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ORIGINAL ARTICLE

# Critical care management of severe sepsis and septic shock: a cost-analysis

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## Abstract

*Background*

Sepsis treatment has been associated with high costs. Furthermore, both the incidence of sepsis and the severity of illness at presentation appear to be increasing. We estimated healthcare costs related to the treatment of patients with sepsis in the intensive care unit (ICU) and aimed to explain variability in costs between individuals.

*Methods*

We performed a prospective cohort study in patients presenting with severe sepsis or septic shock to the ICUs of two tertiary centres in the Netherlands. Resource use was valued using a bottom-up micro-costing approach. Multivariable regression analysis was used to study variability in costs.

*Results*

Overall, 651 patients were included, of which 294 presented with septic shock. Mean costs were €2250 (95% CI €2235-€2266) per day and €29,102 (95% CI €26,598-€31,690) per ICU admission. Of the total expenditure, 74% was related to accommodation, personnel, and disposables, 12% to diagnostic procedures, and 14% to therapeutic interventions. Patients with septic shock had higher costs compared with patients with severe sepsis (additional costs: €69 (95% CI €37-€100) per day, and €8355 (95% CI €3400-€13,367) per admission). Site of infection, causative organism, presence of shock, and immunodeficiency were independently associated with costs, but explained only 11% of the total variance.

*Conclusion*

Mean costs of sepsis care in the ICU were almost €30,000 per case. As costs were poorly predictable, opportunities for cost savings based on patient profiling upon admission are limited.

## Introduction

Over the last decades, both the reported incidence of sepsis in the general population and the severity of disease at presentation to hospital are rising.[1,2] These increases may be explained by an ageing population that brings about more chronic comorbidities. Alternatively, raised awareness amongst doctors as a result of the Surviving Sepsis Campaigns may have resulted in overdiagnosis of sepsis to some extent.[1,2] Sepsis patients who develop organ failure are considered to have severe sepsis, whereas those with advanced circulatory compromise are considered to be in septic shock.[3] In either case, management in a critical care facility is required. As the technological possibilities to provide effective life support to critically ill patients have advanced, both individual patients and the general public demand access to the 'best' possible care. Hence, doctors in intensive care units (ICUs) are faced with increasingly difficult decisions to stop or deny further treatment. Taken together, these developments will likely result in a higher demand for sepsis treatment in the ICU, as well as increased expenditures per patient.[1,4,5]

Insight into the costs of sepsis care and its determinants is of major importance in this era of universal restraints on healthcare budgets. Several authors have estimated expenditures for sepsis treatment in different settings and from different perspectives, including estimations of total hospitalisation costs for sepsis and costs of sepsis in developing countries.[4-9] However, only

very few studies have specifically investigated costs of sepsis treatment in ICU settings.[5,6,9] Moreover, available studies predominantly relied on administrative data to identify sepsis cases and did not use individual patient data to generate cost estimates. These methods do not adequately reflect the variation in costs between patients, precluding the possibility to explain individual variability by multivariable modelling.[10] Furthermore, these studies used data which were collected during the 1990s, and may thus no longer be representative of the current healthcare situation.

Although the existing literature is somewhat inconsistent, several characteristics are believed to be associated with high costs of treatment, including advanced age.[5,11] increased severity of illness,[5] a surgical reason for admission,[5,6,11] and some specific sites of infection (especially catheter-related infections).[9] Knowledge about patient and illness characteristics that are associated with excessive healthcare costs might be helpful for clinicians to make informed decisions when considering treatment of critically ill patients with sepsis.

In this study, we estimated the total direct healthcare costs associated with treatment of patients with severe sepsis or septic shock in the ICU using a bottom-up micro-costing approach. Furthermore, we investigated to what extent patient and illness characteristics measured at baseline can explain variability in costs between patients.

## Methods

*Design*

Data were collected within the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project, a prospective cohort study in two tertiary ICUs in the Netherlands.[12] Ethical approval for the study was provided by the Medical Ethics Committee of the University Medical Center Utrecht. They also gave permission for an opt-out procedure to obtain consent from eligible patients (IRB number 10-056).

## Participants

We included consecutive adults presenting to the ICUs of the University Medical Center Utrecht or the Academic Medical Center Amsterdam between January 2011 and October 2013 with severe sepsis or septic shock as their main reason for admission. We used definitions for severe sepsis and septic shock that were compliant with the 2008 Surviving Sepsis Campaign guidelines.[3] We only included patients having community-acquired or nosocomial infections with an onset within 72 hours before ICU admission, and a post-hoc plausibility of infection that was graded as probable or definite by dedicated observers using validated definitions.[12] Cases of unconfirmed (possible) sepsis were excluded, as were patients who had been admitted from or were discharged to another ICU, because data on total resource use and costs in these patients could not be completed.

## Data collection

Trained observers prospectively collected data on patient and illness characteristics, including demographics, chronic comorbidities, admission type, Acute Physiology and Chronic Health Evaluation (APACHE) IV score sites of infection, and causative organisms. The sites of infection were classified into the following main categories based on their frequency of occurrence: community-acquired pneumonia, hospital-acquired pneumonia, secondary peritonitis, urinary tract infection, bloodstream infection, and other.[12] Causative organisms were categorised as Gram-positive bacteria, Gram-negative bacteria, fungi and yeasts, viruses, and unknown.

Data on the utilisation of drugs, fluids, nutrition, and blood products were collected using the bedside patient data management system (Metavision, iMDsoft, Israel). Information about the numbers and types of blood chemistry, microbiology, and imaging tests, as well as source control surgical procedures was extracted from the electronic health records of both participating hospitals. In one of the centres information on the number of performed blood chemistry tests was only partially accessible. Although summary test results were available (for example the daily lowest and highest plasma concentration of sodium), it was not possible to derive the exact number of individual blood specimens that these aggregates originated from. Therefore, the costs associated with blood chemistry for the patients in this centre (enrolling 55% of the total cohort) were estimated following a multivariable imputation procedure based on the complete laboratory dataset of patients in the other participating centre.

## Costs estimations

We studied direct medical costs during the ICU stay only, because we performed our cost-analysis from a healthcare perspective rather than from a societal perspective, which would also include elements such as costs for productivity loss and opportunity costs. We grouped resource use into three main categories: accommodation, diagnostic procedures, and therapeutic interventions. Costs for accommodation were derived from a previous study investigating the costs of ICU stay in the Netherlands.[13] These comprised expenditures for clinical personnel, general disposables, hotel (including basic dietary costs), overhead (including costs for general expenses, administration, energy, maintenance, insurance, and non-clinical personnel), and capital (including investment costs for buildings and inventory). We identified and valued diagnostic and therapeutic resource use for each patient individually using a bottom-up micro-costing approach. Unified internal tariffs of the participating hospitals were used to value each intervention, test, or procedure. Costs for diagnostic procedures were divided into blood chemistry (which also included immunology and biopsy procedures), microbiology, and imaging. Costs for therapeutic interventions were divided in drugs, fluids,

nutrition, blood products, and surgical procedures for source control. In order to calculate total costs per patient and per day, resources use was multiplied by unit price. All costs were expressed in euros and indexed to the 2013 price level.

As we exclusively included patients who had severe sepsis or septic shock as their main reason for admission, we assumed that all costs generated in the ICU were directly sepsis-related. Naturally, many patients had comorbidities, but we considered it not feasible to distinguish costs of sepsis treatment from those resulting from underlying diseases. Nonetheless, we chose to disregard (mainly elective) surgical procedures that were clearly not sepsis-related because, despite their infrequent occurrence, these events may have a disproportional impact on total costs. All surgery and interventional radiology undertaken as a direct consequence of the sepsis episode (for instance as a source control procedure or to treat complications) were included, however.

Because our study aimed to focus exclusively on costs of critical care management, we chose not to include expenditures during the extended ward stay of patients. However, if patients were re-admitted to the ICU following a primary sepsis event, we accumulated costs over consecutive ICU episodes.

*Statistical analysis*

Patient characteristics were compared between groups using the chi-square or the Mann-Whitney U test, as appropriate. Costs per day and per accumulated ICU admission were compared between patients with severe sepsis and septic shock, by different sites of infection, by different causative organisms, and for survivors and non-survivors. Statistical differences in costs between these subgroups were evaluated using the Kruskal-Wallis H test, as appropriate.

We constructed a multivariable linear regression model to explain variability in ICU expenditure between patients. First, univariable linear regression analyses were performed to investigate which patient and disease characteristics were associated with costs. Subsequently, all determinants with a p-value <0.25 in the univariable linear regression analyses were included in a multivariable model. The category with the lowest costs was used as a reference category in these analyses. A manual stepwise backwards regression analysis was then used to select the optimal model to explain variability between patients. The coefficient of determination ($R^2$) was used to assess the explained variability by the model.

Distributions of costs are typically skewed to the right, due to the presence of few people with very high costs. Because this skewed distribution might result in an overestimation of mean costs, we re-sampled the data 5000 times with replacement and estimated 95% confidence intervals based on these bootstrapped samples. Bootstrapped confidence intervals do not depend on the assumption that the underlying data follow a normal distribution and are therefore suitable to use in cost studies.[14] All analyses were performed in SPSS Version 20.0 for Windows (SPSS, Chicago, IL, USA).

## Results

*Figure 1* is the flowchart of patient inclusions. In total, we studied 651 patients (contributing 780 ICU episodes in total), of whom 294 (45%) were admitted with severe sepsis and 357 (55%) with septic shock. Patients presenting with septic shock had similar demographic characteristics and comorbidities, but significantly increased markers of acute disease severity and higher mortality compared with patients with severe sepsis *(table 1)*.

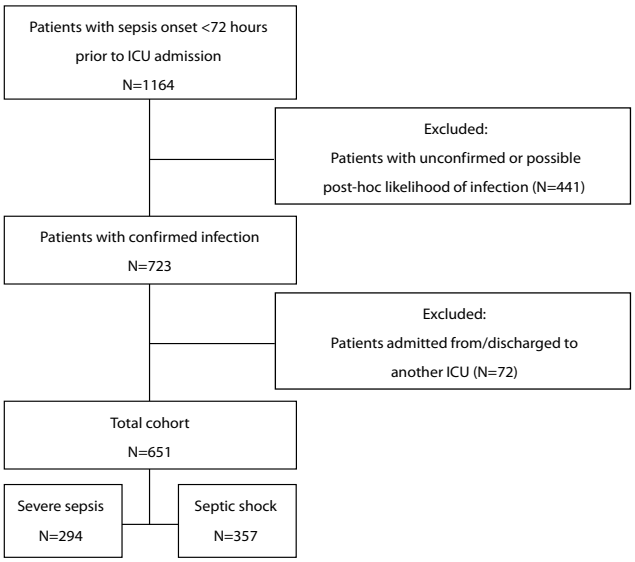


**Figure 1.** Flowchart of patient inclusion
36 patients (12%) admitted with severe sepsis progressed to septic shock during ICU admission. For all analyses, patients stayed in the admission category

*Table 2* shows detailed information on resource use and associated median expenses per admission and per day. The total median costs were €17,659 (IQR €8623-€37,018) per sepsis episode. However, due to a very skewed distribution of costs, mean costs differed considerably from median costs. Overall, we estimated the mean total costs for treatment of an episode of sepsis in the ICU at €2250 (95% CI €2235-€2266) per day and €29,102 (95% CI €26,598-€31,690) per admission. Accommodation represented 74% (€21,654, 95% CI €19,772-€23,445) of these costs, whereas diagnostic procedures accounted for 12% (€3457, 95% CI €3202-€3726) and therapeutic interventions for 14% (€3991, 95% CI €3529-€4487) of the mean total costs per admission. Costs for diagnostic procedures consisted mainly of expenses for laboratory tests. Although the price for several advanced radiological investigations was considerable, these procedures contributed little to the total diagnostic expenditure because they were utilised in less than 25% of admissions. Drugs represented the largest component

**Table 1.** Patient and illness characteristics stratified by sepsis severity

| Variable | Severe sepsis (n=294) | Septic shock (n=357) | Total (n=651) | P-value |
|---|---|---|---|---|
| Gender, male | 160 (54) | 212 (59) | 372 (57) | 0.20 |
| Age, years | 62 (52-71) | 63 (53-71) | 63 (53-71) | 0.64 |
| Comorbidities | | | | |
| - Cardiovascular disease[a] | 88 (30) | 117 (33) | 205 (32) | 0.45 |
| - Chronic obstructive pulmonary disease | 38 (13) | 54 (15) | 92 (14) | 0.43 |
| - Diabetes mellitus | 60 (20) | 71 (20) | 131 (20) | 0.92 |
| - Immune deficiency[b] | 75 (26) | 95 (27) | 170 (26) | 0.79 |
| Surgical admissions | 64 (22) | 96 (27) | 160 (25) | 0.14 |
| APACHE IV score | 81 (64-98) | 94 (77-118) | 87 (71-112) | <0.001 |
| Site of infection | | | | |
| - Community-acquired pneumonia | 88 (30) | 77 (22) | 165 (25) | 0.02 |
| - Hospital-acquired pneumonia | 60 (20) | 55 (15) | 115 (18) | 0.10 |
| - Secondary peritonitis | 33 (11) | 88 (25) | 121 (19) | <0.001 |
| - Urinary tract infection | 25 (9) | 33 (9) | 58 (9) | 0.78 |
| - Bloodstream infection | 29 (10) | 23 (6) | 52 (8) | 0.11 |
| - Other[c] | 59 (2) | 81 (23) | 140 (22) | 0.44 |
| Causative organism | | | | |
| - Gram-positive bacteria | 98 (33) | 125 (35) | 230 (35) | 0.68 |
| - Gram-negative bacteria | 106 (36) | 161 (45) | 260 (40) | 0.02 |
| - Fungi and yeasts | 23 (8) | 13 (4) | 25 (4) | 0.20 |
| - Viruses | 12 (4) | 13 (4) | 25 (4) | 0.84 |
| - Unknown | 55 (19) | 39 (11) | 94 (14) | 0.01 |
| Length of stay, days | | | | |
| - Survivors | 9 (4-14) | 12 (7-22) | 9 (4-18) | <0.001 |
| - Non-survivors | 6 (3-12) | 5 (3-14.5) | 6 (3-14) | 0.28 |
| Use of mechanical ventilation | 253 (86) | 341 (96) | 594 (91) | <0.001 |
| Use of renal replacement therapy | 37 (13) | 131 (37) | 168 (26) | <0.001 |
| ICU mortality | 57 (19) | 148 (42) | 205 (32) | <0.001 |

Continuous variables are expressed as median (IQR). Dichotomous and categorical variables are presented as frequency (%). [a]Cardiovascular disease includes chronic cardiovascular insufficiency, congestive heart failure, myocardial infarction, stroke, cerebrovascular disease and peripheral vascular disease. [b]Immune deficiency includes the presence of acquired immune deficiency syndrome or asplenia, chronic use of immunosuppressive drugs, exposure to chemotherapy or radiotherapy in the last 12 months, and any other documented humoral or cellular deficiency. [c]Other infections includes intra-abdominal infections other than secondary peritonitis, infections of the skin or soft tissue, central nervous system, gastrointestinal tract, upper and lower respiratory tract other than community-acquired pneumonia and hospital-acquired pneumonia, and postoperative wound infections

of the costs associated with therapeutic interventions, although antibiotics only accounted for a small part of these. However, the costs of antimicrobial therapy differed largely between patients, as was the case for advanced imaging. Also, source control procedures were expensive on a case-by-case basis, but contributed little to overall median costs because they were only performed in a minority of patients.

The daily expenditure on both diagnostic procedures and therapeutic interventions was higher during the first two days of admission than on consecutive days *(figure 2)*. By the end of the second day of ICU admission, the additional costs for diagnostic procedures and therapeutic interventions had accumulated to €732 and €300, respectively.

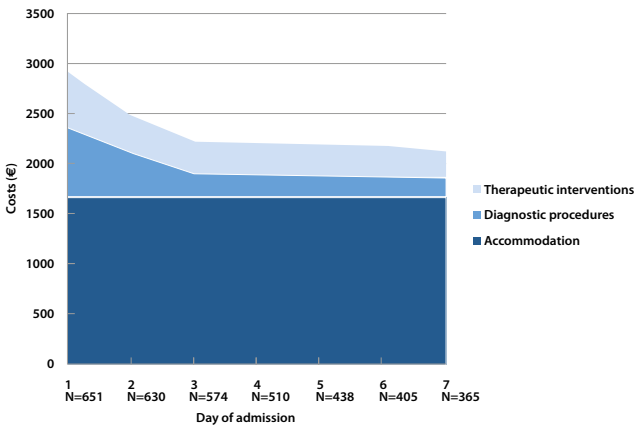


**Figure 2.** Mean costs per day in the first week of admission
The healthcare costs are depicted for patients with severe sepsis and septic shock in the first seven days of ICU admission

**Table 2.** Resource use and costs of treatment for ICU patients with severe sepsis and septic shock

| Cost component | Unit of accounting | Price per unit (€) | Use per patient per day (units of accounting) | Costs per patient per day (€) | Costs per patient per admission (€) |
|---|---|---|---|---|---|
| **Accommodation**[13] | | | | | |
| Hotel | Day | 83 | NA | 83 | 664 (332-1411) |
| Overhead | Day | 572 | NA | 572 | 4576 (2288-9724) |
| Capital | Day | 206 | NA | 206 | 1648 (824-3502) |
| Personnel | Day | 777 | NA | 777 | 6216 (3108-13,209) |
| Disposables | Day | 36 | NA | 36 | 288 (144-612) |
| **Diagnostics** | | | | | |
| Laboratory[a] | | | | | |
| - Blood chemistry | Test | 1.5 (1.3-1.7) | 35 (26-50) | 116 (64-190) | 1277 (704-2439) |
| - Microbiology | Test | 9 (10-11) | 0 (0-8) | 0 (0-80) | 586 (271-1125) |
| Radiology[b] | | | | | |
| - Standard[c] | Procedure | 44 (44-44) | 0 (0-1) | 0 (0-44) | 117 (88-342) |
| - Advanced[d] | Procedure | 182 (165-208) | 0 (0-0) | 0 (0-0) | 208 (0-489) |
| **Therapeutics** | | | | | |
| Drugs | | | | | |
| - Antibiotics[e] | DDD | 7 (2-11) | 3 (0-7) | 9 (1-32 | 84 (31-293) |
| - Other | Dose[f] | 6 (2-19) | 0.8 (0.5-1.4) | 44 (21-155) | 407 (120-1349) |
| Fluids | Litre | 56 (29-90) | 1 (0.4-1.8) | 5 (2-12) | 94 (56-170) |
| Nutrition | Litre | 24 (16-36) | 1.4 (1-1.9) | 13 (5-17) | 77 (16 -219) |
| Blood products | Unit | 215 (215-557) | 0 (0-0) | 0 (0-0) | 215 (0-1186) |
| Source control procedures[g] | Procedure | 691 (471-1276) | 0 (0-0) | 0 (0-0) | 0 (0-0)h |

NA = not applicable. DDD = defined daily dose. All data are expressed as median (IQR). The IQR for price per unit and costs per patient per day for the component of accommodation is not shown as it is not applicable. [a]The number of specimens could not be separated for blood chemistry and microbiology, therefore the unit of accounting is presented per test. The median number (IQR) of specimens for total laboratory was 3.[2-5] [b]Interventional radiology was included under source control procedures. [c]Including X-rays and ultrasounds. [d]Including all MRI scans, CT scans, PET scans, angiography, pyelography, venography and Duplex ultrasonography. [e]Costs for antibiotic prophylaxis were included under 'other'. [f]Total dose per day per 1000 units of measurements (including ml and mg). [g]Including surgical procedures and interventional radiology undertaken to treat (complications of) sepsis in the department of surgery. [h]Median costs per patient per admission were €0 because it was utilised in less than 25% of admissions, but mean costs per patient per admission were €350.

**Table 3.** Costs per day and per admission for subgroups of patients

| Subgroup | N | Costs per day (€) | P-value | Costs per admission (€) | P-value |
|---|---|---|---|---|---|
| Total | 651 | 2250 (2235-2266) | NA | 29,102 (26,598-31,690) | NA |
| Disease severity | | | 0.04 | | <0.001 |
| - Severe sepsis | 294 | 2208 (2188-2227) | | 24,520 (21,288-27,973) | |
| - Septic shock | 357 | 2277 (2255-2298) | | 32,875 (29,615-36,281) | |
| Site of infection | | | <0.001 | | 0.05 |
| - Community-acquired pneumonia | 165 | 2152 (2129-2175) | | 27,913 (23,467-33,105) | |
| - Hospital-acquired pneumonia | 115 | 2266 (2239-2294) | | 33,162 (26,456-40,721) | |
| - Secondary peritonitis | 121 | 2270 (2236-2306) | | 35,554 (29,239-42,352) | |
| - Urinary tract infection | 58 | 2153 (2109-2198) | | 18,331 (14,509-22,360) | |
| - Bloodstream infection | 52 | 2260 (2213-2313) | | 30,471 (22,715-39,535) | |
| - Other[a] | 140 | 2375 (2327-2427) | | 25,546 (22,121-29,168) | |
| Causative organisms | | | <0.001 | | <0.001 |
| - Gram-positive bacteria | 223 | 2217 (2194-2241) | | 28,910 (24,787-33,339) | |
| - Gram-negative bacteria | 267 | 2206 (2182-2231) | | 27,014 (23,820-30,261) | |
| - Fungi and yeasts | 42 | 2440 (2396-2241) | | 59,600 (43,216-78,511) | |
| - Viruses | 25 | 2472 (2389-2560) | | 38,755 (28,368-51,186) | |
| - Unknown | 94 | 2201 (2161-2242) | | 19,294 (15,783-23,209) | |
| Survival status | | | <0.001 | | 0.08 |
| - Survivors | 446 | 2179 (2163-2195) | | 28,824 (26,141-31,522) | |
| - Non-survivors | 205 | 2418 (2385-2451) | | 29,707 (24,854-35,109) | |

NA = not applicable. Costs are expressed as mean (bootstrapped 95% CI). [a]Other infections includes intra-abdominal infections other than secondary peritonitis, infections of the skin or soft tissue, central nervous system, gastrointestinal tract, upper and lower respiratory tract other than community-acquired pneumonia and hospital-acquired pneumonia, and postoperative wound infections.

Patients with septic shock had significantly higher costs per day and per admission compared with patients with severe sepsis *(table 3)*. The additional costs per day and per admission were €69 (95% CI €37-€100) and €8355 (95% CI €3400-€13,367), respectively. This was mainly caused by the longer length of stay of these patients. Differences in costs per admission among patients with different sites of infection were borderline significant, with patients having secondary peritonitis representing the most expensive group. Patients with sepsis caused by fungi or yeasts had twofold higher costs than those with bacterial infections. Furthermore, non-survivors had significantly higher costs per day than survivors, the additional costs were €239 (95% CI €206-€272). But, as non-survivors had a shorter length of stay, overall costs per admission did not differ significantly by survival status.

Male gender, younger age, higher APACHE IV score, and the presence of chronic obstructive pulmonary disease and diabetes mellitus were all associated with increased costs in univariable analyses *(table 4)*. However, none of these variables remained independently associated with costs in multivariable analyses, nor contributed significantly to the total explanatory power of the final cost prediction model. In contrast, the site of infection and its causative organism, the presence of shock at admission, and prior immune deficiency remained independently associated with increased expenditure in the multivariable analysis. Overall, using information available in the first 24 hours of ICU admission and an optimised multivariable prediction model, we could explain only 11.2% of the observed variability in healthcare expenditure between patients.

## Discussion

In this study, the direct healthcare expenditure associated with treatment of severe sepsis and septic shock in the ICU was estimated to be almost €30,000 per admission. Variable

**Table 4.** Multivariable model to explain variability in costs per admission between patients

| Independent variable | Coefficient (€) (95% CI) | $R^2$ change (%) |
|---|---|---|
| Site of infection | | 6.6 |
| - Urinary tract infection | (reference) | |
| - Community-acquired pneumonia | 8058 (1666-14,790) | |
| - Hospital-acquired pneumonia | 11,520 (4477-19,017) | |
| - Secondary peritonitis | 14,532 (7159-22,514) | |
| - Bloodstream infection | 11,462 (2846-21,877) | |
| - Other[a] | 6048 (206-12,261) | |
| Causative organisms | | 2.1 |
| - Unknown | (reference) | |
| - Gram-positive bacteria | 8960 (2476-15,368) | |
| - Gram-negative bacteria | 6731 (1060-12,217) | |
| - Fungi and yeasts | 36,286 (20,119-54,769) | |
| - Viruses | 19,846 (9271-31,675) | |
| Septic shock at admission | 8047 (3374-12,764) | 1.6 |
| Immune deficiency[b] | 7027 (1309-12,711) | 0.8 |

CI = confidence interval; $R^2$ =explained variance. As an example of interpretation, a patient with secondary peritonitis will be predicted to invoke additional costs of almost €15,000 compared with a patient with a urinary tract infection. [a]Other infections included intra-abdominal infections other than secondary peritonitis, infections of the skin or soft tissue, central nervous system, gastrointestinal tract, upper and lower respiratory tract other than community-acquired pneumonia and hospital-acquired pneumonia, and postoperative wound infections. [b]Immune deficiency includes the presence of acquired immune deficiency syndrome or asplenia, the chronic use of immunosuppressive drugs, exposure to chemotherapy or radiotherapy in the last 12 months, and any other documented humoral or cellular deficiency

costs for diagnostic procedures and therapeutic interventions represented only 26% of the total expenditure, whereas the largest component consisted of fixed costs for accommodation, personnel and disposables. Furthermore, we found that patient and illness characteristics at baseline explained only a small part of the observed variability between individuals. Based on these results, it seems impossible to take costs of treatment into account when clinical decisions are made regarding the initiation of ICU treatment. Furthermore, since most independent risk factors for high expenditure are related to fixed patient characteristics, our study does not provide direct approaches to reduce costs. However, improved cost-effectiveness may alternatively be sought in reducing the use of inefficient diagnostic or inefficacious therapeutic procedures, for example by implementing new molecular methods for risk stratification of patients, rapid pathogen detection, and so forth.

Costs of sepsis are of high societal impact. In European countries, approximately 28% of ICU patients have community or hospital-acquired infections.[15] Therefore, a major part of the European budget for ICUs is spent on sepsis care. In the Netherlands, for example, an estimated 8500 patients present to ICUs with severe sepsis or septic shock each year.[16] Extrapolating the costs per sepsis case as estimated in the present study, total direct healthcare expenditure for Dutch society will likely exceed 250 million euros annually. Furthermore, indirect medical costs associated with the sepsis episode due to long-term negative health consequences following ICU treatment may substantially contribute to the total economic burden of disease from the societal perspective.

Our total cost estimate is higher than reported in two previous European studies that have valued the total costs of sepsis treatment in the ICU at €22,800 and €23,297, respectively.[5,6] As one study exclusively enrolled patients having a length of stay longer than 48 hours, the total expenditure per admission they reported may even have been an overestimation of costs for all-comers with sepsis.[5] It seems plausible that expenses for sepsis treatment have risen over the last decade,[1,8] given the expanded possibilities of care due to technological advancements as well as the generally increased burden of disease due to demographic change. However, after correction for inflation and price level variations between countries, our cost estimate remains only slightly higher than these previous projections. Overall, our results thus seem comparable to earlier findings, indicating that our study sample was representative of sepsis patients treated in other European settings.

In contrast to most previous publications,[5,6] but in agreement with at least one other study,[9] we did not find relevant differences in costs for treatment of sepsis in the ICU between survivors and non-survivors. However, we did find higher costs per day for non-survivors as compared with survivors, which probably reflects both a greater severity of illness in these patients and the aggressive attempts of clinicians to prevent death.[6] We also did not find that older patients generate lower costs, as was previously reported by others.[5,11] The suggestion by some authors that elderly patients are treated less aggressively in the ICU was thus not confirmed.[5]

We found that patient and illness characteristics measured in the first 24 hours in the ICU could not be used to reliably predict which individuals would generate high costs. In fact, four variables remained independently associated with increased costs in our multivariable model but together they could explain only 11% of the observed variability in expenditure between patients. These variables were: the presence of shock at admission, infection caused by fungi or yeasts (and to a lesser extent also viral reactivation of cytomegalovirus and herpes simplex virus), site of infection, and immunodeficiency. Urinary tract infections generated the lowest costs and secondary peritonitis the highest costs, followed by hospital-acquired pneumonia and bloodstream infections. This finding matches results of two French studies.[5,9] The significantly higher costs that we found for immune-deficient patients were mainly caused by higher costs for therapeutic interventions, which reflects the difficulties in treating infection in these patients. Other variables that we a-priori selected based on the literature, did not, in contrast to earlier studies,[5,11] remain independently associated with costs in our model. These variables were patient characteristics such as age and the presence of comorbidities, but also surgical admission was not associated with costs, although this was suggested in three earlier studies.[5-6,11]

Strengths of this study relate to the use of data collection as part of a multicentre, prospective cohort study and the accuracy that this entails. This enabled us to provide detailed information about individual cost components, to compare costs between subgroups, and to investigate variability in costs between individuals. However, a limitation of this study is that we derived the daily costs for accommodation, personnel and disposables from the literature. As a result, the intensity of care of individual patients was not reflected in the healthcare expenditure. However, a stable patient acquires less attention from nurses and physicians, but this does not entail lower costs because personnel is present anyway. Secondly, both participating hospitals use protocols for selective decontamination of the digestive tract in ICU patients. Although this intervention has been shown to reduce the incidence of ventilator-associated pneumonia and mortality, use of antibiotic prophylaxis generates costs per se.[17] Nonetheless, selective decontamination of the digestive tract was shown to be cost-effective.[18] Therefore, the adherence to these protocols may hamper the generalisability of our findings.

## Conclusions

In conclusion, total healthcare costs per ICU admission for severe sepsis or septic shock are almost €30,000 per patient. Costs

were poorly predictable by patient and illness characteristics measured at baseline, which limits the development of potential costs saving strategies based on patient profiling at ICU admission.

## Disclosures

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## References

1. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med. 2007;35:1244-50.
2. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013;41:1167-74.
3. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008. Intensive Care Med. 2008;34:17-60.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303-10.
5. Adrie C, Alberti C, Chaix-Couturier C, et al. Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. J Crit Care. 2005;20:46-58.
6. Moerer O, Schmid A, Hofmann M, et al. Direct costs of severe sepsis in three German intensive care units based on retrospective electronic patient record analysis of resource use. Intensive Care Med. 2002;28:1440-6.
7. Sogayar AMC, Machado FR, Rea-Neto A, et al. A multicentre, prospective study to evaluate costs of septic patients in Brazilian intensive care units. Pharmacoeconomics. 2008;26:425-34.
8. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012;40:754-61.
9. Brun-Buisson C, Roudot-Thoraval F, Girou E, Grenier-Sennelier C, Durand-Zaleski I. The costs of septic syndromes in the intensive care unit and influence of hospital-acquired sepsis. Intensive Care Med. 2003;29:1464-71.
10. Tarricone R. Cost-of-illness analysis. What room in health economics? Health Policy. 2006;77:51-63.
11. Braun L, Riedel AA, Cooper LM. Severe sepsis in managed care: analysis of incidence, one-year mortality, and associated costs of care. J Manag Care Pharm. 2004;10:521-30.
12. Klein Klouwenberg PMC, Ong DSY, Bos LDJ, et al. Interobserver Agreement of Centers for Disease Control and Prevention Criteria for Classifying Infections in Critically Ill Patients. Crit Care Med. 2013;41:2373-8.
13. Tan S, Hakkaart-van Roijen L, Al MJ, et al. A microcosting study of intensive care unit stay in the Netherlands. J Intensive Care Med. 2008;23:250-7.
14. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. Stat Med. 2000;19:1141-64.
15. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med. 2006;34:344-53.
16. Van Gestel A, Bakker J, Veraart CPWM, van Hout BA. Prevalence and incidence of severe sepsis in Dutch intensive care units. Crit Care. 2004;8:153-62.
17. de Smet AMGA, Kluytmans JAJW, Cooper BS, et al. Decontamination of the Digestive Tract and Oropharynx in ICU Patients. N Engl J Med. 2009;360:20-31.
18. Oostdijk EAN, de Wit GA, Bakker M, de Smet AMGA, Bonten MJM. Selective decontamination of the digestive tract and selective oropharyngeal decontamination in intensive care unit patients: a cost-effectiveness analysis. BMJ Open. 2013;3:e002529.