Original Report

Three-Year Surveillance Study of Nosocomial Bacterial Resistance in Argentina

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ABSTRACT

Introduction: A national surveillance program (SIR) was introduced in 1996 in Argentina by the Antimicrobial Committee of the Argentinean Society for Microbiology to assess bacterial resistance. The present study reports the rates of nosocomial bacterial resistance found by this program.

Methods: A 2-month point-prevalence study was conducted twice yearly (i.e., April–May and October–November) from 1996 to 1998, by 27 Argentinean centers. Susceptibility testing was carried out by the disk diffusion method following the National Committee for Clinical Laboratory Standards guidelines.

Results: In all, 6343 isolates recovered from 5603 inpatients (≥48-hr hospitalization) were included. Methicillin resistance was 58% and 56% in *Staphylococcus aureus* and coagulase-negative staphylococci (CNS), respectively. Although no vancomycin resistance was found in staphylococci, 2% and 8% of the *S. aureus* and CNS strains, respectively, proved resistant to teicoplanin. No ampicillin resistance was displayed by *Enterococcus faecalis*. High-level gentamicin and streptomycin resistance in enterococci were 33% and 37%, respectively. Acquired glycopeptide resistance in enterococci emerged in 1997 (2%). Imipenem resistance in *Acinetobacter* spp and *Pseudomonas aeruginosa* was 9% and 21%, respectively. Among *Enterobacteriaceae*, 1% and 5% of the *Klebsiella pneumoniae* and *Enterobacter cloacae* isolates, respectively, proved resistant to imipenem. Ceftazidime and cefepime resistance was found in 63% and 33% of the *E. cloacae* strains. Resistance to extended-spectrum cephalosporins was shown by 48%, 26%, and 8% of the *K. pneumoniae*, *Proteus mirabilis*, and *Escherichia coli* isolates, respectively.

Conclusions: The alarming rates of resistance found in this study provide compelling evidence of the need for more rational use of antimicrobial agents in Argentina.

Key Words: *nosocomial infections, resistance, surveillance*

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Nosocomial infections are a worrisome problem worldwide. In addition, antimicrobial resistance results in increased morbidity, mortality, and cost of health care. Thus, the establishment of a system for monitoring bacterial resistance has became one of the most important supports recommended in the guidelines for the prevention of antimicrobial resistance in hospitals.[1] Furthermore, information from routine susceptibility testing of bacterial isolates and surveillance of antibiotic resistance, which provides information on resistance trends, including emerging antibiotic resistance, is essential for clinical practice.[2]

Unfortunately, various strategies applied in hospitals to prevent the spread of antibiotic resistance have not always resulted in increases of bacterial susceptibility to antibiotics.[3] In fact, a number of different antimicrobial

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agents have been rendered ineffective because of the selective pressure of antibiotics leading to the emergence of resistance.[4] Among the most relevant emerging resistance in hospitals from the United States and Europe are methicillin-resistant, and more recently, glycopeptide-resistant staphylococci, gentamicin- and glycopeptide-resistant enterococci, as well as the resistance to fluoroquinolones, extended-spectrum cephalosporins, and carbapenem displayed by gram-negative bacilli.[5]

The antibiotic susceptibility profiles of bacterial isolates are unknown in much of the developing world.[6] Despite several efforts made to design and establish a national surveillance system of nosocomial infections in Argentina, currently, there is no systematically controlled program. Therefore, reliable data on nosocomial infection rates from hospitals are scarce. Nevertheless, some data on antimicrobial resistance have been available in Argentina for several years.[7] A national surveillance program (SIR) was introduced in 1996 in Argentina by the Antimicrobial Committee of the Argentinean Society for Microbiology to assess bacterial resistance. The present study reports the rates of nosocomial bacterial resistance yielded by this program from 1996 to 1998.

MATERIALS AND METHODS

A 2-month point-prevalence study was conducted twice yearly (April–May and October–November) from 1996 to 1998 by 27 Argentinean centers. Antimicrobial susceptibility data of clinically relevant isolates from inpatients (≥48-hr hospitalization) were collected on a computerized system (SIR) designed by a member (C. Bantar) of the Antimicrobial Committee. Sex, age, hospital ward, and the type of specimen were recorded for every patient. Underlying clinical condition, source and type of the infection, as well as previous antimicrobial therapy were also recorded when available. For calculation of resistance rates, the system excluded duplicate isolates (i.e., an isolate of the same bacterial species with the same susceptibility pattern in the same patient, whatever the isolation site, within a 6-mo period).

Organisms were identified according to standard procedures.[8] Susceptibility testing was carried out by the disk diffusion method following the National Committee for Clinical Laboratory Standards (NCCLS) guidelines.[9] Ampicillin, ampicillin-sulbactam, cephalothin, cefoxitin, piperacillin, piperacillin-tazobactam, cefotaxime, ceftazidime, cefepime, imipenem, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin, and amikacin were tested against gram-negative rods. Penicillin, oxacillin, erythromycin, trimethoprim-sulfamethoxazole, rifampin, minocycline, ciprofloxacin, gentamicin, vancomycin, and teicoplanin were assayed against staphylococci, whereas the enterococci were tested for detection of resistance to ampicillin, nitrofurantoin, vancomycin, teicoplanin, ciprofloxacin, and high levels of gentamicin and streptomycin. *Staphylococcus aureus* ATCC 25923, *Escherichia coli*, both ATCC 35218 and ATCC 25922, *Enterococcus faecalis* ATCC 29212, and *Pseudomonas aeruginosa* ATCC 27853 were used as the controls.

RESULTS

In all, 6343 isolates recovered from 5603 inpatients were included. The overall species distribution (%) of the isolates collected during the point-prevalence studies performed from 1996 to 1998 was as follows: *S. aureus*, 22.7%; *E. coli*, 18.3%; *P. aeruginosa*, 13.4; coagulase-negative staphylococci (CNS), 9.4% (includes *Staphylococcus epidermidis* [38%] and other species [62%]); *Klebsiella pneumoniae*, 9.2%; *Enterococcus* spp, 7.2% (includes *E. faecalis* [68%], *Enterococcus faecium* [6.3%], and *Enterococcus* sp [27%]); *Acinetobacter* spp, 5.9%; *Enterobacter cloacae*, 4.6%; *Proteus mirabilis*, 3.3%; *Serratia marcescens*, 1.3%, and other species, 4.7%.

Figure 1 shows the frequency of the different species recovered from blood cultures of all the patients enrolled in the two prevalence studies performed in 1998. The most relevant differences, with the relative frequency of the species recovered from all the specimens collected between 1996 and 1998 (overall prevalence), were found in *E. coli* and *P. aeruginosa*, which declined from ranks 2 and 3 among the overall prevalence to ranks 5 and 6 in blood cultures, respectively. By contrast, *K. pneumoniae* and *E. cloacae* rose from ranks 5 and 9 to ranks 3 and 4, respectively. Staphylococci accounted for nearly one-half of all nosocomial bacteremias (42%). In fact, CNS rose from rank 4 in overall prevalence to rank 1 in blood cultures.

Table 1 presents the resistance profiles of the *Enterobacteriaceae* species, most frequently recovered. Although a high rate of resistance was displayed by all species against the majority of the drugs, the most remarkable findings were the resistance to ampicillin-sulbactam,

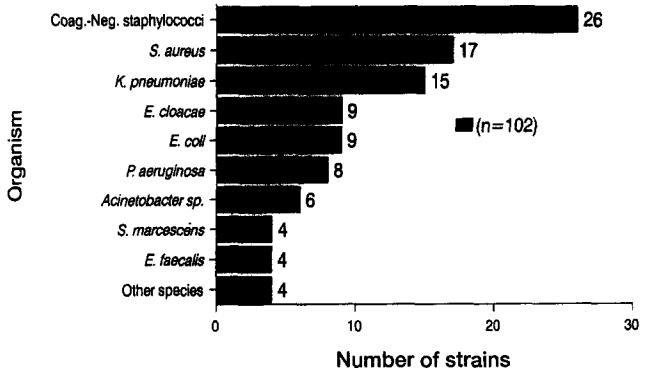

Figure 1. Species distribution in bloodstream infection from patients hospitalized in Argentina during 1998.

Table 1. Resistance Profiles of the *Enterobacteriaceae* Species Most Frequently Recovered between 1996 and 1998 from Hospitalized Patients in Argentina

	*Percentage of Resistance Displayed by the Following Species**				
Drug	E. coli *(n = 1164)*	P. mirabilis *(n = 211)*	K. pneumoniae *(n = 586)*	E. cloacae *(n = 293)*	S. marcescens *(n = 83)*
Ampicillin	63	59	NA	NA	NA
Ampicillin-sulbactam	43	43	70	NA	NA
Cephalothin	33	39	66	NA	NA
Cefoxitin	8.5	10	16	NA	NA
Cefotaxime	8	26	48	67	19
Ceftazidime	6	8.5	42	63	13
Cefepime	6	13.5	37	33	5
Piperacillin	40	39	68	50	29
Piperacilin-tazobactam	11	5	43	45	19.5
Imipenem	0	0	1	5	0
Trimethoprim-sulfamethoxazole	36	50	36	43	26
Gentamicin	15	38	54	46	20
Amikacin	7	10	41	31	19
Ciprofloxacin	13	24	18	38	6

*All *E. coli*, *P. mirabilis*, and *K. pneumoniae* strains resistant to any extended-spectrum cephalosporin were considered as clinically resistant to all β-lactams, with the exception of imipenem.
NA = not applicable.

cephalothin, and extended-spectrum cephalosporins by *E. coli*, *P. mirabilis*, and *K. pneumoniae*. In addition, an appreciable rate of resistance to ciprofloxacin was observed in all the *Enterobacteriaceae* species. Furthermore, a worrisome emerging resistance to imipenem was detected in *K. pneumoniae* and *E. cloacae*.

Resistance patterns of *P. aeruginosa* and *Acinetobacter* spp are depicted in Table 2. Because *P. aeruginosa* was one of the most prevalent pathogens isolated both from all wards and from the intensive care unit (ICU), a comparative analysis of resistance rates between the ICU and all the ward settings was performed for this species. Increased resistance rates showed by strains recovered from the ICU versus those displayed by isolates from all wards showed statistical significance with all antibiotics ($P < 0.05$, χ^2 test). The most pronounced difference was observed in the imipenem resistance, 21% versus 36% in all wards and ICU, respectively. Imipenem and cefepime were the most active antibiotics against *P. aeruginosa* in all wards (21% and 25% resistance, respectively). However, no drugs proving effective against more than 65% of the strains were shown in the ICU setting (i.e., the lowest resistance rate in the ICU was 36%). Imipenem was the only antibiotic exhibiting suitable in vitro activity against *Acinetobacter* spp (9% resistance). Indeed, none of the other antimicrobial agents assayed overcame the 35% susceptibility rate.

Table 3 shows the resistance profiles of staphylococci and enterococci. High rates of oxacillin resistance were seen in both *S. aureus* and CNS (58% and 56%, respectively). This resistance was also associated with resistance to gentamicin, erythromycin, and, to a lesser degree, rifampin, trimethoprim-sulfamethoxazole, and ciprofloxacin. Although no strains of staphylococci

Table 2. Resistance Patterns of *Pseudomonas aeruginosa* and *Acinetobacter* spp Strains Recovered between 1996 and 1998 from Hospitalized Patients in Argentina

	Percentage of Resistance by the Following Species		
	P. aeruginosa *Isolated from*:*		
Drug	*All Wards (n = 850)*	*ICU (n = 206)*	Acinetobacter *spp (n = 375)*
Ampicillin-sulbactam	NA	NA	65
Ceftazidime	30	38	83
Cefepime	25	36	83
Imipenem	21	36	9
Piperacillin	41	50	92
Piperacillin-tazobactam	35	43	84
Gentamicin	51	63	83
Amikacin	36	48	74
Ciprofloxacin	40	53	83

*Increased resistance rates shown by *P. aeruginosa* strains recovered from ICU versus those displayed by isolates from all wards proved statistically significant with all antibiotics.
ICU = intensive care unit; NA = not applicable.

Table 3. Resistance Profiles of Staphylococci and Enterococci Strains Recovered between 1996 and 1998 from Hospitalized Patients in Argentina

	Percentage of Resistance Displayed by		
Drug	S. Aureus *(n = 1441)*	*CNS (v = 226)*	Enterococcus *spp* (n = 457)*
Penicillin	95	95	NA
Ampicillin	NA	NA	8†
Oxacillin	58	56	NA
Erythromycin	56	50	NA
Rifampin	38	44	NA
Minocycline	12	5	NA
Trimethoprim-sulfamethoxazole	40	41	NA
Vancomycin	0	0	2‡
Teicoplanin	2	8	2‡
Ciprofloxacin	45	31	54
Nitrofurantoin	NA	NA	7
Gentamicin	53	50	33§
Streptomycin	NA	NA	37§

*Includes *Enterococcus faecalis* (n = 305), *Enterococcus faecium* (n = 29), and *Enterococcus* sp (n = 123); †no ampicillin resistance was detected in *E. faecalis*, but in 95% of the *E. faecium* strains; ‡glycopeptide resistance was detected only in E. faecium; §high-level resistance.
CNS = coagulase-negative staphylococci; NA = not assayed.

displaying decreased susceptibility to vancomycin were found, an alarming emergence of teicoplanin resistance was observed in both *S. aureus* and CNS (2% and 8%, respectively). Minocycline proved quite active against these species (12% and 5% resistance, respectively). No ampicillin resistance was detected in *E. faecalis*, whereas this feature was observed in 95% of the *E. faecium* strains. The high-level gentamicin resistance rates were 33% and 70%, respectively. The overall acquired glycopeptide resistance in enterococci was 2%, albeit such a resistance was shown only by *E. faecium*. In fact, 9 of 29 strains (31%) reported as *E. faecium* were resistant to vancomycin.

DISCUSSION

Although a clear relation between the overuse of antibiotics and the emergence of bacterial resistance has been difficult to establish, there are several recent studies suggesting that antibiotic control efforts may decrease bacterial resistance and nosocomial infections.[10] Unfortunately, the misuse of antibiotics, and the poor control of drug prescriptions, leading to increased bacterial resistance in developing countries, including Latin America, have been described.[6,11] Therefore, the high rates of resistance yielded by this study are not surprising.

The high prevalence of *Enterobacteriaceae* isolates resistant to ampicillin-sulbactam may be attributable to an overproduction of a broad-spectrum β-lactamase. Bantar et al have recently characterized 48 successive *E. coli* strains resistant to amoxicillin-sulbactam recovered from oupatients with urinary tract infection in Argentina.[12] These authors found that 96% of the strains harbored a TEM-1-like β-lactamase, suggesting that an overproduction of this enzyme was responsible for the resistance. Whether a similar mechanism may be applicable to *K. pneumoniae* and *P. mirabilis* in Argentina remains unknown. Furthermore, an alarming rate of resistance to extended-spectrum cephalosporins was observed in these species. The presence of extended spectrum β-lactamases in Argentina was first reported by Casellas et al, in 1989.[13] Two indigenous novel extended spectrum β-lactamases in Argentina were described, CTX-M-2 and PER-2.[14,15] Recent epidemiologic studies performed by Galas et al demonstrated that CTX-M-2 (64-70%) and to a lesser degree, SHV-1 derivates (i.e. SHV-2 and SHV-5, 11-20%) and PER-2 (5-10%), were the most prevalent extended spectrum β-lactamases among a number of Argentinean *K. pneumoniae* and *E. coli* strains.[16,17] In addition, these extended spectrum β-lactamases also have been detected within strains of *E. cloacae* and *S. marcescens* in up to 20% of the isolates, but the rank of prevalence among these species was PER-2, CTX-M-2, and SHV-1-derivates in *E. cloacae* and CTX-M-2 and SHV-1 derivates in *S. marcescens*.[18] This fact is important, since the presence of an extended spectrum β-lactamase may be overlapped by the current production of a group I β-lactamase in these species. Emerging resistance to carbapenems by *K. pneumoniae* and *E. cloacae* is of concern, since this class of antibiotics remains as the only choice in almost one-half of Argentinean isolates belonging to these species. Studies are ongoing in Argentina to elucidate the mechanism responsible for this resistance.

Pseudomonus aeruginosa, especially the ICU isolates, exhibited high resistance rates against most of the drugs. Significant differences between all wards and the ICU may be attributable, in part, to the increased use of antibiotics in the ICU. Indeed, the emergence of antibiotic-resistant *P. aeruginosa* associated with the use of different antipseudomonal agents recently has been

described.[19] Although imipenem proved the most active drug, resistance rates from all wards and the ICU were as high as 21% and 36%, respectively. A study performed on 22 imipenem-resistant *P. aeruginosa* strains from Argentina suggested that this resistance was associated with deficient OprD expression.[20]

Acinetobacter spp proved resistant to all the antibiotics tested, with the exception of imipenem. Nevertheless, 9% of strains were shown to be resistant to this drug. In fact, a novel plasmid-mediated carbapenemase, ARI-2, has been detected in several of these strains isolated from one of the centers belonging to the SIR participants group.[21]

High rates (>50%) of methicillin-resistant staphylococci were found in this study. This is both a therapeutic and an economic problem. Indeed, a recent study performed in 41 ICUs in the United States demonstrated that the overuse of vancomycin was heavily determined by a mean resistance rate of 32% in *S. aureus*.[22] Although no staphylococci strains displaying decreased susceptibility to vancomycin were found, an alarming emergence of teicoplanin resistance was observed in both *S. aureus* and CNS (2% and 8%, respectively). Corso et al have performed a clonal typing study among 148 isolates of methicillin-resistant *S. aureus* collected by 13 hospitals from Argentina.[23] These authors stated that the prevalent clone (62% of the isolates) had a pulsed-field gel electrophoresis pattern similar to that of the Brazilian isolates, (the clone XI::B::B). This clone also was resistant to gentamicin, macrolides, rifampin, tetracycline, trimethoprim-sulfamethoxazole, and ciprofloxacin.

Ampicillin resistance was not detected in *E. faecalis*. By contrast, 95% of the *E. faecium* strains exhibited this feature. High-level gentamicin resistance in enterococci increased to 33% in this study, as compared with the 20% of resistance reported by Bantar et al in 1991.[24] The first enterococcus strain proving acquired glycopeptide resistance described in Argentina and in Latin America was an *E. faecium* isolate recovered from a child in 1996. The strain possessed the vanA gene and was reported in 1998.[25] However, a significant emergence of glycopeptide-resistant enterococci (2%) since 1997 is demonstrated in the present study, and the resistance rates continue to increase (unpublished data). Glycopeptide resistance was detected only in *E. faecium* and all of the isolates possessed the vanA gene (data not shown).

CONCLUSION

The alarming rates of resistance found in this study compel researchers to establish more rational guidelines for the use of antimicrobial agents. Furthermore, special efforts should be undertaken to definitively establish a national program for prevention and control of nosocomial infections in Argentina.

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