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ORIGINAL ARTICLE

Empirical therapy of bloodstream infection in university hospital

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ABSTRACT

The primary bloodstream infections (BSI) are important causes of morbidity and mortality in developing countries, due to severity of the disease and inadequate empirical therapeutical regimens.

The main objective of this pilot study was to retrospectively assess appropriateness of prescribing antibiotics for treating laboratory-confirmed BSI in two intensive care units (ICU) located in a large university hospital, according to susceptibility profile of the isolated agents.

During the study period (January 1st, 2011 to August 31st, 2012) a total of 47 patients had laboratory-confirmed BSI, and 57 pathogens were isolated in blood cultures. Twenty-two patients (47%) were female and 25 male (53%), mean age of 58 years (range 23-84). Regarding types of patients, 19 (40%) suffered from clinical conditions and 28 (60%) underwent surgical procedures. The mean time to initiate empirical treatment was 38 hours, with no statistically significant difference in patient type. Empirical treatment was considered adequate in 58% of cases, inappropriate in 23%, and was not started before culture results in 19%, with no statistically significant difference between patient types. Of the 57 pathogens isolated from blood cultures, 42 (74%) were Gram-negative and 15 (26%) Gram-positive, and the most prevalent agent was *Acinetobacter baumannii* (n=18; 31.6%), followed by *Klebsiella pneumoniae* (n=5; 8.8%), *Pseudomonas aeruginosa* (n=5; 8.8%), *Serratia marcescens* (n=5; 8.8%) and coagulase-negative staphylococci (n=5; 8.8%). *Staphylococcus aureus* was isolated in only 7% of the samples. As for multidrug resistance, the overall percentage was 53% (30/57), and *Acinetobacter baumannii* (78% - 14/18), *Pseudomonas aeruginosa* (60% - 3/5) and *S. aureus* (100%, 4/4) presented the lowest sensitivity profile.

Thus, a larger prospective study is suggested to confirm these preliminary data. The final results may be used to guide the revision of treatment protocols and intensification of preventive measures.

Keywords: *Bloodstream infection, empirical therapy, multidrug resistance, sensitivity profile, therapy appropriateness.*

INTRODUCTION

Primary bloodstream infections (BSI) are important causes of morbidity and mortality in developing countries, due to severity of the disease and an increased number of agents resistant to the commonly prescribed antimicrobials (MACHARASHVILI et al., 2009). Among the infections caused by Gram-positive organisms, the high percentage of methicillin--resistant *Staphylococcus aureus* (MRSA) and the emergence of glycopeptide-resistant strains are a concern (SIEVERT et al., 2002). Among the Gram-negative agents, increasing rates of carbapenem resistance and the emergence of polymyxin-B-resistant strains challenge physicians in the difficult task of treating patients with such infections (CLÍMACO, 2011).

Early and appropriate treatment of the BSI is essential to reduce mortality of patients, and it is recommended to start empirical treatment as soon as possible, employing antimicrobial regimen for the most prevalent agents in the organization and considering their sensitivity (KALLEL et al., 2010). On the other hand, the indiscriminate use of antibiotics, no compliance to clinical protocols and neglecting the need to adjust treatment after antibiogram results can induce the emergence of multidrug--resistant strains (JACOBY, 2008).

The main objective of this pilot study was to examine the appropriateness of prescriptions for laboratory-confirmed BSI in intensive care units (ICU) of a large university hospital, according to microbial sensitivity.

MATERIAL AND METHODS

This is a retrospective study including all patients in two ICU that presented laboratory-confirmed BSI (according to the

National Healthcare Safety Network – NHSN – 2011 criteria) in the period from January 1st, 2011 to August 31st, 2012. Data were obtained from the database of the Nosocomial Infection Control Committee (NICC) and from search in medical records to complement pieces of information. Treatment was considered adequate when the antibiogram showed at least one antimicrobial agent in use with sensitive profile to the isolated microorganism. In cases in which more than one species was isolated, the treatment was only considered adequate when there was at least one antibiotic agent with sensitive profile for each microorganism.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 15.0. Regarding the statistical analysis, a descriptive analysis was performed using frequency and percentage for categorical variables and mean for continuous variables. The "t" test was applied after verifying data normality using the Kolmogorov-Smirnov test, to compare the mean length of stay and time to initiate treatment between the surgical and clinical groups, as well as to compare the mean time to initiate therapy considering the outcome death. The Fisher's test (two-tailed "p") was used to compare appropriateness of treatment and frequency of death among surgical and clinical groups and to analyze death frequency, considering the appropriateness of treatment.

About ethical aspects, the NICC performed its duties as defined by the Ordinance 2616/98, assessing and controlling regularly the antimicrobial prescription.

RESULTS

From January 2011 to August 2012, 47 patients from two ICUs had laboratory-confirmed BSI and 57 pathogens were isolated in blood culture. Two patients had three pathogens isolated in blood cultures, six patients had two agents and 39 had one species identified. Twenty-two (47%) patients were female and 25 (53%) male, mean age of 58 years (range 23-84 years). Regarding the indication for hospitalization, 19 (40%) patients suffered from clinical conditions and 28 (60%) underwent surgical procedures. As to length of stay in ICU up to diagnosis of BSI, the overall mean was 15 days (range 2-116 days); for clinical patients, the mean was 14 days, and for surgical patients, 15 days (p=0.70).

Data on time to start empirical treatment were available for 18 patients, as access to medical records was only possible in 21 cases, and in three records this information was not available The overall average was 38 hours, ranging from 1 to 105 hours (Figure 1). Considering indication for hospital admission, clinical and surgical patients had a mean time to initiate treatment of 49 and 32 hours, respectively, with no statistically significant difference between the groups (p=0.33).

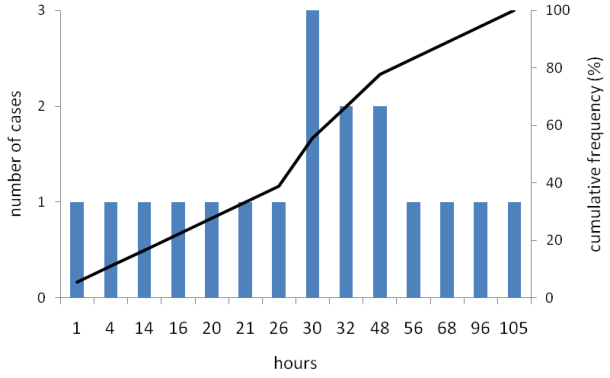

Figure 1 - Distribution of laboratory-confirmed BSI cases in two intensive care units of a university hospital, from January 1st, 2011 to August 31, 2012, per time to initiate empirical treatment.

A total of 57 pathogens were isolated in blood cultures, 42 (74%) were Gram-negative and 15 (26%) Gram-positive (Table 1). Of the 18 isolated strains of *Acinetobacter baumannii,* 15 (83%) were resistant to cefepime, 14 (78%) to imipenem and meropenem and 15 (83%) to piperacillin/tazobactam; four were tested for tigecycline, and one was resistant. Out of five strains of *Pseudomonas aeruginosa*, three had resistant or intermediate profile to cefepime, imipenem and meropenem, and only one showed resistance to piperacillin/tazobactam. In the Enterobacteriaceae family (5 *Klebsiella pneumoniae*, 5 *Serratia marcescens,* 6 *Enterobacter spp.*, 1 *E. coli* and 1 *Proteus vulgaris*), 6 (33%) showed resistance to cefepime, 10 (56%) to piperacillin/tazobactam and 2 (11%) to carbapenem. The following were isolated from the genus Enterococcus: four strains of *Enterococcus faecalis* (one was resistant to vancomycin), one strain of *Enterococcus faecium* (resistant to vancomycin) and one of *Enterococcus gallinarum* (intrinsically resistant). From nine strains of the genus Staphylococcus, four were *S. aureus* (all oxacillin-resistant), two *S. epidermidis* (one resistant to oxacillin), two *S. haemolyticus* (all oxacillin-resistant) and one *S. hominis* (oxacillin-resistant). Among these, three were tested for vancomycin with sensible result.

Table 1 – Distribution of etiologic agents Jan 1st, 2011 to Aug 31st, 2012

ETIOLOGIC AGENT	n	%
Gram-negative bacilli	***42***	***73,7***
Acinetobacter baumannii	*18*	*31,6*
Enterobacter spp.	*6*	*10,5*
Klebsiella pneumoniae	*5*	*8,8*
Pseudomonas aeruginosa	*5*	*8,8*
Serratia marcescens	*5*	*8,8*
Escherichia coli	*1*	*1,8*
Proteus vulgaris	*1*	*1,8*
Stenotrophomonas maltophilia	*1*	*1,8*
Gram-positive cocci	***15***	***26,3***
Enterococcus spp.	*6*	*10,5*
Coagulase-negative staphylococci	*5*	*8,8*
Staphylococcus aureus	*4*	*7,0*
TOTAL	***57***	***100,0***

As to overall percentage of multidrug resistance, 30 (53%) out of 57 isolates were multiresistant. As to specific profile, the following was found: *Acinetobacter baumannii* (78% - 14/18), *Enterobacter spp.* (50% - 3/6), *Enterococcus spp.* (50% - 3/6), *Klebsiella pneumoniae* (20% - 1/5), *Pseudomonas aeruginosa* (60% - 3/5), *Serratia marcenses* (20% - 1/5), *S. aureus* (100%, 4/4) and coagulase-negative staphylococci (0% - 0/5).

Empirical treatment was considered adequate in 58% of cases, inadequate in 23% and no early empirical treatment before culture results was initiated in 19%. For statistical analysis, the groups with inadequate treatment and no treatment were considered together. Taking into account treatment suitability, there was no statistically significant difference between clinical and surgery groups (p=0.37).

Of the 18 patients we gathered information in medical records, three died in the first 14 days after onset of symptoms. There was no difference in survival when comparing the clinical and surgical patient groups (p=0.62) and appropriate, inappropriate and no treatment (p=0.31). Likewise, there was no difference comparing the mean time to initiating treatment between the groups survival versus death (p=0.75).

DISCUSSION

Despite the small sample (47 patients and 57 isolates from blood cultures) and the limited methodological design (retrospective study), the findings of the present study are similar to those reported by MONTRAVERS et al. (2001). In their cohort of 1043 patients receiving antimicrobials for various reasons at the ICU, 21% of drug regimens were initiated after culture results, and the choice was deemed inappropriate in 22% of patients. The authors also demonstrated a higher percentage of adequacy in hospitals adopting treatment protocols. After multivariate analysis, the absence of such protocols was considered a predictor of mortality (OR=1.64, 95% CI: 1.01 to 2.69). The use of treatment protocols for empirical use of antimicrobials is a practice that encourages their rational use and results in reducing mortality from bacteremia in ICU (MONTRAVERS et al., 2011). Recommendations should differ between organizations since the distribution of pathogens causing infections and the susceptibility profile varies widely between hospitals (LAWRENCE et al., 2005).

In another prospective study (ENOCH et al., 2010) that included 203 episodes of bacteriemia by Gram-negative agents, the results were more satisfactory, considering the appropriate treatment was initiated in 80% of cases and orientation about treatment protocol were correct in 95% of them. The group of patients receiving inadequate treatment showed higher mortality (OR=2.63, 95%CI: 1.09 to 6:34).

This study also points to the need for periodic review of empirical prescriptions to ensure quality of care provided to patients. For the Infectious Diseases Society of America – IDSA - antimicrobial stewardship refers to "coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration". According to this organization, the main objectives of this management would be to reach "optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains".

Our data showed a mean time interval to initiate empirical treatment of 38 hours after onset of symptoms. This piece of information was obtained for 18 patients after searching medical records and was calculated by observing the medical and nursing notes about the exact time of onset of symptoms considered as a criterion for BSI (fever, shivering, hypotension, or oliguria) and checking the nursing first administration of the antibiotic(s) prescribed. KUMAR et al. (2006) found a mean of six hours to start treatment after onset of hypotension in a group of 2731 adults with septic shock. In this study, the prescription for the first hour of hypotension was associated with a survival rate of 79.9%, and each hour of delay in treatment within the first six hours of hypotension was associated with a reduction of 7.6% in survival.

As for the percentage of resistant strains, the 18 strains of *Acinetobacter baumannii* had a profile similar to that of the SENTRY study (percentage of resistance observed x Sentry = cefepime: 83% vs. 77%, meropenem: 78% vs. 66%; imipenem: 78% vs. 68%, piperacillin -tazobactam: 83% vs. 86%). Other-Gram negative agents were less frequently isolated, making it difficult to compare. As for Gram-positive, from nine strains of the genus Staphylococcus, only one (11%) was sensitive to oxacillin, and all four strains of *Staphylococcus aureus* were resistant to this drug. Another study (NAVES et al., 2012) conducted at a Brazilian university hospital showed a percentage of 56.8% of methicillin-resistant *S. aureus* (MRSA).

This pilot study confirms the relevance and necessity of a prospective study with a significant sample to confirm these preliminary findings. It is assumed that a considerable percentage of empirical treatments of BSI is being performed improperly, for not covering the main pathogens responsible for these infections or because of late start of medication. The results of a larger study could be used to review treatment protocols, as well to encourage intensification of preventive measures and continuing education of health professionals on the rational use of antimicrobials and hospital infection control.

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