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The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- Bloodstream infections cause significant morbidity and mortality worldwide
- Monitoring organism distribution and antibiotic susceptibility of bacterial bloodstream infection (BSI) pathogens helps inform empiric treatment and prevention strategies
- Epidemiologically important multiple-drug resistant organisms (MDROs) include oxacillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), and multidrug-resistant (MDR) gram-negative bacilli, including extended-spectrum beta-lactamase (ESBL) producers and carbapenem-resistant *Enterobacteriaceae* (CRE); MDR non-fermenters, such as *Acinetobacter* spp., are also major threats
- The SENTRY Antimicrobial Surveillance Program has been ongoing for 20 years, collecting consecutive, clinically significant isolates of bacterial pathogens that cause BSIs in North America, Europe, Latin America, and the Asia-Pacific region
- We report trends in organism distribution and antibiotic resistance among BSI isolates submitted to the SENTRY Program since its inception in 1997, with emphasis on trends in the proportion of BSIs due to specific MDROs

Materials and Methods

- From 1997-2016, each SENTRY participating center submitted bacterial isolates and clinical data for consecutive episodes of BSI each month
- Isolate identification was confirmed at the central reference laboratory (JMI Laboratories, North Liberty, Iowa) using conventional methods
- Susceptibility testing was performed against more than 20 antimicrobial agents at JMI Laboratories, using reference broth microdilution methods and interpretive MIC breakpoints as described by the Clinical and Laboratory Standards Institute (CLSI)
  - Food and Drug Administration breakpoints were used if CLSI breakpoints were not available
- Quality control was performed as recommended by CLSI, and results were all within established ranges
- This report describes the organism distribution and antimicrobial susceptibility trends among the 273,381 BSI isolates collected from 232 SENTRY participating centers in North America (70 medical centers in the United States and Canada), Latin America (18 centers in 7 countries), Europe (65 centers in 23 countries), and the Asia-Pacific region (79 centers in 12 countries) between January 1997 and December 2016
- Multidrug resistance (MDR) among gram-negative bacilli was defined using the Centers for Disease Control and Prevention criteria (nonsusceptibility to at least 1 drug in ≥ 3 major antibiotic classes), and pandrug resistance was defined as nonsusceptibility to a drug in all antibiotic classes
- ESBL-phenotype was defined as *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* spp. with aztreonam, ceftazidime, or ceftriaxone MIC values of ≥2 mg/L.
- CRE was defined as resistance to doripenem, imipenem, or meropenem for all organisms except *P. mirabilis* and indole-positive Proteeae, for which imipenem was excluded from the definition.

Results

- Among the 273,381 BSI isolates collected, the most common pathogen overall was *S. aureus*, followed by *E. coli*, *K. pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* (Table 1)
- Pathogen frequency varied somewhat over time and by region, hospital or community-onset status, and age (Tables 1-4); however, *S. aureus* and *E. coli* remained predominant
- The percentage of *S. aureus* resistant to oxacillin (MRSA) increased until 2005–2008, then declined among both hospital- and community-onset BSIs and in all regions (Figure 1)
- The % VRE declined after 2012 and was 16.4% overall in 2013–2016 (Figure 2)
- Daptomycin resistance among *S. aureus* and enterococci (DRE) remained rare (<0.1%)

Table 1. Rank order (%) of pathogens causing bloodstream infection worldwide in the SENTRY Program by 4-year period, 1997–2016

Rank	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	All years
1	*S. aureus* (22.5)	*S. aureus* (22.7)	*E. coli* (20.0)	*E. coli* (21.3)	*E. coli* (24.0)	*S. aureus* (20.7)
2	*E. coli* (18.7)	*E. coli* (20.2)	*S. aureus* (19.4)	*S. aureus* (18.8)	*S. aureus* (18.7)	*E. coli* (20.5)
3	*K. pneumoniae* (6.8)	*K. pneumoniae* (6.6)	*K. pneumoniae* (7.8)	*K. pneumoniae* (8.5)	*K. pneumoniae* (9.9)	*K. pneumoniae* (7.7)
4	*P. aeruginosa* (5.1)	*E. faecalis* (5.6)	*P. aeruginosa* (5.4)	*E. faecalis* (5.3)	*P. aeruginosa* (5.4)	*P. aeruginosa* (5.3)
5	*E. faecalis* (5.0)	*P. aeruginosa* (5.4)	*E. faecalis* (5.1)	*P. aeruginosa* (5.2)	*E. faecalis* (5.0)	*E. faecalis* (5.2)
6	*S. epidermidis* (4.8)	*S. epidermidis* (3.9)	*S. epidermidis* (3.4)	*E. faecium* (3.8)	*S. epidermidis* (4.1)	*S. epidermidis* (3.8)
7	*S. pneumoniae* (4.2)	*S. pneumoniae* (3.5)	*E. cloacae* (3.3)	*S. epidermidis* (3.1)	*E. faecium* (3.4)	*E. cloacae* (2.9)
8	*E. cloacae* (2.9)	*E. cloacae* (3.1)	*E. faecium* (3.1)	*E. cloacae* (2.8)	*E. cloacae* (2.1)	*S. pneumoniae* (2.8)
9	*E. faecium* (1.7)	*E. faecium* (2.2)	*A. baumannii*[a] (2.4)	*A. baumannii*[a] (2.4)	*A. baumannii*[a] (2.0)	*E. faecium* (2.8)
10	*S. agalactiae* (1.5)	*P. mirabilis* (1.7)	*S. pneumoniae* (2.2)	*S. pneumoniae* (1.9)	*S. pneumoniae* (1.9)	*A. baumannii*[a] (2.0)

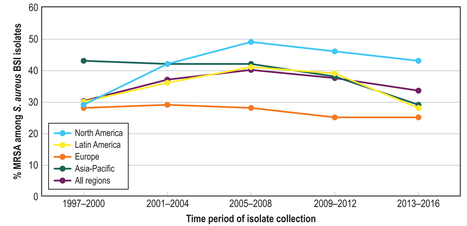
[a] *Acinetobacter baumannii-calcoaceticus* species complex

Table 2. Rank order (%) of pathogens causing bloodstream infection worldwide in the SENTRY Program by region, 1997–2016

Rank	North America	Latin America	Europe	Asia-Pacific
1	*S. aureus* (24.5)	*S. aureus* (20.1)	*E. coli* (24.1)	*E. coli* (26.0)
2	*E. coli* (16.9)	*E. coli* (17.1)	*S. aureus* (17.6)	*S. aureus* (17.1)
3	*K. pneumoniae* (7.3)	*K. pneumoniae* (9.5)	*K. pneumoniae* (6.5)	*K pneumoniae* (10.8)
4	*E. faecalis* (6.6)	*P. aeruginosa* (6.9)	*P. aeruginosa* (5.8)	*P. aeruginosa* (5.4)
5	*P. aeruginosa* (4.4)	*A. baumannii*[a] (4.4)	*S. epidermidis* (5.6)	*E. faecalis* (3.2)
6	*E. faecium* (3.5)	*E. cloacae* (3.4)	*E. faecalis* (4.8)	*A. baumannii*[a] (3.2)
7	*S. pneumoniae* (3.3)	*E. faecalis* (3.4)	*E. faecium* (2.8)	*E. cloacae* (3.0)
8	*E. cloacae* (3.0)	*S. epidermidis* (3.3)	*E. cloacae* (2.7)	*S. pneumoniae* (3.0)
9	*S. epidermidis* (2.7)	*S. pneumoniae* (2.5)	*S. pneumoniae* (2.4)	*S. epidermidis* (2.9)
10	*S. agalactiae* (2.0)	*S. marcescens* (1.9)	*P. mirabilis* (1.8)	*E. faecium* (2.3)

[a] *Acinetobacter baumannii-calcoaceticus* species complex

Figure 1. 20-year trend in % MRSA among all *S. aureus* BSI



- The % MDR among *Enterobacteriaceae* increased steadily over the surveillance period, from 6.2% in 1997-2000 to 15.8% in 2013-2016, and was highest in Latin America (Figure 3) and highest among hospital-onset BSI (but increased over time in both hospital-onset and community onset BSI) (Figure 4)
- ESBL *E. coli*, ESBL-*Klebsiella* spp., and CRE phenotypes also increased over the surveillance period (Figure 5)
- MDR rates were highest among the non-fermentative gram-negative organisms (*P. aeruginosa* at 26.3% and *Acinetobacter baumannii-calcoaceticus* complex at 70.6%); 48 isolates of *A. baumannii-calcoaceticus* (0.9%) and 9 isolates of *P. aeruginosa* (<0.1%) were pandrug resistant
- Colistin was the only agent with predictable activity against *A. baumannii-calcoaceticus* complex (96.9% susceptible; Table 5)
- The antimicrobial activity of selected agents against the 107,617 *Enterobacteriaceae* are in Table 6
- Some trending analysis may have limitations due to inconsistent participation of certain countries, especially in the Asia-Pacific and eastern European regions

Figure 2. 20-year trend in % VRE among *Enterococcus* spp. BSI

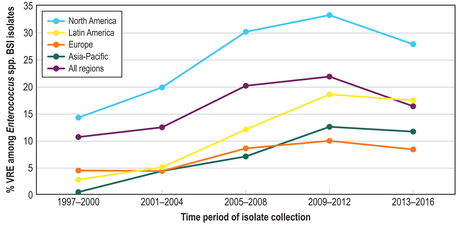


Figure 3. 20-year trend in % MDR among *Enterobacteriaceae* BSI

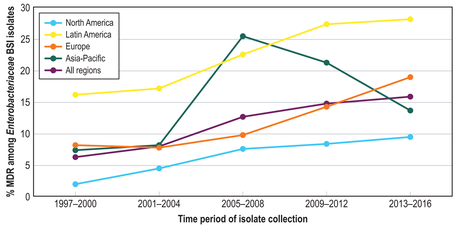


Figure 4. 20-year trend in % MDR among *Enterobacteriaceae* BSI, by community versus hospital-onset infection

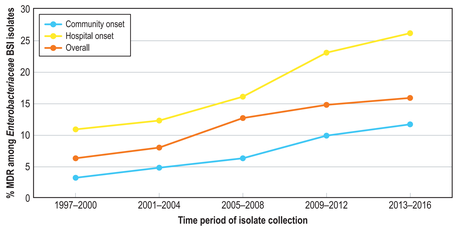


Table 3. Rank order of pathogens causing bloodstream infection worldwide submitted to the SENTRY Program by age group, 1997–2016

Rank	<1 year	1-5 years	6-18 years	19-49 years	50-64 years	>64 years
1	*S. aureus*	*S. aureus*	*S. aureus*	*S. aureus*	*S. aureus*	*E. coli*
2	*E. coli*	*S. pneumoniae*	*E. coli*	*E. coli*	*E. coli*	*S. aureus*
3	*K. pneumoniae*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*	*K. pneumoniae*	*K. pneumoniae*
4	*E. faecalis*	*K. pneumoniae*	*K. pneumoniae*	*P. aeruginosa*	*P. aeruginosa*	*E. faecalis*
5	*S. epidermidis*	*P. aeruginosa*	*S. epidermidis*	*E. faecalis*	*E. faecalis*	*P. aeruginosa*

Table 4. Rank order (%) of pathogens causing BSI worldwide submitted to the SENTRY Program by community or hospital onset, 1997–2016

Rank	Community onset (N=102,638)	Hospital onset (N=103,945)
1	*E. coli* (29.1)	*S. aureus* (18.2)
2	*S. aureus* (28.5)	*E. coli* (13.1)
3	*K. pneumoniae* (8.2)	*K. pneumoniae* (7.9)
4	*E. faecalis* (5.5)	*P. aeruginosa* (6.7)
5	*S. pneumoniae* (5.4)	*E. faecalis* (5.6)
6	*P. aeruginosa* (4.3)	*S. epidermidis* (4.3)
7	*E. cloacae* (2.7)	*E. faecium* (3.2)
8	*S. epidermidis* (2.6)	*E. cloacae* (3.4)
9	*P. mirabilis* (2.2)	*A. baumannii*[a] (3.0)
10	*E. faecium* (2.1)	*P. mirabilis* (1.1)

[a] *Acinetobacter baumannii-calcoaceticus* species complex.

Table 5. Activity of antimicrobial agents when tested against 5,333 *Acinetobacter baumannii-calcoaceticus* species complex isolates submitted to the SENTRY Program between 1997–2016

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI %S	CLSI %R
Amikacin	>32	>32	45.7	50.1
Ampicillin-sulbactam	>16	>16	36.5	51.7
Cefepime	>16	>16	35.5	53.4
Ceftazidime	>16	>16	32.8	61.5
Ciprofloxacin	>2	>2	32.4	67.0
Colistin	≤0.5	2	96.9	3.1
Doripenem	>4	>4	42.8	53.1
Doxycycline	≤1	>8	67.5	31.0
Gentamicin	>8	>8	39.0	55.6
Imipenem	2	>8	55.4	41.6
Levofloxacin	>4	>4	34.6	57.1
Meropenem	2	>8	52.1	43.8
Minocycline	≤1	>8	81.5	10.0
Piperacillin-tazobactam	>64	>64	30.8	59.8
Tetracycline	8	>8	42.4	44.4
Tigecycline	0.5	2		
Tobramycin	4	>8	52.4	44.4
Trimethoprim-sulfamethoxazole	>1	>1	41.7	58.3

Figure 5. 20-year trend in % ESBL and CRE among BSI

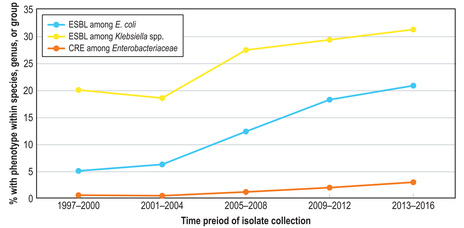


Table 6. Activity of antimicrobial agents when tested against 107,617 *Enterobacteriaceae* isolates submitted to the SENTRY Program between 1997–2016

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI %S	CLSI %R
Amikacin	≤4	≤4	97.4	1.3
Ampicillin-sulbactam	16	>16	49.4	33.5
Aztreonam	≤0.12	16	86.5	11.9
Cefepime	≤0.5	4	89.3	7.7
Ceftazidime-avibactam	0.12	0.25	99.7	0.3
Ceftriaxone	≤0.25	>8	83.5	15.7
Ciprofloxacin	≤0.5	>2	80.9	17.5
Colistin	≤0.5	>4		
Doripenem	≤0.12	≤0.12	98.3	1.4
Doxycycline	2	>8	66.5	24.5
Gentamicin	≤2	>8	87.9	11.0
Imipenem	≤0.5	1	95.2	1.7
Levofloxacin	≤0.5	>4	82.5	15.1
Meropenem	≤0.12	≤0.12	98.8	1.0
Minocycline	2	>8	77.2	14.3
Piperacillin-tazobactam	2	16	90.0	5.6
Tetracycline	≤4	>8	64.0	33.2
Tigecycline	0.25	1	98.4	0.2
Tobramycin	0.5	>8	86.4	10.5
Trimethoprim-sulfamethoxazole	≤0.5	>1	74.7	25.3

Conclusions

- *S. aureus* and *E. coli* were the predominant BSI pathogens worldwide during this 20-year surveillance period, accounting for >40% of all BSI isolates submitted to the SENTRY Program
- Important resistance phenotypes among gram-positive pathogens (MRSA, VRE, or DRE) have been stable or declining over the past 4-8 years
- MDR gram-negative bacilli, including ESBL and CRE phenotypes, continue to increase as a proportion of BSI isolates
- MDR gram-negative bacilli currently pose the greatest threat among common bacterial BSI pathogens

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