Pathogens and antimicrobial susceptibility patterns in Canadian critically ill patients with bloodstream infections: a descriptive study

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Abstract

Background: Surveillance of antimicrobial resistance is vital to guiding empirical treatment of infections. Collating and reporting routine clinical isolate testing data may offer more timely information about resistance patterns than traditional surveillance network methods. We report on the epidemiology of bloodstream infections and susceptibility profiles from routine clinical specimens in a Canadian multi-centre cohort of critically ill patients.

Methods: We conducted a descriptive, secondary analysis of critically ill patients diagnosed with bloodstream infections in 14 intensive care units (ICUs) in Canada using data collected from the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) retrospective cohort study.

Results: 1,416 pathogens were isolated from 1202 patients. The most common organisms were *Escherichia coli* (217, 15.3%), *Staphylococcus aureus* (175, 12.4%), coagulase negative staphylococci (117, 8.3%), *Klebsiella pneumoniae* (86, 6.1%) and *Streptococcus pneumoniae* (85, 6.0%), but the contribution of individual pathogens varied by ICU. Gram negative susceptibility rates were high for carbapenems (95.4%), tobramycin (91.2%) and piperacillin-tazobactam (90.0%); however, the proportion of specimens susceptible to these agents ranged from 75.0-100%, 66.7-100% and 75.0-100%, across ICUs. Fewer Gram negative bacteria were susceptible to fluoroquinolones (84.5%, range 64.1-97.2%). Twelve percent of enrolled patients had infections caused by highly-resistant microorganisms, with significant inter-ICU variation (range: 3%-24%).

Interpretation and Conclusion: Data from routinely collected specimens reveal the pathogens and susceptibility profiles of bloodstream infections in Canada. Expanding data sharing across more ICUs, with serial measurement and prompt reporting could provide much-needed guidance for empiric treatment for patients as well as system-wide methods to limit antimicrobial resistance.

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Introduction

Current and accurate data about the epidemiology of bloodstream infections (BSIs) and antimicrobial susceptibility patterns are needed to guide appropriate empirical antimicrobial treatment and improve patient outcomes.(1) BSIs are associated with considerable morbidity, mortality and cost. In North America, an estimated 575,000 – 677,000 episodes and 79, 000 – 94,000 deaths per year are attributable to nosocomial BSIs; these infections are the sixth and seventh leading causes of death in Canada and the United States, respectively.(2) Data on BSI epidemiology are especially vital in intensive care unit settings where these infections are most common, antibiotic resistance is most prevalent, and timely appropriate antibiotic therapy is necessary to prevent morbidity and mortality.(3,4)

Epidemiological data about BSIs are usually provided by national microbiology surveillance networks. The Canadian Ward Surveillance Study (CANWARD) is a typical example of such a network. CANWARD collects clinical isolates from infected inpatients and outpatients at a number of geographically distributed tertiary-care medical centres across Canada. Each centre is asked to provide a minimum number of respiratory, urine, wound and blood isolates per month based on set criteria, as well as limited patient demographic data (age, sex. hospital location, specimen source).(5) These isolates are then sent to a central coordinating laboratory for antimicrobial susceptibility testing, and results are analyzed centrally to assess the national epidemiology of infections, including resistance patterns. Strengths of these monitoring networks are that they offer broad geographic coverage and standardized testing methods, and measurement of exact minimum inhibitory concentrations; however, these strengths often come at the expense of timeliness as they rely on referral of microbial isolates to a centralized laboratory, direct microbiology laboratory testing, and reporting into a centralized database.(6)

Routine diagnostic data from local hospital laboratories, by contrast, may offer a timely and direct source of epidemiological and susceptibility pattern data because they can be extracted from available data.(6) These databases also offer the added benefit of being potentially linkable to detailed clinical and outcome data, which are more difficult to capture in surveillance networks, and additionally, provide the opportunity to assess trends in epidemiological and susceptibility data at a local level, which can help inform decision-making practices of hospitals that contribute data. The European Antimicrobial Resistance Surveillance Network (EARS-Net) has harnessed routine culture data to assess periodic trends in antimicrobial resistant organisms across Europe.(7) The proof-of-concept objective of our study was to use routine microbiology testing data to describe the epidemiology of BSIs and corresponding antimicrobial susceptibility profiles from a recent Canadian multi-centre cohort of critically ill patients.

Methods

Study sites and patients

This was a secondary analysis of the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) multi-site retrospective (8) cohort study of critically ill patients diagnosed with bloodstream infections in 14 intensive care units (ICUs) in Canada. The participating ICUs were located within tertiary-care

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teaching hospitals and spanned 10 cities and 6 provinces. Patients who had a blood culture that grew a pathogenic organism during their ICU admission were eligible for inclusion. The cohort was accrued by looking back from December 2013 to identify the most recent consecutive critically ill patients who had bloodstream infections (up to a maximum of 100 patients per ICU). Only one episode of bacteremia was included per patient, but all organisms isolated in blood culture sets over the first 24 period from the index blood culture were considered to be contributors to the index bacteremia. The BALANCE cohort was designed to examine prevailing treatment durations for bacteremia without a deep-seated focus, and so patients were excluded if they had endocarditis, osteomyelitis, septic arthritis, undrained abscess or unremoved prosthetic material. Patients were also excluded if they had a single positive culture with a common contaminant (coagulase negative staphylococci, *Corynebacterium spp.*, *Bacillus spp.*, *Propionobacterium spp., Aerococcus spp., Micrococcus spp.*).(9-12) Approval was granted by Research Ethics Boards of all participating ICUs, and informed consent was waived.

Data collection and measures

Experienced Canadian Critical Care Trials Group-affiliated research coordinators at each ICU retrospectively abstracted data on cultured pathogen(s) and susceptibility testing results, source of bloodstream infection, antimicrobial treatment, and clinical outcomes. Data were entered into a web-based, secure electronic case report form and checks were made to minimize missing and invalid data.

Susceptibility testing was done according to Clinical Laboratory Standards Institute (CLSI) guidelines at accredited laboratories.(13) The setting of acquisition for the bloodstream infection was classified as community-acquired if it was diagnosed on a blood culture obtained within 48 hours of hospital admission, hospital-acquired if obtained more than 48 hours after hospital admission, and ICU-acquired if obtained more than 48 hours after ICU admission. The patient's source of infection was based on a review of history, physical, laboratory findings, and clinician notes. Lastly, we defined highly resistant microorganisms (HRMOs) using a modified version of that proposed by de Smet *et al*(14): methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci* spp, penicillin-resistant *Streptococcous pneumoniae*, extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *Acinetobacter* spp; or Enterobacteriaceae resistant to at least two of fluoroquinolones, aminoglycosides or trimethoprim-sulfamethoxazole, *Acinetobacter* spp resistant to at least two of fluoroquinolones, aminoglycosides or ceftazidime; or non-Enterobacteriaceae resistant to at least three of fluoroquinolones, aminoglycosides, carbapenems, ceftazidime or piperacillin.

Statistical Analysis

To examine variability in proportion of patients with specific pathogens and antibiotic resistance profiles across ICUs, comparisons were made using Pearson's $\chi 2$ or Fisher exact tests, and excluded one ICU site that contributed only five patients to the cohort. All other analyses include all patients. Binomial exact methods were used to calculate 95% confidence intervals (CI). For the antimicrobial susceptibility analysis, isolates were defined as either susceptible or resistant to an antimicrobial; intermediate susceptibility isolates were categorized as resistant. Analyses were conducted using Stata v12 (StataCorp. College Station, TX).

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Results

Patient Description

Overall, 1,202 critically ill patients were included in the analysis. Patients were an average of 60 (SD=17) years old, mostly male (748, 62.2%), and admitted for medical (933, 77.6%), surgical (136, 11.3%) or trauma-related (72, 6.0%) reasons. Patients had a mean acute physiology and chronic health evaluation (APACHE) II score of 23 (SD= 9) at admission and most had at least one comorbidity (1110, 92.3%). In total, 479 patients died (39.9%). Half (602, 50.1%) of these infections were community-acquired, 18.3% (220) were hospital-acquired, and 31.6% (380) were ICU-acquired. Pneumonia/lung infections (453, 37.7%), urinary tract infections (243, 20.2%), and vascular catheters (241, 20.2%) were the most common sources of these infections. For the remaining patients, the source of bacteremia was intra-abdominal (189, 15.7%), hepato-biliary (78, 6.5%), skin or soft tissue (97, 8.1%), other infections (62, 5.2%) or unknown (186, 15.5%). Most patients (1,025, 85.3%) were infected with one unique organism, but 148 patients (12.3%) had polymicrobial bloodstream infections.

Pathogen Description

In total, 1,416 pathogens were isolated from the 1202 patients. Overall, 39.4% (558) of the isolated pathogens were Gram negative bacilli, 47.1% (667) were Gram positive cocci, 5.7% (81) other bacteria, and 6.6% (94) yeast. The most frequently isolated individual pathogens are shown in **Table 1**; the five most common organisms were *Escherichia coli* (217, 15.3%), *Staphylococcus aureus* (175, 12.4%), coagulase negative staphylococci (117, 8.3%), *Klebsiella pneumoniae* (86, 6.1%) and *Streptococcus pneumoniae* (85, 6.0%). Mortality varied by infective organism group from 31.5% (*Klebsiella* spp) to 64.5% (*Candida* spp).

Escherichia coli was the most frequently isolated Gram negative bacilli for both community- and hospital-acquired infections, while *Pseudomonas aeruginosa* was more common in ICU-acquired infections (**Table1**). *Enterococcus* spp were the most frequently isolated Gram positive organisms in ICU-acquired infections. A lower proportion of coagulase negative staphylococci were detected in patients who acquired their infection in the community (6.2%) or hospital (6.0%) relative to the ICU (13.0%) (X^2= 18.89, P <0.001). Similarly, there were lower proportions with yeast in the community (2.9%) or hospital (8.3%) relative to ICU-acquired bloodstream infections (11.6%) (X^2= 34.48, P <0.001). By contrast, *Streptococcus pneumoniae* was more frequently cultured in community-acquired infections (11.4%) relative to hospital- (1.1%) and ICU- (0.2%) acquired infections (X^2=73.52, P <0.001).

In patients where the source of bloodstream infection was identified to be urinary- and hepato-biliary-related, infections were caused by Gram negative bacteria, primarily *Escherichia coli* and *Klebsiella pneumoniae* (**Figure 1**). Excluding *Staphylococcus aureus*, Gram positive cocci contributed to a greater relative proportion of infections for other sites including vascular catheter and intra-abdominal (**Figure 1**).

There was also substantial variation in the pathogens isolated across 13 ICUs (X^2= 450.66, P <0.001) (**Figure 2**). The proportion of *Staphylococcus aureus* isolates ranged from 5.3%-27.0%, coagulase negative staphylococci

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from 0.8%-25.6%, other Gram positive cocci 15.4%-33.1%, Gram negative bacilli 16.7%-50.9%, *Candida spp* from 0.0%-20.2% and other bacteria, 0.0%-9.8%.

Susceptibility Patterns

Antimicrobial testing and susceptibility profiles of the pathogens are shown in **Table 2**. Among specimens testing positive for *Staphylococcus aureus*, only 76.4% were susceptible to methicillin and 73.4% were susceptible to fluoroquinolones, but 95.0% were susceptible to trimethoprim-sulfamethoxazole, and 93.9% were susceptible to doxycycline. Only a third of specimens (32.9%) positive for coagulase negative staphylococcus were susceptible to methicillin, while the majority were susceptible to doxycycline (87.5%). *Enterobacteriaceae* susceptiblity rates were high for aminoglycosides (90.9 to 97.8%) and for carbapenems (98.6%). By comparison, fewer non-Enterobacteriaceae were susceptible to carbapenems (80.9%).

We observed variability in susceptibility profiles across the 13 ICUs when examining all Gram negative bacteria (**Figure 3**). Overall, susceptibility rates were high for carbapenems (95.4%), tobramycin (91.2%) and piperacillin-tazobactam (90.0%); however, the proportion of specimens susceptible to these agents ranged from 75.0-100%, 66.7-100% and 75.0-100%, respectively, across the participating ICUs. Fewer Gram negative bacteria were susceptible to fluoroquinolones (overall susceptibility: 84.5%, range across ICUs: 64.1-97.2%).

Highly resistant microorganisms (HRMOs)

Overall, 145 patients (12.1%) had bloodstream infections caused by HRMOs, most commonly ESBL producing *Enterobacteriaceae* (54, 4.5%), and methicillin-resistant *Staphylococcus aureus* (41, 3.4%). 30 patients (2.5%) were infected with Enterobacteriaceae resistant to at least two of fluoroquinolones, aminoglycosides or trimethoprim-sulfamethoxazole, and 23 patients (1.9%) were infected with vancomycin-resistant *Enterococci* spp. Only 4 patients (0.3%) had carbapenem-resistant Enterobacteriaceae. There was significant variability across the 13 ICUs in the proportion of patients infected with HRMOs, ranging from 2.6% to 24.0% (X^2= 57.50, P < 0.001) (**Figure 4**).

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Interpretation

Traditional surveillance networks use labour and time intensive testing methods, and thus there is a scarcity of current data on the profile of pathogens, and antimicrobial susceptibility of those pathogens, causing serious bacterial infections in Canada. Here we present the epidemiology of bloodsteam infections in a geographically diverse cohort of critically ill, Canadian patients using routine pathogen and susceptibility data extracted from readily available microbiology testing databases. More than 100 unique organisms were isolated; 47% of which were Gram positive cocci, 39% Gram negative bacilli, 7% yeast and the remainder other bacteria, with significant variation in isolated organisms across acquisition settings, source of infection, and ICU site. We noted high susceptibility rates (>95%) for carbapenems against Enterobacteriaceae and amikacin against non-Enterobacteriaceae; despite this, one in eight patients had infections caused by highly resistant microorganisms, with the proportion varying significantly across ICU sites from 3% to 24%.

Overall, when we pooled data from all ICU sites, we found that the 5 most frequently isolated pathogens (*Escherichia coli*, *Staphylococcus aureus*, coagulase negative staphylococci, *Klebsiella pneumonia* and *Streptococcus pneumonia)* were similarly amongst the ten most frequently isolated pathogens in blood cultures from the Canadian Ward Surveillance Study (CANWARD), as reported between 2007 and 2009(15). A noted difference, however, was the higher ranking of relative frequency of *Candida* spp in our cohort. This difference is likely reflective of the different settings for data collection, with CANWARD including isolates from a range of settings including medical and surgical wards, ICUs, emergency rooms and hospital-affiliated outpatient clinics.(1) *Candida spp* infections have been shown to be more prevalent in ICU settings: a recent point prevalence study in North American ICUs found that 18% of patients had fungal infections.(16)

Similarly, antimicrobial susceptibility testing data showed consistent findings with other Canadian studies (15), and with American and European ICU data from SENTRY.(3) Carbapenems were the most active antimicrobial agents against *Enterobacteriaceae* (>95% susceptible) in our cohort, followed by gentamicin, piperacillin/tazobactam and tobramycin (>90% susceptible). Despite this, we noted several ICU sites where these agents offered lower likelihood of adequate coverage (susceptibility rates as low as 67% and 75%). Similar heterogeneity in antimicrobial susceptibility rates have been reported recently between hospitals.(4,17) This finding emphasizes the importance of looking to local hospital antibiograms for guidance in selecting empiric treatment regimens. However, some of this variation may relate to imprecision in estimates with small sample sizes, and so it is also important to conduct studies such as this one to examine updated resistance rates over larger patient populations.

In addition to variability in susceptibility profiles, we observed significant variation in both the isolated causative organisms for patients' bloodstream infections and the proportion of highly resistant microorganisms (HRMOs) across ICU sites. Hypothesized hospital-level factors contributing to this variation in HRMOs include differing infection prevention and control programs, antimicrobial usage practices, hospital size, staffing (nurse ratios, infection prevention and/or hospital epidemiology staffing) and characteristics of the patient populations served, among others.(18-21) All ICU sites contributing data to this study were located within academic/teaching hospitals, suggesting that this variability is not due to hospital teaching status. HRMO rates were lowest in the provinces of Manitoba and Quebec (5% each), and highest in Ontario, British Columbia and Alberta (15%, 16% and 20% respectively), suggesting that this variability may be driven by geographical differences in hospital practices, patient populations or strain prevalence (data not shown). Further investigation of this heterogeneity is warranted to determine if there are effective strategies that may reduce HRMOs in highly prevalent settings.

Overall, 41 patients (3.4%) had methicillin-resistant *Staphylococcus aureus* (MRSA) and 23 patients (1.9%) had vancomycin-resistant enterococci (VRE) infections in our study cohort; these proportions are higher than those reported by the Canadian Nosocomial Infection Surveillance Program (CNISP).(22-24) This discrepancy may be attributable to the inclusion of more recent data in our study, as trend data from CNISP have shown increasing rates of VRE colonization and infection in Canada over time.(23) Recent CANWARD and CNISP surveillance data, however, show a decline in MRSA infection in Canada starting in 2008 through to 2012, which may be due to shifts in epidemic strains and/or improvements in infection control practices.(1,24) Differences may also be attributable to the differing patient populations as resistance rates are known to be higher in ICU settings.(25) Only four patients in our study had carbapenem-resistant *Enterobacteriaceae* (CPE), all from differing ICU sites,

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suggesting sporadic and less frequent occurrence than in Europe.(26) These differences may be due in part to increased detection and reporting in Europe (only two-thirds of *Enterobacteriaceae* were tested for carbapenem-resistance in our study), resulting from the recent EuSCAPE initiative aimed at improving understanding of the epidemiology of CPE and building laboratory capacity for diagnosis and surveillance.(26) In Ontario, Canada, Fattouh *et al* (2015) have shown that 14% of CPE may go undetected based on current CLSI recommendations.(27)

This study has several limitations, given the secondary use of these data. The primary objective of the cohort was to study antibiotic treatment durations for bacteremia without deep-seated infection, and thus some bacteremias were excluded (endocarditis, osteomyelitis, septic arthritis, undrained abscess or unremoved prosthetic material); although, these represent a small minority. With regards to antimicrobial susceptibility testing, the use of routine microbiological testing data rather than data expressly collected for the purpose of resistance surveillance means that: first, not all organisms were tested for susceptibility to all potentially relevant agents, and second, there may be variability in susceptibility testing methods across ICU/hospital sites (although methods are generally standardized across Canada using CLSI guidelines).

In summary, we describe the epidemiology of BSIs and corresponding antimicrobial susceptibility profiles in a Canadian multi-centre cohort of critically ill patients using routine microbiological testing data. While this was a time-limited, single retrospective study, it provides proof-of-concept that routine susceptibility testing information from clinical isolates can be harnessed for antimicrobial resistance surveillance at the local level, and offers theoretical advantages of timeliness, efficiency of resources, and ability to examine local trends compared to traditional microbiology surveillance networks. As a result, we recommend that future data sharing could expand to a larger sample of ICUs across Canada, be serially conducted, and have data promptly analyzed and reported; this would further improve the geographical representation and timeliness of these data. Such work is urgently needed to guide empiric treatment guidelines for patients as well as broader system-wide prevention methods to limit the spread of antimicrobial resistance.

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FIGURE LEGENDS:

Figure 1. The distribution of organisms by source of infection in critically ill patients with bloodstream infections (N=1,416) SSTI- skin and/or soft tissue infection. CoNS - coagulase negative staphylococci; α-hemolytic strep. - Alpha hemolytic streptococci.

Figure 2. The variation in isolated pathogens across 13 ICU sites among patients with bloodstream infections (N=1,410). Arrows represent the range in proportion of the particular pathogen across ICU sites, and the red dots represent the overall proportion of the pathogen isolated for all ICU's combined. CoNS – coagulase negative staphylococci; α-hemolytic strep - Alpha hemolytic streptococci.

Figure 3. Variation in susceptibility patterns to antibacterial agents in patients with Gram negative bloodstream infections (N=558) across 13 intensive care unit sites. Error bars represent 95% confidence intervals.

Figure 4. Variation in the proportion of patients with highly resistant microorganisms (HRMOs) (N=145) across 13 intensive care unit sites. Error bars represent 95% confidence intervals. ICU – intensive care unit.

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Table 1. The most frequently isolated organisms from critically ill ICU patients with bloodstream infections, overall and by setting of acquisition

			Setting		
	Organism	**Overall (N=1,416) n (%)**	**Community (N=712) n (%)**	**Hospital (N=266) n (%)**	**ICU (N=438) n (%)**
1	*Escherichia coli*	217 (15.3)	*147 (20.6)*	*46 (17.3)*	24 (5.5)
2	*Staphylococcus aureus*	175 (12.4)	*91 (12.8)*	*28 (10.5)*	*56 (12.8)*
3	*Enterococcus spp*	156 (11.0)	34 (4.8)	*40 (15.0)*	*82 (18.7)*
4	Coagulase negative staphylococcus	117 (8.3)	44 (6.2)	16 (6.0)	*57 (13.0)*
5	*Klebsiella spp*	108 (7.6)	65 (9.1)	22 (8.3)	21 (4.8)
6	*Candida spp*	94 (6.6)	21 (2.9)	22 (8.3)	51 (11.6)
7	*Streptococcus pneumoniae*	85 (6.0)	*81 (11.4)*	3 (1.1)	1 (0.2)
8	*Pseudomonas aeruginosa*	71 (5.0)	18 (2.5)	18 (6.8)	35 (8.0)
9	*Enterobacter spp*	51 (3.6)	16 (2.2)	10 (3.8)	25 (5.7)
10	Alpha hemolytic streptococci (viridans group)	47 (3.3)	29 (4.1)	9 (3.4)	9 (2.1)
11	Beta hemolytic streptococcus: group A *(pyogenes*)	26 (1.8)	23 (3.2)	1 (0.4)	2 (0.5)
12	Beta hemolytic streptococcus: group B (*agalactiae*)	24 (1.7)	18 (2.5)	5 (1.9)	1 (0.2)
13	*Serratia marcescens*	24 (1.7)	8 (1.1)	1 (0.4)	15 (3.4)
14	*Streptococcus anginosus* group	20 (1.4)	12 (1.7)	3 (1.1)	5 (1.1)
15	*Bacteroides spp*	19 (1.3)	11 (1.5)	6 (2.3)	2 (0.5)
16	*Clostridium spp*	17 (1.2)	9 (1.3)	5 (1.9)	3 (0.7)
17	*Proteus spp*	17 (1.2)	12 (1.7)	2 (0.8)	3 (0.7)
18	*Stenotrophomonas maltophilia*	16 (1.1)	3 (0.4)	5 (1.9)	8 (1.8)
19	*Bacillus species* (aerobic spore forming)	13 (0.9)	6 (0.8)	3 (1.1)	4 (0.9)
20	*Acinetobacter spp*	9 (0.6)	0 (0.0)	2 (0.8)	7 (1.6)
21	*Morganella spp*	8 (0.6)	3 (0.4)	2 (0.8)	3 (0.7)
22	*Hemophilus influenzae*	7 (0.5)	7 (1.0)	0 (0.0)	0 (0.0)
23	*Prevotella spp*	6 (0.4)	1 (0.1)	2 (0.8)	3 (0.7)
24	Other	89 (6.3)	53 (7.4)	15 (5.6)	21 (4.8)

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Table 2. The number and proportion of pathogens tested for and susceptible to antibacterial agents in critically ill patients with bloodstream infections (N=1,313)

Pathogen	Antimicrobial	Tested, n (%)	Susceptible, n(%)
Staphylococcus aureus **(N=175)**	Cefazolin/Cloxacillin/Oxacillin	174 (99.4)	133 (76.4)
	Clindamycin	134 (76.6)	100 (74.6)
	Erythro-/Azithro-/Clarithromycin	126 (72.0)	85 (67.5)
	Fluoroquinolones	94 (53.7)	69 (73.4)
	Penicillin	112 (64.0)	17 (15.2)
	Trimethoprim/sulfamethoxazole	159 (90.9)	151 (95.0)
	Doxycycline	115 (65.7)	108 (93.9)
	Vancomycin	115 (65.7)	115 (100.0)
Coagulase negative staphylococci (N=117)	Cefazolin/Cloxacillin/Oxacillin	85 (72.7)	28 (32.9)
	Clindamycin	68 (58.1)	29 (42.6)
	Erythro-/Azithro-/Clarithromycin	64 (54.7)	24 (37.5)
	Fluoroquinolones	53 (45.3)	15 (28.3)
	Penicillin	47 (40.2)	2 (4.3)
	Trimethoprim/sulfamethoxazole	55 (47.0)	30 (54.5)
	Doxycycline	48 (41.0)	42 (87.5)
	Vancomycin	71 (60.7)	71 (100.0)
Enterobacteriaceae (N=432)	Amikacin	186 (43.1)	182 (97.8)
	Amoxicillin-clavulanate	183 (42.4)	112 (61.2)
	Ampicillin/Amoxicillin	399 (92.4)	129 (32.3)
	Carbapenems	284 (65.7)	280 (98.6)
	Cefazolin	360 (83.3)	201 (55.8)
	Ceftazidime	257 (59.5)	229 (89.1)
	Ceftriaxone	424 (98.2)	356 (86.8)*
	Fluoroquinolones	413 (95.6)	349 (84.5)
	Gentamicin	422 (97.7)	398 (94.3)
	Piperacillin/Tazobactam	428 (99.1)	363 (91.0)**
	Trimethoprim/sulfamethoxazole	391 (90.5)	327 (83.6)
	Tobramycin	352 (81.5)	320 (90.9)
Non-enterobacteriaceae (N=126)	Amikacin	31 (24.6)	30 (96.8)
(*primarily *P. aeruginosa, n=71)	Carbapenems	68 (54.0)	55 (80.9)
	Ceftazidime	89 (70.6)	79 (88.8)
	Fluoroquinolones	96 (76.2)	81 (84.4)
	Gentamicin	82 (65.1)	73 (89.0)
	Piperacillin/tazobactam	82 (65.1)	70 (85.4)
	Trimethoprim/sulfamethoxazole	56 (44.4)	28 (50.0)
	Tobramycin	71 (56.4)	66 (93)
Streptococci (N=213)	Ceftriaxone/Cefotaxime	116 (54.5)	114 (98.3)
	Clindamycin	106 (49.8)	93 (87.7)

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	Erythro-/Azithro-/Clarithromycin	89 (41.8)	65 (73.0)
	Fluoroquinolones	77 (36.2)	77 (100)
	Penicillin	160 (75.1)	149 (93.1)
	Septra	44 (20.7)	36 (81.8)
	Vancomycin	109 (51.2)	108 (99.1)
Enterococci (N=156)	Ampicillin/Amoxicillin	153 (98.1)	97 (63.4)
	Vancomycin	142 (91.0)	119 (83.8)
Yeast (N=94)	Fluconazole	29 (30.9)	27 (93.1)

* excludes 14 patients with missing susceptibility testing from denominator. ** excludes 29 patients with missing susceptibility testing data from denominator

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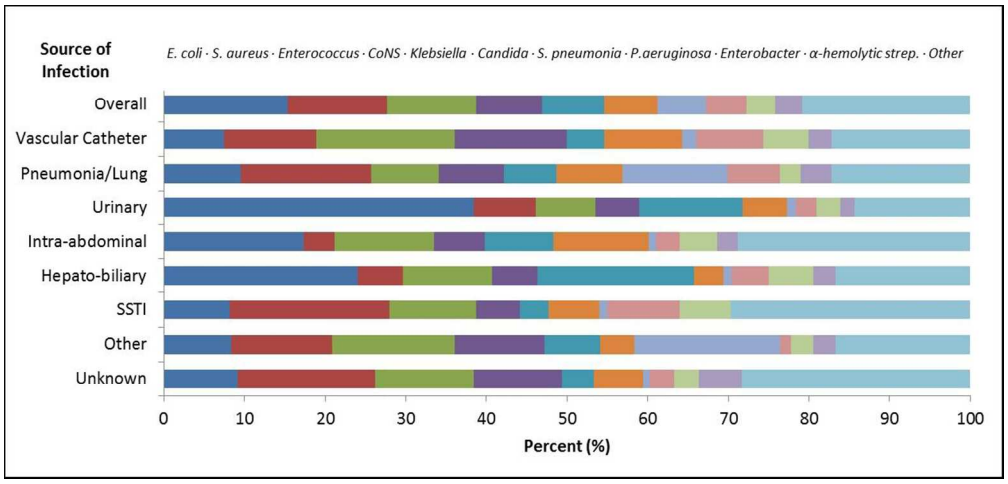

Figure 1. The distribution of organisms by source of infection in critically ill patients with bloodstream infections (N=1,416) SSTI- skin and/or soft tissue infection. CoNS - coagulase negative staphylococci; α-hemolytic strep. - Alpha hemolytic streptococci.

212x100mm (150 x 150 DPI)

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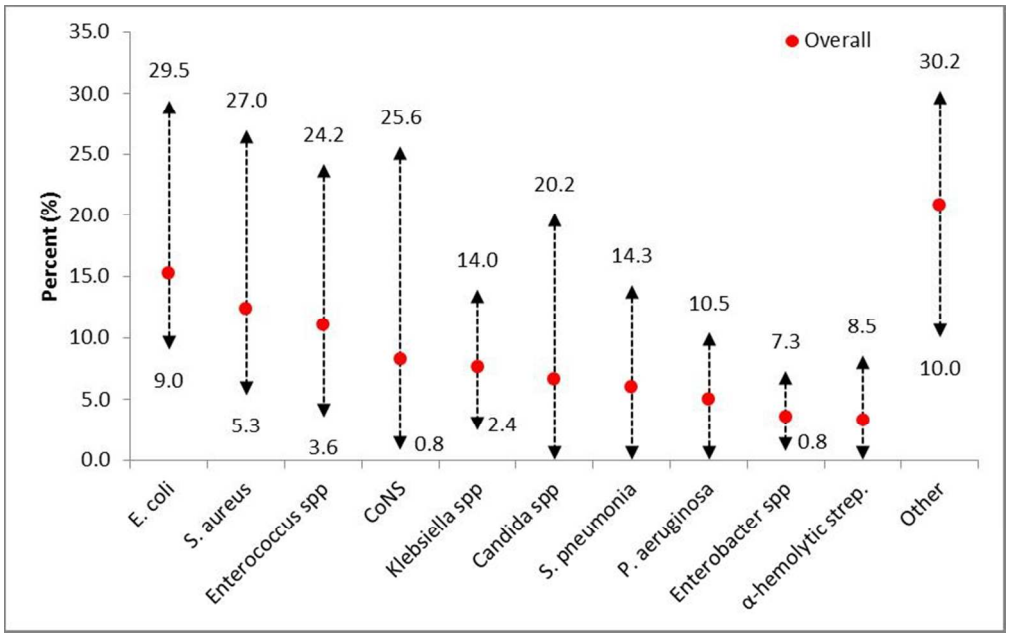

Figure 2. The variation in isolated pathogens across 13 ICU sites among patients with bloodstream infections (N=1,410). Arrows represent the range in proportion of the particular pathogen across ICU sites, and the red dots represent the overall proportion of the pathogen isolated for all ICU's combined. CoNS – coagulase negative staphylococci; α-hemolytic strep - Alpha hemolytic streptococci.

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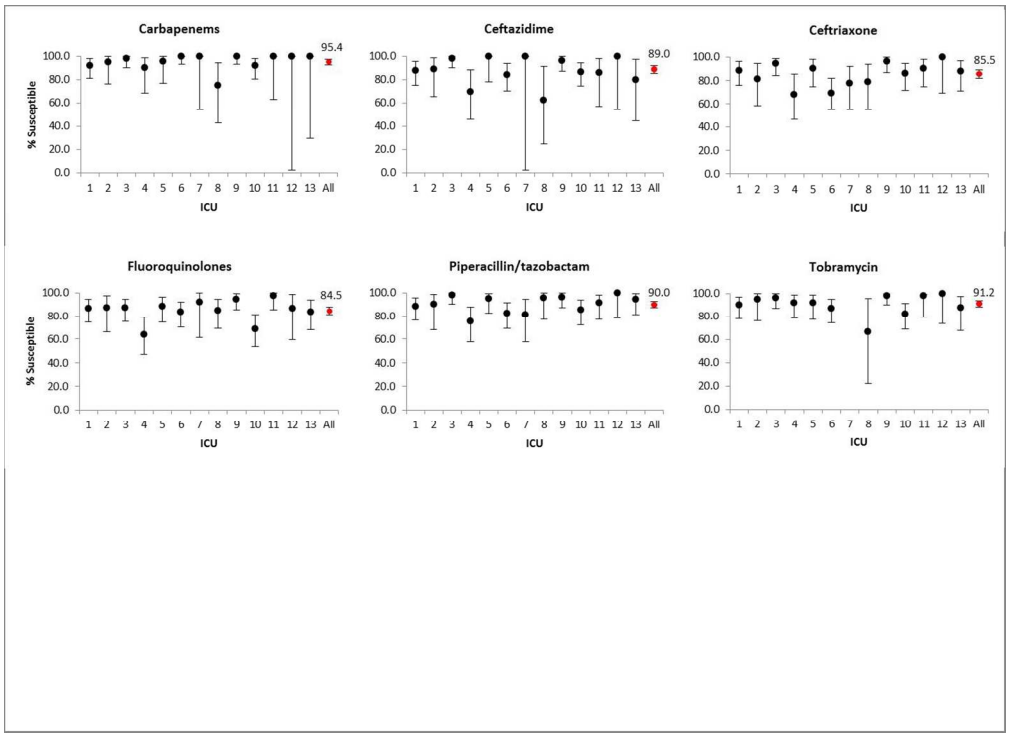

Figure 3. Variation in susceptibility patterns to antibacterial agents in patients with Gram negative bloodstream infections (N=558) across 13 intensive care unit sites. Error bars represent 95% confidence intervals.

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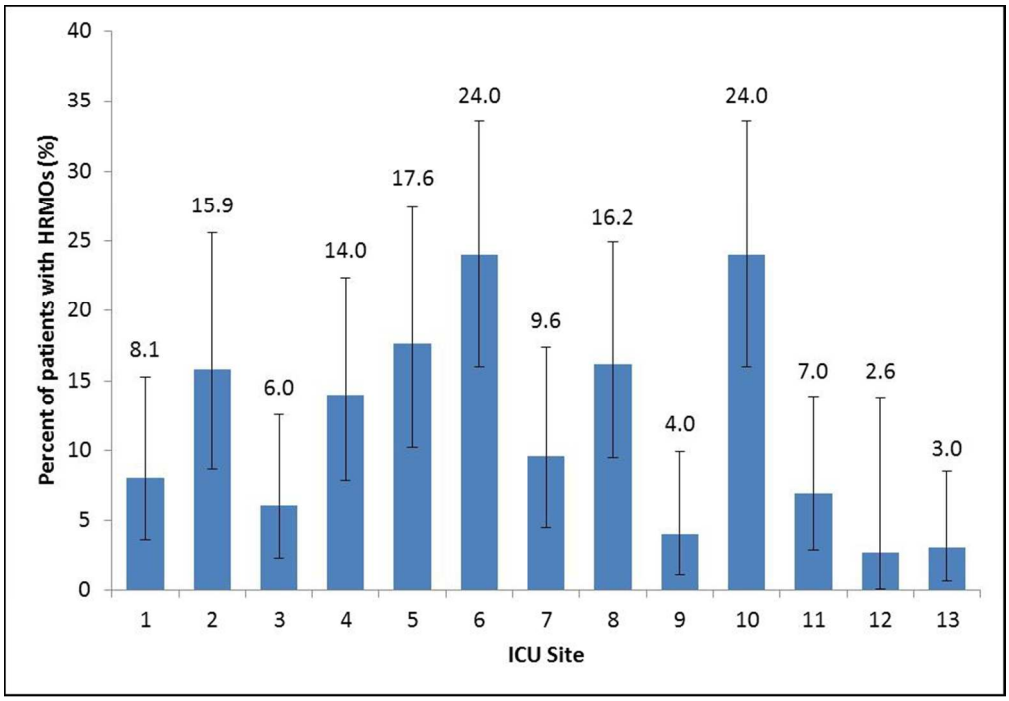

Figure 4. Variation in the proportion of patients with highly resistant microorganisms (HRMOs) (N=145) across 13 intensive care unit sites. Error bars represent 95% confidence intervals. ICU – intensive care unit.

165x114mm (150 x 150 DPI)

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