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Frequency of Occurrence and Antimicrobial Susceptibility of Bacterial Isolates Causing Bloodstream Infections Worldwide: Report from 8 years of the SENTRY Antimicrobial Surveillance Program (1997-2004)

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AMENDED ABSTRACT

Background:Geographic and year-to-year variations on the frequency of pathogens causing bloodstream infection (BSI) were assessed during the 8 years of the SENTRY Program. Geographic patterns of antimicrobial susceptibility (S) for 2004 was also analyzed.
Methods: The first 20 unique and clinically relevant BSI isolates from > 80 medical centers worldwide were sent to a monitor each month. The isolates were tested for S (>30 antimicrobials) by CLSI broth microdilution methods.
Results: 125,126 isolates were processed in 1997-2004. The rank order for all years is summarized in the table.

	Rank position/% of total by region (n)			
Organism	North America (NA; 55,177)	Europe (EU; 39,078)	Latin America (LA; 16,554)	Asia-Pacific (AP; 14,317)
S. aureus (SA)	1/26.1	2/19.7	1/21.8	2/20.2
E. coli (EC)	2/17.7	1/22.6	2/18.0	1/21.3
Enterococcus spp.	3/10.6	4/7.4	9/3.7	5/5.6
Coag-neg staphylococci (CoNS)	4/10.4	3/13.6	3/13.3	3/10.2
Klebsiella spp. (KSP)	5/7.8	5/7.2	4/9.8	4/9.5
P. aeruginosa (PSA)	6/4.4	6/6.2	5/6.7	6/5.2
S. pneumoniae	7/4.2	8/2.9	8/3.8	8/4.4
Enterobacter spp.	8/3.8	7/4.3	6/5.3	7/4.4
ß-haemolytic streptococci	9/3.7	11/2.0	10/1.9	9/2.9
Viridans gr. streptococci	10/1.5	10/2.2	11/1.0	11/2.4
Acinetobacter spp. (ASP)	11/1.4	9/2.5	7/4.2	9/2.9

The main regional variation occurred with enterococci (3rd in the USA to 9th in LA) and ASP (4.2% [7th] in LA and 1.4-2.9% in other regions). The rank order and frequencies were very stable through the years within each region, except for a decrease of CoNS (14.6% in 1997 to 8.9% in 2004) and an increase of enterococci (7.6% in 2001 to 9.2% in 2004) frequencies. Oxacillin resistance (R) among SA in 2004 varied from 26% in EU to 41% in LA (50% in the USA), while vancomycin-R varied from 24% in the USA to only 5-6% in LA and EU. Strains with an ESBL phenotype were lowest in the USA and EU (5 - 6%) but 13% in LA among EC; and 11% in the USA but 22% in EU and 40% in LA among KSP. Cefepime remained active against EC and KSP in the USA, 97-99% S. R to ciprofloxacin rose to 16-17% among EC from EU and USA. Carbapenem-R rates for PSA and ASP were lower in the USA (12 and 3%, respectively) compared to LA (25 and 7%) and EU (23 and 44%).
Conclusions: The frequency of pathogens causing BSI was very similar from region to region and over the 8 years monitored, but great variation was observed in the antimicrobial S patterns.

INTRODUCTION

The interactions of extremely ill patients, modern medical technology and heavy antimicrobial use have increased the frequency of serious infections and antimicrobial resistance among many nosocomial pathogens. Nosocomial bloodstream infection (BSI) is one such infection. Many BSIs are related to the use of intravascular devices and prudent use of such devices usually minimizes these infections. However, in the United States (USA), nosocomial BSIs cause as many as 3.5 million additional hospital days stay per year, accounting for 3.5 billion dollars in added costs. In addition, the mortality rate directly attributable to BSIs varies from 14 to as high as 38%.

The increasing rates of antimicrobial resistance are creating serious dilemmas for treatment of bacteremic patients, requiring the development of new therapeutic options, advanced diagnostic tests and preventive strategies. Despite such advances, accurate empiric treatment remains critical to minimize inappropriate antimicrobial therapy that may lead to poor clinical outcome.

The SENTRY Antimicrobial Surveillance Program (1997 to present) has monitored BSI pathogens, among other yearly objectives, on a worldwide scale. In the present study, we assessed geographic and year-to-year variation on the frequency of pathogens causing BSI during the eight years of the SENTRY Program. Geographic variation of antimicrobial susceptibilities in the year 2004 was also analyzed.

MATERIALS AND METHODS

The geographic regions in this study included North America (31 – 34 centers per year in the USA and Canada [1997-2003]), Europe (25 – 30 centers per year in 17 nations), Latin America (10 centers per year in six nations) and Asia-Pacific (12 - 17 centers per year in nine nations). The period evaluated included 1997 to 2004 for all regions except for the Asia-Pacific region where data from 1998 to 2003 were included in this report. Each medical center was asked to send to the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA or Women's and Children's Hospital, Adelaide, Australia) the first 20 consecutive strains (one per patient, prevalence format) isolated each month.

All isolates were identified by the participant laboratories and confirmed by the monitoring facility. Each strain was tested by a reference broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) methods and criteria. Current quality control testing was performed using the following organisms: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, *Klebsiella pneumoniae* 700603, *Enterococcus faecalis* ATCC 29212, *Haemophilus influenzae* ATCC 49247 and *Streptococcus pneumoniae* ATCC 49619. All QC results were within published ranges.

Klebsiella spp., *E. coli* and *Proteus mirabilis* isolates with increased MIC values (≥ 2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase (ESBL)-producing phenotypes and submitted to a clavulanate inhibition test (disk approximation and/or Etest) for confirmation of ESBL production.

RESULTS

- A total of 125,126 isolates were processed over the eight years (1997-2004), including 55,177 from North America, 39,078 from Europe, 16,554 from Latin America and 14,317 from the Asia-Pacific region (six-years only). The rank orders during the entire period are summarized in Tables 1 to 4.
- *S. aureus* and *E. coli* were the most frequently isolated pathogens isolated from BSIs in all regions evaluated. These two species were responsible from 39.8% (Latin America) to 43.8% (USA) of cases evaluated.
- In North American medical centers approximately two-thirds of BSIs were caused by Gram-positive bacteria while in all other regions the proportions of Gram-positive and Gram-negative bacteria were very similar.
- The main regional variation in pathogen frequency occurred with enterococci, which ranked 3rd in North America (Table 1) and 9th in Latin America (Table 3); and also *Acinetobacter* spp. which represented 4.2% (7th) of isolates in Latin America, but only 1.4 - 2.9% in other regions (Tables 1 to 4).
- The rank order and frequencies were very stable across the years within each region, except for a world-wide decrease of CoNS and an increase of enterococci occurrence in all regions (Tables 1 to 4).
- Oxacillin resistance among *S. aureus* varied from 26% in Europe to 50% in the USA, while vancomycin resistance among enterococci varied from as high as 24% in the USA to only 2 - 5% for the other continents (Table 5).
- Among *S. aureus*, resistance to quinupristin/dalfopristin was detected only in Europe (0.3%) and in the Asia-Pacific region (0.4%), while only one isolate non-susceptible to daptomycin was detected in all regions evaluated in 2004 (USA; daptomycin MIC of 2 µg/ml). No resistance to vancomycin, teicoplanin or linezolid was detected in 2004 (Table 5).

Table 1. Frequency of occurrence of bacterial isolates causing bloodstream infections in North America.

	% by years (no. tested)		
Organism	1997 (7,857)	2004 (5,524)	8-year period (55,177)
1. *S. aureus*	22.9	26.4	26.1
2. *E. coli*	18.6	18.7	17.7
3. *Enterococcus* spp.	9.5	12.7	10.6
4. CoNS	12.8	8.7	10.4
5. *Klebsiella* spp.	7.5	5.1	7.8
6. *P. aeruginosa*	4.6	4.5	4.4
7. *S. pneumoniae*	5.6	3.3	4.2
8. *Enterobacter* spp.	4.0	4.5	3.8
9. ß-haemolytic streptococci	3.5	4.1	3.7
10. viridans group streptococci	1.6	1.0	1.5

Table 2. Frequency of occurrence of bacterial isolates causing bloodstream infections in Europe.

	% by years (no. tested)		
Organism	1997 (4,670)	2004 (5,672)	8-year period (39,078)
1. *E. coli*	20.6	23.2	22.6
2. *S. aureus*	19.9	20.8	19.7
3. CoNS	17.4	11.0	13.6
4. *Enterococcus* spp.	7.2	7.8	7.4
5. *Klebsiella* spp.	6.0	7.2	7.2
6. *P. aeruginosa*	5.5	6.3	6.2
7. *Enterobacter* spp.	3.8	4.4	4.3
8. *S. pneumoniae*	2.2	2.9	2.9
9. *Acinetobacter* spp.	2.4	2.5	2.5
10. viridans group streptococci	2.9	1.8	2.2

- *E. coli* strains with an ESBL phenotype ranged from 4.5 - 6.1% in the USA and Europe to 12.9% in Latin America; while among *Klebsiella* spp., ESBL rates varied from 10.6 - 12.4% in the USA and the Asia-Pacific region to 22.4% in Europe to a very high rate of 39.8% in Latin America (Table 6).

Table 3. Frequency of occurrence of bacterial isolates causing bloodstream infections in Latin America.

	% by years (no. tested)		
Organism	1997 (1,650)	2004 (2,312)	8-year period (16,554)
1. *S. aureus*	20.5	23.1	21.8
2. *E. coli*	16.9	17.4	18.0
3. CoNS	15.1	14.4	13.3
4. *Klebsiella* spp.	10.6	9.6	9.8
5. *P. aeruginosa*	5.6	7.2	6.7
6. *Enterobacter* spp.	6.0	4.9	5.3
7. *Acinetobacter* spp.	5.3	4.7	4.2
8. *S. pneumoniae*	1.9	3.2	3.8
9. *Enterococcus* spp.	3.0	4.2	3.7
10. *P. mirabilis*	1.0	1.1	1.1

Table 4. Frequency of occurrence of bacterial isolates causing bloodstream infections in Asia-Pacific region.

	% by years (no. tested)		
Organism	1998 (1,569)	2003 (2,506)	6-year period (14,317)
1. *E. coli*	19.1	21.2	21.3
2. *S. aureus*	20.8	20.1	20.2
3. CoNS	9.2	7.1	10.2
4. *Klebsiella* spp.	9.3	10.3	9.5
5. *Enterococcus* spp.	3.9	7.1	5.6
6. *P. aeruginosa*	4.5	5.1	5.2
7. *Enterobacter* spp.	5.2	4.6	4.4
8. *S. pneumoniae*	5.4	4.2	4.4
9. *Acinetobacter* spp.	3.3	3.2	2.9
10. ß-haemolytic streptococci	2.2	3.1	2.9

Table 5. Antimicrobial susceptibility pattern of the most frequently isolated Gram-positive pathogens in 2004 according to geographic region.

	% susceptible/resistant[a] (no. tested)			
Organisms/antimicrobial agent	North America[b]	Europe	Latin America	Asia-Pacific[c]
S. aureus	(1,459)	(1,179)	(534)	(504)
Oxacillin	50/50	74/26	59/41	60/40
Erythromycin	36/63	71/28	55/45	55/44
Clindamycin	68/32	85/15	63/36	73/27
Ciprofloxacin	52/46	71/28	60/39	65/35
Levofloxacin	54/45	72/28	61/37	65/35
Trimethoprim/sulfamethoxazole	98/2	97/3	80/20	86/14
Quinupristin/dalfopristin	100/0	99.7/0.3	100/0	99.5/0.4
Teicoplanin	100/0	100/0	100/0	100/0
Vancomycin	100/0	100/0	100/0	100/0
Linezolid	100/-[d]	100/-	100/-	100/-
Daptomycin	>99.9/-	100/-	100/-	100/-
CoNS	(248)	(624)	(334)	(179)
Oxacillin	19/81	24/76	25/75	16/84
Erythromycin	21/78	39/61	32/67	40/59
Clindamycin	52/46	71/29	57/41	71/29
Ciprofloxacin	42/57	43/52	51/45	53/41
Levofloxacin	42/56	44/48	52/38	54/38
Trimethoprim/sulfamethoxazole	59/41	60/40	53/47	59/41
Quinupristin/dalfopristin	100/0	99.4/0.3	98/0.3	100/0
Teicoplanin	95/0.8	97/0.3	95/0.3	94/0
Vancomycin	100/0	100/0	100/0	100/-
Linezolid	100/-	100/-	100/-	100/-
Daptomycin	99.6/-	100/-	99.7/-	99.4/-
Enterococcus spp.	(704)	(443)	(98)	(177)
Ampicillin	69/31	69/31	88/12	73/27
Levofloxacin	44/56	55/42	63/36	57/42
Doxycycline	41/15	44/24	46/18	-/-
Chloramphenicol	90/10	73/21	70/28	74/19
Gentamicin (HL)	65/35	69/31	65/35	61/39
Streptomycin (HL)	64/36	56/44	77/23	76/24
Quinupristin/dalfopristin	30/65	28/59	10/82	27/59
Teicoplanin	78/18	96/3	95/5	98/2
Vancomycin	76/24	94/5	95/5	97/2
Linezolid	99.1/0.7	100/-	100/-	100/0
Daptomycin	99.7/-	100/-	100/-	98/-

a. According to CLSI criteria.
b. Includes isolates from the USA only.
c. Isolates from 2003.
d. - = no interpretive criteria have been published by the CLSI.

- Cefepime remained very active against *E. coli* and *Klebsiella* spp. collected in the USA (97 - 99%), but resistance to ciprofloxacin achieved 16 - 23% among *E. coli* isolated in 2004, worldwide (Table 6).
- Ceftazidime resistance among *Enterobacter* spp. (stably derepressed AmpC) occurred in 15% of strains in the USA, lower than 27% in Latin America and Europe as well as 30% in the Asia-Pacific region (Table 6).
- The frequencies of imipenem-non-susceptible *P. aeruginosa* and *Acinetobacter* spp. strains were lowest in the USA (12 and 3%, respectively) compared to Latin America (25 and 7%) and Europe (23 and 44%; Table 6).
- Amikacin and tobramycin showed similar activity against *Acinetobacter* spp. in North America and Asia-Pacific regions, but tobramycin showed higher rates of susceptibility in Europe and Latin America. These results may be explained by the broader use of amikacin in these two regions (Table 6).
- In general, resistance rates among *P. aeruginosa* and *Acinetobacter* spp. were significantly lower in the USA compared to the other regions evaluated (Table 6).

Table 6. Antimicrobial susceptibility pattern of the most frequently isolated Gram-negative pathogens in 2004 according to geographic region.

	% susceptible/resistant[a] (no. tested)			
Organisms/antimicrobial agent	North America[b]	Europe	Latin America	Asia-Pacific[c]
E. coli	(1,031)	(1,316)	(402)	(531)
Ceftriaxone	98/2(3.8)[d]	96/3(6.1)[d]	89/10(12.9)[d]	95/4(7.5)[d]
Ceftazidime	97/2(4.5)[d]	97/2(5.7)[d]	92/7(11.7)[d]	96/2(6.6)[d]
Cefepime	99/1	98/2	92/6	96/3
Cefoxitin	90/4	91/4	90/5	92/4
Piperacillin/tazobactam	97/2	95/2	95/1	97/2
Imipenem	100/0	100/0	100/0	99.8/0
Ciprofloxacin	84/16	83/17	77/23	82/17
Levofloxacin	84/15	84/13	77/21	82/15
Gentamicin	91/8	94/6	89/10	86/14
Klebsiella spp.	(483)	(407)	(221)	(259)
Ceftriaxone	94/4(10.1)[d]	82/13(22.4)[d]	64/32(39.8)[d]	92/5(12.0)[d]
Ceftazidime	92/8(10.6)[d]	85/14(22.1)[d]	73/20(38.0)[d]	92/7(12.4)[d]
Cefepime	97/2	89/10	71/24	95/4
Cefoxitin	88/7	87/7	84/7	92/5
Piperacillin/tazobactam	93/6	83/14	74/20	90/7
Imipenem	99/1	99/0	99.5/0	100/0
Ciprofloxacin	92/8	87/12	77/19	89/10
Levofloxacin	93/6	87/10	82/16	92/8
Gentamicin	93/6	89/8	83/15	91/9
Enterobacter spp.	(250)	(247)	(113)	(116)
Ceftriaxone	85/7	71/18	68/26	70/18
Ceftazidime	82/15	68/27	70/27	63/30
Cefepime	98/1	96/1	81/18	91/3
Piperacillin/tazobactam	84/6	72/13	74/20	66/19
Imipenem	99.5/0.6	98/1	100/0	99.1/0
Ciprofloxacin	93/6	79/17	82/15	89/8
Levofloxacin	93/4	83/13	83/14	91/5
Gentamicin	94/4	89/10	81/16	90/10
P. aeruginosa	(284)	(355)	(167)	(128)
Ceftazidime	86/11	74/20	67/26	77/15
Cefepime	84/7	76/14	67/17	81/11
Piperacillin/tazobactam	89/11	78/22	79/21	88/12
Imipenem	88/6	77/9	75/14	81/12
Ciprofloxacin	78/18	67/31	59/38	81/19
Levofloxacin	76/18	63/30	59/38	79/19
Amikacin	98/2	88/8	78/21	92/6
Tobramycin	93/6	73/25	65/35	83/16
Polymyxin B	100/0	100/0	100/0	99.2/0.8
Acinetobacter spp.	(99)	(136)	(109)	(80)
Ceftazidime	55/37	30/65	30/63	66/31
Cefepime	59/30	35/43	36/55	68/25
Ampicillin/sulbactam	72/19	39/48	64/22	68/29
Imipenem	97/1	56/37	93/7	74/20
Ciprofloxacin	60/39	32/68	39/61	60/40
Levofloxacin	63/34	33/57	40/51	64/20
Amikacin	79/15	42/57	40/56	66/31
Tobramycin	77/21	48/46	59/38	66/29
Polymyxin B	100/0	100/0	99.1/0.9	95/5

a. According to CLSI criteria.
b. Includes isolates from the USA only.
c. Isolates from 2003.
d. Percent of isolates with ESBL phenotype (MIC, ≥ 2 µg/ml).

CONCLUSIONS

- *S. aureus* and *E. coli* represent the main causes of BSIs among hospitalized patients.
- The frequencies of pathogens causing BSI were very similar from region to region and over the eight years within each region.
- Conversely, significant regional variations were observed among antimicrobial susceptibility patterns. Resistance rates were generally higher among Gram-positive pathogens and lower among Gram-negative pathogens for North America (USA) compared to other continental samples of BSI isolates.

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