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Application of Pharmacodynamic Profiling for the Selection of Optimal β-lactam Regimens in a Large University Hospital

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ABSTRACT

Background: Infections caused by drug-resistant Gram-negative bacteria (GNB) are increasing worldwide and as a result, the selection of appropriate empiric antibiotics (ATBs) has been made increasingly difficult. The present study aimed to identify optimized dosing regimens of intravenous (IV) ATBs, defined by cumulative fraction response (CFR), against *E. coli* (EC), *K. pneumoniae* (KP), *P. aeruginosa* (PA), and *A. baumannii* (AB) at 2,300-bed University Hospital.

Materials and Methods: The minimum inhibitory concentrations (MIC) of EC, KP, PA, and AB from clinical specimens, 250 each, were determined. Pharmacodynamic profiling using Monte Carlo Simulation was performed for standard, high dosage, and prolonged infusions (PI) of ceftriaxone, cefepime, ceftazidime, imipenem, meropenem, and doripenem. A CFR of ≥90% was targeted as providing a sufficiently high ATB exposure.

Results: When considering the Enterobacteriaceae, the % susceptible for the cephalosporins ranged from 60% for ceftriaxone to 86% for cefepime, as a result only the 2 g q8 h regimens of ceftazidime and cefepime provided high CFRs. In contrast, all the carbapenems had % susceptible and CFRs ≥90% for EC and KP. While cefepime and ceftazidime demonstrated higher % susceptibility (82-83%) for PA relative to that of the carbapenems (61-69%) only doripenem 2 g q8 h (4 h PI) achieved an optimal CFR (92%) against this organism. Due to the MIC profiles and dismal susceptibilities of AB (16-22%), none of the regimens studied achieved CFRs > 65%.

Conclusions: The pharmacodynamic profiling undertaken in the current study provides insights that allow prescribers to select more appropriate empirical antibiotic regimens for the treatment of infection caused by these common GNB pathogens at this Thai hospital. While higher doses and PI of β-lactams improve exposures against EC, KP and PA, this approach will not sufficiently enhance their potency against AB, thus alternative therapies should be considered for this organism.

1. Background

Antibiotic-resistant bacteria are increasing worldwide. In Asia, inclusive of Thailand, multidrug-resistant (MDR) Gram-negative bacteria such as *Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli*, and *Klebsiella pneumoniae*, are the most problematic causative pathogens of hospital-acquired infection.[1,2] The common site of infection is hospital-acquired/ventilator-associated pneumonia (HAP/VAP). The study conducted by the International Nosocomial Infection Control Consortium from January 2004 through December 2009 in 422 intensive care units (ICU) of 36 countries in Latin America, Asia, Africa, and Europe reported the frequency of resistance of *P. aeruginosa* isolates to imipenem was 47.2%, *K. pneumoniae* isolates to ceftazidime was 76.3%, and *E. coli* isolates to ceftazidime was 66.7%.[3] The authors also mentioned that the higher rate of resistant Gram-negative bacteria in these studied countries was higher than the resistance rate in the ICU of United States. Without the appropriate empirical antibiotics for the treatment of MDR bacterial infections, the morbidity and mortality consequences are obvious. The resistance of these

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pathogens to available antibiotics including carbapenem leads to the failure of treatment. Chung DR, *et al.*, focused on HAP and VAP cases in Asian countries, and demonstrated that the major bacterial isolates were *Acinetobacter* spp., *P. aeruginosa*, *Staphylococcus aureus*, and *K. pneumoniae*. The study showed high rates of drug-resistant i.e.; imipenem resistance rates of *Acinetobacter* spp. and *P. aeruginosa* were 67.3% and 27.2%, respectively and multidrug-resistant rates were 82% and 42.8% while extensively drug-resistant rates were 51.1% and 4.9%. All-cause mortality rate was 38.9% and the discordant initial empirical antimicrobial therapy increased the likelihood of pneumonia-related mortality.[4]

The current study aimed to explore the optimal dosing regimens of β-lactam antibiotics (ATBs) against *P. aeruginosa, A. baumannii, E. coli*, and *K. pneumoniae* from clinical isolates of Siriraj Hospital, the University Hospital in Thailand, according to susceptibility pattern and MIC distribution.

2. Materials and Methods

In Siriraj Hospital, 2300-bed University Hospital, there were 83,747 in-patient admissions per year (20% was patients of the internal medicine department and 21% was patients of the urgical department). These 2 departments had major hospital-acquired infection complications from Gram-negative bacteria especially *E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii*.

2.1. Microbiology

A total of 1,000 Gram-negative isolates, 250 each (*E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii*) collected between January 2011 and January 2012 from both medical and surgical patients across the institutional care units were analyzed in the present study. The organisms were collected according to the type of infection, which primarily included bloodstream infection, pus, body fluid infection and respiratory infection. Each clinical specimen was processed at the microbiology laboratory, Siriraj Hospital, according to standard microbiology procedures and cultured using 5% (v/v) sheep blood agar, chocolate agar and MacConkey agar, where appropriate. The organisms were identified by using the Vitek 2® system (bioMérieux, Missouri, USA). MICs of 6 ATBs, ceftriaxone (CRO), ceftazidime (CAZ), cefepime (FEP), doripenem (DOR), imipenem (IPM) and meropenem (MEM), were determined by E-test (bioMérieux). CRO was not tested for AB and PA. The quality control of MIC testing was performed using the reference strains *E. coli* ATCC 35218 and *P. aeruginosa* ATCC 27853 according to Clinical and Laboratory Standards Institute (CLSI).[5] MIC_{50} and MIC_{90} were determined and susceptibility was interpreted based on CLSI breakpoints[5] where applicable.

2.2. Antimicrobials

As a result of escalating resistance for these common Gram-negative bacteria in our hospital setting, the appropriateness of the commonly utilized β-lactam regimens such as ceftriaxone 2 g every 24 hours, ceftazidime 1 g every 8 hours (0.5-hour infusion), cefepime 2 g every 12 hours (0.5-hour infusion), imipenem 0.5 g every 8 hours (0.5-hour infusion), meropenem 1 g every 8 hours (0.5-hour infusions), and doripenem 0.5 g every 8 hours (1-hour infusion) for empirical treatment was questioned. Therefore for the purposes of defining the most optimal regimen of these β-lactams against the target pathogen, the following pharmacodynamic profiling assessments were undertaken with a variety of antibiotic regimens:

- ceftriaxone 1 g every 24 hours (0.5-hour infusion)
- ceftriaxone 2 g every 24 hours (0.5-hour infusion)
- ceftazidime 1 g every 8 hours (0.5-hour and 3-hour infusion)
- ceftazidime 2 g every 8 hours (0.5-hour infusion)
- cefepime 2 g every 12 hours (0.5-hour infusion)
- cefepime 2 g every 8 hours (0.5-hour and 3-hour infusion)
- doripenem 0.5 g every 8 hours (1-hour and 4-hour infusions)
- doripenem 1 g every 8 hours (1-hour and 4-hour infusions)
- doripenem 2 g every 8 hours (1-hour and 4-hour infusions)
- imipenem 0.5 g every 8 hours (0.5-hour infusion)
- imipenem 0.5 g every 6 hours (0.5-hour)
- imipenem 1 g every 8 hours (0.5-hour and 3-hour infusions)
- meropenem 1 g every 8 hours (0.5-hour and 3-hour infusions)
- meropenem 2 g every 8 hours (0.5-hour and 3-hour infusions)

2.3. Pharmacokinetic Model

Steady-state exposures were determined for each antibiotic regimen using serum pharmacokinetic (PK) parameters obtained from published population pharmacokinetic studies of infected and/or critically-ill patients as shown in Table 1.[6–11] While more recent references could have been selected, we have made use of the citations noted because the newer studies provide similar PK profiles as such incorporation of newer data would not substantially change the interpretation of the PD profiles. Thus the outputs from the current MCS are contemporary despite older PK data as it is not the PK profile that changes over time but the susceptibility of the pathogen under study. Moreover, we have chosen to use the previously utilized PK data so that comparisons could be made to our previously published work and highlight the importance of the changing MIC distribution of the organism populations. The methodology used to simulate steady-state antibacterial exposures has been previously described in the published study by DeRyke CA, *et al.*[12]

2.4. Monte Carlo Simulation

A 5,000 patient Monte Carlo simulation (Crystal Ball 7; Decisioneering Inc., Denver, CO) was performed for each regimen, and the probability of a simulated patient achieving the pharmacodynamic target, referred to as probability of target attainment (PTA), was calculated over a range of doubling MICs between 0.008 and $\geq$ 64 mg/L. Pharmacodynamic targets were defined as $fT > MIC$ of at least 50% of the dosing interval for cephalosporins and $fT > MIC$ of at least 40% of the dosing interval for carbapenems[13] (imipenem, meropenem, and doripenem).

Probability of target attainment (PTA)* for each regimen was used to calculate the cumulative fraction of response (CFR)** for each antibiotic regimen against the bacteria population as previously described.[12] A CFR of at least 90% for a regimen was defined as optimal against that bacterial population.

Table 1
Summary of the pharmacokinetic parameter estimates used during Monte Carlo simulations[3–8]

Antibiotics	Parameters Mean (SD)			
	CL_T (L/h)	V_c (L)	K_{12} (h^{-1})	K_{21} (h^{-1})
Ceftriaxone	2.48 (0.7)	5.9 (1.3)	2.58 (1.4)	1.02 (0.5)
Ceftazidime	5.57 (1.9)	4.67 (1.2)	4.99 (3.1)	2.2 (0.8)
Cefepime	6.04 (0.4)	22.97 (15.6)	11.2 (8.1)	35.63 (19.5)
Imipenem	10.0 (2.1)	8.89 (4.8)	1.35 (0.9)	1.83 (1.3)
Meropenem	13.96 (8.9)[b]	13.25 (4.9)	1.55 (0.6)	1.48 (0.3)
Doripenem	14.5 (23.6)[c]	8.29 (0.9)	1.34 (1.0)	1.05 (1.1)

CL_T; total body clearance, V_c; volume of distribution in the central compartment, K_{12}; transfer rate constant from the central compartment to the peripheral compartment, K_{21}; transfer rate constant from the peripheral compartment to the central compartment.

Probability of target attainment (PTA); In Monte Carlo simulations, the probability that at least a specific value of a pharmacodynamic index (e.g. 30% *f*T>MIC) is achieved at a certain (minimum inhibitory) concentration.[14]

**The Cumulative fraction of response (CFR)*; the expected population probability of target attainment for a specific drug dose and a specific population of microorganisms.[14]

This study was approved by the Siriraj Institutional Review Board.

3. Results

The MIC_{50}, MIC_{90} and range of MICs for each of the study antibiotics against the four Gram-negative bacteria are displayed in Table 2. Against the Enterobacteriaceae the cephalosporin MICs are shifted to the right indicating a loss of potency relative to that of the carbapenems. Interpretation of these data according to the current susceptibility breakpoints for the cephalosporins ranged from 60% for ceftriaxone to 86% susceptible for cefepime, whereas the carbapenems displayed >97% susceptibility (Table 3). As a result of the MIC distributions for the *E. coli* and *K. pneumoniae* among the cephalosporin treatments examined only the 2 g q8 h regimens of ceftazidime and cefepime provided high CFRs (Table 4). In contrast, all the carbapenem regimens displayed CFRs >95% for these organisms.

When considering *P. aeruginosa* as the target pathogen, cefepime and ceftazidime demonstrated higher % susceptibility (82-83%) relative to that of the carbapenems (61-69%); however, when considering the pharmacodynamic profile and dosing regimens only doripenem 2 g q8 h (4 h PI) achieved an optimal CFR (92%) against this organism (Tables 3 and 4). As a result of the low potency (i.e., susceptibilities of 16-22%) of all tested antibiotics against *A. baumannii*, none of the cephalosporin or carbapenem regimens investigated achieved CFRs > 65%.

Table 2
MIC_{50}, MIC_{90} of all antibiotics against *E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii*

Organisms/Antibiotics	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
K. pneumoniae			
DOR	< 0.008 - 16	0.023	0.032
MEM	0.008 - 8	0.023	0.047
IPM	0.032 - 8	0.125	0.19
FEP	0.008 - > 256	0.032	16
CAZ	0.032 - > 256	0.19	32
CRO	< 0.008 - 32	0.064	>32
E. coli			
DOR	0.008 - 8	0.016	0.023
MEM	0.008 - 8	0.016	0.032
IPM	0.032 - 16	0.125	0.19
FEP	< 0.008 - > 256	0.047	16
CAZ	0.016 - > 256	0.19	16
CRO	< 0.008 - 32	0.064	>32
P. aeruginosa			
DOR	0.016 - 32	0.25	>32
MEM	0.016 - 32	0.5	>32
IPM	0.064 - 32	1	>32
FEP	0.25 - > 256	1.5	>256
CAZ	0.5 - > 256	1	>256
A. baumannii			
DOR	0.032 - 32	>32	>32
MEM	0.125 - 32	>32	>32
IPM	0.125 - 32	>32	>32
FEP	0.5 - > 256	64	>256

DOR; doripenem, MEM; meropenem, IPM; imipenem, FEP; cefepime, CAZ; ceftazidime, CRO; ceftriaxone.

Table 3
The susceptibility of antibiotics against *E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii* (250 isolates for each organism)

Organisms	% susceptible to antimicrobial agents					
	DOR	MEM	IPM	FEP	CAZ	CRO
K. pneumoniae	98.8	98.4	97.6	86	69.2	67.2
E. coli	99.6	99.6	99.6	84.8	74.4	60.4
P. aeruginosa	68.8	62	61	82.7	82.4	NA
A. baumannii	17.2	16.4	16	21.6	NA	NA

DOR; doripenem, MEM; meropenem, IPM; imipenem, FEP; cefepime, CAZ; ceftazidime, CRO; ceftriaxone.

Table 4
Summary of cumulative fraction of response (CFR) for selected intravenous antibiotic regimens against *E. coli*, *K. pneumoniae*, *A. baumannii, and P. aeruginosa*.

Antibiotic Regimen (infusion duration)[a]	CFR (%)[b]			
	EC	*KP*	*AB*	*PA*
ceftriaxone[c]				
1g q24h	60.1	66.5	NA	NA
2g q24h	60.2	66.9	NA	NA
ceftazidime[c]				
1g q8h	75.6	72.4	NA	79.8
2g q8h	62.4	85.1	NA	85
2g q8h (3 hours)	95	88.7	NA	86.1
cefepime[c]				
2g q12h	84.1	84.1	19.2	75.8
2g q8h	88.3	91.1	23.6	80
2g q8h (3 hours)	90.1	92.7	25.2	82
imipenem[d]				
0.5g q8h	96.1	95.1	15.6	53.8
0.5g q6h	97.7	97.2	16	59.3
1g q8h	99.3	99.1	16.3	63.9
1g q8h (3 hours)	99.6	99.9	16.7	70.7
meropenem[d]				
1g q8h	99.8	99.6	17	65.5
1g q8h (3 hours)	99.9	99.8	19.3	70.6
2g q8h	99.9	99.9	24.2	72.4
2g q8h (3 hours)	100	100	35.6	79.5
doripenem[d]				
0.5g q8h (1 hour)	99.3	98.6	17.3	70
0.5g q8h (4 hours)	99.8	99.6	18.7	78.1
1g q8h (1 hour)	99.7	99.3	27	78.6
1g q8h (4 hours)	99.9	99.8	32.1	84.3
2g q8h (1 hour)	99.8	99.6	49.1	84.6
2g q8h (4 hours)	100	99.9	64.1	92.3

q_h = every __ hours.
[a] All antibiotics simulated as 0.5 hour infusions unless noted after dosing regimen.
[b] CFR is reported as a percent of 5,000 simulated patients.
[c] Pharmacodynamic target was 50% freeT>MIC.
[d] Pharmacodynamic target was 40% freeT>MIC.
NA; Not appropriate to performed

4. Discussion

Consistent with the increasing prevalence of drug-resistant Gram-negative bacteria worldwide, the present study demonstrated similar tendencies for *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* among isolates collected from patients admitted to a large Thai teaching hospital. In the absence of novel antibiotics with activity against such organisms, it is critical to understand how dosing regimen selection may affect the ability of antibiotics to achieve bactericidal exposure against pathogens with increasing MICs. Herein, we present the results of a pharmacodynamic profiling study designed to evaluate the currently available intravenous β-lactam antibiotics against four of the most frequently isolated Gram-negative organisms in the hospital setting.

E. coli and *K. pneumoniae* displayed reduced susceptibility to the most commonly utilized cephalosporins, ceftriaxone and ceftazi-

dime, while these organisms showed a much higher susceptibility profile to cefepime. While this observation might be due to the higher intrinsic activity of cefepime, it should also be noted that unlike ceftriaxone and ceftazidime, the institutional use of cefepime at Siriraj hospital has been historically low due to the higher acquisition cost of this product. Due to its reduced potency, both the 1 and 2 g daily doses of ceftriaxone, the most commonly utilized empirical treatment for suspected *E. coli* based infections at the institution showed an unacceptably low CFR of 60%. Based on the results of this pharmacodynamic analysis the use of ceftriaxone for the empirical treatment of hospital-acquired infection suspected to be due to *E. coli* should be avoided. As a result of its potency and the use of an extended infusion time, cefepime of 2 g every 8 h with 3-hour PI achieved optimal CFR against both *E. coli* and *K. pneumoniae* (90% & 92%, respectively), whereas a similar regimen of ceftazidime, 2 g every 8 h with 3-hour PI, achieved sufficiently high CFRs only against *E. coli*. Unlike the cephalosporins, all of the standard, high dosage & PI regimens of carbapenems achieved optimal CFR against *E. coli* and *K. pneumoniae*.

Unlike Enterobacteriaceae, the non-fermenters displayed a very different pharmacodynamic profile to the test agents investigated. As would be expected from the MIC distribution of *A. baumannii* against both the cephalosporin and the carbapenems, none of the regimens examined in the present study produced optimal CFRs. While the CFRs for the *P. aeruginosa* were higher than that observed for *A. baumannii*, the most aggressive doing regimens of cefepime and ceftazidime of 2 g every 8 h with 3-hour PI only approached 82 and 86%, respectively. When considering the carbapenems only the doripenem dose of doripenem 2 g q8 h (4 h PI) delivered a CFR above 90% for *P. aeruginosa*. These data highlight the challenges facing clinicians when attempting to optimize the pharmacodynamic profile of these commonly utilized parenteral β-lactams agents against these prominent nosocomial non-fermenting Gram-negative pathogens.

The data derived from our current investigation are very similar to the observations reported previously from the Asia-Pacific region regarding the both the Enterobacteriaceae and non-fermenters.[15] When specifically focusing on *P. aeruginosa* due to the prevalence and multi-drug resistance profile of this organism it is important to note that only the high prolonged infusion dose of doripenem reliably produce a CFR in excess of the 90% target value.[15]

When considering the currently defined β-lactam pharmacodynamic profiles in this Thai tertiary care institution it is interesting to note the resemblance of these data to not only that of the Asia-Pacific region but other analysis conducted using isolates collected in Europe, South America and the United States.[15–19] When taken collectively these global data show that the utilization of high dose β-lactams administered using the prolonged infusion technique enhances the pharmacodynamic profile of all agents, however, it also displays the relatively poor target attainment achieved for an increasing portion of the organisms studied due to escalating resistance. While clinicians should advocate for pharmacodynamically optimized regimens, escalating MIC values are increasing circumventing this optimization process despite the utilization of high dose therapies.

While these Thai data appear to be similar to that reported from across the globe, it must be recognized that data derived from this university hospital or any other single institution may not be fully representative of all institutions due to variations in the underlying diagnosis or co-morbid conditions of the patients served as well as antibiotic utilization. Additionally it should also be recognized that the MICs derived in the current analysis were obtained from clinical isolates sent to the laboratory for work-up without differentiating between infection and colonization; however, this collection did represent a sample of organisms with the potential to cause serious infections in the nosocomial setting.

In conclusion, while surveillance data may broadly guide the physician to select more appropriate empirical antibiotic regimens based on laboratory defined criteria, pharmacodynamic assessments such as the one derived from this Thai institution provide additional insights into dosing strategies that may further optimize drug exposure in an effort to maximize the probability of microbiologic and clinical success. As such, the application of known pharmacodynamic principles for the β-lactams should be routinely utilized clinical practice when considering empiric dosing regimens in an attempt to improve the probability of treatment success for Gram-negative bacterial infections.

Conflict of interest: Drs. Koomanachai and Kiratisin participate on the speaker bureau of Takeda and MSD. Dr. Nicolau is on the speaker bureau and has received grant support from MSD. The other authors have no conflict of interest associated to this article.

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