Pharmacodynamic profiling of antimicrobials against Gram-negative respiratory isolates from Canadian hospitals

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BACKGROUND: With diminishing antimicrobial potency, the choice of effective empirical therapy has become more challenging. Thus, the pharmacodynamic evaluation of potential therapies is essential to identify optimal agents, doses and administration strategies.
METHODS: Monte Carlo simulation was conducted for standard and/or prolonged infusion regimens of cefepime, ceftazidime, ceftriaxone, ciprofloxacin, doripenem, ertapenem, meropenem and piperacillin/tazobactam. Minimum inhibitory concentrations were obtained for *Escherichia coli* (n=64 respiratory isolates), *Enterobacter cloacae* (n=53), *Klebsiella pneumoniae* (n=75) and *Pseudomonas aeruginosa* (n=273) throughout Canada. The cumulative fraction of response (CFR) was calculated using bactericidal targets for each regimen against each species. A CFR ≥90% was defined as optimal.
RESULTS: All cefepime, doripenem, ertapenem and meropenem regimens achieved optimal exposures against Enterobacteriaceae, whereas target attainment was organism and dose dependent for the other agents. Prolonged infusion doripenem and meropenem 1 g and 2 g every 8 h, along with standard infusion doripenem and meropenem 2 g every 8 h, were the only regimens to attain optimal exposures against *P aeruginosa*. Ciprofloxacin had the lowest CFR against *P aeruginosa*, followed by cefepime. Among the *P aeruginosa* isolates collected in the intensive care unit (ICU) compared with the wards, differences of 0.5% to 10% were noted in favour of non-ICU isolates for all agents; however, marked differences (10% to 15%) in CFR were observed for ciprofloxacin in favour of ICU isolates.
CONCLUSION: Standard dosing of cefepime, doripenem, ertapenem and meropenem has a high likelihood of obtaining optimal pharmacodynamic indexes against these Enterobacteriaceae. For *P aeruginosa*, aggressive treatment with high-dose and/or prolonged infusion regimens are likely required to address the elevated resistance rates of respiratory isolates from Canada.

Key Words: *Canada; Gram negative; Monte Carlo simulation; Pharmacodynamics; Respiratory*

Le profil pharmacodynamique des antimicrobiens contre les isolats respiratoires Gram négatif des hôpitaux canadiens

HISTORIQUE : Puisque la puissance des antimicrobiens diminue, il est plus difficile de choisir une thérapie empirique efficace. Il est donc essentiel de procéder à l'évaluation pharmacodynamique des thérapies potentielles afin de déterminer les agents optimaux, les doses et les stratégies d'administration.
MÉTHODOLOGIE : Les chercheurs ont procédé à une simulation de Monte Carlo sur des schémas standards ou prolongés de perfusion de céfépime, de ceftazidime, de ceftriaxone, de ciprofloxacine, de doripénem, d'ertapénem, de méropénem et de pipéracilline-tazobactam. Ils ont obtenu les concentrations inhibitrices minimales à l'égard de l'*Escherichia coli* (n=64 isolats respiratoires), de l'*Enterobacter cloacae* (n=53), du *Klebsiella pneumoniae* (n=75) et du *Pseudomonas aeruginosa* (n=273) partout au Canada. Ils ont calculé la fraction cumulative de réponse (FCR) au moyen des cibles bactéricides de chaque posologie contre chaque espèce. La FCR optimale était définie comme égale ou supérieure à 90 %.
RÉSULTATS : Toutes les posologies de céfépime, de doripénem, d'ertapenem et de méropénem ont assuré une exposition optimale contre les entérobactériacées, mais pour ce qui est des autres agents, l'atteinte de la cible était fonction de l'organisme et de la dose. Les seules posologies à garantir une exposition optimale contre le *P aeruginosa* étaient une perfusion prolongée de 1 g et de 2 g de doripénem et de méropénem toutes les huit heures, ainsi qu'une perfusion standard de 2 g de doripénem et de méropénem toutes les huit heures. La ciprofloxacine présentait la FCR la plus faible contre le *P aeruginosa*, suivie de la céfépime. Parmi les isolats de *P aeruginosa* prélevés à l'unité de soins intensifs (USI) par rapport à ceux prélevés dans les unités d'hospitalisation, ils ont remarqué des différences de 0,5 % à 10 % en faveur des isolats prélevés hors de l'USI pour tous les agents. Cependant, ils ont observé des différences marquées (10 % à 15 %) de la FCR de la ciprofloxacine en faveur des isolats prélevés à l'USI.
CONCLUSION : La dose standard de céfépime, de doripénem, d'ertapénem et de méropénem s'associe à une forte probabilité d'indices pharmacodynamiques optimaux contre ces entérobactériacées. Dans le cas du *P aeruginosa*, un traitement dynamique au moyen de fortes doses ou de perfusions prolongées s'imposera peut-être pour contrer le taux de résistance élevé des isolats respiratoires du Canada.

Gram-negative bacilli are often implicated as causative pathogens in pneumonia (1). Unfortunately, resistance rates among Gram-negative pathogens are rising, and infections due to these resistant strains have been associated with increased mortality, longer hospital stays and higher hospital costs (2). As resistance rates increase, the effective antimicrobial armamentarium against these pathogens dwindles (3), and antimicrobial surveillance becomes vital in determining the role of various antibiotics in the treatment of serious Gram-negative infections. Moreover, it has been found that inadequate empirial therapy is associated with increased patient morbidity and mortality (4). For these reasons, it is prudent that clinicians prescribe antimicrobial regimens that have a high likelihood of achieving microbiological success until susceptibilities are known and de-escalation can occur.

The ability of an antimicrobial dosing regimen to attain bactericidal exposures is often predictive of microbiological response. Although microbiological success does not always equate to clinical success, considering it does not take into account host or process factors, previous pharmacodynamic modelling predictions have shown a correlation between microbiological and clinical success (5,6). As

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TABLE 1
MIC_{50}, MIC_{90} and percentage of susceptibility (% S) of respiratory *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolates collected in Canada in 2009

	E cloacae (n=53)		*E coli* (n=64)		*K pneumoniae* (n=75)		*P aeruginosa* (n=273)		
Antimicrobial	MIC_{50}	% S	MIC_{50}	% S	MIC_{50}	% S	MIC_{50}	MIC_{90}	% S
Cefepime	0.25	100	0.25	93.8	0.25	94.7	4	16	75.5
Ceftazidime	0.5	85.0	0.25	86.0	0.25	94.7	4	32	78.0
Ceftriaxone	0.25	75.5	0.25	82.8	0.25	94.7	32	>64	25.3
Ciprofloxacin	0.06	96.2	0.06	70.3	0.06	90.7	0.5	8	65.2
Doripenem	0.03	98.1 (98.1)	0.03	100 (100)	0.03	100 (100)	0.5	8	82.4
Ertapenem	0.03	98.1 (88.7)	0.03	100 (96.9)	0.03	100 (94.6)	8	32	NT
Meropenem	0.03	100 (98.1)	0.03	100 (100)	0.3	100 (100)	0.5	8	85.3
Piperacillin/ tazobactam	2	88.7	2	98.4	4	96.0	4	>64	89.0

All minimum inhibitory concentration (MIC) values required to inhibit the growth of 50% and 90% of organisms (MIC_{50} and MIC_{90}) are expressed as µg/mL. % S calculated for each carbapenem against E coli, K pneumoniae *and* E cloacae *using new breakpoints are provided in parentheses, where applicable. NT Not tested*

such, Monte Carlo simulation, an interpretation of in vitro potency and pharmacokinetics, has been used to analyze the ability of various antimicrobial dosing regimens to achieve maximal bactericidal pharmacodynamic exposures against target pathogens.

The objective of the current PASSPORT (Probability of target attainment of Antibacterial agents Studied for Susceptibility and Pharmacodynamic Optimization in Regional Trials) was to use pharmacodynamic modelling techniques to assess the profile of a variety of dosing regimens for common intravenous antibiotics against contemporary *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolates collected in Canada during 2009.

METHODS

Microbiology and susceptibility testing

A total of 53 *E cloacae*, 64 *E coli*, 75 *K pneumoniae* and 273 *P aeruginosa* nonduplicate respiratory isolates were collected in the Canadian Ward (CANWARD) surveillance study (www.can-r.ca). Each site submitted unique (one organism per infection site per patient), consecutive, clinically significant isolates during 2009. The minimum inhibitory concentrations (MICs) were assessed using broth microdilution according to the Clinical and Laboratory Standards Institute (CLSI)-defined methodology, and were classified as susceptible, intermediate or resistant according to CLSI interpretive criteria for each antimicrobial, if available. Otherwise, the United States Food and Drug Administration susceptibility breakpoints were used. New breakpoints for the carbapenems against Enterobacteriaceae were approved by the CLSI in 2010. The susceptibility breakpoints were changed to ≤1 µg/mL for doripenem and meropenem, and to ≤0.25 µg/mL for ertapenem. Per cent susceptibility was also calculated and reported for comparison using these new breakpoints.

Antimicrobials

Antimicrobials were included in the pharmacodynamic model if they had comparative MIC data available from CANWARD. The following intravenous regimens were simulated, which included approved regimens as well as off-label high-dose, prolonged and continuous infusion regimens:

- Cefepime 1 g every 6 h and every 8 h (0.5 h and 3 h infusions), 1 g and 2 g every 12 h (0.5 h infusion), and 2 g every 8 h (0.5 h and 3 h infusions).
- Ceftazidime 1 g and 2 g every 8 h (0.5 h and 3 h infusions).
- Ceftriaxone 1 g and 2 g every 24 h (0.5 h infusion).
- Ciprofloxacin 0.4 g every 8 h and every 12 h (1 h infusion).
- Doripenem 0.5 g, 1 g and 2 g every 8 h (1 h and 4 h infusions).
- Ertapenem 1 g every 24 h (0.5 h infusion).
- Meropenem 0.5 g every 6 h (0.5 h and 3 h infusions); 0.5 g, 1 g and 2 g every 8 h (0.5 h and 3 h infusions).
- Piperacillin/tazobactam 3.375 g and 4.5 g every 6 h and every 8 h (0.5 h infusion); 3.375 g every 8 h (4 h infusion); 4.5 g every 6 h (3 h infusion); and 9 g, 13.5 g and 18 g every 24 h (continuous infusion).

Monte Carlo simulation

Steady-state exposures were determined, as previously described (7), for each antimicrobial regimen using serum pharmacokinetic parameters obtained from published population pharmacokinetic studies of infected and/or critically ill adult patients (8-15). The pharmacokinetic parameters used for each antimicrobial are available from a previous PASSPORT publication (16), with the exception of ceftriaxone (7). A 5000-patient Monte Carlo simulation (Crystal Ball 2000, Decisioneering Inc, USA) was conducted for each regimen as previously described (7,16). The volume of the central compartment, total body clearance, k_{21} and k_{12} were assumed to follow log-Gaussian distributions, while the unbound fraction was assumed to follow a uniform distribution in which any value within the simulated range had an equal probability of occurring. The Monte Carlo simulation determined the probability of a simulated patient achieving the predefined pharmacodynamic target at a specific MIC dilution. This is referred to as the probability of target attainment (PTA), which was calculated over a range of doubling MICs between 0.008 µg/mL and 256 µg/mL. The pharmacodynamic targets were defined as the percentage of the dosing interval in which the free drug concentration is above the MIC ($fT>MIC$) – at least 40% for carbapenems, 50% for penicillins and 60% for cephalosporins (17,18). For ciprofloxacin, a ratio of the area under the concentration curve to MIC of at least 125 was the pharmacodynamic target used (19).

PTAs for each antimicrobial regimen were used to determine the cumulative fraction of response (CFR) against the entire bacterial population. The regimen's simulation-derived PTA was multiplied by the percentage of isolates at each MIC dilution and summed to obtain the CFR. A CFR ≥90% was considered to be optimal against the bacterial population.

RESULTS

The MIC required to inhibit the growth of 50% and 90% of organisms, as well as the susceptibility rates for all respiratory isolates, are shown in Table 1. By using the new carbapenem breakpoints, the per cent susceptibility changed minimally (<2%) for doripenem and meropenem against all three Enterobacteriaceae; however, for ertapenem, a larger change (3% to 10%) in susceptibility was noted. Piperacillin/tazobactam had the highest susceptibility rate (89.0%) against *P aeruginosa*, followed closely by meropenem (85.3%) and doripenem (82.4%).

A summary of CFRs for all antimicrobial regimens against *E cloacae*, *E coli*, *K pneumoniae* and *P aeruginosa* are presented in Table 2.

TABLE 2
Cumulative fraction of response (CFR) of intravenous antimicrobial regimens against *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*

Antibiotic regimen (infusion duration)	CFR,%			
	E cloacae	*E coli*	*K pneumoniae*	*P aeruginosa*
Cefepime				
1 g q 12 h*†	95.6	90.7	92	56
2 g q 12 h*†	97.4	93.6	93.9	70.9
1 g q 8 h	98.2	93.8	94.4	68.3
2 g q 8 h*†	99.2	96.3	96	80.7
1 g q 6 h	99.2	95.4	95.5	76
1 g q 8 h (3 h)	99.2	94.9	95.3	72.8
2 g q 8 h (3 h)	99.7	97.1	96.6	84.6
1 g q 6 h (3 h)	99.8	96.3	96	81.3
Ceftazidime				
1 g q 8 h	85	86.2	94.7	75
2 g q 8 h*†	87.3	89.1	95.5	85.1
1 g q 8 h (3 h)	85.3	87	94.8	81.1
2 g q 8 h (3 h)	91.8	93.2	97.1	91.5
Ceftriaxone				
1 g q 24 h*	73	81.7	94.1	NT
2 g q 24 h*	76.9	84.1	94.7	NT
Ciprofloxacin				
0.4 g q 12 h (1 h)	96.2	66.8	88.1	45.8
0.4 g q 8 h (1 h)*†	96.2	67.5	89	52.8
Doripenem				
0.5 g q 8 h (1 h)	97.4	99	98.8	79.8
1 g q 8 h (1 h)	98.5	99.6	99.4	86.5
2 g q 8 h (1 h)	99.2	99.8	99.7	91.6
0.5 g q 8 h (4 h)	99.1	100	100	89.4
1 g q 8 h (4 h)	99.7	100	100	94.3
2 g q 8 h (4 h)	99.9	100	100	97.8
Ertapenem				
1 g q 24 h	96.2	99.6	99.3	NT
Meropenem				
0.5 g q 8 h	99.4	100	100	78
0.5 g q 6 h*	99.7	100	100	82.2
1 g q 8 h*†	99.7	100	100	84.5
2 g q 8 h	99.9	100	100	90.2
0.5 g q 8 h (3 h)	99.9	100	100	85.2
0.5 g q 6 h (3 h)	100	100	100	87.9
1 g q 8 h (3 h)	100	100	100	90.3
2 g q 8 h (3 h)	100	100	100	94.9
Piperacillin/tazobactam				
3.375 g q 8 h	80.7	89.2	81.1	67.4
4.5 g q 8 h*	83.4	91.5	85.4	71.7
3.375 g q 6 h	87	94.8	90.3	76.3
4.5 g q 6 h*	89.4	96.1	92.9	79.2
3.375 g q 8 h (4 h)	90.6	98	96	81.9
4.5 g q 6 h (3 h)	94.8	98.4	97.6	85.1
9 g q 24 h (CI)	89.2	97.4	95	80.8
13.5 g q 24 h (CI)	92.4	98.3	96.7	83.1
18 g q 24 h (CI)	94.5	98.4	97.5	84.8

*All antibiotics simulated as 0.5 h infusion unless noted after dosing regimen. *Recommended by the Association of Medical Microbiology and Infectious Disease Canada guidelines for the treatment of hospital-acquired pneumonia for those with risk factors for multidrug-resistant pathogens, suspected* P aeruginosa *or severe illness. †Recommended by the Infectious Disease Society of America for the treatment of hospital-acquired pneumonia for those with late-onset disease or risk factors for multidrug-resistant pathogens. CI Continuous infusion; NT Not tested; q Every*

Cefepime, doripenem, ertapenem and meropenem at standard doses were able to to achieve optimal exposures against Enterobacteriaceae species; however, there was discordance with regard to which standard dosing regimens obtained optimal CFRs for ceftazidime, ceftriaxone, ciprofloxacin and piperacillin/tazobactam against the three Enterobacteriaceae**.** The percentage of susceptibility was in agreement with the antimicrobial's ability to attain optimal exposures.

Against *P aeruginosa*, increasing the dose and/or prolonging the infusion duration had the greatest predicted impact on the PTA. The only regimens that obtained optimal exposures were high-dose, standard infusion doripenem and meropenem (2 g every 8 h), prolonged infusion of doripenem and meropenem (1 g and 2 g every 8 h), and prolonged infusion ceftazidime (2 g every 8 h). Ciprofloxacin has the lowest predicted CFR (45.8% to 52.8%) of all the tested antimicrobials against this *P aeruginosa* population. When comparing isolates collected in the intensive care unit (ICU) with those collected outside of the ICU (Table 3), the CFRs were generally in favour of the non-ICU isolates (0.5% to 10%). Interestingly, for ciprofloxacin, there were distinct differences (approximately 10% to 15%) in CFR, which were in favour of isolates collected within the ICU.

DISCUSSION

Resistance among several Gram-negative pathogens continues to be a growing issue associated with worse clinical outcomes (20,21). With few novel antimicrobials on the horizon (3), pharmacodynamic optimization of currently available agents is essential to maximize efficacy and minimize further development of resistance. The present study evaluated numerous intravenous treatment options from the pharmacodynamic perspective to identify optimal empirical agents and dosing regimens against core Canadian respiratory pathogens. The design of the study predicted microbiological success by calculating the CFR using the pharmacodynamic properties of each included antimicrobial.

Minimal studies have been undertaken to determine the target attainment of antimicrobials against Gram-negative pathogens in Canada (22); however, surveillance studies reporting susceptibility and resistance rates have been published (23,24). If the percentage of susceptibility was in concordance with the CFR of the standard dosing regimens against all three Enterobacteriaceae species tested, susceptibility rates should be relatively accurate at determining whether a regimen is an optimal empirical choice. Although this was true for all three Enterobacteriaceae species, the CFRs for standard dosing regimens against *P aeruginosa* were typically lower than the reported percentage of susceptibility. Of note, the MIC distributions used in this pharmacodynamic evaluation were obtained nationally from a contemporary collection of *E cloacae*, *E coli*, *K pneumoniae* and *P aeruginosa* isolates; however, individual hospital or local resistance rates might vary considerably from the national surveillance.

To attain reliable empirical therapy against *P aeruginosa* or other resistant organisms, adjustments in doses or infusion times can affect the efficacy of the beta-lactams. It has been shown that the percentage of the dosing interval in which the free drug concentration remains above the MIC of the infecting organism (*f*T>MIC) is the pharmacokinetic/pharmacodynamic parameter that best predicts efficacy (25). To optimize this parameter, and ultimately antimicrobial efficacy of the beta-lactams, prolonged infusion of 3 h to 4 h can be used rather than the standard 0.5 h to 1 h infusion. Although the susceptibility of the organism is often taken into account, the dose, infusion time and the antimicrobial MIC should be considered. While the safety and efficacy of these high doses, in conjunction with prolonged infusion, have not been evaluated in well-controlled clinical trials, data from animal and limited human studies support the safe attainment of in vivo exposures sufficient for these higher MIC organisms (26,27).

By simulating higher doses, prolonged infusions or a combination of both, an increase in predicted CFR was observed for all beta-lactam antibiotics; however, the more susceptible the population, the less of a difference dose and infusion optimization made. Accordingly, the

largest impact of dose and infusion optimization was observed against *P aeruginosa*. Despite improvements in CFR, only ceftazidime (2 g every 8 h as a 3 h infusion), doripenem (2 g every 8 h as a 1 h or 4 h infusion; 1 g every 8 h as a 4 h infusion), and meropenem (2 g every 8 h as a 0.5 h or 3 h infusion; 1 g every 8 h as a 3 h infusion) met the a priori definition of optimal against *P aeruginosa*. This necessitates the importance of aggressive empirical dosing if the patient has risk factors for *P aeruginosa* or other multidrug-resistant organisms. Additionally, the CFRs for the *P aeruginosa* isolates collected in the ICU were generally lower than the isolates collected outside of the ICU, indicating a shift to the right in MIC distributions. This, however, was not true for ciprofloxacin, which had higher CFRs in the ICU population compared with the non-ICU population. While it is not known why the ICU isolates were more susceptible to ciprofloxacin, the CFR results were consistent with the ciprofloxacin MIC distributions for the ICU and non-ICU isolates.

When comparing CFRs with the recommended treatments for hospital-acquired pneumonia, some recurring themes become evident. In general, regardless of whether evaluating using the Infectious Disease Society of America (28) or the Association of Medical Microbiology and Infectious Disease Canada (AMMI) guidelines (1), the recommended antimicrobials and dosing regimens are sufficient to attain reliable coverage, with few caveats against the Enterobacteriaceae species, but not *P aeruginosa*. Even the higher or more frequent doses recommended by AMMI for severe illness or the most aggressive doses endorsed by the Infectious Disease Society of America fall short of obtaining a CFR ≥90% against *P aeruginosa*. This reiterates the need for empirically optimizing an antimicrobial's pharmacodynamics for individuals with risk factors for multidrug-resistant pathogens including pseudomonas. Additionally, although ciprofloxacin is often thought to be an antipseudomonal fluoroquinolone and is recommended as monotherapy by AMMI for patients with mild to moderate hospital-acquired pneumonia at risk for resistant pathogens, it had the lowest CFR even when given three times daily (52.8%). Moreover, ciprofloxacin failed to attain reliable coverage against *E coli* (0.4 g every 12 h, [66.8%]; 0.4 g every 8 h [67.5%]).

The present pharmacodynamic evaluation was intended to offer guidance to clinicians as they initiate empirical therapy for respiratory infections in Canada. These data emphasize that the currently recommended antimicrobial dosing regimens generally attain acceptable exposures to achieve the requisite pharmacodynamic targets against the Enterobacteriaceae species; however, they fall short of obtaining optimal bactericidal exposures against *P aeruginosa*. Higher dosages in conjunction with prolonged infusion improved the activity of all beta-lactams in achieving their pharmacodynamic target against all tested organisms; however, the dose optimization made the largest impact on *P aeruginosa* isolates. This emphasizes the importance of aggressive dosing of appropriate antibiotics when patients are at risk for multidrug-resistant pathogens including *P aeruginosa*.

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TABLE 3
Comparison of the cumulative fraction of response (CFR) for antibiotic regimens against *Pseudomonas aeruginosa* respiratory isolates collected in the ICU compared with those collected outside of the ICU

	CFR,%	
	P aeruginosa	
Antibiotic regimen (infusion duration)	ICU (n=81)	Non-ICU (n=192)
Cefepime		
1 g q 12 h*†	56.1	56
2 g q 12 h*†	70.5	71
1 g q 8 h†	68	68.4
2 g q 8 h*†	80.1	81
1 g q 6 h	75.5	76.2
1 g q 8 h (3 h)	72.4	72.9
2 g q 8 h (3 h)	83.9	84.9
1 g q 6 h (3 h)	80.7	81.5
Ceftazidime		
1 g q 8 h	69.3	77.4
2 g q 8 h*†	80	87.2
1 g q 8 h (3 h)	75.2	83.6
2 g q 8 h (3 h)	88.3	92.9
Ciprofloxacin		
0.4 g q 12 h (1 h)	54.1	42.4
0.4 g q 8 h (1 h)*†	61.2	49.3
Doripenem		
0.5 g q 8 h (1 h)	77.3	80.8
1 g q 8 h (1 h)	84.8	87.2
2 g q 8 h (1 h)	90.5	92
0.5 g q 8 h (4 h)	87.5	90.2
1 g q 8 h (4 h)	93.4	94.7
2 g q 8 h (4 h)	97.5	97.9
Meropenem		
0.5 g q 8 h	71.8	80.6
0.5 g q 6 h*	76.7	84.6
1 g q 8 h*†	79.3	86.7
2 g q 8 h	86	92
0.5 g q 8 h (3 h)	79.9	87.5
0.5 g q 6 h (3 h)	83.1	89.9
1 g q 8 h (3 h)	85.8	92.1
2 g q 8 h (3 h)	91.6	96.2
Piperacillin/tazobactam		
3.375 g q 8 h (0.5 h)	59.2	70.9
4.5 g q 8 h (0.5 h)*	64	75
3.375 g q 6 h (0.5 h)	69	79.5
4.5 g q 6 h (0.5 h)*†	72.5	82.1
3.375 g q 8 h (4 h)	75.2	84.8
4.5 g q 6 h (3 h)	80.1	87.2
9 g q 24 h (CI)	83.6	83.8
13.5 g q 24 h (CI)	76.9	85.7
18 g q 24 h (CI)	79.6	86.9

*All antibiotics simulated as 0.5 h infusion unless noted after dosing regimen. *Recommended by the Association of Medical Microbiology and Infectious Disease Canada guidelines for the treatment of hospital-acquired pneumonia for those with risk factors for multidrug-resistant pathogens, suspected* P aeruginosa *or severe illness; †Recommended by the Infectious Disease Society of America for the treatment of hospital-acquired pneumonia for those with late-onset disease or risk factors for multidrug-resistant pathogens. CI Continuous infusion; ICU Intensive care unit; q Every*

REFERENCES

1. Rotstein C, Evans G, Born A, et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. Can J Infect Dis Med Microbiol 2008;19:19-53.
2. Slama TG. Gram-negative antibiotic resistance: There is a price to pay. Crit Care 2008;12(Suppl 4):S4.
3. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Disease Society of America. Clin Infect Dis 2009;49:1-12.

4. Kollef MH. Inadequate antimicrobial treatment: An important determinant of outcome for hospitalized patients. Clin Infect Dis 2000;31:S131-8.
5. Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of antiinfectives with pharmacodynamics and Monte Carlo simulation. Pediatr Infect Dis J 2003;22:982-92
6. Kuti JL, Ong C, Lo M, Melnick D, Soto N, Nicolau DP. Comparison of probability of target attainment calculated by Monte Carlo simulation with meropenem clinical and microbiological response for the treatment of complicated skin and skin structure infections. Int J Antimicrob Agents 2006;28:62-8.
7. DeRyke CA, Kuti JL, Nicolau DP. Pharmacodynamic target attainment of six β-lactams and two fluoroquinolones against *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella* species collected from United States intensive care units in 2004. Pharmacotherapy 2007;27:333-42.
8. Ikawa K, Morikawa N, Uehara S, et al. Pharmacokinetic-pharmacodynamic target attainment analysis of doripenem in infected patients. Int J Antimicrob Agents 2009;33:276-9.
9. Crandon JL, Ariano RE, Zelenitsky SA, Nicasio AM, Kuti JL, Nicolau DP. Optimization of meropenem dosage in the critically ill population based on renal function. Intens Care Med 2011;37:632-8.
10. Young RJ, Lipman J, Gin T, Gomersall CD, Joynt GM, Oh TE. Intermittent bolus dosing of ceftazidime in critically ill patients. J Antimicrob Chemother 1997;40:269-73.
11. Lodise TP, Lomaestro B, Rodvold KA, Danziger LH, Drusano GL. Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation. Antimicrob Agents Chemother 2004;48:4718-24.
12. Nicasio AM, Ariano RE, Zelenitsky SA, et al. Population pharmacokinetics of high-dose, prolonged infusion cefepime in adult critically ill patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 2009;53:1476-81.
13. Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong ELY, Gin T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 2001;47:421-9.
14. Forrest A, Ballow CH, Nix DE, Birmingham MC, Schentag JJ. Development of a population pharmacokinetic model and optimal sampling strategies for intravenous ciprofloxacin. Antimicrob Agents Chemother 1993;37:1065-72.
15. Burkhardt O, Kumar V, Katterwe D, Majcher-Peszynska J, Derendorf H, Welte T. Ertapenem in critically ill patients with early-onset ventilator associated pneumonia: Pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother 2007;59:277-84.
16. Koomanachai P, Bulik CC, Kuti JL, Nicolau DP. Pharmacodynamic modeling of intravenous antibiotics against Gram-negative bacteria collected in the United States. Clin Ther 2010;32:766-79.
17. Drusano GL. Antimicrobial pharmacodynamics: Critical interactions of 'bug and drug'. Nat Rev Microbiol 2004;2:289-300.
18. Crandon JL, Bulik CC, Kuti JL, Nicolau DP. Clinical pharmacodynamics of cefepime in patients infected with *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2010;54:1111-6.
19. Forrest A, Nix D, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37:1073-81.
20. Giamarellos-Bourboulis EJ, Papadimitriou E, Galanakis N, et al. Multidrug resistance to antimicrobials as a predominant factor influencing patient survival. Int J Antimicrob Agents 2006;27:476-81.
21. Obritsch MD, Fish DN, MacLaren R, Jung R. National surveillance of antimicrobial resistance in *Pseudomonas aeruginosa* isolates obtained from intensive care unit patients from 1993 to 2002. Antimicrob Agents Chemother 2004;48:4606-10.
22. Zelenitsky SA, Ariano RE, Zhanel GG. Pharmacodynamics of empirical antibiotic monotherapies for an intensive care unit (ICU) population based on Canadian surveillance data. J Antimicrob Chemother 2011;66:343-9.
23. Legace-Wiens PRS, DeCorby MR, Baudry PJ, Hoban DJ, Karlowsky JA, Zhanel GG. Differences in antimicrobial susceptibility in *Escherichia coli* from Canadian intensive care units based on regional and demographic variables. Can J Infect Dis Med Microbiol 2008;19:282-6.
24. Zhanel GG, MeCroby M, Laing N, et al. Antimicrobial-resistant pathogens in intensive care units in Canada: Results of the Canadian National Intensive Care Unit (CAN-ICU) Study, 2005-2006. Antimicrob Agents Chemother 2008:52:1430-7.
25. Fluckiger U, Segessenmann C, Gerber AU. Integration of pharmacokinetics and pharmacodynamics of imipenem in a human-adapted mouse model. Antimicrob Agents Chemother 1991;35:1905-10.
26. Crandon JL, Bulik CC, Nicolau DP. In vivo efficacy of 1- and 2-gram human simulated prolonged infusions of doripenem against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2009;53:4352-6.
27. Bulik CC, Quintiliani R Jr, Pope JS, et al. Pharmacodynamics and tolerability of high-dose, prolonged infusion carbapenems in adults with cystic fibrosis – A review of 3 cases. Respir Med CME 2010;3:146-9.
28. American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.