A-34

# Carbapenem and Cefepime Activity Tested Against Ceftazidime- and Ceftriaxone-Resistant *Enterobacter* spp. Isolates From North America, Latin America, Asia-Pacific, and Europe, 1997-2000: Report From the SENTRY Antimicrobial Surveillance Program.

A.H. Mutnick,[1,2] M.L. Beach,[1] R.N. Jones,[1,3] The SENTRY Program Participants Group. [1]The JONES Group/JMI Laboratories, North Liberty, IA [www.jmilabs.com]; [2]University of Iowa, College of Pharmacy, Iowa City, IA; and [3]Tufts University School of Medicine, Boston, MA

## AMENDED ABSTRACT

**Background:** The SENTRY Program was initiated in 1997 as a global network of hospitals to monitor the predominant bacterial and fungal pathogens as well as antimicrobial susceptibility patterns associated with 4 infection types: blood stream (BSI), lower respiratory (LRTI), cutaneous (SSTI) and urinary tract (UTI). Data representing all *Enterobacter* spp. strains collected during the years of 1997 - 2000 were obtained for continental geographic areas.
**Methods:** A total of 4,634 *Enterobacter* spp. isolates were tested against cefepime (CPM), ceftazidime (CTAZ), ceftriaxone (CTRI), and imipenem (IMP). North America (NA) represented the largest provider of isolates with 2,217 (47.8%) followed by Europe (EU; 1,185 strains; 25.6%), Latin America (LA; 737 strains; 15.9%) and Asia-Pacific (APAC; 495 strains; 10.7%). BSI represented the largest number of isolates with 2,334 (50.4%) isolates, followed by LRTI with 1,307 (28.2%), cutaneous with 537 (11.6%), and UTI with 456 (9.8%).
**Results:** IMP, a carbapenem, continues to maintain wide coverage for ceftazidime-ceftriaxone-resistant *Enterobacter* spp. (CCR-ES) during the initial 4 years of data collection. IMP-R rates range from nil in LA, EU and APAC to only 0.2% in NA. CPM also continues to show susceptibilities for *Enterobacter* spp. (overall) of 88.6 - 96.8% in EU, NA and APAC, but in LA the susceptibility declined to 77.5% among CCR-ES. These LA results are quite distinct from the other geographic areas; where CPM-R rates range from only 0.9% (NA) to 6.9% (EU). A concurrent, associated concern was the number of ESBL-phenotypes identified in *Klebsiella* spp. strains in the 4 areas. An ESBL rate as low as 5.8% was identified from NA and compared to 19.2 and 22.7% from APAC and EU. LA had an ESBL rate of 41.8% corresponding to the higher CCR-ES CMP-R rate of 12.1%.
**Conclusions:** The data reveal that CPM continues to be an effective agent against CCR-ES in 3 of the 4 geographic areas representing the SENTRY Program. Various factors responsible for the significant decrease in susceptibility for CPM in LA include the prevalence of CTX-M ESBL-producing isolates. Further epidemiologic investigations into this area are needed and may implicate problems centering around aseptic care/personal hygiene and infection control practices. IMP continues to provide very good coverage against CCR-ES in all four geographic areas.

## INTRODUCTION

The SENTRY Antimicrobial Surveillance Program was initiated in 1997, with the primary purpose of monitoring antimicrobial resistance trends of both nosocomial- and community-acquired pathogens obtained from four infection sites: bloodstream (BSI), lower respiratory tract (LRTI), cutaneous (SSTI), and urinary tract (UTI) over large geographic areas: North America (NA), Latin America (LA), Europe (EU), and the Asia-Pacific (APAC) regions. Currently, over 80 sentinel hospitals throughout the SENTRY Program network share bacterial isolates with the designated monitor and referral laboratories to assure validated reference identification, susceptibility testing methods and molecular epidemiology throughout the tenure of the study.

The purpose of this study was to evaluate the potency and susceptibility patterns for cefepime (CPM) compared to the third-generation cephalosporins, ceftazidime (CTAZ) and ceftriaxone (CTRI), as well as to the carbapenem, imipenem (IMP) tested against *Enterobacter* spp. strains by the SENTRY Program over the four-year period from 1997 to 2000.

## MATERIALS AND METHODS

Between 1997 and 2000, a total of 4,634 strains of *Enterobacter* spp. were collected from the SENTRY Program to evaluate the potencies and susceptibilities of CPM, CTAX, CTRI, and IMP against these strains from BSI, LRTI, SSTI, and UTI. The antimicrobials were tested using broth microdilution methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS).

Organisms were inoculated into cation-adjusted Mueller-Hinton broth and incubated for 24 hours at 35ºC in ambient air. The MIC panels were interpreted manually and results validated using the appropriate American Type Culture Collection (ATCC) quality control strains in accordance with NCCLS documents. These strains included *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212.

## RESULTS

- NA (2,217 strains) had the largest number of organisms obtained with BSI (1,068) > LRTI (730) > SSTI (234) > UTI (185); followed by EU (1,185 strains) with BSI (608) > LRTI (287) > SSTI (161) > UTI (129); then LA (737 strains) with BSI (420) > LRTI (140) > SSTI (100) > UTI (77); and finally APAC (495 strains) with BSI (238) > LRTI (150) > UTI (65) >SSTI (42) (Table 1).

**Table 1.** Occurrence of *Enterobacter* spp. strains by geographic area and site of infection (4,634 strains; SENTRY Antimicrobial Surveillance Program, 1997-2000).

| | No. by site of infection: | | | |
|---|---|---|---|---|
| Geographic region (no. tested) | BSI | LRTI | SSTI | UTI |
| North America (2,217) | 1,068 | 730 | 234 | 185 |
| Latin America (737) | 420 | 140 | 100 | 77 |
| Asia-Pacific (495) | 238 | 150 | 42 | 65 |
| Europe (1,185) | 608 | 287 | 161 | 129 |
| All regions (4,634) | 2,334 | 1,307 | 537 | 456 |

- CPM (95.3-99.7% susceptible) and IMP (>99.9-100.0%) continued to demonstrate very high activity against *Enterobacter* spp. strains in all four geographic regions. In contrast, ceftazidime resistance (CTAZ-R) rates of 20.0 to 32.3% and ceftriaxone resistance (CTRI-R) rates of 11.8 to 27.5% were observed (Table 2).

**Table 2.** Antimicrobial activity and spectrum of cephalosporins tested against *Enterobacter* spp. strains from four geographic regions (SENTRY Antimicrobial Surveillance Program, 1997-98).

| | MIC (µg/ml) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1997 | | 1998 | | 1999 | | 2000 | | All years | | |
| Geographic region (no. tested) / Antimicrobial | 50% | 90% | 50% | 90% | 50% | 90% | 50% | 90% | 50% | 90% | % resistant[a] |
| N America (2,217) | | | | | | | | | | | |
| Ceftazidime | 0.5 | >16 | 0.5 | >16 | 0.5 | >16 | 0.25 | >16 | 0.5 | >16 | 20.0 |
| Ceftriaxone | ≤0.25 | >32 | ≤0.25 | >32 | 0.5 | >32 | ≤0.25 | >32 | ≤0.25 | >32 | 11.8 |
| Cefepime | ≤0.12 | 2 | ≤0.12 | 2 | ≤0.12 | 2 | ≤0.12 | 1 | ≤0.12 | 2 | 0.3 |
| Imipenem | 0.5 | 2 | 0.5 | 2 | 0.5 | 1 | 0.25 | 1 | 0.5 | 1 | <0.1 |
| L America (737) | | | | | | | | | | | |
| Ceftazidime | 0.5 | >16 | 1 | >16 | 0.5 | >16 | 1 | >16 | 0.5 | >16 | 32.2 |
| Ceftriaxone | 0.5 | >32 | 0.5 | >32 | 0.5 | >32 | 0.5 | >32 | 0.5 | >32 | 27.5 |
| Cefepime | 0.25 | 8 | ≤0.12 | 16 | ≤0.12 | 8 | 0.25 | 8 | ≤0.12 | 8 | 4.7 |
| Imipenem | 0.5 | 2 | 0.5 | 1 | 0.5 | 1 | 0.25 | 1 | 0.5 | 2 | 0.0 |
| Asia-Pacific (495) | | | | | | | | | | | |
| Ceftazidime | NT | NT | 1 | >16 | 0.5 | >16 | 0.5 | >16 | 0.5 | >16 | 32.3 |
| Ceftriaxone | NT | NT | 0.5 | >32 | 0.5 | >32 | 0.5 | >32 | 0.5 | >32 | 19.2 |
| Cefepime | NT | NT | ≤0.12 | 4 | ≤0.12 | 8 | ≤0.12 | 4 | ≤0.12 | 4 | 2.4 |
| Imipenem | NT | NT | 0.5 | 1 | 0.5 | 2 | 0.5 | 1 | 0.5 | 1 | 0.0 |
| Europe (1,185) | | | | | | | | | | | |
| Ceftazidime | 0.25 | >16 | 0.5 | >16 | 0.5 | >16 | 0.5 | >16 | 0.5 | >16 | 24.9 |
| Ceftriaxone | ≤0.25 | 32 | 0.5 | >32 | ≤0.25 | >32 | ≤0.25 | >32 | ≤0.25 | >32 | 16.5 |
| Cefepime | ≤0.12 | 4 | ≤0.12 | 4 | ≤0.12 | 4 | ≤0.12 | 4 | ≤0.12 | 4 | 2.3 |
| Imipenem | 1 | 2 | 0.5 | 2 | 0.5 | 1 | 0.5 | 1 | 0.5 | 2 | 0.0 |

a. Resistance as defined by the NCCLS [2002]: ceftazidime and cefepime at >16 µg/ml; ceftriaxone at >32 µg/ml; and imipenem at >8 µg/ml.
b. Not tested (NT) in 1997.

- IMP demonstrated very low resistance rates in all four geographical regions when tested against ceftazidime- and ceftriaxone-resistant *Enterobacter* spp. (CCR-ES) strains (Table 3).

**Table 3.** Antimicrobial activity of cefepime and imipenem tested against ceftazidime- and ceftriaxone-resistant[a] *Enterobacter* spp. in the four SENTRY Program regions (1997-2000).

| | | MIC (µg/ml) | | % by category | |
|---|---|---|---|---|---|
| Geographic region (no. tested) | Antimicrobial | 50% | 90% | Susceptible | Resistant |
| N America (441) | Cefepime | 2 | 8 | 96.8 | 0.9 |
| | Imipenem | 0.5 | 1 | 99.8 | 0.2 |
| L America (240) | Cefepime | 4 | >16 | 77.5 | 12.1 |
| | Imipenem | 0.5 | 1 | 100.0 | 0.0 |
| Asia-Pacific (156) | Cefepime | 2 | 8 | 91.7 | 5.1 |
| | Imipenem | 0.5 | 1 | 100.0 | 0.0 |
| Europe (306) | Cefepime | 2 | 16 | 88.6 | 6.9 |
| | Imipenem | 0.5 | 2 | 99.0 | 0.0 |

a. Defined as all non-susceptible isolates (MIC, ≥16 µg/ml) to both cephalosporins [NCCLS, 2002].

- There were three different levels of risk for use of CPM in CCR-ES (Amp C phenotypes) isolate infections (Table 4): 1) in NA there was a low level of risk with resistance rates of 0.9%; 2) in EU and APAC there was a moderate level of risk with resistance rates of 5.1 to 6.9%; and 3) in LA there was a higher level of risk with a resistance rate of 12.1%. Increasing risk indicates the potential coexistent presence of a second ß-lactamase (ESBL) or an AMP mutation.

- Extended-spectrum ß-lactamase (ESBL) phenotype occurrence rates in *Klebsiella* spp. (reservoir species) varied among the four geographic regions, with the lowest rate in NA (5.8%) < APAC (19.2%) < EU (22.7%) < LA (41.8%). These rates correlate with the diminished utility of the “fourth-generation” cephalosporin by region.

**Table 4.** Comparison of cefepime resistance rates among CCR-ES and ESBL-phenotype rates among *Klebsiella* spp. by geographic region.

| | CCR-ES | *Klebsiella* spp. |
|---|---|---|
| Region | Cefepime-resistant (%)[a] | ESBL rate (%)[b] |
| N America | 0.9 | 5.8 |
| Asia-Pacific | 5.1 | 19.2 |
| Europe | 6.9 | 22.7 |
| L America | 12.1 | 41.8 |

a. Rate of strains with MIC at ≥32 µg/ml [NCCLS, 2002].
b. ESBL-phenotype rate as an average of three substrates (aztreonam, ceftazidime, ceftriaxone) used to determine % of ESBL-phenotype isolates with MICs at ≥2 µg/ml [NCCLS, 2002]. The numbers of *Klebsiella* spp. strains screened were: North America (3,837 strains), Asia-Pacific (1,091 strains), Europe (1,865 strains) and Latin America (1,440 strains).

## CONCLUSIONS

- IMP, representing carbapenems, continues to be a very useful agent in the treatment of CCR-ES throughout all four geographic regions participating in the SENTRY Antimicrobial Surveillance Program.
- CPM has utility in the treatment of CCR-ES throughout NA (USA and Canada), however, moderate to high risks of resistance are currently present in EU, APAC and LA.
- Continued use of longitudinal surveillance antimicrobial programs is necessary to track the development of resistance patterns and to prevent the increase in healthcare costs associated with increases in infectious disease-related mortality throughout the world.

## SELECTED REFERENCES

1. Jones RN, Jenkins SG, Hoban DJ, et al. In vitro efficacy of six cephalosporins tested against *Enterobacter*iaceae isolated at 38 North American medical centres participating in the SENTRY Antimicrobial Surveillance Program, 1997-1998. *Int J Antimicrob Agents* 2000; 15:111-8

2. National Committee for Clinical Laboratory Standards. 2000. Methods for dilution antimicrobial tests for bacteria that grows aerobically. Approved standard M7-A5. Wayne, PA:NCCLS.

3. National Committee for Clinical Laboratory Standards. 2002. Performance standards for antimicrobial susceptibility testing. Supplemental tables, M100-S12. Wayne, PA:NCCLS.

4. Cosgrove SE, Kaye KS, Eliopoulous GM, et al. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. *Arch Intern Med* 2002; 162:185-90.

5. Naumiuk L, Samet A, Dziemaszkiewicz E. Cefepime in vitro activity against derepressed extended-spectrum beta-lactamase (ESBL)-producing and non-ESBL-producing *Enterobacter* cloacae by a disc diffusion method. *J Antimicrob Chemother* 2001; 4:321-2.

6. Gottlieb T, Wolfson C. Comparison of the MICs of cefepime for extended-spectrum ß-lactamase-producing and non-extended-spectrum ß-lactamase-producing strains of *Enterobacter* cloacae. *J Antimicrob Chemother* 2000; 46:300-2.

7. Sanders WE, Tenney JH, Kessler RE. Efficacy of Cefepime in the Treatment of Infections Due to Multiply Resistant *Enterobacter* Species. *Clin Inf Dis* 1996; 23:454-61.

8. Winokur PL, Canton R, Cassellas JM, Legakis N. Variations in the Prevalence of Strains Expressing an Extended-Spectrum ß-lactamase Phenotype and Characterization of Isolates from Europe, the Americas, and the Western Pacific Region. *Clin Inf Dis* 2001; 32 (Suppl 2):S94-S103.