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Interim susceptibility testing for ceftaroline, a new MRSA-active cephalosporin: selecting potent surrogate β-lactam markers to predict ceftaroline activity against clinically indicated species☆,☆☆

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ABSTRACT

Ceftaroline, the bio-active form of parenterally administered ceftaroline fosamil, is a unique broad-spectrum cephalosporin with in vitro and in vivo activity against methicillin-resistant *Staphylococcus aureus* and was approved for clinical use by the United States Food and Drug Administration in October 2010. In over a year since ceftaroline fosamil approval, no widely used commercial susceptibility test system has added this new compound to its product, therefore requiring use of alternative agar diffusion methods for clinical microbiology laboratories that want to test clinical isolates for ceftaroline susceptibility. An alternative strategy of applying a surrogate β-lactam class marker agent was assessed here, using results from 14,902 organisms (2008–2010) sampled in the USA. Very high and acceptable accuracy (≥99.75%) was observed for predicting ceftaroline susceptibility as follows: 1) use of imipenem or meropenem minimum inhibitory concentrations (MICs) at ≤8 μg/mL (susceptible and intermediate categories) when testing *S. aureus*; 2) use of ceftriaxone MIC at ≤2 μg/mL (susceptible and intermediate categories) when testing *Streptococcus pneumoniae* as well as other streptococci (*S. pyogenes* and *S. agalactiae*); and 3) use of ceftriaxone, or cefepime, or ceftazidime at ≤2 μg/mL (susceptible category) when testing *Haemophilus influenzae*. Only when testing indicated Enterobacteriaceae species using ceftriaxone susceptibility results did the ceftaroline-nonsusceptible errors increase (4.11%). These presented analyses offer a validated surrogate marker strategy for ceftaroline susceptibility testing, pending development and validation by the commonly used automated systems and agar diffusion commercial methods.

1. Introduction

Ceftaroline (formerly TAK-599 [prodrug fosamil form], T-91825, and PPI903M), the bio-active form of parenterally administered ceftaroline fosamil, is a broad-spectrum cephalosporin with a uniquely high binding affinity for the altered penicillin-binding protein (PBP2a) responsible for methicillin resistance among staphylococci (Ishikawa et al., 2003; Jones et al., 2010b; Sader et al., 2005; Zhanel et al., 2009). Unlike other cephalosporins that are considered inactive against methicillin-resistant *Staphylococcus aureus* (MRSA), ceftaroline has demonstrated in vitro potency and clinical success against this important pathogen (Corey et al., 2010; Zhanel et al., 2009) and has a clinical indication for use in acute bacterial skin and skin structure infections including for methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA (Corey et al., 2010; Teflaro Package Insert, 2012) as well as community-acquired bacterial pneumonia (CABP) (for MSSA, but not for MRSA) (File et al., 2010; Jones et al., 2011; Teflaro Package Insert, 2012; Zhanel et al., 2009). Therefore, the use of oxacillin and/or cefoxitin test results to predict ceftaroline resistance or susceptibility among other β-lactams does not apply and direct testing of this novel cephalosporin would be the desired method to predict clinical success per criteria approved in the United States Food and Drug Administration (US-FDA) product package insert (Teflaro Package Insert, 2012) or the recently approved criteria of the Clinical and Laboratory Standards Institute (CLSI, 2013).

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Ceftaroline MIC (μg/mL)	Imipenem MIC (μg/mL)							
	≤0.12	0.25	0.5	1	2	4	8	>8
≥4								
2	3	1	2	2	1	2	9	161
1	120	328	425	306	226	189	159	435
0.5	1210	586	399	176	64	23	15	23
0.25	3388	25	9	5	3			
0.12	295							
≤0.06	29							

Fig. 1. Scattergram of ceftaroline MIC values compared to imipenem MIC results when tested against 8619 *S. aureus* (4624 or 53.6% were MRSA) from the USA. Solid bolded horizontal and vertical lines indicate breakpoints for each agent (CLSI, 2012b, 2013; Teflaro Package Insert, 2012).

Those *Staphylococcus aureus* susceptibility criteria are a ceftaroline minimum inhibitory concentration (MIC) at ≤1 μg/mL and a zone diameter of ≥24 mm when using methods published by the CLSI (CLSI, 2012a,b, 2013). Nonsusceptible results (MIC, ≥2 μg/mL) have not been characterized as either intermediate or resistant by the US-FDA owing to limited clinical experience with infections caused by *S. aureus* having those MIC levels (Corey et al., 2010; Teflaro Package Insert, 2012).

Similarly, ceftaroline exhibits a high binding affinity to altered PBPs associated with β-lactam MIC elevations in streptococci, particularly *Streptococcus pneumoniae* (File et al., 2010; Jones et al., 2010a,c, 2011; Ramirez and Anzueto, 2011; Sader et al., 2005). This resulting potency advantage compared to ceftriaxone expands the spectrum of ceftaroline against CABP pathogens and translated to high clinical success rates (File et al., 2010).

As the vast majority (>80%) of clinical microbiology laboratories do not use reference/standardized CLSI methods, alternative strategies for testing newly released antimicrobials must be developed owing to long-term delays in the development and US-FDA approval of commercial susceptibility testing products (e.g., Vitek, Vitek 2, BD Phoenix, MicroScan, Sensititre, Etest, etc.). As some antimicrobials may present immediate therapeutic advantages, one strategy is to test a surrogate agent (usually in the same class) as a predictor of susceptibility and/or resistance. This testing option has been most recently applied to doripenem (Jones et al., 2007), but has also been used for other β-lactams (cefotetan, cefpodoxime) (Barry and Jones, 1987; Jones and Zurenko, 1993), new fluoroquinolones (Jones and Pfaller, 2001), investigational lipoglycopeptides (dalbavancin) (Jones et al., 2006), and by the CLSI in Table 1 of document M100-S23 (CLSI, 2013). The most challenging obstacle for assessing ceftaroline activity has been to select an appropriate antimicrobial class (β-lactams) agent when testing *S. aureus* (MRSA strains), where no other marketed β-lactam has demonstrated clear in vitro and clinical utility. However, some carbapenems have shown measurable potencies versus MRSA that may be usable, as would advanced-spectrum cephalosporins (ceftriaxone, ceftazidime, or cefepime) when testing *Streptococcus* spp. or other indicated species (Teflaro Package Insert, 2012). This study investigates the optimal use of candidate β-lactams as surrogate predictors of ceftaroline activity/susceptibility (not resistance), allowing the earliest guided clinical use in medical centers having FDA-approved commercial susceptibility testing systems reporting quantitative MIC values or category interpretations using the CLSI (2013) and US-FDA breakpoint criteria (Teflaro Package Insert, 2012).

2. Materials and methods

The organisms tested in the ceftaroline resistance surveillance programs from 2008 to 2010 were analyzed to select a surrogate marker agent for ceftaroline. The species selected were 3954 *S. pneumoniae* (2008–2010), 769 *Haemophilus influenzae* (2010 only), 8619 *S. aureus* (2008–2010; 53.6% MRSA), and 1560 Enterobacteriaceae (2010 only; *Escherichia coli* and *Klebsiella* spp.), for a total of 14,902 strains, all tested by the CLSI M07-A9 method in a good laboratory practice facility (JMI Laboratories, North Liberty, IA, USA) (CLSI, 2012b). Concurrent quality control (QC) strains *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and 29213, *H. influenzae* ATCC 49247, and *S. pneumoniae* ATCC 49619 were used, and all QC results were within published ranges (CLSI, 2013) for ceftaroline and candidate surrogate β-lactams.

Analysis focused on the use of a surrogate agent to predict ceftaroline susceptibility while minimizing, where possible, false-susceptibility to ≤1.5% and false-intermediate rates to ≤5%. Comparisons used published breakpoint criteria for each agent (CLSI, 2013; Teflaro Package Insert, 2012). With the exception of testing the Enterobacteriaceae and *S. aureus*, ceftaroline only has susceptible and nonsusceptible criteria precluding total cross-resistance calculations (CLSI, 2013; Teflaro Package Insert, 2012). By using the most potent β-lactam surrogate agents against each pathogen, the interpretive error was found to be far below the listed target accuracy limits above (see tables and figures). The following are the CLSI (2013) breakpoints for ceftaroline (susceptible/intermediate/resistant): for *S. aureus*, ≤1/2/≥4 μg/mL; for Enterobacteriaceae, ≤0.5/1/≥2 μg/mL; for *S. pneumoniae*, ≤0.5/—/— μg/mL; for β-hemolytic streptococci, ≤0.5/—/— μg/

Ceftaroline MIC (μg/mL)	Meropenem MIC (μg/mL)							
	≤0.12	0.25	0.5	1	2	4	8	>8
≥4								
2			1	2	3	2	5	168
1	3	9	47	264	613	328	311	613
0.5	277	165	416	771	579	184	71	33
0.25	3212	166	20	14	13	3	2	
0.12	287	7	1					
≤0.06	28	1						

Fig. 2. Scattergram of ceftaroline MIC values compared to meropenem MIC results when tested against 8619 *S. aureus* (4624 or 53.6% were MRSA) from the USA. Solid bolded horizontal and vertical lines indicate breakpoints for each agent (CLSI, 2012b, 2013; Teflaro Package Insert, 2012).