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REVIEW ARTICLE

The Economic and Humanistic Burden of Severe Sepsis

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Abstract Sepsis and severe sepsis in particular remain a major health problem worldwide. Their cost to society extends well beyond lives lost, as the impact of survivorship is increasingly felt. A review of the medical literature was completed in MEDLINE using the search phrases "severe sepsis" and "septic shock" and the MeSH terms "epidemiology", "statistics", "mortality", "economics", and "quality of life". Results were limited to human trials that were published in English from 2002 to 2014. Articles were classified by dominant themes to address epidemiology and outcomes, including quality of life of both patient and family caregivers, as well as societal costs. The severity of sepsis is determined by the number of organ failures and the presence of shock. In most developed countries, severe sepsis and septic shock account for disproportionate mortality and resource utilization. Although mortality rates have decreased, overall mortality continues to increase and is projected to accelerate as people live longer with more chronic illness. Among those who do survive, impaired quality of life, increased dependence, and rehospitalization increase healthcare consumption and, along with increased mortality, all contribute to the humanistic burden of severe sepsis. A large part of the economic burden of severe sepsis occurs after discharge. Initial inpatient costs represent only 30 % of the total cost and are related to severity and length of stay, whereas lost productivity and other indirect medical costs following hospitalization account for the majority of the economic burden of sepsis. Timeliness of treatment as well as avoidance of intensive care unit (ICU)-acquired illness/morbidity lead to important differences in both cost and outcome of treatment for severe sepsis and represent areas where improvement in care is possible. The degree of sophistication of a health system from a national perspective results in significant differences in resource use and outcomes for patients with serious infections. Comprehensive understanding of the cost and humanistic burden of severe sepsis provides an initial practical framework for health policy development and resource use.

Key Points for Decision Makers

The incidence of severe sepsis and its overall mortality is projected to accelerate as people live longer with more chronic illnesses.

The majority of the economic burden of severe sepsis occurs after hospital discharge; initial inpatient costs represent only 30 % of the total cost and are related to severity and length of stay.

Impaired quality of life, increased healthcare consumption, and subsequent increased mortality all contribute to the humanistic burden of severe sepsis and affects caregivers as well.

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1 Introduction

Severe sepsis represents a significant global problem with an estimated number of deaths between 15 and 19 million per year worldwide [1], with significant variance in its prevalence throughout the world [2, 3].

1.1 Severe Sepsis in Adults

The incidence of sepsis is rising rapidly. In the USA, between 2004 and 2009, the annual incidence was in the range of 300–1031 per 100,000 population [4], depending on which approach to identification was used [5–8]. Regardless of methodology, the incidence of sepsis increased an average of 13 % annually, as compared with 8.7 % annually between 1979 and 2000, while the case fatality rate decreased [7]. On reviewing the study done by Lagu et al [9], the differences in methodology become readily apparent, as they report a constant and more rapid increase (17.8 % per year) in the number of cases of severe sepsis between 2003 and 2007. There was a decrease in the proportion of septic patients with no or one organ dysfunction, while the proportion of patients with three or four documented organ dysfunctions rose. Aside from improvements in care, a likely explanation is better recognition, documentation and coding of organ dysfunction by healthcare providers.

This trend is also supported by data from Australia and New Zealand [10], where the proportion of patients with severe sepsis and septic shock admitted to an intensive care unit (ICU) rose each year from 7.2 % (in 2000) to 11.1 % (in 2012), representing a relative increase in the number of cases of approximately 3.7 % per year. During this time, the length of ICU stay was approximately 7 days. The mean mortality in septic patients decreased from 35 % in 2000 to 18.4 % in 2012, while the actual number of deaths increased each year.

In Europe, severe sepsis and septic shock also represent a significant portion (between 10 and 45 %) of all ICU admissions [11]. Although it is difficult to treat Europe as a homogeneous region, it is safe to say their models of care for the critically ill, independent of nationality, differ in comparison to North America through differences in bed availability, which affect directly patient disposition. As such, in Europe, patients with severe sepsis and septic shock are more likely to be admitted to an ICU after spending approximately 1 day on the wards. Once admitted, however, their length of stay is longer, at 7.8 days vs. 4.2 in the USA [12].

Population-based studies in the developed world suggest that the burden of critical illness is higher than generally appreciated and will continue to increase as the population ages [1]. This may be related to a difference in immune response [13] or a result of the presence of comorbidities [14]. Regardless, there is a clear increase in the rates of severe sepsis with age [5, 15], along with an increase in mortality [5, 14]. This multi-year trend in increasing hospitalizations for severe sepsis is likely to continue as life expectancy continues to rise worldwide and an aging population with multiple comorbidities becomes more susceptible to developing sepsis [16].

Among those with an increasing number of hospitalizations are patients with end stage renal disease. Between 1993 and 2006, US Renal Data System showed an increase of 34 % in infections and a doubling of infections due to vascular access [17], and by 2010, this number increased even further [18]. The type of vascular access is a major determinant of risk of infection, with non-tunneled catheters having a 10- to 50-fold higher odds ratio of becoming infected than arteriovenous fistulas [19].

As advances in the management of malignancies and organ failures have led to a substantial increase in the survival of patients with cancer so has the number of patients with solid [20] and hematological malignancies [21, 22] requiring ICU admission due to infection and sepsis. In these patients, bloodstream infections are an important cause of mortality and are usually associated with Gram-negative bacteria and the presence of multidrug resistant organisms. For organ transplant patients, sepsis is the most common cause of ICU admission (47 %) and an independent predictor of inpatient mortality (68 %) [23].

1.2 Sepsis in Children

Sepsis is the leading cause of death in infants and children worldwide, with an annual mortality of approximately 1.6 million [5]. The pediatric population represents a very diverse group, with age influencing the epidemiology of severe sepsis more than any other single characteristic [24]. Respiratory infections and primary bacteremia are the most common infections [25].

From 1995 to 2005, the number of pediatric hospitalizations for severe sepsis in the USA grew by 81 % to more than 75,000 cases annually, with the majority of this increase resulting from doubling of severe sepsis cases in newborns, from 4.5 to 9.7 cases per 1000 births [25]. During this time, the median length of stay remained stable at 31 days, while mortality decreased from 10.3 to 8.9 % [24, 26]. Despite improved survival rates, the burden of severe sepsis in children remains very high, with 47 % of survivors readmitted at least once at a median of 3 months after discharge. More than 30 % of these readmissions were in children without comorbidities, and an additional 6.5 % of patients died during these readmissions [27].

The incidence of sepsis in pediatric patients in Europe has not been well studied. One of the better sepsis epidemiological databases comes from the Italian Pediatric Sepsis Study Group, representing a 1-year period in 15 of the 22 Italian pediatric ICUs, where the incidence of sepsis was found to be 11.6 %. The most common site of infection was respiratory (47.8 %), followed by bloodstream (24 %) and central nervous system (16.2 %), with a mortality of 15 % compared with 4.7 % in children without sepsis. Presence of a chronic comorbidity was associated with an almost three-fold increase in mortality, 24 vs. 8.9 % [28]. Other major factors for sepsis in children are chronic comorbidities, cancer, immunosuppression and presence of central venous access.

The majority of pediatric sepsis occurs in low- and middle-income countries, but there is very little epidemiological research. Most data comes from World Health Organization statistics, which rank pneumonia, diarrheal disease, neonatal sepsis, malaria and measles as the top killers of children, with 80 % of pediatric deaths classified as sepsis [29]. By far, the highest burden is from neonatal sepsis, with an estimated 1 million babies dying annually. The highest numbers of neonatal deaths are in South/Central Asian countries, and the highest rates are generally in Sub-Saharan Africa. Unfortunately, with few exceptions, there has been little progress in reducing such deaths over the past 10–15 years [30].

1.3 Maternal Sepsis

For the most part, maternal sepsis deaths mirror those of neonatal sepsis, with low- and middle-income countries having the highest rates because of poor access to prenatal care. In comparison, in industrialized countries, maternal death rates including those due to sepsis are low, but as would be expected among patients of lower socioeconomic status, there is a higher rate of morbidity and mortality because of poor access to care, as well as the presence of comorbidities, such as diabetes or hypertension.

The best epidemiological data comes from the USA, where the incidence of sepsis and severe sepsis were found to be 10 per 10,000 live births and 4.9 per 10,000 live births, respectively [31], and accounted for 11.5 % of all inhospital deaths [32].

2 Methods

Our review examines recent (2002–2014) literature on severe sepsis with a focus on its epidemiology and impact, both clinical and economic, on patients and health systems. Different methodologies and wide variations in healthcare delivery make it difficult to estimate the true cost of severe sepsis, both from an economic and humanistic perspective. This review emphasizes the most severe forms of sepsis (severe sepsis and septic shock), which are usually treated in the ICU and are a common cause of death and disability. Although inpatient costs for severe sepsis are high, significant medical costs occur after discharge. Both clinical outcomes and associated societal costs are the focus of this review.

A MEDLINE search using the phrases “severe sepsis” and “septic shock” and the MeSH terms “epidemiology”, “statistics”, “mortality”, “economics”, and “quality of life” provided the foundation for our review. We analyzed human trials published in English between 2002 and 2014 and classified articles by dominant themes to address epidemiology, acute therapies, mortality and quality of life of both patient and family caregivers, as well as societal costs. Differences in medical care, patient outcomes and cost relative to the level of development of the health systems for those countries with published data were considered.

3 Economic Burden of Sepsis

In August 2013, the Agency for Healthcare Research and Quality (AHRQ) published a statistical brief from the Healthcare Cost and Utilization Project describing the amount of money hospitals spent to treat patients according to their medical condition. Septicemia ranked in the top four most costly conditions for hospitals within all four payer groups (Medicare, Medicaid, private insurance, uninsured) and number one when combining the groups [33]. Across all payer groups, adult sepsis cost hospitals US$20,000 per patient in 2011 (approximately US$21,000 in 2014 dollars according to inflation rates provided by the Bureau of Labor and Statistics and its consumer price index) [34]. Sepsis in the pediatric population is estimated to cost between US$29,829 and US$65,639 per case, with higher costs mostly attributed to neonatal and infant ICU care, which is highly specialized [5, 35].

However, the cost of severe sepsis may be greater than that reported by the AHRQ for generalized septicemia. The Nationwide Inpatient Sample database was used to identify 2,828,917 US hospitalized adult patients with severe sepsis between the years of 2003 and 2007 [36]. Overall the rate of severe sepsis increased 71 % over the 5-year period, giving an annual rate of 17.8 %. The authors identified an approximate cost per case of severe sepsis as US$34,000 in 2007 dollars (approximately US$38,000 in 2014 dollars). A more recent publication [37] retrospectively evaluated a cohort of severe sepsis adult patients hospitalized in 2011 identified using the University Health System Consortium Clinical Database Resource Manager (Chicago, IL, USA). Based on the 56,997 patients identified, the average cost of hospitalization per patient was US$26,304 (approximately US$28,000 in 2014 dollars).

3.1 Direct Costs Associated with Severe Sepsis

3.1.1 Sepsis Onset and Severity in Relation to Length of Stay

Direct medical costs are the medically related resources used to directly provide treatment. Using sepsis as an example, direct medical costs may include physician and nursing care, medications administered, laboratory tests, diagnostic imaging, intravenous supplies, hemodynamic monitoring devices, and other general costs associated with occupying an ICU bed. Over 3 decades of research and crossing international borders, multiple studies have consistently shown that the per-day hospital costs of sepsis are high compared with other conditions that require ICU care, costs increase as sepsis severity increases, and sepsis requires a longer ICU stay compared with other conditions.

A French study from 1998 [38] followed patients presenting to a single medical ICU with sepsis and found total direct costs of €26,256, €35,185 and €27,083 (2001 €) for sepsis, severe sepsis and septic shock, respectively. The authors noted that cost differences were largely influenced by length of stay and whether the syndrome was present upon admission or acquired while in the ICU. When comparing the daily cost of all patients according to severity and mode of acquisition (patients who had sepsis syndrome upon admission vs. patients who acquired the syndrome while in the ICU), the costs generally went up as severity increased. This difference was most significant for those who acquired sepsis while in the ICU (Table 1). Costs due to drugs, fluids and consumables increased as sepsis severity increased (33, 41 and 44 % for sepsis, severe sepsis and septic shock, respectively). The authors concluded the biggest impact on the direct costs of sepsis is its mode of acquisition (sepsis on admission vs. ICU-acquired) as the latter patients had much longer length of stays. This study also shows how the severity of sepsis can impact the overall length of stay and how the length of stay is a large contributor to the overall cost of care.

The increased direct cost of ICU acquired sepsis was further supported in a review of six ICUs located in France [39] from 1997 to 2000. The average cost of having severe sepsis at ICU admission was €14,500 compared with the average cost of €32,700 for acquiring sepsis while in the ICU. Further, the average cost of severe sepsis was €22,800 compared with €9600 for ICU patients without severe sepsis (2001 €). If a patient was admitted to the ICU with severe sepsis, improved and subsequently developed a secondary episode of severe sepsis, the average cost was further increased to €36,600, and this difference was largely driven by ICU length of stay. The overall ICU cost per day remained greater for those with ICU-acquired severe sepsis compared with severe sepsis at the time of ICU admission (at least €1300 compared with €800) [40]. More recently, a 2007 German-based study looking at costs within 51 ICUs found patients with sepsis to have a higher daily ICU direct cost than patients without sepsis [€1090 ± 422 vs. €745 ± 255 (2003 €), $p < 0.0001$] [41]. Among a subset of patients with an underlying diagnosis of cancer, there is again a significant difference between the cost of caring for a patient without severe sepsis and caring for a patient with severe sepsis [42, 43].

Length of stay was again noted to drive direct hospital costs in a retrospective cohort study using Medicare patient data from 2000 to 2002 [44]. Here ICU patients with severe sepsis were compared with ICU patients without severe sepsis. Severely septic patients spent almost twice as long in the hospital as patients without severe sepsis (16.5 vs. 8.5 days) and more than twice as long in the ICU (10 vs.

Table 1 LOS (days), cost (2001 €) and cost per day of all septic patients, patients with sepsis syndrome upon admission or sepsis syndrome acquired in the ICU

	All patients	Sepsis on ICU admission	ICU-acquired sepsis
Patients with sepsis			
LOS	37	29	58
Cost	26,256	17,261	39,908
Cost per day	710	595	688
Patients with severe sepsis			
LOS	43	35	52.5
Cost	35,185	21,461	42,132
Cost per day	818	613	802
Patients with septic shock			
LOS	34	25.2	48
Cost	27,083	17,705	44,851
Cost per day	796	702	934

ICU intensive care unit, *LOS* length of stay

4.6 days). Total costs were 2.5 times higher (US$34,436 vs. US$13,895) and daily costs were US$2,087 and US$1,635 per day for patients with severe sepsis and patients without severe sepsis, respectively (2002 dollars). The difference in daily costs supports the conclusion that severe sepsis is more expensive compared with an average of other ICU admissions. On a daily basis, the cost of an ICU bed, an ICU nurse, and physician is likely to be the same regardless of the reason for admission. The difference may be attributable to the number of drugs, fluids, lab tests and ancillary services a severe sepsis patient utilizes.

3.1.2 Itemized Breakdown of Direct Costs

Further detail into the direct costs of sepsis was provided by a Brazilian study that itemized cost according to allocation blocks of clinical support services, consumables, staff and hospital fee (Fig. 1) [45]. The authors found that hospital fee only made up 12 % of the overall costs associated with sepsis. The remaining blocks of clinical support services, consumables and staff consumed 31, 36 and 21 %, respectively. In other words, 33 % of the costs were as a result of hotel and staff costs. A breakdown analysis of direct costs was also provided in the previously mentioned German study from 2007 [41]. The top three expenditures

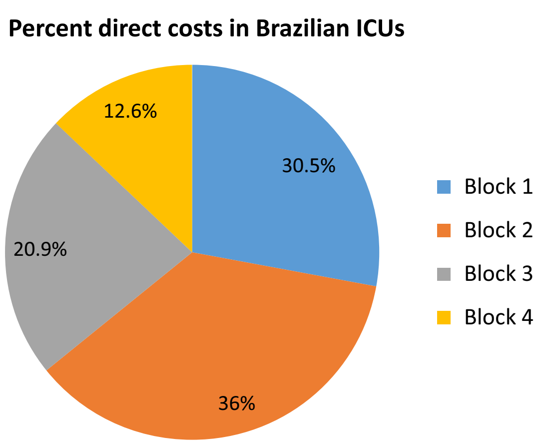

Fig. 1 Direct costs from Brazilian intensive care units (ICUs). Data obtained from [45]. *Block 1* (30.5 %) = clinical support services: electrophysiology (0.1 %), lab tests (1 %), cultures (0.3 %), parenteral and enteral nutrition (18.1 %), dialysis methods (3.4 %), respiratory physiotherapy (0.7 %), invasive and noninvasive ventilation (6.1 %), X-ray (0.8 %). *Block 2* (36.1 %) = consumables: intravenous or oral medications (including antibiotics) (32.8 %), colloids (0.3 %), albumin (2.6 %), fresh frozen fresh plasma (0.1 %), packed red blood cells (0.3 %). *Block 3* (20.9 %) = staff: standard monitoring (6 %), sample blood or other fluids collected (0.5 %), central venous catheter (5.3 %), pulmonary artery catheter (1.7 %), dialysis catheter (intravenous or peritoneal) (2.8 %), intracranial pressure monitoring (0.01 %), arterial catheter (0.8 %), clothes changes (1.7 %), caring for drainages (0.1 %), cardiopulmonary resuscitation (0.1 %), tracheotomy (0.6 %), laparotomy (0.3 %), neurosurgery (0.4 %), thoracotomy (0.2 %), other surgeries (0.1 %). *Block 4* (12.6 %) = hospital fees (12.6 %)

were staffing (55 % of total direct cost), medication (19 % of total direct cost) and diagnostics (12 % of total direct cost) (Fig. 2). A 2001 Swiss study identified a mean hospitalization cost of 41,790 Swiss Francs (CHF) (US$44,000) (2001 CHF and US$). Half of this cost was the result of staffing costs and an additional 20 % was the result of medication costs (Fig. 3) [46]. Additionally, the authors found that the proportion of total costs attributed to drugs, fluids and consumables increased with patient severity, while the proportion of medical and nursing staff costs decreased.

The studies above highlight the difficulty in comparing the direct costs associated with severe sepsis. Depending upon the study, the cost of staff alone varies between 21 % [45] to 55 % [41]. This discrepancy can be explained by non-uniform definitions of "staffing" between studies, differing healthcare systems and reimbursement models, and worldwide variability regarding staff compensation.

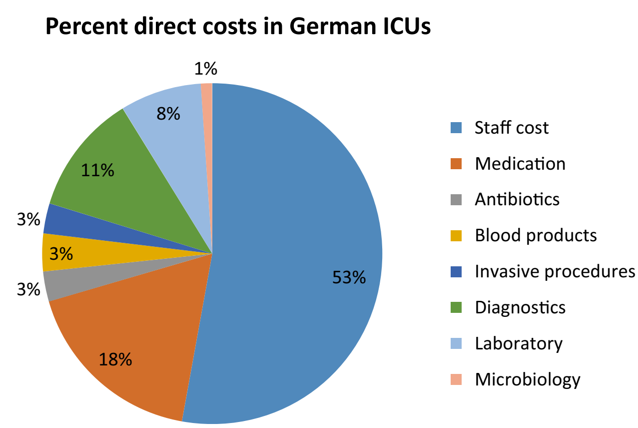

Fig. 2 Direct costs in German intensive care units (ICUs). Data obtained from [41]. Medication = drugs, fluids, nutrition. Invasive procedures includes diagnostic procedures (including imaging), renal replacement therapy, and mechanical ventilation

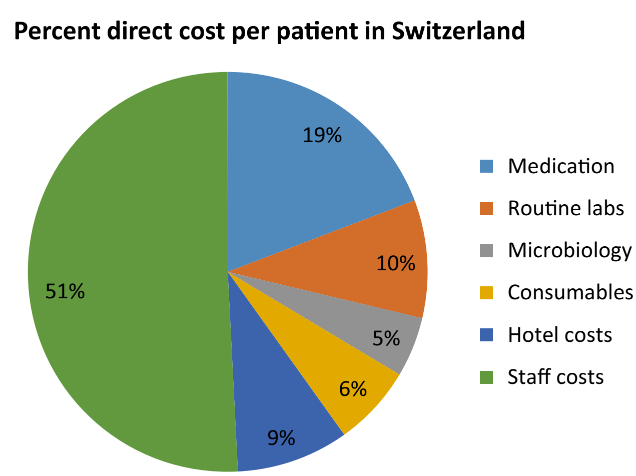

Fig. 3 Direct costs in Swiss intensive care units (ICUs). Data obtained from [46]

3.1.3 Impact of Drug Utilization on Cost

Medication utilization has the potential to impact the total direct costs of severe sepsis. Opportunities to minimize waste are worth implementing when trying to reduce costs. Services like sedation stewardship, clinical pharmacist involvement and specialized dietician participation may mitigate cost [47–58].

Nazer et al. [59] recently evaluated medication utilization and medication cost in cancer patients with sepsis and septic shock admitted in 2010 to a single ICU in Jordan. The number, type and total cost for each medication utilized were retrospectively assessed. A total of 116 cases of sepsis or septic shock were identified. The total cost of the medications prescribed for this cohort of patients was €291,030 and the mean number of medications prescribed per patient was 11.7 (SD ±4.7) (2010 €). The most commonly prescribed medication classes were acid suppressive therapy, antibacterial agents and vasopressors. The most costly medications classes were antifungals, which were prescribed in 55 patients (47.4 %), and colony stimulating factors, which were prescribed in 37 patients (31.9 %). Non-survivors had higher medication costs than survivors (€3664 vs. €1430, $p = 0.0001$), a finding which has been noted in prior studies [45].

Future therapies, such as novel biologics, may become available that reduce the severity of illness for some patients. Once introduced into the marketplace, these therapies are likely to be expensive and may not necessarily have cost-neutral or cost-effective outcomes associated with their use [60, 61]. Therefore, indiscriminate use in patients with anticipated marginal benefits will skew the cost discussion and ultimately limit or delay the development and use of beneficial therapies [62, 63].

Such therapies, if considered a standard of care, would benefit from judicious oversight over their utility [64].

Every health system must deal with these realities on the basis of their unique circumstances, but rationing will ultimately occur along with the expected misapplication of scarce resources and delay the development of the science of medicine, to the detriment of all [65–67]. A goal of health systems should be to ensure novel, expensive therapy is applied to those patients who ultimately benefit [68].

3.2 Indirect Costs Associated with Severe Sepsis

Indirect non-medical costs are financial opportunities lost as a result of productivity changes because of illness or death and may include personal income lost during hospitalization and subsequent outpatient recovery. Indirect medical costs may include healthcare expenditures after hospital discharge and can include durable medical equipment or outpatient medication.

3.2.1 Productivity Loss

The sepsis syndrome has long-lasting and untoward effects on both individuals and society in general, including nontrivial productivity loss due to work absenteeism, sepsis mortality and early retirement [46, 69]. Yearly productivity loss in Germany due to temporary morbidity was conservatively estimated to be €151 million (1998 prices), assuming 44,000 new severe sepsis cases per year [89]. Permanent morbidity due to severe sepsis cost €447 million, and premature death cost €2024 million, with the total indirect cost estimated at €2622 million per year. A Swiss study conservatively estimated the indirect burden of disease to be CHF347 million per year (2001 prices) [75]. In both studies, direct hospital costs made up only about 30 % of the total cost, and productivity loss due to premature death accounted for the largest portion of total cost (56 % in the German paper and 67 % in the Swiss paper) (Figs. 4, 5).

Using the two studies above, one can extrapolate the total (direct plus indirect) cost burden of severe sepsis in the USA. The mean hospital cost per case of severe sepsis in the USA is approximately US$20,000 [34], and approximately 1 million cases of severe sepsis are expected in 2014 [5]. The nationwide hospital cost is therefore approximately US$20 billion [34]. Assuming this represents only 30 % of the economic burden of disease [46, 69], the total cost of the disease to the USA is roughly US$67 billion per year. The total cost could be even higher if the direct cost per case is revised upwards [9].

3.2.2 Healthcare Expenditure After Hospital Discharge

Other studies have estimated that the majority of healthcare expenditure for an episode of severe sepsis occurs after hospital discharge. Weycker et al. [70] estimated long-term mortality and medical care charges among patients with severe sepsis annually for 5 years after an index admission for sepsis. Inpatient and outpatient medical and pharmaceutical charges were tracked. The mean cost of the index admission was US$44,600. By 180 days after the index admission, mean cumulative total medical charges were US$68,300. At 1 year, 3 years and 5 years, the mean cumulative total medical charges were US$78,500, US$103,600 and US$118,800, respectively (Fig. 6). A Canadian study of sepsis survivors found that the majority of healthcare costs in the year following discharge is attributed to subsequent hospital admissions [71].

Survivors of severe sepsis utilize greater healthcare resources compared with prior to their sepsis episode. This was demonstrated in a recently published study where the healthcare use of older severe sepsis survivors (mean age 78) was compared with their own pre-sepsis resource use [34].

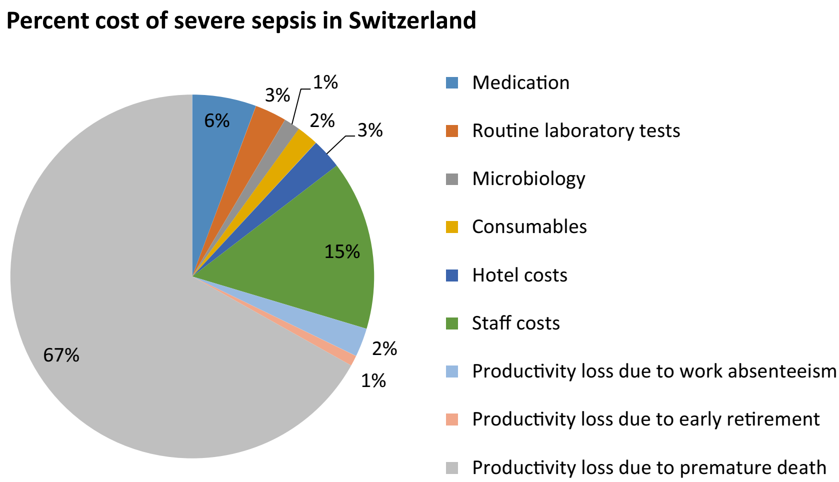

Fig. 4 All costs of severe sepsis in Switzerland. Data obtained from [46]

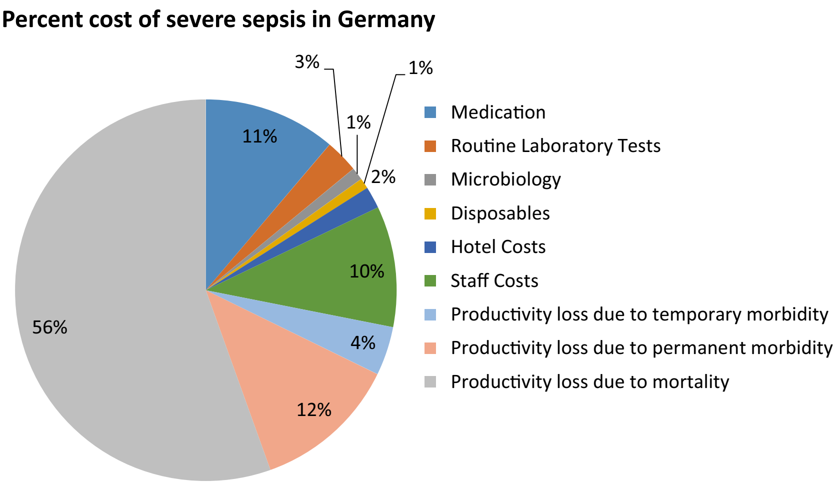

Fig. 5 Total costs of severe sepsis in Germany. Data obtained from [41]

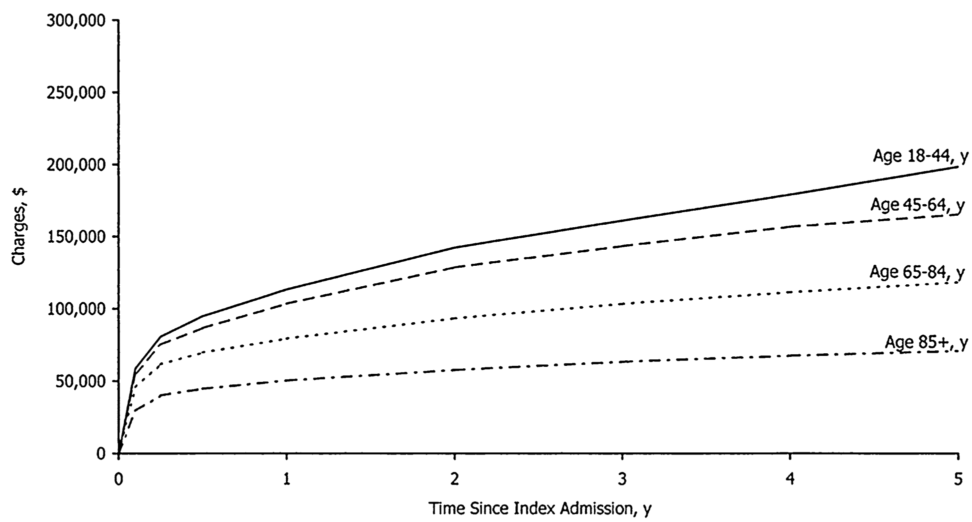

Fig. 6 Cumulative total medical care charges among patients with severe sepsis, by age at index admission. Charges are given in 2000 US dollars. Reprinted with permission from Weycker et al. [70]

This design helps to distinguish between resource utilization due to patients' propensity to use care and resource utilization due to sequelae of severe sepsis. Patients spent a median of 9 more days admitted to an inpatient healthcare facility the year after surviving an episode of severe sepsis compared with the year prior. The rate of hospitalization was increased by 0.51 hospitalizations per patient-year, and the rate of inpatient healthcare use was increased by 23.7 days per patient-year (Fig. 7). Additionally, only 20 % of severe sepsis survivors remained alive for a full year after severe sepsis without being rehospitalized.

4 Humanistic Cost of Sepsis

4.1 Mortality After Hospital Discharge

There is an increased risk of death after a sepsis episode that persists up to 5 years after hospitalization [72, 73]. In the study by Weycker et al. [70], mortality was 21.2 % for the index admission, 51.4 % at 1 year and 74.2 % at 5 years. A recent systematic review of the literature noted patients with sepsis have ongoing significant mortality once discharged from the ICU and that 28-day mortality as an end point for clinical studies may lead to inaccurate inferences [74].

The mechanisms behind the increased mortality that persists for years after an episode of sepsis are being investigated. Survivors of severe sepsis exhibit profound immune suppression, deemed “post-septic immunosuppression”, resulting in increased morbidity [74, 75]. Using a mouse model, survivors of sepsis demonstrated 100 % mortality when challenged 3 or 15 days post-sepsis recovery with intratracheal *Aspergillus fumigatus*. The increased mortality correlated with changes in cytokines and Toll-like receptor expression and alterations in lung leukocyte populations. The authors speculate that the lung becomes predisposed to nosocomial infections for extended periods of time after severe sepsis via mechanisms that include alterations in inflammatory cytokines and an increase in immunomodulatory chemokines. Additionally, there is mounting evidence that sepsis survivors have ongoing subclinical inflammation related to cytokine dysregulation, which is associated with an increased risk of death [76].

4.2 The Post-Sepsis Syndrome

The post-sepsis syndrome refers to the constellation of long-term physical and psychological problems experienced by the sepsis survivor. This includes insomnia, hallucinations, disabling muscle and joint pains, extreme fatigue, poor concentration, decreased cognitive functioning, and loss of self-esteem [77, 78]. Much effort has been directed to better understand the burden of problems borne by the sepsis survivor.

In a landmark observational study published in 2010 in *JAMA*, Iwashyna et al. [79] used data from the Health and Retirement Study to identify 516 individuals who survived severe sepsis hospitalizations and interviewed patients to assess for discharge cognitive impairment after the index hospitalization. The mean age at hospitalization was 77 years. The authors found that survivors of severe sepsis had a clinically and statistically significant increase in moderate to severe cognitive impairment. Among all severe sepsis survivors, 6.1 % had moderate to severe cognitive impairment according to the survey just prior to severe sepsis. The prevalence increased to 16.7 % after severe sepsis (Fig. 8). Worsened cognitive or physical function was seen in 59.3 % of survivors at the first post-sepsis survey. After controlling for changes in level of cognitive impairment after severe sepsis, 1.3 new functional limitations were seen for patients without prior limitations, and 1.2 new limitations were seen for those with baseline mild to moderate limitations. New deficits were relatively more severe among patients who were in better health prior to

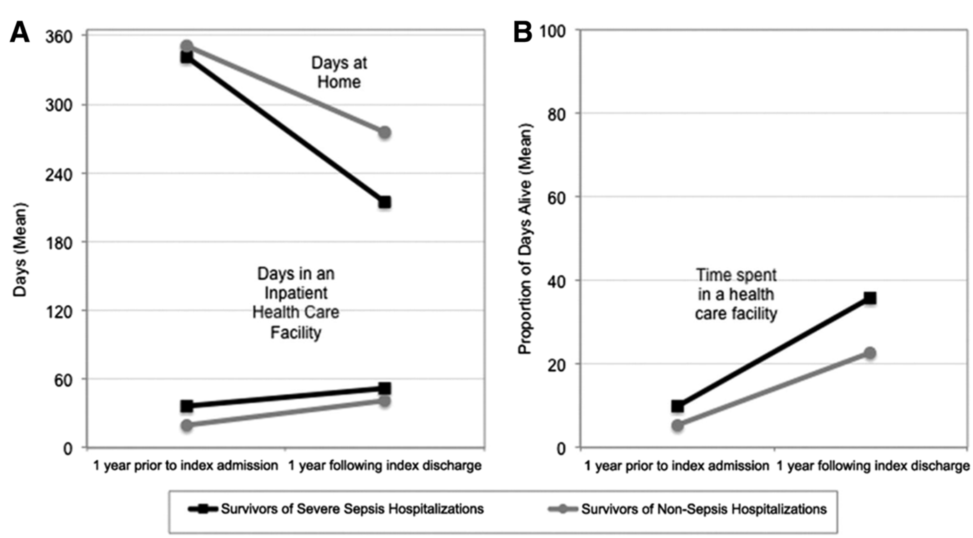

Fig. 7 Difference-in-differences analysis of healthcare use in the severe sepsis and cohorts of patients without sepsis. Reprinted with permission of the American Thoracic Society. Copyright© 2015 American Thoracic Society. Prescott et al. [97]. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society

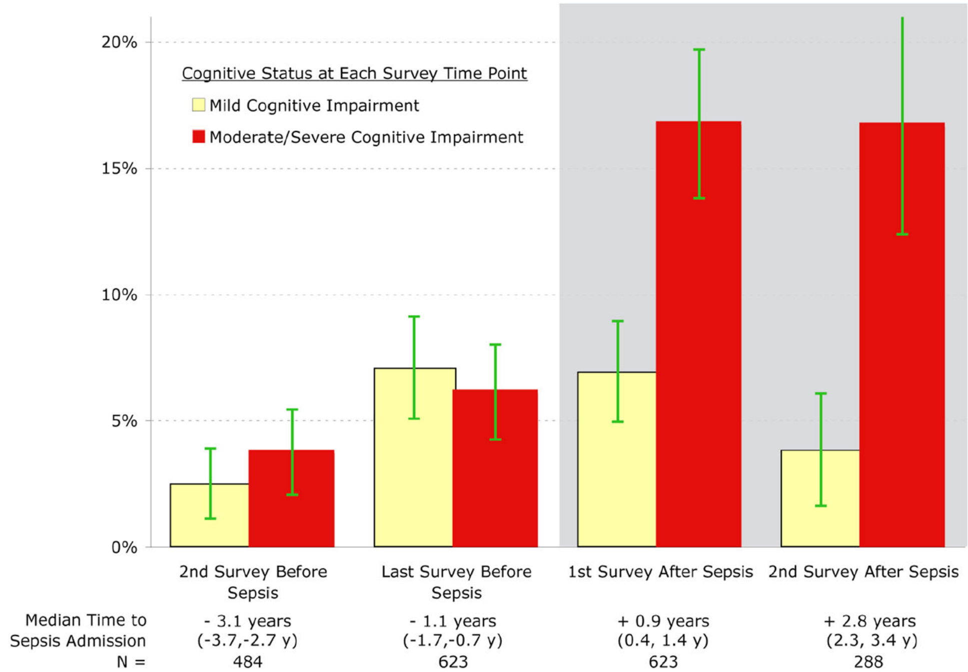

Fig. 8 Cognitive impairment among survivors of severe sepsis at each survey time point (95 % confidence intervals for the proportions are shown). Reprinted with permission from Iwashyna et al. [79]

the index episode. When compared with other non-sepsis hospitalizations, the cognitive and functional changes were worse after severe sepsis. Patients hospitalized without severe sepsis and no functional limitations prior to hospitalization developed an average of 0.48 new functional limitations. Patients with mild to moderate functional limitations at baseline developed 0.43 new functional limitations after hospitalization which did not involve sepsis.

Based upon the above study, Iwashyna et al. [72] subsequently measured the absolute number of the population of Medicare beneficiaries who survive at least 3 years after an index severe sepsis episode in 2005 and estimated the likely numbers with cognitive dysfunction and functional disability. The absolute number of individuals that survived severe sepsis by at least 3 years was found to be >600,000 individuals. The authors then estimated a substantial 2008 population burden of older adults with moderate to severe cognitive impairment (>100,000 persons) and functional impairment (>500,000 persons) after severe sepsis.

Recently published work has found a bidirectional relationship exists between pneumonia and cognition which may explain how a single episode of infection in well-appearing older individuals accelerates decline in chronic health conditions and loss of functional independence [80].

4.3 Quality of Life Among Sepsis Survivors

Within the last decade, several studies have attempted to quantify the impact of sepsis on health-related quality of life (HR-QoL) [74, 81–84]. Granja et al. [81] administered the EuroQol five-dimension (EQ-5D) health-related questionnaire to 104 ICU sepsis survivors and 133 ICU non-sepsis survivors. The authors reported in 2004 that survivors from severe sepsis and septic shock have a similar EQ-5D to that of survivors from critical illness admitted without sepsis at 6 months after ICU discharge. Sepsis survivors reported significantly fewer problems in the anxiety/depression dimension, and there were no significant differences in the other dimensions.

However, more recent work casts doubt upon the findings of the above study. In 2008, Hofhuis et al. [82] reported a prospective study where 170 patients with severe sepsis were administered the Short-Form 36 questionnaire at ICU admission (via use of patient proxies), during hospital stay and at 3 and 6 months after ICU discharge. The results were compared with those of an age-matched general Dutch population. A significant decline of HR-QoL during ICU stay was noted for severe sepsis patients, with gradual improvement during the 6 months after ICU discharge. However, at 6 months, recovery was still incomplete in the physical functioning, role-physical and general health dimensions compared with preadmission status. The study also noted that severe sepsis patients frequently have a lower HR-QoL before critical illness occurs, compared with the general population.

In a 2009 paper, Karlsson et al. [83] investigated quality of life before and after severe sepsis in adult patients in Finland. The cumulative 2-year mortality was 1.5 times higher than the hospital mortality. Severe sepsis survivors had lower quality of life than the age- and sex-adjusted population even 1.5 years after the index sepsis episode. In keeping with prior studies, the quality of life in most patients before ICU admission was already lower than that in the general population [83].

A systematic review of the literature published in 2010 concluded that survivors of sepsis consistently demonstrate impaired quality of life [74]. The worsening quality of life and increasing morbidity and mortality was consistently seen across trials of all sizes, nationalities, varying severities of illness, and patient populations.

Symptoms of depression were recently evaluated in a prospective longitudinal cohort study of 439 older Americans who had survived severe sepsis [84]. The prevalence of substantial depressive symptoms was high among severe sepsis survivors at 28 %, but interestingly this was not significantly increased from the pre-sepsis baseline. However, this percentage is considerably higher than the prevalence of substantial depressive symptoms in the community and correlates with prior studies that indicate patients who develop severe sepsis have a lower HR-QoL at baseline.

The above studies highlight the "hidden public health disaster" of long-term sepsis survival [85]. However, more difficult to quantitate is the downstream social impact. Like all life-threatening illnesses, severe sepsis can change family dynamics, disrupt work or school, and bring a household into financial hardship. Ongoing study is required to better understand and mitigate the untoward effects of the sepsis syndrome.

5 Conclusions

Severe sepsis is a common disease worldwide which has a major impact on morbidity, mortality and costs of medical care. Although inpatient costs for severe sepsis are high, the majority (70 %) of medical costs occur beyond the hospital. Medical costs are further compounded by a diminished quality of life for those afflicted and increased caregiver burden [72, 86–88].

The post-sepsis syndrome is a major determinant of the humanistic burden of the disease and affects previously healthy patients as well. There is little information in the existing medical literature regarding the incremental cost for patients who suffer from the post-sepsis syndrome, though upcoming studies may provide some insight [89].

The outcome of severe sepsis and associated costs are very dependent on the sophistication and development of the health systems within which patients reside. Among less developed nations, excess mortality related to a lack of application of "basic medical care" primarily afflicts children. Large improvements in mortality for these populations could be anticipated with small increases in spending to provide basic medical care and access to health facilities. In the developed world, excess mortality and morbidity come at a high cost to an elderly population or those already afflicted with serious chronic illness.

The outcomes for many patients, especially the elderly and chronically ill, are poor despite already large expenditures on the care of these patients, and further monetary expenditures on behalf of this group are unlikely to significantly improve outcomes [90]. Avoidance of ICU acquired illness and optimal use of fluids and mechanical ventilation are simple evidence-based strategies that can reduce cost [91–93]. For the developed world, enhanced patient selection for advanced medical care, especially in the ICU, has great potential to alleviate suffering and reduce cost [93].

Considering the diminished quality of life and associated costs for many survivors, the concept of incremental cost per quality-adjusted life-year is important from both the patient-centric and societal perspective [83]. If the efforts of friends, family or others called upon to fill in the gaps in necessary care not provided by any part of the health system were included in cost analyses, their productivity loss would act as multipliers to the crude estimates that do exist [94–96]. In developed countries, a better understanding of the costs and outcomes of sepsis may lead to improved allocation of healthcare resources toward a goal of better health for all.

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