220

IDSA 2003

The JONES Group/JMI Laboratories
North Liberty, IA, USA; www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

Global Patterns of Susceptibility for 21 Commonly Used Antimicrobial Agents Tested Against 48,440 *Enterobacteriaceae* in the SENTRY Antimicrobial Surveillance Program (1997-2001)

HS SADER, DJ BIEDENBACH, RN JONES
The JONES Group/JMI Laboratories, North Liberty, IA

ABSTRACT

Background: *Enterobacteriaceae* remain an important cause of nosocomial and community-acquired infections, and antimicrobial resistance (R) has increased steadily among these pathogens over the last decade. The objectives of the present study were to evaluate and compare the contemporary, global spectrum of activity for commonly used antimicrobial agents as potential treatments of *Enterobacteriaceae* infections.

Methods: A total of 48,440 *Enterobacteriaceae* isolates collected consecutively from patients hospitalized in participant SENTRY Program sites (four international regions; Asia-Pacific, Europe, Latin America, and North America) were tested by the reference broth microdilution method against 27 antimicrobial agents.

Results: The most active compounds could be divided into 3 groups based on their spectrum of activity. The highest group included meropenem and imipenem, with 99.9% susceptibility (S) rates. The second group included amikacin (97.3% S) and cefepime (97.2% S); and a third level activity group (89.8% - 91.7% S) had a rank order of susceptibility: gatifloxacin = levofloxacin (91.7% S) > ceftazidime (91.4% S) > ceftriaxone (91.2% S) > aztreonam (91.1% S) > gentamicin (90.6% S) > piperacillin/tazobactam = ciprofloxacin (90.5% S) > tobramycin (89.8%).

Conclusion: The important findings of this study were: 1) carbapenem resistance remained very rare among contemporary (1997-2001) *Enterobacteriaceae*; 2) cefepime and amikacin were very active (less than 2% R) among potentially unrestricted agents; and 3) the activity of the newer fluoroquinolones (gatifloxacin and levofloxacin) was very similar to or superior to that of ciprofloxacin against the current, worldwide clinical isolates of *Enterobacteriaceae*. Comprehensive multicenter surveillance programs remain important to monitor the comparative activity of antimicrobial agents currently used in clinical practice.

INTRODUCTION

The increasing incidence of antimicrobial resistance among nosocomial and community-acquired pathogens has produced a major challenge for the successful therapy of many bacterial infections. Infections caused by resistant bacteria are associated with higher rates of hospitalization, greater length of stay, and higher rates of morbidity and mortality. The best approach for reducing infection-related complications appears to be the selection of the initial, often empiric, broad-spectrum therapeutic regimen.

Enterobacteriaceae remain an important cause of both nosocomial and community-acquired infections, and antimicrobial resistance has increased incrementally among these pathogens in the last decade. The most important *Enterobacteriaceae* resistance problems that impact on clinical treatment are extended-spectrum ß-lactamases (ESBLs) in *Klebsiella* species and *Escherichia coli*; stably derepressed (AmpC) ß-lactamase-mediated resistance among *Enterobacter* spp. and *Citrobacter freundii*; and fluoroquinolone resistance due to altered topoisomerase targets among most clinically important *Enterobacteriaceae* species.

Antimicrobial resistance surveillance programs provide important quantitative information, both for the development of empiric antimicrobial therapy recommendations and for the design of interventions to control or minimize antimicrobial resistance. Due to the comprehensive nature of the SENTRY Antimicrobial Surveillance Program, critical analysis of its results become very helpful to assess the contemporary spectrum of the most clinically important antimicrobial agents. Thus, the results presented here can assist physicians and hospital formulary committees to choose the most appropriate classes of antimicrobial agents, and also the most appropriate compound within a specific class for first-line therapy or as a reserved treatment.

MATERIALS AND METHODS

The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor all prevalent pathogens and antimicrobial resistance patterns of nosocomial and community-onset infections via a broad network of sentinel hospitals distributed by geographical location and bed capacity. The monitored core infections included bloodstream infections, community-acquired respiratory infections, pneumonia in hospitalized patients, wounds or skin and soft tissue infections, and urinary tract infections in hospitalized patients. We report here the antimicrobial susceptibility patterns of all *Enterobacteriaceae* isolates collected during the first five years (1997-2001) of the SENTRY Program worldwide.

Individual strains were collected consecutively from patients hospitalized in participant SENTRY Program medical centers in four international regions: Asia-Pacific region (15-17 sites), Europe (17-32 sites), Latin America (10 sites), and North America (32-38 sites). All isolates were identified by the participant laboratories and confirmed by monitoring facilities (Iowa, USA; Adelaide, Australia; Utrecht, The Netherlands). Each strain was tested by a reference broth microdilution method against more than 30 antimicrobial agents; only agents with the widest potential clinical utility and in vitro activity are reported here. Interpretation of quantitative MIC results was in accordance with National Committee for Clinical Laboratory Standards (NCCLS) methods and criteria.

RESULTS

- Among 48,440 *Enterobacteriaceae* isolates *E. coli* was the most frequently isolated pathogen (46.1%), followed by *Klebsiella* spp. (21.3%) and *Enterobacter* spp. (12.2%; Table 1).
- The most active compounds were the carbapenems, meropenem (MIC_{90}, ≤0.06 µg/ml) and imipenem (MIC_{90}, 1 µg/ml), which were active against 99.9% of the strains at the susceptible breakpoints (Table 2).
- Cefepime was the most active compound among other ß-lactams with a MIC_{90} of 1 µg/ml. This "fourth-generation" cephem inhibited 97.2% of *Enterobacteriaceae* isolates at the susceptible breakpoint (only 1.9% resistance). Ceftazidime, ceftriaxone, aztreonam and piperacillin/tazobactam followed cefepime in their rank order of susceptibility rates (90.5 - 91.4%).
- The fluoroquinolones showed an antimicrobial spectrum very similar to the third group of ß-lactams, with susceptibility rates ranging from 90.5% for ciprofloxacin to 91.7% for the newer agents, gatifloxacin and levofloxacin (Table 3).
- Amikacin (MIC_{90}, 8 µg/ml) was the widest spectrum aminoglycoside with 97.3% susceptibility (most similar to cefepime) among tested strains, followed by gentamicin (MIC_{90}, 4 µg/ml; 90.6% susceptibility) and tobramycin (MIC_{90}, 8 µg/ml; 89.8% susceptibility; see Table 3).

Table 1. Frequency of occurrence for *Enterobacteriaceae* isolates in SENTRY Antimicrobial Surveillance Program medical centers worldwide for the years 1997-2001 (48,440 strains).

Organism or group	No. of occurrences	% of all isolates
1. *E. coli*	22,327	46.1
2. *Klebsiella* spp.[a]	10,329	21.3
3. *Enterobacter* spp.[b]	5,889	12.2
4. *P. mirabilis*	2,434	5.0
5. *Serratia* spp.[c]	2,412	5.0
6. *Salmonella* spp.[d]	1,779	3.8
7. *Citrobacter* spp.[e]	1,276	2.6
8. *Morganella morganii*	675	1.4
9. *Shigella* spp.[f]	469	1.0
10. Indole-positive *Proteus* spp.[g]	244	0.5
11. *Providencia* spp.[h]	217	0.4
12. *Pantoae agglomerans*	217	0.4
13. *Hafnia alvei*	81	0.2
14. *Yersinia* spp.[i]	28	<0.1
15. Other species[j]	63	0.1

a. Includes *K. ornithinolytica* (12 strains), *K. oxytoca* (1,580 strains), *K. ozaenae* (23 strains), *K. pneumoniae* (8,471 strains), *K. rhinoscleromatis* (one strain), *K. terrigena* (two strains), and *Klebsiella* spp., NOS (240 strains).
b. Includes *E. aerogenes* (1,367 strains), *E. amnigenus* (21 strains), *E. asburiae* (20 strains), *E. cancerogenus* (three strains), *E. cloacae* (4,064 strains), *E. gergoviae* (20 strains), *E. hornaechei* (six strains), *E. intermedium* (nine strains), *E. sakazakii* (46 strains), *E. taylorae* (eight strains), and *Enterobacter* spp., NOS (325 strains).
c. Includes *S. fonticola* (13 strains), *S. liquefaciens* (90 strains), *S. marcescens* (2,217 strians), *S. odorifera* (eight strains), *S. plymuthica* (eight strains), *S. rubidaea* (13 strains), and *Serratia* spp., NOS (63 strains).
d. Includes 29 serotypes or serovers with 186 isolates of *S. typhi*.
e. Includes *C. amalonaticus* (32 strains), *C. braakii* (25 strains), *C. fameri* (two strains), *C. freundii* (727 strains), *C. koseri* (424 strains), and *Citrobacter* spp., NOS (66 strains).
f. Includes *S. boydii* (13 strains), *S. dysenteriae* (six strains), *S. flexneri* (135 strains), *S. sonnei* (278 strains), and *Shigella* spp., NOS (37 strains).
g. Includes *P. penneri* (31 strains), *P. vulgaris* (168 strains), and *Proteus* spp., NOS (45 strains).
h. Includes *P. alcalifaciens* (four strains), *P. rettgeri* (58 strains), *P. rustigianii* (two strains), *P. stuartii* (138 strains), and *Providencia* spp., NOS (15 strains).
i. Includes *Y. enterocolitica* (26 strains) and one strain each of *Y. ruckeri* and *Yersinia* spp.
j. Fourteen other species or genus groups with one to 17 strains each.

Table 2. Comparative activity of 15 ß-lactams tested against 48,440 *Enterobacteriaceae* isolated in SENTRY Antimicrobial Surveillance Program centers and tested by reference MIC methods from 1997-2001 worldwide.

	Cumulative % inhibited at MIC (µg/ml) of:												
Antimicrobial agent	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	% S/R[a]
Ampicillin	-[b]	-	-	-	-	18.8	30.1	33.1[c]	38.2	-	-	-	33.1/61.8
Amoxicillin/Clavulanate	-	-	-	-	-	28.2	48.3	64.9	75.7	-	-	-	64.9/24.3
Piperacillin	-	-	-	-	21.7	41.1	51.7	59.8	63.3	65.9	69.3	73.4	63.3/26.6
Piperacillin/Tazobactam	-	-	-	13.0	36.9	69.1	82.5	87.4	90.5	93.0	95.2	-	90.5/4.8
Ticarcillin	-	-	-	-	10.0	23.8	39.0	43.8	45.7	48.1	52.6	60.6	45.7/47.4
Ticarcillin/Clavulanate	-	-	-	-	14.5	36.8	56.2	66.1	75.1	82.2	88.2	93.3	75.1/11.8
Cefazolin	-	-	-	-	-	48.3	61.4	66.4	69.8	-	-	-	66.4/30.2
Cefuroxime	-	0.2	0.7	3.4	12.3	32.8	64.3	76.7	81.4	-	-	-	76.7/18.6
Cefoxitin	-	-	0.1	0.5	8.1	39.7	66.4	76.0	81.4	84.7	-	-	76.0/18.6
Aztreonam	-	75.6	84.1	86.5	87.8	88.8	89.8	91.2	92.5	-	-	-	91.1/7.5
Ceftriaxone	-	-	83.5	86.2	87.6	88.6	89.8	91.2	92.9	94.7	-	-	91.2/5.3
Ceftazidime	-	34.6	58.6	66.0	70.7	88.8	90.2	91.4	92.7	-	-	-	91.4/8.6
Cefepime	-	82.8	87.6	90.2	92.3	94.3	96.0	97.2	98.1	-	-	-	97.2/1.9
Imipenem	4.7	46.2	70.0	85.7	93.8	98.6	99.9	99.9	-	-	-	-	>99.9/<0.1
Meropenem	90.8	96.4	98.8	99.4	99.7	99.8	99.9	99.9	-	-	-	-	>99.9/<0.1

a. Susceptibility (S) and resistance (R) interpretive criteria of the NCCLS.
b. - = untested MIC level.
c. Underline indicates the susceptible breakpoint (NCCLS).

Table 3. Comparative activity of six aminoglycosides and fluoroquinolones tested against 48,440 *Enterobacteriaceae* isolated in SENTRY Antimicrobial Surveillance Program centers (1997-2001) worldwide and processed by reference MIC methods.

	Cumulative % inhibited at MIC (µg/ml) of:										
Antimicrobial agent	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	% S/R[a]
Amikacin	-[b]	-	0.2	1.8	26.4	69.3	88.8	95.0	97.3[c]	98.5	97.3/1.5
Gentamicin	-	-	-	-	-	88.9	90.6	91.9	-	-	90.6/8.1
Tobramycin	-	0.4	6.8	40.8	72.8	80.1	89.8	92.1	94.6	-	89.8/7.9
Ciprofloxacin	-	-	86.9	88.9	90.5	91.7	-	-	-	-	90.5/8.3
Gatifloxacin	70.9	78.7	84.7	88.0	90.1	91.7	94.1	-	-	-	91.7/5.9
Levofloxacin	-	-	-	88.4	90.4	91.7	93.8	-	-	-	91.7/6.2

a. Susceptibility (S) and resistance (R) interpretive criteria of the NCCLS.
b. - = untested MIC level.
c. Underline indicates the susceptible breakpoint (NCCLS).

CONCLUSIONS

- The results of this study clearly showed three groups of antimicrobial agents in terms of spectrum of activity against *Enterobacteriaceae*, each with >90% susceptibility rates.
  - Group I are the carbapenems (imipenem and meropenem), which possess near complete in vitro activity against the *Enterobacteriaceae* (48,440 isolates).
  - Group II includes cefepime and amikacin, with 97.2-97.3% susceptibility rates. Either one of these compounds would represent an excellent option for empiric mono- or combination therapy for suspected *Enterobacteriaceae* infection.
  - Group III was active against approximately 90% of *Enterobacteriaceae* strains (7% less than Group II agents) evaluated in the present study. This group includes the ß-lactams ceftazidime, ceftriaxone, aztreonam and piperacillin/tazobactam; two aminoglycosides (gentamicin and tobramycin); and all fluoroquinolones evaluated (ciprofloxacin, gatifloxacin and levofloxacin).
- The newer fluoroquinolones, such as gatifloxacin and levofloxacin, offered several advantages over ciprofloxacin and showed significant in vitro activity (2.1 - 2.4% reduced resistance rates) and antimicrobial spectrum advantages when directly compared to ciprofloxacin worldwide.
- Comprehensive multicenter surveillance networks, such as the SENTRY Program, remain important in monitoring the comparative activity of antimicrobial agents currently in use in clinical practice.

SELECTED REFERENCES

Barradell LB, Bryson HM. Cefepime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; 47:471-505.

Harris AD, Smith D, Johnson JA, Bradham DD, Roghmann MC. Risk factors for imipenem-resistant *Pseudomonas aeruginosa* among hospitalized patients. *Clinical Infectious Disease* 2002; 1:34:340-345.

Jones RN. Resistance patterns among nosocomial pathogens. Trends over the past few years. *Chest* 2001; 119:397S-404S.

Jones RN. Microbiology of newer fluoroquinolones: Focus on respiratory pathogens. *Diagnostic Microbiology and Infectious Disease* 2002; 44:213-220.

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.

Perry CM, Ormrod D, Hurst M, Onrust SV. Gatifloxacin: A review of its use in the management of bacterial infections. *Drugs* 2002; 62:169-207

Zhanel GG, Ennis K, Vercaigne L, Walkty A, Gin AS, Embil J, Smith H, Hoban DJ. A critical review of the fluoroquinolones: Focus on respiratory infections. *Drugs* 2002; 62:13-59.