Pathogen Frequency and Resistance Patterns in Brazilian Hospitals: Summary of Results from Three Years of the SENTRY Antimicrobial Surveillance Program

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Background: Pathogen frequency and resistance patterns may vary significantly from country to country and also in different hospitals within a country. Thus, regional surveillance programs are essential to guide empirical therapy and infection control measures. Methods: Rank order of occurrence and antimicrobial susceptibility of pathogenic species causing bloodstream infections (BSI), lower respiratory tract infections (LRTI), wound or skin and soft tissue infections (WSSTI), and urinary tract infections (UTI) in hospitalized patients were determined by collecting consecutive isolates over a specified period of time, as part of the SENTRY Antimicrobial Resistance Surveillance Program (SENTRY). All isolates were tested by reference broth microdilution. Results and Conclusions: A total of 3,728 bacterial strains were obtained from January, 1997, to December, 1999, from 12 Brazilian hospitals located in 4 states. The largest number of isolates were obtained from patients with BSI (2,008), followed by LRTI (822 cases), UTI (468 cases), and WSSTI (430 cases). *Staphylococcus aureus* was the most frequently isolated pathogen in general (22.8% - 852 isolates), followed by *E. coli* (13.8% - 516 cases) and *Pseudomonas aeruginosa* (13.3% - 496 cases). *Staphylococcus aureus* was also the most common species isolated from BSI (23.6%) and WSSTI (45.8%), and *P. aeruginosa* was the most frequent species isolated from patients with LRTI (29.4%). The main bacterial resistance problems found in this study were: imipenem resistance among *P. aeruginosa* (69.8% susceptibility) and *Acinetobacter* spp. (88.1% susceptibility); ESBL production among *K. pneumoniae* (48.4%) and *E. coli* (8.9%); resistance to third generation cephalosporins among *Enterobacter* spp. (68.1% susceptible to ceftazidime) and oxacillin resistance among *S. aureus* (34.0%) and coagulase negative staphylococci (80.1%). Only the carbapenems (88.1% to 89.3% susceptibility) showed reasonable activity against the *Acinetobacter* spp. isolates evaluated.

Key Words: SENTRY, antimicrobial resistance, nosocomial infection, surveillance program.

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The euphoria generated by the discovery of antibiotics led to confident predictions that bacterial diseases would soon be conquered and safely forgotten. Scientists felt free to attack other pressing health problems such as viral diseases. However, bacterial pathogens have become increasingly resistant to a variety of antibiotics. This increase in antimicrobial resistance has demanded the development of new and more potent antimicrobial agents and more research in the area of mechanisms of bacterial resistance. A better

understanding of the dissemination of bacterial resistance to antimicrobial agents is necessary to control the problem.

In general, resistance to increasingly used antimicrobial agents in commonly isolated pathogens is a result of selective pressure caused by the frequent use of these agents [1]. Due to the change in resistance patterns that are occurring in Brazil and worldwide, ongoing surveillance of predominant pathogens and antimicrobial susceptibilities is needed in order to optimize patient care. The SENTRY Antimicrobial Resistance Surveillance Program (SENTRY) started in January, 1997, and was designed to monitor nosocomial and selected community-acquired infections via a worldwide surveillance network of sentinel hospitals distributed equally by geographic location and size [2-4].

This report will focus on the antimicrobial susceptibilities of predominant pathogens causing bloodstream infections, pneumonia, wound infections, and urinary tract infections in Brazil.

Materials and Methods

Bacterial strains

SENTRY has enrolled 3 Brazilian sites per year. During 1997 and 1998, the sites were located in Rio de Janeiro, Florianópolis, and São Paulo. In 1999, a site located in the city of Porto Alegre replaced the site located in Rio de Janeiro. Bacterial samples collected between January, 1997, and December, 1999, were evaluated in this study. Only 1 isolate per patient judged to be clinically significant by local criteria was collected. The target numbers of isolates for the evaluated infections to be collected from hospitalized patients at each participating center were: (1) Bloodstream infection (BSI) - 20 consecutive isolates in each calendar month during the 24-month period from January 1, 1997, through December 31, 1998; (2) Lower respiratory tract infection (LRTI) - 100 consecutive isolates over a 6-month period each year, from July 1, through December 31; (3) Wound or skin and soft tissue infection (WSSTI) - 50 consecutive isolates over a 3-month period each year, from April 1, 1997, through June 30, 1997; (4) Urinary tract infection (UTI) - 50 consecutive isolates over a 3-month period each year, from February 1, 1997, through May 1, 1997.

Organism identification

All pathogens were identified at the participating center using routine methods for that laboratory and were confirmed at the coordinating laboratory using automated or conventional methods if needed.

Susceptibility testing

Antimicrobial susceptibility testing was performed at the coordinating laboratory using broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS) [5]. Antimicrobial agents were obtained from respective manufacturers as laboratory grade powder and included macrolides (erythromycin, azithromycin, clarithromycin), the streptogramin quinupristin-dalfopristin, glycopeptides (vancomycin, teicoplanin), fluoroquinolones (gatifloxacin, ciprofloxacin, levofloxacin, trovafloxacin), aminoglycosides (amikacin, gentamicin, tobramycin), carbapenems (imipenem, meropenem), a monobactam (aztreonam), cephalosporins (cefepime, cefuroxime, cefotaxime, ceftriaxone, ceftazidime, cefoxitin, cefaclor), penicillins (ampicillin, penicillin, amoxicillin, oxacillin), ß-lactamase inhibitor combinations (amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam), and other drugs including clindamycin, chloramphenicol, tetracycline, rifampin, and trimethoprim-sulfamethoxazole.

Quality control

Quality control was performed utilizing strains from the American type culture collection (ATCC), including *S. pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

Results

The species distribution of the pathogens evaluated in this study is summarized in Table 1. A total of 3,728 strains were obtained from the Brazilian centers participating in SENTRY in 1997, 1998, and 1999. Based on the study design, the largest number of isolates were obtained from patients with BSI (2,008 cases), followed by LRTI (822 cases), UTI (468 cases), and WSSTI (430).

Table 2 summarizes the susceptibility testing results obtained with the 5 most frequent Gram-negative species listed in the order of occurrence. *P. aeruginosa* was the second most common Gram-negative with almost 500 isolates evaluated (496 strains; 13.3%). This pathogen showed extremely high rates of resistance to the majority of the antimicrobial agents tested. The most active compound against this pathogen in Brazil was the carbapenem, meropenem (MIC_{50}, 1mg/mL; 74.4% susceptibility). Ciprofloxacin also showed low MIC results (MIC_{50}, 0.5 mg/mL); however, the percentage of isolates susceptible to this compound was lower (58.7%). The spectrum rank order of the antimicrobial agents against *P. aeruginosa* in terms of percentage of susceptibility was: meropenem (74.4%) > piperacillin/tazobactam (70.8%) > imipenem (69.8%) > amikacin (62.1%) > cefepime (59.7%) > ceftazidime (59.5%) > ciprofloxacin (58.7%).

The cephalosporins and other b-lactams, except for ampicillin, were active against most of the *E. coli* isolates. Cefepime was the most active of the cephalosporins (95.9% susceptible) and the carbapenems imipenem and meropenem were the most active b-lactams overall (100.0% susceptible). On the other hand, resistance rates to fluoroquinolones were relatively high with only 89.1% of strains being susceptible to ciprofloxacin (MIC_{90}, >2 mg/mL). Susceptibility to aminoglycosides varied from 97.3% for amikacin (MIC_{90}, 8 mg/mL) to 90.5% for tobramycin (MIC_{90}, 4 mg/mL).

Antimicrobial resistance rates were much higher among the 318 *Klebsiella* spp. isolates (Table 2). The carbapenem, imipenem was the most active compound (MIC_{90}, 0.5 mg/mL; 100% susceptibility). Although the potency of meropenem (MIC_{50}, ≤0.06 mg/mL) was higher than that of imipenem (MIC_{50}, 0.25 mg/mL), one isolate with an intermediate MIC for meropenem (8 mg/mL) and susceptible MIC for imipenem (4 mg/mL) was detected (Table 2). Cefepime showed the highest percentage of susceptible strains (76.7%) among b-lactams, other than the carbapenems.

Table 1. Occurrence of the major pathogens isolated in Brazil in 1997, 1998, and 1999

	% Occurrence in				
Organisms in rank order	**BSI (2008)[a]**	**LRTI (822)[b]**	**SSTI (430)[c]**	**UTI[d] (468)**	**All sites (3728)**
S. aureus	23.6	21.0	45.8	1.9	22.8 (852)
E. coli	11.3	4.4	7.2	47.6	13.8 (516)
P. aeruginosa	7.5	29.4	10.5	12.6	13.3 (496)
K. pneumoniae	8.9	9.2	4.2	9.8	8.5 (318)
Enterobacter spp.	8.3	6.8	6.7	5.8	7.5 (279)
CoNS[e]	12.0	0.5	3.0	0.6	7.0 (261)
Acinetobacter spp.	6.8	10.8	2.8	3.0	6.7 (252)
Enterococcus spp.	2.7	4.0	8.4	5.1	4.0 (147)
Serratia spp.	2.5	3.3	2.8	2.7	2.7 (102)
Proteus spp.	0.7	-	3.5	5.1	1.4 (54)

[a] BSI: blood stream infection; [b] LRTI: lower respiratory tract infection; [c] WSSTI: wound or skin and soft tissue infection; [d] UTI: urinary tract infection; [e] CoNS: Coagulase-negative staphylococci.

Table 2. Antimicrobial susceptibility pattern of the most frequent Gram-negative bacilli collected from hospitalized patients in Brazil - SENTRY Program 1997, 1998, and 1999

Antimicrobial class/agent	Pathogen (prevalence rank/ no. tested)									
	E. coli (2/516)		*P. aeruginosa* (3/496)		*K. pneumoniae*. (4/318)		*Enterobacter* spp. (5/279)		*Acinetobacter* spp. (7/252)	
	$MIC_{50}/_{90}$	% Susc.[a]	$MIC_{50}/_{9}$	% Susc [a]	$MIC_{50}/_{90}$	% Susc [a]	$MIC_{50}/_{90}$	% Susc [a]	$MIC_{50}/_{90}$	% Susc [a]
Cephalosporins										
Cefazolin	≤2/>16	84.1	>16/>16	0.0	>16/>16	45.0	>16/>16	2.9	>16/>16	0.4
Cefuroxime	4/16	87.0	>16/>16	0.0	8/>16	50.6	>16/>16	37.3	>16/>16	3.6
Cefoxitin	4/8	93.6	>32/>32	0.2	4/16	84.3	>32/>32	5.4	>32/>32	1.2
Ceftriaxone	≤0.25/≤0.25	92.6 (7.8)[b]	>32/>32	4.8	≤0.25/>32	58.8 (48.4)[b]	0.5/>32	69.5	>32/>32	12.7
Ceftazidime	0.25/1	94.6 (8.9)[b]	8/>16	59.5	1/>16	68.2 (48.4)[b]	0.5/>16	68.1	>16/>16	26.6
Cefepime	≤0.12/0.25	95.9	8/>16	59.7	0.25/>16	76.7	≤0.12/8	91.4	>16/>16	34.1
Other b-lactams										
Ampicillin	>16/>16	42.2	>16/>16	0.2	>16/>16	2.5	>16/>16	5.7	>16/>16	4.4
Aztreonam	≤0.12/0.25	93.2 (8.5)[b]	16/>16	42.7	0.25/>16	59.7 (45.6)[b]	0.25/>16	68.5	>16/>16	6.7
Ticarcillin/Clavulanate	8/128	69.4	64/>128	52.0	32/>128	48.7	8/>128	54.5	128/>128	28.6
Piperacillin/Tazobactam	2/16	92.4	16/>64	70.8	4/>64	67.0	4/>64	67.4	>64/>64	30.2
Imipenem	0.12/0.5	100.0	2/>8	69.8	0.25/0.5	100.0	0.5/2	99.6	1/>8	88.1
Meropenem	≤0.06/≤0.06	100.0	1/>8	74.4	≤0.06/0.12	99.7	≤0.06/0.25	100.0	1/>8	89.3
Aminoglycosides										
Amikacin	4/8	97.3	8/>32	62.1	2/>32	79.2	2/>32	82.4	>32/>32	31.7
Gentamicin	1/4	92.6	4/>16	55.6	1/>16	64.8	1/>16	77.4	16/>16	49.6
Tobramycin	1/4	90.5	1/>16	55.8	1/>16	55.7	1/>16	69.2	4/>16	56.3
Fluoroquinolones										
Ciprofloxacin	0.03/>2	89.1	0.5/>2	58.7	0.06/1	94.3	0.06/>2	83.2	>2/>2	35.3
Gatifloxacin	≤0.03/2	90.1	2/>4	55.0	0.06/1	95.6	0.06/4	86.4	4/>4	40.5
Levofloxacin	0.5/4	89.5	1/>4	57.1	0.5/1	94.7	0.5/>4	84.9	4/>4	36.9
Trovafloxacin	≤0.03/4	89.1	4/>4	52.6	0.06/1	93.4	0.06/>4	81.7	4/>4	43.7
Grepafloxacin	≤0.25/>2	88.9	1/>2	54.0	≤0.25/0.5	93.5	≤0.25/>2	78.9	>2/>2	39.4
Others										
Tetracycline	≤4/>8	59.5	>8/>8	1.0	≤4/>8	73.9	≤4/>8	66.7	≤4/>8	64.7
Trimethoprim/ Sulfathoxazole	≤0.5/>2	53.7	2/>2	3.2	≤0.5/>1	65.6	≤0.5/>2	72.0	2/>2	32.1

[a] Percentage of susceptible strains according to NCCLS criteria [NCCLS 2000;] [b] Percentage of strains with MIC ≥ 2 mg/mL indicating possible ESBL production.

Table 3. Percentages of *E. coli* and *K. pneumoniae* considered ESBL producers based on the NCCLS criteria.

Site of infection	% ESBL Producing strains (n/total)	
	E. coli	*K. pneumoniae*
Bacteremia	8.4% (19/226)	52.2% (93/178)
Pneumonia	30.6% (11/36)	48.7% (37/76)
Urinary tract	5.8% (13/223)	45.6% (21/46)
Wound, skin, and soft tissue	12.9% (4/31)	50.0% (9/18)
Total	**9.1% (47/516)**	**50.3% (160/318)**

[a] Strains with increased MICs (≥ 2 mg/mL) for ceftazidime, aztreonam, ceftriaxone or cefotaxime indicating possible ESBL production.

Table 4. Antimicrobial susceptibility *E.coli* and *K. pneumoniae* strains classified as ESBL-producers based on the NCCLS criteria

Antimicrobial class/agent	Pathogens (%)			
	E. coli [a] (47)		K. pneumoniae [a] (160)	
	$MIC_{50}/_{90}$	% Susc.	$MIC_{50}/_{90}$	% Susc.
b-lactams				
Cefoxitin	4/32	76.6	4/32	78.1
Ticarcillin/ Clavulanate	128/>128	8.5	128/>128	8.1
Piperacillin/ Tazobactam	16/>64	51.1	64/>64	39.4
Imipenem	0.25/0.5	100.0	0.25/0.5	100.0
Meropenem	≤0.06/0.12	100.0	≤0.06/0.12	99.4
Aminoglycosides				
Amikacin	16/32	74.5	16/>32	63.1
Gentamicin	16/>16	36.2	16/>16	36.9
Tobramicin	>16/>16	19.1	>16/>16	19.4
Fluoroquinolones				
Ciprofloxacin	0.25/>2	70.2	0.25/1	90.6
Levofloxacin	0.5/>4	70.2	0.5/2	91.3
Gatifloxacin	≤0.03/>4	74.5	0.06/2	92.5
Others				
Tetracycline	>8/>8	40.4	≤4/>8	66.3
Trimethoprim / Sulfathoxazole	>1/>1	27.7	>1/>1	46.3

[a] ESBL-producing strains should be considered resistant to all cephalosporins based on the NCCLS [2000].

Table 5. Antimicrobial susceptibility pattern of the most frequent Gram-positive cocci from hospitalized patients in Brazil - SENTRY Program 1997, 1998, and 1999

Antimicrobial class/agent	Pathogen (prevalence rank/ no. tested)					
	S. aureus (1/852)		CoNS[a] (6/261)		*Enterococcus* spp. (8/147)	
Cephalosporins						
Cefazolin	≤2/>16	66.0[b]	4/>16	19.9[b]	>16/>16	-
Ceftriaxone	4/>32	66.0[b]	16/>32	19.9[b]	>32/>32	-
Cefepime	4/>16	66.0[b]	8/>16	19.9[b]	>16/>16	-
Ceftazidime	8/>16	51.8	>16/>16	19.9[b]	>16/>16	-
Other b-lactams						
Oxacilliin	0.5/>8	66.0	>8/>8	19.9	>8/>8	-
Ampicillin	16/>16	9.9	16/>16	12.6	1/4	98.0
Penicillin	16/>32	9.2	16/>32	8.1	2/16	89.1
Amoxicillin/Clavulanate	2/>16	68.1	4/>16	19.9[b]	1/2	89.1[c]
Piperacillin/Tazobactam	2/>64	66.0[b]	4/>64	19.9[b]	4/>64	89.1[c]
Imipenem	≤0.06/>8	66.0[b]	1/>8	19.9[b]	2/8	-
MLS						
Clindamycin	0.25/>8	66.5	>8/>8	46.4	>8/>8	-
Erythromycin	1/>8	45.3	>8/>8	39.1	>8/>8	6.1
Doxycycline	0.5/>8	81.0	1/8	85.8	4/8	55.1
Fluoroquinilones						
Ciprofloxacin	0.5/>2	65.6	2/>2	49.8	2/>2	49.0
Gatifloxacin	0.12/4	89.3	0.5/2	92.7	0.5/>4	73.5
Trovafloxacin	≤0.03/1	90.3	0.25/4	75.9	0.25/>4	72.1
Others						
Gentamicin	1/>16	64.8	16/>16	41.4	16/>16	27.2
Gentamicin (HL)[d]	≤500/≤500	-	≤500/≤500	-	≤500/>1000	72.8
Streptomycin (HL)[d]	≤1000/2000	-	≤1000/2000	-	≤1000/>2000	70.1
Rifampin	0.25/2	71.1	0.25/>2	67.8	>2/>2	20.4
Chloramphenicol	8/>16	58.8	8/>16	50.6	8/>16	60.5
Tetracycline	≤4/>8	62.3	≤4/>8	75.1	>8/>8	35.4
Trimethoprim/ Sulfametoxale	≤0.5/>2	68.0	2/>2	40.2	≤0.5/2	76.9
Quinupristin/dalfopristin	0.25/0.5	99.8	0.25/1	98.9	8/>8	3.4
Teicoplanin	1/2	99.8	2/16	88.9	0.25/0.5	99.3
Vancomycin	1/1	100.0	1/2	100.0	1/2	99.

[a] CoNS: Coagulase-negative staphylococci.
[b] Susceptibility predicted by the oxacillin result.
[c] Susceptibility predicted by the penicillin result.
[d] High level aminoglycoside resistance screen.

Table 6. Antimicrobial susceptibility pattern of oxacillin-resistant *Staphylococcus aureus* strains from hospitalized patients in Brazil

Antimicrobial agent	Oxacillin-resistant *Staphylococcus aureus* (290)		
	MIC_{50} (mg/mL)	MIC_{90} (mg/mL)	% Susceptible
Clindamycin	>8	>8	7.2
Erythromycin	>8	>8	2.4
Doxycycline	8	8	47.9
Ciprofloxacin	>2	>2	7.2
Gatifloxacin	2	4	69.3
Gentamicin	>16	>16	4.5
Rifampin	2	>2	20.3
Chloramphenicol	>16	>16	21.7
Tetracycline	>8	>8	10.3
Trimethoprim / sulfamethoxale	>1	>1	8.3
Quinupristin/dalfopristin	0.5	1	99.3
Teicoplanin	2	2	99.3
Vancomycin	1	1	100.0

The percentage of *E. coli* and *K. pneumoniae* producing ESBLs remains very high in Brazil. Utilizing the screening concentrations recommended by the NCCLS [5] to predict isolates of *K. pneumoniae* and *E. coli* suspected of harboring ESBLs (MICs ≥2 mg/mL to ceftazidime or aztreonam or ceftriaxone), 9.1% of *E. coli* and 50.3% of *Klebsiella* met these criteria (Table 3).

Table 4 summarizes the antimicrobial susceptibility results of the ESBL-producing strains. Only the carbapenems showed excellent activitiy against these pathogens. ESBL-producing strains also showed high rates of resistance to cefoxitin, a cefamycin stable to hydrolysis by ESBLs; and to piperacillin/tazobactam, a b-lactam-b-lactamases inhibitor combination. Cefoxitin was active against only 78.1% of the *K. pneumoniae* and 76.6% of the *E. coli* isolates at £ 8 mg/mL, suggesting that other mechanisms of resistance, such as the production of *AmpC* enzymes (strains with cefoxitin MICs, ≥32 mg/mL) and/or alteration in the outer membrane might be associated to the ESBL production. Ticarcillin/clavulanic acid was active against only 8.1% of the *K. pneumoniae* (MIC_{90}, >128 mg/mL) and 8.5% of the *E. coli* isolates (MIC_{90}, >128 mg/mL). Piperacillin/tazobactam showed *in vitro* activity higher than that of ticarcillin/clavulanic acid, but only 39.4% of *K. pneumoniae* (MIC_{90}, >64 mg/mL) and 51.1% of *E. coli* (MIC_{90}, >64 mg/mL) were susceptible to this compound. The fluoroquinolones were very active against ESBL-producing *K. pneumoniae* (>90% susceptibility), but not against *E. coli* isolates (70.2% to 74.5% susceptibility).

Enterobacter spp. (279 isolates analyzed) showed high rates of resistance to broad spectrum penicillins with or without b-lactamase inhibitors (67.4% susceptibility to piperacillin/tazobactam) and third-generation cephalosporins (68.1% susceptibility to ceftazidime). However, cefepime (91.4% susceptibility) remains very active against this pathogen in Brazil. Aminoglycoside resistance was also elevated among *Enterobacter* spp. (69.2 to 82.4% susceptibility), and the most active fluoroquinolone against this pathogen was gatifloxacin (86.4% susceptibility).

Acinetobacter spp. was the fifth most frequent Gram-negative bacilli genus isolated in general (6.7% of the isolates), and the third most common pathogen isolated from hospitalized patients with pneumonia (10.8% of the isolates, Table 1). In our study, the carbapenems were active against nearly 90% of *Acinetobacter* spp. isolates (MIC_{50}, 1 mg/mL and

Table 7. Antimicrobial activity and spectrum of drugs tested against the 5 most prevalent Gram-negative pathogens causing bloodstream infections in Brazil

Antimicrobial class/agent	Pathogen (prevalence rank/ n° tested)									
	E. coli *(3/226)*		K. pneumoniae. *(4/178)*		Enterobacter *spp.(5/167)*		P. aeruginosa *(6/150)*		Acinetobacter *spp.(7/137)*	
	$MIC_{50}/_{90}$	% Susc.[a]	$MIC_{50}/_{90}$	% Susc [a]	$MIC_{50}/_{90}$	% Susc [a]	$MIC_{50}/_{90}$	% Susc [a]	$MIC_{50}/_{90}$	% Susc [a]
Cephalosporins										
Cefazolin	≤2/>16	82.7	>16/>16	42.1	>16/>16	2.4	>16/>16	0.0	>16/>16	0.0
Cefuroxime	16/>16	40.7	16/>16	49.4	16/>16	40.7	>16/>16	0.0	>16/>16	6.6
Cefoxitin	4/8	93.4	4/16	86.5	>32/>32	4.8	>32/>32	0.7	>32/>32	1.5
Ceftriaxone	≤0.25/0.5	92.0 (8.0)[b]	2/>32	56.2 (51.1)[b]	≤0.25/>32	74.3	>32/>32	6.7	>32/>32	16.1
Ceftazidime	0.25/1	93.8 (8.4)[b]	1/>16	69.1 (48.4)[b]	0.25/>16	73.7	4/>16	66.7	>16/>16	38.0
Cefepime	≤0.12/0.25	96.0	0.25/>16	74.7	≤0.12/8	91.0	4/>16	66.7	16/>16	44.5
Other b-lactams										
Ampicillin	>16/>16	39.4	>16/>16	4.5	>16/>16	6.0	>16/>16	0.0	>16/>16	6.6
Aztreonam	≤0.12/0.25	92.9 (8.4)[b]	0.5/>16	59.6 (47.2)[b]	≤0.12/>16	74.9	8/>16	52.7	>16/>16	10.9
Ticarcillin/Clavulanate	8/128	68.1	32/>128	47.8	4/>128	59.9	64/>128	64.0	64/>128	39.4
Piperacillin/ Tazobactam	2/16	91.2	4/>64	68.0	2/>64	70.7	8/>64	74.0	64/>64	40.1
Imipenem	0.12/0.25	100.0	0.25/0.5	100.0	0.5/2	99.4	2/>8	82.0	0.5/4	90.5
Meropenem	≤0.06/≤0.06	100.0	≤0.06/0.12	100.0	≤0.06/0.25	100.0	0.5/>8	82.7	1/4	92.0
Aminoglycosides										
Amikacin	4/8	96.5	2/>32	75.8	2/>32	81.4	4/>32	70.0	>32/>32	42.3
Gentamicin	1/2	91.6	1/>16	60.7	1/>16	75.4	2/>16	62.0	4/>16	51.8
Tobramycin	1/4	90.7	2/>16	52.8	1/>16	70.7	1/>16	60.7	2/>16	67.9
Fluoroquinolones										
Ciprofloxacin	0.03/0.5	91.6	0.06/0.5	95.5	0.06/>2	86.2	0.25/>2	67.3	>2/>2	44.5
Gatifloxacin	≤0.03/0.5	92.5	0.06/0.5	96.6	0.06/4	88.6	1/>4	66.7	4/>4	48.2
Levofloxacin	0.5/0.5	92.0	0.5/1	94.9	0.5/4	87.4	0.5/>4	68.0	4/>4	47.4
Trovafloxacin	≤0.03/0.5	91.6	0.06/0.5	94.9	0.06/4	84.4	0.5/>4	64.0	1/>4	50.4
Grepafloxacin	≤0.25/≤0.25	95.8	≤0.25/0.5	92.6	≤0.25/>2	80.6	0.5/>2	65.7	≤0.25/>2	51.7
Others										
Tetracycline	≤4/>8	60.2	≤4/>8	78.7	≤4/>8	70.7	>8/>8	1.3	≤4/>8	70.1
Trimethoprim/ Sulfathoxazole	2/>2	46.9	≤0.5/>2	61.0	≤0.5/>2	73.7	2/>2	4.0	2/>2	38.7

[a] Percentage of susceptible strains according to NCCLS criteria [NCCLS 2000].
[b] Percentage of strains with MIC ≥ 2 mg/mL indicating possible ESBL production.

Table 8. Antimicrobial activity and spectrum of drugs tested against the most prevalent Gram-positive pathogens causing bloodstream infections in Brazil - SENTRY program 1997 to 1999

	Pathogen (prevalence rank/ no. tested)					
Antimicrobial class/agent	***S. aureus* (1/473)**		**CoNS[a] (2/241)**		***Enterococcus* spp. (8/54)**	
Cephalosporins						
Cefazolin	≤2/>16	70.6[b]	4/>16	19.9[b]	>16/>16	-
Ceftriaxone	4/>32	70.6[b]	16/>32	19.9[b]	>32/>32	-
Cefepime	4/>16	70.6[b]	8/>16	19.9[b]	>16/>16	-
Ceftazidime	8/>16	55.1	>16/>16	19.9[b]	>16/>16	-
Other b-lactams						
Oxacillin	0.5/>8	70.6	>8/>8	19.9	>8/>8	-
Ampicillin	16/>16	12.3	16/>16	13.3	1/4	94.4
Penicillin	16/>32	11.6	16/>32	8.3	4/16	85.2
Amoxicillin/Clavulanate	2/>16	70.6[b]	4/>16	19.9[b]	1/4	85.2[c]
Piperacillin/Tazobactam	2/>64	70.6[b]	4/>64	19.9	4/>64	85.2[c]
Imipenem	≤0.06/>8	70.6[b]	1/>8	19.9	2/8	-
MLS						
Clindamycin	0.25/>8	70.8	>8/>8	45.6	>8/>8	-
Erythromycin	1/>8	49.5	>8/>8	39.4	>8/>8	1.9
Doxycycline	0.5/>4	84.3	1/8	86.7	4/8	63.0
Fluoroquinolones						
Ciprofloxacin	0.5/>2	70.6	1/>2	50.2	2/>2	38.9
Gatifloxacin	0.12/4	89.0	0.25/2	92.9	0.5/>4	66.7
Trovafloxacin	≤0.03/1	90.7	0.25/4	75.9	0.25/>4	64.8
Others						
Gentamicin	1/>16	68.5	16/>16	41.1	16/>16	-
Gentamicin (HL)[d]	≤500/≤500	-	≤500/≤500	-	≤500/>1000	63.0
Streptomycin (HL)[d]	≤1000/2000	-	≤1000/2000	-	≤1000/>2000	68.5
Rifampin	0.5/2	77.8	0.25/>2	68.0	>2/>2	20.4
Chloramphenicol	8/>16	63.6	16/>16	49.8	8/>16	53.7
Tetracycline	≤4/>8	66.6	≤4/>8	76.3	>8/>8	37.0
Trimethoprim/ Sulfamethoxazole	≤0.5/2	72.7	2/>2	39.0	≤0.5/2	68.5
Quinn/Dalf.	0.25/0.5	99.6	0.25/1	98.8	4/>8	5.6
Teicoplanin	1/2	99.6	2/16	88.4	≤0.12/0.5	98.1
Vancomycin	1/1	100.0	2/2	100.0	1/2	98.1

[a] CoNS: coagulase-negative staphylococci.
[b] Susceptibility predicted by the oxacillin result.
[c] Susceptibility predicted by the penicillin result.
[d] High level aminoglycoside resistence screen.

Table 9. Comparison of the antimicrobial susceptibility of *Pseudomonas aeruginosa* isolates collected from various infection sites

Antimicrobial agents	% Susceptible				
	BSI[a] (150)	LRTI[b] (242)	WSSTI[c] (45)	UTI[d] (59)	All sites (496)
Cefepime	66.7	59.9	55.6	44.1	59.7
Ceftazidime	66.7	59.5	55.6	44.1	59.5
Piperacillin/tazobactam	74.0	70.7	71.1	62.7	70.8
Imipenem	82.0	66.9	64.4	54.2	69.8
Meropenem	82.7	71.1	75.6	66.1	74.4
Gentamicin	62.0	55.0	62.2	25.4	55.6
Amikacin	70.0	61.6	68.9	39.0	55.8
Ciprofloxacin	67.3	59.9	57.8	32.2	58.7
Gatifloxacin	66.7	54.1	51.1	32.2	55.0

[a] BSI: bloodstream infection.
[b] LRTI: lower respiratory tract infection.
[c] WSSTI: wound or skin and soft tissue infection.
[d] UTI: urinary tract infection.

Table 10. Comparison of the antimicrobial susceptibility of *Enterobacter* spp. isolates collected from various infection sites

Antimicrobial agents	% Susceptible				
	BSI[a] (167)	LRTI[b] (56)	WSSTI[c] (29)	UTI[d] (27)	All sites (279)
Cefepime	91.0	89.3	100.0	88.9	91.4
Ceftazidime	73.7	62.5	69.0	44.4	68.1
Piperacillin/tazobactam	70.7	66.1	65.5	51.9	67.4
Imipenem	99.4	100.0	100.0	100.0	99.6
Meropenem	100.0	100.0	100.0	100.0	100.0
Gentamicin	75.4	76.8	89.7	59.3	77.4
Amikacin	81.4	85.7	93.1	70.4	82.4
Ciprofloxacin	86.2	85.7	89.7	51.9	83.2
Gatifloxacin	88.6	89.3	93.1	59.3	86.4

[a] BSI: bloodstream infection.
[b] LRTI: lower respiratory tract infection.
[c] WSSTI: wound or skin and soft tissue infection.
[d] UTI: urinary tract infection.

Table 11. Comparison of the antimicrobial susceptibility of *S. aureus* isolates collected from various infection sites

Antimicrobial agents	% Susceptible Strains			
	BSI[a] (473)	LRTI[b] (173)	WSSTI[c] (197)	All sites (852)
Oxacillin	70.6	52.0	66.0	66.0
Cefepime	70.6	52.0	66.0	66.0
Ceftriaxone	70.6	52.0	66.0	66.0
Ceftazidime	55.1	44.4	49.3	51.8
Clindamycin	70.8	52.0	68.5	66.5
Trimethoprim / Sulfametoxazole	72.7	53.6	67.5	68.0
Ciprofloxacin	70.6	50.3	33.0	65.6
Gatifloxacin	89.0	89.0	89.8	89.3
Teicoplanin	99.6	100.0	100.0	99.8
Vancomycin	100.0	100.0	100.0	100.0

[a] BSI: bloodstream infection.
[b] LRTI: lower respiratory tract infection.
[c] WSSTI: wound or skin and soft tissue infection.

Table 12. Comparison of the antimicrobial susceptibility of chromosomally inducible b-lactamase producing isolates collected from various infection sites

Antimicrobial agents	% Susceptible	
	All isolates[a] (442.0)	Ceftazidime-resistant strains[a] (120.0)
Cefepime	92.5	80.0
Ceftazidime	72.9	-
Piperacillin/tazobactam	68.6	15.8
Imipenem	99.3	100.0
Meropenem	100.0	100.0
Gentamicin	71.3	42.5
Amikacin	79.0	51.7
Ciprofloxacin	76.5	50.8
Gatifloxacin	80.3	58.3

[a] Include *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., *Proteus vulgaris*, and *Morganella morganii*.

MIC_{90}, >8 mg /mL for both imipenem and meropenem; Table 2). Tetracycline showed some *in vitro* activity (64.7% susceptibility). The next most active compound was tobramycin, which inhibited 56.3% of the isolates tested (MIC_{50}, 4 mg/mL). Interestingly, gentamicin (MIC_{50}, 16 mg/mL; 49.6% susceptibility) showed higher *in vitro* activity than amikacin (MIC_{50}, >32 mg/mL; 31.7% susceptibility). All other compounds were active against ≤ 40% of the isolates (Table 2).

The results of the antimicrobial susceptibility of three most frequently isolated Gram-positive cocci are shown on Table 5. In general, 34% of *S. aureus* isolates were resistant to oxacillin. The broad-spectrum b-lactams showed similar spectrum to that shown by oxacillin, except for ceftazidime, which was active against only 51.8% of *S. aureus* isolates. In addition, cross-resistance to other antimicrobial classes was very common among oxacillin-resistant strains (Tables 5 and 6). Clindamycin, trimethoprim/sulfamethoxazole, ciprofloxacin, and gentamicin were active against less than 10% of oxacillin-resistant *S. aureus* (ORSA) (Table 6). On the other hand, 69.3% of ORSA isolates were susceptible to the new quinolone gatifloxacin (MIC_{90}, 4 mg/mL). Vancomycin was uniformly active against *S. aureus* strains; however, reduced susceptibility to teicoplanin and quinupristin/dalfopristin was detected in 1 isolate (Table 6).

Resistance rates to b-lactams were much higher among CoNS and less than 20% of the strains were considered susceptible to oxacillin and broad-spectrum b-lactams (Table 5). Gatifloxacin was active against 92.7% of the CoNS isolates (MIC_{90}, 2 mg/mL) and decreased susceptibility to vancomycin was not detected among CoNS (MIC_{90}, 2 mg/mL). The vast majority of enterococci isolates were represented by *E. faecalis* and only 1 isolate with reduced susceptibility to glycopeptides was detected during the period of the program (Table 5). In addition, ampicillin resistance was very low among enterococci (98.0% susceptibility). On the other hand, almost 30% of the enterococci isolates evaluated showed high level resistance to gentamicin or streptomycin (Table 5).

Tables 7 and 8 show the antimicrobial susceptibility of the most frequently isolated species from BSI, while Tables 9, 10, and 11 exhibit the antimicrobial susceptibility of specific species (*P. aeruginosa*, *Enterobacter* spp., and *S. aureus*, respectively) according to the site of infection. Table 12 shows the antimicrobial susceptibility of chromosomally inducible b-lactamase producing strains (*Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Proteus vulgaris*, *Morganella morganii*, and *Providencia* spp.) broken down according to the ceftazidime susceptibility.

Discussion

As resistance to antibiotics continues to increase, surveillance has become a well-recognized necessity, and should combine local, national, and international efforts. Multicenter surveillance program monitoring at the hospital, or even at ward level, is also critical to understanding the relative importance of risk factors, the evolution of resistance over time, as well as for the development and assessment of preventive measures [1, 6].

Gram-negative bacilli and *S. aureus* were the predominant pathogens causing infections in the Brazilian medical centers participating in the SENTRY. Since the isolates were consecutively collected according to the site of infection, our results show the most frequently isolated species in the sites of infection evaluated. The rank order of occurrence differed slightly from that reported for North American centers participating in SENTRY [1]. In general, the most important discrepancies were a higher prevalence of *Acinetobacter* spp. and a lower prevalence of *Enterococcus* spp. in Brazil, when compared to North American centers. The top 10 pathogens in the present study accounted for almost 90% of all isolates. Among isolates from BSI, 38.3% were due to Gram-positive cocci, but *Enterococcus* spp. was isolated in only 2.7% of the cases. In contrast, in the U.S., the Gram-positive cocci were responsible for 46% of the BSI cases and *Enterococcus* spp. was isolated in almost 10% of cases [1].

The resistance rates were generally higher in Brazil when compared to those of North America, especially among the Gram-negative rods [7, 8]. The main resistance problems detected in this study were: 1) extremely high rates of ESBL-producing Enterobacteriaceae; 2) carbapenem resistance among non-fermentative Gram-negative bacilli, especially *P. aeruginosa*; 3) and high rates of stably derepressed Bush-Jacoby-Medeiros group 1 strains among Enterobacteriaceae.

The epidemic rate of ESBL-producing strains of *K. pneumoniae* and *E. coli* in Brazil is of great concern. Although the rates of ESBL-producing strains may vary significantly from region to region, or even from hospital to hospital within the same geographic region, the Brazilian rates are much higher than rates seen in most other parts of the world. In the U.S., ESBL-production rates are usually less than 5% for *K. pneumoniae* and less than 2% for *E. coli* [1]. In Europe the prevalence of ESBL-producing *K. pneumoniae* may be as high as 15% to 20%, or even higher in isolates from ICUs [9, 10]. In contrast, in the present study, approximately 9% of *E. coli* and 50% of *K. pneumoniae* were characterized as ESBL producers. Other Brazilian studies have validated the SENTRY results by showing similar rates of ESBL-producing strains in several hospitals around the country [11]. Although the extensive dissemination of a plasmid harboring the ESBL gene cannot be completely disregarded, the great genomic variability demonstrated by the ESBL-producing strains strongly suggests the continued selection of resistant mutants [12, 13]. Some studies have shown that among other identified risk factors, the use of third-generation cephalosporins, especially ceftazidime, is related to the appearance of ESBL-producing strains [14, 15].

Although these enzymes are usually inhibited by b-lactamase inhibitors, such as clavulanic acid and tazobactam, a significant percentage of ESBL-producing strains showed *in vitro* resistance to b-lactam-b-lactamase inhibitor combinations, including piperacillin/tazobactam. A low activity of b-lactam-b-lactamase inhibitor combinations against ESBL-producing strains has been documented in other studies and the mechanisms of resistance involved are not completely elucidated [16-18]. Thus, clinical studies are necessary to clarify the role of b-lactam-b-lactamase inhibitor combinations in the treatment of infections due to ESBL-producing strains. Actually, some authors have advocated that the b-lactamase-inhibitor combinations might be used to prevent the emergence of ESBL-producing strains. In a case control-control study conducted in an intensive care unit to investigate the risk acquisition of ESBL-producing strains, b-lactamase-inhibitor therapy was shown to be a protective factor [15]. Other investigators have been able to decrease the rate of colonization with ESBL-producing *K. pneumoniae* by using piperacillin/tazobactam, rather than ceftazidime, in the empirical treatment for nosocomial infections [15, 19].

In summary, Table 4 shows that there are very few therapeutic options to treat infections due to ESBL-producing strains in Brazil. Only the carbapenems were active against >75% of ESBL-producing *E. coli*, while the quinolones represent a reasonable alternative to the carbapenems against *K. pneumoniae*. All quinolones evaluated inhibited more than 90% of ESBL-producing *K. pneumoniae* with similar *in vitro* activity. In addition, the finding of an isolate of *K. pneumoniae* with intermediate MIC for meropenem is of great concern since widespread carbapenem resistance among Enterobacteriaceae would have catastrophic consequences.

The antimicrobial susceptibility results for Gram-positive cocci showed very high rates of oxacillin resistance among staphylococci with cross-resistance to most antimicrobial agents, except the glycopeptides. On the other hand, our study showed very low rates of resistance to ampicillin and glycopeptides among enterococci. The high rate of susceptibility to ampicillin may reflect the higher prevalence of *E. faecalis* as the cause of enterococci infections in the hospitals evaluated. These results are different from those reported by the SENTRY in the U. S., where both the proportion of *E. faecium* and the prevalence of glycopeptide resistance are much higher [2].

Isolates from BSI were analyzed separately because they are more likely to represent isolates from true infections and because the number of isolates from this

site was significantly higher. The antimicrobial susceptibilities of isolates from BSI (Tables 7 and 8) were very similar to that found when all isolates were analyzed together (Tables 2 and 5). One of the highest discrepancies was noted in the carbapenem susceptibility of *P. aeruginosa*. While 82.0% of isolates from BSI were susceptible to imipenem (Table 7), less than 70% of all *P. aeruginosa* evaluated was susceptible to this compound (Table 2). A tendency of higher rates of resistance among isolates from UTI was also noted for this pathogen. In contrast, the highest rates of susceptibilities were detected among isolates from BSI (Table 9). Similarly, *S. aureus* from BSI presented higher rates of susceptibility when compared to *S. aureus* from LRTI (Table 11).

Resistance rates to third-generation cephalosporins and b-lactam-b-lactamases inhibitor combinations were high among *Enterobacter* spp. and other species that produce large amounts of inducible Bush-Jacoby-Medeiros group 1 (*Amp*C) b-lactamase (Table 10)[20]. More than 440 isolates of *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Proteus vulgaris*, *Morganella morganii*, and *Providencia* spp. were analyzed as a group and the antimicrobial susceptibility pattern of this group was very similar to that showed by *Enterobacter* spp. (Table 12). When the ceftazidime-resistant strains (stably derepressed Bush-Jacoby-Medeiros group 1) were analyzed separately (120 isolates), we verified that only the carbapenems (100% susceptibility) and cefepime (80% susceptibility) showed reasonable activity against this group of multiresistant organisms. The newer quinolones gatifloxacin and levofloxacin were active against 57.5% of the isolates (MIC_{50}, 2 mg/mL), and all other compounds were active against less than 50% of the strains (Table 12).

SENTRY is one of the largest and most comprehensive surveillance programs in place worldwide. This program has been contributing to the better understanding of antimicrobial resistance in several areas of the world. Due to the lack of regional data, Brazilian physicians relied on susceptibility data from the U. S. and Europe to guide their empiric antimicrobial therapy and also to direct infection control measures. SENTRY has analyzed more than 4,000 clinical isolates (3,728 from nosocomial infections and 612 isolates from community acquired infections) from four Brazilian cities in 3 consecutive years. This Program has detected important differences in the antimicrobial susceptibilities in Brazil, North America, and Europe, further emphasizing the importance of having regional data to guide empiric therapy. In addition, the program has performed molecular typing in several groups of resistant organisms (data not shown). The results from this part of the Program allow us to better understand the mode of dissemination of antimicrobial resistance, and to guide the infection control measures necessary to control the problem [9-11,21].

Antimicrobial resistance may vary significantly within a country and SENTRY evaluate only a small percentage of Brazilian hospitals. However, the leading objective of the Program is to detect the main problems within the country and to guide more regional programs. A broader study that evaluated more than 36 Brazilian hospitals focusing on BSI found that the antimicrobial resistance problems detected by SENTRY are widespread and not restricted to only those hospitals evaluated by the Program [11].

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