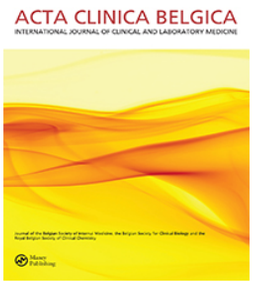

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Original Articles

COSTS AND LENGTH OF STAY ASSOCIATED WITH ANTIMICROBIAL RESISTANCE IN ACUTE KIDNEY INJURY PATIENTS WITH BLOODSTREAM INFECTION

D.M. Vandijck [1,2], S.I. Blot [1,2], J.M. Decruyenaere [1,2], R.C. Vanholder [1,3], J.J. De Waele [1,2], N.H. Lameire [1,3], S. Claus [3], J. De Schuijmer [4], A.W. Dhondt [3], G. Verschraegen [1,4], E.A. Hoste [1,2]

Key words: economic, costs, length of stay, acute kidney injury, bloodstream infection, antimicrobial resistance, intensive care

ABSTRACT

Introduction: Antimicrobial resistance negatively impacts on prognosis. Intensive care unit (ICU) patients, and particularly those with acute kidney injury (AKI), are at high risk for developing nosocomial bloodstream infections (BSI) due to multi-drug-resistant strains. Economic implications in terms of costs and length of stay (LOS) attributable to antimicrobial resistance are underevaluated. This study aimed to assess whether microbial susceptibility patterns affect costs and LOS in a well-defined cohort of ICU patients with AKI undergoing renal replacement therapy (RRT) who developed nosocomial BSI.

Methods: Historical study (1995-2004) enrolling all adult RRT-dependent ICU patients with AKI and nosocomial BSI. Costs were considered as invoiced in the Belgian reimbursement system, and LOS was used as a surrogate marker for hospital resource allocation.

Results: Of the 1330 patients with AKI undergoing RRT, 92 had microbiologic evidence of nosocomial BSI (57/92, 62% due to a multi-drug-resistant microorganism). Main patient characteristics were equal in both groups. As compared to patients with antimicrobial-susceptible BSI, patients with antimicrobial-resistant BSI were more likely to acquire Gram-positive infection (72.6% vs 25.5%, $P<0.001$). No differences were found neither in LOS (ICU before BSI, ICU, hospital before BSI, hospital, hospital after BSI, and time on RRT; all $P>0.05$) or hospital costs (all $P>0.05$) when comparing patients with antimicrobial-resistant vs antimicrobial-susceptible BSI. However, although not statistically significant, patients with BSI caused by resistant Gram-negative-, *Candida*-, or anaerobic bacteria incurred substantial higher costs than those without.

Conclusion: In a cohort of ICU patients with AKI and nosocomial BSI undergoing RRT, patients with antimicrobial-resistant vs antimicrobial-susceptible Gram-positive BSI did not have longer hospital stays, or higher hospital costs. Patients with resistant "other" (i.e. Gram-negative, *Candida*, or anaerobic) BSI were found to have a distinct trend towards increased resources use as compared to patients with susceptible "other" BSI, respectively.

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INTRODUCTION

In the current health care situation, optimization in terms of a more appropriate allocation of scarce resources is gaining in importance. As such, from an economic point of view, the intensive care unit (ICU) has become more and more a matter of debate and controversy because of the societal burden associated with treating these patients, already presumed to have harmful prognosis (1, 2).

So far, in the ICU, bloodstream infections (BSI) implicate a significant problem, being the third most prevalent hospital-acquired infection observed, and antimicrobial resistance among its causal pathogens is increasing in incidence (3, 4). The latter has been widely shown to negatively impact clinical and economic outcome (5-9). However, earlier studies reporting on the financial effects of antimicrobial resistance in BSI patients were generally performed in either small or heterogeneous populations with a wide variety of underlying comorbidities, only included standard costs for health care-related services, or resource use was limited to inpatient length of stay (5, 10). Salient literature is available with inconsistent results, and as a matter of fact, the real consequences of antimicrobial resistance in terms of costs have never been fully elucidated (11). Hence, to make valid conclusions, studies with specific and well-defined cohorts are needed.

Critically-ill patients with acute kidney injury (AKI) necessitating renal replacement therapy (RRT) are amongst the most severely-ill subgroup of patients admitted to the ICU (12-16). Because of having at least one extra intravascular access to perform RRT, BSIs are more frequently diagnosed within this subgroup compared to general ICU patients (17). As a result, they are more likely to receive antimicrobials, which on its turn increases the likelihood for developing multi-drug resistance (17, 18). Because multi-drug-resistant infections commonly are associated with the infusion of new and more costly antimicrobials, we hypothesized that these infections are associated with a higher health-economic burden, respectively. This hypothesis was tested in a cohort of critically-ill patients with AKI undergoing RRT, and whose course was complicated with a nosocomial BSI.

METHODS

Study setting and patient population

The study was conducted in the ICU of the Ghent University Hospital, a tertiary academic referral centre with 1060 beds. The ICU has 56 beds and includes a medical, surgical, burns, and cardiac-surgical unit.

All patients (age 18 years or older) admitted to one of these ICUs between 1 January 1995 and 31 December 2004 with AKI treated with RRT, and who developed nosocomial BSI during the period RRT was performed were retained for analysis. In case RRT was initiated before admission to the ICU, or for indications other than AKI (e.g. chronic renal failure), patients were excluded.

Study design

Patient baseline characteristics and economic outcomes were compared between patients with antimicrobial-resistant and antimicrobial-susceptible BSI. Long-term renal impairment, defined by the Acute Dialysis Quality Initiative as either loss of kidney function or end-stage kidney disease (i.e. need for dialysis treatment for more than 4 weeks or 3 months, respectively), was also compared between both groups (19). This is a secondary analysis of a study that aimed to compare clinical outcomes in this particular cohort (20).

Costs were available from the hospital's cost accounting system, and were obtained from each patient's hospital invoice. Therefore, our results reflect the total costs indicated on a patient's hospital invoice. Additionally, we further subdivided the total hospital costs into 5 categories as they are used in the Belgian health care system: (i) fixed hospitalization cost (including hotel costs and fees for health care personnel), (ii) cost for pharmacy products, (iii) cost for blood and blood derivates, (iv) cost for medical interventions (e.g. procedures, consultations, laboratory, radiology), and (v) diverse medical costs. All costs were corrected and updated following the Belgian Health Care Index applicable for the last year of study. Expenditures were calculated in euros. Length of stay (LOS) was used as a surrogate marker of hospital resources use. The LOS was calculated as the number of days between admission and discharge from either the ICU or hospital. Additionally, LOS in the ICU and hospital before onset of BSI, ICU and hospital after onset of BSI, as well as time on dialysis and time on dialysis before onset of BSI, were calculated. No patients were lost during follow-up.

The study was approved by the ethics committee of our hospital, and conducted in accordance with the declaration of Helsinki.

Data collection and definitions

RRT was instituted in critically-ill patients with AKI

according to by convention proposed criteria (14, 17, 21). In patients with severe haemodynamic repercussions (defined as the need for a high dose of vaso-active drugs, and as judged by the attending intensivist and nephrologist), a continuous mode of RRT (continuous venovenous haemofiltration, - dialysis, or - haemodiafiltration) was used; intermittent RRT was used in those without. Indications for, as well as the choice of RRT modality were made in communication with the attending nephrologist. Respiratory failure was defined as the need for mechanical ventilation. Severity of illness was calculated by means of the Acute Physiology and Chronic Health Evaluation (APACHE) II score (22).

Blood cultures were taken on a routine basis every time infection was clinically suspected or when a patient's body temperature was 38.5°C or above. In this way only clinically significant episodes of nosocomial BSI were enrolled in the study database. Blood cultures were executed following the BacT/Alert procedure (Organon Technika Corp, Durnham, NC). Peripheral venous puncture and a 10mL inoculum were considered standard. All microbiologically documented nosocomial BSIs were prospectively screened by the local hospital infection control team. Clinical significance, nosocomial or community acquisition and presumed inciting source of BSI were recorded in this database. BSI was considered nosocomial when micro-organisms were cultured from a blood sample drawn equal or greater than 48 hours after initial hospital admission. For the purpose of the study, only BSIs acquired during the period that the patient received RRT were taken into account. In accordance to the Centers for Disease Control and Prevention definitions, cultures isolating coagulase-negative staphylococci (CNS) were considered as significant BSI when cultured from at least two blood cultures drawn on separate occasions (23). The source of BSI was determined by the intensivists and microbiologists, based on isolation of the micro-organism from the presumed portal of entry and clinical evaluation. BSIs of unknown origin were defined as primary BSI. In case of an identified source other than an intravascular catheter, BSIs were defined as secondary. Intravascular catheter-related BSI was also classified as primary (23, 24).

Throughout the study period antimicrobial susceptibility was determined according to the methods for disk diffusion testing by the National Committee for Clinical Laboratory Standards (25). No major changes in microbiologically laboratory techniques were carried out over the study period. Antimicrobial resistance was defined as in-vitro resistance to ceftazidime for Gram-negative bacteria. In our hospital ceftazidime resistance is considered to be an indicator of epidemic extended-spectrum ß-lactamase-producing strains and/or hyper-producers of ß-lactamases, and is, therefore, a sign of infection with organisms that are resistant to multiple drugs (11, 26, 27). Because susceptibility patterns for *Pseudomonas aeruginosa* vary, these isolates were considered resistant when there was resistance to one or more of the following antipseudomonal antibiotics: ceftazidime, imipenem, ciprofloxacin, or piperacillin (5, 28-30). Staphylococci were defined as resistant when resistance was found for methicillin; other Gram-positive bacteria were defined as resistant in case of ampicillin resistance. *Candida* species were defined resistant when in-vitro resistance was detected for fluconazole, and anaerobic bacteria were defined as resistant when there was resistance to metronidazole.

Antimicrobial therapy was considered appropriate if the drugs administered had in-vitro and clinical activity against the isolated strain identified as the cause of BSI, and when initiated within 48 hours after sampling the positive culture (31-33).

For patients who developed more than one episode of BSI during the same hospitalization, only the first was retained for analysis. When two or more micro-organisms grew from one set of blood cultures, this was defined as a polymicrobial BSI.

With the exception of cost data, all data were collected prospectively.

Statistical analysis

It was considered that LOS departed from normal distribution and is thus expressed as median and interquartile range. Other variables have been similarly expressed unless otherwise indicated. Univariate analysis of continuous variables was performed with the Student's *t* or Mann-Whitney *U* test. The Chi-square or Fisher's exact test was used for comparison of dichotomous variables. Prevalence rate of the first episode of BSI per year and per 1000 days of RRT was evaluated for even distribution by the Kruskall Wallis statistic. Relationships between total cost and multi-drug resistance were assessed using multivariate linear regression analysis. Covariates included in this model were length of hospital stay, APACHE II score, and antimicrobial resistance. Statistical significance was set at a two-sided *P*-value <0.05. For all analyses, SPSS 12.0.0 (SPSS Inc. Chicago, IL, USA) statistical software was used.

RESULTS

Over the 10-year study period, 1330 ICU patients were diagnosed with AKI undergoing RRT. From this cohort, 92 patients developed at least 1 episode of nosocomial BSI (5 patients with first episode of BSI per 1000 RRT days), incurring 109 micro-organisms. Incidence rates of BSI per year were equally distributed over the study period (P=0.361). Thirteen patients (14.1%) had polymicrobial BSI. BSI was caused by antimicrobial-susceptible micro-organisms in 35 patients (38.0%) and by antimicrobial-resistant micro-organisms in 57 patients (62.0%).

Baseline characteristics of the study cohort

For patients with susceptible vs resistant BSI, all baseline characteristics, with the exception of need for vaso-active therapy at start of dialysis (60.0% vs 82.5%, P=0.017) and initiation of appropriate antimicrobial treatment (85.7% vs 63.2%, P=0.020), were equal between both groups (table 1). Gram-positive bacteria were more frequent in BSIs with antimicrobial-resistant bacteria (72.6% vs 25.5%, P<0.001), while Gram-negative bacteria, and fungal micro-organisms were more frequent in BSIs with antimicrobial-susceptible bacteria (Gram-negatives 48.9% vs 22.6%, P=0.004; and fungi 19.1% vs 1.6%, P=0.002). Anaerobic micro-organisms were also more frequently observed to be antimicrobial-susceptible (6.4% vs 3.2%, P=0.365). Among the Gram-positives, CNS, *Staphylococcus aureus*, and Streptococci/Enterococci accounted, 32/57 (56.1%), 14/57 (24.6%), and 11/57 (19.3%) of BSIs respectively, of which antimicrobial resistance was present in 100% of BSIs with CNS, 85.7% of BSIs with *Staphylococcus*

Table 1: Baseline characteristics of critically-ill patients with AKI who developed nosocomial BSI during RRT

Variable	Critically-ill AKI patients undergoing RRT with antimicrobial susceptible BSI	Critically-ill AKI patients undergoing RRT with antimicrobial-resistant BSI	P
Demographics			
n	35 (38.0)	57 (62.0)	
Age	61 (52.0-69.1)	58 (46.0-66.9)	0.295
Female sex	9 (25.7%)	14 (24.6%)	0.803
APACHE II	28 (18.0-37.0)	25 (17.0-30.5)	0.356
Vaso-active therapy at start of RRT	21 (60.0)	47 (82.5)	0.017
Mechanical ventilation at start of RRT	24 (68.6)	43 (75.4)	0.472
Appropriate antimicrobial therapy	30 (85.7)	36 (63.2)	0.020

Variables are given as No (%) or as median (interquartile range)
BSI, bloodstream infection; AKI, acute kidney injury; RRT, renal replacement therapy; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit

Table 2: LOS of critically-ill patients with AKI who developed nosocomial BSI during RRT

Variable	Critically-ill AKI patients undergoing RRT with antimicrobial-susceptible BSI	Critically-ill AKI patients undergoing RRT with antimicrobial-resistant BSI	P
LOS			
LOS Hospital before BSI (days)	15.0 (6.0-32.0)	19.0 (10.0-28.5)	0.421
LOS ICU before BSI (days)	13 (2.0-22.0)	15 (7.0-25.5)	0.103
LOS RRT to BSI (days)	6 (1.0-21.0)	11 (5.0-21.5)	0.021
LOS ICU (days)	25 (10.0-63.0)	34 (21.0-47.0)	0.381
LOS Hospital (days)	44 (18.0-78.0)	42 (25.0-81.5)	0.618
LOS Hospital after BSI (days)	14 (3.0-60.0)	16 (5.5-56.0)	0.579
LOS on RRT (days)	21 (9.0-42.0)	20 (12.5-39.0)	0.806
Mortality			
ICU mortality	22 (62.9)	31 (54.4)	0.516
Hospital mortality	25 (71.4)	39 (68.4)	0.819

Variables are given as median (interquartile range)
BSI, bloodstream infection; AKI, acute kidney injury; RRT, renal replacement therapy; LOS, length of stay

Table 3: Total hospital costs of critically-ill patients with AKI undergoing RRT and who developed nosocomial BSI due to Gram-positive vs other organisms

Variable	Antimicrobial-susceptible organisms	Antimicrobial-resistant organisms	P
Gram-positive bacteria	67,020 (41,497-135,920)	58,084 (33,824-96,305)	0.363
Other organisms	33,360 (22,569-87,211)	56,654 (42,750-117,317)	0.185

Variables are given as median (interquartile range)
BSI, bloodstream infection; RRT, renal replacement therapy

Table 4: Linear regression analysis adjusted for covariates to assess relationship with total hospital costs

Variable	β-coefficient ± SE	95% CI	P
LOS Hospital	751 ± 58	637 ± 866	<0.001
APACHE II (per 5 points increase)	2,437 ± 1,784	-1,114 – 5,988	0.176
Antimicrobial-resistance	2,213 ± 7,231	-12,177 – 16,604	0.760

R2 = 0.681
Costs are given in euros
SE, standard error; CI, confidence interval; LOS, length of stay; APACHE, Acute Physiology and Chronic Health Evaluation

aureus, and 9.1% of BSIs with Streptococci/Enterococci. BSI caused by antimicrobial-resistant micro-organisms was more often of primary origin (57.9% vs 20.0%, *P*<0.001) as compared to nosocomial BSI caused by antimicrobial-susceptible micro-organisms.

Economic characteristics of the study cohort

Patients infected with resistant pathogens were on RRT longer before onset of BSI than patients infected with susceptible pathogens (11.0 days (5.0-21.5) vs 6.0 days (1.0-21.0), *P*=0.021) (table 2). However, no differences were found regarding LOS in ICU before onset of BSI (*P*=0.103), in ICU (*P*=0.381), in hospital (*P*=0.618), in hospital before onset of BSI (*P*=0.421), in hospital after onset of BSI (*P*=0.579), and time on RRT (*P*=0.806). Also, the proportion of patients reaching RIFLE outcome classes "loss" (40.0% vs 36.8%, *P*=0.827) and "end-stage kidney disease" (5.7% vs 8.8%, *P*=0.705), and ICU and in-hospital mortality (62.9% vs 54.4%, *P*=0.516, and 71.4% vs 68.4%, *P*=0.819) were comparable between both groups.

Similarly, economic outcomes were comparable between critically-ill AKI patients who developed either susceptible or resistant BSI during RRT. Although not statistically significant, median total hospital costs were higher for patients with antimicrobial-resistant BSI (€56,597 vs €46,300, *P*=0.383). Interestingly, when further subdividing antimicrobial classes, among antimicrobial-resistant "other" organisms (i.e. Gram-negative, *Candida*, and anaerobic bacteria) there was a distinct trend towards higher hospital costs, whereas among Gram-positive strains there was not (table 3). Linear regression analysis revealed that longer length of hospital stay, but not multi-drug resistance, was independently associated with higher costs (table 4).

As shown in figure 1, a micro-organism's susceptibility pattern did not negatively impact hospitalization cost (*P*=0.901), pharmacy cost (*P*=0.667), cost for blood and blood derivates (*P*=0.984), cost for medical inter-

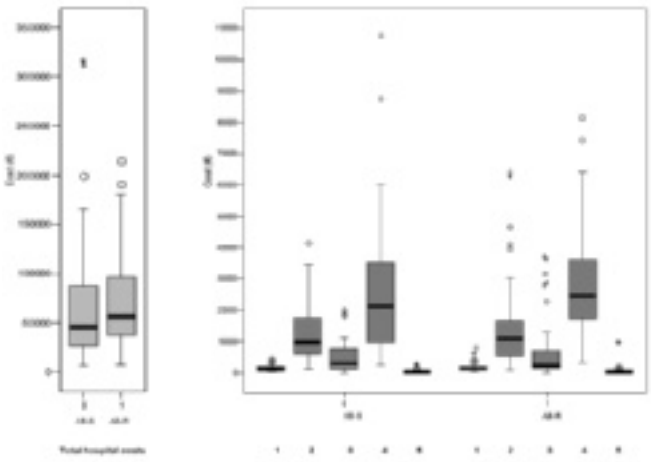

Figure 1: Economic outcomes of critically-ill patients with AKI who developed antimicrobial-susceptible (*n*=57) vs antimicrobial-resistant (*n*=35) BSI during RRT

AB-S, antimicrobial-susceptible BSI; AB-R, antimicrobial-resistant BSI
1 = fixed hospitalization costs; 2 = pharmacy products; 3 = blood and blood derivates; 4 = medical interventions; 5 = diverse medical costs

ventions (P=0.283), nor diverse medical costs (P=0.635), respectively. Even when corrected for LOS, total costs were comparable between patients with susceptible and resistant BSI (all P>0.05).

DISCUSSION

In this report studying the impact of microbial susceptibility patterns in AKI patients undergoing RRT and whose course was complicated with a nosocomial BSI, no statistical evidence was found for higher health care resources use, in terms of hospital LOS and cost, for BSIs caused by antimicrobial-resistant pathogens; however, among the subgroup of patients having antimicrobial-resistant "other" BSI, a clear trend towards higher costs was observed, whereas for antimicrobial-resistant Gram-positive BSIs there was not.

Taking care for patients in the ICU can be extremely resource intensive, particularly for those patients developing AKI (34-35). However, the literature on the financial implications of treating AKI or its sometimes associated complications (such as antimicrobial-resistant infections) is scarce. As such, questions may arise with respect to the exceedingly expensive efforts made which may not provide a worthwhile benefit when one accounts for the large resources spent for the small health gains.

In this study we found that antimicrobial resistance occurred in almost two-thirds of AKI patients with BSI, whereas this rate is 46% in non-RRT patients in our unit (P=0.028; unpublished data). Although this rate might be considerably high, this rate is comparable to that reported in other studies on BSIs in general ICU patients (36). Further, in-hospital mortality was comparable between both groups.

Although antimicrobial resistance could, theoretically, lead to a trend towards increased health care expenditures, the present study could not demonstrate substantial differences in economic outcomes neither in LOS, a 'rudimentary' marker of hospital resources use, nor in total hospital costs or its 5 subcategories. A possible factor contributing to our findings is that in the group of patients with resistant BSI, coagulase-negative staphylococci were the most prevalent. This micro-organism is assumed to have less impact on outcome compared to other micro-organisms (37). Additionally, primary BSIs were also observed more frequently in this group. As already confirmed by others, BSIs with either unknown or catheter-related origin are associated with better outcome compared to secondary BSIs (38, 39). On the other hand, only clinically relevant BSIs, i.e. these requiring treatments were included in the study. Also, BSIs with coagulase-negative staphylococci are typically treated with glycopeptides for a recommended period of 10 to 14 days (40). As our cohort concerned a population of critically-ill patients with already higher average costs and LOS than a general ICU population, it is, however, more difficult to find a potential increase of the variables under study. Also, the effect of intrinsically more costly antimicrobials might be dampened, because profound dose adjustments are often needed in these patients.

To be able to correctly interpret and fit the economic analyses performed within a broader perspective, some extra information should be provided regarding the Belgian health care setting. In Belgium, a so-called 'third payer' principle is used. As such, hospitals directly invoice to the public insurance institute by means of fixed charges (predetermined by the federal government) for each procedure or resource item used during a patient's hospitalization. Hospital invoices include the part reimbursed by the insurance institutions, as well as the individual co-payment by the patient. The same principle is applied for the per diem cost (i.e. hotel and nursing costs) of hospital stay. Importantly, the reimbursement of a considerable number of medical procedures/interventions is, however, limited in time (e.g. 21 days in case of mechanical ventilation, 40 days of acute RRT, 5 days of haemodynamic monitoring). Especially when studying patients with considerable length of ICU stay such as in this particular cohort this might lead to a substantial underestimation of the real costs incurred, as in this way hospital invoices do not reflect the real total cost spent. Furthermore, using the patient's hospital invoice does not take into account the additional nursing and medical time that is spent to these patients. Moreover, differences in workload inflicted in other departments are also not considered. Here, correcting costs for workload by means of the Therapeutic Intervention Scoring System scores could, at least partly, be a solution to meet this bias (41). Nonetheless, this study reflects the actual economic impact of antimicrobial-resistant BSIs applicable to the Belgian health care system; however, this may be different in countries with other reimbursement systems. Such peculiarities, specific to national billing and reimbursement systems, hamper detailed comparisons with other studies. Nevertheless, the Belgian health care setting is relevant within a broader international context as its health care-related costs are in accordance with these in other West-European countries (42). Lastly, we could

not provide persuasive evidence that antimicrobial strains incurred greater resources use; however, this lack of statistical significance is probably due to underpowering of the cohort studied.

The advantages of our study include the long study period, the prospective collection of the analyzed data, and the homogeneity of the patient cohort. To our knowledge, there are no studies available detailing on this subject within such a specific and well-defined cohort. Previous studies report on (heterogeneous) patient populations with different underlying conditions, and with both community- or hospital-acquired infections (28, 43).

CONCLUSION

In this well-defined homogenous cohort of critically-ill patients with AKI undergoing RRT and with nosocomial BSI, we found high rates of antimicrobial-resistant micro-organisms that did, for patients with Gram-positive BSI; however, not negatively impact on LOS, a surrogate marker for use of hospital resources, nor on hospital costs, whereas for Gram-negative, *Candida*, or anaerobic BSI there rather was a trend towards increased costs.

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