Risk factors for recurrence and death after bacteraemia: a population-based study

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Abstract

Although most bacteraemic outcome studies have focused on mortality, a repeated episode(s) is another important outcome of bacteraemia. We sought to characterize patient factors and microbial species associated with recurrence and death from bacteraemia. Population-based surveillance for bacteraemia was conducted in a Canadian health region during 2000–2008. Episodes of bacteraemia were extracted and characterized. Transition intensities of both recurrence and death were estimated by separate multivariate Cox proportional hazards models. We identified 9713 patients with incident episodes of bacteraemia. Within 1 year: 892 (9.2%) had recurrent bacteraemia, 2401 (24.7%) had died without a recurrent episode and 330 (3.4%) had died after a recurrent episode. Independent risk factors for recurrence within 1 year (hazard ratio; 95% confidence interval) were: increasing Charlson comorbidity scores (score 1–2: 2.2; 1.8–2.7 and score 3+: 3.4; 2.8–4.2), origin of infection (nosocomial: 2.1; 1.8–2.6 and healthcare-associated: 2.4; 2.0–2.8), microorganism (polymicrobial: 1.5; 1.2–2.0 and fungal: 2.8; 1.9–4.2) and focus of infection (verified urogenital: 0.4; 0.3–0.6). Independent risk factors for death within 1 year included: a recurrent bacteraemic episode 3.6 (3.1–4.0), increasing age and different foci of infection. This study identifies patient groups at risk of having a recurrent episode and dying from these infections. It adds recurrent bacteraemia as an independent risk factor of death within 1 year and may help to target patients for prevention or changes in management.

Keywords: Bacteraemia, bloodstream infection, epidemiology, mortality, population-based, recurrence, risk factors
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Introduction

Bacteraemia is a leading cause worldwide of morbidity and mortality [1]. Bacteraemic outcome studies have focused on predictors of mortality, and factors predisposing individuals to bacteraemia are well described in many different settings [2–4]. However, a repeated bacteraemic episode(s), after surviving the primary infection, is another important outcome. Several previous hospital-based studies have investigated this entity and found that recurrence rates range between 2% and 17%, and that mortality is not higher [5–9]. These studies are limited by the inclusion of highly selected patients or microorganisms and so may not be widely generalizable.

Population-based surveillance is widely recognized as an optimal means for establishing the epidemiology of an infectious disease. To our knowledge there are only two population-based studies that have investigated recurrent bacteraemia. The first comprised 8672 adults in Denmark with incident bacteraemia; it reported a rate of recurrence of 12% and identified the main risk factors for recurrence as: bacteraemia that was healthcare-associated or nosocomial; polymicrobial bacteraemia or fungaemia; patients with Charlson comorbidity index scores of ≥1; an infectious focus

either unknown or in the gastrointestinal tract or liver/biliary tract, endocarditis, or related to an intravenous catheter [10]. Another recent study, of Gram-negative bloodstream infections from the United States in 944 adults and children, found recurrence rates after 1, 5 and 10 years of 6%, 9% and 15%, respectively [11].

There is a limited body of literature reporting on the epidemiology of recurrent bacteraemia in non-selected populations and reports from other jurisdictions are needed. The objectives of this study were to determine (i) the incidence of all recurrent bacteraemias occurring in a large, non-selected population in Canada, and (ii) independent risk factors for both recurrence and death.

Methods

Study population

The Calgary Zone of Alberta Health Services provides all publicly funded medical and surgical care to the residents of the cities of Calgary and Airdrie and a large surrounding area (population 1.2 million) in the Province of Alberta, Canada. Only patients requiring liver, heart or lung transplantation surgery are routinely referred elsewhere for care. All persons who resided in the Calgary Zone and who developed a bacteraemic infection during 2000–2007 were included.

The Conjoint Health Research Ethics Board at the University of Calgary approved this study and waived the requirement for individual written informed consent.

Study protocol

We used an active, population-based surveillance cohort design. All data were obtained using the Electronic Surveillance System (ESS) [12]. This database contains all patients with bacteraemia in the Calgary Zone and has been developed through a linkage between the regional and provincial microbiology, hospital, disease registry and vital statistics databases. Demographic, microbiological and mortality outcome data are available for all patients and further information on comorbidities are available for those admitted to any of the main regional acute-care centres.

Definitions

The Electronic Surveillance System defines an episode of bacteraemia as growth of pathogenic bacteria or fungus from at least one aerobic/anaerobic set of blood culture bottles; for common skin contaminants including diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, viridans group streptococci and micrococci, isolation of the organism from at least two different blood samples within a 5-day period was required to fulfil the criteria for bacteraemia [13]. Performance of blood culture was at the discretion of the attending medical team and was not dictated by study protocol.

We defined an incident episode of bacteraemia by isolation of one or more clinically important pathogens within a 48-h period. Re-isolation of the same species within 30 days was considered to be from the same episode [10,14–16]. Recurrent episodes of bacteraemia were those where a different species was isolated more than 48 h after the index episode or the same species was isolated more than 30 days after the index episode. The incident non-recurrent episodes and the incident recurrent episodes refer to the initial bacteraemic episode with or without later recurrence, respectively. The second bacteraemic episode is referred to as the recurrent episode.

Polymicrobial bacteraemia was defined as an episode with more than one clinically important blood culture isolate detected within 48 h [15].

Nosocomial bacteraemias were those with incident positive culture collected ≥48 h after hospital admission or within 48 h of discharge. Community-onset infections were those where incident positive culture was obtained within 48 h of admission or >48 h after discharge from hospital [17]. Community-onset bacteraemias were further classified as community-acquired or healthcare-associated according to a modification of the definitions of Friedman *et al.* [12,18]. The focus of infection was based on microbiological findings from other sites within 48-h of the drawing of the blood culture. Comorbidities were determined and Charlson score was calculated using discharge data by application of a previously validated algorithm [19,20].

Statistical analyses

We pursued two different analysis strategies. The focus of the first analysis was the separate evaluation of covariate effects on both recurrence and death (before recurrence). To that extent, transition intensities (cause-specific hazards) for both recurrence and death were estimated by separate multivariate Cox proportional hazards models (Fig. 1). The second analysis modelled covariate effects on mortality in a multivariate Cox proportional hazards model where recurrence was included as a time-dependent covariate. The following prognostic factors (at incident bacteraemia) were considered for modelling the (separate) cause-specific hazards (Table 1): age (categories: 0–8, 19–64, 65–79, 80+ years), Charlson comorbidity index (categorized: 0, 1–2, 3+, unknown), sex, origin of infection (categories: community-acquired, nosocomial, healthcare-associated), microorganism(s) (monomicrobial Gram-positive, mo-

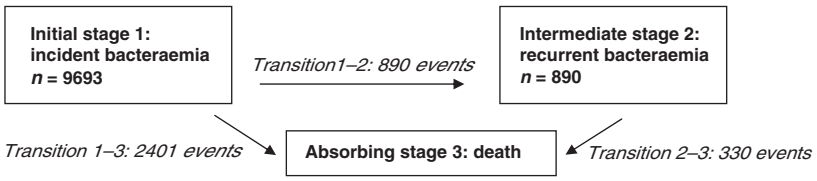

FIG. 1. Unidirectional illness–death model for transition intensities; all transitions censored at 1 year from initial stage.

TABLE 1. Baseline characteristics of patients with incident episodes of bacteraemia

Prognostic factor		*n*	%
Age (at incident bacteraemia)	0–18[a]	935	10
	19–64	4210	43
	65–79	2727	28
	80+	1837	19
	Unknown/missing	4 (excluded)	0
Charlson comorbidity index (at incident bacteraemia)	0[a]	3250	33
	1–2	2907	30
	3+	2278	23
	Unknown/missing	1278 (separate category)	13
Sex	Female[a]	4452	46
	Male	5259	54
	Unknown/missing	2 (excluded)	0
Origin of infection (at incident bacteraemia)	Community-acquired[a]	4370	45
	Nosocomial	2344	24
	Healthcare-associated	2999	31
Microorganism(s) (at incident bacteraemia)	Monomicrobial Gram-negative[a]	3825	39
	Monomicrobial Gram-positive	4591	47
	Monomicrobial anaerobic	501	5
	Polymicrobial	632	7
	Fungal	150	2
	Unknown/missing	14 (excluded)	0
Focus of infection (at incident bacteraemia)	Unverified[a]	6990	72
	Verified UG	1583	16
	Verified non-UG	1005	10
	Multifocal	135	1

In all, 892 patients had recurrent bacteraemia within 1 year, 2401 patients died before experiencing recurrence and 330 patients died after recurrence (within 1 year).
UG, urogenital.
[a]Refers to reference category.

nomicrobial Gram-negative, monomicrobial anaerobic, polymicrobial, fungal and unknown) and focus (unverified, verified urogenital (UG), verified non-UG and multifocal). The estimated effects of prognostic factors were expressed as hazard ratios (HRs) and reported with 95% CI. As a consequence of the missing values, 20 observations were excluded from the Cox regression analysis, leaving 9693 patients with incident bacteraemia—890 with recurrent bacteraemia. Statistical analyses were performed using STATA® (version 11.1/SE; StataCorp, College Station, TX, USA).

Results

During 2000–2007, a total of 9713 patients had incident episodes of bloodstream infection; 892 (9%) had recurrent episodes within 1 year. The baseline characteristics of patients with incident episodes of bacteraemia are displayed in Table 1. The median age of the patients was 62 years (interquartile range, 43–76 years) with no significant difference between the incident episodes with no later recurrence and the incident episodes that later recurred.

Recurrent episodes were found in 834 adult patients and 58 children (<18 years). Of the 892 patients who experienced recurrence before death within 1 year, 95 (11%), 204 (23%), 528 (59%), 710 (80%) and 804 (90%) had a recurrent episode within 10, 30, 90, 180 and 270 days, respectively.

Monomicrobial bacteraemia accounted for 8268 (94%) of the incident episodes with no later recurrence, 813 (91%) of the incident episodes that later recurred and 819 (92%) of the recurrent episodes, respectively. The proportion of fungaemia was higher in recurrent episodes (6%) compared with incident episodes that later recurred (3%) and incident episodes with no later recurrence (1%), respectively. Incident episodes with no later recurrence displayed more monomicrobial Gram-negative isolates compared with incident episodes that later recurred. Incident episodes that later recurred displayed more monomicrobial anaerobic isolates compared with recurrent episodes, but fewer monomicrobial Gram-positive isolates. In 751 patients (84%) both episodes were monomicrobial, and the same microorganism was retrieved in both episodes in 273 patients (273/751, 36%). Among these 273 paired episodes the most frequent microorganisms were *Staphylococcus aureus* (90/273, 33%),

coagulase-negative staphylococci (66/273, 24%) and *Escherichia coli* (55/273, 20%).

A number of selected conditions were identified as predictors for acquiring a recurrent episode within 1 year, and these are shown in Table 2. Healthcare-associated bacteraemia, Charlson comorbidity index score of ≥ 3 and fungaemia were the most important predictors. Among 29 patients with recurrence and fungaemia at the incident episode, *Candida albicans* was the most prevalent microorganism, accounting for 38% of the episodes, followed by *Candida glabrata* (35%). The remaining eight episodes were the result of the following microorganisms: *Candida kefyr*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans* and *Saccharomyces cerevisiae*. Monomicrobial anaerobic bacteraemia and a verified UG focus of infection lowered the risks of recurrence in relation to the reference category. Sex and age of the patient were not important predictors of recurrence.

In the Cox regression analysis for mortality (Table 3), we found increasing age and increasing Charlson comorbidity index score to be important predictors of death. Also, factors regarding the origin of infection, the focus of infection and the microorganisms involved were independent predictors for death. A verified UG focus of infection had a lower risk of death than the reference category.

Adding recurrence as a time-dependent variable to the Cox regression analysis for mortality did not change the hazard ratios of the different prognostic factors notably. But, having experienced a recurrent episode of bacteraemia was also a strong independent predictor for death within 1 year (Table 4).

Discussion

In this article, we report novel population-based data describing the recurrence rates and risk factors for recurrence and death of bacteraemia in a large Canadian population. We found that 9% of patients with bacteraemia experienced a recurrence, of which 59% occurred within 3 months. Similar findings have been reported in the two contemporary studies investigating the epidemiology of recurrent bacteraemia in non-selected populations—Jensen *et al.* [10] and Al-Hasan *et al.* [11] (Gram-negative bacteraemia)—with which we were able to make a comparison.

Our results are also in accordance with the greater number of non-population-based studies. Studies of Miller and Farr [21], and Capdevila *et al.* [22] found recurrent bacteraemia rates of 10% and 9%, respectively. Wendt *et al.* [23], and Mylotte and McDermott [24] both reported recurrence rates in patients with recurrent Gram-negative bacteraemia comparable with ours (13% and 10%, respectively). Others have studied recurrences only in selected pathogens [5–8,25,26]. Definitions of recurrence and follow-up periods differ among these studies. Our follow up of 1 year was identical to that used by Jensen *et al.* [10], but most previous studies [5,22–24] applied short follow-up periods, albeit 3-months or even 10 years of follow up have also been applied [11,25,26]. Unfortunately, no gold standard to determine the follow-up period exists. What determines the optimal follow-up period is probably the weight of factors that may significantly change the longevity of the host such as comorbidity and extreme age. Therefore, differences in

TABLE 2. Risks of recurrent bacteraemia within 1 year in 9693 patients with bacteraemia (890 events)

Prognostic factor		HR (95% CI)	p-value
Age (at incident bacteraemia)	0–18[a]	1	
	19–64	1.30 (0.98–1.72)	0.069
	65–79	1.35 (1.01–1.81)	0.044
	80–	0.97 (0.70–1.35)	0.867
Charlson comorbidity index (at incident bacteraemia)	0[a]	1	
	1–2	2.17 (1.77–2.65)	<0.001
	3+	3.40 (2.77–4.19)	<0.001
	Unknown/missing	2.61 (2.06–3.30)	<0.001
Sex	Female[a]	1	
	Male	1.11 (0.97–1.27)	0.132
Origin of infection (at incident bacteraemia)	Community-acquired[a]	1	
	Nosocomial	2.14 (1.77–2.59)	<0.001
	Healthcare-associated	2.37 (2.00–2.80)	<0.001
Microorganism(s) (at incident bacteraemia)	Monomicrobial Gram-negative[a]	1	
	Monomicrobial Gram-positive	1.17 (1.00–1.38)	0.049
	Monomicrobial anaerobic	0.53 (0.24–0.83)	0.005
	Polymicrobial	1.52 (1.18–1.97)	0.001
	Fungal	2.82 (1.90–4.18)	<0.001
Focus of infection (at incident bacteraemia)	Unverified[a]	1	
	Verified UG	0.43 (0.33–0.56)	<0.001
	Verified non-UG	0.97 (0.79–1.20)	0.799
	Multifocal	1.28 (0.78–2.10)	0.337

HR, hazard ratio; CI, confidence interval; UG, urogenital.
[a]Refers to reference category.

TABLE 3. Risks of mortality without recurrence within 1 year in 9693 patients with bacteraemia (2398 events)

Prognostic factor		HR (95% CI)	p-value
Age (at incident bacteraemia)	0–18[a]	1	
	19–64	1.59 (1.21–2.10)	0.001
	65–79	2.74 (2.08–3.60)	<0.001
	80–	4.24 (3.22–5.59)	<0.001
Charlson comorbidity index (at incident bacteraemia)	0[a]	1	
	1–2	2.76 (2.40–3.18)	<0.001
	3+	5.27 (4.58–6.06)	<0.001
	Unknown/missing	1.46 (1.18–1.80)	<0.001
Sex	Female[a]	1	
	Male	0.97 (0.89–1.05)	0.431
Origin of infection (at incident bacteraemia)	Community-acquired[a]	1	
	Nosocomial	2.12 (1.90–2.38)	<0.001
	Healthcare-associated	1.79 (1.61–2.00)	<0.001
Microorganism(s) (at incident bacteraemia)	Monomicrobial Gram-negative[a]	1	
	Monomicrobial Gram-positive	0.95 (0.86–1.04)	0.276
	Monomicrobial anaerobic	1.37 (1.16–1.63)	<0.001
	Polymicrobial	1.29 (1.11–1.50)	0.001
	Fungal	1.66 (1.29–2.13)	<0.001
Focus of infection (at incident bacteraemia)	Unverified[a]	1	
	Verified UG	0.61 (0.54–0.70)	<0.001
	Verified non-UG	1.28 (1.13–1.45)	<0.001
	Multifocal	1.62 (1.23–2.15)	0.001

HR, hazard ratio; CI, confidence interval; UG, urogenital.
[a]Refers to reference category.

TABLE 4. Risks of mortality within 1 year with recurrence as time-dependent variable in 9693 patients with bacteraemia (2728 events)

Prognostic factor		HR (95% CI)	p-value
Age (at incident bacteraemia)	0–18[a]	1	
	19–64	1.54 (1.21–1.96)	<0.001
	65–79	2.58 (2.02–3.28)	<0.001
	80–	3.91 (3.07–4.99)	<0.001
Charlson comorbidity index (at incident bacteraemia)	0[a]	1	
	1–2	2.70 (2.36–3.08)	<0.001
	3+	4.96 (4.35–5.66)	<0.001
	Unknown/missing	1.45 (1.19–1.76)	<0.001
Sex	Female[a]	1	
	Male	0.98 (0.91–1.06)	0.586
Origin of infection (at incident bacteraemia)	Community-acquired[a]	1	
	Nosocomial	2.04 (1.83–2.28)	<0.001
	Healthcare-associated	1.81 (1.63–2.01)	<0.001
Microorganism(s) (at incident bacteraemia)	Monomicrobial Gram-negative[a]	1	
	Monomicrobial Gram-positive	0.93 (0.83–1.02)	0.116
	Monomicrobial anaerobic	1.31 (1.11–1.54)	0.001
	Polymicrobial	1.27 (1.10–1.47)	0.001
	Fungal	1.48 (1.17–1.86)	0.001
Focus of infection (at incident bacteraemia)	Unverified[a]	1	
	Verified UG	0.61 (0.54–0.70)	<0.001
	Verified non-UG	1.26 (1.12–1.42)	<0.001
	Multifocal	1.46 (1.12–1.91)	0.005
Recurrent bacteraemia	Within 1 year	3.55 (3.13–4.02)	<0.001

HR, hazard ratio; CI, confidence interval; UG, urogenital.
[a]Refers to reference category.

terminology and follow-up periods may influence the recurrence rates.

Different studies have shown that patients with serious underlying conditions are at greater risk of recurrence. Recurrent *Streptococcus pneumoniae* and Gram-negative bacteraemia have been associated with immune deficiency caused by, for example, cancer, congenital B-cell or T-cell defects, and human immunodeficiency virus infection [5,24]. Jensen *et al.* [10] found a Charlson comorbidity index score of ≥ 1 and a focus of infection in the abdomen, endocarditis, or an unknown focus to be independent risk factors of recurrence. They also described characteristics of the microbiological findings and the iatrogenic factors as important predictors of recurrent episodes. Our current data support these findings. We identified several patient and microorganism characteristics as well as the iatrogenic factor as independent risk factors of recurrent bacteraemia (Table 2). For example, a patient with a nosocomial origin, an unverified focus of infection and a Charlson score of 1–2 had a more than tenfold increased HR for recurrent bacteraemia compared with a patient with a community-acquired origin, a verified UG focus of infection and a Charlson score of 0.

Previous population-based studies of bacteraemia have identified advancing age, comorbidities, focus of infection

other than UG, polymicrobial infection, nosocomial acquisition and inappropriate empirical antibiotic treatment as being associated with death [16,27,28]. Similar results have been documented in a few contemporary population-based studies of bacteraemia attributed to one specific microorganism [4,29,30]. Our observation of risk factors of death within 1 year compares with (the trends of) the adjusted ORs of 30-day case fatality found by Pedersen *et al.* [16], the adjusted 30-day Mortality Rate Ratios found by Søgaard *et al.* [28] and the adjusted 180-day Mortality Rate Ratios found by Hanon *et al.* [27] as well as the adjusted ORs of in-hospital death found in the studies of bacteraemia attributed to one specific microorganism [4,29,30]. Moreover, our present study is important in that we add recurrent bacteraemia as a strong independent risk factor (HR 3.6; 95% CI 3.1–4.0) of death within 1 year (Table 4).

Though we did not investigate incidence rates in this study, recent population-based studies of bacteraemia have estimated incidence rates of bacteraemia to be between 125 per 100 000 person-years in Finland [31] to 156 per 100 000 person-years in females and 237 per 100 000 person-years in males in Olmsted County, MN [32]. From Northern Denmark, Søgaard *et al.* [33] recently reported an increase of the overall annual incidence rate of 46%, from 114 to 166 episodes per 100 000 person-years from 1992 to 2006. In Calgary, Canada, Laupland *et al.* [34] compared incidence and in-hospital case fatality of community-acquired bacteraemia (82/100 000; 13%) with incidence and in-hospital case fatality after trauma (70/100 000; 12%), after myocardial infarction (161/100 000; 9%) and after stroke (150/100 000; 13%) during 2000–2004.

Our study has several characteristics that make its results robust. The study had a population-based design with public hospitals accounting for >99% of all hospital admissions. In addition, our cohort was much larger than those of "selected population" studies (341–1205 patients). Finally, we used a strict set of definitions and ensured almost complete follow up with the exception of Charlson comorbidity index scores.

Although a rigorous population-based design was used, there are some study limitations that merit discussion. Only patients who had a positive blood culture were included in this study. Patients who may have had bacteraemia but from whom no sample was submitted for culture would not have been identified in this study. The rates presented should therefore be viewed as conservative estimates of all true bacteraemias in the population studied. Another limitation is that each patient was not clinically assessed to determine a potential focus of infection; this was based, crudely, on the presence of positive cultures from other sites. Therefore, we were not able to elucidate to what extend reduction in the rates of, for example, catheter-related bacteraemias had occurred [35]. Third, no clinical information was available to evaluate the clinical state of the patients at the time of admission or the development of any clinical complications such as septic shock, disseminated intravascular coagulation, renal failure, or respiratory failure in connection with the incident bacteraemic episode. Finally, data on antimicrobial chemotherapy and details of dosing as well as timing of and duration of therapy were not available. This is potentially a major factor in determining recurrence and certainly in determining mortality.

Future research should include detailed information on antimicrobial chemotherapy (timing of the empirical treatment, dosage regimens and duration of therapy) to extend our understanding of predictors of recurrent bacteraemia as well as predictors of death.

In summary, this study confirms the major burden of recurrence and mortality associated with bacteraemia and identifies patient-groups at increased risk of having a recurrent episode and dying from these infections. This study also adds recurrent bacteraemia as an independent risk factor of death within 1 year.

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Transparency Declaration

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