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Letter to the Editor

Predictors of 14-day mortality in patients with bloodstream infections caused by Enterobacteriaceae strains: a mathematical PK/PD analysis

Dear Editor,

Bloodstream infections (BSI) caused by Enterobacteriaceae strains are of great concern in clinical settings. Furthermore, the presence of extended-spectrum β-lactamases (ESBLs) in these microorganisms has added potential difficulties in treating these infections.

Quantitative pharmacodynamics (PD) parameters have been proposed to evaluate clinical and microbiological outcomes.[1] Changes in minimum inhibitory concentration (MIC) and pharmacokinetics (PK) parameters affect these PD ratios. Currently, a great concern is how to optimize antimicrobial use due to a restricted number of new antimicrobial drugs against Gram-negative rods. The evaluation of the PK/PD relationship has received great consideration because it has led to optimization of dosage regimens and improvement of outcomes.[2]

Currently, limited human studies are available on the relevance of PK/PD parameters in terms of outcome for complicated bacteremia caused by Gram-negative rods. With this study, we sought to assess the risk factors associated with 14- and 28-day mortality, and the adequacy of beta-lactam therapy in a group of patients with bloodstream infection (BSI) caused by Enterobacteriaceae. Moreover, a mathematical PD model was utilized to evaluate whether a lack of ideal PD goal impact on mortality rates.

A retrospective cohort study was performed in a university-affiliated hospital (Hospital São Paulo) in São Paulo, Brazil. Adult patients were eligible if they had a documented nosocomial bloodstream infection caused by an Enterobacteriaceae strain, were treated with beta-lactam antibiotics for at least 72 h by the attending physician, and had a creatinine clearance ≥ 30 mL/min. Immunocompromised patients were excluded. Briefly, immunocompromised patients were those on chemotherapy, those who were neutropenic (ANC < 500 cells/mm^3), and those with AIDS. Infection was defined by the CDC criteria. We analyzed only the first episode of bacteremia from each patient. Data collected from patients' medical records included demographic characteristics, comorbidities, antimicrobial treatment, presence of ESBL, presence of septic shock, delay in starting adequate antimicrobial therapy, achievement of PD goal, and in-hospital mortality. Delay to start adequate antimicrobial therapy was defined as the therapy starting > 48h after collection of blood culture.

A mathematical PD model was employed. Briefly, MICs were determined using the automated BD Phoenix. % T > MIC was estimated mathematically based on the equation % T > MIC = ln[Dose* f/Vd*MIC)]*[V/Cl]*[100/DI], where V is the volume of distribution in liters at steady state, DI is the dosing interval (h), ln is the natural logarithm, f is the fraction of unbound drug, and Cl is the total body clearance in liters per hour.[3] V and Cl were taken from published population pharmacokinetic studies.[4-6] For cephalosporins and carbapenens, %T > MIC of free drug at 50% and 40% of the dosing interval were the PD targets, respectively.[7]

The first microorganism obtained from each patient's bloodstream was used for all microbiologic assessments. Identification and MICs were determined for each isolate by automated BD Phoenix.

Categorical variables were compared using the chi-square test, and continuous variables were compared by Student's t-test. A p-value < 0.1 was considered to be statistically significant. To determine independent predictors of mortality, logistic regression analysis was performed. Variables considered for model inclusion were adjusted by age and comorbidities. A p-value < 0.05 was considered to be statistically significant in multivariate analyses. All calculations were computed using MedCalc, version 11.6, Mariakerke, Belgium.

During the study period, 76 adult patients with bacteremia caused by Enterobacteriaceae who received ≥ 72 h of β-lactam therapy were identified. Twelve patients were excluded because they were immunocompromised, thus 64 patients were evaluated. 40 patients were male (62.5%), and the median age was 64 years. The 14- and 28-day mortality rates were 25% (16/64) and 35.9% (23/64), respectively. The most common microorganisms isolated were *Klebsiella pneumoniae* (39; 60.9%) and Proteus mirabilis (14; 21.8%). 30 patients (46.8%) had ESBL-positive strains. Imipenem was the most utilized antimicrobial drug

(31/64, 48.4%) followed by cefepime (23/64, 35.9%). The $MIC_{50/90}$ for cefepime, imipenem and piperacillin/tazobactam were > 16/> 16, 1/1, > 64/> 64 and > 16/> 16, 4/4, ≤ 4/> 64 for *Klebsiella pneumonia* and *Proteus mirabilis*, respectively. Only 15 (23.4%) patients had a delay to start adequate antimicrobial therapy. Only nine patients (14%) did not achieve the PD goal. Only two variables were independently associated with 14-day mortality in logistic regression analysis: lack of PD goal (OR 9.26; 95%CI 1.50 57.17; p = 0.01) and presence of septic shock (OR 14.58; 95%CI 3.28-64.82; p = 0.0004). With regard to 28-day mortality, only presence of septic shock (OR 4.90; 95% CI 1.36-17.62; p = 0.01 was significant. We also performed a subgroup analysis of predictors of 14-day mortality focused on patients with ESBL-producing microorganisms (30 patients). In this subset of patients, only the variable PD goal not achieved was independently associated with 14-day mortality (OR 13.71; 95% CI 1.38-136.21; p = 0.02).

Several factors have been demonstrated as predictors of mortality among patients with Enterobacteriaceae bacteremia, e. g. septic shock, neutropenia, higher APACHE II score, comorbidities, and older age.[8-9] This is one of the first cohorts to evaluate outcomes and characteristics of patients with bacteremia caused by Enterobacteriaceae focused on characteristics of antimicrobial therapy, e.g. PD goal.

Our study demonstrated that failure to achieve PD goal, as well as presence of septic shock, is associated with 14-day mortality, but only the later variable was associated with 28-day mortality (Table 1). Surprisingly, the delay to start adequate therapy was not associated with mortality. Conversely, the presence of ESBLs did not impact on mortality rates, probably because the vast majority of patients were treated with carbapenems in our cohort. Interestingly, despite the reduced number of patients evaluated, we found that failure to achieve PD goal was a predictor of 14-day mortality among patients with infections caused by ESBL-producing microorganisms. This finding suggests that achievement of PD goal may be important among a subset of patients with infections caused by pathogens with higher MICs.

Carbapenems and cefepime were the only antibiotics utilized in our cohort. The restricted use of ceftazidime in recent years in our hospital by the antimicrobial management program and the great prevalence of ESBL may be the likely reason for this situation. Interestingly, we found a non-significant lower mortality rate among the patients who used meropenem (6.2%), when compared with those who used cefepime (37.5%) and imipenem (56.2%).

The utilization of hospital-specific susceptibility data (MIC) distribution provides reliable information for designing empirical antimicrobial dosing regimens. In recent years, the combination of MIC with antimicrobial drugs' pharmacokinetic properties has provided clinically relevant information.[3]

A similar tool to analyze PD adequacy was utilized by Mohr et al.[10] In their study, the authors analyzed 19 patients with serious infections and assessed the achievement of the PD goal which was achieved with the initial antimicrobial selection in only 3/19 (15.7%) patients. The authors concluded that standard empiric therapy is often sub-optimal. However, in their study the authors utilized a %T > MIC of 100 as the PD goal for beta-lactams. We utilized a lower PD goal in this study as defined elsewhere, and we found a greater achievement of PD goal (89%). Despite this fact, failure to achieve this PD goal was a predictor of mortality in our cohort.

Our study has several limitations. First, we utilized clearance and volume of distribution from previous population pharmacokinetics studies. However, since the beta-lactam drugs utilized had predominantly renal clearance, we think that those values may be suitable surrogate markers for actual beta-lactam clearance and volume of distribution. Moreover, despite

Table 1 - Analysis of factors associated with 14-day mortality in patients with BSI caused by Enterobacteriaceae

Variable	Non-survivors (n = 16)	Survivors (n = 48)	Univariate p	Multivariate OR (95%CI) p
Age, median, SD	66 (+/-16)	63 (+/-16)	0.47	
Male sex	9 (56.2)	31 (64.6)	0.76	
Comorbidities, ≥ 2	9 (56.2)	0 (62.5)	0.88	
Antibiotic				
Cefepime	6 (37.5)	14 (29.17)	0.62	
Imipenem	9 (56.2)	27 (56.2)	0.81	
Meropenem	1 (6.2)	7 (14.5)	0.27	
ICU	15 (93.7)	29 (60.4)	0.02	4.43 (0.46-42.11) 0.19
ESBL	8 (50)	22 (45.8)	1.00	
Delay to adequate treatment > 48h	2 (12.5)	13 (27.1)	0.39	
Septic shock	10 (62.5)	5 (10.4)	0.0001	14.58 (3.28-64.82) 0.0004
PD goal not achieved	6 (37.5)	3 (6.2)	0.0007	9.26 (1.50-57.17) 0.01

BSI, bloodstream infection; ESBL, extended-spectrum beta-lactamase; PD, pharmacodynamics.

the great variability of PK data among patients, we sought to utilize data from PK studies undertaken in hospitalized patients similar to our patients. Secondly, our study was restricted to the analysis of only three beta-lactam drugs and these findings cannot be extrapolated to other beta-lactams. Finally, the broth microdilution method, which is considered the gold standard microbiological method, was not employed in our study.

In conclusion, our study demonstrated that failure to achieve a PD goal and presence of septic shock were predictors of 14-day mortality, but only the latter variable was predictor of 28-day mortality among patients with bloodstream infections caused by Enterobacteriaceae strains. As far as we know, this is the first study analyzing this subject in this specific population. Hence, taking into account the difficulties in performing more accurate bedside PK/PD analysis, we consider our data relevant. Our results highlight the increasing importance of adequate PD targets in the treatment of serious nosocomial infections. Further well-designed studies are warranted to better assess this interesting subject.

Conflict of interest

All authors declare to have no conflict of interest.

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