The complex pathogenesis of bacteremia
From antimicrobial clearance mechanisms to the genetic background of the host

Eirini Christaki[1,2,*] and Evangelos J Giamarellos-Bourboulis[3,4]

[1]Third Department of Internal Medicine; Aristotle University of Thessaloniki; Papageorgiou General Hospital; Thessaloniki, Greece; [2]Infectious Diseases Division; Warren Alpert Medical School of Brown University; Providence, RI USA; [3]Fourth Department of Internal Medicine; Medical School; University of Athens; Athens, Greece; [4]Integrated Research and Treatment Center; Center for Sepsis Control and Care; Jena University Hospital; Jena, Germany

Bacteremia develops when bacteria manage to escape the host immune mechanisms or when the otherwise well-orchestrated immune response fails to control bacterial spread due to inherent or acquired immune defects that are associated with susceptibility to infection. The pathogenesis of bacteremia has some characteristic features that are influenced by the genetic signature of the host. In this review, the host defense mechanisms that help prevent bacteremia will be described and the populations who are at risk because of congenital or acquired deficiencies in such mechanisms will be defined. A special mention will be made to novel insights regarding host immune defense against the most commonly isolated organisms from patients with community-acquired bloodstream infections.

Introduction

Bacteremia is defined as the presence of viable bacteria in the bloodstream and can occur in daily activities like toothbrushing and some minor medical procedures like dental work but also during infection.[1] In the first case, it is a transient and clinically benign condition where the host immune mechanisms eliminate the bacteria from the blood. However, when those mechanisms fail or in the presence of anatomic lesions, turbulent cardiac blood flow and foreign material, bacteremia can lead to infection and sepsis. The incidence of bloodstream infections (BSI) either of community-acquired origin or of hospital-acquired origin has dramatically increased.[2,3] The incidence rate of community-acquired bacteremia (CAB) varies according to the geographic location and it is reported to be 31.1 episodes per 100 000/year in northeast Thailand,[4] 92 episodes per 100 000/year in northern Denmark,[5] 153 episodes per 100 000/year in Olmsted County in the United States[6] and 101.2 episodes per 100 000/year in Victoria, Canada.[7] The etiology varies according to age, geographic location, ecologic environment, and co-morbid illnesses.[4,8,9] The incidence is greater in males (especially older males), very young,

*Correspondence to: Eirini Christaki; Email: eirini.christaki@gmail.com

and elderly patients.[6,7] Infections of the respiratory tract, of the urinary tract, and intraabdominal infections are the commonest sites of origin of bacteremia.[3,10] However, 10% of cases are classified as primary bacteremia of undefined origin.[3] *Escherichia coli*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* are the most frequently isolated pathogens.[3,10,11] Community-acquired bloodstream infections are often associated with severe sepsis and septic shock, occurring at a rate of approximately 10.2 episodes per 1000 intensive care unit (ICU) admissions.[12] In a study of 112 patients with sepsis and septic shock due to community-acquired BSI, APACHE II, and hypoalbuminemia were independent risk factors for mortality.[13] Mortality from BSI ranges between 4% and 41.5% in different studies, depending on age, severity of illness, and presence of severe sepsis or septic shock.[3-5,7,9-12] Despite an increase in the prevalence of BSI in ICU patients from 9 to 24.4 episodes per 1000 ICU admissions between 1993 and 2007, associated mortality decreased by almost 20% in the same time period.[10] Similar trends have also been noted in other studies.[4,5,14]

In this review, we will describe the host defense mechanisms that help prevent bacteremia and the populations who are at risk because of congenital or acquired deficiencies in such mechanisms. A special mention will be made to novel insights regarding host immune defense against the most commonly isolated organisms from patients with CAB.

Host Immune Defense Mechanisms to Prevent Bacteremia

Innate immune mechanisms
Pathogen recognition and host response

In order for bacteria to cause bacteremia, they must evade the host immune mechanisms either in the site of infection or in the bloodstream. Innate immune cells recognize microorganisms through sensing of common microbial structures known as pathogen-associated molecular patterns (PAMPs), like lipotechoic acid, lipopeptides, lipopolysaccharide (LPS), peptidoglycan, flagellin, and nucleic acids.[15] Receptors on the surface of immune and non-immune cells, the so-called pattern recognition receptors (PRRs), recognize and attach PAMPs.[16] Toll-like receptors (TLRs) are an important family of PRRs and have a major role in host defense against bacteria. The transmembrane

TLR2 and TLR4 are of crucial importance, since they bind the most common bacterial surface molecules like peptidoglycan, lipotechoic acid, lipopetides, and LPS.[17] TLR2-deficient mice are more susceptible to *S. aureus* infection than wild type mice.[18] PRRs are not only found on the cell surface but also in the cytoplasm, like the nucleotide-oligomerization domain leucine-rich repeat proteins (NOD-LRRs). Activation of Nod-like receptors (NLRs) like NLRP3 through PAMPs leads to oligomerization and recruitment of adaptor proteins leading to the formation of a multiprotein complex called the "inflammasome" which contributes to the production of pro-inflammatory cytokines like IL-1β and antimicrobial peptides. NOD2-deficient mice showed impaired bacterial clearance and larger skin lesions after cutaneous *S. aureus* infection compared with wild-type controls.[19] Other important PRRs for the initiation of the innate immune response are also the C-type lectin-receptors (CLRs) and recruiting domain helicases like the retinoic-acid-inducible-gene I (RIG-I)-helicases.[20]

Attachment of PRRs to their ligands activates downstream signaling pathways via intracellular adaptor proteins, like myeloid differentiation factor 88 (MyD88), that lead to the activation of transcription factors that modulate gene expression and pro-inflammatory cytokine production.[21] Moreover, a transmembrane receptor of blood neutrophils and monocytes, triggering receptor expressed on myeloid cells (TREM), magnifies the TLR- and NLR-mediated inflammatory response to microbial products.[22] A major pathway of inflammatory response is driven by the cellular transcription factor nuclear factor kappa B (NFκB), which migrates to the cell nucleus and forms a complex with DNA, resulting in the expression of pro-inflammatory cytokines.[23] TNFα is rapidly produced by activated blood cells and has direct proinflammatory and procoagulant properties, which are further enhanced by other cytokines like IL-1, IL-2, IL-6, IL-8, and IFN-γ.[24] In addition, novel molecular pathways are being identified as elementary in the antibacterial host defense. Nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) is a transcription factor that induces antioxidant responses and other cytoprotective defenses, like glutathione and heme-oxygenase-1 biosynthesis, in response to inflammatory and oxidative stress. There is evidence that activation of the Nrf2 pathway in innate immune cells preserves antibacterial defenses and leads to decreased systemic bacterial burden after experimental cecal ligation and puncture (CLP).[25]

Host–pathogen interface

The first barrier to pathogen invasion is the skin and mucosal surfaces. Microbes most commonly enter the body through the skin, the gastrointestinal tract, and the respiratory tract.[26] Antigen-presenting cells residing in the epithelium (mainly dendritic cells) capture bacterial antigens and present them to T lymphocytes. Specifically for the skin, Langerhans cells (dendritic cells that reside in the skin epithelium) bind and endocytose bacterial antigens, then they migrate to the lymph nodes were they present part of the antigens to naïve T lymphocytes which then differentiate to effector cells.[27] This mechanism is lost in the event of trauma, burn, or the use of medical devices and renders the host susceptible to infection. Loss of the skin

and mucosal surface barrier to bacterial invasion, with the use of medical devices like urinary catheters and intravenous catheters, contributed to the morbidity and mortality associated with *E. coli* bacteremia.[28,29] In one study, host factors outweighed bacterial virulence factors in predicting the outcome in adults and neonates with *E. coli* bacteremia.

Most infections caused by *S. aureus* involve the skin and soft tissue but often this organism can cause bacteremia, pneumonia, endocarditis, osteomyelitis, and sepsis.[30-32] Moreover methicillin-resistant *S. aureus* (MRSA) poses a major threat to public health given its worldwide spread, virulence, and difficult to treat invasive and life-threatening infections related to this organism.[31,33,34] About one-third of the population is colonized with *S. aureus* as shown in one US study[35] and it is well established that colonization with *S. aureus* is a risk factor for subsequent infection.[36,37] Host immune defense against *S. aureus* originates in the skin where there are cutaneous host innate immune mechanisms that detect and combat microbial pathogens.[27,38,39] Keratinocytes express TLR 1, 2, and 6 and NOD2 receptors, which recognize and bind *S. aureus*-derived lipoptides, lipotechoic acid, and peptidoglycan-derived muramyl dipeptide, leading to cytokine production and neutrophil recruitment.[40] These cells also produce antimicrobial peptides with bacteriostatic or bactericidal activity, like β-defensin 3 (hBD3), RNase 7, or human cathelicidin (LL-37), all of which have potent activity against *S. aureus*.[41-43] Such antimicrobial peptides are also produced after activation of keratinocytes by *Staphylococcus epidermidis* via a TLR-2-dependent mechanism, a finding that suggests that commensal organisms also contribute in *S. aureus* killing in the skin.[44,45]

Cellular innate immune response

The first and most important cellular host defense against invading pathogens is neutrophils. Neutrophils migrate rapidly from the blood to the site of infection and this recruitment is mediated by chemoattractants, like IL-8, granulocyte chemotactic protein 2 (GCP2), leukotriene B_4 (LTB_4), which are secreted by monocytes, macrophages, keratinocytes, mast cells, endothelial, and other host immune cells. Recognition and subsequent phagocytosis of invading microorganisms by neutrophils is mediated through PRRs and facilitated by antibody-Fc and complement receptors that bind to complement and antibody-coated microbes.[46] After phagocytosis, microorganisms contained in phagosomes are killed by NADPH oxidase-dependent and myeloperoxidase-dependent reactive oxygen species or by antimicrobial peptides of cytoplasmic granules.[46,47] In addition, the role of neutrophil extracellular traps (NETs), a novel mechanism of neutrophil antimicrobial defense has been described and is currently under investigation.[48-50] NETs comprise of histones, chromatin, azurophilic granule, and cytosolic proteins and were shown to bind and destroy pathogens like *S. aureus*.[49,50] Of the human neutrophil peptides (HNPs), the one with the greatest activity against *S. aureus* is HNP2.[51] Also, calprotectin (S100A8/S100A9), a protein complex found in neutrophilic cytoplasm, inhibits. *S. aureus* growth via Mn^{2+} and Zn^{2+} chelation.[52] Phagocytosis also enhances neutrophil apoptosis which is necessary for the resolution of the inflammatory response.[53] Neutrophils have a major role in the control and

clearance of extracellular bacteria like *S. aureus*.[54,55] Congenital (leukocyte adhesion deficiency disorders, severe congenital neutropenia, myeloperoxidase deficiency, chronic granulomatous disease) or acquired (after chemotherapy) deficiency in the number or function of neutrophils predisposes to invasive infections, not only by *S. aureus* but also from gram-negative bacteria and fungi.[47]

Other cells with phagocytic potential include tissue macrophages, dendritic cells, and natural killer (NK) cells. Apart from phagocytosis, after their activation, macrophages secrete a number of chemotactic, inflammatory, and immunoregulatory molecules that direct the migration of other immune cells to the site of infection or act systemically regulating their response, hence playing a major role in the crosstalk between the innate and adaptive immune systems.[26] The role of NK and NKT cells in bacteremia and sepsis is also of considerable importance as evidenced by an increasing number of relevant experimental and human studies.[56,57] The pathogenesis of sepsis in patient populations is characterized by marked heterogeneity. It seems that both the innate and adaptive immune responses differ between patients in relation to the underlying type of infection. A prospective study including 505 patients was conducted by the Hellenic Sepsis Study Group. Flow cytometry analysis of white blood cell count subsets was conducted in blood sampled within the first 24 h from diagnosis. The primary study endpoint was the differences in immune responses between sepsis and severe sepsis/shock as these are related with the underlying type of infection leading to sepsis. From the total of 505 enrolled patients, 183 had acute pyelonephritis, 97 had community-acquired pneumonia (CAP), 100 had intrabdominal infections, 61 had BSIs, and 64 had hospital-acquired pneumonia. Increased apoptosis of natural killer T cells was the main change of the immune response upon transition from sepsis to severe sepsis/shock in patients with BSI contrary to the other types of infections.[58] No profound explanation exists for this finding. Indirect evidence comes from an animal model of lethal ehlrichiosis. Although depletion of NKT cells did not affect final outcome, it prevented the advent of signs of toxic shock and prevented the development of excess levels of circulating TNFα.[59]

The role of complement

One of the first and most potent host immune barriers which all human pathogens, including bacteria, fungi, viruses, and parasites, encounter is the complement system. After bacterial infection, complement is activated through the classical, alternative, and mannose-binding lectin (MBL) pathways. Antigen-antibody complexes and C-reactive protein (CRP) bind to phosphorylcholine on the bacterial cell surface; amyloid P and bacterial cell wall components bind the C1q complex, which in turns activates the classic complement pathway, which includes C1, C2, C3, and C4. The alternative pathway is activated by microbial elements (bacterial cell surface) and involves factor B, factor D, properdin, and C3. Cleavage of C3 results in the production of opsonins that prepare pathogens for phagocytosis, anaphylatoxins, and the creation of a membrane attack complex that lyses target cells. One major example is the role of complement in the innate immune defense against *S. pneumoniae*.[60-62] CAP caused by this

species is associated with bacteremia in 10–30% of cases.[63] One of the main mechanisms of *S. pneumoniae* clearance from the systemic circulation is opsonophagocytosis mediated by complement components.[62,64] There is evidence that that classic complement pathway has a more critical role in host immune defense against *S. pneumoniae* compared with the alternative pathway.[65] In more detail, Brown et al. studied mice genetically deficient of different complement components and demonstrated that C1q$^{-/-}$ mice (deficient in the classical complement pathway) were more susceptible to pneumococcal infection than Bf$^{-/-}$ mice (deficient in the alternative complement pathway).[65] A defect in the classical complement pathway may limit primary adaptive immune responses which are known to be paramount in invasive pneumococcal infection.[66] However, the alternative pathway has been found to amplify the activation of the classical/MBL complement pathway, thus playing an important role in the natural antibody-mediated opsonization of *S. pneumoniae*.[67] In a pneumococcal otitis media model, where three types of complement-deficient and wild-type mice were used, Bf/C2$^{-/-}$ mice had higher bacterial burden in the blood 24 h after transtympanic infection than C1qa$^{-/-}$ and Bf$^{-/-}$ mice, whereas wild-type mice exhibited no bacteremia. In addition, complement-deficient mice exhibited decreased capacity for C3-mediated opsonization and complement-mediated opsonophagocytosis, which could be related to dissemination of *S. pneumoniae* to the bloodstream in these animals, indicating a critical role for both the classical and alternative pathways in host immune defense against pneumococcal otitis.[68]

To avoid potentially injurious excessive activation of the complement system, the host uses regulatory proteins, like C4b-binding protein (C4bp), which inhibits the classic and lectin pathways. Many bacteria use these host regulatory proteins in order to escape complement-mediated killing. Despite their diversity, pathogens share common mechanisms of complement escape. Examples of such strategies are the expression of host complement regulator binding proteins, the secretion of proteases, and the release of complement inhibitors. Moreover, each microbial pathogen often uses multiple strategies to evade immune recognition and complement attack. Using such complement escape proteins, bacteria like *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Borrelia burgdoferi*, and fungi like *Candida* species, can evade host immune response and disseminate to the blood.[69] Many of the individual proteins used by pathogens to prevent and inhibit complement activation and attack have been molecularly and functionally characterized in the last decade. For example, it was recently shown that an *E. coli* outer membrane protein, NlpI, contributes in high-level bacteremia by facilitating blockade of classical complement-mediated killing, via C4bp deposition on the bacterial surface.[70] In addition, Prc, another *E. coli* bacterial periplasmic protease was also found to have a critical role in the evasion of complement-mediated killing.[71] Hence, when immune mechanisms fail to control bacterial spread either due to bacterial evasion of host immune strategies or due to a breach or defect in the otherwise well-orchestrated immune response, bacteremia can develop (**Fig. 1**).
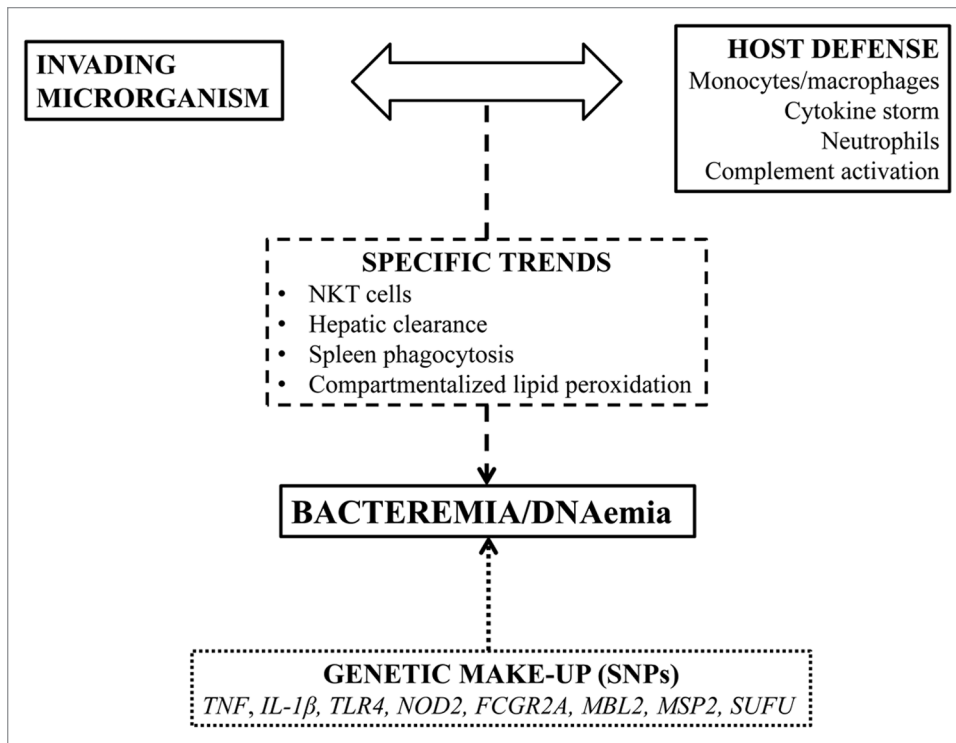
Figure 1. The complex interactions between the invading microorganism and the host defense mechanism ending in bacteremia. These interactions present some unique features in pathogenesis and they are under the influence of the genetic make-up of the host.

Adaptive immune response

As opposed to innate immune defense, the adaptive immune response is stimulated later during the infection process and encompasses B cell- and T cell-specific responses. Central to cellular adaptive immune responses is the presentation of exogenous antigens or microbes to lymphocytes by antigen presenting cells, most commonly dendritic cells and monocyte/macrophages via an MHC-I or II dependent manner. T-helper cells that express the CD4 molecule recognize antigens in the context of MHC class II molecules. Upon antigenic stimulation, naïve CD4+ cells expand and differentiate into Th1, Th2, and Th17 cells.[72] Th1 response promotes cell-mediated immune responses via the production of pro-inflammatory cytokines like IFN-γ, TNF-α, IL-2, and IL-1β. Th2 cells produce IL-4, IL-10, IL-13, and support antibody mediated immune responses. Th17 cells produce IL-17, Il-21, IL-22, IL-26, mediate neutrophil recruitment and activation, contribute to abscess formation, and are critical for the clearance of extracellular bacteria.[39,72] In addition, Th17 responses induced by bacteria and fungi result in the secretion of antimicrobial peptides that contribute to mucosal host defense.[73] CD8+ T cells destroy target cells with cytolysis, produce potent inflammatory cytokines like IFN-γ and TNF-α, and they are the major effector cells against intracellular bacteria. When activated by antigens expressed on infected cells and co-stimulators, they differentiate into cytolytic cells (CTLs) and secrete proteins that form pores in the infected cell membrane and mediate apoptosis of these cells.[74]

B-cell responses lead to the production of antibodies directed against specific antigenic components of a certain pathogen.[26] Immunoglobulin molecules consist of the Fc constant region that binds to Fc receptors on the surface of immune cells and is responsible for most of their effector functions and the Fab variable antigen-binding region with which the antibody binds with great specificity to the optimal target molecule and which is characterized by massive diversity. Antibodies interact with the binding of pathogens or toxins to the host cell receptors, hence neutralizing their effect and limiting microbial infectivity. Also, they opsonize bacteria and thus facilitate neutrophil or macrophage phagocytosis, mediate antibody-dependent killing of pathogens by NK cells or granulocytes and also activate complement. After the second encounter with the same antigen, B cells produce larger amounts of antibodies that often show increased heavy chain isotype switching. Moreover, the antigen–antibody binding affinity increases with repeated stimulation (affinity maturation), thus increasing the yield of the antibody response during a secondary infection.[75]

The importance of liver and spleen

The liver and the spleen function as filters of bacteria from the bloodstream and the spleen is a major site of antibody production. As a consequence, patients with anatomic or functional asplenia have increased risk of disseminated infections with encapsulated bacteria.[76] Moreover, the significance of liver function to contain bacteremia has been increasingly recognized recently due to both its metabolic function and its ability to clear bacteria. Within the first six hours after induction of experimental pneumonia by *S. pneumoniae* in mice, the transcriptomic profile of the liver is modulated so that the liver metabolism is shifted toward increased production of high-density lipoproteins (HDLs). These are conceived as soluble receptors for pneumolysin.[77] Moreover, a series of animal studies have shown that HDLs are a mechanism of protection in endotoxemia since they bind LPS whereas low circulating HDL is related with an increased infection risk among critically ill patients.[78] This role of HDL may also have direct therapeutic implications. When reconstituted HDL was administered in the setting of experimental endotoxemia in healthy volunteers, LPS-induced activation of coagulation was attenuated.[79] However, the therapeutic role of reconstituted HDL has not yet been studied in any randomized trial in sepsis. Hepatic clearance is also of major importance to contain bacteremia by *Pseudomonas aeruginosa*. Early after induction of bacteremia, the liver bacterial load increases dramatically to an extent depending

on the number of inoculated bacteria. The inability of the liver to contain bacteria is linked with the induction of hepatic apoptosis in the event of severe large-scale bacteremia and it affects not only the liver but also the renal and myocardial function. Hepatic clearance in this situation is related to the function of Kupffer cells. Loss of Kupffer cells after pre-treatment with gadolinium paves the way for earlier animal death.[80]

The importance of this early modulation of liver function in response to bacteremia has also being confirmed in a recent study where experimental findings were confirmed in the clinical setting. Early after challenge of rats with *P. aeruginosa*, lipid peroxidation in the liver was increased compared with sham-treated animals. On the contrary, lipid peroxidation in the kidney was decreased. Lipid peroxidation was assessed by measurement of malondiadehyde (MDA). Changes of MDA were not statistically related with tissue bacterial load showing that they represent some compartmentalization of the lipid peroxidation process, which is a unique characteristic in pathogenesis. When MDA was measured in serum from patients with sepsis, this compartmentalization was further confirmed: serum MDA was greater in patients with acute liver dysfunction and lower in patients with acute renal dysfunction.[81]

Bacteremia and DNAemia

Bacteremia is traditionally conceived as the presence of pathogenic bacteria in the bloodstream. To this end, the traditional commercialized systems to culture blood mandate the inoculation of large quantities of blood, as much as 10 to 20 ml, in pre-prepared media. With current techniques, detection of bacteremia in severe infections fails to a great extent. Prospective observational studies report an incidence of less than 20% of positive blood cultures among patients with severe sepsis and/or septic shock.[82,83] These findings broad up the question how of is it possible for a host to present with severe infection with a negative blood culture? The reply to this question is related to the extent of bacteremia and to the duration of bacteremia, that greatly differ between patients. The presence of bacteria in the bloodstream is not always constant. Transient episodes of bacteremia seem to be adequate to disseminate the infection within remote tissues. Furthermore, current research conducted with animal models implies that systemic spread of microorganisms takes place from the primary source of infection. In all these models, animals are considered to suffer from bacteremia, yet blood culture results are not always reported; instead, the presence of bacteremia is indirectly documented by the isolation of microorganisms from tissues far from the primary infection site.[84,85]

The extent of bacteremia is another important factor linked with final outcome. Current blood culture systems are not able to quantify circulating bacteria in the bloodstream. Few animal studies are also available to this same end.[86] Molecular identification of circulating bacteria is a proposed alternative allowing to identify not only the presence of pathogens but also to quantify the amount of circulating bacteria. This is done indirectly by the measurement of the number of copies of specific bacterial genes. One well-studied example is the autolysin gene (*lytA*) of *S. pneumoniae*. *lytA* is a single-copy gene and its measurement is an indirect estimation of the number of circulating bacteria. Analysis of samples coming from 93 patients with CAP allowed to discriminate two patterns; patients with low-level gene copies i.e., less than 10^3 copies of *lytA* and patients with high-level gene copies i.e., $\geq 10^3$ copies/ml of *lytA* in the bloodstream. The incidence of bacteremia was 24.2% among patients with low-level gene copies and 66.6% among patients with high-level gene copies ($P < 0.0001$). Similarly patients with high number of copies had a greater incidence of acute renal dysfunction (55.5% vs. 15.1%), septic shock (44.4% vs. 9.1%), and greater mortality (25.9% vs. 6.1%).[87]

These findings regarding the significance of the number of copies of *lytA* are confirmed in two more studies; the first enrolled 45 patients[88] and the second enrolled 304 patients.[89] The first study showed that the number of gene copies is an indicator of the presence of *S. pneumoniae* as the causative pathogen for CAP but also of the degree of the inflammation of the host. Using receiver operator characteristics (ROC) curve analysis, the authors concluded that the use of gene copies is a more reliable marker than the white blood cell count and serum CRP for the systemic inflammatory response syndrome stimulated by CAP.[88] In the second study, it was confirmed that patients with more than 10^3 gene copies/ml in the bloodstream carried a greater risk for severe disease (odds ratio = 5.22).[89]

Similar findings to those reported for the detection of bacteremia using the copy number of specific genes of *S. pneumoniae* have also been reported for patients with bacteremia by *S. aureus* and by *Acinetobacter baumannii*. In a prospective study of 20 patients with secondary methicillin-resistant *S. aureus* (MRSA) bacteremia of various origins, the number of copies of *mecA* conferring resistance to methicillin on patient follow-up was reversibly related with the response to anti-MRSA antimicrobial coverage.[90] In a similar fashion, the copies of *Oxa-51* were measured in the blood of 34 survivors and 17 non-survivors with *A. baumannii* bacteremia. The authors have prospectively measured the number of copies during the disease course and found that any increase of the absolute copy numbers of *Oxa-51* in the bloodstream was an independent predictor of unfavorable outcome.[91] However, the clinical relevance of DNAemia is still not yet clear and further research is warranted in order to determine its exact role in the diagnosis and prognosis of BSIs.

Genetic susceptibility to bacteremia

Genes encoding for immune receptors and cytokines

Most genes of the human genome carry single nucleotide polymorphisms (SNPs) at specific exonic or intronic regions. The frequency of these SNPs is usually below 1% of the general population. Some of these SNPs are carried at greater frequencies even exceeding 20% mostly at a heterozygotes state bringing up the question whether this may impose on a certain disease phenotype. Regarding infectious diseases, the question generated is whether SNPs of genes encoding for all the above described molecules i.e., receptors and cytokines may induce susceptibility to severe infections.

The most broadly studied gene is *TNF*. SNPs of this gene involve the −308 position at the promoter region where a

substitution of guanine (G) for adenosine (A) takes place (rs1800629). A meta-analysis of 25 studies provided contradictory results regarding the role of this SNP for the physical course of sepsis.[92] We tried to decipher the role of this SNP for susceptibility to infection in 213 intubated patients all of whom developed ventilator-associated pneumonia. The rationale of the study was that if this SNP is important, it should have a clear impact on a patient population with a major risk factor (i.e., intubation) for the development of infection. The study did not focus only on the rs1800629 SNP but on the *TNF* haplotype as defined by all three SNPs at the –376, –308, and –238 promoter positions of the *TNF* gene. In all these SNPs G to A substitutions are reported. Results revealed that carriers of any A allele of the three SNPs developed VAP earlier after intubation compared with carriers of only wild-type G alleles and that this was related with lower production of TNFα and of IL-6 by circulating monocytes.[93] Unpublished data of our group report on the significance of these haplotypes for the natural course of 83 patients with infective endocarditis and secondary gram-positive bacteremia. Carriage of the GGG wild-type haplotype was related with a significantly greater risk for unfavorable outcome (odds ratio = 3.29, *P* = 0.041). A large study on 774 medical patients in ICUs, studied the associations of several gene SNPs with the risk for development of bacteremia. Two gene SNPs were associated with a greater risk for BSI. These SNPs were at the position 299 of *TLR4* encoding for TLR4 and at the position 702 of *NOD2* encoding for the CARD15 (caspase activation recruitment domain 15) of the NLRP3 inflammasome PRR. Carriers of these gene SNPs had a greater risk for the acquisition of BSI (13.5% vs. 7.6% of wild-type and of *TLR4* and 12.6% vs. 7.1% of wild-type and of *NOD2*). This risk was even greater for patients carrying both SNPs (25.0% vs. 7.6%). Carriage of these SNPs was also linked with susceptibility for earlier acquisition of BSI after ICU admission.[94] Although this study does not report for an effect of carriage of the Asp299Gly SNP of *TLR4* in cytokine production, it has been shown that monocytes of healthy controls who carry only this SNP allele are able for greater production of TNFα but not of IL-10 compared with monocytes of patients who carry only WT alleles after stimulation with LPS.[95]

Signaling of TLR2 and TLR4 stimulation is down-stream linked with the adaptor protein TIRAP. One SNP has been described for *TIRAP* at position 180 where serine is substituted by leucine. Heterozygozity for this SNP is linked with protection against the development of pneumococcal bacteremia as defined in a cohort of 901 patients from Kenya. Odds ratio for the development of bacteremia was 0.34 (*P* = 0.003) among heterozygotes for this SNP.[96]

Another important SNP linked with susceptibility for bacteremia has been reported from a study enrolling recipients of kidney transplants. The SNP is found at position –511 of *IL-1*β where either a C allele or a T allele exists. Carriage of the C allele is associated with increased risk for bacteremia (66.7% vs. 45.% for non-infected patients, *P* = 0.015).[97]

Genes encoding for other components of the immune response

Genetic association studies have tried to investigate the existence of a link between host factors related with protection against encapsulated microorganisms and the development of bacteremia. These factors primarily refer to the receptor of IgG and the MBL pathway.

One SNP exists after one point mutation of *FCGR2A* encoding for the FcγRIIA receptor of IgG2. This SNP leads to a substitution of arginine with histidine at position 131 of FcγRIIA ending in poor IgG2 binding capacity. This SNP was studied in 1262 patients with CAP and compared with 1224 healthy controls. The overall SNP frequency did not differ between patients and controls. However, among patients with CAP due to *S. pneumoniae* the frequency of SNP carriage was significantly greater among those who developed bacteremia compared with those who did not develop bacteremia. More precisely, among those who developed pneumococcal bacteremia 35.3% were homozygotes and 43.5% heterozygotes for the SNP. This translates to an odds ratio of 2.9 for bacteremia for patients homozygous for the SNP (*P* = 0.00016) and 2.83 for patients heterozygous for the SNP (*P* = 0.0012.).[98]

As described above, the mannose complement pathway is of major importance for the host response against bacteria particularly for encapsulated bacteria. Two major structural SNPs of *MBL2* and *MASP2* have been found to be associated with the physical course of bacteremia. *MBL2* encodes for MBL2. Structural SNPs exist at codons 52 (CGT or TGT haplotypes), 54 (GGG or GAC haplotypes), and 57 (GGA or GAA haplotypes) of exon 1 of *MBL*. These SNPs were studied in a cohort of 145 patients with bacteremia and they were compared with 400 healthy controls. Although the overall frequency of SNPs did not differ between groups, carriers of the GAA haplotype at codon 57 had a 4.2-fold greater risk for the acquisition of gram-positive BSI.[99]

MASP2 encodes for the serine protease of MBL2. rs2273346 of *MASP2* was analyzed in a large cohort of ICU patients. Although carriage of the SNP was not associated with the risk for the development of bacteremia, after adjustment for co-morbidities, it was independently associated with in-hospital mortality (odds ratio = 2.35, *P* = 0.02).[94]

SNPs of *SUFU* have very recently been reported to impact on the physical course of bacteremia. This gene encodes for a negative regulator of the Sonic hedgehog signaling pathway (SHH). This pathway is of major importance for the maturation of CD4 lymphocytes. A total of 69 SNPs of *SUFU* were studied in a cohort of 250 patients with bacteremia by *Enterobacteriaceae*, mainly by *E. coli* and *K. pneumoniae*. The primary study endpoint was the significance of these SNPs for the development of organ failure. It was found that four of the studied SNPs (rs10786691, rs12414407, rs10748825, and rs7078511) were protective against the development of renal dysfunction and two of the studied SNPs (rs12414407 and rs10748827) against the development of ARDS.[100]

Conclusions

BSI is a complex and life-threatening entity. Pathogenesis is multifactorial. Based on the presented analysis, bacteremia develops as a result of imbalances in the complex interplay between the invading microorganism and the host defense mechanisms.

This interplay encompasses some characteristics that are unique for BSI and it seems to be directly influenced by the genetic background of the host.

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