A Pharmacodynamic Strategy to Optimize Empirical Antibiotic Therapy for Gram-Negative Bacteria in a Brazilian Intensive Care Unit

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Pharmacodynamic analyses were proposed to determine optimal empirical antibiotic therapy against Gram-negative bacteria isolated in a Brazilian ICU. Due to high resistance rates, standard regimens of cefepime, ciprofloxacin, meropenem, and piperacillin/tazobactam were not able to attain significant bactericidal CFR. Prolonged infusion of meropenem achieved 88% CFR, making it a possible empirical regimen in this ICU until susceptibilities become available. Still, even through administration of high dose prolonged infusions, 12.0% of simulated subjects did not achieve bactericidal exposure, suggesting that combination therapy would frequently be required in this setting. In conclusion, we recommend that in the presence of identified resistance problems among Gram-negative bacteria in a unit or hospital, MIC testing of formulary agents should be conducted along with pharmacodynamic simulation to assist in choosing an optimal antibiotic and dosage regimen for empirical use of severe infections until cultures and susceptibilities become available.

Key-Words: Pharmacodynamics, resistance, carbapenem, meropenem.

Inadequate antimicrobial therapy for severe infections is associated with increased mortality, prolonged stay in the intensive care unit (ICU), and increased risk of septic shock and bacteremia [1,2]. In most studies, the definition of inadequate antimicrobial therapy is based solely on a lack of *in vitro* susceptibility of the causative pathogen to the antibiotic administered. As a result, the use of a local antibiogram to determine empirical drug regimen combinations that would provide the greatest likelihood of at least one microbiologically active agent seems practical [3-5]. However, the simple classification of S, I, or R provides little information on the underlying level of susceptibility or resistance (i.e., the minimum inhibitory concentration [MIC]) [6]. This methodology also precludes a clear appreciation of the optimal dosage to administer, as it may be possible to overcome low levels of resistance in some patients with dosage enhancements [7]. As an alternative, we propose the determination of unit (or hospital) specific MIC distributions and use of pharmacodynamic modeling via Monte Carlo simulation to provide the best estimate of achieving optimal empirical antibiotic therapy.

In view of these facts and increasing resistance rates in Brazil, we set out to investigate which Gram-negative bacteria caused infections in an adult ICU of a tertiary care medical center (Hospital Samaritano) in São Paulo, Brazil and to determine the MIC distributions of several antibiotic therapies so that an optimal antibiotic and dosage regimen could be chosen empirically.

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Over a 9-month interval in 2004, Gram-negative bacteria (n=43) were collected consecutively from adults treated for documented infections in the ICU of the referred hospital. During this period all possibilities of nosocomial outbreaks were ruled out by investigators and were validated externally by the hospital infection control service. Bacteria were isolated from the following infection sources: blood/catheter, n=22 (51%); urine, n=10 (23%), bronchoalveolar lavage, n=8 (19%), and abdominal/wound, n=3 (7%). MIC testing was performed by E-test® methodology (ABBiodisk, Solna, Sweden). Reported MICs that fell within intervals for standard broth microdilution values reassigned the value of the next highest tube dilution based on these intervals. *Pseudomonas aeruginosa* was the most commonly isolated Gram-negative pathogen (Table 1). For all 43 Gram-negatives isolated, susceptibility rates were greatest for meropenem (81.4%), followed by piperacillin/tazobactam (53.5%), cefepime (48.9%), and ciprofloxacin (39.5%). The range of MICs isolated is also listed in Table 1.

Pharmacodynamic analyses were conducted via a 5000 subject Monte Carlo simulation (Crystal Ball 2000 v.2.2, Decisioneering Inc., Denver, CO, USA) for standard intravenous dosage regimens of cefepime, ciprofloxacin, meropenem, and piperacillin/tazobactam (dosage and antimicrobial drugs routinely used in the unit). All standard dosage regimens were simulated as 30-minute infusions via a 1-compartment intravenous infusion model. Estimates of pharmacokinetic parameters and dispersion were derived from studies in healthy volunteers as reported in past OPTAMA studies [8, 9]. The bactericidal cumulative fraction of response (CFR) was calculated for each drug regimen against the bacteria population as a single group. Bactericidal CFR was defined as free drug concentrations above the MIC for a percentage of the dosing interval (% $fT>MIC$) of 40% for meropenem, 50% for the other β-lactams and as a ratio of total drug area under the curve (AUC)/MIC greater than or equal

Table 1. Frequency and antibiotic MIC range of 43 Gram-negative bacteria collected consecutively in the adult ICU of a Brazilian hospital over a 9 month period in 2004

		MIC (μg/mL) range			
Bacteria	**N (%)**	**Cefepime**	**Ciprofloxacin**	**TZP**	**Meropenem**
P. aeruginosa	15 (35)	2->256	0.064->32	4->256	0.125->32
E. coli	10 (23)	0.032-256	0.006->32	1.5-8	0.012-0.047
E. cloacae	6 (14)	0.094-192	0.012->32	4->256	0.032-0.094
A. baumannii	6 (14)	3->256	0.125->32	3->256	0.25-16
Klebsiella spp.	3 (7)	0.032-256	0.012-6	0.75-4	0.023-0.064
Other	3 (7)	0.125->256	0.008-1.5	0.75->256	0.023->32

TZP=piperacillin/tazobactam.

Table 2. Cumulative fractions of response (CFR) at varied % *f*T>MIC exposures for frequently used β-lactam regimens in a ICU in Brazil

% *f*T>MIC	**Cefepime 2g q12h**	**Meropenem 1g q8h**	**TZP 4.5g q8h**	**TZP 4.5g q6h**
20	59.6	85.5	51.6	53.0
30	54.0	83.5	49.3	50.8
40[a]	48.1	80.7	46.9	49.2
50[b]	47.2	73.2	37.0	47.5
60	44.5	65.3	21.8	43.4
70	41.4	60.3	10.7	33.0
80	38.6	57.0	4.3	21.9
90	35.6	54.0	1.1	13.0
100	32.6	50.3	0.38	7.1

TZP=piperacillin/tazobactam; all regimens admonistered as 30 minute infusions. [a]Bactericidal exposure for meropenem defined as 40% T>MIC. [b]Bactericidal exposures for the penicillins and cephalosporins defined as 50% *f*T>MIC.

to 125 for ciprofloxacin. CFR at alternative % *f*T>MIC exposures were also calculated and reported. For those drug regimens with the highest bactericidal CFR, pharmacodynamically enhanced dosage strategies were explored to increase the CFR.

Bactericidal CFR was greatest for meropenem 1g every 8 hours (80.7%), followed by piperacillin/tazobactam 4.5 g every 6 hours (47.5%), cefepime 2 g every 12 hours (47.2%), piperacillin/tazobactam 4.5 g every 8 hours (37.0%), and ciprofloxacin 400 mg every 12 hours (34.9%). CFR at alternative % *f*T>MIC targets are listed in Table 2. While standard meropenem regimens provided the highest CFR and one similar to percent susceptibility, neither estimate should be considered optimal for empirical therapy. Thus, higher doses as prolonged infusions were simulated to improve CFR. A dose of 2 g administered as a 3-hour prolonged infusion every 8 hours achieved 88.0% likelihood of bactericidal CFR. Similar CFR probabilities were achieved up to 70% *f*T>MIC exposure with this regimen (i.e., 84.2%, 83.2%, and 80.4% at 50%, 60%, and 70% *f*T>MIC, respectively). Accordingly, this regimen would provide the greatest likelihood of optimal empirical therapy for patients in this ICU. Still, even through administration of high dose prolonged infusions, 12.0% of simulated subjects did not achieve bactericidal exposure, suggesting that combination therapy with an aminogylcoside would frequently be required in this setting.

The hospital antibiogram provides extremely valuable information for tracking emerging resistance throughout medical centers and has been proposed as useful tool for choosing empirical antibiotic therapy. However, in the presence of increasing resistance rates, the antibiogram provides little information on how to empirically dose antibiotics to improve the likelihood of optimal therapy and outcomes [6]. The currently proposed strategy for this ICU was designed to extend the interpretation of appropriate antibiotic therapy from simply *in vitro* susceptibility testing to a quantitative assessment of achievable *in vivo* antibiotic exposure. Although not routinely used, this approach is not novel; pharmacodynamic simulations in conjunction with MIC data have been used on several occasions to recommend specific dosage regimens on national, hospital and even individual patient levels [7, 10-14]. It was not under the scope of this analysis to collect outcome data; however, it was our intention that any beneficial regimen emerging from this simulation model could be implemented into the unit's daily practice to provide optimal empirical therapy and improve outcomes. We made these data available for the hospital's staff and started a discussion forum for implementing prescription changes.

In conclusion, we recommend that in the presence of identified resistance problems among Gram-negative bacteria

in a unit or hospital, MIC testing of formulary agents should be conducted along with pharmacodynamic simulation to assist in choosing an optimal antibiotic and dosage regimen for empirical use against severe infections until cultures and susceptibilities become available.

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