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# *Acinetobacter* spp. Infections: The Latin American Scenario by the SENTRY Antimicrobial Surveillance Program (1997-2006)

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SENTRY ANTIMICROBIAL SURVEILLANCE

## AMENDED ABSTRACT

**Objectives:** To evaluate the frequency of occurrence, the antimicrobial susceptibility profile and the temporal evolution of antimicrobial resistance among *Acinetobacter* spp. isolated in Latin America. *Acinetobacter* spp. is an important nosocomial pathogen in Latin America and exhibits high rates of acquired resistance to many antimicrobial agents.

**Methods:** Consecutive non-duplicate bacterial pathogens were collected in the last decade (1997-2006) from hospitalized patients in 10 Latin American medical centers (7 countries). The antimicrobial susceptibility profile to > 20 antimicrobial agents was evaluated by CLSI broth microdilution methods and interpreted by CLSI M100-S18 (2008) or US-FDA package insert criteria for Enterobacteriaceae (tigecycline).

**Results:** A total of 1,807 isolates were collected during the 10-year period. The highest number of isolates were collected from Brazil (52.9%) > Argentina (18.7%) > Chile (14.3%) and Mexico (6.2%). Most isolates were collected from bloodstream (57.2%) followed by respiratory tract (31.9%) infections. The activities of selected drugs are shown in Table 3. Polymyxin B, tigecycline and imipenem demonstrated the highest in vitro activity against *Acinetobacter* spp. A significant increase ($p < 0.05$) in the resistance rates for imipenem (8.8-27.0%), meropenem (8.3-31.7%), cefepime (66.3-71.3%), ceftazidime (71.0-79.1%), amikacin (71.0-79.1%) was observed when comparing the 1997 and 2006 results.

**Conclusions:** Polymyxin B remains the most active drug against *Acinetobacter* spp. in the Latin American countries evaluated by the SENTRY Program and tigecycline was also active. An important reduction in the susceptibility rates to some broad-spectrum antimicrobials, including the carbapenems, was observed, limiting therapeutic options available.

## INTRODUCTION

*Acinetobacter* spp. is an opportunistic pathogen that frequently causes sepsis, pneumonia and urinary tract infection in debilitated patients. It has also been responsible for many hospital outbreaks, most of them occurring in intensive care units. The frequency of multidrug-resistant (MDR) *Acinetobacter* spp. isolates has increasingly been reported often during the last decade. Carbapenem (imipenem and/or meropenem) resistance in this species is now observed more commonly worldwide, and constitutes a sentinel event for emerging antimicrobial resistance. Several factors favor the acquisition of MDR *Acinetobacter* spp. such as: i) its ability to survive in environmental and human reservoirs; ii) the common acquisition of genetic elements like integrons and transposons; and iii) its intrinsic resistance to many antimicrobial agents due to the interplay of decreased permeability and constitutive expression of active efflux systems. The production of naturally occurring AmpC ß-lactamases and acquired oxacillinases with carbapenemase properties also contribute resistance profiles for this pathogen.

The main objective of this study was to evaluate the frequency of occurrence, the antimicrobial susceptibility profile and the temporal evolution of antimicrobial resistance among *Acinetobacter* spp. isolated in Latin America by the SENTRY Antimicrobial Surveillance Program.

## MATERIALS AND METHODS

Bacterial strains: Consecutive non-duplicate bacterial pathogens were collected in the last decade (1997-2006) from hospitalized patients in Latin American medical centers. All isolates were identified at the participating institution by routine methodologies in use at each laboratory. Upon receipt at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), isolates were subcultured to ensure viability and purity. Confirmation of species identification was performed with the Vitek system (bioMerieux Vitek, St Louis, MO) or conventional methods, as required.

Medical centers: The participant medical centers included thirteen cities in seven countries: São Paulo (1997-2006), Brasília (1999-2006), 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 (1997-2006); Mexico City (three sites, 1997-2001), Guadalajara (2004-2006), and Durango (2005-2006) in Mexico; and Caracas in Venezuela (1998-2004).

Susceptibility testing: *Acinetobacter* spp. isolates were tested against several antimicrobial agents including tigecycline by broth microdilution methods using fresh Mueller-Hinton broth as described by the Clinical and Laboratory Standards Institute (CLSI; M7-A7, 2006). Susceptibility results were interpreted according to CLSI document M100-S18 (2008) for all comparison agents. USA-FDA tigecycline breakpoints for Enterobacteriaceae (≤2 and ≥8 mg/L for susceptible and resistant, respectively) were used for comparison purposes only. Isolates resistant to ampicillin/sulbactam (MIC, ≥32/16 mg/L), ceftazidime (MIC, ≥32 mg/L), cefepime (MIC, ≥32 mg/L), imipenem (MIC, ≥16 mg/L), ciprofloxacin (MIC, ≥4 mg/L), and amikacin (MIC, ≥32 mg/L) were considered MDR isolates. Concurrent quality control (QC) was performed using the following organisms: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213 and all QC results were within published CLSI ranges.

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

## RESULTS

- A total of 1,807 *Acinetobacter* spp. isolates were collected from Latin American medical centers during the 10-year period. The occurrence of *Acinetobacter* spp. isolates varied over the years with a drop in isolate numbers collected between 1999 and 2003, followed by an increase starting in 2004. Nearly 36.8% of *Acinetobacter* spp. isolates were collected between 2004 and 2006 (Table 1). This increase was associated with a higher number of bloodstream isolates collected from medical centers in Argentina, Brazil, Chile, and Mexico.
- The highest number of isolates were collected from Brazil (52.9%) > Argentina (18.7 %) > Chile (14.3%) and Mexico (6.2%); see Table 1.
- Bloodstream (57.2%) was the most common body site of *Acinetobacter* spp. infection, followed by lower respiratory tract (31.9%) and skin and soft tissue (7.5%); see Table 2.
- The antimicrobial susceptibility profile of the 1,807 Latin American *Acinetobacter* spp. isolates is shown in Table 3. Overall, polymyxin B ($MIC_{50,}$ 0.5 mg/L; 98.8% susceptible) and tigecycline ($MIC_{50,}$ 0.5 mg/L; 98.1% susceptible) demonstrated the highest in vitro activity followed by imipenem ($MIC_{50,}$ 1 mg/L; 83.5% susceptible) and meropenem ($MIC_{50,}$ 2 mg/L; 81.0% susceptible).
- A significant increase ($p < 0.05$) in the resistance rates for imipenem (8.8-27.0%), meropenem (8.3-31.7%), cefepime (66.3-71.3%), ceftazidime (71.0-79.1%), amikacin (64.2-70.4%) was observed when comparing 1997 and 2006 susceptibility results (Table 4).

**Table 1.** *Acinetobacter* spp. isolates collected from Latin American medical centers according to the year and nation of isolation (SENTRY Antimicrobial Surveillance Program, 1997-2006).

| Nation/ Year (no tested) | Argentina No. (%) | Brazil No. (%) | Chile No. (%) | Colombia No. (%) | Mexico No. (%) | Venezuela No. (%) | Uruguay No. (%) |
|---|---|---|---|---|---|---|---|
| 1997 (193) | 43 (2.4) | 81 (4.5) | 30 (1.7) | 8 (0.4) | 11 (0.6) | 0 (0.0) | 20 (1.1) |
| 1998 (215) | 46 (2.5) | 104 (5.8) | 35 (1.9) | 10 (0.6) | 5 (0.3) | 15 (0.8) | _[a] |
| 1999 (129) | 21 (1.2) | 67 (3.7) | 7 (0.4) | 12 (0.7) | 1 (0.1) | 21 (1.2) | _[a] |
| 2000 (140) | 36 (2.0) | 72 (4.0) | 8 (0.4) | 14 (0.8) | 1 (0.1) | 9 (0.5) | _[a] |
| 2001 (168) | 40 (2.2) | 91 (5.0) | 21 (1.2) | _[a] | 0 (0.0) | 16 (0.9) | _[a] |
| 2002 (166) | 35 (1.9) | 86 (4.8) | 29 (1.6) | _[a] | 9 (0.5) | 7 (0.4) | _[a] |
| 2003 (129) | 15 (0.8) | 86 (4.8) | 13 (0.7) | _[a] | 8 (0.4) | 7 (0.4) | _[a] |
| 2004 (203) | 17 (0.9) | 132 (7.3) | 37 (2.0) | _[a] | 14 (0.8) | 3 (0.2) | _[a] |
| 2005 (234) | 38 (2.1) | 120 (6.6) | 47 (2.6) | _[a] | 29 (1.6) | _[a] | _[a] |
| 2006 (230) | 47 (2.6) | 117 (6.5) | 32 (1.8) | _[a] | 34 (1.9) | _[a] | _[a] |
| Total (1,807) | 338 (18.7) | 956 (52.9) | 259 (14.3) | _[a] | 112 (6.2) | 78 (4.3) | 20 (1.1) |

a. No medical centers located in this nation submitted isolates to the SENTRY Program in that year.

**Table 2.** *Acinetobacter* spp. isolates collected from Latin American medical centers according to the year of isolation and body site of infection (SENTRY Antimicrobial Surveillance Program, 1997-2006).

| Year (No. Tested) | No. of isolates tested (%[a]) by body site: Blood (1033) | Respiratory Tract (576) | Skin and Soft Tissue (136) | Urinary Tract (44) |
|---|---|---|---|---|
| 1997 (193) | 87 (4.8) | 65 (3.6) | 26 (1.4) | 15 (0.8) |
| 1998 (215) | 107 (5.9) | 75 (4.2) | 21 (1.2) | 12 (0.7) |
| 1999 (129) | 61 (3.4) | 48 (2.67) | 16 (0.9) | 4 (0.2) |
| 2000 (140) | 66 (3.7) | 59 (3.3) | 11 (0.6) | 4 (0.2) |
| 2001 (168) | 75 (4.2) | 78 (4.3) | 4 (0.2) | 3 (0.2) |
| 2002 (166) | 90 (5.0) | 60 (3.3) | 16 (0. 9) | 0 (0.0) |
| 2003 (129) | 120 (6.6) | 2 (0.1) | 0 (0.0) | 3 (0.2) |
| 2004 (203) | 119 (6.6) | 54 (3.0) | 21 (1.2) | 3 (0.2) |
| 2005 (234) | 149 (8.3) | 64 (3.5) | 21 (1.2) | 0 (0.0) |
| 2006 (230) | 159 (8.8) | 71 (3.9) | 0 (0.0) | 0 (0.0) |
| Total (1,807) | 1,033 (57.2) | 576 (31.9) | 136 (7.5) | 44 (2.4) |

a. Percentage was calculated using the total number of *Acinetobacter* spp. isolates collected as the denominator.

**Table 3.** Antimicrobial susceptibility profile to selected agents of 1,807 *Acinetobacter* spp. isolates collected from Latin American medical centers (SENTRY Antimicrobial Surveillance Program, 1997-2006).

| | MIC (mg/L)[a] $MIC_{50}$ | $MIC_{90}$ | % Susceptible[b] | % Resistant[b] |
|---|---|---|---|---|
| Amikacin | >32 | >32 | 34.9 | 59.5 |
| Ampicillin/sulbactam[c] | 16 | 32 | 45.5 | 39.6 |
| Cefepime | 16 | >16 | 35.1 | 48.2 |
| Ceftazidime | > 16 | >16 | 27.9 | 63.8 |
| Ciprofloxacin | ≥4 | ≥4 | 30.5 | 69.0 |
| Imipenem | 1 | >8 | 83.5 | 15.3 |
| Meropenem | 2 | >8 | 81.0 | 15.3 |
| Piperacillin/tazobactam | > 64 | > 64 | 27.1 | 68.1 |
| Polymyxin B[d] | 0.5 | 1 | 98.8 | 1.2 |
| Tigecycline[e] | 0.5 | 2 | 98.1 | 0.0 |

a. MIC determined by broth microdilution according to CLSI recommendations (2006).
b. Susceptibility and resistance rates were calculated according to the CLSI guidelines (2008).
c. Ampicillin/sulbactam was tested from 2003.
d. Polymyxin B was tested since 2001.
e. Tigecycline was tested since 2003.

**Table 4.** Resistance rates of selected antimicrobial agents tested against *Acinetobacter* spp. isolates collected from Latin American medical centers according to the year of isolation (SENTRY Antimicrobial Surveillance Program, 1997-2006).

| Antimicrobial Agents | Year (N of isolates tested) %Resistant[a] 1997 (193) | 1998 (215) | 1999 (129) | 2000 (140) | 2001 (168) | 2002 (166) | 2003 (129) | 2004 (203) | 2005 (234) | 2006 (230) |
|---|---|---|---|---|---|---|---|---|---|---|
| Amikacin | 64.2 | 73.0 | 62.8 | 67.1 | 62.5 | 57.8 | 48.8 | 65.0 | 69.7 | 70.4 |
| Ampicillin/sulbactam[b] | - | - | - | - | - | - | 53.5 | 45.3 | 56.8 | 61.3 |
| Cefepime | 66.3 | 72.6 | 51.2 | 67.1 | 64.3 | 62.7 | 54.3 | 69.0 | 62.8 | 71.3 |
| Ceftazidime | 71.0 | 82.3 | 62.8 | 64.3 | 70.2 | 67.5 | 55.8 | 72.9 | 77.8 | 79.1 |
| Ciprofloxacin | 72.5 | 70.7 | 65.1 | 65.7 | 72.0 | 65.1 | 52.7 | 67.5 | 76.5 | 76.1 |
| Imipenem | 8.8 | 13.0 | 11.6 | 15.7 | 16.1 | 21.7 | 7.8 | 8.4 | 27.4 | 27.0 |
| Meropenem | 8.3 | 13.0 | 10.9 | 16.4 | 17.9 | 25.3 | 7.3 | 13.3 | 34.2 | 31.7 |
| Piperacillin/tazobactam | 75.1 | 80.5 | 63.6 | 70.1 | 73.2 | 69.3 | 58.1 | 73.4 | 77.4 | 76.5 |
| Polymyxin B[c] | - | - | - | - | 4.2 | 0.6 | 1.5 | 0.5 | 0.4 | 0.4 |
| Tigecycline[d] | - | - | - | - | - | - | 0.0 | 0.0 | 0.0 | 0.0 |

a. Resistance rates were calculated including intermediate and resistant isolates according to the CLSI guidelines (2007).
b. Ampicillin/sulbactam was tested from 2003.
c. Polymyxin B was tested since 2001.
d. Tigecycline was tested since 2003.

- Among the 1,807 *Acinetobacter* spp. isolates collected, 70 (3.9%) exhibited the MDR phenotype. These isolates were mainly collected from Argentinean sites (44 of 70 isolates; 62.9%) followed by Brazilian medical centers (23 of 70 isolates; 32.9%). Proportionally, the percentage of MDR isolates was much higher in Argentina (44 of 338 isolates; 13.0%) compared to Brazil (23 of 956 isolates; 2.4%).
- Sixty-two of the 70 (88.6%) MDR *Acinetobacter* spp. isolates were collected in the years 2005 and 2006, suggesting the occurrence of outbreaks in the monitored medical centers in Argentina and Brazil.

## CONCLUSIONS

- Polymyxin B and tigecycline remain the most active antimicrobials against *Acinetobacter* spp. in the Latin American countries (SENTRY Program; 1997-2006).
- An important reduction in the susceptibility rates to some broad-spectrum antimicrobials, including the carbapenems, was observed that limits therapeutic options.
- The elevated numbers of MDR *Acinetobacter* spp. strains in Argentina and Brazil may reflect wide clonal dissemination within participating medical centers.

## SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement.* Wayne, PA: CLSI.
3. Jones RN, Ferraro MJ, Reller LB, Schreckenberger PC, Swenson JM, Sader HS (2007). Multicenter studies of tigecycline disk diffusion susceptibility results for *Acinetobacter* spp. *J Clin Microbiol* 45: 227-230.
4. Poirel L, Nordmann P (2006). Carbapenem resistance in *Acinetobacter baumannii*: Mechanisms and epidemiology. *Clin Microbiol Infect* 12: 826-836.
5. Tygacil Package Insert (2005). Philadelphia (PA): Wyeth Pharmaceuticals Inc. (June, 2005).
6. Vila J, Marti S, Sanchez-Cespedes J (2007). Porins, efflux pumps and multidrug resistance in *Acinetobacter baumannii*. *J Antimicrob Chemother* 59: 1210-1215.