

Distribution and antimicrobial susceptibility profile of pathogens recovered from the bloodstream of Canadian patients: results from the CANWARD study (2007–23)

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Objectives: Bloodstream infections are associated with significant morbidity and mortality. The purpose of this study was to determine the most common pathogens causing bacteraemia among Canadian patients and to evaluate their antimicrobial susceptibility profiles.

Methods: Annually from 2007 to 2023, bloodstream isolates from patients admitted to or evaluated at Canadian hospitals were collected by sentinel laboratories (CANWARD surveillance study). Antimicrobial susceptibility testing was performed by broth microdilution.

Results: In total, 26 067 bloodstream isolates were obtained over 17 years of the CANWARD study (14 954 from inpatients, 11 107 from outpatients, no patient location for six isolates). The five most common pathogens were *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae*. There was little variation in pathogen distribution over time but certain pathogens were more common among inpatients (e.g. *Candida albicans*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*) while others were more common among outpatients (e.g. *Streptococcus pyogenes*, *Streptococcus agalactiae*). The proportion of ESBL-producing *E. coli* increased from 4.5% (2007–09) to 12.7% (2019–23). The proportion of ESBL-producing *K. pneumoniae* increased from 2.0% (2007–09) to 7.1% (2018–23). Vancomycin susceptibility among *Enterococcus faecium* decreased from 84.9% (2007–09) to 69.0% (2019–23). In contrast, the proportions of *S. aureus* that were MRSA and *P. aeruginosa* that had a difficult-to-treat resistance phenotype were relatively stable.

Conclusions: There has been little variation in the pathogens commonly causing bacteraemia among Canadian patients over the course of the CANWARD study, but some resistant phenotypes (e.g. ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, VRE) are being encountered more frequently in recent years.

Introduction

Bacteraemia is defined as the presence of viable bacteria in the blood.¹ Bloodstream infections may be classified as either primary (no documented source of infection) or secondary (due to a localized/focal infection), and are associated with significant patient morbidity and mortality.^{1–6} The mortality rate among patients with bacteraemia in several publications has ranged between 14.3% and 33.2%, and is influenced by many variables including the source of infection, the pathogen, patient

comorbidities and the severity of illness.^{2–6} Mortality is particularly high among bacteraemic patients with septic shock.⁷ Multiple studies have demonstrated an increase in mortality when there is a delay in the initiation of appropriate empiric antimicrobial therapy among patients with bacteraemia.^{2,3,8} Of concern, in recent years bloodstream infections due to certain antimicrobial-resistant organisms, including *Enterobacterales* that harbour an ESBL, have been observed with increasing frequency.^{9–12} Antimicrobial resistance, in turn, has been associated with patients receiving inappropriate empiric treatment.²

When patients present to an emergency department with sepsis or develop sepsis while admitted to a hospital, clinicians are faced with the task of selecting appropriate empiric antimicrobial therapy prior to culture results being known. Information used in making therapeutic decisions includes consideration of the likely source of infection (and the most common pathogens causing that infection), severity of illness and patient risk factors for harbouring an antimicrobial-resistant pathogen. Data from national surveillance studies can serve as an additional tool to help define the most likely pathogens a clinician will encounter should the patient prove to be bacteraemic. There has not been a large-scale surveillance study investigating the epidemiology and susceptibility profile of bloodstream isolates recovered from Canadian patients published in recent years. The purpose of this study was to determine the most common pathogens recovered from the bloodstream of patients admitted to or evaluated at Canadian hospitals and to assess whether the pathogen distribution and the susceptibility profile of the most frequently recovered bloodstream pathogens has changed over time.

Materials and methods

Bacterial isolates

Bloodstream isolates were obtained as a part of the CANWARD surveillance study, January 2007 to December 2023. CANWARD is an ongoing national Public Health Agency of Canada-PHAC/Canadian Antimicrobial Resistance Alliance partnered surveillance study evaluating *in vitro* activities of antimicrobial agents against bacterial pathogens isolated by clinical laboratories from patients attending tertiary care hospitals across Canada.¹³ Each isolate included was considered clinically significant by protocols in place at the submitting laboratory. The CANWARD surveillance study sets annual quotas for bloodstream isolates and requires isolates be collected consecutively, one per patient, from both in- and outpatients attending emergency rooms (ERs), hospital clinics, medical/surgical wards and intensive care units each year. All isolates are shipped to the CANWARD coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where their identities are confirmed by colonial appearance, spot testing,¹⁴ and/or MALDI-TOF mass spectrometry (Bruker Daltonics, Billerica, MA, USA) as required. Tertiary care hospitals in 8 of the 10 Canadian provinces participated in the CANWARD surveillance study, with the number of hospitals varying between 8 and 15 depending on the study year. The CANWARD surveillance study receives annual approval by the University of Manitoba Research Ethics Board (H2009:059).

Antimicrobial susceptibility testing

Following two subcultures from frozen stock, antimicrobial susceptibility testing was performed by broth microdilution using in-house prepared 96-well microtitre panels, as described by CLSI.¹⁵ MICs were interpreted using current CLSI breakpoints, when available.¹⁶ Putative ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* were identified as isolates with a ceftaxime and/or ceftazidime MIC of ≥ 1 mg/L. ESBL-production was verified using the CLSI phenotypic confirmatory disk test.¹⁵ Difficult-to-treat resistance (DTR) among *Pseudomonas aeruginosa* was defined as isolates testing not susceptible (intermediate or resistant) to all of the following antimicrobials: meropenem, piperacillin-tazobactam, ceftazidime and ciprofloxacin.¹⁷

Statistical analysis

The Cochran–Armitage Test of trend was used to determine whether changes in antimicrobial susceptibility over time were statistically significant. Statistical analysis was performed using JMP Pro version 18.0.2.

Results

In total, 26 067 bloodstream isolates were recovered from Canadian patients as part of the CANWARD Study between 2007 and 2023. Of these isolates, 14 954 (57.4%) were obtained from inpatients (intensive care unit, surgical ward or medical ward) and 11 107 (42.6%) were obtained from outpatients (ER or clinic). The distribution of isolates by specific ward type was as follows: 3823 (14.7%) from patients in an intensive care unit, 2003 (7.7%) from patients on a surgical ward, 9128 (35.0%) from patients on a medical ward, 9485 (36.4%) from patients in an ER and 1622 (6.2%) from clinic patients. The ward type was not available for six isolates. Stratified by age, 2581 isolates (9.9%) were obtained from patients ≤ 17 years old, 11 373 isolates (43.6%) were obtained from patients 18–64 years old, and 12 110 isolates (46.5%) were obtained from patients ≥ 65 years old (no age documented for three patients). Stratified by biological sex, 14 834 isolates (56.9%) were obtained from male patients while 11 231 isolates (43.1%) were obtained from female patients (no biological sex documented for two patients).

The 10 most common pathogens recovered from the bloodstream of patients admitted to or evaluated at Canadian hospitals are listed in Table 1. The five most frequently isolated organisms were *E. coli* (24.5% of isolates), *Staphylococcus aureus* (17.3% of isolates), *K. pneumoniae* (7.9% of isolates), *Staphylococcus epidermidis* (4.7% of isolates) and *Streptococcus pneumoniae* (4.3% of isolates). These pathogens accounted for 58.7% of all bloodstream isolates in CANWARD. The pathogen distribution differed when comparing inpatients with outpatients (Table 1). While *E. coli*, *S. aureus* and *K. pneumoniae* were the pathogens most frequently recovered from both inpatients and outpatients, a higher proportion of bloodstream infections due to *E. coli* was found among outpatients. *Enterococcus faecium*, *Pseudomonas aeruginosa*, *Enterobacter cloacae* and *Candida albicans* were more commonly isolated from inpatients, while *S. pneumoniae*, *Streptococcus pyogenes* and *Streptococcus agalactiae* were more frequently isolated from outpatients. The pathogen distribution also varied depending on the specific ward type (Table 2). Among inpatients, *C. albicans* was more frequently recovered from patients admitted to an intensive care unit or a surgical ward. In general, *P. aeruginosa* and *E. cloacae* were more frequently isolated from patients in the intensive care unit, a surgical ward, or a medical ward relative to an ER or clinic. Conversely, the top 10 pathogens recovered from ER patients included *S. pyogenes* and *S. agalactiae*, and a relatively higher proportion of *E. coli* and *S. pneumoniae*.

The pathogen distribution stratified by patient age and biological sex is presented in Table 3. The most common bloodstream pathogen among patients ≤ 17 years of age was *S. aureus*, while *E. coli* was most common among patients ≥ 65 years of age. The overall pathogen distribution by biological sex was comparable between males and females, but the proportion of bloodstream infections due to *E. coli* was higher for females. The top 10 bloodstream pathogens among Canadian patients, stratified by study time period, is provided in Table 4. There was some minor variability in pathogen distribution over the course of the study, but *E. coli*, *S. aureus* and *K. pneumoniae*, were consistently the most common pathogens recovered.

Table 1. Top 10 pathogens causing bloodstream infections among patients admitted to or evaluated at Canadian hospitals (CANWARD)

All locations		Inpatient ^a		Outpatient ^b	
Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen	Number (% of total)
<i>Escherichia coli</i>	6379 (24.5)	<i>Escherichia coli</i>	3055 (20.4)	<i>Escherichia coli</i>	3323 (29.9)
<i>Staphylococcus aureus</i>	4515 (17.3)	<i>Staphylococcus aureus</i>	2609 (17.4)	<i>Staphylococcus aureus</i>	1904 (17.1)
<i>Klebsiella pneumoniae</i>	2060 (7.9)	<i>Klebsiella pneumoniae</i>	1210 (8.1)	<i>Klebsiella pneumoniae</i>	850 (7.7)
<i>Staphylococcus epidermidis</i>	1215 (4.7)	<i>Staphylococcus epidermidis</i>	866 (5.8)	<i>Streptococcus pneumoniae</i>	696 (6.3)
<i>Streptococcus pneumoniae</i>	1108 (4.3)	<i>Enterococcus faecalis</i>	778 (5.2)	<i>Staphylococcus epidermidis</i>	349 (3.1)
<i>Enterococcus faecalis</i>	1091 (4.2)	<i>Pseudomonas aeruginosa</i>	698 (4.7)	<i>Enterococcus faecalis</i>	312 (2.8)
<i>Pseudomonas aeruginosa</i>	1003 (3.8)	<i>Enterococcus faecium</i>	504 (3.4)	<i>Streptococcus pyogenes</i>	306 (2.8)
<i>Enterobacter cloacae</i>	687 (2.6)	<i>Enterobacter cloacae</i>	484 (3.2)	<i>Pseudomonas aeruginosa</i>	305 (2.7)
CoNS ^c	603 (2.3)	<i>Candida albicans</i>	480 (3.2)	<i>Streptococcus agalactiae</i>	255 (2.3)
<i>Enterococcus faecium</i>	602 (2.3)	<i>Streptococcus pneumoniae</i>	412 (2.8)	CoNS	232 (2.1)
Other ^d	6804 (26.1)	Other	3858 (25.8)	Other	2575 (23.2)

^aInpatient = isolates obtained from patients on surgical wards, medical wards and intensive care units.

^bOutpatient = isolates obtained from patients seen in clinics or an emergency room.

^cCoNS, coagulase-negative staphylococci (not speciated).

^dOther: *Abiotrophia* spp., *Achromobacter* spp., *Acinetobacter* spp., *Aerococcus* spp., *Aeromonas* spp., *Aggregatibacter* spp., *Agrobacterium* spp., *Alcaligenes* spp., *Arcanobacterium* spp., *Bacillus* spp., *Brevibacillus* spp., *Brevibacterium* spp., *Burkholderia* spp., *Campylobacter* spp., *Candida* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Cedecea* spp., *Chryseobacterium* spp., *Citrobacter* spp., *Clostridium* spp., *Comamonas* spp., *Corynebacterium* spp., *Cronobacter* spp., *Cryptococcus* spp., *Cupriavidus* spp., *Cutibacterium* spp., *Delftia* spp., *Dermabacter* spp., *Diphtheroids*, *Eikenella* spp., *Elizabethkingia* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Flavobacterium* spp., *Gemella* spp., *Gordonia* spp., *Granulicatella* spp., *Haemophilus* spp., *Hafnia* spp., *Jeptogalococcus* spp., *Klebsiella* spp., *Kocuria* spp., *Kytococcus* spp., *Lactobacillus* spp., *Lactococcus* spp., *Leclercia* spp., *Leifsonia* spp., *Lelliottia* spp., *Leuconostoc* spp., *Listeria* spp., *Macroccoccus* spp., *Micrococcus* spp., *Moraxella* spp., *Morganella* spp., *Mycobacterium* spp., *Neisseria* spp., *Ochrobactrum* spp., *Paenibacillus* spp., *Pantoea* spp., *Paracoccus* spp., *Pasteurella* spp., *Phenylobacterium* spp., *Pluralibacter* spp., *Proteus* spp., *Providencia* spp., *Pseudomonas* spp., *Ralstonia* spp., *Raoultella* spp., *Rhodococcus* spp., *Roseomonas* spp., *Rothia* spp., *Saccharomyces* spp., *Salmonella* spp., *Serratia* spp., *Shigella* spp., *Sphingobacterium* spp., *Sphingomonas* spp., *Staphylococcus* spp., *Stenotrophomonas* spp., *Stomatococcus* spp., *Streptococcus* spp., *Trichosporon* spp., *Trueperella* spp., *Vibrio* spp., *Weissella* spp., *Yersinia* spp.

Antimicrobial susceptibility for the top 10 bacterial pathogens recovered from the bloodstream of Canadian patients, subdivided by study time period, is presented in Table 5. Coagulase-negative staphylococci (not speciated) were excluded from this table as antimicrobial susceptibility testing was not performed for these. The proportion of *E. coli* isolates that were ESBL-producers increased over the course of the study, from 4.5% (2007–09) to 12.7% (2019–23). There was a corresponding reduction in susceptibility of ceftriaxone over the 17 years of the study and a slight reduction in piperacillin-tazobactam susceptibility. Among *E. coli* isolates, susceptibility to ciprofloxacin, ertapenem and meropenem, remained fairly constant, with ertapenem, meropenem and piperacillin-tazobactam demonstrating the highest susceptibility rates. The proportion of *K. pneumoniae* isolates that were ESBL-producers also increased over time (from 2.0% in 2007–09 to 7.1% in 2018–23), although to a lesser extent than was observed for *E. coli*. Ertapenem, meropenem and gentamicin demonstrated good *in vitro* activity versus *K. pneumoniae* (>95% of isolates testing susceptible) over the course of the study. Susceptibility rates for most antimicrobials were either stable or improved slightly for bloodstream isolates of *P. aeruginosa*. The proportion of isolates with a DTR phenotype varied between 1.9% and 3.3% for most of the study (excluding the 2007–09 time period) with no clear temporal trend.

The proportion of *S. aureus* isolates that were MRSA declined early in the study but has since remained relatively stable at 17.4% to 19.4% (2010–23). Over 97% of *S. aureus* bloodstream isolates remained susceptible to ceftiofur, daptomycin, doxycycline, linezolid, trimethoprim-sulfamethoxazole and vancomycin over the course of the CANWARD Study. The proportion of *S. pneumoniae* isolates that tested susceptible to penicillin (oral breakpoints) varied from 86.1% to 92.7%, without a clear trend to increasing or decreasing susceptibility over time. Irrespective of the study time period, over 98% of bloodstream *S. pneumoniae* isolates tested susceptible to ceftriaxone (non-meningitis breakpoints), levofloxacin and vancomycin. An increase in the proportion of *E. faecium* bloodstream isolates that were vancomycin resistant was observed over the study years, with a corresponding reduction in vancomycin susceptibility from 84.9% (2007–09) to 69.0% (2019–23).

The proportion of isolates with a common antimicrobial-resistant phenotype, stratified by ward type, is presented in Table 6. MRSA, ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, *P. aeruginosa* demonstrating DTR and VRE were all more frequently recovered from inpatients (intensive care unit, surgical ward, or medical ward) in comparison with outpatients (ER or clinic).

Table 2. Top 10 pathogens causing bloodstream infections among patients admitted to or evaluated at Canadian hospitals (CANWARD), stratified by hospital location

Hospital location			Surgical ward			Medical ward			ER			Clinics		
ICU														
Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen	Number (% of total)	Number (% of total)
<i>Staphylococcus aureus</i>	592 (15.5)	<i>Escherichia coli</i>	395 (19.7)	<i>Escherichia coli</i>	2103 (23.0)	<i>Escherichia coli</i>	3006 (31.7)	<i>Staphylococcus aureus</i>	318 (19.6)					
<i>Escherichia coli</i>	557 (14.6)	<i>Staphylococcus aureus</i>	372 (18.6)	<i>Staphylococcus aureus</i>	1645 (18.0)	<i>Staphylococcus aureus</i>	1586 (16.7)	<i>Escherichia coli</i>	317 (19.5)					
<i>Staphylococcus epidermidis</i>	327 (8.6)	<i>Klebsiella pneumoniae</i>	180 (9.0)	<i>Klebsiella pneumoniae</i>	755 (8.3)	<i>Klebsiella pneumoniae</i>	740 (7.8)	<i>Klebsiella pneumoniae</i>	110 (6.8)					
<i>Klebsiella pneumoniae</i>	275 (7.2)	<i>Enterococcus faecalis</i>	118 (5.9)	<i>Enterococcus faecalis</i>	445 (4.9)	<i>Streptococcus pneumoniae</i>	643 (6.8)	CoNS	95 (5.9)					
<i>Enterococcus faecalis</i>	215 (5.6)	<i>Staphylococcus epidermidis</i>	103 (5.1)	<i>Staphylococcus epidermidis</i>	436 (4.8)	<i>Streptococcus pyogenes</i>	283 (3.0)	<i>Staphylococcus epidermidis</i>	77 (4.7)					
<i>Pseudomonas aeruginosa</i>	191 (5.0)	<i>Candida albicans</i>	93 (4.6)	<i>Pseudomonas aeruginosa</i>	432 (4.7)	<i>Staphylococcus epidermidis</i>	272 (2.9)	<i>Enterococcus faecalis</i>	63 (3.9)					
<i>Candida albicans</i>	190 (5.0)	<i>Pseudomonas aeruginosa</i>	75 (3.7)	<i>Enterobacter cloacae</i>	283 (3.1)	<i>Enterococcus faecalis</i>	249 (2.6)	<i>Pseudomonas aeruginosa</i>	57 (3.5)					
<i>Enterococcus faecium</i>	162 (4.2)	<i>Enterococcus faecium</i>	68 (3.4)	<i>Enterococcus faecium</i>	274 (3.0)	<i>Pseudomonas aeruginosa</i>	248 (2.6)	<i>Streptococcus pneumoniae</i>	53 (3.3)					
CoNS ^a	157 (4.1)	<i>Enterobacter cloacae</i>	62 (3.1)	<i>Streptococcus pneumoniae</i>	266 (2.9)	<i>Streptococcus agalactiae</i>	221 (2.3)	<i>Enterobacter cloacae</i>	52 (3.2)					
<i>Enterobacter cloacae</i>	139 (3.6)	<i>Klebsiella oxytoca/Raoultella</i> spp.	55 (2.7)	<i>Candida albicans</i>	197 (2.2)	Viridans group streptococci	178 (1.9)	Viridans group streptococci	37 (2.3)					
Other	1018 (26.6)	Other	482 (24.1)	Other	2292 (25.1)	Other	2059 (21.7)	Other	443 (27.3)					

^aCoNS, coagulase-negative staphylococci (not specified).

Table 3. Top 10 pathogens causing bloodstream infections among patients admitted to or evaluated at Canadian hospitals (CANWARD), stratified by patient age and biological sex

Patient age	Biological sex					
	≤17 years old			≥65 years old		
	18–64 years old			Male		
Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen	Number (% of total)	Pathogen
<i>Staphylococcus aureus</i>	350 (13.6)	<i>Staphylococcus aureus</i>	2367 (20.8)	<i>Escherichia coli</i>	3678 (30.4)	<i>Escherichia coli</i>
<i>Escherichia coli</i>	335 (13.0)	<i>Escherichia coli</i>	2366 (20.8)	<i>Staphylococcus aureus</i>	1798 (14.8)	<i>Staphylococcus aureus</i>
<i>Staphylococcus epidermidis</i>	328 (12.7)	<i>Klebsiella pneumoniae</i>	891 (7.8)	<i>Klebsiella pneumoniae</i>	1062 (8.8)	<i>Klebsiella pneumoniae</i>
<i>Streptococcus pneumoniae</i>	192 (7.4)	<i>Streptococcus pneumoniae</i>	564 (5.0)	<i>Enterococcus faecalis</i>	600 (5.0)	<i>Staphylococcus epidermidis</i>
<i>Klebsiella pneumoniae</i>	107 (4.1)	<i>Staphylococcus epidermidis</i>	472 (4.2)	<i>Pseudomonas aeruginosa</i>	514 (4.2)	<i>Streptococcus pneumoniae</i>
<i>Enterococcus faecalis</i>	89 (3.4)	<i>Pseudomonas aeruginosa</i>	429 (3.8)	<i>Staphylococcus epidermidis</i>	415 (3.4)	<i>Pseudomonas aeruginosa</i>
<i>Staphylococcus hominis</i>	82 (3.2)	<i>Enterococcus faecalis</i>	402 (3.5)	<i>Streptococcus pneumoniae</i>	352 (2.9)	<i>Enterococcus faecalis</i>
<i>Streptococcus agalactiae</i>	81 (3.1)	<i>Enterobacter cloacae</i>	319 (2.8)	<i>Enterobacter cloacae</i>	294 (2.4)	<i>Enterobacter cloacae</i>
<i>Streptococcus pyogenes</i>	81 (3.1)	<i>Enterococcus faecium</i>	294 (2.6)	<i>Enterococcus faecium</i>	282 (2.3)	CoNS
Viridans group streptococci	77 (3.0)	CoNS ^a	280 (2.5)	<i>Proteus mirabilis</i>	256 (2.1)	<i>Enterococcus faecium</i>
Other	859 (33.3)	Other	2989 (26.3)	Other	2859 (23.6)	Other

^aCoNS, coagulase-negative staphylococci (not speciated).

Table 4. Top 10 pathogens causing bloodstream infection among patients admitted to or evaluated at Canadian hospitals (CANWARD), stratified by study time period

Study years		2010–12		2013–15		2016–18		2019–23	
Organism	Number (% of total)	Organism	Number (% of total)	Organism	Number (% of total)	Organism	Number (% of total)	Organism	Number (% of total)
<i>Escherichia coli</i>	1850 (22.5)	<i>Escherichia coli</i>	1156 (22.2)	<i>Escherichia coli</i>	1000 (25.0)	<i>Escherichia coli</i>	1030 (26.9)	<i>Escherichia coli</i>	1343 (27.9)
<i>Staphylococcus aureus</i>	1457 (17.7)	<i>Staphylococcus aureus</i>	870 (16.7)	<i>Staphylococcus aureus</i>	761 (19.1)	<i>Staphylococcus aureus</i>	660 (17.2)	<i>Staphylococcus aureus</i>	767 (15.9)
<i>Klebsiella pneumoniae</i>	597 (7.3)	<i>Klebsiella pneumoniae</i>	383 (7.4)	<i>Klebsiella pneumoniae</i>	316 (7.9)	<i>Klebsiella pneumoniae</i>	302 (7.9)	<i>Klebsiella pneumoniae</i>	462 (9.6)
CoNS ^a	474 (5.8)	<i>Staphylococcus epidermidis</i>	310 (6.0)	<i>Staphylococcus epidermidis</i>	205 (5.1)	<i>Staphylococcus epidermidis</i>	205 (5.4)	<i>Pseudomonas aeruginosa</i>	199 (4.1)
<i>Streptococcus pneumoniae</i>	470 (5.7)	<i>Candida albicans</i>	258 (5.0)	<i>Streptococcus pneumoniae</i>	170 (4.3)	<i>Enterococcus faecalis</i>	141 (3.7)	<i>Enterococcus faecalis</i>	187 (3.9)
<i>Enterococcus faecalis</i>	388 (4.7)	<i>Streptococcus pneumoniae</i>	222 (4.3)	<i>Enterococcus faecalis</i>	164 (4.1)	<i>Enterobacter cloacae</i>	129 (3.4)	<i>Staphylococcus epidermidis</i>	185 (3.8)
<i>Pseudomonas aeruginosa</i>	332 (4.0)	<i>Enterococcus faecalis</i>	211 (4.1)	<i>Pseudomonas aeruginosa</i>	160 (4.0)	<i>Streptococcus pneumoniae</i>	127 (3.3)	Viridans group streptococci	153 (3.2)
<i>Staphylococcus epidermidis</i>	310 (3.8)	<i>Pseudomonas aeruginosa</i>	189 (3.6)	<i>Enterobacter cloacae</i>	102 (2.6)	<i>Pseudomonas aeruginosa</i>	123 (3.2)	<i>Enterococcus faecium</i>	145 (3.0)
<i>Enterobacter cloacae</i>	193 (2.3)	<i>Enterobacter cloacae</i>	123 (2.4)	<i>Enterococcus faecium</i>	96 (2.4)	<i>Enterococcus faecium</i>	94 (2.5)	<i>Enterobacter cloacae</i>	140 (2.9)
Viridans group streptococci	162 (2.0)	<i>Enterococcus faecium</i>	114 (2.2)	<i>Streptococcus agalactiae</i>	90 (2.3)	<i>Klebsiella oxytoca</i> <i>Raoultella</i> spp.	87 (2.3)	<i>Streptococcus pneumoniae</i>	119 (2.5)
Other	1988 (24.2)	Other	1370 (26.3)	Other	930 (23.3)	Other	932 (24.3)	Other	1116 (23.2)

^aCoNS, Coagulase-negative staphylococci (not speciated)

Table 5. Temporal trends in the antimicrobial susceptibility profile of common bacterial pathogens recovered from the bloodstream of patients admitted to or evaluated at Canadian hospitals (CANWARD)

	% Susceptible (n/N)					
Organism	2007–09	2010–12	2013–15	2016–18	2019–23	P value
<i>Escherichia coli</i>						
ESBL ^a	4.5 (84/1850)	4.9 (57/1156)	9.7 (97/1000)	10.2 (105/1030)	12.7 (170/1343)	<0.001
Amoxicillin-clavulanate	94.6 (1448/1531)	82.1 (949/1156)	81.8 (818/1000)	75.9 (782/1030)	62.5 (671/1073)	<0.001
Cefazolin	69.0 (1277/1850)	74.9 (866/1156)	74.3 (743/1000)	69.8 (719/1030)	61.1 (821/1343)	<0.001
Ceftazidime	95.4 (1015/1064)	94.6 (1093/1156)	92.3 (923/1000)	89.5 (922/1030)	86.2 (1157/1343)	<0.001
Ceftriaxone	93.5 (1730/1850)	92.7 (1072/1156)	89.0 (890/1000)	88.2 (908/1030)	84.4 (1133/1343)	<0.001
Ciprofloxacin	75.8 (1402/1850)	76.0 (879/1156)	75.4 (754/1000)	75.8 (781/1030)	72.5 (974/1343)	0.062
Ertapenem	99.8 (1526/1529)	99.9 (1155/1156)	99.8 (998/1000)	99.4 (1024/1030)	99.7 (1339/1343)	0.165
Gentamicin	89.1 (1648/1849)	89.9 (1039/1156)	90.3 (903/1000)	91.3 (940/1030)	90.6 (1217/1343)	0.076
Meropenem	100 (1850/1850)	100 (1156/1156)	100 (1000/1000)	99.9 (1029/1030)	99.9 (1341/1343)	ND ^b
Piperacillin-tazobactam	96.6 (1788/1850)	97.3 (1125/1156)	96.9 (969/1000)	93.8 (966/1030)	95.1 (1277/1343)	<0.001
SXT ^c	70.1 (1296/1850)	72.2 (835/1156)	73.0 (730/1000)	74.5 (767/1030)	71.6 (962/1343)	0.1222
<i>Staphylococcus aureus</i>						
MRSA ^a	24.4 (356/1457)	19.9 (173/870)	17.9 (136/761)	17.4 (115/660)	19.4 (149/767)	<0.001
Ceftobiprole ^d	100 (1456/1456)	100 (382/382)	100 (243/243)	100 (660/660)	100 (766/766)	ND
Clindamycin ^e	80.2 (1168/1456)	86.6 (744/859)	89.2 (677/759)	94.1 (621/660)	94.9 (727/766)	0.038
Daptomycin	100 (1456/1456)	99.9 (858/859)	100 (759/759)	99.8 (659/660)	99.7 (764/766)	ND
Doxycycline	No data	99.2 (482/486)	98.7 (750/760)	98.8 (652/660)	99.0 (758/766)	0.698
Linezolid	100 (1456/1456)	100 (859/859)	100 (759/759)	100 (660/660)	99.9 (765/766)	ND
SXT	97.2 (1415/1456)	99.2 (861/868)	99.2 (754/760)	99.4 (656/660)	98.4 (754/766)	0.003
Vancomycin	99.9 (1455/1456)	100 (859/859)	99.9 (758/759)	99.8 (659/660)	100 (766/766)	ND
<i>Klebsiella pneumoniae</i>						
ESBL ^a	2.0 (12/597)	4.4 (17/383)	6.3 (20/316)	8.3 (25/302)	7.1 (33/462)	<0.001
Amoxicillin-clavulanate	97.6 (483/495)	92.1 (352/382)	91.8 (290/316)	88.4 (267/302)	88.0 (315/358)	<0.001
Cefazolin	86.3 (515/597)	86.7 (332/383)	84.5 (267/316)	81.8 (247/302)	82.2 (379/461)	0.018
Ceftazidime	98.2 (327/333)	95.3 (365/383)	93.7 (296/316)	92.7 (280/302)	91.5 (422/461)	<0.001
Ceftriaxone	97.7 (583/597)	94.8 (363/383)	92.7 (293/316)	91.7 (277/302)	91.5 (422/461)	<0.001
Ciprofloxacin	88.6 (529/597)	88.5 (339/383)	88.6 (280/316)	88.1 (266/302)	88.7 (409/461)	0.957
Ertapenem	99.6 (493/495)	98.7 (378/383)	98.1 (310/316)	98.7 (298/302)	98.9 (456/461)	0.272
Gentamicin	97.7 (583/597)	96.6 (370/383)	95.3 (301/316)	95.7 (289/302)	96.5 (445/461)	0.179
Meropenem	99.8 (596/597)	99.7 (382/383)	99.1 (313/316)	99.3 (300/302)	99.1 (457/461)	ND
Piperacillin-tazobactam	94.3 (563/597)	92.2 (353/383)	93.4 (295/316)	89.4 (270/302)	93.9 (433/461)	0.379
SXT	91.6 (547/597)	90.1 (344/382)	88.9 (281/316)	88.7 (267/301)	88.5 (408/461)	0.064
<i>Streptococcus pneumoniae</i>						
Amoxicillin-clavulanate	99.1 (435/439)	96.8 (209/216)	98.8 (163/165)	97.6 (121/124)	99.1 (116/117)	ND
Ceftriaxone	100 (439/439)	99.1 (214/216)	100 (165/165)	100 (124/124)	99.1 (116/117)	ND
Clarithromycin	87.4 (383/438)	74.9 (161/215)	71.5 (118/165)	81.5 (101/124)	76.9 (90/117)	0.002
Levofloxacin	99.8 (438/439)	98.6 (213/216)	99.4 (162/163)	100 (124/124)	100 (117/117)	ND
Penicillin (IV) ^f	99.3 (436/439)	97.4 (188/193)	100 (165/165)	100 (124/124)	99.1 (116/117)	ND
Penicillin (oral) ^g	86.1 (378/439)	87.0 (168/193)	92.7 (153/165)	89.5 (111/124)	88.0 (103/117)	0.1719
SXT	89.6 (398/444)	84.7 (182/215)	83.4 (136/163)	87.1 (108/124)	82.1 (96/117)	0.032
Vancomycin	100 (445/445)	100 (216/216)	100 (163/163)	100 (124/124)	100 (117/117)	ND
<i>Staphylococcus epidermidis</i>						
Ceftobiprole ^c	100 (310/310)	100 (169/169)	100 (75/75)	100 (204/204)	99.4 (177/178)	ND
Clindamycin	55.8 (173/310)	54.5 (168/308)	60.0 (120/200)	64.7 (132/204)	66.9 (119/178)	0.002
Daptomycin	100 (310/310)	100 (308/308)	100 (200/200)	100 (204/204)	99.4 (177/178)	ND
Doxycycline	No data	96.4 (135/140)	96.0 (192/200)	96.6 (197/204)	91.0 (162/178)	0.035
Linezolid	100 (310/310)	100 (308/308)	100 (200/200)	100 (204/204)	100 (178/178)	ND
SXT	59.0 (183/310)	57.3 (177/309)	61.5 (123/200)	64.7 (132/204)	67.4 (120/178)	0.020
Vancomycin	100 (310/310)	100 (308/308)	100 (200/200)	100 (204/204)	100 (178/178)	ND

Continued

Table 5. Continued

Organism	% Susceptible (n/N)					P value
	2007–09	2010–12	2013–15	2016–18	2019–23	
<i>Enterococcus faecalis</i>						
Amoxicillin-clavulanate ^h	99.0 (309/312)	100 (208/208)	99.4 (162/163)	100 (141/141)	100 (132/132)	ND
Daptomycin	98.7 (378/383)	98.5 (202/205)	98.2 (160/163)	97.2 (137/141)	99.5 (184/185)	ND
Linezolid	99.5 (381/383)	94.1 (193/205)	99.4 (162/163)	100 (82/82) ⁱ	98.4 (182/185)	ND
Vancomycin	100 (383/383)	100 (205/205)	100 (163/163)	100 (141/141)	100 (185/185)	ND
<i>Pseudomonas aeruginosa</i>						
DTR ^{a,j}	5.5 (18/329)	2.6 (5/189)	1.9 (3/160)	3.3 (4/123)	2.0 (4/198)	ND
Ceftazidime	88.1 (290/329)	90.5 (171/189)	91.3 (146/160)	86.2 (106/123)	83.3 (165/198)	0.088
Ceftolozane-tazobactam	99.7 (328/329)	98.9 (187/189)	98.8 (158/160)	98.4 (121/123)	98.5 (195/198)	ND
Ciprofloxacin	71.7 (238/332)	84.1 (159/189)	81.9 (131/160)	94.3 (116/123)	91.9 (182/198)	<0.001
Colistin ^k	92.6 (262/283)	97.4 (184/189)	92.5 (148/160)	100 (123/123)	97.0 (192/198)	0.014
Meropenem	82.5 (274/332)	86.8 (164/189)	83.8 (134/160)	91.1 (112/123)	79.8 (158/198)	0.850
Piperacillin-tazobactam	88.6 (294/332)	91.0 (172/189)	90.0 (144/160)	91.9 (113/123)	87.4 (173/198)	0.875
Tobramycin	93.6 (308/329)	94.2 (178/189)	98.8 (158/160)	97.6 (120/123)	91.4 (181/198)	0.874
<i>Enterobacter cloacae</i>						
Ceftazidime	86.7 (91/105)	81.3 (100/123)	82.2 (83/101)	82.9 (107/129)	71.4 (100/140)	0.009
Ceftriaxone	77.7 (150/193)	76.4 (94/123)	74.3 (75/101)	80.6 (104/129)	70.0 (98/140)	0.286
Ciprofloxacin	92.2 (178/193)	90.2 (111/123)	93.1 (94/101)	96.1 (124/129)	91.4 (128/140)	0.592
Ertapenem	95.2 (157/165)	89.4 (110/123)	96.0 (97/101)	92.2 (119/129)	88.6 (124/140)	0.109
Gentamicin	98.4 (190/193)	96.7 (119/123)	98.0 (99/101)	98.4 (127/129)	95.7 (134/140)	ND
Meropenem	100 (193/193)	99.2 (122/123)	100 (101/101)	100 (129/129)	99.3 (139/140)	ND
Piperacillin-tazobactam	81.9 (158/193)	82.9 (102/123)	89.1 (90/101)	82.9 (107/129)	77.9 (109/140)	0.486
SXT	91.7 (177/193)	91.9 (113/123)	91.1 (92/101)	94.6 (122/129)	87.1 (122/140)	0.384
<i>Enterococcus faecium</i>						
Amoxicillin-clavulanate ^h	16.5 (22/133)	15.9 (18/113)	7.4 (7/95)	11.7 (11/94)	8.4 (10/119)	0.027
Daptomycin ^l	100 (152/152)	100 (112/112)	100 (95/95)	98.9 (93/93)	97.9 (142/145)	ND
Linezolid	97.4 (148/152)	83.0 (93/112)	93.7 (89/95)	84.0 (79/94)	90.3 (131/145)	0.084
Vancomycin	84.9 (129/152)	76.8 (86/112)	78.9 (75/95)	72.3 (68/94)	69.0 (100/145)	0.001

^aValues provided in the table indicate the percent of isolates with a particular resistance phenotype (e.g. ESBL, MRSA or DTR).

^bND, not done. Statistical analysis was not performed due to too few isolates testing not susceptible.

^cSXT, trimethoprim-sulfamethoxazole.

^dHealth Canada breakpoints were applied for ceftobiprole (MIC ≤4 mg/L is considered susceptible). While these breakpoints were used for both *S. aureus* and *S. epidermidis*, they are only approved for use by Health Canada versus *S. aureus* (i.e. breakpoints not defined for *S. epidermidis*).

^eTesting for inducible clindamycin resistance was not performed.

^fCLSI parenteral non-meningitis breakpoints were applied to determine IV penicillin susceptibility.

^gCLSI oral penicillin breakpoints were applied to determine oral penicillin susceptibility.

^hCLSI ampicillin breakpoints were used to determine susceptibility to amoxicillin-clavulanate.

ⁱData provided are for 2017 and 2018 only. No data available for isolates obtained from 2016.

^jDTR was defined as isolates testing not susceptible (intermediate or resistant) to all of the following antimicrobials: meropenem, piperacillin-tazobactam, ceftazidime and ciprofloxacin.

^kFor colistin versus *P. aeruginosa*, CLSI does not have a susceptible breakpoint. The percentages provided in the table reflect the proportion of *P. aeruginosa* isolates testing intermediately susceptible to colistin.

^lFor daptomycin versus *E. faecium*, CLSI does not have a susceptible breakpoint. The percentages provided in the table reflect the proportion of *E. faecium* isolates testing susceptible-dose dependent.

Discussion

The most common bloodstream pathogens recovered from patients admitted to or evaluated at Canadian hospitals between 2007 and 2023 in descending order of frequency were *E. coli*, *S. aureus*, *K. pneumoniae*, *S. epidermidis* and *S. pneumoniae*.

The data presented here are generally in keeping with other publications in the literature. Pfaller *et al.*¹⁸ evaluated the frequency of occurrence and antimicrobial susceptibility profile of bacterial pathogens recovered from the bloodstream of patients at 16 sentinel hospitals in the USA (10 sites), Europe (4 sites), Mexico

Table 6. Distribution of antimicrobial-resistant phenotypes among patients admitted to or evaluated at Canadian hospitals (CANWARD), stratified by ward type

Organism/Phenotype	% with phenotype (n/N)				
	Ward type ^a				
	ICU	Surgical ward	Medical ward	ER	Clinic
<i>E. coli</i> (% ESBL)	9.2 (51/557)	9.1 (36/395)	10.2 (214/2103)	6.6 (199/3006)	4.1 (13/317)
<i>S. aureus</i> (% MRSA)	22.8 (135/592)	25.5 (95/372)	23.2 (381/1645)	16.8 (267/1586)	16.0 (51/318)
<i>K. pneumoniae</i> (% ESBL)	8.0 (22/275)	3.3 (6/180)	7.3 (55/755)	2.7 (20/740)	3.6 (4/110)
<i>P. aeruginosa</i> (% DTR) ^b	7.3 (14/191)	6.7 (5/75)	2.3 (10/432)	1.2 (3/248)	3.5 (2/57)
<i>E. faecium</i> (% VRE) ^c	29.0 (47/162)	17.9 (12/67)	24.6 (67/272)	15.9 (11/69)	10.7 (3/28)

^aNo location data were provided for one *E. coli* and two *S. aureus* isolates. Vancomycin susceptibility was not determined for four *E. faecium* isolates.
^bDTR was defined as isolates testing not susceptible (intermediate or resistant) to all of the following antimicrobials: meropenem, piperacillin-tazobactam, ceftazidime and ciprofloxacin.
^cVRE were defined as *E. faecium* isolates having a vancomycin MIC of ≥ 8 mg/L.

(1 site) and South Korea (1 site) between 2012 and 2017. The five most common pathogens across all study years were *S. aureus*, *E. coli*, *Enterococcus* spp., *Klebsiella* spp. and coagulase-negative staphylococci.¹⁸ Ohnuma et al.² assessed the distribution of pathogens causing bloodstream infections among patients at 183 hospitals in the USA using data from the Premier Healthcare database (2016–20). The top five pathogens recovered from bacteraemic patients in this publication were *E. coli*, *S. aureus*, *Streptococcus* spp., *Klebsiella* spp. and *Enterococcus* spp.² Of note, coagulase-negative staphylococci were excluded from this analysis due to challenges in determining whether they represented true pathogens or contaminants. Variation in the rank order of pathogens across studies is potentially explained by differences in the study populations (including differences in the proportion of inpatients versus outpatients) and protocols.

While the rank order of the top five pathogens varied slightly over different time periods of our study, the organisms themselves were fairly consistent. Older data in the literature support the consistency of pathogens recovered from bacteraemic patients going back to at least the 1990s. Weinstein et al.⁵ evaluated 843 episodes of bacteraemia among 707 patients at three healthcare centres in the USA between 1992 and 1993. The five most common pathogens recovered from patients in their study were *S. aureus*, *E. coli*, coagulase-negative staphylococci, *K. pneumoniae* and *Enterococcus* spp.⁵

E. coli, *S. aureus* and *K. pneumoniae* were the pathogens most frequently recovered from the bloodstream of both inpatients and outpatients in our study. However, among outpatients (ER and clinic patients), a greater proportion of bloodstream infections were due to *S. pneumoniae* and beta-haemolytic streptococci (e.g. *S. agalactiae* and *S. pyogenes*) relative to inpatients. Among inpatients (ICU, medical wards and surgical wards), a relatively greater proportion of bloodstream infections were due to *E. faecium*, *P. aeruginosa*, *E. cloacae* and *C. albicans*. We hypothesize that differences in the pathogen distribution by ward location may be related to differences in the presenting clinical syndromes. We presume that bacteraemia due to community-acquired pneumonia and soft tissue infections

would be more common among outpatients and bacteraemia due to complicated post-operative infections, device-related infections (central line infections and urinary catheter infections), hospital-acquired pneumonia and ventilator-associated pneumonia would be more common among inpatients. It is also possible that inpatients would have received prior antimicrobial treatment, predisposing them to more antimicrobial-resistant organisms.

Over 17 years of the CANWARD study, we observed an increase in the proportion of *E. coli* and *K. pneumoniae* bloodstream isolates that harboured an extended-spectrum beta-lactamase enzyme. The increase in infections due to ESBL-producing *E. coli* described here has similarly been reported in the USA and other parts of the world.^{9–12} It is thought to be due, at least in part, to successful spread of the ST131 clone.¹¹ In a prior evaluation of 671 ESBL-producing *E. coli* clinical isolates obtained as a part of CANWARD (all specimen types, 2007–18), ST131 was the most frequent sequence type, accounting for 62.4% (419/671) of isolates.⁹ Further, CTX-M-type beta-lactamases were the dominant enzymes encountered, with 92% (617/671) of ESBL-producing *E. coli* possessing one of these (most commonly CTX-M-15, CTX-M-14 or CTX-M-27).⁹ We also observed an increase in the proportion of *E. faecium* isolates that were vancomycin resistant over time. An increase in bloodstream infections due to vancomycin-resistant Enterococci among Canadian patients has been previously reported by the Canadian Nosocomial Infection Surveillance Program.¹⁹ This may be linked to a change in infection control practices, including discontinuation of screening and isolation for VRE at some acute care facilities in Canada.¹⁹

There are several important limitations to this work that deserve attention. The sites participating in the CANWARD study and the number of bloodstream isolates requested from participating sites on an annual basis varied somewhat depending on the study year. This potentially may have influenced trends in pathogen distribution and antimicrobial susceptibility over time. There were no unified criteria across all study sites for determining clinical significance of isolates (e.g. requirement that bacteria considered common blood culture contaminants such as coagulase-negative staphylococci be recovered from at least

two sites). Rather, this attribution was made by the submitting site based on local criteria. As such, it cannot be excluded that some of the organisms described here were actually contaminants rather than true pathogens. In early study years, CANWARD received a number of bloodstream isolates that were simply identified as coagulase-negative staphylococci, while in later years coagulase-negative staphylococci were typically identified to the species level. We speculate that this is due to the widespread implementation of MALDI-TOF across Canada for organism identification over the last two decades. It is possible that some of the coagulase-negative staphylococci isolates may have in fact been *S. epidermidis*, thereby introducing some error into the number of *S. epidermidis* isolates reported here. Some clinically relevant antimicrobials were not included on the susceptibility panels used here due to space limitations. Susceptibility data were not available for certain antimicrobials versus a small number of isolates. Finally, clinical information on patients from whom the isolates were obtained was not collected. Hence, we were unable to stratify pathogen distribution by source of bacteraemia/presenting clinical syndrome.

In summary, the most common pathogens recovered from the bloodstream of patients admitted to or evaluated at Canadian hospitals between 2007 and 2023 were *E. coli*, *S. aureus*, *K. pneumoniae*, *S. epidermidis* and *S. pneumoniae*. The distribution of pathogens did not vary much over the course of the study, but some variation in the pathogen distribution was observed when comparing inpatients with outpatients. ESBL-producing *E. coli* and *K. pneumoniae* isolates were recovered more frequently in later study years, with a corresponding reduction over time in the susceptibility of third generation cephalosporins versus these species. An increase in the proportion of *E. faecium* bloodstream isolates that were resistant to vancomycin was also observed over time. However, the proportion of *S. aureus* isolates that were MRSA and *P. aeruginosa* isolates that had a DTR phenotype remained fairly stable over the course of the study. Knowledge of the common pathogens causing bloodstream infections and their susceptibility profiles may assist clinicians in selecting empiric antimicrobial therapy for patients presenting with severe sepsis, although local/institution level data remains preferable for guiding treatment decision.

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Transparency declarations

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