10 Years of Surveillance of Bloodstream Infections in North American Medical Centers by the SENTRY Antimicrobial Surveillance Program (1997-2006)

HS SADER, JE ROSS, TR FRITSCHE, RN JONES
JMI Laboratories, North Liberty, IA, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370
fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Objectives: We assessed the prevalence and antimicrobial susceptibility (S) of pathogens causing bloodstream infections (BSI) in North America (NA).

Methods: The first 20 unique and clinically relevant BSI isolates were collected from 60 medical centers (25-30/year) and sent to a central monitor each month. Isolates were S tested by CLSI broth microdilution methods. Variations of prevalence and S rates over time were analyzed. Strains with selected S patterns were chosen for characterization of resistance (R) mechanisms and epidemic clonality (PFGE).

Results: 66,204 strains were processed. S rates of the most common Gram-negative bacilli are shown in the table. ESBL phenotypes among *E. coli* and *Klebsiella* spp. (KSP) increased from 2 and 5% in 1999 to 6 and 14% (includes KPC enzymes) in 2006, respectively. The most common Gram-positive cocci were (rank order among all / no. of isolates / % of total): *S. aureus* (1 / 17,284 / 26%) > *Enterococcus* spp. (ESP; 3 / 7,285 / 11%) > coag.-neg. staphylococci (CoNS; 4 / 6,470 / 10%) > *S. pneumoniae* (SPN; 7 / 2,828 / 4%). Rank order and the frequencies were stable over time, except for a decrease in CoNS and an increase in ESP. MRSA and VRE rates varied from 22 and 13% in 1997 to 49 and 30% in 2006. *E. faecium* prevalence increased from 2 to 5%, and vancomycin-R from 40 to 70%. Among SPN, penicillin-S varied from 71 (2006) to 81% (1998 and 2002), while erythromycin/clindamycin S dropped significantly from 90/98% in 1998 to 75/91% in 2006.

		% S (1997)/% variation through 2006:			
Rank Order	Organism (no. tested: 1997/2006)	Ciprofloxacin	Gentamicin	Ceftazidime	Imipenem
2	*E. coli* (1461/922)	98/-20	96/-6	99/-3	100/NC
5	*Klebsiella* spp. (592/548)	96/-9	96/-4	96/-7	100/-5
6	*P. aeruginosa* (359/274)	89/-3	88/+8	87/+1	88/NC
8	*Enterobacter* spp. (312/300)	94/-2	95/-5	98/-2	100/-1
11	*Acinetobacter* spp. (ASP;117/137)	79/-19	80-12	74/-19	94/-14

Abbreviations: NC = No change

Conclusions: The following R phenotypes showed substantial increase during the study period: MRSA, VRE, and ESBL and ciprofloxacin-R (Table) among all species. R rates among ASP showed greatest increase and large year-to-year variation caused by epidemic outbreaks of R clones.

INTRODUCTION

Bloodstream infections (BSI) are one of the most common nosocomial infections and the mortality rate directly attributable to this type of infection varies from 14 to as high as 38%. In the United States (USA), nosocomial BSIs cause as many as 3.5 million additional hospital stay days per year, accounting for 3.5 billion dollars in additional costs.

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

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 assess the prevalence and antimicrobial susceptibility of pathogens causing BSI in North American hospitals during the first 10 years of the SENTRY Program.

MATERIALS AND METHODS

The first 20 unique and clinically relevant BSI isolates were collected from 60 medical centers (25-30/year) and sent to a central monitor each month (JMI Laboratories, North Liberty, IA). Isolates were susceptibility tested by Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) broth microdilution methods. Variations of prevalence and susceptibility rates over time were analyzed. Strains with selected susceptibility patterns were chosen for characterization of resistance mechanisms and epidemic clonality (PFGE and ribotyping).

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 CLSI methods and criteria. Current quality control testing was performed using the following organisms: *Escherichia coli* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, *Klebsiella pneumoniae* 700603, *Enterococcus faecalis* ATCC 29212, *Haemophilus influenzae* ATCC 49247 and *Streptococcus pneumoniae* ATCC 49619.

Klebsiella spp., *E. coli* and *Proteus mirabilis* isolates with elevated 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 66,204 isolates were processed over the 10 years (1997-2006). Approximately 60% of BSIs overall were caused by Gram-positive organisms and this proportion remained stable during the study period (Tables 1 and Figure 1).
- Tables 2-4 show the antimicrobial susceptibility patterns of the most frequently isolated pathogens for the overall period.

Table 1. Frequency of occurrence of organisms causing bloodstream infections (1997-2006).

Pathogen	Rank order	No. tested	Prevalence
S. aureus	1	17,284	26.1
E. coli	2	11,550	17.4
Enterococcus spp.	3	7,285	11.0
CoNS	4	6,470	9.8
Klebsiella spp.	5	5,398	8.2
P. aeruginosa	6	2,963	4.5
S. pneumoniae	7	2,828	4.0
Enterobacter spp.	8	2,662	4.0
ß-haemolytic streptococci	9	2,467	3.7
Serratia spp.	10	1,149	1.7
Acinetobacter spp.	11	978	1.5
Viridans group streptococci	12	971	1.5
Others	-	4,399	6.6
Total		66,204	

- *S. aureus* was the most frequently isolated pathogen from BSIs during the 10-year period, with a prevalence varying from 22.9 to 28.7% (26.1% overall; Figure 1).
- The prevalence of MRSA and VRE increased significantly from 22.4 and 13.0% in 1997 to 48.6 and 29.6% in 2006, respectively (Figure 2). Among *E. faecium* strains, vancomycin resistance rates were approximately 70% in the last three years.
- *E. coli* was the second most frequently isolated pathogen and its prevalence decreased from 18.6% in 1997 to 15.9% in 2006. In contrast, the prevalence of enterococci increased from 9.5 to 12.9% (Figure 1).
- *E. coli* strains with an ESBL-phenotype ranged from 2.1% (1997) to 4.9% (2006). Among *Klebsiella* spp., the ESBL rate increased from 4.7% in 1997 to 14.2% in 2006 (8.0% overall; Figure 3).

Table 2. Activity of antimicrobial agents tested against Gram-positive organisms (1997-2006).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
S. aureus (17,283)				
Oxacillin	0.5	>8	≤0.06->8	62.5 / 37.5
Erythromycin	>4	>4	≤0.06->4	45.8 / 42.9
Clindamycin	≤0.25	>8	≤0.25->8	72.1 / 27.6
Levofloxacin	≤0.5	>4	≤0.5->4	59.0 / 40.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	97.3 / 2.7
Quinupristin/dalfopristin	0.25	0.5	≤0.06-2	99.8 / 0.0
Linezolid	2	2	≤0.06-16	>99.9 / -
Vancomycin	1	1	≤0.12-4	>99.9 / 0.0
Enterococcus spp. (7,283)				
Ampicillin	≤2	>16	≤2->16	73.0 / 27.0
Gentamicin (HL)	≤500	>1000	≤500->1000	69.5 / 30.5
Streptomycin (HL)	≤1000	>2000	≤1000->2000	62.1 / 37.9
Quinupristin/dalfopristin	>2	>2	0.12->2	27.9 / 66.2
Levofloxacin	>4	>4	≤0.03->4	45.2 / 53.9
Linezolid	2	2	≤0.06->16	98.5 / 0.4
Teicoplanin	0.25	>16	≤0.12->16	83.9 / 14.1
Vancomycin	1	>16	≤0.12->16	80.9 / 18.2
CoNS (6,470)				
Oxacillin	>2	>2	≤0.06->2	24.2 / 75.8
Erythromycin	>4	>4	≤0.06->4	27.3 / 65.2
Clindamycin	≤0.25	>8	≤0.25->8	59.1 / 40.2
Levofloxacin	≤2	>4	≤0.03->4	45.2 / 49.1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	75.8 / 24.2
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-8	99.3 / 0.1
Linezolid	1	2	≤0.06->8	>99.9 / -
Vancomycin	1	2	≤0.12-8	>99.9 / 0.0
S. pneumoniae (2,628)				
Penicillin	≤0.03	1	≤0.03->16	76.0 / 9.9
Ceftriaxone	≤0.25	1	≤0.25-8	97.6 / 0.9
Erythromycin	0.12	>2	≤0.06->2	84.8 / 14.8
Clindamycin	≤0.25	≤0.25	≤0.25->8	96.4 / 3.4
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	76.8 / 16.2
Levofloxacin	1	1	0.06->4	99.7 / 0.2
Linezolid	1	1	≤0.06-2	100.0 / -
Vancomycin	0.25	0.5	≤0.12-1	100.0 / -
ß-haemolytic streptococci (2,467)				
Penicillin	0.03	0.06	≤0.008-0.25	99.8 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25-1	99.9 / -
Erythromycin	0.12	>2	≤0.06->2	78.4 / 20.9
Clindamycin	≤0.25	≤0.25	≤0.25->8	91.9 / 7.7
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->8	- / -
Levofloxacin	0.5	1	0.06->4	99.3 / 0.6
Linezolid	1	1	≤0.06-2	100.0 / -
Vancomycin	0.5	0.5	≤0.12-1	100.0 / -
Viridans group streptococci (971)				
Penicillin	0.06	1	≤0.015-32	69.6 / 5.5
Ceftriaxone	≤0.25	1	≤0.25-16	93.4 / 3.2
Erythromycin	≤0.25	4	≤0.25->32	55.6 / 40.3
Clindamycin	≤0.25	≤0.25	≤0.25->8	92.2 / 7.7
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5->8	- / -
Levofloxacin	1	2	≤0.03->4	96.3 / 3.0
Linezolid	1	1	≤0.06-8	99.9 / -
Vancomycin	0.5	1	≤0.12-2	99.9 / -

a. According to CLSI M100-S17.

Table 3. Activity of antimicrobial agents tested against Enterobacteriaceae (1997-2006).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
E. coli (11,550)				
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	98.6 / 0.8 (2.3)[b]
Cefepime	≤0.12	≤0.12	≤0.12->16	99.5 / 0.4
Ampicillin/sulbactam	4	32	≤0.25->32	59.8 / 20.0
Piperacillin/tazobactam	2	4	≤0.12->256	96.9 / 1.5
Imipenem	≤0.5	≤0.5	≤0.5-4	100.0 / 0.0
Levofloxacin	≤0.03	0.5	≤0.03->4	91.2 / 8.0
Gentamicin	≤2	≤2	≤2->16	94.9 / 4.4
Polymyxin B	≤1	≤1	≤1->8	99.5 / 0.5
Klebsiella spp. (5,398)				
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	94.9 / 2.5 (8.0)[b]
Cefepime	≤0.12	0.25	≤0.12->16	97.8 / 1.5
Ampicillin/sulbactam	4	>16	≤0.25->16	76.2 / 15.7
Piperacillin/tazobactam	2	16	0.25->256	93.1 / 4.7
Imipenem	0.12	0.5	≤0.06->8	99.0 / 0.9
Levofloxacin	0.12	0.5	≤0.03->4	93.9 / 4.9
Gentamicin	≤2	≤2	≤2->16	94.5 / 4.1
Polymyxin B	≤1	≤1	≤1->8	98.4 / 1.6
Enterobacter spp. (2,662)				
Ceftriaxone	≤0.25	32	≤0.25->32	81.9 / 9.6
Cefepime	≤0.12	2	≤0.12->16	98.5 / 0.9
Ampicillin/sulbactam	16	>32	1->32	29.0 / 45.9
Piperacillin/tazobactam	2	64	0.25-256	83.7 / 6.7
Imipenem	0.5	1	≤0.06->8	99.7 / 0.2
Levofloxacin	0.25	0.5	≤0.03->4	94.6 / 3.5
Gentamicin	≤2	≤2	≤2->16	93.0 / 5.6
Polymyxin B	≤1	>8	≤1->8	81.1 / 18.9
Serratia spp. (1,149)				
Ceftriaxone	≤0.25	2	≤0.25->32	96.1 / 1.0
Cefepime	≤0.12	0.5	≤0.12->16	99.5 / 0.4
Ampicillin/sulbactam	>16	>16	2->16	10.5 / 68.0
Piperacillin/tazobactam	2	4	≤0.5->256	95.5 / 1.3
Imipenem	0.5	2	≤0.06->8	99.7 / 0.3
Levofloxacin	0.25	1	≤0.03->4	97.6 / 1.3
Gentamicin	≤2	≤2	≤2->16	95.3 / 3.1
Polymyxin B	>8	>8	≤0.5->8	4.5 / 95.5

a. According to CLSI M100-S17.
b. Percentage of strains with ESBL-phenotype.

- Ciprofloxacin resistance also increased approximately six-fold from 2.1% (1997) to 12.4% (2006) among *E. coli* and from 2.9% (1997) to 22.5% (2006) among *Klebsiella* spp. (data not shown).

Figure 1. Yearly frequency of occurrence for BSI pathogens in North America (1997-2006).

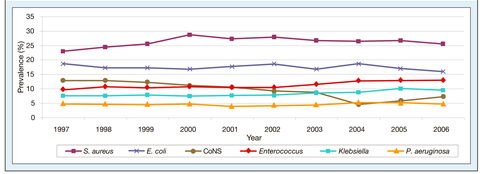
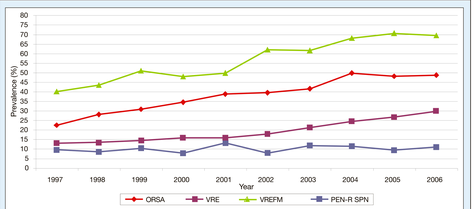
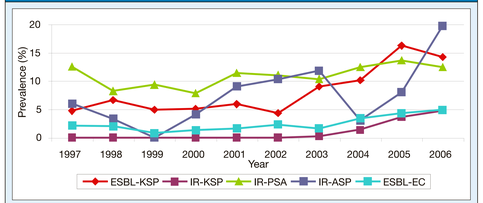


Figure 2. Yearly frequency of occurrence of selected resistance phenotypes among Gram-positive pathogens (1997-2006).



Abbreviations and definitions: MRSA, methicillin-resistant *Staphylococcus aureus* (oxacillin MIC >4 µg/ml); PEN-R SPN, penicillin-resistant *Streptococcus pneumoniae* (penicillin MIC ≥2 µg/ml); VRE, *Enterococcus* spp. with vancomycin MIC ≥8 µg/ml (non-susceptible); VREFM, *Enterococcus faecium* with vancomycin MIC ≥8 µg/ml (non-susceptible).

Figure 3. Yearly frequency of occurrence of selected resistance phenotypes among Gram-negative pathogens (1997-2006).



Abbreviations and definitions: ESBL-EC, *Escherichia coli* with an ESBL-phenotype (MIC ≥2 µg/ml for ceftriaxone or ceftazidime); ESBL-KSP, *Klebsiella* spp. with an ESBL-phenotype; IR-ASP, *Acinetobacter* spp. with imipenem MIC ≥8 µg/ml; IR-KSP, *Klebsiella* spp. with imipenem MIC ≥8 µg/ml; IR-PSA, *Pseudomonas aeruginosa* with imipenem MIC ≥8 µg/ml.

- Imipenem-non-susceptible *Klebsiella* spp. (KPC strains) emerged in 2003 and the frequency of this organism increased rapidly, reaching 4.7% in 2006 (Figure 3).
- The yearly frequencies of imipenem-non-susceptible *P. aeruginosa* remained stable during the study period while the yearly frequencies of imipenem-non-susceptible *Acinetobacter* spp. varied due to the occurrence of clonal dissemination in certain institutions (Figure 3).

Table 4. Activity of antimicrobial agents tested against non-fermentative Gram-negative bacilli (1997-2006).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
P. aeruginosa (2,963)				
Ceftazidime	2	16	≤0.12->16	86.4 / 9.9
Cefepime	2	16	≤0.12->16	88.0 / 4.7
Piperacillin/tazobactam	4	64	≤0.5->256	90.9 / 9.1
Imipenem	1	8	≤0.12->8	89.2 / 6.2
Levofloxacin	0.5	>4	≤0.03->4	80.5 / 14.4
Gentamicin	≤2	4	≤2->16	90.1 / 6.9
Amikacin	≤4	8	≤4->32	97.6 / 1.4
Polymyxin B	≤1	2	≤1->4	99.7 / 0.3
Acinetobacter spp. (978)				
Ceftazidime	8	>16	≤0.12->16	63.0 / 28.0
Cefepime	4	>16	≤0.12->16	66.3 / 21.3
Ampicillin/sulbactam	4	>16	≤0.25->16	72.4 / 19.6
Imipenem	0.25	4	≤0.06->8	91.6 / 5.0
Levofloxacin	≤0.5	>4	≤0.5->4	68.5 / 28.4
Gentamicin	≤2	>8	≤2->8	70.8 / 26.3
Amikacin	≤4	32	≤4->32	86.9 / 9.2
Polymyxin B	≤1	≤1	≤1->8	98.6 / 1.4
S. maltophilia (472)				
Ceftazidime	8	>16	0.5->16	59.2 / 27.2
Levofloxacin	1	4	0.06->4	86.2 / 5.5
Minocycline	≤1	2	≤1-4	100.0 / 0.0
Ticarcillin/clavulanate	16	128	≤1->128	56.3 / 12.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	99.4 / 0.6

a. According to CLSI M100-S17.

CONCLUSIONS

- *S. aureus*, *E. coli* and *Enterococcus* spp. represent the most frequent causes of BSIs in North American hospitals (statistics are dominated by the USA).
- The following resistance patterns showed significant increases during the study period:
  - MRSA and VRE (mainly vancomycin-resistant *E. faecium*)
  - *Klebsiella* spp. and *E. coli* with ESBL-phenotypes
  - Fluoroquinolone resistance among Enterobacteriaceae
  - Carbapenem resistance among *Acinetobacter* spp.
- Carbapenem resistances have emerged among some Enterobacteriaceae, mainly *K. pneumoniae*, and have rapidly increased thus becoming endemic in the Northeast USA.

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