Economic and Social Burden of Severe Sepsis

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Introduction

Sepsis is highly prevalent within intensive care units (ICUs) and is associated with elevated rates of morbidity and mortality [1–3], and high costs [4–7]. For these reasons, healthcare providers, managers, government authorities, and insurance companies have focused their attention on strategies that could reduce the economic and social burden of sepsis. In the healthcare system, ICUs consume a considerable amount of resources and have frequently been considered the target for efforts to reduce escalating medical expenses.

The direct cost of caring for patients with sepsis has been shown to be 6-fold higher than caring for ICU patients without sepsis [8]. According to data from the US, each septic patient consumes, during hospitalization, about US$ 25,000, corresponding to approximately $ 17 billion annually [9]. These figures may increase when patients progress to septic shock and multiple organ dysfunction and require highly expensive therapeutic and diagnostic interventions, and a longer hospital stay [10].

In parallel, indirect costs have also been estimated as being excessively elevated. These costs, also called social costs, result from the productivity loss associated with absenteeism or early mortality. Indirect costs are those resulting from lack of productivity of an employee who is hospitalized or in ambulatory care or temporarily hindered from work. Indirect costs of sepsis have been estimated as 2–3 times the direct costs.

This chapter will describe the main studies addressing the direct and indirect costs of sepsis, as well as the cost and cost-effectiveness of sepsis treatment protocols.

Concepts

Before describing the main data regarding the cost of sepsis management, we will review some concepts related to health economic analyses which will be used in this chapter. The reason for this brief review is to standardize these concepts and to provide the reader with guidelines for reporting or interpreting economic analyses. This concern is not unfounded. Heyland and co-workers demonstrated that, from more than 1,000 studies that addressed intensive care costs, only three met minimal criteria for scientific rigor [11]. Many of the concepts and guidelines we will use were proposed in 1996 by the US Public Health Service Panel on Cost-effectiveness in Health and Medicine (PCEHM) for the conduct and reporting of economic analyses [12].

1) **Costs** – Usually expressed in monetary terms, costs are a measure of what we forfeit to achieve a utility or acquire an item.

2) **Direct costs** – Direct costs are those resulting directly from health interventions. They are divided into medical and non-medical costs. Direct medical costs stem from hospitalization, complementary exams, medications, prostheses and ortheses, among other products and services. Non-medical direct costs typically include the costs of transporting the patient to the hospital and fees for the temporary hiring of personnel to look after the patient during the recovery period

3) **Indirect costs** – As mentioned, indirect costs result from the productivity loss associated with absenteeism or early mortality. Indirect costs are those resulting from lack of productivity of an employee who is hospitalized or is in ambulatory care or temporarily hindered from work.

4) **Opportunity-cost** or economic opportunity loss – This represents the value of a product forgone to produce or obtain another product. Opportunity cost is a key concept in economics because it implies the choice between desirable, yet mutually exclusive results. The notion of opportunity cost plays a crucial part in ensuring that scarce resources are used efficiently.

5) **Top-down and bottom-up approaches** – There are two approaches to estimating unit costs: The top-down and the bottom-up approaches. The top-down approach divides the total expenditure on a service by units of activity. Units of activity are specific to the services for costing, for example, the cost per day of a hospital stay or the cost of a general practice consultation. The top-down approach also uses aggregated data along with a population-attributable fraction to calculate the attributable costs. The bottom-up approach is more comprehensive and involves more detailed costing of all the elements used to cost the service. The different resources used to deliver the service are identified and a value is assigned to each, these values are then summed and linked to an appropriate unit of activity to generate the unit cost. A number of reports and papers provide more details on how to measure and value costs [13–15].

6) **Developing the cost estimate (micro-costing)** – three basic steps are required to build a cost estimate (micro-costing) including identification, quantification, and valuation. The first step is building a resource use profile by determining which health care services are relevant for each therapy (identification). The next step is achieved by identifying the frequency of use and the proportion of users for each health care service in the profile (quantification). The last step is to apply a unit cost to each resource used (valuation).

7) **Quality-adjusted life-year (QALY) -** The QALY is a measure of health outcomes, known as a utility, which incorporates both the duration and quality of survival. Quality of life must be expressed as a numeric value ranging from 0 to 1, and the duration of time that a patient exists in that state is adjusted by the quality of life of being in that state.

8) **Efficacy versus effectiveness** – Efficacy describes the clinical effects under ideal circumstances (usually a controlled clinical trial). Effectiveness describes the clinical effects under typical 'real world' circumstances, where patients are not carefully selected and practice is not carefully monitored.

9) **Cost–effectiveness analysis** (CEA) – This produces a ratio, such as the cost per year of life gained, where the denominator reflects the gain in health from a specific intervention (e.g., life-years gained, number of additional survivors, or number of pneumonias averted) and the numerator reflects the cost in dollars of obtaining that gain [16].

10) **Cost utility** – This is a type of cost-effectiveness where effects are expressed as utilities, such as quality-adjusted survival, facilitating comparisons across different diseases and interventions (e.g., QALYs). From here forward, we use the standard terminology in which CEA refers to both cost-effectiveness and cost-utility analyses.

11) **Cost (burden) of illness** – Direct and indirect costs related to a specific disease.

12) **Budget impact analysis** – While economic evaluation of the efficient allocation of healthcare resources plays a useful role to healthcare purchasers, it is unable to address the issue of affordability. In addition to maximizing efficiency, healthcare purchasers must also strive to simply remain within their annual budgets.

13) **Perspective** – It is important to know the perspective of an analysis in order to determine what the content of the cost profile will be. In many countries, the societal perspective is the one of choice for an economic analysis and indirect costs play a larger role in the decision-making process. In other countries the perspective of a third party payer responsible for the cost of comprehensive care is frequently the viewpoint of the analysis and direct medical costs are those that drive the decision process.

14) **Friction cost method** - This is a modification of the human capital method to calculate indirect costs. Whereas in the human capital method the economic costs (productivity losses) are calculated for the period from the beginning of the illness until the end of the age of gainful employment, this period is shortened in the friction cost method to the so called 'friction period', which corresponds to the length of time until the position in question is filled again.

Direct Costs of Sepsis Management

Direct medical costs associated with severe sepsis primarily consist of hospital costs. The main components of these costs can be divided into blocks according to the proposal by Edbrooke and co-workers [6]. These and other authors reported that personnel costs (for nurses, physicians, technicians, and assistants) consume from 45 to 60 % of the total ICU budget. Compared with the large proportion of personnel costs, other fixed costs (such as non-clinical support services, equipment, and rent and maintenance costs for building and properties) have a minor impact on the total costs of intensive care. Variable costs including drugs, other consumables, laboratory and diagnostic services, amounted to only 30 % of total costs [6].

Comparing this cost distribution per ICU patient-day with severe sepsis patient-day, personnel related costs are still extremely relevant. However, as demonstrated in **Figure 1**, drugs amount to 40 % of total costs [4]. Combining these data, we can easily conclude that an effective reduction in costs for a patient with severe sepsis in the ICU, could be achieved either by shortening length of stay, since a large proportion

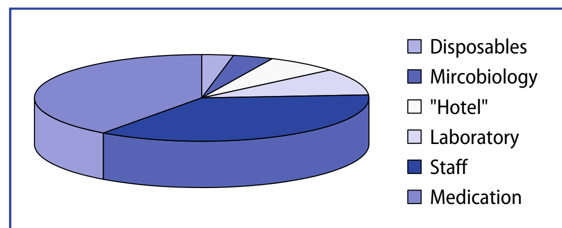

Fig. 1. Distribution of costs for intensive care unit (ICU) treatment of severe sepsis from three German university hospitals (1997 – 2000) [4].

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of costs are fixed, or by reducing drug consumption. Later on, we will discuss how an integrated protocol of sepsis management could impact on those variables.

Some studies have reported the costs of sepsis management. For instance, Angus et al. [9] reported a total hospital cost of US$ 22,100 in a retrospective study in ICU and non-ICU septic patients in the United States. In this study, ICU septic patients were more severely ill, with longer lengths of stay (23.3 vs. 15.6 days, $p < 0.0001$) and cost more ($29,900 vs. $13,900, $p < 0.0001$) than non-ICU patients, In similar populations, Braun et al. [17] and Moerer et al. [4] reported even higher costs ranging from US$ 26,820 to €23,296 per patient. Costs have also varied depending on severity of the disease and outcome. Chalfin et al. [18] analyzed 1,405 patients and estimated mean total charges of $38,304 in survivors and $49,182 in non-survivors. Similarly, Brun-Buisson et al. [10], in an elegant study, reported costs from €26,256 to €35,185 depending on the severity of illness. However, a simple and direct comparison among all those studies is not feasible. Country-specific health care systems, reimbursement rates and regulations, as well as different cost and pricing factors prevent an easy comparison. Additionally, the case mix for sepsis should be taken into account. Therefore, in contrast to the findings of clinical studies, results of economic evaluations cannot be readily transferred from one country to another.

Direct Costs of Sepsis Management in Developing Countries: A Brazilian Experience

We performed a multicenter, prospective study to evaluate costs of septic patients in Brazilian ICUs [19]. Twenty-one ICUs and 524 septic patients were enrolled in this study. By using a bottom-up approach we collected every diagnostic and therapeutic intervention performed in these patients daily. Standard unit costs (year 2006 values) were based on the Brazilian Medical Association (AMB) price index for medical procedures and the BRASINDICE price index for medications, solutions and hospital consumables. Medical resource utilization was also assessed daily using the Therapeutic Intervention Scoring System (TISS)-28. Direct costs outside the ICU and indirect costs were not included.

The median total cost of sepsis was US$ 9632 (interquartile [IQ] range 4583–18387; 95 % CI 8657, 10672) per patient, while the median daily ICU cost per patient was $ 934 (IQ 735–1170; 95 % CI 897, 963). The median daily ICU cost per patient was significantly higher in non-survivors than in survivors ($ 1094 [IQ 888–1341; 95 % CI 1058, 1157] and $ 826 [IQ 668–982; 95 % CI 786, 854], $p < 0.001$). Interestingly in our study, the costs of non-survivors increased day-by-day while the costs of survivors decreased after the first few days (**Fig. 2**). In other words, we observed an increasing pattern in daily costs associated with death while survivors showed a decreasing pattern, indicating an increased use of resources in non-survivors. To our knowledge, this pattern of increasing daily costs has not previously been demonstrated. These data support that a surviving patient will use less sophisticated therapy upon his or her convalescence, as opposed to the non-survivors. This finding also suggests that those patients who receive effective treatment and respond to it will develop less organ dysfunction and consequently have reduced costs. In this context, an evidence-based approach can rationally provide the most effective management, increasing survival rates and, at the least, not increasing expenses.

For patients admitted to public and private hospitals, we found median sequential organ failure assessment (SOFA) scores at ICU admission of 7.5 and 7.1, respectively

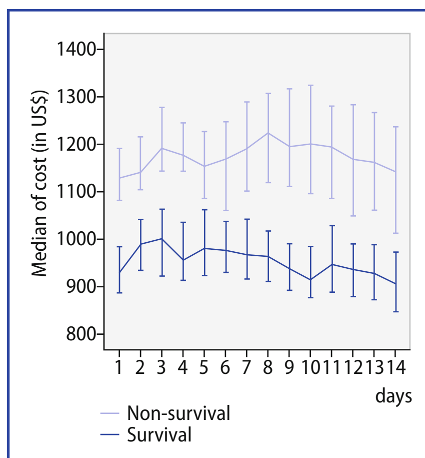


Fig. 2. Median daily ICU costs including error bars (95 % CI) for surviving and non-surviving septic patients. From [19] with permission

(p = 0.02), and the mortality rate was 49.1 % and 36.7 %, respectively (p = 0.006). Patients admitted to public and private hospitals had a similar length of stay of 10 (IQ 5 – 19) days versus 9 (IQ 4 – 16) days (p = 0.091), and the median total direct costs for public ($US 9773; IQR 4643 – 19 221; 95 % CI 8503, 10 818) versus private ($US 9490; IQR 4305 – 17 034; 95 % CI 7610, 11 292) hospitals did not differ significantly (p = 0.37).

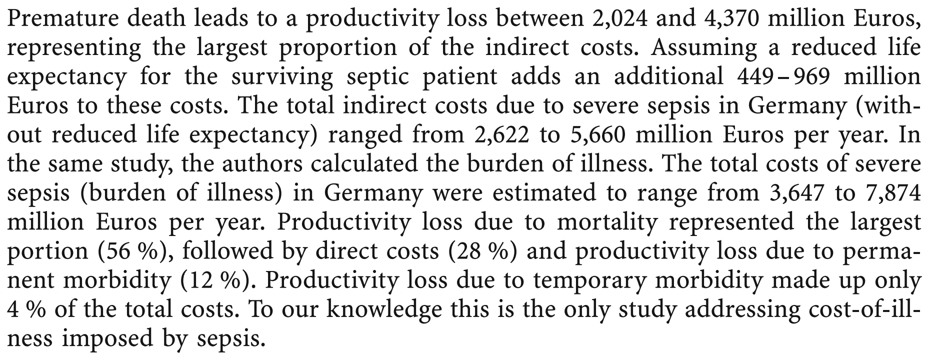
This study provides the first economic analysis of the direct costs of sepsis in Brazilian ICUs and reveals that the cost of sepsis treatment is high and, despite similar ICU management and resource allocation, there was a significant difference regarding patient outcome between private and public hospitals [19]. These data reinforce the need for a national campaign in order to standardize management and decrease the heterogeneity with which these patients are treated in Brazilian institutions.

In another country, Cheng et al. [20] collected data from 10 Chinese ICUs and found a median length of stay of 7 days (3 – 14), with a mean hospital cost of US$ 11,390 – 11,455 per case of severe sepsis (mean cost per case per hospital day $ 502 – 401 USD).

Indirect Costs and Burden of Illness

Severe sepsis causes indirect costs as a consequence of productivity loss due to temporary unfitness for work, premature retirement, or premature death. All three kinds of work absenteeism are affected by severe sepsis [4]. Indirect costs of illness are calculated according to the human capital approach or friction cost approach (see these concepts above). Expected future productivity losses due to permanent morbidity or mortality could be discounted using a yearly discount rate of 5 %. Lower (0 %) and higher (10 %) discounting rates are tested in the scope of the sensitivity analysis [21].

In a retrospective study, using electronic charts from three German ICUs, Schmid and co-workers [21] reported the indirect costs associated with severe sepsis in that country. The annual prevalence of severe sepsis was considered to range from 44,000 to 95,000 cases. The productivity loss due to temporary morbidity ranged from 151 to 326 million Euros. Productivity loss due to permanent morbidity due to severe sepsis was 447 – 964 million Euros (upper and lower end of severe sepsis incidence).



Premature death leads to a productivity loss between 2,024 and 4,370 million Euros, representing the largest proportion of the indirect costs. Assuming a reduced life expectancy for the surviving septic patient adds an additional 449–969 million Euros to these costs. The total indirect costs due to severe sepsis in Germany (without reduced life expectancy) ranged from 2,622 to 5,660 million Euros per year. In the same study, the authors calculated the burden of illness. The total costs of severe sepsis (burden of illness) in Germany were estimated to range from 3,647 to 7,874 million Euros per year. Productivity loss due to mortality represented the largest portion (56 %), followed by direct costs (28 %) and productivity loss due to permanent morbidity (12 %). Productivity loss due to temporary morbidity made up only 4 % of the total costs. To our knowledge this is the only study addressing cost-of-illness imposed by sepsis.

Impact of Therapeutic Strategies on Costs

As mentioned before, several factors can increase costs in the ICU, including length of stay (fixed costs mainly personnel), severity of disease, and drugs. Hence, interventions which could reduce length of stay and/or severity may attenuate costs. In general, cost-effective analyses are carried out to evaluate new interventions, such as drugs and devices. For example, there are several studies addressing the costs and cost-effectiveness of drotrecogin alfa (activated) [activated protein C] and evidence-based sepsis protocols, mainly based on the Surviving Sepsis Campaign guidelines [22].

Drotrecogin alfa (activated) has been indicated for patients with severe sepsis at high risk of death [22]. This recommendation is based on two randomized clinical trials (RCTs), PROWESS (Protein C Worldwide Evaluation in Severe Sepsis) [23] and ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis) [24]. There is an ongoing RCT evaluating the efficacy of this drug only in patients with septic shock (ClinicalTrials.gov Identifier: NCT00604214). The first economic evaluation of drotrecogin alfa (activated) treatment for severe sepsis was carried out by Manns et al. [25]. These authors collected clinical and cost information, including data from a three-year follow-up in a cohort of patients who had been admitted to an ICU with severe sepsis and had received conventional care. They estimated the cost-effectiveness of this drug for ICU patients with severe sepsis using a Markov analysis. For all patients, the cost per life-year gained by treating patients with drotrecogin alfa (activated) was $27,936; it was significantly more cost-effective to treat patients with an APACHE II score of 25 or more ($19,723 per life-year gained) than to treat those with an APACHE II score of 24 or less ($575,054 per life-year gained). However, the cost per quality-adjusted life-year gained was higher ($43,319 to $53,989) because of the reduction in ongoing health-related quality of life for survivors of sepsis. These authors concluded that the use of drotrecogin alfa (activated) in patients with severe sepsis, with greater severity of illness, and a reasonable life expectancy is cost effective (< 50 thousand dollars).

One year later, Angus et al. [26] also published a cost-effectiveness analysis based on data collected prospectively as part of a multicenter international trial. Analyses were conducted from the United States societal perspective, limited to healthcare costs, and using a 3 % annual discount rate. Over the first 28 days (short-term Base Case), drotrecogin alfa (activated) increased the costs of care by $9,800 and survival by 0.061 lives saved per treated patient. Projected to lifetime (lifetime Reference Case), drotrecogin alfa (activated) increased the costs of care by $16,000 and quality-

adjusted survival by 0.33 quality-adjusted life-years per treated patient. Thus, drotrecogin alfa (activated) cost $48,800 per quality-adjusted life-year (with 82 % probability that the ratio is <$100,000 per quality-adjusted life-year). For more severely ill patients with APACHE II score higher 24, drotrecogin alfa (activated) cost $27,400 per quality-adjusted life-year. The authors concluded that this intervention had a cost-effectiveness profile similar to many well-accepted healthcare strategies.

More recently, Dhainaut et al. [27] reported another cost-effectiveness analysis in 'real life', by using an observational study design involving adult patients recruited before and after licensing of drotrecogin alfa (activated) in France. The incremental cost-effectiveness ratios gained were as follows: €20,278 per life-year gained and €33,797 per quality-adjusted life-year gained. There was a 74.5 % probability that this compound would be cost-effective if they were willing to pay €50,000 per life-year gained. An interesting commentary [28] accompanying this paper, highlighted some limitations of the study [27] that should be evaluated in every cost-effective analysis. First, the authors based their economic evaluation only on non-RCT data, even when RCT data [23] were available. Second, the study was only powered to find differences in costs, but not in effectiveness. Finally, they did not consider sensitivity analyses using the PROWESS data. Despite these limitations, the authors of the commentary concluded that the results appear to confirm that the use of drotrecogin alfa (activated) in the 'real world' is cost-effective [28].

Three other studies [29–31] have reported similar results regarding the cost-effectiveness ratio of drotrecogin alfa (activated). Importantly there is a consensus that this compound is only cost-effective in the more severely ill septic patients.

Taken together, these studies suggest that the use of drotrecogin alfa (activated) in severely ill septic patients is associated with a cost-effectiveness ratio in the range of other funded interventions. ICU managers and clinicians should decide if this intervention should or should not be incorporated in their units/institutions by considering the incremental costs and the opportunity cost of this intervention in relation to others not currently funded.

In contrast, there are some recent publications evaluating the costs and cost-effectiveness of integrated protocols using the Surviving Sepsis Campaign guidelines. Shorr et al. [32] evaluated the economic impact of an evidence-based sepsis protocol in their institutions. One hundred and twenty patients were assessed before (60) and after (60) the protocol implementation. In addition to increased survival rates, the median total hospital costs were significantly lower with use of the protocol ($16,103 vs. $21,985, $p = 0.008$), mainly because of shorter length of stay. They concluded that implementation of a sepsis management protocol was able both to improve mortality rate and to substantially save money.

Similarly, but using a cost-effectiveness analysis, Talmor et al. [33] carried out a cohort study evaluating the impact of the Multiple Urgent Sepsis Therapies (MUST) protocol (based on early goal-directed therapy [34]). These authors reported an association between adoption of this integrated sepsis protocol and increased in-patient survival at a moderate increase in treatment costs. The cost for treating a patient with an integrated sepsis protocol was approximately $8,800 greater than for treating patients before it. These increased costs in the study cohort were driven by higher ICU costs associated with increased ICU length of stay. The authors also plotted differences in costs versus differences in QALY (**Fig. 3**). They were able to demonstrate that the MUST protocol was largely localized in the upper-right quadrant, which means incremental increases in costs and in QALY, falling within acceptable standards for cost-effectiveness.

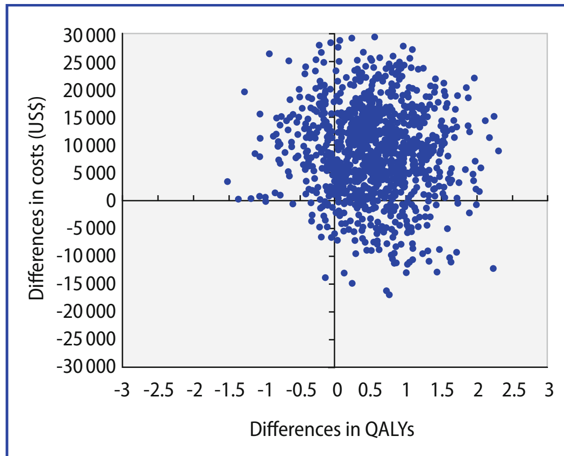


Fig. 3. Analysis of quality-adjusted life expectancy (QALY) versus cost. Base case cost-effectiveness distributions of the 1,000 simulations. Quadrants to the right of the y-axis represent regions where treating patients with the MUST protocol is associated with net QALYs gained. From [33] with permission

A recent systematic review was carried out to identify critical care interventions that are cost-effective [35]. The authors reviewed every cost-effectiveness analysis study related to this field. Methodological and analytical characteristics included the study perspective, discounting of future costs and life years, and performance of sensitivity analyses. They also converted all non-US currency ratios into US currency. Nineteen original cost-effectiveness studies (1993–2003) were included, which were directly related to the management of the critically ill patient in the ICU and presented cost per QALY or cost per life-year incremental cost-effectiveness ratios. Three interventions fell within accepted cost-effectiveness ratios including drotrecogin alfa (activated) for patients with sepsis, mechanical ventilation, and admission to the ICU itself. However, when selected populations were analyzed, such as drotrecogin alfa (activated) for septic patients and an APACHE score of < 25, mechanical ventilation in patients > 40 yrs old with stroke, and admission to the ICU for patients with hematologic malignancies, the cost-effectiveness ratio was unfavorable.

Conclusion

In summary, there is a relatively strong body of data demonstrating that the management of sepsis is costly. Cost-effectiveness analysis studies are crucial to evaluate the economic impact of critical care interventions. Although critical care support requires an expensive and complex structure, cost-effectiveness analyses are rare in the medical literature. This fact is largely because there is a scarcity of evidence of the effectiveness of critical care interventions and as a result of difficulty in measuring quality of life and utility, which are recommended for use in cost-effectiveness analyses. Additional well recognized obstacles include heterogeneic practice patterns, and the difficulty in measuring burden of critical illness. Despite these factors, managers and clinicians should be empowered by health economic studies before making decisions. Cost-effectiveness analyses are good examples of ‘phase 4’ studies which should be carried out in order to help us in the process of accepting different critical care interventions and/or incorporating a new drug or device into current practice.

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