, and total ICU costs were nearly $8 billion nationally (30% of all hospital costs for children) [13].

Angus et al. [14] performed a study of the use of ICU services at the end of life for children and adults and found that one in five Americans overall died while using ICU services in the United States in 1999. Although many more adults than children died, children were more likely than adults to receive ICU services at the end of life. Nearly half of infants and one third of older children who died in 1999 received ICU care. Subsequent preliminary analyses of the pediatric sample from this population found that 29% of children aged 1 to 19 years who died did so after receiving ICU care, and, among hospitalized children who died, ICU care was much more common for those without a history of chronic illness [15].

Despite the limitations of a geographic definition of critical illness, our understanding of the magnitude of critical illness among children is enhanced by information about the provision of pediatric critical care services [16]. Only 9% of counties in the United States have PICUs, and 99% of the PICUs are located in urban counties [17]. The number of hospital beds overall for children has been decreasing since the 1980s in the United States, but ICU beds for children have been increasing. In 1989, Pollack and others identified 276 pediatric-specific ICUs in the United States, with an average of 528 admissions per year [18]. Pediatric intensivists were available to 73% of the units, and reported mortality rate was 5.5%. In 2001, Randolph and colleagues found 349 PICUs, with an average of 672 admissions per year [12]. Pediatric intensivists were available to 94% of the units, and reported mortality rate was 2.9%. The number of available PICU beds between 1995 and 2001 increased by 24% and outpaced population growth of children by 17.5%. The number of beds per child varied substantially by region—from 1 per 15,250 children in Arkansas, Louisiana, and Texas to 1 per 27,440 in New England. Whether this variation reflects different regional pediatric critical care needs is unknown.

The reason for the increasing numbers of PICU beds is also unclear and likely multifactorial. It may reflect changes in referral patterns, with an increasing number of smaller hospitals providing care for patients previously transferred to larger units. Although this would be somewhat surprising in light of increasing evidence that higher volume units have better severity-adjusted outcomes than their smaller counterparts [19–21], health care financing affords incentives to provide intensive care services even at smaller hospitals. On the other hand, patients who remain at smaller hospitals may be less severely ill than those who are transferred to tertiary care and may merely require additional monitoring that is not available on the wards of many hospitals.

Perhaps the most important factor in the increasing demand for PICU services is an increasing number of children in the population living with chronic medical conditions. Success in the treatment of extremely low-birth-weight babies, children with neurodevelopmental abnormalities, cancer, or cystic fibrosis, and organ transplant recipients has lead to longer life expectancies and decreased mortality rates. These successes have also led to an increased number of children living at increased risk of critical illness [22–26]. In a population-based study at a tertiary PICU in New York, almost half (45%) of all unscheduled admissions to the PICU were for patients with chronic health conditions, 32% of whom received technology-assisted care (such as mechanical ventilation, oxygen, tracheostomies, and intravenous therapies) [27]. Children with chronic conditions were 3.3 times more likely than healthy children to have an unscheduled PICU admission, and those receiving technology-assisted care were 373 times more likely. The most common conditions were neurologic, accounting for 15% of all unscheduled admissions. Similarly, 23% of all admissions (both scheduled and unscheduled) to a large, tertiary PICU had preexisting neurodevelopmental disorders [28]. Although hospital mortality rate was only 3%, patients were discharged with significantly greater needs for ventilatory and nutritional technology support than they had on admission. In addition to increasing the number of PICU admissions, children with chronic illness may require lengthy PICU stays. Indeed, former premature babies admitted to the PICU consumed more health care resources than their nonpremature counterparts, including longer lengths of stay and higher rates of mechanical ventilation [29].

Epidemiology of Mechanical Ventilation and Acute Respiratory Distress Syndrome/Acute Lung Injury

The provision of mechanical ventilation (MV) for acute respiratory failure was a major motivating factor in the development of ICUs and is one of the hallmarks of critical care. National estimates of respiratory failure among infants and children have been derived from analyses of administrative records of patients receiving mechanical ventilation. Of course, some patients are ventilated in the ICU for reasons other than respiratory failure (such as extreme hemodynamic instability or after prolonged surgery). Therefore, the incidence of MV is higher than the incidence of respiratory failure. Rates of mechanical ventilation were higher in neonates than in any other age group (80,000 babies per year, or 1.8 % of U.S. neonates) [30]. Although very-low-birth weight babies had extremely high rates of MV (52%/year), one third of ventilated neonates were of normal birth weight. Hospital mortality rate was 11.1%, and total U.S. hospital costs were $4.4 billion in 1994. Preliminary work examining older children found that 35,000 children aged 1 to 19 years were ventilated in the United States in 1999 [31]. Duration of MV was 4 or more days for over one third of patients. Most were ventilated for medical (as opposed to surgical) reasons, and the most common associated condition was severe sepsis (in 35%). Hospital mortality rate (13.8%) was higher than that of neonates, and estimated national hospital costs were lower ($1 billion).

The epidemiology of ARDS and ALI is being systematically assessed in adults. A recent study found that the age-adjusted incidence in patients 15 years and older in King County, Washington, was 86.2/100,000/year (which projects to 190,600 cases per year nationally) in 1999–2000 [5]. Hospital mortality rate was 38.5%, and both incidence and mortality rate increased with age. The most common risk factor for development of ALI was severe sepsis (present in 79% of cases of ALI). Efforts to understand the epidemiology of pediatric ARDS are hampered by a lower incidence in children and challenges in defining ARDS in infants and very young children. The only prospective population-based study of ARDS in children found only 7 new cases of ARDS in 3 months (February, April, and June) in 94 ICUs in Germany. These cases represented 1.5% of ventilated children and a population-based prevalence of 5.5/100,000 children (with an incidence of 3.1/100,000/year) [32]. Based on this incidence, the authors estimated that 500 children develop ARDS in Germany annually.

Epidemiology of Sepsis

Not only is the treatment of sepsis an integral component of critical care, but sepsis also provides a good example of how defining a syndrome, even broadly, facilitates its study and determines its characteristics. In 1992, the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference met to standardize the definitions of sepsis and severe sepsis so that they might be more clearly applied in research and clinical practice [33]. The group defined *sepsis* as a systemic inflammatory response syndrome resulting from infection, *severe sepsis* as sepsis associated with organ dysfunction, hypoperfusion, or hypotension, and *septic shock* as sepsis with arterial hypotension despite adequate fluid resuscitation [33]. These definitions now frequently serve as criteria for inclusion in randomized, controlled trials for sepsis therapies [34–40] and are increasingly employed by medical practitioners around the world. One of the significant advantages of this standard terminology is that it has allowed us to begin to understand the magnitude of sepsis. Sepsis and severe sepsis are much more common than previously realized, and they are important causes of serious morbidity and mortality in both children and adults.

The U.S. Centers for Disease Control and Prevention (CDC) lists septicemia (*a systemic disease associated with organisms or their toxins in the blood*) as the seventh leading cause of death for children aged 1–4 years and eighth for children aged 5–9 years [41]. Other investigators have examined severe sepsis specifically, applying consensus definitions to large administrative datasets containing records of U.S. hospitalizations. In 1995, over 42,000 children younger than 20 years old were hospitalized with severe sepsis in the United States, and 4,400 of them died (for a hospital mortality rate of 10.3%) [42]. Compared with other conditions in the CDC's list of leading causes of death, severe sepsis deaths exceeded all but three among infants and all but one among older children. Almost half of children with severe sepsis (48%) were less than 1 year old. Severe sepsis was more common among boys than girls and more common in children with underlying illness. In preliminary analyses of data from 1999, incidence rates of severe sepsis increased by 11% over the 4-year period, and hospital mortality rate decreased [43]. The increased incidence was secondary to increased numbers of very-low-birth-weight babies in the United States and an increased rate of sepsis among those babies. Although hospital mortality rate from 1995 to 1999 was unchanged among previously healthy children, it decreased to 9.0% overall in 1999 because of lower mortality among children with underlying illness. The three most common pathogens for children with severe sepsis in the United States were *Staphylococcus* (all types), *Streptococcus* (all types), and fungus, although viral etiologies were not examined [42].

In a single-center study in Montreal, Proulx et al. [44] examined the incidence of sepsis and related conditions in a university pediatric intensive care unit. This group examined 1,058 admissions to their PICU between 1991 and 1992 and identified 245 cases of sepsis (23% of all PICU admissions), 46 cases of severe sepsis (4%), and 25 cases of septic shock (2%). Mortality rate among the children with sepsis was 6% [44].

Multiple organ dysfunction (MOD) is often associated with severe sepsis. Details about its pathophysiology are poorly understood, and its effects on mortality are still being studied [45,46]. Kutko et al. [47] studied 96 cases of septic shock in 80 patients at a large academic PICU over 2 years to determine the impact of MOD on mortality in septic shock. Over 70% of sepsis cases occurred in patients with cancer (19% of whom had undergone a bone marrow transplant), and half occurred in patients with neutropenia. Indwelling catheters were present in over 58% of cases. Multiple organ dysfunction was present in almost 73% of cases at some point in time during the PICU course, and the mortality rate for this group was 36%. In Proulx's sepsis cohort, discussed above, 29% developed MOD, with a mortality rate of 32% [44]. A finding common among these studies is that there were few or no deaths among children who were previously healthy and no deaths among patients without MOD.

Epidemiology of Status Asthmaticus

As the most common chronic disease among children, asthma's epidemiology has been extensively studied, and increasing numbers of investigators have examined the epidemiology of status asthmaticus. Asthma affects 5% to 7% of U.S. children. Its prevalence increased from 1980 to 1996 and leveled off between 1997 and 2000. It is one of the most common reasons for pediatric hospitalization in the United States [48], and hospitalization rates increased between 1980 and the mid-1990s [49,50]. In 2000, there were 152,000 pediatric hospital admissions for asthma, which generated total U.S. hospital charges of $835 million (2% of U.S. health care charges for children) [51]. Although status asthmaticus is a common reason for ICU admission, an average of only 8% of children hospitalized with asthma at pediatric centers require PICU care [52]. The use of invasive MV varies substantially by center (from 3% to 47% of PICU patients [7]), by region of the United States (from 6% to 27% of PICU patients at pediatric centers [52]), and by year (from 8% to 18% of ICU patients between 1992 and 2001 in a single state [53]). This variation persists even when controlling for severity of illness [7], and children with Medicaid insurance have higher rates of tracheal intubation and longer lengths of stay than patients with commercial insurance, even when controlling for severity of illness [54].

Mortality rates for children with asthma are increasing [49,50,55,56], but death is still uncommon after patients are admitted to the hospital. Two recent, large studies found 0.3%–0.4% hospital mortality rate among patients admitted to tertiary PICUs [7,52] and a 2.8% mortality rate among tracheally intubated patients [7]. Mortality is highest for adolescents (twice that of younger children), and children of African American decent are more than four

times as likely to die from asthma as white children [49]. Risk factors for asthma-related death include previous life-threatening attacks, severe disease, recent hospital admission or emergency room visit, poor adherence to medical regimens [57,58], and prior history of asthma-induced respiratory failure requiring mechanical ventilation [59]. Some patients with near-fatal asthma (requiring mechanical ventilation or resulting in unconsciousness) have been found to have decreased sensitivity to hypoxia and blunted perception of dyspnea [60].

Conclusion

Improving definitions of the syndromes that characterize critical illness, the development of efficient information technology, and the creation of extensive databases that include PICU patients have enabled large-scale epidemiologic research to be conducted in critical care. As evident from the discussion, however, this work is incomplete. We need better estimates of basic critical care syndromes and interventions, such as ARDS and continuous renal replacement therapy. We also need to examine further reasons for variation in care, the relationship between risk factors of disease, hospital course, and postdischarge outcome, and how public health and medical interventions affect the incidences and outcomes of critical illnesses in children.

Recent and impending developments in the health care of children will affect the epidemiology of pediatric critical illness. Populations of children known to be at high risk for critical illness (e.g., premature babies, technology-dependent or immunosuppressed children) continue to grow. New vaccines may decrease the rate of severe sepsis in previously healthy children. Genetic and immunologic analyses will identify children at high or low risk of severe illness and sequelae. They will enhance our therapeutic effectiveness by allowing us to provide specific treatments to children based on more robust information regarding the likelihood of responsiveness [61]. The success of pediatric critical care study networks will increase our knowledge about the efficacy and effectiveness of interventions for critical illness and will enhance our understanding of the natural history of critical illness. The thoughtful use of the tools of clinical epidemiology can facilitate these advances, help us refine application, and let us understand their ramifications.

References

1. Jacobs P, Noseworthy TW. National estimates of intensive care utilization and costs: Canada and the United States. Crit Care Med 1990; 18:1282–1286.
2. Cowan CA, Lazenby HC, Martin AB, et al. National health expenditures, 1999. Health Care Finance Rev 2001;22:77–110.
3. Merrill CT, Elixhauser A. Hospitalization in the United States, 2002. HCUP Fact Book No. 6. Report No. AHRQ, Publication No. 05–0056. Rockville, MD: AHRQ; 2005.
4. Kersten A, Milbrandt EB, Rahim MT, et al. How big is critical care in the US? Crit Care Med 2003;31(Suppl):A8.
5. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685–1693.
6. Goss CH, Brower RG, Hudson LD, Rubenfeld GD. Incidence of acute lung injury in the United States. Crit Care Med 2003;31:1607–1611.
7. Roberts JS, Bratton SL, Brogan TV. Acute severe asthma: differences in therapies and outcomes among pediatric intensive care units. Crit Care Med 2002;30:581–585.
8. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med 2000;160:41–46.
9. Bungard TJ, McAlister FA, Johnson JA, Tsuyuki RT. Underutilisation of ACE inhibitors in patients with congestive heart failure. Drugs 2001;61:2021–2033.
10. Sim I, Cummings SR. A new framework for describing and quantifying the gap between proof and practice. Med Care 2003;41: 874–881.
11. Bickell NA, McEvoy MD. Physicians' reasons for failing to deliver effective breast cancer care: a framework for underuse. Med Care 2003;41:442–446.
12. Randolph AG, Gonzales CA, Cortellini L, Yeh TS. Growth of pediatric intensive care units in the United States from 1995 to 2001. J Pediatr 2004;144:792–798.
13. Garber N, Watson RS, Linde-Zwirble WT, et al. The size and scope of intensive care for children in the US. Crit Care Med 2003;31(Suppl): A78.
14. Angus DC, Barnato AE, Linde-Zwirble WT, et al. Use of intensive care at the end of life in the United States: an epidemiologic study. Crit Care Med 2004;32:638–643.
15. Watson RS, Linde-Zwirble WT, Hartman ME, et al. ICU use at the end-of-life in US children. Crit Care Med 2002;30(Suppl):A147.
16. Odetola FO, Clark SJ, Freed GL, Bratton SL, Davis MM. A national survey of pediatric critical care resources in the United States. Pediatrics 2005;115:e382–e386.
17. Odetola FO, Miller WC, Davis MM, Bratton SL. The relationship between the location of pediatric intensive care unit facilities and child death from trauma: a county-level ecologic study. J Pediatr 2005; 147:74–77.
18. Pollack MM, Cuerdon TC, Getson PR. Pediatric intensive care units: results of a national survey. Crit Care Med 1993;21:607–614.
19. Tilford JM, Simpson PM, Green JW, Lensing S, Fiser DH. Volume-outcome relationships in pediatric intensive care units. Pediatrics 2000;106:289–294.
20. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346: 1128–1137.
21. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals: estimating potentially avoidable deaths. JAMA 2000;283:1159–1166.
22. Newacheck PW, Taylor WR. Childhood chronic illness: prevalence, severity, and impact. Am J Public Health 1992;82:364–371.
23. Reiss J, Gibson R. Health care transition: destinations unknown. Pediatrics 2002;110:1307–1314.
24. Feudtner C, Hays RM, Haynes G, Geyer JR, Neff JM, Koepsell TD. Deaths attributed to pediatric complex chronic conditions: national trends and implications for supportive care services. Pediatrics 2001; 107:e99.
25. Hack M. Consideration of the use of health status, functional outcome, and quality-of-life to monitor neonatal intensive care practice. Pediatrics 1999;103:319–328.
26. Noble L. Developments in neonatal technology continue to improve infant outcomes. Pediatr Ann 2003;32:595–603.
27. Dosa NP, Boeing NM, Ms N, Kanter RK. Excess risk of severe acute illness in children with chronic health conditions. Pediatrics 2001; 107:499–504.
28. Graham RJ, Dumas HM, O'Brien JE, Burns JP. Congenital neurodevelopmental diagnoses and an intensive care unit: defining a population. Pediatr Crit Care Med 2004;5:321–328.
29. Slonim AD, Patel KM, Ruttimann UE, Pollack MM. The impact of prematurity: a perspective of pediatric intensive care units. Crit Care Med 2000;28:848–853.
30. Angus DC, Linde-Zwirble WT, Griffin M, Clermont G, Clark RH. Epidemiology of neonatal respiratory failure in the US: projections from California and New York. Am J Respir Crit Care Med 2001;164: 1154–1160.

31. Watson RS, Linde-Zwirble WT, Hartman ME, Clermont G, Angus DC. Epidemiology of mechanical ventilation in non-infant US children. Crit Care Med 2002;30(Suppl):A131.

32. Bindl L, Dresbach K, Lentze MJ. Incidence of acute respiratory distress syndrome in German children and adolescents: a population-based study. Crit Care Med 2005;33:209–212.

33. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–874.

34. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862–871.

35. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368–1377.

36. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 1999;27:723–732.

37. Reinhart K, Meier-Hellmann A, Beale R, et al. Open randomized phase II trial of an extracorporeal endotoxin adsorber in suspected Gram-negative sepsis. Crit Care Med 2004;32:1662–1668.

38. Molnar Z, Mikor A, Leiner T, Szakmany T. Fluid resuscitation with colloids of different molecular weight in septic shock. Intensive Care Med 2004;30:1356–1360.

39. Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. Intensive Care Med 2003;29: 834–840.

40. Busund R, Koukline V, Utrobin U, Nedashkovsky E. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intensive Care Med 2002;28:1434–1439.

41. Center for Disease Control and Prevention. National Vital Statistics Report, vol 50, no. 16. Atlanta, GA: CDC; 2002:1–36.

42. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003;167:695–701.

43. Watson RS, Linde-Zwirble WT, Lidicker J, et al. The increasing burden of severe sepsis in U.S. children. Crit Care Med 2001;29(Suppl):A8.

44. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. Chest 1996;109:1033–1037.

45. Al Zwaini EJ. Neonatal septicaemia in the neonatal care unit, Al-Anbar governorate, Iraq. East Mediterr Health J 2002;8:509–514.

46. Ali Z. Neonatal bacterial septicaemia at the Mount Hope Women's Hospital, Trinidad. Ann Trop Paediatr 2004;24:41–44.

47. Kutko MC, Calarco MP, Flaherty MB, et al. Mortality rates in pediatric septic shock with and without multiple organ system failure. Pediatr Crit Care Med 2003;4:333–337.

48. McCormick MC, Kass B, Elixhauser A, Thompson J, Simpson L. Annual report on access to and utilization of health care for children and youth in the United States—1999. Pediatrics 2000;105:219–230.

49. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics 2002;110:315–322.

50. Fulwood R, Parker S, Hurd SS. Asthma—United States, 1980–1987. MMWR Morbid Mortal Weekly Rep 1990;39:493–497.

51. Owens PL, Thompson J, Elixhauser A, Ryan K. Care of Children and Adolescents in U.S. Hospitals. Report No. AHRQ Publication No. 04–0004. Rockville, MD: AHRQ; 2003.

52. Bratton SL, Odetola FO, McCollegan J, Cabana MD, Levy FH, Keenan HT. Regional variation in ICU care for pediatric patients with asthma. J Pediatr 2005;147:355–361.

53. Hartman ME, Linde-Zwirble WT, Watson RS, Angus DC. Changes in incidence, management, and care of pediatric status asthmaticus over the last decade. Crit Care Med 2005;33(Suppl):A4.

54. Bratton SL, Roberts JS, Watson RS, Cabana M. Intensive care of pediatric asthma: differences in outcome and Medicaid insurance. Pediatr Crit Care Med 2002;3:234–238.

55. Centers for Disease Control and Prevention. Asthma mortality and hospitalization among children and young adults, United States, 1980–1993. MMWR CDC Surveill Summ 1996;45(17):350–353.

56. Serafini U. Can fatal asthma be prevented? A personal view. Clin Exp Allergy 1992;22:576–588.

57. Greenberger PA, Patterson R. The diagnosis of potentially fatal asthma. N Engl Reg Allergy Proc 1988;9:147–152.

58. Lowenthal M, Patterson R, Greenberger PA, Grammer LC. The application of an asthma severity index in patients with potentially fatal asthma. Chest 1993;104:1329–1331.

59. Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick J, Sutherland DC. A case–control study of deaths from asthma. Thorax 1986;41: 833–839.

60. Kikuchi Y, Okabe S, Tamura G, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994;330:1329–1334.

61. Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet 2004;364:1505–1512.