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Selection of a Surrogate Carbapenem Testing Agent for Initial Susceptibility Testing of Doripenem

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Abstract

Background: Doripenem (DOR), a broad-spectrum parenteral investigational carbapenem (CARB), has potency and pharmacokinetic and pharmacodynamic (PK/PD) features most similar to imipenem (IPM) and meropenem (MEM). Due to potential delays in commercial susceptibility (S) products post US FDA release, surrogate CARB or related markers offer immediate guidance to DOR use.

Methods: Cross-S analysis of CLSI MICs compared IPM, MEM, and ertapenem (ETP) to DOR for 7 groups of recent isolates: staphylococci (STAPH; *S. aureus* [SA] and oxacillin-susceptible coagulase-negative staphylococci (CoNS), 6304), enterococci (ESP; 3491 including 2253 *E. faecalis* [EF]), Enterobacteriaceae (ENT; 6560), *P. aeruginosa* (PSA; 1494), *Acinetobacter* spp. (ACB; 600), *H. influenzae* (HI; 109), and *S. pneumoniae* (SPN; 750). Target accuracy was ≥90% categorical agreement and ≤1.5% false-S (very major; VM) error. Candidate DOR break points were those published for other CARBs.

Results: Per CLSI interpretive guidelines, oxacillin (OXA) is the β-lactam surrogate for STAPH and ampicillin (AMP) for IPM to predict ESP-S. DOR-S is predicted with 100% agreement by OXA (STAPH), but AMP results (for all ESP or EF) produced VM error. Among CARB surrogates, MEM was the best DOR surrogate for ENT (99.7%), ACB (92.7%), and PSA (89.1%). PSA accuracy was compromised, as some IPM- intermediate/resistant (I/R) and MEM-I/R were DOR-S. Respiratory-specific ETP break points predict DOR versus HI and SPN (99.9%-100.0% accuracy).

		Error rates (%)			
Organism	Surrogate (no.)	Minor	Major	Very Major	% Absolute agreement
SA	OXA (5647)[a]	-	0.0	0.0	100.0
ESP	AMP (3491)	-	0.3	13.1[b]	86.6
ENT	MEM (6558)[a]	0.2	<0.1	0.0	99.7
	IPM (6560)	0.3	0.1	0.0	99.6
	ETP (6559)	0.4	0.4	0.0	99.2
PSA	MEM (1494)[a]	9.6	1.3	<0.1	89.1
	IPM (1494)	11.8[b]	5.8[b]	0.0	82.4
ACB	MEM (600)[a]	7.3	0.0	0.0	92.7
	IPM (600)	8.3	0.5	0.5	90.7
HI	ETP (109)[a]	0.0	0.0	0.0	100.0
SPN	ETP (750)[a]	0.1	0.0	0.0	99.9

[a]Proposed surrogate for DOR testing.
[b]Unacceptable

Conclusions: Proposed surrogate testing agents until DOR commercial systems are available provide 89.1%-100.0% absolute categorical agreement with <0.1% VM error. These include OXA for STAPH; MEM for ENT, PSA and ACB; and ETP for HI and SPN. This option is particularly attractive for centers wanting to utilize this CARB to treat indicated multidrug-R pathogens.

Introduction

To facilitate the initial introduction of a new antimicrobial agent into a medical center formulary, the determination of in vitro susceptibility can be determined by other agents in the same or a similar class. Examples of this successful application of surrogate marker testing have been the uses of levofloxacin or ciprofloxacin to predict gatifloxacin susceptibility, cefoxitin to predict cefotetan susceptibility, and most recently, vancomycin as a surrogate for dalbavancin susceptibility test results. This process has become particularly important because of delays in the availability of newly approved compounds in the panels produced by the market-dominating diagnostic products such as Vitek or Vitek 2 (bioMerieux, Hazelwood, Missouri) and MicroScan WalkAway (Dade Berhing, West Sacramento, California). In the United States, more than 80% of all antimicrobial susceptibility testing has been performed by MIC methods products, most by automated devices.

Doripenem, a novel parenteral investigational carbapenem, has an expanded spectrum and potency when compared with currently marketed agents of the same class, especially when tested in vitro against *Pseudomonas aeruginosa* and some other non-fermentative Gram-negative bacilli. This investigational carbapenem appears safe, less likely to select resistances, possesses pharmacokinetic and pharmacodynamic (PK/PD) features similar to imipenem or meropenem, and has developed methods for in vitro susceptibility testing. Because of the urgent need for therapeutic antimicrobials active against *Acinetobacter baumannii* and *P. aeruginosa*, doripenem, if approved by the US Food and Drug Administration (US-FDA), could be a valuable compound among the available carbapenems.

In this report, the results of simultaneously testing doripenem, ertapenem, imipenem, and meropenem by reference broth microdilution methods are summarized. Analyses of these data considered the surrogate application of an existing carbapenem to predict doripenem susceptibility against potentially indicated species or genus groups by cross-susceptibility plots. A total of 19,308 organisms were compared in these studies to validate potential surrogate guides to doripenem therapies.

Materials and Methods

- The organisms were derived from patients hospitalized in Europe and the Americas (North and South). Organism groupings studied in the cross-susceptibility validation were: oxacillin (methicillin)-susceptible *Staphylococcus aureus* (MSSA; 5647 strains), oxacillin (methicillin)-susceptible coagulase-negative staphylococci (MS-CoNS; 657 strains), *Enterococcus* spp. (3491; includes 2253 *Enterococcus faecalis*), Enterobacteriaceae (6560 strains), *P. aeruginosa* (1494 strains), *Acinetobacter* spp. (600 strains), *Haemophilus influenzae* (109 strains), and *Streptococcus pneumoniae* (750 strains).
- Cross-susceptibility of the bacterial groups primarily sought to select a doripenem surrogate agent among tested carbapenems and to minimize false-susceptible (very major) errors to ≤1.5% and false-resistant (major) errors to ≤3%, while maintaining absolute categorical agreement at ≥90%. Minor errors were defined as an intermediate result by one of the compared carbapenems. All MIC values for marketed carbapenems were compared with those of doripenem by regression statistics and by scattergram plots (see Figures 1-4). Error rates (as percentages) were determined using all organisms tested as the denominator. Categorical agreement was calculated using doripenem break point concentrations comparable with imipenem and meropenem, based on similar PK/PD parameters. Where ertapenem was used as a surrogate marker, its break points, published by the Clinical and Laboratory Standards Institute (CLSI), were utilized. Susceptibility tests were performed using reference broth microdilution methods described by the CLSI M7-A7 and M100-S17 documents. All quality-control (QC) MIC results were within CLSI-recommended ranges for six QC strains (*Escherichia coli* ATCC 25922, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *P. aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247).

Results

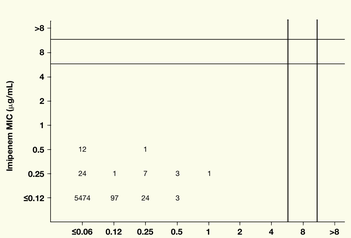
- No interpretive errors were identified using oxacillin as a surrogate for doripenem activity against staphylococci (all MIC values at ≤1 μg/mL; Table 1 and Figure 1). Also, the use of imipenem as a surrogate marker for doripenem versus MSSA (Figure 1) and MS-CoNS did not have interpretive error.

Table 1. Possible Carbapenem or Other β-lactam Surrogate Agents for Laboratory Doripenem Susceptibility Testing

		Error rates (%)			
Organism	Surrogate (no.)	Minor	Major	Very Major	% Absolute Categorical Agreement
MSSA	Oxacillin (5647)[a]	-	0.0	0.0	100.0
MS-CoNS	Oxacillin (657)[a]	-	0.0	0.0	100.0
Enterococci	Ampicillin (3491)	-	0.3	13.1[b]	86.6
Enterobacteriaceae	Meroperem (6558)[a]	0.2	<0.1	0.0	99.7
	Imipenem (6560)	0.3	0.1	0.0	99.6
	Ertapenem (6559)	0.4	0.4	0.0	99.2
P. aeruginosa	Meroperem (1494)[a]	9.6	1.3	<0.1	89.1
	Imipenem (1494)	11.8[b]	5.8[b]	0.0	82.4
Acinetobacter spp.	Meroperem (600)[a]	7.3	0.0	0.0	92.7
	Imipenem (600)	8.3	0.5	0.5	90.7
H. influenzae	Ertapenem (109)[a]	0.0	0.0	0.0	100.0
S. pneumoniae	Ertapenem (750)[a]	0.1	0.0	0.0	99.1

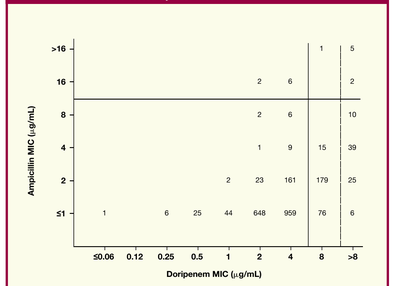
MSSA = oxacillin-susceptible *S. aureus*; CoNS = oxacillin-susceptible coagulase-negative staphylococci.
[a]Proposed surrogate marker carbapenem or penicillin for doripenem testing if doripenem diagnostic devices are not available.
[b]Unacceptable levels of error.

Figure 1. Scattergram Comparing Doripenem and Imipenem MIC Results for 5647 MSSA Tested by CLSI Methods



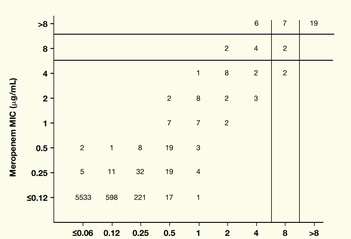
- A comment in CLSI M100-S17 states "ampicillin susceptibility can be used to predict imipenem susceptibility providing the species is confirmed to be *E. faecalis*." Table 1 and Figure 2 clearly demonstrate that doripenem susceptibility cannot be accurately predicted by ampicillin for all *Enterococcus* spp. (Table 1; 13.1% very major errors), or if only the 2253 *E. faecalis* strains were analyzed separately (Figure 2; 3.6% very major and 12.0% minor errors).

Figure 2. Scattergram Comparing Doripenem and Ampicillin MIC Results for 2253 *E. faecalis* Tested by CLSI Methods



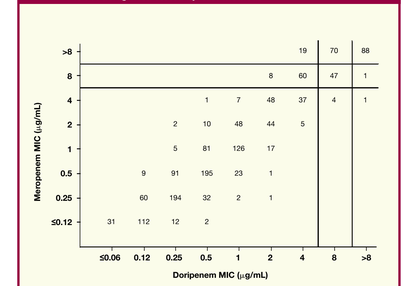
- The overall absolute categorical agreement for Enterobacteriaceae (Table 1) ranged from 99.2% (ertapenem) to 99.7% (meropenem; Figure 3). No very major errors were detected for any of the existing carbapenems (ertapenem, imipenem, and meropenem) used as surrogate markers for doripenem susceptibility.

Figure 3. Scattergram Comparing Doripenem and Meropenem MIC Results for 6558 Enterobacteriaceae Tested by CLSI Methods



- For *P. aeruginosa* (Table 1), both imipenem and meropenem could be used to predict doripenem susceptibility with only 0.0 to <0.1% very major error. Overall, error rates for imipenem (17.6%) and meropenem (10.9%) were elevated because of the greater potency of doripenem against this species. Nearly all errors were predicting doripenem as resistant (major error) or intermediate (minor error) when the actual doripenem MIC was likely to be ≤4 μg/mL (susceptible, see Figure 4).

Figure 4. Scattergram Comparing Doripenem and Meropenem MIC Results for 1494 *P. aeruginosa* Tested by CLSI Methods



- *Acinetobacter* spp. susceptibility to doripenem could be predicted with acceptable accuracy (0.0%-0.5% very major error) by either imipenem (90.7% absolute categorical agreement) or meropenem (92.7%), see Table 1. Similarly, ertapenem would be best utilized as the doripenem surrogate for *H. influenzae* and *S. pneumoniae* (Table 2) having ≥99.9% categorical confidence.

Table 2. Comparisons of Doripenem Activity With That of Ertapenem When Tested Against Key Respiratory Tract Pathogens (*S. pneumoniae* and *H. influenzae*)

		Occurrences at Doripenem MIC (μg/mL)[a]						
Organism (no. tested)	Ertapenem MIC (μg/mL)	0.06	0.12	0.25	0.5	1	2	4
H. influenzae (109)	0.5[b]	-	-	-	-	-	-	-
	0.25	-	-	-	-	-	-	
	0.12	-	-	-	-	-	-	
	≤0.06	80	18	7	4	-	-	-
S. pneumoniae (750)	4	-	-	-	-	-	1	-
	2	-	-	-	-	-	2	-
	≤1[b]	638	17	21	47	23	-	-

[a]For comparison purposes, the break point for imipenem (≤4 μg/mL) was used for doripenem when testing *H. influenzae*, and the break point for ertapenem (≤1 μg/mL as susceptible and ≥4 μg/mL as resistant) was used for *S. pneumoniae*.
[b]CLSI susceptible break points.

Conclusions

- These analyses for doripenem susceptibility, predicted by other carbapenem tests, confirm that the doripenem spectrum against these pathogen groups was equal to or greater than ertapenem, imipenem, and meropenem.
- Risks of serious categorical errors (major and very major) would be considered extremely rare for those surrogate agents (0.0%-1.4%) recommended in Table 1 and also unusual for other listed carbapenem markers (0.0%-5.8%).
- The utilization of these cited surrogate β-lactams (Table 1) to predict doripenem activity should allow its early therapeutic use against indicated species found among the 8 analysis groups.
- In contrast to the possible US FDA regulatory delays that may negatively influence MIC testing via commercial devices, the disk diffusion method can be quickly adopted by clinical microbiology laboratories by having published susceptible break points in US FDA disk and antimicrobial product package inserts.

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