Susceptibility Patterns of *Klebsiella* spp. isolated in Latin America: Results of the SENTRY Antimicrobial Surveillance Program (1997-2006)

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ABSTRACT

Backgroud:
We evaluated the antimicrobial susceptibility (S) patterns of the *Klebsiella* (KSP) collected from 7 Latin American countries.

Methods:
3,516 KSP clinical isolates collected between 1997 and 2006 by the SENTRY Program were studied. Antimicrobial S testing against > 20 antimicrobials was performed using the CLSI broth microdilution methods. Trends of resistance between 1997 and 2006 for each antimicrobial agent were analyzed by the chi-square test.

Results:
K. pneumoniae (KPN; 3122/88.8%) and *K. oxytoca* (358/10.2%) were the most frequent species. Most of the KSP isolates were collected from blood (61.0%) and respiratory tract (18.8%). Brazil (BR; 41.7%), Argentina (ARG; 23.1%) and Chile (15.7%) contributed with the largest number of isolates. ESBL phenotype was observed in 45.5% of KPN (1,422 isolates), and was more frequently observed in ARG (59.2%) and BR (58.8%). Most of the KSP isolates with elevated (≥8 µg/ml) polymyxin B (PB) MICs were collected from BR (60.0%) and ARG (26.7%), and recovered from bloodstream infections (76.7%). A significant decrease in S rates to CIP (82.5-71.0% *p*= <0.0005) and LEV (85.2-72.8% *p*=0.00009) was observed in 2006 compared to 1997. In contrast, there was an increase in the S rates to piperacillin/tazobactam (58.6/74.0% *p*=0.0008) and ticarcillin/clavulanic acid (47.4/57.9% *p*=0.0008) in the same period.

Antimicrobial Agent	(%) inhibited at MIC (µg/ml) ≤1	2	4	≥8	% S
Imipenem	98.6	0.8	0.3	0.3	99.7
Meropenem	98.3	0.7	0.3	0.7	99.3
Levofloxacin	82.7	2.4	2.9	12.0	85.1
Ciprofloxacin	82.5	2.5	6.1	9.0	82.5
Polymyxin B	95.8	2.3	0.5	2.0	95.8

Conclusion:
The carbapenems and PB remain the best therapeutic options for treatment of KSP infections in LA, especially due to the high prevalence of ESBL phenotype in this region. The emergence of KSP isolates showing reduced susceptibility to PB is of great concern.

INTRODUCTION

Klebsiella spp. is an important etiologic agent of community- and nosocomial-acquired infections, especially those involving the urinary and respiratory tracts. Furthermore, the prevalence of ESBL-producing *Klebsiella* spp. is particularly elevated in some geographic regions, such as Latin America. The therapeutic options for treatment of infections caused by ESBL-producing *Klebsiella* spp. are severely limited and, to date, the carbapenems are the most reliable agents for treatment of such infections. However, in certain geographic areas, the high prevalence of ESBL-producing *Klebsiella* spp. has led to the increased use of carbapenems, which may compromise the clinical efficacy of these compounds in a near future.

The aim of the present study was to evaluate the antimicrobial susceptibility patterns of the *Klebsiella* spp. isolated in 7 Latin American countries in 10 years of the SENTRY Antimicrobial Surveillance Program.

METHODS

Bacterial strains: A total 3,516 *Klebsiella* spp. clinical isolates were evaluated between 1997 and 2006 by the SENTRY Antimicrobial Surveillance Program. These isolates were recovered from diverse body sites of infection, mainly bloodstream and respiratory tract. Only one isolate per patient was evaluated. All isolates were identified at the participating institution by the routine methodology in use at each laboratory and confirmed at the coordinator center (JMI Laboratories, North Liberty, IA) by the Vitek System (bioMerieux, Hazelwood, MO) and/or biochemical tests where needed.

Medical centers: The participant medical centers included eleven cities in seven countries: São Paulo (1997-2006), Rio de Janeiro (1997-1998), Brasília (2001-2006), Florianópolis (1997-2006) and Porto Alegre (1999-2006) in Brazil; Bueno Aires and San Isidro in Argentina (1997-2006); Santiago in Chile (two sites, 1997-2006); Montevideo in Uruguay (1997); Medelin in Colombia (1997-2000); Mexico City (three sites, 1997-2001), Guadalajara (2004-2006) and Durango (2005-2006) in Mexico; and Caracas in Venezuela (1998-2004).

Susceptibility testing: Antimicrobial susceptibility testing was performed and interpreted using reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI). Microdilution panels and broth for inoculation were produced by TREK Diagnostics (Cleveland, OH, USA). Quality control strains tested were: *Escherichia coli* ATCC 25922 and 35218 and *Pseudomonas aeruginosa* ATCC 27853. Isolates with increased MIC values (≥ 2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as ESBL phenotype according to CLSI criteria.

Statistical analysis: Trends of susceptibility rates between 1997 and 2006 for each antimicrobial agent were analyzed by the chi-square test and values of p <0.05 were considered statistically significant.

RESULTS

- Brazilian medical centers contributed with the largest number of isolates (41.7%) followed by medical centers in Argentina (23.1%) and Chile (15.7%).
- The vast majority of isolates were *K. pneumoniae* (88.8%) and *K. oxytoca* (10.2%).
- The majority of strains were isolated from bloodstream infections (62.9%), followed by lower respiratory tract (19.6%), urinary tract (8.7%) and skin and soft tissue infections (8.2%).

Table 1. Antimicrobial potency and spectrum of drugs tested against *Klebsiella* spp. isolated in Latin America (SENTRY Program 1997-2006).

Antimicrobial agent	1997-2001 MIC_{50}	1997-2001 MIC_{90}	1997-2001 % Susceptible	2002-2006 MIC_{50}	2002-2006 MIC_{90}	2002-2006 % Susceptible	1997-2006 MIC_{50}	1997-2006 MIC_{90}	1997-2006 % Susceptible
Piperacillin/tazobactam[a]	4	>64	68.4	4	>64	74.4	4	>64	71.4
Cefuroxime	4	>16	56.3	4	>16	56.8	4	>16	56.5
Cefoxitin	4	32	84.2	≤4	16	83.6	4	16	83.9
Ceftriaxone	≤0.25	>32	64.3	≤0.25	>32	62.4	≤0.25	>32	63.3
Ceftazidime	≤1	>16	68.5	≤1	>16	70.9	≤1	>16	69.7
Cefepime	≤0.12	>16	78.2	≤0.12	>16	74.3	≤0.12	>16	76.2
Imipenem	0.25	0.5	99.8	0.25	0.5	99.6	0.25	0.5	99.7
Meropenem	≤0.06	0.12	99.6	≤0.06	≤0.12	99.0	≤0.06	0.12	99.3
Aztreonam	≤0.12	>16	63.9	≤0.12	>16	65.8	≤0.12	>16	64.8
Amikacin	2	32	81.4	2	32	85.2	2	32	83.3
Gentamicin	≤2	>16	67.4	≤2	>8	66.2	≤2	16	66.8
Tobramicin	1	>16	60.3	0.5	>16	64.0	0.5	>16	62.1
Ciprofloxacin	≤0.25	>2	86.6	≤0.25	>4	78.4	≤0.25	>2	82.5
Levofloxacin	≤0.5	4	89.1	≤0.5	>4	81.1	≤0.5	>4	85.1
Polymyxin B[a]	≤1	≤1	95.7	≤1	≤1	95.8	≤1	≤1	95.8

a. Isolate showing MIC ≤2 µg/ml was considered susceptible.

- Imipenem (MIC_{90}, 0.5 µg/ml; 99.7% susceptible) and meropenem (MIC_{90}, 0.12 µg/ml; 99.3% susceptible) were the most active compounds, followed by polymyxin B (MIC_{90}, ≤1 µg/ml; 95.8% susceptible), levofloxacin (MIC_{90}, >4 µg/ml; 85.1% susceptible), and ciprofloxacin (MIC_{90}, >2 µg/ml; 82.5% susceptible). The susceptibility rates for broad-spectrum cephalosporins varied from 63.3% (ceftriaxone) to 76.2% (cefepime; Table 1).
- Comparison of 1997 and 2006 susceptibility rates revealed a significant decrease in susceptibility to ciprofloxacin (82.5 to 71.1%; *p*=<0.0005) and levofloxacin (85.2 to 72.8%; *p*=0.00009). On the other hand, an increase in the susceptibility rates for piperacillin/tazobactam (58.6 to 74.0%; *p*=0.0008) was observed in the same period (Table 2).
- Polymyxin B was highly active against *Klebsiella* spp., inhibiting 1,984 (95.8%) isolates at concentrations of 2 µg/ml or less. Thirty isolates (2.0%) showed elevated polymyxin B MIC values (≥8 µg/ml). Most of these strains were isolated in Brazil (60.0%) and Argentina (26.7%), and recovered from bloodstream infections (76.7%).
- The antimicrobial susceptibility profiles of *Klebsiella* spp. isolates showing elevated polymyxin B MIC values (≥8 µg/ml) are found in Table 3. Twenty of 30 *Klebsiella* spp. were screened as ESBL producers and displayed elevated resistance rates to aztreonam and broad-spectrum cephalosporins.
- Among *K. pneumoniae* isolates, 45.5% (1,422) exhibited an ESBL phenotype. The prevalence of ESBL phenotypes were highest in Argentina (46.2%) followed by Brazil (43.5%) and Mexico (37.7%; Figure 1).
- The annual rates of *K. pneumoniae* isolates screened as ESBL producers did not vary significantly during the study period except for the year 2003, when the lowest rate was observed (31.6%; data not shown).

Table 2. Susceptibility rates of *Klebsiella* spp. isolated in Latin America in 1997 and 2006 (SENTRY Program 1997-2006).

Antimicrobial agents	Year of isolation (no. tested) 1997 (331)	2006 (311)
Piperacillin/tazobactam	58.6	74.0
Cefuroxime	52.6	55.0
Cefoxitin	81.0	84.9
Ceftriaxone	62.8	58.8
Ceftazidime	66.8	70.1
Cefepime	77.0	68.8
Imipenem	99.4	99.7
Meropenem	99.4	99.7
Aztreonam	63.1	66.2
Amikacin	79.8	84.6
Gentamicin	62.8	64.3
Tobramycin	57.7	63.3
Ciprofloxacin[a]	82.5	71.1
Levofloxacin[a]	85.2	72.8

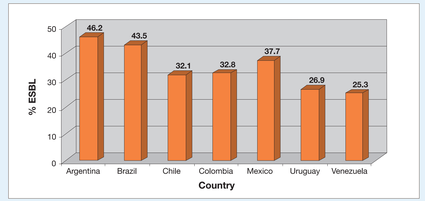
a. Variation was statistically significant (p <0.005).

Table 3. Resistance rates for selected antimicrobial agents tested against *Klebsiella* spp. showing elevated polymyxin B MIC values (≥8 µg/ml) according to the country of isolation (SENTRY Program 1997-2006).

Nation	AZT[a]	CAZ[a]	CRO[a]	FEP[a]	PTZ[a]	CIP[a]	LEV[a]	IMP[a]	MER[a]
Argentina (n=8)	62.5	25.0	50.0	50.0	37.5	50.0	50.0	0.0	0.0
Brazil (n=18)	72.2	38.9	77.7	50.0	22.2	44.4	27.7	0.0	0.0
Chile (n=2)	50.0	50.0	5.0	50.0	50.0	50.0	50.0	0.0	0.0
Mexico (n=1)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Venezuela (n=1)	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

a. Abbreviations: AZT, aztreonam; CAZ, ceftazidime; CRO, ceftriaxone; FEP, cefepime, PTZ, piperacillin/tazobactam; CIP, ciprofloxacin; LEV, levofloxacin; IMP, imipenem; and MER, meropenem.

Figure 1. Prevalence of ESBL phenotype among *K. pneumoniae* strains.



CONCLUSIONS

- A high geographic prevalence of *Klebsiella* spp. isolates showing an ESBL phenotype was observed in the Latin American medical centers participating in the SENTRY Program.
- The observed increase in the susceptibility rate for piperacillin/tazobactam may indicate a change in the ESBL types produced by *Klebsiella* spp.
- Carbapenem-resistant *Klebsiella* spp. strains have recently emerged in the Latin American region.
- The *Klebsiella* spp. isolates (4.2%) showing elevated polymyxin B MIC values are of great concern since this agent would constitute an important alternative treatment of the carbapenem-resistant (0.3%) *Klebsiella* spp.

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