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Evaluation of Six Broad-Specrum ß-Lactams Tested Against Recent Clinical Isolates from India: A 10 Medical Center Survey

India Antimicrobial Resistance Study Group, D. Mathai, D.J. Biedenbach, R.N. Jones.
Christian Medical College Hospital, Vellore, India; Univ of Iowa, Iowa City, IA; The JONES Group/JMI Laboratories, N. Liberty, IA [www.jmilabs.com]

AMENDED ABSTRACT

Background: Systematically obtained resistance data for ß-lactams remains very limited in India. These data from standardized quantitative and comprehensive testing are urgently needed to educate physicians making therapeutic choices.

Methods: 10 centers located in diverse regions collected 100 consecutive common pathogens (n=859) in 10 categories: *E. coli* (EC); *Klebsiella* spp. (KS); *Enterobacter* spp. (EB); *C. freundii*, *Serratia* spp.; *Acinetobacter* spp. (ACB); *P. aeruginosa* (PSA); other Enterobacteriaceae usually *Salmonella* (SAL); oxa-susc *S. aureus* and CoNS. The 6 ß-lactams were: cefpirome (CR), cefotaxime (CT), ceftazidime (CZ), imipenem (IM), piper/tazo (P/T), piperacillin (P) or oxacillin using Etest (NCCLS). Selected resistant phenotypes were retested and referred to monitors for confirmation and molecular testing.

Results: Among enteric strains, best susceptibility (S) rates were recorded for IM (100%) and P/T (96%) with cephalosporin activity highest for CR > CZ > CT. P/T was the most active (81%) against PSA > P = IM (77%) > CZ (67%) > CR (54%), with ACB showing the greatest S to IM (99%). Absolute susceptibility was observed among staph for all agents except CZ (67 to 96%). P-resist strains were usually inhibited by P/T and high ESBL phenotype rates were found among EC (61%) and KS (57%), many of which (85%)were inhibited by clavulanate and co-resist to fluoroquinolones (FQ) and aminoglycosides (AG). Intra- and inter-center clonal ESBL transmission was observed and species-to-species dissemination into EB (12%), CF (4%), SAL (2%) or proteae (7%).

Conclusions: Very high rates of inhibitable ESBL phenotypes with dissemination was observed in nearly all Indian hospitals. Longitudinal monitoring of resistance rates in India should be continued to address this nation-wide crisis.

INTRODUCTION

ß-lactam antimicrobials (penicillins with enzyme inhibitors, cephalosporins, monobactams, carbapenems) by their broad spectrum of activity, favorable pharmacokinetics and wide margin of or without therapeutic safety, have become preferred first line agents as empiric treatment of serious infections world wide. In India, nearly twenty structurally different molecules are available among the penicillin and cephalosporin classes, with over 90 brands being marketed to medical practitioners. The orally-active ß-lactams are frequently used to treat community-acquired infections and the parenteral forms of ureidopenicillins (with or without ß-lactamase inhibitors), and advanced generation cephalosporins, are usually reserved for treatment of serious nosocomial infections. With the increasing and widespread use of these classes in several monitored nations, pathogens have acquired stepwise or novel resistances that render some ß-lactams inactive. Examples of these resistance mechanisms are: extended spectrum ß-lactamase (ESBL) production, penicillin binding protein site alteration, stable derepression of chromosomal amp C cephalosporinases, porin protein loss in bacterial membranes, and production of novel metallo-enzymes. Failure to detect and limit the spread of such emerging resistant strains have resulted in their dissemination between bacterial species, patients and geographically distinct areas.

In India, sources of country-based information on antimicrobial resistance have been limited to: 1) consensus statements of expert panels; 2) a limited selection of antimicrobials tested; or 3) a summary of antibiograms based on questionnaire responses obtained from participating laboratories. Laboratory-supported, prospective antimicrobial resistance surveillance studies have been restricted to a few selected community-acquired pathogens monitored at multiple institutions or at a national reference laboratory. Nation-wide resistance rates have been inferred from studies that differ in laboratory practices and often lack the needed reliability of central monitoring. Furthermore, within India and some other nations, the limited controls on prescription habits, non-standardized antimicrobial manufacturing, and breakdowns of infection control practices due to compromised fiscal resources, offer the high potential for emerging resistant pathogens and their unimpeded spread.

"Fourth-generation" cephalosporins such as cefpirome and cefepime (not marketed in India) may have advantages over earlier agents in their class against pathogens that cause serious clinical infections. Following their clinical availability, several national surveillance programs were initiated world wide in 1997-1999 to provide antimicrobial comparative activity data against 10 commonly occurring hospital pathogen groups. This report from monitored medical centers in India follows the same standardized and comprehensive testing protocol utilized before. The objectives were to provide reliable quantitative information for making local, national and regional spectrum comparisons, and to benchmark the prevailing rates of ß-lactam resistance.

Table 1. Distribution of genus and species groups (859 strains) tabulated in the study of ß-lactam resistances in 10 medical centers in India.

Species or genus group	No. of strains (%)
1. *Klebsiella* spp.	145 (16.9)
2. *P. aeruginosa*	138 (16.1)
3. *E. coli*	132 (15.4)
4. *S. aureus*	96 (11.2)
5. *Acinetobacter* spp.	90 (10.5)
6. *Enterobacter* spp.[a]	84 (9.8)
7. *Salmonella* spp.[b]	63 (7.3)
8. Indole-positive *Proteae*	40 (4.7)
9. *C. freundii*	29 (3.4)
10. Coagulase-negative staphylococci	23 (2.7)
11. *Serratia* spp.	15 (1.7)
12. *P. mirabilis*	4 (0.5)

a. Includes 74 unspeciated strains and *Pantoea agglomerans* (10 strains; formerly *E. agglomerans*).

b. Includes *S. paratyphi* (one strain), *S. typhi* (12 strains), *S. typhimurium* (10 strains) and 40 unspeciated *Salmonella* isolates.

FIG. 1: Geographic locations of participant medical centers (10 sites).

MATERIALS AND METHODS

Participant sites. Ten clinical laboratories associated with medical centers were recruited. The national coordinator was HMR India, Ltd. (Mumbai). Figure 1 provides the geographic location of the enrolled laboratories in India. The distribution of bed capacities among the hospitals was: ≤ 399 beds (four), 400-1,000 (three), > 1,000 (three). Five sites were teaching medical centers (three central/state government, and two private), two were non-government community hospitals, and three were corporate hospitals.

Formulary practices were monitored by a questionnaire concerning parenteral ß-lactam use prior to the initiation of the study. The unrestricted use of various ß-lactams studied in this protocol was as follows (% of all sites): cefotaxime (100%), ceftazidime (90%), piperacillin (80%), cefpirome (30%), piperacillin/tazobactam (20%) and imipenem (20%).

The international monitor (Iowa, USA) provided protocols, reference procedures, reagent manuals (Etest, AB BIODISK, Solna, Sweden), and materials for storage and strip application. The routine methods and susceptibility test interpretations used in these participant sites were: NCCLS [2000a and b; 2001] in seven laboratories and the British Society of Chemotherapy method was used in only three locations.

Organisms tested. One hundred organisms were targeted for processing in each laboratory, grouped into 10 general categories: *E. coli* (10 strains); *Klebsiella* spp. (10 strains); *Enterobacter* spp. (10 strains); *Citrobacter freundii* (10 strains); *Serratia* spp. (10 strains); *Acinetobacter* spp. (10 strains); *Pseudomonas aeruginosa* (10 strains); oxacillin-susceptible (≤ 2 µg/ml) *Staphylococcus aureus* (10 strains); oxacillin-susceptible (≤ 0.25 mg/ml) coagulase-negative staphylococci (10 strains); and other Enterobacteriaceae (variable number of strains). The latter category was opened to allow testing of a greater variety of species.

Susceptibility testing methods. All laboratories utilized the Etest method (AB BIODISK) following manufacturer procedures and protocol design. Six antimicrobials were tested against each strain: cefpirome, cefotaxime, ceftazidime, imipenem, piperacillin/tazobactam, piperacillin (Gram-negative species) or oxacillin (staphylococci).

Quality control was performed using provided strains: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213. Each strain was processed at least once weekly or ≥ five times during the study interval. All results were recorded on standardized forms and then forwarded to national and international monitors. Additional quality assurance was initiated in the form of the required referral of strains presenting with defined resistance profiles. The following clinical isolates needed confirmation by repeated local tests as well as reference testing by the national and/or international monitor: 1) all Enterobacteriaceae or oxacillin-susceptible staphylococci not susceptible to cefpirome (MIC, > 16 µg/ml) or imipenem (MIC, > 4 µg/ml); and 2) any unusual pattern of multiple resistance of interest to the participant or monitors (generally ESBL phenotypes and enteric bacilli not susceptible to carbapenems).

Additional investigations. Confirmation of referred resistance patterns was accomplished by testing each strain by the original method (Etest) and two more alternative tests (reference broth microdilution, disk diffusion) to resolve any discords. The ESBL criteria were a MIC for cefotaxime or ceftazidime at ≥ 2 µg/ml among *E. coli*, *Klebsiella* spp. and selected other enteric isolates. These strains were also tested by Etest ESBL strips to confirm inhibitor (clavulanic acid) -susceptible enzymes compared to those inhibitor-resistant strains that may harbor other ß-lactamases, usually of Amp C derivation.

Phenotypically related resistant strains of the same species in the same institution received further molecular characterization by PFGE and /or ribotyping (Riboprinter, Qualicon, Wilmington, DE). Detected clonally related isolates were further tested to determine the extent of co-resistances between non-ß-lactam antimicrobial classes and the dissemination of resistance genes between species or genera.

RESULTS

• Table 1 lists the species and genus groups tested. *Klebsiella* spp., *P. aeruginosa*, and *E. coli* were the largest samples averaging 13 to 15 isolates per participant site (Figure 1).

•Quality control results (Table 2) illustrates the high level of protocol/method (Etest) accuracy. Overall "in control" results ranged from 91.0 to 97.9%.

•Table 3 shows the high rate of ß-lactamase-mediated resistances in the Enterobacteriaceae (especially *E. coli* and *Klebsiella* spp.)
- Only 18.9% of *E. coli* were piperacillin-susceptible and ESBL phenotypes were noted in 61% of isolates.
- Against *Klebsiella* spp., imipenem (IMP, 100% susceptible) and piperacillin/tazobactam (P/T; 77% susceptible) were most active. ESBL's were suspect in 56 to 57% of isolates.
- IMP, P/T and cefpirome were most active against *C. freundii*, *Enterobacter* spp. and indole-positive *Proteae*. *Serratia* spp. susceptibility ranged from 93% (four drugs) to 100% (cefpirome and IMP).
- *Salmonella* spp. had a 26% rate of non-susceptibility to piperacillin. Chromosomal or plasmid Amp C and ESBL phenotypes were noted at a rate of 3 - 8%.
- *Acinetobacter* spp. isolates were generally resistant to all ß-lactams (36 - 48% susceptible) except IMP (99% susceptible).
- *P. aeruginosa* strains were most susceptible to P/T (81%) followed by piperacillin alone, IMP, ceftazidime and cefpirome (54% susceptible).
- Among the 119 staphylococci tested, all drugs were active except ceftazidime which often had intermediate MIC values (67 - 96% susceptible overall).

• Table 4 demonstrates possible intra- and inter-institutional dissemination of *E. coli* or *Klebsiella* spp. strains having ESBL phenotypes. ESBL-like organisms were detected by MIC screen and ESBL Etest in nine of 10 medical centers monitored, most isolates unique to each institution (data not shown).

• ESBL phenotypes were also noted in *Providencia* spp. and *Enterobacter* spp. These ESBL containing isolates were confirmed by a cefepime Etest strip with and without clavulanic acid (Table 5). Three medical centers had high rates of ESBL phenotypes in *E. coli* and *Klebsiella* spp. with presumed spread to *Enterobacters* or *Citrobacters*, each possessing a similar co-resistance pattern.

• Table 6 summarizes the in vitro findings of the India isolates by ranking the broad-spectrum ß-lactams against all tested strains. The rank order was similar to earlier investigations in the Asia-Pacific region using an identical study design/method. The consensus rank order favors the spectrum of carbapenems > "fourth-generation" cephalosporins (cefpirome or cefepime) > piperacillin/tazobactam > "third-generation" cephalosporins including ceftazidime.

CONCLUSIONS

• This ten center in vitro protocol in India, qualified by internal quality assurance practices, reveals alarming levels of resistance among various Gram-negative bacilli.
- -ESBL's
- -Amp C
- -Fluoroquinolones (secondary testing)
- -Aminoglycosides (secondary testing)

• Urgent attention is required in the form of formulary and infection control interventions to reduce endemic ß-lactam resistance rates or possibly reduce the spread of highly resistant phenotypes.

• This study should establish a baseline or benchmark for ß-lactam resistance patterns in India and follow up studies of similar design are encouraged.

Table 2. Quality control results from 10 laboratories participating in the India resistance surveillance trial.

Antimicrobial tested	% of study results within QC ranges (median MIC in µg/ml) for:[a] *S. aureus* ATACC 29213	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853
Cefotaxime	100.0 (1.5)	89.6 (0.064)	89.6 (12)
Cefpirome	100.0 (1.0)	87.5 (0.064)	95.8 (1.5)
Ceftazidime	97.9 (6.0)	91.7 (0.25)	89.6 (1.5)
Imipenem	95.8 (0.047)	95.8 (0.19)	89.6 (3.0)
Oxacillin	93.6 (0.25)	NT[b]	NT[b]
Piperacillin	NT[b]	93.8 (0.19)	100.0 (2.0)
Piperacillin/Tazobactam	100.0 (0.75)	87.5 (1.5)	87.5 (2.0)
Total	97.9	91.0	92.0

a. Ranges of MIC results from NCCLS [2001] tables or provided by investigator/manufacturer publications.
b. NT = not tested.

Table 3. Antimicrobial spectrum and activity of six ß-lactams when tested against 855 strains from hospitals in India.[a]

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category[b] Susceptible	Resistant
E. coli (132)	Cefotaxime	128	>256	0.023->256	41.1	54.8(61.3)[c]
	Cefpirome	48	>256	0.023->256	44.9	52.8
	Ceftazidime	16	96	≤0.016->256	42.1	35.7(61.1)[c]
	Piperacillin	>256	>256	1.0->256	18.9	78.2
	Piperacillin/Tazobactam[d]	8.0	32	0.38->256	80.5	4.1
	Imipenem	0.25	0.38	0.094-1.5	100.0	0.0
Klebsiella spp. (145)	Cefotaxime	8.0	>256	≤0.016->256	51.6	43.7(55.6)[c]
	Cefpirome	2.0	192	≤0.016->256	60.0	34.8
	Ceftazidime	8.0	>256	0.023->256	51.9	41.5(57.0)[c]
	Piperacillin	>256	>256	0.38->256	34.1	61.5
	Piperacillin/Tazobactam[d]	4.0	64	0.38->256	76.7	9.3
	Imipenem	0.25	0.5	0.125-1.5	100.0	0.0
Citrobacter freundii (29)	Cefotaxime	1.0	>256	0.023->256	69.2	23.1
	Cefpirome	1.0	16	≤0.016-96	89.3	3.6
	Ceftazidime	3.0	>256	≤0.016->256	60.7	39.3
	Piperacillin	48	>256	1->256	46.4	42.9
	Piperacillin/Tazobactam[d]	2.0	8.0	0.25->256	90.5	4.8
	Imipenem	0.5	2.0	0.125-3.0	100.0	0.0
Enterobacter spp. (84)	Cefotaxime	3.0	>256	0.032->256	54.7	30.7
	Cefpirome	0.75	64	≤0.016->256	76.6	13.6
	Ceftazidime	1.5	>256	0.032->256	54.3	39.5
	Piperacillin	24	>256	0.5->256	49.4	40.7
	Piperacillin/Tazobactam[d]	3.0	128	0.125->256	76.6	11.7
	Imipenem	0.38	1.5	0.125-2	100.0	0.0
Indole-positive *Proteae* (40)	Cefotaxime	8.0	>256	≤0.016->256	52.0	28.0
	Cefpirome	1.5	>256	0.023->256	71.9	28.0
	Ceftazidime	4.0	>256	≤0.016->256	50.0	40.6
	Piperacillin	12	>256	0.19->256	53.1	40.6
	Piperacillin/Tazobactam[d]	0.5	1.5	0.032->256	96.3	3.7
	Imipenem	1.0	3.0	0.023-4	100.0	0.0
Salmonella spp. (63)	Cefotaxime	0.094	0.125	0.023->256	95.2	3.2(3.2)c
	Cefpirome	0.094	0.19	0.023->256	98.4	0.0
	Ceftazidime	0.38	0.75	0.064->256	96.8	3.2(8.1)c
	Piperacillin	2.0	64	0.38->256	74.2	9.7
	Piperacillin/Tazobactam[d]	1.5	3.0	0.38->256	93.3	5.0
	Imipenem	0.19	0.38	0.094-0.5	100.0	0.0
Serratia spp. (15)	Cefotaxime	0.38	2.0	0.094-32	93.3	0.0
	Cefpirome	0.125	0.25	0.047-2.0	100.0	0.0
	Ceftazidime	0.19	0.75	0.094->256	93.3	6.7
	Piperacillin	2.0	16	0.5->256	93.3	6.7
	Piperacillin/Tazobactam[d]	1.5	4.0	0.38-64	93.3	0.0
	Imipenem	0.5	1.0	0.25-1.0	100.0	0.0
Acinetobacter spp. (90)	Cefotaxime	24	>256	0.064->256	36.7	46.8
	Cefpirome	32	>256	0.047->256	48.3	50.6
	Ceftazidime	16	>256	0.125->256	41.6	48.3
	Piperacillin	>256	>256	0.25->256	36.0	53.9
	Piperacillin/Tazobactam[d]	24	>256	≤0.016->256	48.0	37.3
	Imipenem	0.75	3.0	0.032->32	98.9	1.1
P. aeruginosa (138)	Cefotaxime	32	>256	0.023->256	11.6	49.6
	Cefpirome	8.0	>256	0.25->256	54.3	34.1
	Ceftazidime	3.0	>256	0.064->256	67.4	27.5
	Piperacillin	8.0	>256	0.5->256	77.4	22.6
	Piperacillin/Tazobactam[d]	6.0	>256	≤0.016->256	81.3	18.7
	Imipenem	2.0	>32	0.19->32	76.5	17.6
S. aureus (96)	Cefotaxime	1.5	3.0	0.023-8.0	100.0	0.0
	Cefpirome	1.0	1.5	0.125-2.0	100.0	0.0
	Ceftazidime	8.0	16	1.5->256	66.7	5.2
	Piperacillin/Tazobactam[d]	0.38	0.75	0.047-1.5	100.0	0.0
	Imipenem	0.047	0.094	0.012-1.0	100.0	0.0
	Oxacillin	1.0	2.0	0.023-2.0	100.0	0.0
CoNS (23)[e]	Cefotaxime	0.5	1.5	0.19-1.5	100.0	0.0
	Cefpirome	0.38	0.75	0.19-0.75	100.0	0.0
	Ceftazidime	4.0	8.0	1.0-12	95.7	0.0
	Piperacillin/Tazobactam[d]	0.125	0.25	0.047-0.38	100.0	0.0
	Imipenem	0.023	0.094	0.012-0.25	100.0	0.0
	Oxacillin	0.125	0.25	0.023-0.25	100.0	0.0

a. All tests were performed by the Etest method (AB BIODISK, Solna, Sweden), validated by quality assurance results.
b. Criteria as published by the NCCLS [2001].
c. Percentage in parenthesis represents the proportion of strains having an ESBL phenotype by NCCLS [2001] criteria.
d. Tazobactam at a fixed concentration of 4 µg/ml.
e. CoNS = coagulase-negative staphylococci and NCCLS [2001] interpretive criteria (≤ 0.25 µg/ml).

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Table 4. Examples of molecular epidemiology and co-resistance patterns for selected ESBL phenotypes[a] and confirmed strains isolated from Indian medical centers in the 2000-2001 protocol.

Medical center	Organism	Strain no.	MIC (µg/ml) Cefotaxime	Ceftazidime	Cefpirome	Cefoxitin	ESBL Etest[b]	Co-resistance pattern[c]	Ribotype
I01	*E. coli*	D4/11	>256	24	128	NT[d]	+	AG,FQ	243.2
	E. coli	D4/14	>256	24	128	NT	+	AG,FQ	243.2
I06	*E. coli*	I4/3	>256	16	128	NT	+	FQ	243.2
	E. coli	I4/13	>256	16	64	NT	+	AG,FQ	263.1
	K. pneumoniae	I5/5	>256	64	64	NT	+	AG,FQ	79.2
	K. pneumoniae	I5/6	>256	96	96	NT	+	AG,FQ	79.2
	K. pneumoniae	I5/10	256	96	96	NT	+	AG,FQ	79.2
I09	*E. coli*	B4/6	>256	>256	>256	96	-	AG,FQ	253.7
	E. coli	B4/10	>256	>256	>256	96	-	AG,FQ	253.7
	Klebsiella spp.	B5/3	256	64	>256	NT	+	AG,FQ	283.8
	Klebsiella spp.	B5/11	256	96	>256	NT	+	AG,FQ	283.8
I10	*E. coli*	H4/3	>256	128	>256	NT	+	AG,FQ	243.2
	E. coli	H4/5	32	16	24	NT	+	AG,FQ	243.2
	E. coli	H4/8	>256	16	>256	NT	+	AG,FQ	263.1

a. Phenotypes include all strains having a MIC for cefotaxime and/or ceftazidime at ≥ 2 µg/ml [NCCLS, 2001]. Confirmed strains are phenotype-positive isolates with the enzyme inhibited by 2 µg/ml of clavulanic acid [NCCLS, 2001] using the Etest (AB BIODISK) ESBL strip.
b. A positive test was the reduction of the ceftazidime MIC by ≥ 3 $\log_2$ dilutions in the presence of clavulanic acid (2 µg/ml).
c. Co-resistances for: AG = aminoglycosides (gentamicin MIC > 4 µg/ml); and FQ = fluoroquinolones (ciprofloxacin MIC, > 1 µg/ml).
d. NT = not tested.

Table 5. Listing of species and locations of isolates having ESBL-like enzymes occurring in genera other than Escherichia, Klebsiella or Proteus [NCCLS, 2001].

Medical center	Organism	Strain no.	MIC (µg/ml) Cefotaxime	Ceftazidime	Cefepime MIC (µg/ml) Cefepime	Alone	+ CA[a]	Result	Co-resistance pattern[b]	ESBL in environment[c]
I02	*Enterobacter* spp.	F2/6	>256	>256	>256	>256	4.0	+	AG,FQ	Yes
	Enterobacter spp.	F2/9	>256	>256	>256	48	2.0	+	AG,FQ	Yes
I06	*Enterobacter* spp.	I2/3	64	16	192	12	0.064	+	AG,FQ	Yes
	Enterobacter spp.	I2/4	64	16	>256	16	0.064	+	AG,FQ	Yes
	Enterobacter spp.	I2/6	64	64	128	12	0.064	+	AG,FQ	Yes
	Enterobacter spp.	I2/7	128	96	>256	48	0.064	+	AG,FQ	Yes
I09	*P. stuartii*	B1/10	24	>256	96	12	0.19	+	AG,FQ	Yes

a. CA = clavulanic acid at 2 µg/ml on an Etest (AB BIODISK) strip.
b. Co-resistances for: AG = aminoglycosides (gentamicin MIC, > 4 µg/ml); and FQ = fluoroquinolones (ciprofloxacin MIC, > 1 µg/ml).
c. Yes indicates proven ESBL phenotypes with similar antibiogram (excludes fluoroquinolones; chromosomal mechanisms) occurred in *E. coli* or *Klebsiella* spp. isolates in the same medical center during this investigation.

Table 6. Concensus rank order of spectrum for similar studies with ß-lactams in selected nations in Asia (1998-99) and India (2000-2001).

Antimicrobial agent/group	Rank order of spectrum by nation: India	Indonesia	Malaysia/Singapore	Thailand	Concensus
Carbapenems					
Imipenem	1	1	1	1	1
Cephalosporins					
Fourth generation					
Cefepime	NT[b]	2	2	2	2
Cefpirome	3	3	3	4	2
Third generation					
Ceftazidime	4	5	6	6	4
Cefotaxime[c]	5	6	5	5	5
Beta-lactamase inhibitor Combinations					
Piperacillin/tazobactam	2	3	4	3	3
Penicillins					
Piperacillin	6	NT	NT	NT	6

a. Modified from Jones [2000] and excludes Korea and the Western Pacific island nations of Japan, Taiwan, and the Philippines.
b. NT = not tested.
c. Ceftriaxone was tested in some nations.