An analysis of 7 years of blood cultures: epidemiology, microbiology and mortality

N. Deborah Friedman [1], Tali Braun [2], Noga Fallach [2], Yehuda Carmeli [2,3]

Authors:
N. Deborah Friedman [1],
Departments of Medicine and Infectious Diseases,
Barwon Health,
Geelong, VIC, Australia

Tali Braun [2],
Division of Epidemiology,
Tel Aviv Sourasky Medical Center,
Tel Aviv, Israel, [2]

Noga Fallach [2],
Division of Epidemiology,
Tel Aviv Sourasky Medical Center,
Tel Aviv, Israel, [2]

Yehuda Carmeli [2,3]
Division of Epidemiology,
Tel Aviv Sourasky Medical Center,
Tel Aviv, Israel, [2]
National Center for Infection Control,
Ministry of Health,
State of Israel.[3]

Corresponding Author:
A/Professor N. Deborah Friedman, Departments of Medicine and Infectious Diseases, Barwon Health, Bellerine st, Geelong, VIC 3220, Australia
Ph: +61 3 4215 2340
Email: Deborahf@barwonhealth.org.au

Abstract

Background: We sought to analyze the epidemiology, microbiology and outcomes of medical patients with blood cultures collected.

Methods: Analysis of prospectively collected data from internal medicine admissions with and without blood cultures collected over 7 years at Tel Aviv Sourasky Medical Centre in Israel.

Results: Blood cultures were drawn in 35% of medical admissions. Twenty one percent of admissions with blood cultures collected had at least 1 positive blood culture, 6621 admissions (4%) had at least 1 bloodstream infection (BSI), while 5908 admissions (3.5%) yielded a blood culture contaminant. Seventy-three percent of BSIs were of community-onset, and 27% were hospital-acquired. The most common pathogens responsible for BSI were *Escherichia coli, Staphylococcus aureus,* and *Klebsiella pneumoniae*. Forty two percent of *S. aureus* BSI episodes were caused by methicillin-resistant strains, while among *K. pneumoniae* BSI episodes, 49.4% were caused by extended-spectrum β lactamase producers, and 5.6% were caused by carbapenem-resistant strains. Patients with BSI were of older age, had lower Norton risk scale scores and higher length of hospital stay, with 30-day and 1-year mortality rates approximately 2.5 times higher than the overall internal medicine patient population. Hospital-acquired BSI in particular carried a substantially higher length of stay and mortality.

Conclusions: Among medical admissions of median age 73 years, the incidence of BSI was 4%. Nearly three-quarters of BSIs were of community-onset. MRSA and ESBL-producers accounted for half of *S. aureus* and *K. pneumoniae* BSI episodes. Patients with BSI, particularly hospital-acquired BSI, spend longer in hospital and have substantially higher mortality.

Key Words: Blood culture, bacteremia, epidemiology, mortality, microbiology

Introduction

Dating from the early 1900s, pioneering work by Dr. Emanuel Libman, [1] contributed to our understanding of the use of blood cultures to aid in the diagnosis of febrile illnesses of uncertain origin. [2] In contemporary medicine blood cultures have an important role in the diagnosis of serious bloodstream infections (BSI), [3] which have an estimated mortality ranging from 14% to up to 50%, and are a major cause of morbidity and mortality worldwide. [4-7]

Reith and Squier in 1932 described blood culture contamination in 48 of 113 (42%) of positive cultures. [8] More contemporary studies in unselected hospitalized patients have shown that while only 7.5% to 12.4% of all blood culture sets are positive; of these, contamination rates range from as little as 0.6% to over 6%. [3, 9-12] Contaminated blood cultures result in longer hospitalizations, unnecessary treatment and testing and increased costs, [3, 12, 13] and remain an ongoing source of frustration for clinicians and microbiologists alike.

According to previously used classifications, nearly equal proportions of bacteremias were community-acquired and nosocomial. The acceptance of the entity of health care-associated infections (HCAIs), [14] has altered these proportions somewhat, such that bloodstream infections of community-onset (a combination of community-acquired and HCAIs) comprise 60-70% of bloodstream infections. [7, 14, 15]

The pretest probability of bacteremia is dependent upon the clinical syndrome; where conditions such as cellulitis have a low pretest probability of BSI (<5%), while pneumococcal pneumonia (20-30%), sepsis (30-50%) and bacterial meningitis (80-90%) have a higher pretest probability of BSI. [16-21] Among patients on an internal medicine service, the pretest probability of bacteremia has been estimated to be 5%. [20]

The Tel Aviv Sourasky Medical Center is a 1440-bed tertiary care teaching hospital in Tel Aviv, Israel which contains 9 internal medical units. This study was undertaken to describe the epidemiology, microbiology and outcomes of medical inpatients from which blood cultures were collected over a 7-year period.

Materials and Methods

Blood cultures

According to institutional protocol, when clinically indicated, two sets of aerobic blood cultures should be drawn with anaerobic cultures reserved for cases where suspicion exists for anaerobic infection. In this study only aerobic blood culture bottles were analyzed as the yield from anaerobic cultures is low, and most medical patients do not have anaerobic cultures collected.

Cultures are performed using BacT/ALERT® FA bottles incubated in the BacT/ALERT® Microbial Detection System (Biomerieux, Marcy-l'Etoile – France).

Data collection

Data were extracted from a hospital computerized database of prospectively collected clinical and microbiological data of adult internal medicine admissions from July 1st 2008 through June 30, 2015. Patients under 18 years of age and those with incomplete data were excluded from the analysis. Data collected included; total number of inpatient admissions, basic patient demographics, epidemiology and microbiology of positive cultures, length of hospital stay, Norton score, Charlson comorbidity index, results of aerobic blood cultures drawn, and 30 day and 1 year mortality.

Definitions

An episode of suspected bacteremia was defined as all blood cultures taken within 48 hours of consecutive blood cultures (i.e. any blood culture drawn ≥48 hours after

previous blood cultures was considered the indicator of a new episode). We internally validated the use of this definition on a subset of patients.

True bacteremia versus contamination: True bacteremia was defined as a recognized pathogen cultured from 1 or more blood cultures. For surveillance purposes each positive blood culture at this institution is assessed according to an electronic algorithm based on the number of cultures positive, and the organisms cultured as true-positives, or contaminants. [22]

BSI was defined according to the criteria for laboratory-confirmed BSI proposed by the Centers for Disease Control and Prevention (Atlanta, GA, USA).[22] Community-onset bacteremia included both community-acquired (CA) bacteremia and health care-associated (HCA) bacteremia. CA bacteremia was defined as a BSI detected at the time of hospital admission or within the 48 hours after hospital admission.

HCA bacteremia was defined as a BSI detected at the time of hospital admission or within 48 hours after hospital admission in a patient with significant exposure to healthcare.[14] Hospital-acquired bacteremia was defined as BSI detected after hospitalization for 48 hours or longer. The Norton risk scale was calculated on admission based on the following 5 domains (scored between 1 and 4 points); physical condition, mental condition, level of activity, mobility, and continence. The final score ranges between 5 and 20 points, where a score of 14 and below denotes a high-risk of developing a pressure ulcer. [23] The Charlson chronic comorbidity index was calculated for each patient at the time of admission. [24]

Data Analysis

Categorical variables were described using numbers and percentages. Continuous variables were described by median and interquartile range. Age, length of hospital stay, Norton risk scale, Charlson comorbidity index and mortality were calculated and compared for 3 separate populations; the entire admitted cohort, those without BSI (includes those patients with no blood cultures collected, and those with negative or contaminated blood cultures), and those with BSI. Wilcoxon rank sum test was performed to check for differences between patients with and without BSI. A Chi-square test was conducted to check for differences between patients with and without BSI in 30 day and 1 year mortality.

Ethical Considerations

This project was exempted from ethical approval as it was performed as a deidentified quality improvement project in the area of infection control, and patient medical records were not reviewed. Informed consent was not required in this retrospective cohort study where review of patient medical records was not undertaken.

Results

Demographics

Over the 7-year period from 2008-2015, there were a total of 167,783 admissions to internal medicine. There were 377 admissions of patients less than 18 years of age, and 42 admissions with incomplete data, which were excluded leaving a total of 167,364 admissions, for analysis. There were 85,569 male admissions (51.1%) and 81,795 female admissions (48.9%), which were evenly distributed through the 9 medical units. From these admissions, there were 59,263 admissions (35.4%) in which blood cultures were collected, and in 12,529 admissions there was at least 1 positive blood culture.

Comparisons of patient populations

The total cohort of internal medical admissions and the subset of admissions without BSI were similar with regards to age,

comorbid conditions and length of hospital stay. The median age of all admitted patients was 73 years (range 18-110), while patients with BSI were older and had lower Norton risk scale results. Charlson comorbidity index scores were the same for all patients. The length of hospital stay for patients with BSI was significantly higher than that of other internal medical admissions. (Table 1)

Table I. Characteristics of Internal Medicine patients with and without BSI

Characteristics	**Total Internal medicine admissions (n=167,364)**	**Internal medicine admissions without [a]BSI (n=160,743)**	**Internal medicine admissions with BSI (n=6621)**	***P* value for the difference between admissions with and without BSI**
Age Median (Years) (interquartile range, IQR)	73 (58-63)	73 (58-63)	78 (65-86)	<0.0001
Length of hospital stay (days) Median (IQR)	3.3 (1.8-7 days)	3.2 (1.8-6.7)	9 (5-21)	<0.0001
Norton risk scale Median (IQR)	18 (13-20)	18 (13-20)	14 (10-18)	<0.0001
Charlson comorbidity index Median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.8906

[a]BSI= bloodstream infection

Epidemiology of positive blood cultures

In 12,529 admissions with positive blood cultures there were 6621 admissions with a BSI (incidence of BSI 6621/167364, 4%), which included 7022 episodes of BSI and 11,583 blood culture bottles, which grew a true pathogen (62.2% of total 18,625 positive blood culture bottles). 5117 episodes (including 8340 blood culture bottles) were community-onset BSIs (73%), while 1905 episodes (including 3243 blood culture bottles) were hospital-acquired BSI episodes (27%). Hospital-acquired BSIs had significantly higher inpatient length of stay compared with community-onset BSIs. (Table 2)

There were 5908 admissions with blood cultures that yielded contaminants (incidence 5908/167364, 3.5%). This included 6496 episodes and 7042 blood culture bottles (37.8% of total 18,625 positive blood culture bottles), which were contaminants. The epidemiology of blood cultures yielding contaminants was almost indistinguishable from the epidemiology of blood cultures yielding a BSI. In the 6496 episodes of suspected bacteremia, which yielded contaminants, 4699 episodes (including 4954 blood culture bottles) were community-onset (72.3%), while 1797 (including 2088 blood culture bottles) were hospital-acquired episodes yielding conta-minants (27.7%). Furthermore, conta-minants comprised 7.9% of community-onset positive blood cultures, and 7.2% of hospital-acquired positive blood cultures.

Table II. Characteristics of Internal Medicine patients with BSI based on epidemiology

Characteristics	Internal Medicine admissions with BSI[a] (n=6621)[b]	Community-onset (CO) admissions with BSI (n=4978)	Hospital-acquired (HA) admissions with BSI (n=1504)	*P* value for the difference between admissions with CO and HA BSI
Age Median (Years) (interquartile range, IQR)	78 (65, 86)	79 (65, 86)	77 (65, 84.5)	NS
Length of hospital stay (days) Median (IQR)	9 (5, 21)	6.8 (4.1, 12.1)	30.6 (17.9, 55.8)	<0.001
Norton risk scale Median (IQR)	14 (10, 18)	14 (10, 19)	14 (10, 17)	NS
Charlson comorbidity index Median (IQR)	1 (0, 2)	0 (0, 2)	2 (0, 3)	NS
30-day mortality (%)	1665 (25.2%)	1117 (22.4%)	414 (27.5%)	<0.001
1-year mortality (%)	3435 (51.9%)	2246 (45.1%)	1091 (72.5%)	<0.001

[a]BSI= bloodstream infection, [b]139 admissions included both community-onset and hospital-acquired BSIs, and were excluded from this analysis, NS= not significant due to the calculated small effect size.

Mortality

Both the 30-day and 1-year mortality of admitted internal medicine patients increased in a stepwise fashion from all admissions to admissions with a BSI. (Table 3) Among all admitted patients the 30-day mortality was 10.6% while patients with a BSI had a 30-day mortality of 25.2%. (*P*<0.0001) The difference in 1-year mortality between patients with and without BSI was also statistically significant (51.9% versus 26.2%, P<0.0001). When analyzed by BSI epidemiology, hospital-acquired BSIs had significantly higher mortality compared with community-onset BSIs. (Table 2)

Microbiology of blood cultures

The most frequent pathogens isolated in BSIs were in descending order; *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. (Table 4) Susceptibility data revealed that 42% (366/871) of *S. aureus* BSI episodes were caused by strains resistant to methicillin, and that 10.5% (13/124) of *Enterococcus faecium* BSI episodes were caused by vancomycin-resistant strains. Penicillin resistance was present in 1.7% (3/179) of *Streptococcus pneumoniae* BSI episodes.

Among Gram-negative bacteria, ceftazidime resistance as a marker of EBSL-production was present in 49.4% (382/774) of *K. pneumoniae* BSI episodes, and 26.3% (531/2019) of *E.coli* BSI episodes. Carbapenem resistance was present in 67.5% (228/338) of *Acinetobacter baumanni* BSI episodes, 19.9% (86/433) of *Pseudomonas aeruginosa* BSI episodes and 5.6% (43/774) of *K. pneumoniae* BSI episodes.

Table III. Mortality of Internal Medicine patients with and without BSI

	All Internal medicine admissions (n=167,364)		**Admissions without BSI[a] (n=160,743)**		**Admissions with BSI (n=6621)**	
Medical Unit	One year Mortality (%)	30 Day Mortality (%)	One year Mortality (%)	30 day Mortality (%)	One Year Mortality (%)	30 Day Mortality (%)
1	2358 (12)	5748 (29.2)	2158 (11.3)	5368 (28.2)	200 (28.9)	380 (55)
2	1887 (9.8)	5101 (26.5)	1719 (9.3)	4724 (25.5)	168 (23.3)	377 (52.3)
3	2255 (12.5)	5122 (28.3)	2039 (11.7)	4744 (27.3)	216 (30.9)	378 (54.1)
4	1585 (8.8)	4674 (25.9)	1425 (8.2)	4283 (24.8)	160 (20.4)	391 (49.9)
5	1539 (9.3)	4333 (26.2)	1372 (8.7)	3947 (24.9)	167 (22.5)	386 (52)
6	1922 (10.1)	5213 (27.3)	1734 (9.5)	4815 (26.3)	188 (24.7)	398 (52.3)
7	2038 (10.6)	5078 (26.5)	1837 (10)	4695 (25.5)	201 (25.7)	383 (49)
8	1954 (10.3)	5137 (27)	1757 (9.6)	4728 (25.9)	197 (24.8)	409 (51.6)
9	2233 (12.2)	5214 (28.4)	2065 (11.7)	4881 (27.6)	168 (25.9)	333 (51.3)
Total	17,771 (10.6%)	45,620 (27.3%)	16,106 (10%)	42,185 (26.2%)	1665 (25.2%)	3435 (51.9%)

[a]BSI= bloodstream infection

Table IV. Epidemiology and Microbiology of 12,898 bacteria isolated from blood cultures

Organisms	**Community-Onset**	**Hospital-Acquired**
Gram Positive Bacteria	**4133**	**1104**
Staphylococcus aureus	1142	517
Enterococcus spp.	661	271
Coagulase-negative *Staphylococcus*	574	168
Streptococcus Group B	362	4
Streptococcus pneumonia	275	3
Streptococcus Group A	269	4
Other Beta hemolytic Streptococci	391	100
Streptococcus viridans group	140	3
Streptococcus gallolyticus	61	3
Streptococcus milleri group	44	5
Listeria monocytogenes	39	2
Streptococcus infantarius	30	
Streptococcus salivarius	26	
Granulicatella spp.	24	1
Other Streptococci	42	6
Streptococcus pasteurianus	12	9
Other Gram-positive bacteria	41	8
Gram Negative Bacteria	**5650**	**1642**
Escherichia coli	3009	231
Klebsiella pneumonia	813	423
Pseudomonas aeruginosa	391	258
Proteus spp.	310	131
Enterobacter spp.	178	59
Acinetobacter baumannii	149	279
Citrobacter spp.	85	16
Serratia spp.	57	43
Providencia spp.	56	88
Morganella spp.	55	17
Haemophilus influenza	54	4
Klebsiella oxytoca	53	8
Salmonella spp.	35	
Aeromonas spp.	29	4
Salmonella Typhi	28	
Stenotrophomonas maltophilia	17	8
Neisseria spp.	23	3
Burkholderia cepacia	15	6
Achromobacter spp.	10	4
Actinobacillus spp.	9	
Eikenella corrodens	4	
Kingella spp.	2	
Other Gram-negative bacteria	268	33
Fungi	**122**	**159**
Yeast spp.	114	157
Candida glabrata	2	
Aspergillus niger	1	
Candida albicans	1	
Candida krusei	1	1
Cryptococcus spp.	1	
Cryptococcus neoformans	1	
Microsporum	1	1
Other	65	23
Total contaminants	658 (7.8%)	235 (7.2%)
Total	9970	2928

Single blood cultures

There were 1306 BSI episodes (18.6% of total BSI episodes) where only a single blood culture was collected. Among monomicrobial bacteremias originating from a single collected blood culture bottle, there were 323 episodes of *Escherichia coli* BSI, 156 episodes of bacteremia due to *S. aureus*, 134 bacteremias due to *K. pneumoniae*, 81 episodes of BSI caused by *P.aeruginosa*, and 56 episodes of BSI caused by Yeast species. Notably there were also BSI caused by *Salmonella* spp., Group D *Streptococcus, Listeria* spp., *Capnocytophagia* spp., *Pasteurella* spp., and *Neisseria* spp. The majority of polymicrobial BSIs from single blood cultures contained 2 or more gastrointestinal organisms in combination.

In 176 of 1306 BSI episodes (13.5%) originating from a single blood culture, the patient died within 48 hours. The microbiological causes for these deaths included; *E. coli* (30), *A. baumanii* (27), *K. pneumoniae* (24), *S. aureus* (20), *P. aeruginosa* (19), and *Enterococcus* spp. (15). In 72 episodes (5.5%) another blood culture was collected, within 72 hours of the single blood culture (and therefore was considered part of a different episode of suspected bacteremia), and in 58 episodes (4.4%) patients were discharged from the hospital within 48 hours of a single positive blood culture. In the remaining 1176 bacteremic patients (90%) there was no reason identified for further blood cultures not being collected.

Discussion

In this study we determined that 4% of internal medicine admissions had a BSI. This rate is lower than that found in Leibovici's study from 1991, where 21% of selected internal medicine patients with febrile illness were bacteremic.[25] Our bacteremia rate is in keeping both with the moderately low (5%) pretest probability of bacteremia estimated by Aronson in the 1980s for medical patients, and is roughly in keeping with other positive blood culture rates in unselected patient populations. [7, 9-11, 20]

The rate of contaminants isolated from blood cultures in this study was nearly 40% of positive blood cultures, which is similar to previous estimates. [7, 9-11] Of concern, contaminants have been shown to increase costs substantially, such that the ultimate costs may greatly exceed those of the test itself.[3, 13] Blood culture contaminants have a major effect on unnecessary or broad-spectrum antibiotic use. [3] A blood culture cohort study investigating the isolation of coagulase-negative staphylococci found that physicians used antibiotics to treat nearly half of patients with contaminated blood cultures, with vancomycin being misused in 34% of patients. [26]

The mortality of patients without BSI admitted to internal medicine units in this study was demonstrated to be approximately 10% within 30 days and 26% over 1 year. This is similar to hospital mortality rates for all admitted patients, which has been measured at approximately 11%. [27] In this study, mortality increased substantially for patients with BSI where the 30-day mortality was 2.5 times higher compared with the overall admitted population. This is not unexpected. The 30-day mortality of bloodstream infections due to ESBL-producing *E. coli* and *K. pneumoniae* has been shown to be 19.4% and 31.8% respectively. [28, 29] In addition, in this study, patients with HA BSI had a significantly higher mortality than patients with community-onset BSI. It has been demonstrated that community-acquired BSI due to *S. aureus* carries a crude mortality of 14%, [30] and a 28 day mortality of up to 27%, [31] while nosocomial BSIs have been shown to have crude mortality rates of 34-50% during hospitalization. [30-32]

The epidemiological results from this study reveal that among a large cohort of patients with BSI, nearly three-quarters of

infections have their onset in the community. Previous studies of smaller cohorts from USA and Israel have similarly shown that infections of community-onset comprise 60-70% of bloodstream infections. [7, 14, 15] In contrast, in their research, Weinstein and colleagues demonstrated in the 1980s that two-thirds of BSIs were nosocomial, while in the 1990s the proportion of nosocomial BSIs had dropped to 52%. [6, 7] The increasing shift of healthcare delivery to the community has dramatically increased the proportion of infections, which are of community-onset.

The microbiological results arising from this study are also of interest. We found that the most common organisms causing BSI among internal medical inpatients were *E. coli*, *S. aureus* and *K. pneumoniae*. These results are identical to the results presented by Weinstein et al in 1997, indicative that little has changed in terms of the most common pathogens isolated from blood cultures. [6] However, we also identified that over 40% of episodes of BSI due to *S. aureus* were caused by methicillin-resistant strains, and that nearly 50% of *K.pneumoniae* BSI episodes were caused by ESBL-producing strains. These MRSA rates are lower than those found in South Korea, similar to those found in Greece, but higher than the average of 31% for European countries. [33, 34] A multifaceted prevention program, such as the one used in Geneva, or the United Kingdom's program involving mandatory reporting of MRSA bacteremia rates offer some optimism of methods that may successfully tackle high rates of MRSA among *S. aureus*. [35, 36] The high rates of ESBLs in this study, particularly among *E.coli* and *K.pneumoniae*, are of great microbiological and clinical importance, [37] and are in keeping with previously published Israeli experience with increasing Gram-negative resistance. [38] These rates of ESBL-producing bacteria are similar to rates seen in South Korea, Chile and Brazil but higher than rates reported by the CDC among health care-associated infections. [33, 39, 40]

In this study, we also analyzed the collection of and results arising from single aerobic blood cultures. Approximately 13% of patients with bacteremia detected on a single culture died within 48 hours of their single blood culture, and first positive blood cultures yielding pathogens such as *S. aureus* or yeast were largely not followed by collecting further cultures. These results point to a system problem in the practice of blood culture collection, which requires attention to promote change. While single blood cultures may detect >90% of BSI episodes, [7] they are insufficiently sensitive for detecting some infections, and are difficult to interpret. [41]

There are limitations to this study. Given the large volume of data, the medical records of patients were not examined. Therefore clinical details that may be relevant to this population were not analyzed. We utilized both the Charlson comorbidity index and the Norton scale to measure the comorbidities of admitted internal medicine patients. Without examining medical records we are unable to explain why the Charlson comorbidity index results did not reveal differences between our patient populations where there were clear differences in mortality. The Charlson index scores have previously been shown to calibrate poorly with the outcome of antibiotic-resistant bacterial infections, [42] which may relate to the fact that the comorbid conditions used in assigning points are not directly relevant to patients with BSIs. [24]

Nonetheless, we found that patients with BSI had lower Norton scales. Functional measures are known to be strong predictors of 90 day and 2-year mortality after hospitalization, [43] and while the Norton risk scale was created to predict the risk of developing a pressure area, the Norton risk scale on admission has also been shown to predict mortality within 1 year or more. [44]

In a population of internal medical inpatients, 73% of BSIs are of community-onset and the mortality of BSI, especially

hospital-acquired BSI among predominantly elderly patients is high. The collection of single blood cultures is not uncommon in this patient population and poses a risk to patients. The most common pathogens responsible for BSI were *E. coli, S. aureus* and *K. pneumoniae.*

Declaration of interest:

There are no conflicts of interest relevant to this research. There was no funding for this research

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