Annals of Clinical Microbiology and Antimicrobials

BioMed Central

Research

Prevalence and antimicrobial susceptibilities of bacteria isolated from blood cultures of hospitalized patients in the United States in 2002

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Published: 10 May 2004

Annals of Clinical Microbiology and Antimicrobials 2004, **3**:7

Received: 21 January 2004
Accepted: 10 May 2004

This article is available from: http://www.ann-clinmicrob.com/content/3/1/7

Abstract

Background: Bloodstream infections are associated with significant patient morbidity and mortality. Antimicrobial susceptibility patterns should guide the choice of empiric antimicrobial regimens for patients with bacteremia.

Methods: From January to December of 2002, 82,569 bacterial blood culture isolates were reported to The Surveillance Network (TSN) Database-USA by 268 laboratories. Susceptibility to relevant antibiotic compounds was analyzed using National Committee for Clinical Laboratory Standards guidelines.

Results: Coagulase-negative staphylococci (42.0%), *Staphylococcus aureus* (16.5%), *Enterococcus faecalis* (8.3%), *Escherichia coli* (7.2%), *Klebsiella pneumoniae* (3.6%), and *Enterococcus faecium* (3.5%) were the most frequently isolated bacteria from blood cultures, collectively accounting for >80% of isolates. In vitro susceptibility to expanded-spectrum β-lactams such as ceftriaxone were high for oxacillin-susceptible coagulase-negative staphylococci (98.7%), oxacillin-susceptible *S. aureus* (99.8%), *E. coli* (97.3%), *K. pneumoniae* (93.3%), and *Streptococcus pneumoniae* (97.2%). Susceptibilities to fluoroquinolones were variable for *K. pneumoniae* (90.3–91.4%), *E. coli* (86.0–86.7%), oxacillin-susceptible *S. aureus* (84.0–89.4%), oxacillin-susceptible coagulase-negative staphylococci (72.7–82.7%), *E. faecalis* (52.1%), and *E. faecium* (11.3%). Combinations of antimicrobials are often prescribed as empiric therapy for bacteremia. Susceptibilities of all blood culture isolates to one or both agents in combinations of ceftriaxone, ceftazdime, cefepime, piperacillin-tazobactam or ciprofloxacin plus gentamicin were consistent (range, 74.8–76.3%) but lower than similar β-lactam or ciprofloxacin combinations with vancomycin (range, 93.5–96.6%).

Conclusion: Ongoing surveillance for antimicrobial susceptibility remains essential, and will enhance efforts to identify resistance and attempt to limit its spread.

Background

Bloodstream infections cause significant morbidity and mortality worldwide and are among the most common healthcare-associated infections [1-6]. It is estimated that 2 million patients per year in the United States acquire infections while in hospitals, approximately 350,000 (10–20%) of these infections involve the bloodstream, and 90,000 (4.5%) are fatal [1,6,7]. Advances in medicine, efforts to control medical costs, and incentives for outpatient care have resulted in an increasingly concentrated population of seriously ill patients in hospitals. The incidence of bloodstream infections in patients treated in United States hospitals has been reported to correlate with increasing use of central venous catheters, patient illness (e.g., oncology, burn/trauma, and high-risk nursery), and other predisposing factors, including microorganism, intensive-care unit (ICU) stay, hand washing practices of medical staff, and adherence to infection control practices [1,5,6,8]. Respiratory, genitourinary tract, and intra-abdominal foci are often identifiable sources of bloodstream infections [9]. Bacteremia due to *Enterobacteriaceae* other than *Escherichia coli* are associated with increased mortality compared with bloodstream infections due to Gram-positive species [5]. Gram-negative and polymicrobial bacteremia can result in septic shock and mortality is greater with high-grade bacteremia and polymicrobial infection [4,5,10]. Efforts need to be extended to prevent and control serious hospital-acquired infections.

The National Nosocomial Infections Surveillance (NNIS) system reported that from 1986 to 1997, coagulase-negative staphylococci and *Staphylococcus aureus* were the most common organisms isolated from blood cultures of intensive-care unit (ICU) patients, followed by *Enterococcus* spp., *Candida albicans*, and *Enterobacter* spp. [11]. However, only 50% of all positive blood cultures represent true bloodstream infection [5]. Importantly, although coagulase-negative staphylococci are the most frequently isolated organism from blood cultures, they are clinically significant <15% of the time [5]. Coagulase-negative bacteremia is often the result of long-term use of indwelling central and peripheral catheters as well as other prosthetic devices, the ubiquity of these bacteria as normal skin flora, and the ability of these relatively avirulent organisms to adhere to the surface of biomaterials [5]. Previous studies have reported that *S. aureus* and *E. coli* are the two most common, clinically significant causes of bloodstream infections in patients in the United States and Europe [4,5,12,13] and that 6–18% of bloodstream infections are polymicrobial [4,5]. Bacteremia may be transient or indicative of true systemic infection (i.e., sepsis syndrome) with an initial focal source such as the lungs (e.g., pneumonia) or the urinary tract [10].

The potential for antimicrobial resistance is one consideration for physicians when selecting a regimen with which to treat patients. This is particularly important for the treatment of systemic infections as initial antimicrobial chemotherapy is almost invariably empiric and must be based on knowledge of the most frequently isolated etiological agents and their antimicrobial susceptibility patterns. Early initiation of appropriate antimicrobial treatment is critical in decreasing morbidity and mortality among patients with bloodstream infections [14]. The current study reports the prevalence and antimicrobial susceptibility profiles of blood culture isolates from the United States using The Surveillance Network (TSN) Database-USA (Focus Technologies, Herndon, VA).

Methods

In the current study, results from the TSN Database-USA from January 1 to December 31, 2002 were used to estimate the prevalence of specific bacterial species as blood culture isolates in the United States and to determine rates of antimicrobial susceptibility for commonly tested agents among the most prevalent species identified. TSN assimilated antimicrobial susceptibility testing and patient demographic data from a network of 268 hospitals in the United States in 2002 [15]. All blood culture isolates were identified at the participating institutions by routine methods in use at each laboratory. Antimicrobial susceptibility testing of patient isolates was conducted onsite by each participating laboratory as a part of their routine diagnostic testing. An inpatient isolate was defined as such by each laboratory participating in TSN. Data from patients in nursing facilities and hospital outpatients were excluded from the current analysis.

Laboratories contributing to TSN databases are all nationally-accredited and are invited to participate in TSN based on factors such as hospital type (e.g., university teaching hospital, community hospital) and antimicrobial susceptibility testing method used as well as the bed size, patient population, and geographic location of the hospital(s) they serve [15]. Only data generated using nationally approved (Food and Drug Administration-approved) testing methods with MIC results interpreted according to NCCLS [16] recommendations are included in TSN Database-USA. In addition, a series of quality-control filters (proprietary critical rule sets) are used to screen susceptibility test results for patterns indicative of testing error; suspect results are removed from analysis for laboratory confirmation. TSN reflects current testing in United States laboratories and is the antimicrobial susceptibility testing data considered when clinical decisions in participating institutions are made. The TSN database presumes the evidence of infection, but no clinical correlates are applied universally. In TSN, any result from the same patient with the same organism identification and the same

Table 1: Frequencies of occurrence of bacterial species or groups isolated from blood cultures of hospitalized patients in the United States in 2002

Rank	Bacterial species or group	No. of isolates	% of total no. of isolates
1	Coagulase-negative staphylocci	34,640	42.0
2	*S. aureus*	13,618	16.5
3	*E. faecalis*	6,893	8.3
4	*E. coli*	5,942	7.2
5	*K. pneumoniae*	2,942	3.6
6	*E. faecium*	2,873	3.5
7	Viridans group streptococci	2,773	3.4
8	*Pseudomonas aeruginosa*	2,030	2.5
9	*S. pneumoniae*	1,901	2.3
10	*Enterobacter cloacae*	1,550	1.9
11	*Serratia marcescens*	814	1.0
12	*Acinetobacter baumannii*	733	0.9
13	*Proteus mirabilis*	732	0.9
14	*Streptococcus agalactiae*	626	0.8
15	*Klebsiella oxytoca*	470	0.6
16	*Enterobacter aerogenes*	376	0.5
17	*Stenotrophomonas maltophilia*	256	0.3
18	*Citrobacter freundii*	245	0.3
19	*Streptococcus pyogenes*	211	0.3
20	*Enterococcus avium*	153	0.2
21	Others	2,791	3.4
Total	82,569	100	

susceptibility pattern received within five days is considered a repeat culture and is counted only once in the database. In TSN, all isolates are not tested against all agents and variation can be observed for antimicrobial agents of the same class such as expanded-spectrum cephalosporins (ceftriaxone and cefotaxime) and fluoroquinolones (ciprofloxacin and levofloxacin) for which similar in vitro activities have been previously demonstrated.

Results

Table 1 depicts the frequencies of occurrence of the 20 most common bacterial blood culture isolates in the United States in 2002. A total of 82,569 blood culture isolates were reported to TSN Database-USA in 2002. Coagulase-negative staphylococci accounted for 42.0% of all isolates. Six organisms, coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus faecalis*, *Eschericia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecium* accounted for >80% of all blood culture isolates. Overall frequencies of isolation were 78.1% gram-positive bacteria and 21.9% gram-negative bacteria.

Table 2 provides susceptibility rates for commonly tested antimicrobial agents for the most frequently isolated bacterial species in 2002. Greater than 99% of oxacillin-susceptible *S. aureus* isolates and >98% of oxacillin-susceptible coagulase-negative staphylococci isolates were susceptible to amoxicillin-clavulanate, cefotaxime, ceftriaxone, and cefuroxime. Susceptibilities to ciprofloxacin and levofloxacin, respectively were 88.5% and 89.4% for oxacillin-susceptible *S. aureus* and 82.1% and 82.7% for oxacillin-susceptible coagulase-negative staphylococci. Among viridans group streptococci, ceftriaxone and cefotaxime were equally active based on the susceptibilities of isolates (89.9% and 89.2%, respectively). *S. pneumoniae* susceptibilities to penicillin and trimethoprim-sulfamethoxazole were <70% while susceptibilities to levofloxacin, amoxicillin-clavulanate, and ceftriaxone all exceeded 97%. Greater than 95% of *E. faecalis* isolates and 33% of *E. faecium* isolates from blood were susceptible to vancomycin.

The oxacillin-resistance rate was 49.3% among blood culture isolates of *S. aureus* and 76.7% among blood culture isolates of coagulase-negative staphylococci (data not shown). Among oxacillin-resistant coagulase-negative staphylococci and *S. aureus*, susceptibilities were 32.1–32.6% (range) and 7.3–7.6% for fluoroquinolones, respectively, 48.1% and 80.9% for gentamicin, 13.7% and 5.9% for erythromycin, 47.2% and 29.8% for clindamycin, 56.0% and 90.9% for trimethoprim-sulfamethoxazole, and 100% and 100% for vancomycin (data not shown).

For *E. coli*, ≥ 97% of isolates were susceptible to amikacin, cefepime, cefotaxime, ceftriaxone, and nitrofurantoin;

Table 2: In vitro antimicrobial susceptibility testing results for the most common gram-positive and gram-negative bacterial species or groups isolated from blood cultures of hospitalized patients in the United States in 2002

Gram-positive bacteria	Antimicrobial	Total No.	% Susceptible
Oxacillin-susceptible CoNS[a]	Amoxicillin-clavulanate	1,692	99.8
	Cefotaxime	962	99.7
	Ceftriaxone	228	98.7
	Cefuroxime	131	100
	Ciprofloxacin	1,724	82.1
	Clindamycin	2,290	91.2
	Erythromycin	2,241	59.2
	Gentamicin	1,789	95.7
	Levofloxacin	1,652	82.7
	Ofloxacin	172	72.7
	Penicillin	2,106	31.7
	Trimethoprim-sulfamethoxazole	2,099	89.2
	Vancomycin	2,273	100
Oxacillin-susceptible *S. aureus*	Amoxicillin-clavulanate	1,854	99.7
	Cefotaxime	823	99.6
	Ceftriaxone	602	99.8
	Cefuroxime	424	99.8
	Ciprofloxacin	3,383	88.5
	Clindamycin	5,707	93.3
	Erythromycin	5,707	69.1
	Gentamicin	4,904	97.9
	Levofloxacin	3,903	89.4
	Ofloxacin	811	84.0
	Penicillin	5,532	14.3
	Trimethoprim-sulfamethoxazole	4,660	97.8
	Vancomycin	5,565	100
E. faecalis	Erythromycin	787	13.2
	Levofloxacin	1,793	52.1
	Penicillin	2,372	97.1
	Vancomycin	3,400	95.4
E. faecium	Erythromycin	421	4.0
	Levofloxacin	758	11.3
	Penicillin	913	13.3
	Vancomycin	1,285	32.9
Viridans group streptococci	Cefotaxime	719	89.2
	Ceftriaxone	1,120	89.9
	Clindamycin	1,227	89.0
	Erythromycin	1,681	46.6
	Levofloxacin	661	90.6
	Penicillin	2,005	60.0
	Vancomycin	1,901	100
S. pneumoniae	Amoxicillin-clavulanate	141	97.2
	Cefotaxime	750	96.3
	Ceftriaxone	1,149	97.2
	Cefuroxime	223	70.9
	Clindamycin	634	95.1
	Erythromycin	1,023	75.2
	Levofloxacin	762	99.5
	Ofloxacin	196	95.4
	Penicillin	1,345	68.0
	Trimethoprim-sulfamethoxazole	675	66.8
	Vancomycin	1,190	100
Gram-negative bacteria	Antimicrobial	Total No.	% Susceptible
E coli	Amikacin	3,815	99.1
	Amoxicillin-clavulanate	1,417	79.9
	Ampicillin	5,192	52.2

Table 2: In vitro antimicrobial susceptibility testing results for the most common gram-positive and gram-negative bacterial species or groups isolated from blood cultures of hospitalized patients in the United States in 2002 *(Continued)*

	Cefazolin	5,167	87.5
	Cefepime	2,966	98.3
	Cefotaxime	2,967	97.7
	Ceftazidime	4,067	96.2
	Ceftriaxone	3,820	97.3
	Cephalothin	1,879	61.5
	Ciprofloxacin	4,633	86.7
	Gentamicin	5,171	92.8
	Levofloxacin	4,266	86.0
	Nitrofurantoin	1,356	97.5
	Ofloxacin	456	88.6
	Piperacillin-tazobactam	3,887	95.4
	Tobramycin	4,414	93.5
	Trimethoprim-sulfamethoxazole	5,108	74.8
K. pneumoniae	Amikacin	1,987	97.6
	Amoxicillin-clavulanate	867	86.7
	Cefazolin	2,576	86.3
	Cefepime	1,613	96.5
	Cefotaxime	1,502	93.5
	Ceftazidime	2,134	88.5
	Ceftriaxone	2,104	93.3
	Cephalothin	930	75.3
	Ciprofloxacin	2,370	90.3
	Gentamicin	2,686	91.1
	Levofloxacin	2,264	91.4
	Nitrofurantoin	835	55.0
	Ofloxacin	275	90.2
	Piperacillin-tazobactam	1,997	89.9
	Tobramycin	2,320	90.7
	Trimethoprim-sulfamethoxazole	2,625	87.2
P. aeruginosa	Amikacin	1,563	92.3
	Cefepime	1,450	76.7
	Ceftazidime	1,764	77.2
	Ciprofloxacin	1,734	71.0
	Gentamicin	1,858	77.2
	Levofloxacin	1,475	68.0
	Ofloxacin	199	44.7
	Piperacillin-tazobactam	1,484	91.0
	Tobramycin	1,708	87.5

[a]CoNS, coagulase-negative staphylococci

ceftazidime non-susceptibility, a commonly used phenotypic marker for estimating extended-spectrum β-lactamase (ESBL) rates, was 3.8%. For *K. pneumoniae*, ≥ 90% of isolates were reported susceptible to amikacin, cefepime, cefotaxime, ceftriaxone, ciprofloxacin, levofloxacin, and gentamicin; ceftazidime non-susceptibility was 11.5%. Among *P. aeruginosa*, amikacin, piperacillin-tazobactam, and tobramycin had the highest rates of susceptibility; however, no agent had susceptibilities ≥ 93%.

The susceptibility of *S. aureus* to oxacillin from blood culture isolates also varied by <3% for isolates from intensive-care unit (ICU) patients and non-ICU inpatients. The ciprofloxacin susceptibility rate for *E. coli* was similar for isolates from ICU patients (85.7%) and non-ICU inpatients (86.8%) (Table 3). Similarly, rates of susceptibility to ceftriaxone among *E. coli* were similar for isolates from ICU patients (96.3%) and non-ICU inpatients (97.5%).

Combinations of antimicrobial agents are often prescribed as empiric therapy for suspected or laboratory confirmed bloodstream infections. Frequently prescribed combinations include an expanded-spectrum β-lactam or a fluoroquinolone plus an aminoglycoside for the treatment of infections caused by Gram-negative bacilli while combinations of an expanded-spectrum β-lactam or a fluoroquinolone plus vancomycin are often prescribed for suspected or demonstrated infections caused by Gram-

Table 3: In vitro antimicrobial susceptibility of *S. aureus* to oxacillin and *E. coli* to ciprofloxacin and ceftriaxone in blood culture isolates from ICU and non-ICU inpatients

Organism	Antimicrobial agent	Inpatient location	No. of isolates	% of isolates susceptible to antimicrobial agent
S. aureus	oxacillin	ICU	1,994	48.1
		Non-ICU	9,625	51.2
E. coli	ciprofloxacin	ICU	581	85.7
		Non-ICU	4,052	86.8
	ceftriaxone	ICU	510	96.3
		Non-ICU	3,310	97.5

Table 4: In vitro susceptibilities of blood culture isolates from hospitalized patients in the United States in 2002 to antimicrobial combinations of a β-lactam or ciprofloxacin plus gentamicin or vancomycin

Antimicrobial Combination	Total no. of isolates tested against one or both of the antimicrobials in the combination	% of isolates susceptible to at least one antimicrobial in the combination
Ceftriaxone + gentamicin	53,648	75.5
Ceftazidime + gentamicin	50,238	76.0
Cefepime + gentamicin	50,489	76.1
Piperacillin-tazobactam + gentamicin	50,415	76.3
Ciprofloxacin + gentamicin	55,973	74.8
Ceftriaxone + vancomycin	62,907	93.5
Ceftazidime + vancomycin	62,518	95.4
Cefepime + vancomycin	59,807	96.6
Piperacillin-tazobactam + vancomycin	61,265	96.3
Ciprofloxacin + vancomycin	64,467	94.1

positive pathogens. Beta-lactams or fluoroquinolones are associated with aminoglycosides. Table 4 depicts the percentages of isolates susceptible in vitro to one or both antimicrobials in 10 combinations of agents tested against all blood culture isolates reported to TSN Database-USA in 2002. Combining ceftriaxone, ceftazidime, cefepime, piperacillin-tazobactam or ciprofloxacin with gentamicin demonstrated consistent susceptibility rates for each combination (range, 74.8–76.3%). Similarly, combining ceftriaxone, ceftazdime, cefepime, piperacillin-tazobactam or ciprofloxacin with vancomycin demonstrated consistent susceptibility rates for each combination (range, 93.5–96.6%). Combinations including gentamicin demonstrated lower rates of susceptibility by approximately 20% compared with combinations including vancomycin.

Discussion

S. aureus and *E. coli* were identified in previous studies as the two most common blood culture isolates from hospitalized patients in the United States and Europe [4,5,12,13]. In the current study, coagulase-negative staphylococci were the most common blood culture isolates from laboratories in the United States (42.0% of isolates) (Table 1). However, given that coagulase-negative staphylococci isolated from blood cultures are often contaminants (>85% are clinically insignificant) [5] our results agree generally with those previously published. As TSN collects all laboratory data, year-round, it may present a more accurate description of laboratory testing than do centralized point prevalence studies that often exclude the majority of isolates identified by laboratories in a year [12,13]. Accepting the over-representation of contaminant coagulase-negative staphylococci in clinical laboratories in the United States as observed in TSN Database-USA, the rank order of other pathogens is similar to previous reports describing centralized surveillance studies [12,13] and hospital review studies [4,5]. Six organisms, coagulase-negative staphylococci, *S. aureus*, *E. faecalis*, *E. coli*, *K. pneumoniae*, and *E. faecium* accounted for >80% of blood culture isolates. Previously, SENTRY has reported similar results for laboratories in the United States, Canada, Latin America, and Europe [12,13]. In the current study, overall frequencies of isolation were 78.1% gram-positive bacteria and 21.9% gram-negative bacteria.

Oxacillin-resistant *S. aureus* are extremely important causes of bloodstream infections and evidence has been

presented that oxacillin-resistant *S. aureus* (Table 3) are increasing globally among bloodstream isolates and among isolates from other anatomical sites [12,17]. Fluoroquinolone resistance has increased in a consistent stepwise manner in the United States and Europe for *Enterobacteriaceae*, *P. aeruginosa*, and *S. aureus* [12,13,18,19]. It is important for clinicians to be updated with current data concerning the susceptibility of commonly prescribed agents such as the fluoroquinolones and also to be aware of trends in longitudinal data. The rates of change in resistance by pathogen and region can help set priorities for focused intervention efforts.

Early clinical suspicion, rigorous diagnostic measures, aggressive initiation of appropriate antimicrobial therapy, comprehensive supportive care, and measures aimed at reversing predisposing causes (e.g., amelioration of an underlying disease, removal of foreign bodies, drainage of abscesses) are the cornerstone of successful management of patients with sepsis syndrome [5,10]. The selection of antimicrobials to be used for empiric therapy should be based on the local rates of susceptibility and on the site of infection [10]. Early initiation of appropriate antimicrobial treatment is critical in decreasing morbidity and mortality among patients with bloodstream infections due to gram-negative organisms [14]. The initiation of such therapy is almost always empirical, requiring knowledge of the likely pathogen(s) and their usual antimicrobial susceptibility patterns [10,20]. Combinations of antimicrobial agents are recommended for empiric therapy for patients with bloodstream infections, particularly for those patients with the most adverse prognostic factors [10]. Combination therapy is recommended to cover the broad range of possible pathogens which may be difficult to distinguish clinically, because of the possibility of polymicrobial infections, because they may prevent the emergence of resistance, and because they may have additive or synergistic antimicrobial activity. For the patient with a nosocomial bloodstream infection, initial treatment should consist of an aminoglycoside initially paired with a broad-spectrum β-lactam. Expanded-spectrum cephalosporins are the β-lactam of choice for the non-neutropenic patient because of the greater likelihood of *Klebsiella* and *Staphylococcus* infections in these patients [10]. The regimen of an aminoglycoside paired with a penicillin or cephalosporin having antipseudomonal activity is preferred for neutropenic patients, patients with severe chronic obstructive pulmonary disease or bronchiestatis, patients receiving assisted ventilation, and patients with extensive burns [10].

The in vitro potency of ceftriaxone and cefotaxime against *E. coli* and *Klebsiella* suggests that single-agent therapy directed against those bacteria may be successful even in severely compromised hosts [10]. The superior pharmacokinetic and pharmacodynamic properties that exist for ceftriaxone when compared with cefotaxime may be a consideration when choosing between these two agents [18]. In the nosocomial setting, extensive data also confirmed the efficacy of ceftriaxone with or without an aminoglycoside in serious Gram-negative infections, pneumonia, spontaneous bacterial peritonitis and as surgical prophylaxis [21]. Ceftriaxone, cefotaxime, and cefepime all have similar indications for pneumonia, skin and skin structure infections, and urinary tract infections; however only ceftriaxone and cefotaxime have an indication for the sepsis syndrome. In the current study, susceptibilities of isolates to one or both agents in combinations of ceftriaxone, ceftazdime, cefepime, piperacillin-tazobactam or ciprofloxacin plus gentamicin were consistent (range, 74.8–76.3%) but lower than similar β-lactam or ciprofloxacin combinations with vancomycin (range, 93.5–96.6%). Ceftazidime, cefepime, imipenem and meropenem appear most active against *P. aeruginosa* [10].

Conclusions

In conclusion, susceptibilities to some classes of antimicrobials are decreasing, most notably the fluoroquinolones for *Enterobacteriaceae* and *P. aeruginosa*. Many older antimicrobials including ceftriaxone continue to retain high rates of susceptibility against many important bacterial pathogens such as those commonly isolated from blood cultures. Against the most clinically important gram-positive species including pneumococci, and gram-negative bacilli such as *E. coli* (Table 2) susceptibility to ceftriaxone appears to have changed little, if at all, from 1996 to 2002 [18]. While selective pressure for resistance through antimicrobial use is important, infection control practices are critical to limiting the spread of resistant organisms. The life-threatening nature of bacteremia and sepsis underscores the importance of using timely surveillance data to develop rational antimicrobial therapy recommendations and to design strategies to help control antimicrobial resistance [10,22].

Authors' contributions

JK and MJ conceived the study, provided expert data interpretation and drafted the manuscript. DD analyzed the study data; CT and DS provided expert microbiological analysis and interpretation of study data; GV provided clinical expertise in interpretation of data and drafting manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank the participating institutions in TSN® Database-USA, who make data collection possible and Roche Laboratories, Inc., who financially supported this study.

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