Population-Based Epidemiology and Microbiology of Community-Onset Bloodstream Infections

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SUMMARY

Bloodstream infection (BSI) is a major cause of infectious disease morbidity and mortality worldwide. While a positive blood culture is mandatory for establishment of the presence of a BSI, there are a number of determinants that must be considered for establishment of this entity. Community-onset BSIs are those that occur in outpatients or are first identified <48 h after admission to hospital, and they may be subclassified further as health care associated, when they occur in patients with significant prior health care exposure, or community associated, in other cases. The most common causes of community-onset BSI include *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. Antimicrobial-resistant organisms, including methicillin-resistant *Staphylococcus aureus* and extended-spectrum β-lactamase/metallo-β-lactamase/carbapenemase-producing *Enterobacteriaceae*, have emerged as important etiologies of community-onset BSI.

INTRODUCTION

Bloodstream infection (BSI) is a major cause of infectious disease morbidity and mortality worldwide (1–15). Due to a number of determinants, not limited to changing population de-

TABLE 1 Definitions of bloodstream infection and associated entities

Entity	Definition
Contamination of blood cultures	Blood cultures are positive for growth due to organisms that were not present in the bloodstream
Bacteremia	Presence of viable bacteria in the blood; blood cultures positive for bacterial growth where contamination has been ruled out
Fungemia	Presence of viable fungi in the blood; blood cultures positive for fungal growth where contamination has been ruled out
Transient bacteremia/fungemia	Brief episode of bacteremia/fungemia that is not associated with infection
Bloodstream infection	Bacteremia/fungemia that is associated with infection
Hospital-onset bloodstream infection	Bloodstream infection that is first identified (culture drawn) $\geq$48 h after hospital admission and within 48 h following hospital discharge
Community-onset bloodstream infection	Bloodstream infection occurring in an outpatient or first identified (culture drawn) <48 h following admission to hospital
Health care-associated community-onset bloodstream infection	Community-onset bloodstream infection associated with significant prior health care exposure (as evidenced by recent hospitalization, specialized in-home medical services, care in a hospital-based clinic or hemodialysis unit, or residence in a nursing home)
Community-associated community-onset bloodstream infection	Community-onset bloodstream infection not fulfilling criteria for health care-associated infection
Polymicrobial bloodstream infection	Episode of bloodstream infection associated with two or more different organisms isolated within 48 h of each other

mographics, shifts in health care delivery models, and increasing globalization, the epidemiology of community-onset BSI has been changing in recent decades. In addition, antimicrobial-resistant organisms, most notably methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamase (ESBL)/metallo-β-lactamase-producing *Enterobacteriaceae*, have emerged as important etiologies of community-onset BSI. However, despite its importance and extensive investigation, as a result of inconsistent application of definitions and a reliance on hospital-based studies that are highly subject to a range of potential biases, the burden of community-onset BSI has not been well summarized.

Knowledge of the epidemiology and microbiology of community-onset BSI is needed to assess its impact on the health of the world community and to provide a basis from which development of interventional strategies may be created. Obtaining that epidemiological and microbiological knowledge first requires a detailed understanding of the technical and clinical factors that constitute a community-onset BSI. These factors include how a community-onset BSI is detected and the determinants influencing its ascertainment, including understanding the roles of different organisms as etiologic agents of community-onset BSI, the importance of utilizing study designs that minimize bias, and the use of definitions that are concise, unambiguous, and clinically relevant.

The primary objective of this report was therefore to provide a state-of-the-art review of the population-based incidence and microbiology of community-onset BSI. However, unlike the case with hospital-onset/nosocomial infections, for which widely accepted definitions exist and hospitalized patients represent a captive population for surveillance, establishment of the burden of community-onset BSI is more methodologically challenging and complex. Within this report, we therefore first review methodological issues surrounding establishment of the diagnosis of community-onset BSI. Key themes in this area include the provision of rational and precise definitions, determinants of positivity, and the importance of classification of community-onset BSIs into community-associated and health care-associated community-onset BSIs. In the second part of the report, we conduct a detailed review of the published population-based literature in order to first define the overall and then the species- or organism group-specific burden of community-onset BSI. Following this, we briefly highlight the importance of the emergence of resistant organisms as agents of community-onset BSI.

ESTABLISHING THE PRESENCE OF AND DEFINING COMMUNITY-ONSET BLOODSTREAM INFECTION

There are a number of diagnostic and classification considerations related to ascertainment of the presence of a BSI episode. However, definitions of BSI, especially with regard to community-onset disease, are not consistently used and applied in studies. For this review, precise and unambiguous definitions were identified, and these are listed in Table 1. Although no single definition has been accepted as a reference standard, BSI is generally deemed to be present when an organism associated with disease is cultured from the blood of an infected patient. It is therefore requisite in any definition of BSI that a positive blood culture for one or more organisms be demonstrated. However, a positive blood culture does not necessarily imply BSI. Positive blood cultures may arise in three main different settings, namely, contamination and true positivity in the absence or presence of associated clinical disease. Figure 1 shows the diagnostic hierarchy involved in establishing the presence of a community-onset BSI. It should be noted that organisms that may not be cultured from blood may be detected by using other methods, such as antigen detection or nucleic acid-based techniques. While future definitions may include these cases, present definitions are limited to those that demonstrate growth in blood cultures.

Contamination (pseudobacteremia) occurs when cultures are positive due to organisms not present in the bloodstream and arises as a result of inadequate sterile technique in obtaining and/or processing blood culture specimens. The terms "bacteremia" and "fungemia" are defined by the presence of viable bacteria and fungi in the blood, respectively. These may be operationalized as positive blood cultures in cases where contamination has been excluded. The term "bacteremia" is frequently used interchangeably with "BSI." However, these terms are not synonymous, and there are two important distinctions. First, the term "BSI" is more
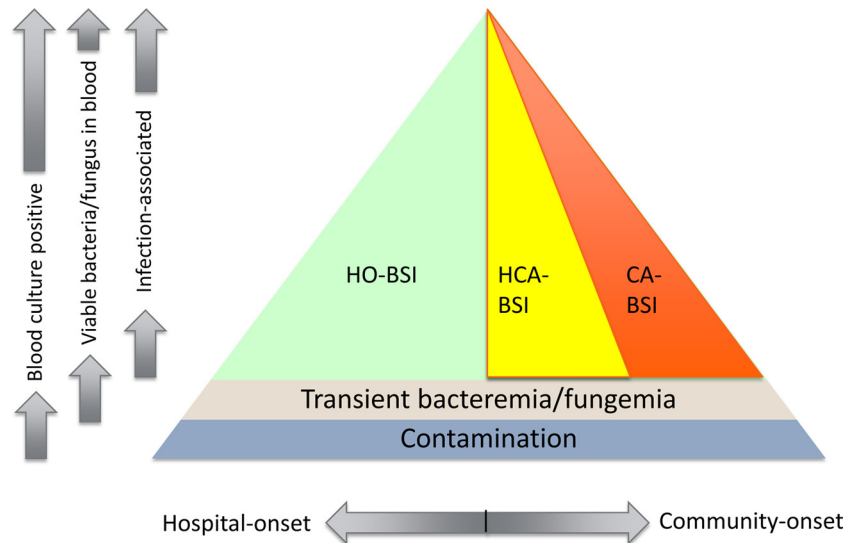
FIG 1 Diagnostic hierarchy from positive blood cultures to community-onset bloodstream infection. BSI, bloodstream infection; HO, hospital onset; HCA, health care associated; CA, community associated. The overall triangular area indicates all positive blood cultures, which may represent contamination (first level), transient bacteremia/fungemia (second level), or "true" BSI (third level). Bloodstream infections are further classified into the three mutually exclusive categories of hospital-associated, health care-associated community-onset, and community-associated community-onset BSIs.

comprehensive, in that it encompasses both bacterial and fungal etiologies. Second, implicit within the term "bloodstream infection" is that the positive blood culture is associated with clinical infection. While most bacteremias are associated with infections, transient bacteremias may occasionally be observed following minor manipulations of nonsterile body surfaces that are not infection associated (16–26).

Determinants of Blood Culture Positivity

Documentation of a positive blood culture is a mandatory step in BSI diagnosis. A blood culture or culture set (one or more bottles) containing broth media is immediately inoculated with a volume of blood collected under aseptic conditions, preferably by venipuncture. While blood may be drawn through indwelling intravascular catheters, at least one set of blood cultures should be collected by venipuncture (27–29). Use of a single needle for blood draw and inoculation is recommended (30, 31). Although there are a number of clinical and laboratory-based determinants that lead to a positive blood culture, this review focuses on the most clinically relevant determinants in community-based patients. An extensive review of this topic was previously published within this journal (32).

Blood culture sampling and bloodstream infection diagnosis. Practices related to sampling of patients with suspected BSI will influence its presence. In the extreme case, if a specimen is not submitted for culture, diagnosis of BSI is precluded. In contrast, liberal sampling for blood cultures may result in higher rates of detection (33). Studies conducted at the population level have correlated the rate of submission of cultures with the rate of detection of BSI (8). However, whether there is a threshold at which this effect is not further observed remains to be determined.

The volume of blood drawn is associated with the probability of detecting a patient with bacteremia. Some conditions, such as endocarditis and septic thrombophlebitis, are associated with a continuous bacteremia where a sustained high organism load is

present in the bloodstream, and cultures will be positive even if small volumes of blood are drawn for culture. However, with most other infections, lower organism loads are present and larger volumes of blood are required to increase the probability of detection. Contemporary studies reviewing multiple 20-ml blood cultures drawn in a 24-h period have indicated that among patients with bacteremia, approximately 70% will have positive cultures after the first draw, 85% after the second, 97% after the third, and >99% after the fourth (34, 35). While the ability to detect positive blood cultures with repeated draws over time may reflect detection of intermittent bacteremia, it most likely reflects a greater total volume of blood drawn (36). Inclusion of an anaerobic bottle as part of a blood culture set enables the detection of anaerobes, increases the probability of detecting facultative anaerobes, and shortens the time to detection for some fastidious organisms (37, 38).

Bloodstream infection may arise as a primary infection or may be secondary to a focal infection at a defined body site, most commonly arising from the respiratory, gastrointestinal, and urogenital tracts (32, 39). Endocarditis, meningitis, and septic shock typically have high rates of blood culture positivity, while other conditions, such as soft tissue infection, have very low rates (40).

Influence of blood culture systems and other laboratory-based determinants. There are many different laboratory protocols and procedures possible for blood culture. However, most modern laboratories utilize automated incubation and detection systems, due to their higher efficiency, lower risk for contamination, and requirement for shorter duration of incubation than those of manual blood culture approaches (35, 41–45). Although various media and detection systems are used with different commercially available automated systems, generally speaking, performances are comparable provided that similar volumes of blood are cultured. However, the use of media containing charcoal or resins improves the recovery of organisms in the presence of an-

timicrobials, and the use of specialized media enhances the recovery of anaerobes, mycobacteria, and fungi (46, 47). A detailed review of these aspects has been published previously (32).

Determining the Significance of Positive Blood Cultures

Following exclusion of contamination, it is important to ascertain whether bacteremia/fungemia is infection associated (i.e., BSI) or not. However, there is no widely accepted "gold standard" for defining these different entities. In most cases, integration of clinical, laboratory, and microbiological factors is required (48).

Factors to consider in classifying positive blood cultures. (i) Identified organism(s). Isolation of organisms from an aseptically obtained and processed blood sample indicates BSI in most cases. However, there are a number of skin commensal organisms that, when growing in blood cultures, represent contaminants (i.e., false-positive blood cultures) in the majority of cases. These organisms include coagulase-negative staphylococci (CoNS), *Bacillus* spp. (not *Bacillus anthracis*), *Micrococcus* spp., *Corynebacterium* spp. (not *Corynebacterium jeikeium*), and *Propionibacterium acnes* (48). Among immunocompetent patients who do not have an indwelling prosthetic device, such as an intravascular catheter, these organisms are rare but possible causes of community-onset BSI (49). Viridans group streptococci are occasional blood culture contaminants, although when not infection associated they may represent transient bacteremia from a dental or upper gastrointestinal source rather than contamination *per se*. In the absence of advanced immune suppression, identification of molds in blood cultures usually indicates environmental contamination. In contrast, isolation of yeasts and dimorphic fungi in blood cultures invariably indicates fungemia and BSI.

(ii) Number and timing of positive cultures. Adequate sampling volume is the single most important factor for detecting BSI. The Clinical and Laboratory Standards Institute (CLSI) guidelines recommend four 10-ml bottles of blood (e.g., two sets of blood cultures, each consisting of an aerobic and an anaerobic bottle, equivalent to 40 ml of blood) to be taken for the initial evaluation in order to detect about 90 to 95% of bacteremias. A third blood culture set (i.e., an additional 20 ml of blood) increases the detection rate to 95 to 99% (39, 50). Recent studies also suggest that even larger blood volumes may need to be cultured in order to achieve the optimal recovery of specific organisms and that larger blood volumes also decrease the detection time for common pathogens (34, 51). Lee and colleagues showed that *Staphylococcus aureus* bacteremia was detected in the first blood culture ~90% of the time, whereas only 60% of *Pseudomonas aeruginosa* bacteremia cases and candidemia cases due to *Candida albicans* were detected with only a single blood culture (34). Similar data were found for polymicrobial episodes, where only 67% of all the organisms present were detected with the first blood culture, but most of them (99.1%) were detected by the third blood culture (34).

For common skin contaminants, the number of positive cultures may be used as a means of differentiating contamination from bacteremia. However, most of the published literature in this regard has focused on hospital-onset coagulase-negative staphylococcal infections (48, 49, 52–55). Based on this literature, a single positive culture represents contamination in 75 to 95% of cases. In a patient with bacteremia, there is a high likelihood (>75%) of a second blood culture growing the same organism as that from the initial draw (39). However, a second blood culture is not usually positive when the initial isolate is a contaminant. Although less well defined, the time to culture positivity has also been used to establish the presence of contamination, with earlier positivity being suggestive of bacteremia (48, 56).

(iii) Transient bacteremia. On occasion, low-grade bacteremia may occur that is transient (i.e., lasting less than 30 min) and not associated with infection. Transient bacteremia is a "true" bacteremia in that viable organisms are present in the bloodstream (i.e., not contaminants), but it is not a BSI because it is not infection associated. There are a number of well-recognized causes of transient bacteremia, and these generally involve manipulation of colonized or contaminated mucosal surfaces, including dental manipulations (16–19), endoscopic gastrointestinal procedures (20–23), and invasive respiratory procedures (24, 25). Transrectal needle prostate biopsy is associated with transient bacteremia in approximately 20% of cases, and this may subsequently evolve into BSI (26).

(iv) Clinical variables. A BSI may be confirmed if an evident infective focus is temporally associated with a positive blood culture. A focus may be documented clinically and/or microbiologically by isolation of the same species from a normally sterile body site, such as cerebrospinal, synovial, or pleural fluid or samples obtained from deep-tissue aspirates. However, determination of a focus of infection is often less overt, and by definition, no focus of infection is present in primary BSI. In these cases, other parameters are often employed to classify positive blood cultures as contaminants or as infection associated or not. The presence of fever and an elevated white blood cell count are often cited as important determinants, but these alone are only weakly associated with BSI. Along with the number of positive blood cultures, the presence of an indwelling catheter, hypotension, and an increasing number of criteria for systemic inflammatory response syndrome (SIRS) will increase the probability of a BSI with potential blood culture contaminants (52, 55). Some criteria utilize whether patients are treated with antimicrobials to define a BSI. However, this factor may simply be a marker of excessive therapy rather than proof of BSI *per se* (57).

Approaches to classification of positive blood cultures. With individual patient care, a clinician determines the presence of a BSI based on an integration of available microbiological, clinical, and radiologic information. However, such an individualized approach has significant limitations for surveillance and research purposes. Use of standardized definitions and algorithms has been developed in an attempt to improve consistency (52), although where a subjective component is included, substantial interobserver variability has been a major problem (58). In part as an attempt to promote consistency, but also efficiency, electronic surveillance systems have been developed and increasingly reported in recent years (59–61).

Classification of Community-Onset Bloodstream Infections

Traditionally, BSIs were classified as community-acquired or nosocomial infections (62). Community-acquired BSIs were those deemed to be present prior to or incubating at hospital admission, and nosocomial BSIs were those acquired after admission to hospital. Two important challenges have arisen with the use of such a binary definition. First, it is very difficult to objectively determine the true acquisition of infecting isolates, and interobserver variation in application of these definitions is a major problem (58). Second, shifts in health care delivery models have changed dra-

matically in recent years, with much higher levels of complex medical care (such as home hemodialysis and outpatient parenteral antimicrobial therapy) being delivered in the community setting. As a result, it is increasingly recognized that community-based patients may have infections that are hospital associated/acquired.

New classification schemes have been developed in order to address the challenges associated with the traditional binary definitions (63, 64). Classification of infections as either community-onset or hospital-onset infections provides a discrete and objective means of classification. In this regard, community-onset infections can be defined as occurring among outpatients or those first identified (cultures drawn) within 2 days (<48 h) of admission to hospital, and hospital-onset infections can be defined as those where culture is first identified 2 or more days (≥48 h) following hospital admission or within 2 days (<48 h) of hospital discharge (63). In addition, community-onset infections may be subclassified further as health care associated or community associated, based on prior exposure of patients to significant health care or not, respectively (65). It is important that while these new categories are likely reflective of the location of acquisition of infection, this is not necessarily the case.

Community-associated versus health care-associated community-onset disease. Morin and Hadler first proposed categorization of community-onset BSI into further subcategories that included previously hospitalized patients (health care-associated community-onset BSI) and those patients not recently admitted, either with or without comorbid medical illnesses (63). Friedman and colleagues later proposed categorizing patients with community-onset BSI into those having either health care-associated or community-acquired disease, and these categories were subsequently widely recognized (65). Their definition of health care-associated community-onset BSI included at least one of the following: patients who had recently been hospitalized and patients who received recent specialized medical services in the home, who attended a hospital-based clinic or hemodialysis unit, or who were nursing home residents. Patients who did not have at least one of these criteria had community-acquired BSI. In order to avoid confusion with the previous binary definitions, we use the term "community-associated disease" in preference to "community-acquired BSI" in referring to community-onset disease not associated with prior health care exposure.

There have been a number of investigations that have sought to validate the entity of health care-associated community-onset BSI as distinct from community-associated and hospital-onset BSIs. Studies not limited to specific etiologies are summarized in Table 2 (50, 65–70). While definitions and study populations have varied to some degree, compared to community-associated BSIs, health care-associated BSIs are more likely in older patients with comorbid illness, have a different distribution of pathogens (higher rates of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and lower rates of *Streptococcus pneumoniae* and *Escherichia coli*), have higher rates of antimicrobial resistance, and are more lethal (65). Health care-associated infections are readily definable using objective criteria and, as a result, are readily applicable for use in electronic surveillance systems (71). However, because not all patients with community-onset BSI are admitted to hospital, surveillance systems that do not ascertain all cases of community-onset BSI, with admittance to hospital or not, will be subject to a selection bias that may challenge the ability to adequately define

the problem and provide a rational basis for devising potential preventative strategies.

BURDEN OF COMMUNITY-ONSET BLOODSTREAM INFECTION

Although not likely recognized by both the lay and medical communities, the burden of community-onset BSI is comparable in magnitude to those of acute myocardial infarction, stroke, and major trauma (4). Most investigations studying the adverse impact of BSI have been performed with selected patient cohorts, such as those admitted to hospital. However, such studies suffer from a number of important limitations, including selection bias and a lack of adequate denominator data (72). As a result, population-based studies have been recognized as an optimal design for establishment of the burden of illness related to an infectious disease (73). In population-based studies, all episodes of infection occurring among residents of a defined geographical region are ascertained, and nonresidents are excluded (74). By including all cases, selection bias is minimized (75). Furthermore, as a result of the ability to define the population at risk, both incidence and mortality rates can be calculated.

Overall Populations

Rare studies have been published that report (or at least contain adequate data to estimate) the overall burden of community-onset BSI at the population level, and these are displayed in Table 3 (1–5). Filice et al. were the first to publish a study investigating BSIs in a nonselected population (1). These investigators did not focus on community-onset BSI, and the value in Table 3 represents an estimate based on the information provided in their report. Importantly, they had a number of cases that remained unclassified, such that the rate of community-onset BSI may have been as high as 6 per 100,000 higher than that reported. Uslan et al. reported an overall case fatality rate of 13.5% in their study, but this rate also included nosocomial cases, so the rate for community-onset cases could not be determined (2). Sogaard et al. found significant increases in incidence over the time of their study, and as a result, the most recent data are displayed in Table 3 (3). In the first study reported from Calgary, it is important that all common skin contaminants were excluded, such that the rate may be a falsely low estimate of the incidence of community-onset BSI in that population (4). In addition, that study did not differentiate between community-associated and health care-associated community-onset BSIs. Subsequent studies conducted in the pediatric (<18 years) population during 2000 to 2006 demonstrated an incidence of community-onset disease of 40 per 100,000 population (26 per 100,000 were community-associated BSIs, and 14 per 100,000 were health care-associated BSIs), an approximate case fatality rate of 5%, and mortality of 2 per 100,000 (76). In an adult cohort studied from 2000 to 2007, 28-day case fatality rates for health care-associated and community-associated BSIs were 19% and 10%, respectively (66). In another analysis of adult patients, during 2003 to 2007, all-cause case fatality rates were 12% (28 days), 17% (90 days), and 25% (365 days) (77). Notably, the study from Victoria evaluated only in-hospital deaths, which likely underestimated the true burden of disease (5).

Several other studies have evaluated BSIs at the population level but have had incomplete case ascertainment, have limited analysis to subpopulations, have not specifically defined rates, or have not

TABLE 2 Studies comparing health care-associated (HCA) and community-associated (CA) community-onset BSIs

First author (reference)	Setting/population	HCA BSI definition	Patient differences (vs CA BSI)	Microbiology (vs CA BSI)	Outcome difference (vs CA BSI)
Friedman (65)	Adults admitted to three hospitals in North Carolina (143 with CA BSI and 186 with HCA BSI)	Community-onset BSI with any specialized therapy in the home, recent attendance at a hospital, hemodialysis, or chemotherapy clinic, recent hospitalization, or residence in a nursing home	More likely to have cancer and renal failure with HCA BSI, and less likely to have HIV infection	Urinary tract infection more common in CA BSI; *Staphylococcus aureus* most common in HCA BSI and *Escherichia coli* and *Streptococcus pneumoniae* most common in CA BSI; MRSA much more common in HCA BSI	3- to 6-month mortality higher (29% versus 16%; $P = 0.019$) for HCA BSI than for CA BSI
Lenz (66)	Adult residents of Calgary, Canada (3,088 with CA BSI and 2,492 with HCA BSI)	Minor modification of criteria of Friedman et al. (60, 65)	Older, more comorbid illness with HCA BSI	Different distribution of pathogens and higher rates of resistant organisms, including MRSA; more polymicrobial infections with HCA BSI	Longer length of stay and higher 28-day case fatality rate (18% versus 10%; $P < 0.001$) with HCA BSI
Al-Hasan (67)	Gram-negative BSI in residents of Olmsted County, MN (306 with HCA BSI and 427 with CA BSI)	Per criteria of Friedman et al. (65)	Patients with HCA BSI were older	Different distribution of infection foci and pathogens; higher rates of resistance with HCA BSI	Higher 28-day case fatality rate (15% versus 4%; $P < 0.001$) with HCA BSI
Son (50)	Patients admitted to nine university hospitals in Korea (380 with CA BSI and 206 with HCA BSI)	Per criteria of Friedman et al. (65)	Patients with HCA BSI more likely to be male and to have comorbidities and immune-suppressant therapy	Different distribution of infection foci and pathogens; higher rates of resistance with HCA BSI	Higher 30-day case fatality rate (18% versus 10%; $P = 0.007$) with HCA BSI
Kollef (68)	Adults admitted to seven hospitals in the United States (728 [64%] with HCA BSI and 415 with CA BSI)	Recent hospitalization, immune suppression, hemodialysis, or nursing home residence	Patients with HCA BSI were older and more likely to be male and to have comorbidities and a higher severity of illness	Different distribution of infection pathogens; higher rates of primary BSI and resistance with HCA BSI	Higher hospital case fatality (14% versus 4%; $P < 0.001$) with HCA BSI
Evans (69)	Adults with spinal cord injury admitted to two hospitals in the United States (110 with HCA BSI and 36 with CA BSI)	Per criteria of Friedman et al. (65)	Patients with HCA BSI were older and more likely to have comorbidities	Trend for higher rates of resistance with HCA BSI	No difference in hospital or 30-day mortality rates
Valles (70)	Adults admitted to three teaching hospitals in Spain (581 with CA BSI and 281 with HCA BSI)	Per criteria of Friedman et al. (65)	Patients with HCA BSI were older and more likely to have comorbidities	Different distribution of pathogens and higher rates of resistance, including MRSA; more polymicrobial infections with HCA BSI	Higher case fatality rate (28% versus 10%; $P < 0.001$) with HCA BSI

TABLE 3 Population-based studies investigating the overall burden of disease associated with community-onset bloodstream infection

First author (reference)	Setting, yr	Annual incidence	Case fatality rate (%)	Mortality per 100,000 population
Filice (1)	Charleston County, SC (population 250,000), 1974–1976	43 per 100,000	Not reported	Not reported
Uslan (2)	Olmsted County, MN (population 124,277), 2003–2005	154 per 100,000 (70 per 100,000 were health care associated, and 84 were community acquired)	Not reported	Not reported
Sogaard (3)	Northern Denmark (population 500,000), 1992–2006	112 per 100,000 (79 per 100,00 were CA, and 34 were HCA) during 2002 to 2006	17 (15 for CA BSI and 22 for HCA BSI) during 2002 and 2006	19 (12 for CA BSI and 7 for HCA BSI) during 2002 to 2006
Laupland (4)	Calgary area, Alberta, Canada (population 1 million), 2000–2004	81.6 per 100,000	13 (in hospital)	11 (in hospital)
Laupland (5)	Victoria area, British Columbia, Canada (population 358,000), 1998–2005	101.2 per 100,000	12.6 (in hospital)	12.8 (in hospital)

clearly differentiated between community- and hospital-onset disease (6–15).

It is difficult to precisely define the contemporary (within the last 20 years) overall burden of community-onset BSI, for a number of potential reasons. First, there are few studies that have been conducted (Table 3). Second, studies were conducted over different periods during the past 4 decades, and it is well documented that the rate of BSI has increased in many jurisdictions, at least up to the early 2000s (3, 6, 8). Third, the demographic profiles of the populations are different. Age and gender standardization alone has been shown to potentially result in differences of 20 to 30% in reported incidences among populations (73), and this may even be observed within different regions of the same country (5). Fourth, and perhaps most importantly, these studies were all reported from high-income Western countries. The burden of community-onset disease may be substantially different elsewhere worldwide (12–15).

Specific Etiologies

Although population-based data are limited in defining the overall community-onset BSI burden, there is a significant and growing number of studies investigating the epidemiology of community-onset BSI with selected pathogens. *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* are the most frequent causes of community-onset BSI and are responsible for more than one-half of all cases overall (1, 2, 4, 5). The following sections review the incidence of community-onset BSI among selected etiologies, with an emphasis on contemporary studies conducted in populations without age restriction.

Escherichia coli. *Escherichia coli* is the most common cause of BSI reported in overall population-based studies (1–9). However, few population-based studies have specifically focused on *E. coli* BSI (78–81). Kennedy and colleagues investigated *E. coli* bacteremia in Canberra, Australia (population 366,000), between 2000 and 2004 (78). The annual incidence was 28 per 100,000, and among infections, 68% were community associated and 13% were health care associated. The incidence of community-onset disease was 23 per 100,000 annually. Laupland et al. investigated *E. coli* BSI in the Calgary area of Canada (population 1.2 million) during 2000 to 2006 and found an incidence of 30.3 per 100,000 annually

(79). Overall, 32% of BSIs were health care associated, and 53% were community associated, for a community-onset incidence of 25.6 per 100,000. During 1998 to 2007, Al-Hasan et al. investigated *E. coli* BSI in Olmsted County, MN (population 124,277) (80). The incidence rates for females and males were 48 and 34 per 100,000, respectively. Fifty-nine percent of cases were community associated, and 32% were health care associated, for incidence rates of approximately 44 and 31 per 100,000 for community-onset disease among females and males, respectively. Williamson and colleagues investigated *E. coli* BSI in Auckland, New Zealand (population 0.5 million), during 2005 to 2011 (81). They reported an incidence of 52 per 100,000, and among infections, 34% were community associated and 40% were health care associated, for an incidence of community-onset disease of 39 per 100,000 annually. They also observed marked differences in incidence based on ethnicity, with the highest rates observed in Pacific peoples and Maoris.

Staphylococcus aureus. *Staphylococcus aureus* is the second most common species causing BSI in population-based studies, and there is an evolving body of literature focusing specifically on this pathogen (2, 6, 8, 9). Table 4 displays studies investigating the burden of community-onset *Staphylococcus aureus* BSI in nonselected populations (63, 82–86). Several other population-based studies, in addition to those presented in Table 3, have been reported but either had older or duplicative data with tabulated studies (87–90), were limited to subgroups such as MRSA only (91–94), included selected age groups (95–101), or did not report or clearly differentiate between community- and hospital-onset disease (102–106). Overall, these data support the estimate that the contemporary incidence of community-onset *Staphylococcus aureus* BSI is approximately 15 per 100,000 in Western countries and is associated with a 30-day all-cause case fatality rate of 20% and a mortality rate of 3 per 100,000 (107). Notably, MRSA strains vary widely internationally, and in some cases MRSA appears to add to and in others replaces the burden due to methicillin-sensitive *S. aureus* (MSSA) (85).

Streptococcus pneumoniae. *Streptococcus pneumoniae* is the third most common overall BSI etiology reported in population-based studies, and there is a significant body of literature focusing

TABLE 4 Contemporary population-based studies investigating the overall burden of *Staphylococcus aureus* community-onset bloodstream infection

First author (reference)	Population, yr	MSSA incidence per 100,000/yr	MRSA incidence per 100,000/yr	Total incidence per 100,000/yr	Mortality (%)
Morin (63)	Four areas in Connecticut, 1998	14.5	2.5	17	10 for MSSA, 14 for MRSA, 11 overall (case fatality rates)
Lyytikainen (82)	Finland, 1995–2001	7	<0.1	7	13 (28-day case fatality rate)
Collignon (83)	Australia, 1999–2002	15	2	17	18 (28-day case fatality rate)
Huggan (84)	Canterbury, New Zealand, 1998–2006	14	<0.3	14	Not reported
Laupland (85) and Tom (86)	Multinational, 2000–2008				30-day case fatality rates of 20.2 for MSSA and 22.3 for MRSA, mortality rates of 3.4 for MSSA and 0.3 for MRSA per 100,000 per year
	Canberra, Australia	14.5	2.0	16.5	
	Calgary, Canada	15.3	2.4	16.5	
	Victoria, Canada	15.1	2.4	17.4	
	Sherbrooke, Canada	13.0	1.8	14.8	
	Northern Denmark	16.2	0	16.2	
	Copenhagen County, Denmark	14.7	0.2	14.9	
	Copenhagen City, Denmark	16.5	0.2	16.7	
	Finland	11.9	0.2	12.1	
	Western Sweden	18.1	0	18.2	
	Overall	15.0	1.0	16.0	

specifically on this pathogen (1–9). Several contemporary studies have been reported from overall populations and are summarized in Table 5 (108–125). Other studies have been conducted in pediatric (126–137) and adult (137–143) subpopulations worldwide.

Although the current annual incidence of community-onset *Streptococcus pneumoniae* BSI likely ranges between 10 and 20 per 100,000 in most Western countries, it is difficult to precisely define an overall rate, for several reasons (4, 5). First, this organism usually causes community-onset disease, with only approximately 10% of cases overall showing hospital-onset disease (144). Studies to date have not typically differentiated between community- and hospital-onset disease. Second, most studies, to date, have focused

TABLE 5 Contemporary studies of invasive disease and/or bloodstream infection due to *Streptococcus pneumoniae* in nonselected populations

First author (reference)	Population, yr	Annual invasive disease incidence per 100,000	BSI rate or proportion (%) of isolates in blood
Rudnick (108)	Toronto, Canada, 1995–2011	9	Not reported
Feemster (109)	Philadelphia, PA, 2005–2008	Not reported	12.3 per 100,000
Helferty (110)	Northern Canada, 1999–2010	25.8	Not reported
Ingels (111)	Denmark, 2000–2010	17.7 (2008–2010)	Not reported
Rosen (112)	Eight U.S. regions, 1998–2009	13.5 (overall; range of 11.2 to 18 between regions during 2009)	Not reported
Harboe (113)	Denmark, 1938–2007	Approximately 20 (1998–2007)	81
Weatherholtz (114)	Navajo Nation, USA, 1995–2006	51 (2004–2006)	Not reported
Motlova (115)	Czech Republic, 2000–2006	2.3–4.3	Not reported
Hsieh (116)	Taiwan, 2007	2.6	≥94
Kellner (117)	Calgary, Canada, 1998–2007	11.2 (2003–2007)	89
Baggett (118)	Two areas in rural Thailand, 2005–2007	Not reported	3.7 per 100,000 (Sa Kaeo Province) and 7.6 per 100,000 (Nakhon Phanom Province)
Bruce (119)	Seven circumpolar regions, 1999–2005	21.6 for Canada (2003–2005), 19.8 for Greenland (2000–2005), 16.2 for Norway (2000–2005), 15.8 for Alaska (2001–2005), 14.6 for Iceland (2000–2005), 11.6 for Finland (2000–2005), 9.1 for Sweden (2003–2005)	Not reported
Heffernan (120)	New Zealand, 1998–2005	12.4	93
Lacapa (121)	Fort Apache Indian Reserve, USA, 1991–2006	87 (2001–2006)	Not reported
Klemets (122)	Finland, 1995–2002	10.6	9.9 per 100,000
Einarsdottir (123)	Iceland, 1975–2004	16.7 (1990–2004)	Not reported
Stephens (124)	Atlanta, GA, 1994–2002	18 (2000–2002)	95
Andresen (125)	Canberra, Australia, 1998–2000	15.2	Not reported

on invasive disease, and while approximately 90% of all invasive *Streptococcus pneumoniae* infections are associated with BSI, these data are not usually reported independently. Third, certain chronic comorbid illnesses, acute coinfections, and a range of ethnic and socioeconomic factors can greatly influence the risk of developing invasive *Streptococcus pneumoniae* infections (109, 110, 137, 145). As a result, populations differing in these characteristics will have different observed rates. Fourth, and most importantly, the epidemiology of invasive *Streptococcus pneumoniae* infection has undergone major changes in recent years, related to implementation of the universal use of protein-conjugate pneumococcal vaccines in infants in many populations. This has led to serotype shifts and major decreases in childhood invasive pneumococcal disease, with a commensurate reduction in disease among nonvaccinated adults due to herd immunity (146).

***Klebsiella* species.** *Klebsiella* species are the fourth most frequent agents of community-onset BSI (2, 4, 5). Meatherall et al. investigated *Klebsiella pneumoniae* BSI in Canada (2000 to 2007) and found a community-onset incidence of 5.2 per 100,000 (3.1 per 100,000 were health care associated, and 2.1 per 100,000 were community associated), with an associated case fatality rate of 14% (147). This is similar to the incidence of 5.7 per 100,000 observed in Victoria, Canada, during 1998 to 2005 (5). In a study investigating *Klebsiella* species BSI from the United States (1998 to 2007), Al-Hasan and colleagues found overall incidence (including hospital-onset disease) rates of 15.4 per 100,000 for males and 9.4 per 100,000 for females (148). Among a cohort of 127 patients, 60 (47%) patients had community-acquired BSI (50 with *Klebsiella pneumoniae*, 9 with *Klebsiella oxytoca*, and 1 with *Klebsiella ornithinolytica*), and 53 (42%) had health care-associated BSI (46 with *Klebsiella pneumoniae* and 7 with *Klebsiella oxytoca*).

***Salmonella enterica*.** Although *Salmonella enterica* is a relatively infrequent cause of BSI in high-income Western countries, it is a frequent cause of BSI in many other areas of the world. In one study conducted during 2000 to 2007 in six regions in Australia, Canada, Denmark, and Finland, an overall rate of 1.02 per 100,000 population was observed; the rate of typhoidal disease (with *S. enterica* serotypes Typhi and Paratyphi) was 0.21 per 100,000, with a disease rate of 0.81 per 100,000 for other serotypes (149). Where data were available, more than 90% of cases were classified as community-onset BSI. A study from northern Denmark during 1994 to 2003 reported an overall incidence of nontyphoidal *Salmonella enterica* BSI of 2.3 per 100,000 population per year (150). A later study demonstrated international travel as a risk factor (151). Tabu et al. reported on non-*S.* Typhi *Salmonella* BSI in Kenya during 2006 to 2009 and reported rates of 78 and 13 per 100,000 population in rural and urban sites, respectively (152). In another study from these investigators, in Kenya during 2007 to 2009, *Salmonella enterica* serovar Typhi incidences were 29 and 247 per 100,000 population in rural and urban sites, respectively (153).

Other *Enterobacteriaceae*. As a group, the *Enterobacteriaceae* are frequent causes of community-onset BSI, largely due to *Escherichia coli* and *Klebsiella pneumoniae*, as previously detailed. *Proteus mirabilis* was among the 10 most frequent species of bacteria causing community-onset BSI in some studies (1, 4). A rate of 1.3 per 100,000 was observed in Calgary, Canada (2000 to 2004) (4), and a rate of approximately 2 per 100,000 was seen in Olmsted County, MN (1998 to 2007) (67). Other *Proteus* species are rare and occur at rates of <0.1 per 100,000 (154). *Enterobacter* species

BSIs were investigated in Olmsted County during 1998 to 2007 and were found to occur at a rate of 3.3 per 100,000 population; 58% and 21% of cases were health care-associated and community-associated BSIs, respectively, for an incidence of community-onset BSI of 2.6 per 100,000 (155). There is increasing recognition of the importance of *Serratia* species as causes of community-onset BSI, with rates of 0.6 and 0.5 per 100,000 observed in Calgary, Canada (2000 to 2005), and Canberra, Australia (1998 to 2007), respectively (156, 157). Few population-based data on *Citrobacter* species have been published, and a rate of ≤1 per 100,000 was estimated for Olmsted County, MN (67). Rare *Enterobacteriaceae* etiologies of community-onset BSI include *Hafnia alvei* (0.1 per 100,000) (158), *Morganella morganii* (0.3 per 100,000) (154), and *Providencia* species (0.15 per 100,000) (154).

***Haemophilus influenzae*.** Prior to widespread use of protein-conjugate serotype b vaccines, *Haemophilus influenzae* was among the predominant causes of community-onset BSI (1). Although now less common, it remains an important cause of invasive disease, and there has been a shift toward non-serotype b etiologies. A multinational study conducted during 2000 to 2008 within Australia, Canada, and Denmark found an incidence of *Haemophilus influenzae* BSI of 1.31 per 100,000, with 89% of infections being community-onset BSIs (159). Incidences were 0.08, 0.22, and 0.98 per 100,000 for serotype b, serotypes a and c to f, and nontypeable *H. influenzae*, respectively. A large study including invasive infections from 14 European countries during 1996 to 2006 identified rates of 0.15, 0.04, and 0.28 for serotype b, serotypes a and c to f, and nontypeable *H. influenzae*, respectively (160). Studies of invasive disease from Canadian regions, including Manitoba (2000 to 2006), northern Canada (2000 to 2005), and Ontario (1989 to 2007), reported rates of 1 to 2, 8, and 1.4 per 100,000, respectively (161–163). The overall incidence of invasive disease in Illinois was reported to be 1.0 per 100,000 in 2004 (164), and an incidence of 1.5 per 100,000 was reported for Iceland during 1990 to 2008 (165). The rate of community-onset BSI due to *Haemophilus influenzae* was approximately 1.5 per 100,000 in a large multiregional study in the United States during 1989 to 2008 (166).

***Pseudomonas aeruginosa*.** *Pseudomonas aeruginosa* is variably listed among the 10 most frequent etiologies of community-onset BSI (2–4). Al-Hasan and colleagues reported overall rates (including hospital-onset disease) of *Pseudomonas aeruginosa* BSI for males and females of 10.8 and 3.7 per 100,000, respectively (167). Eighty-three percent of the cases had a community onset, suggesting an incidence of community-onset BSI of 6 per 100,000 annually. Parkins et al. identified an overall rate (including hospital-onset cases) of *Pseudomonas aeruginosa* BSI of 3.6 per 100,000 in Calgary during 2000 to 2006 (168). Fifty-five percent of cases had a community onset, for an incidence of community-onset BSI of 2 per 100,000 annually (4, 168).

Beta-hemolytic streptococci. Beta-hemolytic streptococci represent a large group of organisms causing community-onset BSI (2, 4, 5). Invasive *Streptococcus pyogenes* (group A) and *Streptococcus agalactiae* (group B) have been studied extensively worldwide, although fewer studies have specifically examined community-onset BSI in nonselected populations (169, 170). A rate of 2.5 per 100,000 was reported for community-onset BSI due to *S. pyogenes* in Connecticut in 1998 (63). A high rate of 11.6 per 100,000 population for *S. pyogenes* BSI was observed during 2000 to 2005 in Fiji, although it is not clear what proportion of cases may have had a hospital onset (171). Respective rates of community-onset BSI

due to *S. pyogenes* and *S. agalactiae* were reported as 2.3 and 2.5 per 100,000 in Victoria, Canada, during 1998 to 2005 (5), and as 3.3 and 2.3 per 100,000 in Calgary, Canada, during 2000 to 2004 (4). Large-colony group C and G streptococci (*Streptococcus dysgalactiae* subsp. *equisimilis*) are also important causes of community-onset BSI, with incidence rates of approximately 2 to 3 per 100,000 observed in Canada, Denmark, and Finland (5, 172–174).

Enterococci. Enterococci, particularly *Enterococcus faecalis*, are consistently reported among the top 10 most frequent isolates in community-onset BSI (2, 4, 5). Incidence rates for *Enterococcus faecalis* community-onset BSI were reported as 3.6 per 100,000 in Victoria, Canada, during 1998 to 2005 (5), and 2.9 per 100,000 in Calgary, during 2000 to 2004 (4). Pinholt et al. examined enterococcal BSI in two Danish regions during 2006 to 2009 and found rates of 7 and 1 per 100,000 for *Enterococcus faecalis* and *Enterococcus faecium*, respectively (175).

Anaerobes. Anaerobes as a group are frequently observed causes of community-onset BSI (2–5). Ngo and colleagues reported on all anaerobic BSIs in Calgary during 2000 to 2008 and found incidence rates of 3.6 and 2.9 per 100,000 for community-associated and health care-associated community-onset BSIs, respectively (176). *Bacteroides fragilis* is the most commonly observed anaerobic species causing community-onset BSI, with reported rates (per 100,000 per year) of 2.4 in Calgary, Canada, from 2000 to 2004 (4), and 2.1 in Victoria, Canada, from 1998 to 2005 (5). *Clostridium* species represent the second most common anaerobes causing community-onset BSI, with a rate of 1.2 per 100,000 (177). *Fusobacterium* species are uncommon but potentially severe causes of community-onset BSI, with rates of approximately 0.3 to 0.5 per 100,000 annually observed in New Zealand (2002 to 2007), Denmark (1998 to 2001), and Canada (2000 to 2008) (178–180).

***Candida* species.** *Candida* species are occasional causes of community-onset BSI and are typically health care associated. While there are many population-based studies reporting incidences of *Candida* species BSI (181–185), few independently report rates of community-onset disease. Incidence rates for community-onset *Candida* species BSI include 0.5 per 100,000 in Calgary, Canada, during 2000 to 2005 (186), approximately 0.4 per 100,000 in Barcelona, Spain, during 2002 to 2003 (187), 4 per 100,000 in Connecticut and Maryland, during 1998 to 2000 (188), and 0.8 in Iceland, during 2000 to 2012 (189).

Coagulase-negative staphylococci and other Gram-positive organisms. Coagulase-negative staphylococci (CoNS) are frequently listed as agents of community-onset BSI and are predominantly related to health care-associated disease (2, 3, 5). However, determination of rates of community-onset BSI is complicated by the fact that CoNS are common blood culture contaminants and ascertainment of a BSI due to CoNS involves a degree of subjective clinical assessment (54). In addition, the vast majority of studies involving CoNS BSI are hospital based. Similar issues challenge the establishment of the incidence of community-onset BSI with viridans group streptococci (190). *Listeria monocytogenes* is a rare but potentially serious cause of community-onset BSI that may be associated with community-based outbreaks related to contaminated food sources. Rates of 0.2 to 0.3 per 100,000 were observed in the United States in the early 2000s (191).

Other Gram-negative bacteria. A number of Gram-negative bacteria not previously listed have been identified as causes of community-onset BSI, but these are either rare or restricted to certain geographical regions worldwide. The incidence of meningococcemia demonstrates considerable geographical and temporal variability and is influenced by the immunization status of populations as well as by outbreaks, such that it is difficult to define an "average" or typical incidence rate for community-onset BSI (192–194). Melioidosis, caused by *Burkholderia pseudomallei*, is a severe illness that is most widely diagnosed in northern Australia and Southeast Asia. Bacteremic melioidosis rates were reported as 4.9 and 14.9 per 100,000 population in two regions of Thailand during 2006 to 2008 (195), 3 per 100,000 in Australia during 1989 to 2003 (196), 0.3 per 100,000 in Singapore during 1989 to 1996 (197), and 4 and 8 per 100,000 in Malaysia during 2000 to 2003 and 2005 to 2008, respectively (198, 199). A number of other Gram-negative bacteria causing community-onset BSI, including *Brucella* species and *Bartonella* species, demonstrate marked geographical variation (200–202).

EMERGENCE OF RESISTANT COMMUNITY-ONSET BLOODSTREAM INFECTIONS

Traditionally, BSIs due to antimicrobial-resistant organisms have been recognized to occur principally among patients admitted to high-acuity hospital environments, especially intensive care units (203, 204). However, the past decade has witnessed the emergence of a number of multiply antimicrobial-resistant pathogens arising in the community setting worldwide. Notable examples include community-onset MRSA (205, 206) and ESBL (207)-, metallo-β-lactamase-, and other carbapenemase-producing *Enterobacteriaceae* (208).

Community-Onset MRSA Bloodstream Infection

Although community-associated MRSA infections were first recognized among injection drug users in Detroit, MI, in the early 1980s (209), MRSA largely remained a hospital-onset pathogen in most jurisdictions worldwide, until recently. Since the turn of the millennium, community-associated MRSA infections have emerged worldwide and have either replaced or added to the MSSA disease burden (205, 206, 210). Five clones have been associated with the majority of disease worldwide, with multilocus sequence type 1 (ST-1)/USA400 and ST-8/USA300 predominantly observed in North America, ST-59 observed in the Asia-Pacific region, ST-80 observed in Europe, and ST-30 distributed broadly worldwide (205). Initially, community-associated MRSA strains were noted to occur in previously healthy individuals, and higher rates were observed among injection drug users, homeless or incarcerated individuals, men who have sex with men, and military recruits. However, in many jurisdictions, strains that initially caused community-onset disease subsequently moved into the hospital environment and now represent the predominant strains causing hospital-onset disease (211).

Several population-based studies have evaluated the epidemiology of community-onset BSI due to MRSA worldwide (88, 93, 94, 210). Klevens et al. investigated invasive MRSA in 9 U.S. communities during 2005 and reported an overall incidence of 31.8 per 100,000 population; 80% or more of cases were bacteremic, 58% were health care associated, and 14% were community associated, suggesting an incidence of approximately 18 per 100,000 for community-onset MRSA BSI (93). In another study comparing rates of MRSA BSI between the United States and the United Kingdom during 2006 to 2007, rates were 21.9 and 3.5 per 100,000 population, respectively (94). In a multinational study investigating all

Staphylococcus aureus BSIs during 2000 to 2008, major shifts were observed, with an increasing incidence of community-onset MRSA BSI (210).

Enterobacteriaceae

A number of multidrug-resistant members of the *Enterobacteriaceae*, in particular *Klebsiella pneumoniae* and *Escherichia coli*, have emerged as important causes of community-onset BSI in recent years. During the 1990s, ESBL-producing *Enterobacteriaceae* were associated with hospital environments and were infrequently recognized causes of community-onset disease. However, since the turn of the millennium, these have emerged as major community-onset pathogens worldwide (207, 212). Series of community-onset BSIs due to a range of ESBL-producing *Enterobacteriaceae* have been reported from around the globe (13, 81, 213–216). Molecular epidemiology studies have identified a globally distributed clone, ST131, and defined the importance of international travel in the acquisition and spread of these infections (217–222). Within the ST131 clone, most of the fluoroquinolone-resistant and ESBL-producing strains have been identified within a highly pathogenic H30 subclone (223–227). Health care-associated BSI due to ESBL-producing *Escherichia coli* has been recognized as a significant complication following transrectal prostate biopsy (228, 229). A number of other resistant *Enterobacteriaceae*, such as those harboring *Klebsiella pneumoniae* carbapenemases and New Delhi metallo-β-lactamases, may result in community-onset BSI, but to date, these have largely caused either hospital-onset or health care-associated infections not associated with BSI (230, 231).

CONCLUSIONS

Community-onset BSI is a major health problem that is associated with a burden of illness similar to those of major trauma, acute stroke, and myocardial infarction (4). While heart disease and stroke, in particular, have garnered great attention and financial support by both public and private organizations, this is much less the case for severe bacterial infections, including community-onset BSI. It is therefore important to document the major burden of disease associated with community-onset BSI in order to bring the greater public attention and awareness that is needed to gain support for enhanced efforts aimed at reducing its major adverse impact. Population-based studies have demonstrated that *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* are responsible for the majority of community-onset BSIs in many jurisdictions, while other key pathogens have important roles in other regions. Demonstration of the importance of these pathogens regionally provides a rational basis for prioritizing future potential preventative strategies, such as immunization, environmental hygiene, and optimized management of chronic comorbid medical diseases. Community-onset BSI will likely increase in importance in the coming years, due to rising rates of health care-associated community-onset BSI related to management of older and increasingly complex patients in the community setting. The emergence of resistant organisms will have a major impact on the epidemiology of community-onset BSI in our increasingly global community in the coming years.

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