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Comparative Activity and Spectrum of Broad-Spectrum ß-Lactams Tested Against 12,295 Staphylococci and Streptococci: Report from the SENTRY Antimicrobial Surveillance Program (North America: 2001-2002)

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ABSTRACT

Background: Knowledge of contemporary susceptibility profiles is important for assuring the continued effectiveness of empiric broad-spectrum antimicrobial therapy. In this report, we evaluated the activity of cefepime (CPM), ceftazidime (CTAZ), ceftriaxone (CTRI), imipenem (IMP), piperacillin/tazobactam (P/T) and other comparator agents tested against a recent (2001-2002) collection of North American isolates of staphylococci and streptococci.

Methods: The collection consisted of 6,129 *S. aureus* (SA); 1,524 coagulase-negative staphylococci (CoNS); 2,935 *S. pneumoniae* (SPN); 1,457 ß-haemolytic (ßHS) and 250 viridans-group streptococci (VGS). All isolates were tested using NCCLS methods and interpretive criteria.

Results: Rank order of *S. aureus* susceptibilities (S) were: vancomycin (VAN; 100%) > linezolid (LIN) = Synercid® (Q/D; >99) > IMP (87) > clindamycin (CM) = gatifloxacin (GATI; 66) > ciprofloxacin (CIP; 56) > oxacillin (OXA; 58) > erythomycin (ERY; 45). CoNS S rates were similar except for GATI (83%), CIP (46), ERY (29) and OXA (24). All agents were active against OXA-S staphylococci (> 98% S). ßHS were exquisitely S (> 99%) to penicillin (PEN) and all other agents except CM (94%) and ERY (81). VGS was less S than other streptococci: VAN (100%) > LIN (> 99) > Q/D (98) > GATI (95) > CM = CPM (92) > CTRI (90) > PEN (75) > ERY (56). SPN remained S to most agents: VAN = LIN (100%) > Q/D (> 99) > GATI (99) > CPM (97) > CTRI (96) > CM (92) > IMP (91) > ERY (74) > PEN (69). Among ß-lactams tested against SPN, CTRI and CPM were very active against both PEN-S (> 99% S) and -intermediate (> 98) strains. PEN-R SPN strains were less S to both newer cephalosporins.

Conclusions: These findings confirm that for the broad-spectrum ß-lactam agents, including CPM and CTRI, the spectrum of activity remains comprehensive for the commonly isolated and indicated Gram-positive pathogens.

INTRODUCTION

ß-lactam antimicrobial agents continue to be among the preferred drugs for treatment of infections caused by susceptible staphylococci and streptococci because of their rapid bactericidal action, high achievable serum levels and broad safety profiles. Unfortunately, staphylococci have become widely resistant to penicillin and, more recently, to oxacillin (North America 38.7% resistant > Latin America 36.0% > Europe 30.4%); likewise, penicillin-resistant *Streptococcus pneumoniae* has been an increasing global problem (Europe 32.5% resistant > Asia-Western Pacific 15.1% > Latin America 13.8% > North America 9.6%) as documented by various investigators concurrent with a decline in susceptibility to macrolides and fluoroquinolones. While ß-haemolytic streptococci remain exquisitely susceptible to most agents, resistance to penicillin and levofloxacin has been documented (0.7% non-susceptible and 0.2% resistant, respectively) and can be problematic for clindamycin and erythromycin (5.3% and 13.8% resistant, respectively) therapy. Resistance among viridans group streptococci has also been recognized for these agents (penicillin 5.9%, levofloxacin 1.3%, erythromycin 29.9% and clindamycin 9.1%).

Broad-spectrum antimicrobial coverage, often including a ß-lactam agent either singly or in combination, has become a standard management approach for the febrile patient with or without a defined infectious source or etiology. Given the importance of Gram-positive bacteria as agents of systemic disease, respiratory tract disease, endocarditis, skin and soft tissue infections and urinary tract infections, among others, knowledge of the contemporary susceptibility profiles of such infectious agents continues to be an important component in the determination of the most appropriate options for empiric therapy. In this report we review the activity of very commonly used cefepime, ceftazidime, ceftriaxone, piperacillin/tazobactam and other comparator agents against a large number (12,295 strains) of contemporary North American isolates of *S. aureus*, coagulase-negative staphylococci (CoNS), *S. pneumoniae*, ß-haemolytic streptococci and viridans group streptococci.

MATERIALS AND METHODS

To assess the trends of resistance of commonly occurring staphylococci and streptococci in North America, isolates (12,295 strains) from the SENTRY Antimicrobial Surveillance Program collected during 2001 and 2002 were evaluated for susceptibility to five broad-spectrum ß-lactams (cefepime, ceftazidime, ceftriaxone, imipenem, piperacillin/tazobactam) along with eight comparator agents (oxacillin, erythromycin, clindamycin, quinupristin/dalfopristin, ciprofloxacin, gatifloxacin, linezolid, vancomycin) representing seven different antimicrobial classes. The SENTRY Program was initiated in 1997 as a global surveillance system for the identification and tracking of antimicrobial resistance patterns of community and nosocomial infections.

Isolates for this study originated from 34 sentinel medical centers in North America (United States [USA] and Canada) and were recovered consecutively from patients with bloodstream infections, community-acquired and nosocomial respiratory infections, wounds or skin and soft tissue infections, and urinary tract infections in hospitalized patients. Isolates were identified by the submitting laboratory and confirmed by the monitoring facility (The JONES Group/JMI Laboratories, Iowa, USA). The collection consisted of 6,129 isolates of *S. aureus*; 1,524 CoNS; 2,935 *S. pneumoniae*; 1,457 ß-haemolytic streptococci (39.6% Lancefield group A, 44.8% group B, 9.1% group G, 2.8% group C, 1.3% group F, and others 2.4%); and 250 viridans group streptococci. All strains were tested by a reference broth microdilution method of the National Committee for Clinical Laboratory Standards (NCCLS) against 13 antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of infections caused by the Gram-positive organisms being studied. Interpretation of quantitative MIC results was in accordance with NCCLS methods and criteria.

RESULTS

- *S. aureus* was the most commonly isolated pathogen (Table 1) with rank order of susceptibility being: vancomycin (100.0%) > linezolid = quinupristin/dalfopristin (> 99.9%) > clindamycin (66.1%) > gatifloxacin (65.9%) > ciprofloxacin (56.1%) > oxacillin (58.3%) > erythromycin (44.9%). CoNS ranked third in frequency and displayed a similar rank order.
- By examining the activities of broad-spectrum ß-lactams when staphylococci are categorized by their oxacillin susceptibility test profile (Table 2), all of the agents tested against oxacillin-susceptible strains showed potent anti-staphylococcal activity (>98% of strains susceptible), specifically for cefepime, imipenem and piperacillin/tazobactam; ceftazidime was less effective than the other agents with 92.7%-94.3% of isolates inhibited at ≤ 8 µg/ml.
- When testing oxacillin-resistant isolates of *S. aureus*, imipenem provided the greatest number of false-susceptible results (68.4%) followed by cefepime (29.9%).
- ß-haemolytic streptococci remained exquisitely susceptible (>99.6%) to penicillin and all other antimicrobial agents tested with the exception of clindamycin (93.5%) and erythromycin (80.8%) (Table 1). Cefepime and ceftriaxone were highly active and equivalent to penicillin in the percentage of isolates being susceptible. The MIC_{50} and MIC_{90} results for piperacillin/tazobactam and ceftazidime were four-fold and eight-fold higher, respectively, than observed for ceftriaxone or cefepime.
- Viridans group streptococci characteristically displayed greater resistance to a variety of antimicrobial agents than other streptococci (Table 1). The susceptibility rank order was: vancomycin (100.0%) > linezolid (99.6%) > quinupristin/dalfopristin (98.4%) > gatifloxacin (95.2%) > clindamycin = cefepime (92.0%) > ceftriaxone (90.4%) > penicillin (75.2%) > erythromycin (56.4%). The differences between erythromycin and clindamycin in both susceptibility rates and potency suggested that the M-phenotype predominates in North America.
- *S. pneumoniae* strains were highly susceptible to most tested agents with the rank order being: vancomycin = linezolid (100.0%) > quinupristin/dalfopristin (99.8%) > gatifloxacin (99.0%) > cefepime (96.6%) > ceftriaxone (96.1%) > clindamycin (91.8%) > imipenem (91.2%) > erythromycin (74.0%) > penicillin (69.2%) (Table 1).
- In this collection of 2,935 isolates, 0.8% of *S. pneumoniae* were observed to be resistant to gatifloxacin with a MIC_{90} of 0.5 µg/ml; the MIC_{90} for ciprofloxacin was 2 µg/ml, or four-fold greater (also levofloxacin, data not shown).
- Among the broad-spectrum ß-lactams evaluated, ceftriaxone and cefepime were highly active in vitro (96.1-96.6%, respectively) against *S. pneumoniae* with fewer isolates being susceptible to imipenem (91.2%), despite the fact that the imipenem MIC_{90} (0.12 µg/ml) was eight-fold lower than that of the other two compounds.
- Examination of *S. pneumoniae* susceptibility results when categored by their penicillin susceptibility (Table 3), revealed that cefepime and ceftriaxone remained highly active against penicillin-susceptible (99.9% and 99.8% susceptible, respectively) and intermediate (99.2% and 98.7% susceptible) strains. Penicillin-resistant strains were predictably less susceptible to both cefepime (81.9%) and ceftriaxone (79.7%).

Table 1. Antimicrobial activity and susceptibility rates of five broad-spectrum ß-lactams and eight comparator agents tested against 12,295 isolates of staphylococci and streptococci (SENTRY Program North America, 2001-2002).

	MIC (µg/ml)		% by category[a]		
Organism group (no. tested)/antimicrobial agent	50%	90%	Susceptible	Intermediate	Resistant
S. aureus (6,129)					
Cefepime	4	>16	70.4[b]	6.0	23.6
Ceftazidime	8	>16	55.3[b]	7.0	37.7
Ceftriaxone	4	>32	59.8[b]	15.1	25.1
Imipenem	≤0.06	>8	86.8[b]	2.3	10.9
Piperacillin/Tazobactam	2	>64	65.1[b]	-[c]	34.9
Oxacillin	0.5	>8	58.3	-	41.7
Erythromycin	>8	>8	44.9	0.5	54.6
Clindamycin	0.12	>8	66.1	0.1	33.8
Quinupristin/Dalfopristin	≤0.25	0.5	>99.9	<0.1	0.0
Ciprofloxacin	0.5	>2	56.1	1.0	42.9
Gatifloxacin	0.12	>4	65.9	15.7	18.4
Linezolid	1	2	>99.9	-	-
Vancomycin	1	1	100.0	0.0	0.0
Coagulase-negative staphylococci (1,524)					
Cefepime	4	>16	81.8[b]	7.8	10.4
Ceftazidime	16	>16	34.1[b]	26.9	39.0
Ceftriaxone	8	>32	52.6[b]	35.4	12.0
Imipenem	0.25	>8	85.2[b]	3.6	11.2
Piperacillin/Tazobactam	2	16	88.3[b]	-	11.7
Oxacillin	4	>8	24.0	-	76.0
Erythromycin	>8	>8	28.6	0.6	70.8
Clindamycin	0.12	>8	59.8	0.2	40.0
Quinupristin/Dalfopristin	≤0.25	0.5	99.8	0.2	0.0
Ciprofloxacin	>2	>2	46.3	2.2	51.5
Gatifloxacin	1	>4	83.0	6.2	10.8
Linezolid	1	1	>99.9	-	-
Vancomycin	2	2	100.0	0.0	0.0

Table 1. Continued.

	MIC (µg/ml)		% by category[a]		
Organism group (no. tested)/antimicrobial agent	50%	90%	Susceptible	Intermediate	Resistant
ß-haemolytic streptococci (1,457)					
Cefepime	≤0.12	≤0.12	99.8	-	-
Ceftazidime	≤2	≤2	-	-	-
Ceftriaxone	≤0.25	≤0.25	99.8	-	-
Imipenem	≤0.5	≤0.5	-	-	-
Piperacillin/Tazobactam	≤1	≤1	-	-	-
Penicillin	≤0.015	0.06	99.6	-	-
Erythromycin	≤0.06	2	80.8	1.2	18.0
Clindamycin	≤0.06	≤0.06	93.5	0.2	6.3
Quinupristin/Dalfopristin	0.25	0.5	100.0	0.0	0.0
Ciprofloxacin	0.5	1	-	-	(0.6)[d]
Gatifloxacin	0.25	0.25	99.7	0.1	0.2
Linezolid	1	1	100.0	-	-
Vancomycin	0.5	0.5	100.0	-	-
S. pneumoniae (2,935)					
Cefepime	≤0.12	1	96.6	3.0	0.4
Ceftazidime	≤2	8	-	-	-
Ceftriaxone	0.12	1	96.1	2.2	1.7
Imipenem	≤0.06	0.12	91.2	7.7	1.1
Piperacillin/Tazobactam	≤1	4	-	-	-
Penicillin	≤0.03	2	69.2	13.2	17.6
Erythromycin	≤0.25	8	74.0	0.9	25.1
Clindamycin	≤0.12	≤0.12	91.8	0.4	7.1
Quinupristin/Dalfopristin	0.5	0.5	99.8	0.1	0.1
Ciprofloxacin	1	2	-	-	(3.4)[d]
Gatifloxacin	0.25	0.5	99.0	0.2	0.8
Linezolid	1	1	100.0	-	-
Vancomycin	0.25	0.5	100.0	-	-
viridans group streptococci (250)					
Cefepime	≤0.12	1	92.0	4.0	4.0
Ceftazidime	≤2	16	-	-	-
Ceftriaxone	≤0.25	1	90.4	5.6	4.0
Imipenem	≤0.06	0.12	-	-	-
Piperacillin/Tazobactam	≤1	4	-	-	-
Penicillin	0.06	2	75.2	20.0	4.8
Erythromycin	≤0.06	>8	56.4	3.2	40.4
Clindamycin	≤0.06	≤0.06	92.0	0.0	8.0
Quinupristin/Dalfopristin	0.5	1	98.4	1.6	0.0
Ciprofloxacin	1	>2	-	-	(16.8)[d]
Gatifloxacin	0.25	0.5	95.2	0.8	4.0
Linezolid	1	1	99.6	-	-
Vancomycin	0.5	1	100.0	-	-

a. Susceptibility assessed using the breakpoint criteria of the NCCLS.
b. Susceptibility of the ß-lactams would be predicted from the oxacillin MIC results.
c. - = indicates no interpretive criteria are published for this category by the NCCLS.
d. Ciprofloxacin resistant result (≥ 4 µg/ml) was presented to predict the proportion of strains with possible topoisomerase target mutations

Table 2. Variations in potency and spectrum for the five broad-spectrum ß-lactams for methicillin (oxacillin)-susceptible and -resistant staphylococci (SENTRY Program North America, 2001-2002; 7,656 isolates).

	MIC (µg/ml) by oxacillin category:					
	Susceptible (no. tested)			Resistant (no. tested)		
Organism/antimicrobial agent	50%	90%	% susceptible[a]	50%	90%	% susceptible[a]
S. aureus		(3,576)			(2,553)	
Cefepime	2	4	99.4	>16	>16	29.9[b]
Ceftazidime	8	8	92.7	>16	>16	2.8[b]
Ceftriaxone	4	4	98.9	>32	>32	4.9[b]
Imipenem	≤0.06	≤0.06	99.8	1	>8	68.4[b]
Piperacillin/Tazobactam	≤1	2	99.4	64	>64	17.0[b]
CoNS[c]		(366)			(1,158)	
Cefepime	1	2	99.2	4	>16	76.4[b]
Ceftazidime	4	8	94.3	>16	>16	15.1[b]
Ceftriaxone	2	4	98.1	16	>32	38.3[b]
Imipenem	≤0.06	≤0.06	99.5	0.5	>8	80.7[b]
Piperacillin/Tazobactam	≤1	≤1	99.7	2	32	84.8[b]

a. Susceptibility criteria as published by the NCCLS.
b. All oxacillin-resistant strains should be considered resistant to other ß-lactams [NCCLS, 2003b], and the susceptibility rates listed are considered false-susceptibility.
c. CoNS = coagulase-negative staphylococci.

Table 3. Impact of penicillin susceptibility category of *S. pneumoniae* strains on the potency and spectrum of five broad-spectrum ß-lactams (SENTRY Program North America, 2001-2002; 2,935 isolates).

	MIC (µg/ml) and susceptibility (%) by penicillin category:[a]								
	Susceptible (n=2,031)			Intermediate (n=386)			Resistant (n=518)		
Antimicrobial agent	50%	90%	Susceptible	50%	90%	Susceptible	50%	90%	Susceptible
Cefepime	≤0.12	≤0.12	99.9	0.25	1	99.2	1	2	81.9
Ceftazidime	≤2	≤2	-[b]	4	8	-	8	>16	-
Ceftriaxone	0.03	0.25	99.8	0.25	1	98.7	1	2	79.7
Imipenem	≤0.06	≤0.06	-	≤0.06	0.12	-	0.25	0.5	-
Piperacillin/Tazobactam	≤1	≤1	-	≤1	2	-	4	4	-

a. Susceptibility criteria of the NCCLS.
b. - = indicates that no interpretive criteria for this category has been established by the NCCLS. Note that imipenem should be considered susceptible if the penicillin result is susceptible, however, no predictions can be made for ceftazidime or piperacillin/tazobactam based on penicillin testing.

CONCLUSIONS

- The appearance of increasing resistance in pathogenic Gram-positive organisms to ß-lactams, macrolides, lincosamides, fluoroquinolones, tetracyclines and, more recently, glycopeptides, is troublesome and has lead to the release of new antimicrobial agents including linezolid and quinupristin/dalfopristin, and the development of other, promising agents (everninomicins, lipopeptides, glycylcyclines, and peptide deformylase inhibitors).
- Knowledge of contemporary susceptibility profiles, both global (as presented here) and local, augment other epidemiologic and medical data in establishing or modifying practice guidelines.
- When using broad-spectrum ß-lactam agents including cefepime and ceftriaxone as empiric therapy for serious infections, the spectrum of activity continues to be comprehensive for the common Gram-positive pathogens, specifically *S. aureus*, CoNS, *S. pneumoniae*, ß-haemolytic streptococci and viridans group streptococci.

SELECTED REFERENCES

Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *New England Journal of Medicine*, 1999; 341:233-239.

Gordon KA, Beach ML, Biedenbach DJ, Jones RN, Rhomberg PR, Mutnick AH. Antimicrobial susceptibility patterns of ß-haemolytic and viridans group streptococci: report from the SENTRY Antimicrobial Surveillance Program (1997-2000). *Diagnostic Microbiology and Infectious Disease*, 2002; 43:157-162.

Hoban DJ, Doern GV, Fluit AC, Roussel-Delvallez M, Jones RN. Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clinical Infectious Diseases* 2001; 32(suppl 2):S81-S93.

Jones RN, Pfaller MA. Macrolide and fluoroquinolone (levofloxacin) resistances among *Streptococcus pneumoniae* strains: significant trends from the SENTRY Antimicrobial Surveillance Program (North America, 1997-1999). *Journal of Clinical Microbiology*. 2002; 38:4298-4299.

Jones RN. Global epidemiology of antimicrobial resistance among community-acquired and nosocomial pathogens: a five-year summary from the SENTRY Antimicrobial Surveillance Program (1997-2001). *Seminars in Respiratory and Critical Care Medicine*, 2003; 24:121-133.

McCormick AW, Whitney CG, Farley MM, Lynfield R, Harrison LH, Bennett NM, Schaffner W, Reingold A, Hadler J, Cieskal P, Samore MH, Lipsitch M. Geographic diversity and temporal trends of antimicrobial resistance in *Streptococcus pneumoniae* in the United States. *Nature Medicine* 2003; 9:424-430.

Mutnick AH, Biedenbach DJ, Turnidge JD, Jones RN. Spectrum and potency evaluation of a new oxazolidinone, linezolid: report from the SENTRY Antimicrobial Surveillance Program, 1998-2000. *Diagnostic Microbiology and Infectious Disease*, 2002; 43:65-73.

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-sixth edition. Approved document M7-A6*. Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2003). *Performance standards for antimicrobial susceptibility testing, 13th informational supplement M100-S13*. Wayne, PA:NCCLS.