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Factors influencing antibiotic treatment cost and outcome in critically ill patients: A "real-life" study

Faktori koji utiču na cenu antibiotske terapije i ishod kod kritično obolelih pacijenata: "*real-life*" studija

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Abstract

Background/Aim. Critically ill patients are at very high risk of developing severe infections in intensive care units (ICUs). Procalcitonin (PCT) levels are eleveted in the circulation in patients with bacterial sepsis and PCT might be useful in guiding antibiotic treatment. The aim of this study was to estimate factors influencing patients survival and treatment cost in ICU with special emphasis on the impact of PCT serum levels use in guiding antimicrobial therapy. **Methods.** The study was conducted from August 2010 to May 2012 in the Intensive Therapy Unit, Clinic of Anesthesiology and Intensive Therapy, Military Medical Academy (MMA), Belgrade, Serbia. All adult critically ill patients with sepsis and/or trauma admitted in the ICU were included in the study. This study included only the cost of antimicrobial therapy in the ICU and the cost for PCT analysis. We used prices valid in the MMA for the year 2012. PCT in serum was measured by homogeneous immunoassay on a Brahms Kryptor analyzer. **Results.** A total of 102 patients were enrolled. The mean patients age was 55 ± 19 years and 61.8% of patients were male. The mean length of stay (LOS) in the ICU was 12 ± 21 days. There was a statistically significant difference ($p < 0.001$) between the sepsis and trauma group regarding outcome (higher mortality rate was in the sepsis group, particularly in the patients with peritonitis who were mostly women). The patients younger than 70 years had better chance of survival. LOS, the use of carbapenems and PCT-measurement influenced the cost of therapy in the ICU. **Conclusions.** The obtained results show that age, the diagnosis and gender were the main predictors of survival of critically ill patients in the ICU. The cost of ICU stay was dependent on LOS, use of carbapenems and PCT-measurement although the influence of these three factors on the outcome in the patients did not reach a statistical significance.

Key words:
critical illness; sepsis; anti-bacterial agents; cost and cost analysis; biological markers.

Apstrakt

Uvod/Cilj. Kritično oboleli pacijenti imaju veliki rizik od razvoja teških infekcija u jedinicama intenzivne terapije (JIT). Nivo prokalcitonina (PCT) u cirkulaciji je povišen kod bolesnika sa bakterijskom sepsom, tako da PCT može biti koristan u praćenju antibiotske terapije. Cilj ove studije bio je da se ustanove faktori koji utiču na ishod i troškove lečenja u JIT u našoj ustanovi sa posebnim naglaskom na uticaj korišćenja serumskog nivoa PCT u vođenju antimikrobne terapije. **Metode.** Studija je sprovedena od avgusta 2010. godine do maja 2012. godine u Jedinici intenzivne terapije Klinike za anesteziologiju i intenzivnu terapiju Vojnomedicinske akademije (VMA) u Beogradu, Srbija. Svi kritično oboleli sa sepsom i/ili traumom koji su primljeni u JIT bili su uključeni u studiju. Studijom su obuhvaćeni samo troškovi antimikrobne terapije u JIT i troškovi PCT analize. Koristili smo cenovnik VMA za 2012. godinu. PCT u serumu je meren tehnikom homogenog imunoeseja na Brams Kriptor analizatoru. **Rezultati.** Studijom su bila obuhvaćena 102 bolesnika. Prosečna starost bolesnika iznosila je 55 ± 19 godina, a 61,8% bolesnika bili su muškarci. Prosečna dužina boravka u JIT (*lenght of stay* – LOS) iznosila je 12 ± 21 dana. Postojala je statistički značajna razlika ($p < 0.001$) između ishoda lečenja u grupi sa sepsom u odnosu na grupu sa traumom. Bolesnici mlađi

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od 70 godina imali su bolju šansu da prežive. Dužina boravka, upotreba karbapenema i merenje PCT uticali su na cenu terapije u JIT. **Zaključak.** Dobijeni rezultati pokazuju da su godine života, dijagnoza i pol bili glavni prediktori preživljavanja kritično obolelih u JIT. Cena terapije zavisila je od dužine boravka u JIT, upotrebe karbapenema i merenja PCT, ali uticaj ovih faktora na ishod lečenja nije dostigao statističku značajnost.

Ključne reči:
kritična stanja; sepsa; antibiotici; cene i analize cena; biološki pokazatelji.

Introduction

Severe infections with multiresistant bacteria represent a medical challenge and a financial burden for hospitals. Sepsis is a frequent cause of intensive care unit (ICU) admission and may also develop in patients admitted to the ICU for other reasons. Critically ill patients are at very high risk of developing severe nosocomial infections with the incidence rate about 5–10-fold higher than in general medical wards [1, 2]. The recent Sepsis Occurence in Acutelly Ill Patients (SOAP) Study across Europe reported that more than 35% of ICU patients had sepsis at some point during the ICU stay, with the mortality rate of 27%. In the USA, approximately 750,000 cases occur each year, at least 250,000 of which are fatal. Septic patients are generally hospitalized for extended periods, sometimes 2–3 weeks [3–6].

The pathophysiology of sepsis is complex and comprises diffuse endothelial and epithelial injury, increased capillary permeability, impaired hemodynamics, microvascular thrombosis, tissue ischemia, apoptosis and multiorgan failure [7–9].

Critically ill patients with sepsis are commonly treated with antimicrobials. Selecting the appropriate initial antimicrobial is most important, since the inappropriate choice may be responsible for therapeutic failure and higher mortality rate in ICU [2]. The use of inappropriate initial antibiotics may occur in 34.3% of cases involving nosocomial-acquired bacteremia. The risk of death increased from 30–60% in ICU bacteremia and 70–100% in gram-negative shock when the initial antimicrobial therapy was inappropriate [7].

The choice of initial empirical anti-infective therapy should be broad enough to cover any likely patogens and guided by local prevalence of microorganisms. Appropriate intravenous antibiotics (e.g. carbapenems, fluoroquinolones) should be initiated as rapidly as possible, preferably within the first hour of establishing diagnosis of sepsis [7, 10, 11]. The most common pathogens that cause sepsis in hospitalized patients are gram-positive bacteria, followed by gram-negative and mixed bacterial microorganisms. Once blood culture profile results become available, de-escalation to the most appropriate single-agent therapy should be performed as soon as possible. This practice reduces the prevalence of antimicrobial resistance or the risk of antibiotic related diarrhea from *Clostridium difficile*, as well as pharmaceutical expenditure [10, 11]. However, conventional microbiology cultures, despite their specificity and accuracy, are time consuming, and a negative result in many cases of bacterial sepsis (50% or more) does not exclude an infective etiology [10, 12, 13]. Procalcitonin (PCT), a prohormone of calcitonin, was shown to be a marker of sepsis. Its levels are elevated in the circulation in patients with bacterial sepsis, due to the failure of suitable proteolysis. PCT has a longer half-life of 24 to 30 hours in circulation, in contrast to other markers of sepsis such as tumor necrosis factor (TNF) or interleukin (IL)-6 [2, 14–16]. The use of PCT is useful in guiding antibiotic treatment, but with some limitations. The results derived from a multicentre randomised controlled trial PRORATA, show that despite lower antibiotic exposure in the PCT group compared to the control group, there was no difference between emerging multidrug-resistant bacteria [17]. The results from a study conducted across Denmark, with 1,200 critically ill patients, show that PCT-guided antimicrobial strategy does not improve a 28-day survival. The authors observed deleterious effects on organ function and length of stay (LOS) in the ICU in the PCT-guided group [15]. Another limitiation for the use of PCT is associated with the cost of analysis.

Pharmacoeconomics is a scientific discipline that evaluates pharmaceutical interventions, taking into account both the cost and the value of health benefits. When performing pharmacoeconomic evaluations of ICU expenditure, it is customary to consider only the direct price of medication. The single most important factor determining the magnitude of cost is the LOS in the ICU, which is influenced by the high mortality in severe sepsis and septic shock patients and the high incidence of nosocomial infections in critically ill patients [18, 19].

The aim of this study was to provide data about the cost and outcome of critically ill patients admitted to our ICU. We analyzed factors that influence survival of critically ill patients and the cost of treatment in the ICU. Moreover, the impact of PCT measurement on the patient survival and cost of treatment was analysed. Our data are derived from real-life clinical population of critically ill patients in the ICU.

Methods

The observational study was conducted from August 2010 to May 2012 in the Intensive Therapy Unit of the Clinic of Anesthesiology and Intensive Therapy of the Military Medical Academy (MMA), tertiary university hospital in Belgrade, Serbia. All adult critically ill patients with sepsis and/or trauma admitted to the ICU were included in the study.

The study was approved by the Ethic Committee in the MMA and performed in accordance with the Declaration of Helsinki. Sepsis, severe sepsis and septic shock were diagnosed according to the criteria proposed by the American College on International Sepsis Definition Conference [20]. Complete medical data for all patients were recorded until their discharge or death.

This study included only the cost of antibacterial therapy in the ICU. We analyzed cost-related expenditures such as a total drug cost and the cost for PCT analysis. Costs related to equipment usage, estates (e.g. cost related to infra-

structure, electricity, etc) and non-clinical support services, as well as indirect cost (productivity loses), were not included. The enrolled patients were assessed during ICU stay. After completion of data collection, all costs were priced. We used prices valid in the MMA for the year 2012. All the costs are presented in RSD (Serbian currency). As we collected data from 2010, we adjusted all values using a 10% average inflation rate to 2012 values, according to Serbian indexes for that period. In order to compare our data with others, we presented costs in euro (€), as well. The exchange rate of 1€ was considered as 115 dinars for the year 2012.

PCT in serum was measured by homogeneous immunoassay (sandwich principle) using time resolved amplified cryptate emission (TRACE) technology on Brahms Kryptor analyzer.

The results are expressed as mean ± standard deviation (SD) for variables that exhibit normal distribution. All costs are reported as median, with the interquartile range (IQR) and 95% confidence interval (CI) [21]. Statistical analyses were conducted using PASW 18.0 (SPSS Inc., Chicago, IL, USA). Binary logistic regression was used to determine the predictors of survival and linear regression was used to determine the predictors of treatment cost. The results were presented with odds-ratio (OR) or *p*-value. Both models were obtained using a stepwise approach, variables were excluded at the selection threshold of 0.1. A probability value of < 0.05 was considered to be statistically significant.

Results

A total of 102 patients were enrolled. The mean patients age was 55 ± 19 years and 61.8% of patients were male. The reasons for ICU admissions were severe trauma, severe trauma and secondary sepsis, severe sepsis due to peritonitis, pancreatitis and other causes. The mean length of ICU stay was 12 ± 21 days (Table 1).

Regression analysis revealed that gender, the diagnosis and age influenced the survival of critically ill patients with sepsis. There was a difference between males and females regarding the diagnosis. In the sepsis group (regardless of underlying cause) there were 49 (58.3%) males *vs* 35 (41.7%) females, whereas in the trauma group (with or without secondary sepsis) males strongly dominated with 14 (77.8%) *vs* 4 (22.2%) of females. In the sepsis group with peritonitis females were dominant. Regression analysis showed that gender influenced the outcome. The mortality rate in males was 42.9% and they had better chances to survive (OR = 2.13). Consequently, there was a statistically significant difference ($p < 0.001$) between the sepsis and the trauma group regarding the outcome; in the trauma group the mortality rate was 17.6% while in the sepsis due to peritonitis, for example, the mortality rate raised to 48%. The outcome, among other parameters, was related to age of the studied population. In survivors, the mean age was lower (44 ± 16 years), compared to non-survivors (66 ± 15 years) ($p < 0.001$). The younger patients (< 70 years) had better chance of survival (Figure 1).

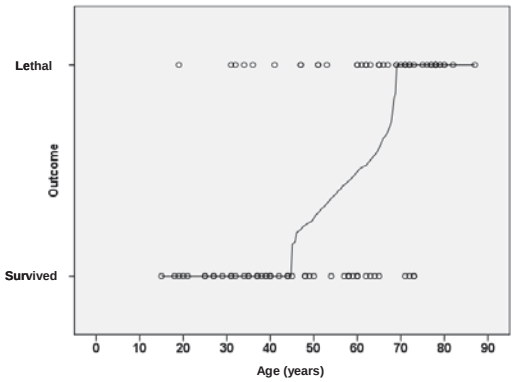

Fig. 1 – Correlation of age and outcome of survivors and non-survivors.

Table 1

Demographic and clinical characteristics of critically ill patients

Characteristics	Value
Total number of patients (n)	102
Age (years), mean ± SD (range)	55 ± 19 (18 - 87)
Sex, n (%)	
male	63 (61.8)
female	39 (38.2)
SAPS II score, mean ± SD	56.82 ± 9.83
APACHE II score, mean ± SD	21.87 ± 4.21
SOFA score, mean ± SD	7.56 ± 2.30
Length of ICU stay in days, mean ± SD (range)	12 ± 21 (2–169)
Severe trauma (ISS 28.73 ± 9.40), n (%)	18 (17.6)
Severe trauma and secondary sepsis, n (%)	17 (16.7)
Severe sepsis due to peritonitis, n (%)	49 (48)
Pancreatitis, n (%)	13 (12.7)
Other causes, n (%)	5 (4.9)
Blood cultures, n (%)	
gram-positive	16 (15.7)
gram-negative	4 (3.9)
mixed	47 (46.1)
fungi	1 (1)
sterile	34 (33.3)
Mortality, n (%)	51 (50)

APACHE II – Acute and Physiology and Chronic Health Evaluation II; SAPS – Simplified Acute Physiology Score II; SOFA – Sequential Organ Failure Assessment; ICU – Intensive Care Unit; ISS – Injury Severity Score.

Examining costs and the outcome in 102 patients in the ICU, irrespective of the underlying cause of admission, we found that the median cost *per* patient was higher in 51 non-survivors compared to 51 survivors (€ 488 *vs* € 358, respectively), but regression analysis showed that survival did not influence ICU cost significantly. In contrast, LOS, the use of carbapenems and PCT-measurement influenced the cost of therapy in the ICU (Figures 2–4 and Table 2).

consultants from the Clinic for Infectious and Tropical Diseases of the MMA, and not attending physicians from the ICU. Our study showed that several combinations of antibiotics were used in the studied period. Some of them included carbapenems and vancomycin or carbapenems and aminoglycosides (gentamycin or amikacin). The other usual combination was cephalosporins with vancomycin.

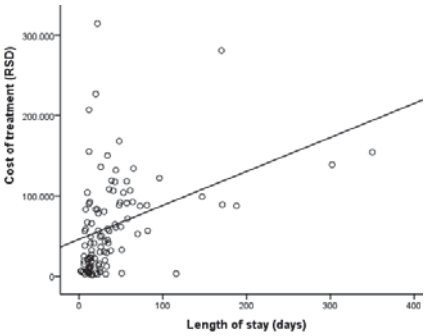

Fig. 2 – Length of stay in Intensive Care Unit.

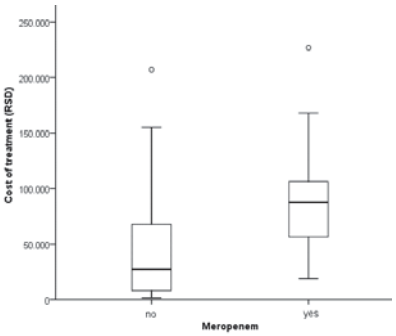

Fig. 3 – Cost of treatment with meropenem.

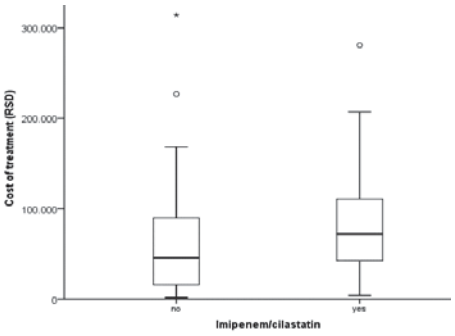

Fig. 4 – Cost of treatment with imipenem/cilastatin.

Table 2

Comparison of cost and outcome in critically ill patients with and with no procalcitonin (PCT) guided antibiotic therapy

Parameter	Survivors (median; IQR; 95% CI)	Non-survivors (median; IQR; 95% CI)
PCT-guided therapy		
- in RSD	75,729.15; 33,984.60-107,941.06; 59,385.51-98,001.47	91,278.23; 56,797.17-125,294.68; 71,138.43-126,056.18
- in €	658.51; 343.97-888.09; 516.40-852.19	793.72; 493.89-1,089.52; 618.60-1,096.14
Non PCT-guided therapy		
- in RSD	71,729.15; 29,984.60-103,941.06; 55,385.51-94,001.47	87,278.23; 52,797.17-121,294.68; 67,138.43-122,056.18
- in €	623.73; 322.78-800.03; 510.20-893.87	758.94; 405.46-989.79; 598.98-1,001.12
LOS in the PCT group (days)	34; 19-57; 28.01-58.57	26; 11-57; 22.29-94.11
LOS in non-PCT group (days)	22; 14-39.50; 18.57-42.67	15; 12-31.5; 13.48-41.16

LOS – lenght of stay in Intensive Care Unit; IQR – interquartile range; CI – 95% confidence interval.

Antibiotics were administered to all patients during ICU stay. Monotherapy was administered to 32 (31.4%) patients. Our analysis showed that the most prescribed antibiotics were carbapenems (58.8%). In the carbapenem group, 56.9% of patients survived. In non-carbapenem group, 43.1% of patients survived. Although there was an obvious trend of increased survival in the carbapenem group, it did not reach a statistical significance. On the other hand, the use of carbapenems (meropenem or imipenem) significantly increased the cost of ICU therapy ($p < 0.001$).

The majority of patients had combined antimicrobial therapy (68.6%). The combination of antibiotics depended on clinical and microbiological data, and antimicrobial therapy was introduced and managed by the infectious disease (ID) specialists. Those ID specialists were

PCT measurement was introduced on the proposal of ID specialists, in order to control the length of antimicrobial therapy, bacterial resistance, and to reduce the use of antimicrobials as well as the cost of antimicrobial therapy. During the follow-up period, the observed patients were divided into two groups: the PCT-guided group of 56 (54.9%) patients and the non-PCT-guided group of 46 (45.1%) patients. Our results show that in the PCT-guided group the cost of antimicrobial therapy in the ICU was significantly higher than in the non-PCT-guided group (761.56 € *vs* 329.98 €, respectively; $p < 0.001$). The differences between the cost and the outcome are shown in Table 2. There was no significant difference between the outcome and the length of use of antibiotics in the two groups. Our results show that 75% of the patients in the PCT-

guided group had combined antibiotic therapy, and 40.5% of them died. In the PCT-guided group, carbapenems were administered in 69.6% of the patients and 56.4% of them survived. The most prescribed was meropenem. In the PCT-guided group, 41.1% of the patients had mixed bacteria in blood culture and 23.2% of them died. Sterile blood cultures were found in 33.9% of the patients and 10.7% of them died.

In the non-PCT guided group, 60.9% of the patients had combined antibiotic therapy and 50% of them died. Carbapenems were administered in 45.7% of the patients in the non-PCT guided group and 33.3% of them survived. In this group, 52.2% of the patients had mixed bacteria in blood cultures, out of whom 45.6% died. The differences between PCT-guided group and non-PCT guided group did not reach a statistical significance.

Discussion

In the present observational study, three factors were identified as the major cost drivers: duration of ICU-LOS; cost of antimicrobial therapy; PCT-measurement.

In our population of critically ill patients, the mortality rate was 50%. This outcome is comparable with that found previously in larger studies, where high mortality rates, between 40% and 70%, were common in ICU if septic shock developed [6, 18, 22, 23]. Moreover, ICU patients had a significantly increased mortality risk and a decrement in the quality of life and continued to die in the months and years after hospital discharge [20, 24, 25].

Patients who stay longer in the ICU are at increased risk of infection and probably would have higher cost since LOS is a major determinant of cost. A prolonged ICU stay consumes a large part of ICU resources. According to the literature, predominantly because of the long ICU-LOS, the cost of treatment for patients with sepsis is considerably higher than treatment for other ICU patients. The ICU direct costs *per* day are generally three to seven times higher than for non-ICU care [26, 27]. A multicenter, prospective pharmacoeconomic study of septic patients, showed that the cost of non-survivors increased day by day, while the cost of survivors decreased after the first few days. These findings suggest that patients who developed less organ dysfunction would have consequent reduced cost [17, 18, 27]. In the United States, the mean hospital cost per patient was estimated at $ 22,100 with higher cost in infants, patients who died, ICU patients, surgical patients and patients with multiple organ dysfunction [5]. In three ICUs in Germany similar results were found and again, total direct hospital costs were higher in non-survivors, surgical patients and patients requiring emergency procedures [26]. Our results also show the tendency of increased ICU cost in non-survivors. The lack of statistical significance may be attributed to the relatively small number of patients and great variability of cost.

Our costs were determined according to the pricing of drugs used during ICU-LOS in the hospital and those values are smaller than mentioned in other studies. This may be explained by the difference in pricing of drugs as well as the difference of the type of costs which were considered in comparing studies and included cost of diagnostic methods, surgical procedures, laboratories tests, microbiological tests, hospital fee, salaries and workload in ICU.

The most frequently used antibiotics in our study were carbapenems, which is in accordance with guidelines for antibotic treatment of sepsis [10, 12]. Carbapenems, especially meropenem, are antibiotics typically used in ICUs worldwide. The results of different studies show that meropenem is a cost-effective alternative to imipenem/cilastatin or piperacillin/tazobactam – the preferred carbapenem unless other factors affect this decision (such as local pathogen resistance) [18, 19, 28–30]. However, in our study carbapenems increased the cost of therapy in the ICU. As mentioned before, our population of patients was not analyzed in controlled environment, so our results were observational and from a follow-up period and may vary from the results derived from predefined study and the control groups. This might be one of the possible explanations of the fact that although there was the obvious trend of increased survival in the carbapenem group, it did not reach a statistical significance. Further controlled studies should be conducted in order to get additional data about clinical and economic benefits of the use of carbapenems in our ICU.

PCT measurement is also important in guiding duration of antibiotic therapy in ICU patients and in differentiating infective and non-infective inflammatory conditions [12, 14, 15, 31]. Since the levels of PCT rise in response to infection, its utility for the diagnosis of infection has been extensively investigated with conflicting results depending on the setting and population studied [17, 32]. The existing literature supports the position that PCT-guided therapy is associated with the average of 2 days of reduction in antibiotic use [33]. We did not have a reduction in antibiotic use in PCT-guided group, despite the fact that the ID specialist was in charge of antibiotic treatment. We are currently missing tools to facilitate the discontinuation of antibiotics in the ICU. In standard practice, duration of antibiotic courses in ICU vary greatly. In critically ill patients on prolonged therapy with broad-spectrum antibiotics, superinfections may occur and should be carefully monitored as possible infectious complications. The duration of antimicrobial therapy should be limited to 7 to 10 days. According to the literature, combination therapy should be used in *Pseudomonas* infections and should be discontinued in 3 to 5 days [7]. The severity of presenting symptoms correlate with the mortality in ICU patients and is used to justify more prolonged therapy. In one recent survey, critical care and infectious disease specialists were not even completely swayed by the evidence that limiting antibiotics attenuates the emergence of resistant Gram-negatives in ICU [5, 34–36]. A small number of antibiotic-free days (e.g. 3 days in a PRORATA trial) might not be sufficient to record a decreased resistance-emergence rate, especially for some ICUs with high cross-transmission rates [17]. Our results show that PCT did not affect the LOS in ICU and that LOS depended on diverse clinical characteristics and reasons for admissi-

ons to ICU. In our population of patients, antibiotic treatment was independent on PCT use and the mean duration was 7 days. These findings are similar to others [35,36].

The price of PCT analysis is about € 35 in our laboratory which is higher than in France, where PCT analysis costs € 10–15, and is comparable to the expenditure of unnecessary antibiotics. Nevertheless, Vandjick et al. [37] reported that the acquisition cost of antibiotics used to treat nosocomial bloodstream infections in ICU in adults was € 114 daily. Clearly, we need more data to confirm the value of PCT as a diagnostic parameter to guide antibiotic therapy.

The main limitation of our study lies in the number of patients and the use of direct medication pricing cost only. Despite this limitation, our results are the real-life results, obtained in population of critically ill patients and those results represent valuable data about clinical and economic aspects of antibiotic usage.

Conclusion

The obtained results show that age, the diagnosis and gender were the main predictors of survival of critically ill patients in the Intensive Care Unit. However, the cost of Intensive Care Unit treatment was not significantly influenced by the survival of patients possibly due to a relatively small number and large variability of treatment cost. In contrast, cost of Intensive Care Unit stay was determined by the lenght of stay, use of carbapenems and procalcitonin-measurement, although the influence of these three factors on the outcome in patients did not reach statistical significance. To our knowledge, this type of cost analysis is rarely, if ever, performed routinely. With direct connecting economic analysis to routine data collections, as we did in our real-life study, the results would be better and more applicable in everyday practice.

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