Studies on Components of Blood & Their Functions

Chapter 5

Bacterial Bloodstream Infections

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Abstract

Bacterial bloodstream infections have received increased attention over the years, and have seen a continuous expansion of the implicated etiologic agents. Of principal concern is the escalating rates of antimicrobial resistance observed in these etiologic agents. In this paper, the authors clarify major terminologies used in connection with bloodstream infections, review bloodstream infections in the context of bacterial etiologic agents and their associated antimicrobial resistance, and present a brief overview of the pathogenesis of bacterial bloodstream infections.

Keywords: Bacteraemia; Septicaemia; Sepsis; Severe sepsis; Septic shock

1. Introduction

Blood is regarded as a sterile tissue. Bloodstream infection (BSI) simply refers to the occurrence of microbes in blood [1,2]. Organisms belonging to the various microbial categories – viruses, parasites, fungi, and bacteria – have all been recovered from blood specimens. Bloodstream infections could be described as polymicrobial or monomicrobial, depending on whether they involve any degree of combinations of these microbes, or only

one microbial etiology. They have far-reaching social and economic consequences, including prolonged length of hospital-stay, high costs to the individual, and in some instances, loss of life. According to a recent report of the Centre for Disease Control (CDC), sepsis affects around 1.5 million individuals in the United States annually, causing the mortality of 250,000 individuals, and accounts for 1 out of every 3 hospital deaths [3]. Sepsis is also the single-most expensive cause of hospitalization in the United States, carrying an annual cost of more than $20 billion [4]. Bloodstream infections are predominantly caused by bacteria, and over the years, there have been a continuous expansion of the bacterial etiologic agents, as well as an escalation in their antibiotic resistance. In this article, we review bloodstream infections with a focus on the bacterial etiological agents, including their antibiotic resistance, epidemiology, clinical significance, and pathogenesis.

2. Terminologies Related to Bloodstream Infections

It is important to distinguish among the several different terminologies related to blood-related infections, as this has been an issue of confusion. These terminologies include viraemia, parasitaemia, fungaemia, bacteraemia, septicaemia, sepsis, severe sepsis, and septic shock. Viraemia, parasitaemia, fungaemia, and bacteraemia respectively refer to the presence of cultivable viruses, parasites, fungi, and bacteria, in blood. Conventional routes through which bacteria enter the body include wounds, infections, surgical procedures, or injections. Bacteraemia has been classified as transient, intermittent, continuous, or breakthrough. Bacteraemia is said to be transient if the bacteria are present in the blood briefly – for a few minutes to hours. In majority of these cases, the bacteria in the blood are few, and the body clears them by itself. Therefore those in whom these occur show no symptoms. This is the most common type of bacteraemia. With regard to intermittent bacteraemia, the bacteria remain present in the blood for longer than is observed in the case of transient bacteraemia, yet their periods of presence are temporally interlaced with periods of bacterial absence. Continuous bacteraemia, like the name suggests, involves the occurrence of bacteria in the blood over a considerably long duration. The terminology ‘breakthrough bacteraemia’ has been used to qualify bacteraemia that occurs in those who are under antimicrobial therapy with a therapeutic agent to which the bacterium isolated from the blood is sensitive. When breakthrough bacteraemia occurs early in therapy, it serves as an indicator that sub-therapeutic concentrations of the antimicrobial had been administered; when it occurs later on in therapy however, it indicates probable deficient drainage of a focus of infection, secondary foci, or flawed host defense mechanisms [1,2]. Septicaemia is the occurrence and multiplication of bacteria in the blood. It is also referred to as blood poisoning, and is characterized by such symptoms as prostration, fever, chills, very fast respiration, and/or heart rate. It could be preceded by localized infections, such as of the urinary tract, lungs, or abdomen. Sepsis is a severe pathology arising from systemic responses of the body to infections – both localized

and disseminated. Severe sepsis is sepsis that is accompanied with acute organ dysfunction [5,6]. Such an organ dysfunction could occur in any organ, and often manifests clinically as kidney injury, metabolic acidosis, or respiratory failure [6]. Septic shock is a type of severe sepsis where the organ dysfunction is associated with the cardiovascular system; in such cases, there is persistent hypotension despite fluid resuscitation [5-7].

3. Bacteraemia: Its Epidemiological Classification and Incidence

Bacteraemia has traditionally been dichotomized into community-acquired and hospital-acquired; the latter is reflective of bacteraemia that must not have been in its incubation period at the time the patient was admitted into inpatient care, and occurs in the course of inpatient stay, or in close proximity to the time of hospital discharge [8]. Noteworthy, though, there have been calls to further dichotomize community-acquired bacteraemia into healthcare-associated and community-associated, given that modifications to patient care have allowed for some measure of amalgamation of inpatient and outpatient care; the healthcare-associated community-acquired bacteraemia, per the proposals, could be used to describe those bactaeremic patients who had had significant healthcare exposure (including procedures), as opposed to those who lack such exposures [1,9]. Several specific traits have been fitted into the criteria for diagnosing healthcare-associated community-acquired bacteraemia, and these keep undergoing refinements by experts [1, 9-18]. Such refinements are are needed, as they have a bearing on treatment regimens.

Notwithstanding the continuous adjustments in the classification of bacteraemia, estimating the incidence of bacteraemia has mainly been contingent on population dynamics. Newer population studies are rare, but past long-term studies had suggested a rising trend in incidence [19-21]. To illustrate, in one tertiary care hospital in Madrid, Spain, the rate escalated from 16.0 to 31.2 episodes per 1,000 admissions between 1985 and 2006 [21]. In another study conducted in Spain from 2006 to 2007, but in tertiary and community hospitals in the city of Andalucia, the minimum estimated annual population-based incidence was 109.2 cases per 100,000 people, or 14.7 episodes per 1000 admissions [16]. Shifting focus away from Spain, in the United States, in the city Minnesota, after adjusting for sex and age, the incidence rate was reported to be 189 per 100,000 person-years for the period spanning from 2003 to 2005 [22]. Another study based on data collected between 2000 and 2004, reported the annual incidence rate of community-onset bacteraemia to be 81.6 per 100,000 people [8].

4. Bacterial Etiology of Bloodstream Infections

4.1. Staphylococcus aureus

Epidemiological evidence from several studies indicate that *Staphylococcus aureus* is probably the most important cause of blood-related infections. For instance, a large septicaemia

study involving 3,779 patients in Ghana [23] identified eight microbial pathogens; *S. aureus* was the predominant organism isolated from both children and adults, comprising an overall proportion of 33.33% of the total number of isolates. Paulsen et al. [24] investigated the epidemiology and outcome of *S. aureus* bloodstream infection (BSI) and sepsis in a county in Norway among 373 patients over a period of five years; 57.4% developed sepsis devoid of organ failure, 29.8% developed severe sepsis, while 12.9% developed septic shock. The all-cause mortality was 14.5% at seven days, 27.3% at thirty days, and 36.2% at 90 days. In a study involving 724 consecutive patients with bacteraemia caused by *S. aureus* in North Carolina [25], 34% developed metastatic infections, and 12% had endocarditis; the mortality rate at twelve weeks was 22%. Moreover, in patients with central venous catheter-associated *S. aureus* bacteraemia, a 71% incidence of thrombosis has been reported [26]. These findings show that *S. aureus* BSI is in tandem with significant morbidity and mortality.

S. aureus is carried as part of the normal flora of the anterior nares, and its carriage constitutes a major risk factor for developing sepsis caused by the microbe. Approximately half of the general population sparingly carry *S. aureus*, 20% are persistent carriers, while the remainder intermittently carry the organism [27-30]. Methicillin-resistant *S. aureus* (MRSA) is of particular concern due to its extensive resistance to antibiotics; MRSA is refractory to all beta-lactam antibiotics, plus many antibiotic groups in routine use, such as chloramphenicol, fluoroquinolones, aminoglycosides, macrolides, and tetracyclines [31-33]. Besides its far-reaching antibiotic resistance, MRSA has attracted a lot of attention due to the relatively high prevalence of its infections and its connection with persistent outbreaks, compared with methicillin susceptible *Staphylococcus aureus* (MSSA) [34-36]. Data from thirty-one countries in Europe within a one-year period indicated the occurrence of 27,711 MRSA BSI episodes, and these were in tandem with 5,503 deaths and 255,683 days of hospital stay; the cost estimated for this length of hospital stay was 44 million Euros [36].

4.2 Streptococcus pneumoniae

Streptococcus pneumoniae, also called the pneumococcus, is a principal cause of bloodstream infections, though not as common as *S. aureus*. Pneumococcal sepsis is usually fatal. In the immunocompetent patient population, host factors that predispose to increased case fatality include diabetes mellitus and liver disease [37-42]. Among the immunocompromised, chronic kidney disease, HIV infection, and malignant disease are linked with increased case fatality [37,43]. *S. pneumoniae* is a normal flora of the nasopharynx, and carriage precedes development of pneumococcal sepsis and other diseases of the organism [44-46]. Carriage of the pneumococcus is especially high among children below age five, and this probably explains why pneumococcal septicaemia and related infections are relatively more frequent in children. In Ghana, a study on community-acquired septicaemia reported that *S. pneumoniae* prevalence in children less than five years old (0.26%) was twice the prevalence in older people

(0.13%) [23]. Though *S. pneumoniae* is predominantly associated with community-acquired invasive infections, there is increasing evidence of its implication in nosocomial infections. One retrospective study in two large teaching hospitals in Spain involving adult patients identified 10.6% (n = 108) of 1,020 episodes of *S. pneumoniae* bacteraemia to be nosocomial in origin [47]. Overall, 31.2%, 11.7%, and 3.9% of the patients respectively developed severe sepsis, septic shock, and multiple organ failure. The principal portals of entry leading to bacteraemia in the patients were pneumonia (70.1%), primary peritonitis (5.2%), and meningitis (5.2%).

Multidrug resistance is now widespread among pneumococci [48-50], and this has negative implications for pneumococcal bloodstream infections, in terms of the severity and treatment. Fortunately, several pneumococcal vaccines have been available, and at present, there are two main types, including the polysaccharide (unconjugated) vaccine and conjugate vaccines. The polysaccharide vaccine contains 23 serotypes, and has an average good efficacy of approximately 60 to 70 percent in protecting against these serotypes [51]. However, its usefulness is limited in the elderly, immunocompromised individuals, and infants. Most of these limitations have been addressed with the development of the conjugate vaccines, which consist of 10 or 13 capsular serotypes of the organism. In addition, the conjugate vaccines have a relatively higher potential in controlling the serotypes most frequently linked with multidrug resistance. It should however be noted that pneumococcal conjugate vaccines are not a panacea for pneumococcal infections, owing to the limited serotype composition and the possible emergence of non-vaccine serotypes post-vaccination.

4.3 Enterococci

Enterococci are increasingly being implicated in infections among patients on hospital admission [52,53]. They have been implicated as the third or fourth frequently encountered pathogens in nosocomial bloodstream infections [52-54], and have maintained their listing in the ten topmost etiologies of community-associated BSI [8,22,55]. During 1998 to 2005 and 2000 to 2004 respectively, incidence rates of community-associated BSIs due to *Enterococcus faecalis* were noted as 3.6 per 100,000 in Victoria, Canada [55], and 2.9 per 100,000 in Calgary [8]. Pinholt *et al*. [56] reported rates of 1 and 7 per 100,000 for *E. faecium* and *E. faecalis* BSIs respectively in two areas in Denmark for the period spanning from 2006 to 2009.

Similar to *S. aureus* and the pneumococcus, antimicrobial resistance is on the rise among the enterococci, and this complicates treatment of their infections. Initial reports had indicated a rising trend of enterococcal resistance to aminoglycosides (high-level) and ampicillin, but the phenomenon that probably attracts the greatest attention is the increased rates at which vancomycin-resistant enterococci (VRE) are isolated [57,58]. Within just a four-year period (1989 to 1993), there was a 20-fold rise in the rates of VRE reported to the National Nosocomial Infection Surveillance System [59]. Besides this, a number of researchers have thereafter

reported 14%–25% of all enterococci isolated from patients in North American hospitals to be vancomycin-resistant [54,60,61]. Of concern, VRE have been implicated in BSI, particularly in severely ill patients on extensive antibiotic therapy during prolonged hospital stays, as well as immunocompromised individuals [62]. Moreover, previous studies, albeit not adjusting for severity of illness, have noted that vancomycin resistance exacerbates mortality [63]. Several studies that addressed that limitation followed, yet their conclusions lacked harmony. Some failed at demonstrating a statistically significant association between vancomycin resistance and increased mortality [64-69], whereas others successfully did [70-73].

4.4. Some other Gram-positive bacteria

A few other Gram-positive bacteria implicated in BSIs include *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis*, the group C beta hemolytic streptococci, viridans group streptococci, coagulase-negative staphylococci (CoNS), *Listeria monocytogenes*, as well as anaerobic bacteria [8,22,55,74-78]. Rates of 2.3–11.6 per 100,000 have been reported for *S. pyogenes* community-onset BSI in somewhat geographically- and temporally-distinct studies [8,22,55,74,79]. The upper limit of the reported range, 11.6, is however blurred by a possible inclusion of hospital-acquired infections. The rates reported for *S. agalactiae* are 2.3 [8] and 2.5 [55] per 100,000, both studies emanating from Canada, with that of Laupland et al. [55] spanning a longer time period (1998 to 2005) than that of Laupland et al. [8] (2000 to 2004). Rates of about 2 to 3 per 100,000 have been reported in Finland, Denmark, and Canada for *Streptococcus dysgalactiae* subsp. *equisimilis* [55,75,76,78]. There are controversies regarding the determination of community-onset viridans group streptococci and coagulase-negative staphylococci BSI, as studies reporting on these pathogens have mostly been conducted in hospital settings [80]. Although CoNS are implicated in both community- and healthcare-associated BSI, they are primarily observed in the latter [22,55,81]. Notably, though, the accurate identification of CoNS as etiologies of BSI is subject to the expertise of the clinician, as they frequently contaminate blood cultures, and this mars the integrity of reported prevalence rates of CoNS community-associated BSIs [82,83]; this challenge in determining precise rates also holds true for the viridans group streptococci. *Listeria monocytogenes*, associated with food contamination, have been implicated in outbreaks of BSI in communities, but this occurs sparingly, and this is seen in rates of 0.2 to 0.3 per 100,000 reported in the United States during the initial part of the twenty-first century [77]. With regard to the anaerobic bacteria, it is *Bacteroides fragilis* that has usually been implicated in community-onset BSI – annual rates in reports emanating from two Canadian cities are 2.1 [55] and 2.4 [84] per 100,000. Next in rank to *B. fragilis* is *Clostridium* species, reported at a rate of 1.2 per 100,000 [85]. Other anaerobic bacteria are rarely implicated [86-88]. As a group though, Ngo et al. [89] reported their BSIs at incidence rates of 3.6 and 2.9 per 100,000 for community- and healthcare-associated community-onset BSIs, respectively in Calgary during 2000 to 2008.

4.5. Gram-negative bacilli

Gram-negative bacilli account for about 25–50% of all BSIs; these proportions are contingent on the geographical location, whether the onset of the infection is in the hospital or community, and other patient risk factors. Those commonly implicated in bloodstream infections include *Proteus, Serratia, Pseudomonas aeruginosa, Neisseria meningitidis, Escherichia coli*, and *Klebsiella pneumoniae*. Of these, *E. coli* is probably the most clinically significant, as it has been singled out together with *S. aureus* and *S. pneumoniae* as etiologies of more than one-half of community-onset BSIs [8,22,55,90]. Data from overall population-based studies suggest *E. coli* as the most implicated etiology of BSI [8,22,55,90-94]. Also, studies that have investigated BSI with a particular focus on *E. coli* have reported high incidence of BSI caused by *E. coli*, with some of these researchers classifying most of the infections as community-associated [95-98]. Laupland et al. [96], whose study spanned from 2000 to 2006 in a Canadian population of 1.2 million, reported a higher incidence of community-associated *E. coli* BSI than healthcare-associated (53% vs. 32%), with an overall incidence of 30.3 per 100,000 annually. This holds true for the study of Kennedy et al. [95] conducted among an Australian population of 366,000 which spanned a relatively shorter period (2000 to 2004) – 68% vs. 13% for community-associated and healthcare-associated were respectively reported, with an annual incidence of 28 per 100,000. In a relatively current study conducted in New Zealand among a population of 500,000 from 2005 to 2011 by Williamson et al. [98] however, a lower incidence of community-associated infections (34%) than healthcare-associated infections (40%) was reported, with an incidence of 52 per 100,000 annually. The study of Williamson et al. [98] compares well with that conducted by Al-Hasan et al. [97] in Olmsted County of the United States, which spanned from 1998 to 2007 among a population of 124,277, and reported that females had a higher incidence of *E. coli* BSI (48 per 100,000) than males (34 per 100,000) and a higher incidence of community-onset infections (approximately 44 and 31 per 100,000) after stratification of the infections by virtue of their being community associated (32%) or healthcare associated (59%).

As is observed in *E. coli*, one group of organisms widely noted for community-associated BSIs is *Klebsiella* species – some studies have acknowledged them as fourth on the list of the paramount community-associated BSI etiologies [8,22,55]. For instance, for the period spanning from 1998 to 2007, in the United States, Al-Hasan et al. [99] reported an overall incidence rate of 9.4 per 100,000 and 15.4 per 100,000 for females and males respectively. In Canada, an incidence rate of 5.2 per 100,000 with a 14% case fatality rate was reported for community-onset BSI caused by *Klebsiella pneumoniae* for the period spanning 2000 to 2007 [100]. Comparably, a rate of 5.7 per 100,000 was reported in another Canadian study for the period spanning 1998–2005 [55]. Of the *Proteus genus, P. mirabilis* is the species that "puts" the *Proteus* genus "on the map" of etiological agents of BSI. It has been listed among the top

ten bacterial agents of community-associated BSI [8,90], at incidence rates less than or equal to 2 per 100,000 [8, 101]. Less than 0.1 per 100,000 has been reported for the other species of the genus [84]. With regard to *Serratia* species, incidence rates of 0.5–0.6 per 100,000 have been reported for community-associated BSI [102,103]. Like *P. mirabilis*, *Pseudomonas aeruginosa* has been tagged by some studies as part of a "top ten", but unlike *P. mirabilis*, its tag is more generic – that of being a part of the top ten culprits of community-associated BSI – not top ten bacterial etiologies [8,22,81]. To illustrate, annual incidence rates of 2 to 6 per 100,000 *P. aeruginosa* community-onset BSIs have been reported [8,104,105]. With regard to *Neisseria meningitidis,* the incidence of its BSI is difficult to estimate, as it exhibits dynamism temporally and geographically, is highly amenable to the immunization status of populations, and is influenced by outbreaks [106-108].

Some other Gram-negative organisms implicated in BSI include *Salmonella enterica*, *Enterobacter* species, *Citrobacter* species, *Morganella morganii*, *Providencia* species, and *Haemophilus influenzae*. With regard to *S. enterica*, the rates of its BSI in a number of geographical areas have been reported to range between 0.21 and 2.3 per 100,000 [109,110], and international travel has been noted to increase its risk of occurrence [111]. In Kenya, one study [112] reported an incidence rate of *S. enterica* serovar Typhi BSI that was higher in urban study sites (247 per 100,000) than the rural (29 per 100,000), but conversely, rates of non-typhoidal Salmonellae BSI in another study [113] was lower in the urban (13 per 100,000) than (78 per 100,000) rural study sites. As regards *Enterobacter* species, one study reported their BSI rate as 3.3 per 100,000 population; of the cases, 21% were community-associated, and 58% were healthcare-associated [114]. Population-based data on *Citrobacter* species are limited. One of the few published studies, conducted in Olmsted County, reported a rate of less than or equal to 1 per 100,000 [101]. The rates at which *Morganella morganii* and *Providencia* species have been reported are low, being respectively 0.3 per 100,000 [84] and 0.15 per 100,000 [84]. *H. influenzae* was a part of the predominant etiologies of community-onset BSIs until the introduction and extensive use of protein-conjugate serotype b vaccines [90]. This has however resulted in the dominance of serotypes not captured in the vaccine in its infections. For instance, for serotypes a, b, and c to f respectively, incidence rates of 0.04 to 8, 0.08 to 2, and 0.04 to 1.4 have been reported [115-119]. Overall, though, some studies have reported incidence rates of 1 to 1.5 per 100,000 [117,120,121], and these emanate from different geographical areas.

Over the years, antimicrobial resistance has been reported among Gram-negative bacteria, including those implicated in BSIs, at exponential rates [122-125]. This probably stems from their propensity for antimicrobial resistance, partly structurally conferred by their outer membranes which are capable of making them less permeable to antibiotics [126]. Moreover, they harbor a pool of antibiotic resistance determinants which they

homogenously and heterogeneously shuttle [127]. Two main mechanisms underlie multidrug resistance in Gram-negative bacteria – the production of extended-spectrum β-lactamases and carbapenemases. In the study conducted in Egypt by Abdallah et al. [123], 48.93% (n = 46) of the 94 Enterobacteriaceae isolated by the researchers were phenotypically demonstrated to be ESBL producers. One of these, belonging to the *Enterobacter* genus, was additionally resistant to meropenem. Genetic investigations revealed the resistance determinant, CTX-M, to be present in 89.13% (n = 41) of the ESBL producers, as opposed to 56.52% (n = 26) and 21.74% (n = 10) which respectively harbored TEM and SHV; almost half (47.83%) of the ESBL producers were resistant to multiple drugs.

5. Microbial Pathogenesis of Sepsis

Identifying a specific agent that exclusively initiates sepsis among Gram-positive bacteria is challenging, owing to the heterogeneity of the group. Nonetheless, a minimum of two pathways have been implicated [128]. One of these involves such structural components as surface proteins, teichoic acids, and the characteristic peptidoglycan cell wall, and the other, inherent toxins released by the organisms during infections, such as exotoxins. The haematogenous presence of these toxins may trigger a cascade of systemic inflammation. Some types of exotoxins that are released act locally, such as the enterotoxins released in host guts. One other bacterial secretion that warrants investigation as a potential precursor of sepsis is the glycocalyx ("slime") produced by some Gram-positive organisms. Among the Gram-negative bacteria, the lipopolysaccharide is the macromolecule that is largely implicated in septic shock [129,130], and has been a target for the development of remedies to mitigate the effects of septic shock [131].

6. Conclusions

At present, bacterial organisms implicated in bloodstream infections constitute an inexhaustible list. A major challenge this presents is the shuttling of antimicrobial resistance determinants among them. Even though vaccines have been developed to mitigate the clinical significance of infections with some of these bacteria, such as *S. pneumoniae* and *H. influenzae*, it is not financially feasible to replicate that in all the major bacteria implicated in bloodstream infections, more especially, given the extensive heterogeneity of each species. Moreover, the development of new antimicrobials, albeit seemingly at its peak, is apparently outpaced by the pervasiveness of antimicrobial resistance. Perhaps, a sound approach in mitigating the burden of bloodstream infections would be to intensify global efforts on infection prevention strategies and the curtailing of irrational antimicrobial use.

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