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

Eirini Christaki1,2,* and Evangelos J Giamarellos-Bourboulis3,4

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

Keywords: bacteremia, bloodstream infection, host defense, single nucleotide polymorphism

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. 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. 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, 92 episodes per 100,000/year in northern Denmark, 153 episodes per 100,000/year in Olmsted County in the United States and 101.2 episodes per 100,000/year in Victoria, Canada. The etiology varies according to age, geographic location, ecologic environment, and co-morbid illnesses. The incidence is greater in males (especially older males), very young, and elderly patients. Infections of the respiratory tract, of the urinary tract, and intraabdominal infections are the commonest sites of origin of bacteremia. However, 10% of cases are classified as primary bacteremia of undefined origin. 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. 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. 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. 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. Similar trends have also been noted in other studies.

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. Receptors on the surface of immune and non-immune cells, the so-called pattern recognition receptors (PRRs), recognize and attach PAMPs. Toll-like receptors (TLRs) are an important family of PRRs and have a major role in host defense against bacteria. The transmembrane

*Correspondence to: Eirini Christaki; Email: eirini.christaki@gmail.com
Submitted 06/07/2013; Revised: 09/15/2013; Accepted: 09/17/2013
http://dx.doi.org/10.4161/viru.26514
TLR2 and TLR4 are of crucial importance, since they bind the most common bacterial surface molecules like peptidoglycan, lipoteichoic acid, lipopetides, and LPS. TLR2-deficient mice are more susceptible to *S. aureus* infection than wild type mice. 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. 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.

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. 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. 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. 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. 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).  

*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. 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 where they present part of the antigens to naïve T lymphocytes which then differentiate to effector cells. 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. 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. 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. About one-third of the population is colonized with *S. aureus* as shown in one US study and it is well established that colonization with *S. aureus* is a risk factor for subsequent infection. Host immune defense against *S. aureus* originates in the skin where there are cutaneous host innate immune mechanisms that detect and combat microbial pathogens. Keratinocytes express TLR 1, 2, and 6 and NOD2 receptors, which recognize and bind *S. aureus*-derived lipopetides, lipoteichoic acid, and peptidoglycan-derived muramyl dipeptide, leading to cytokine production and neutrophil recruitment. 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*. 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.

*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 B₄ (LTB₄), 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. 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. In addition, the role of neutrophil extracellular traps (NETs), a novel mechanism of neutrophil antimicrobial defense has been described and is currently under investigation. NETs comprise of histones, chromatin, azurophilic granule, and cytosolic proteins and were shown to bind and destroy pathogens like *S. aureus*. Of the human neutrophil peptides (HNP), the one with the greatest activity against *S. aureus* is HNP2. Also, calprotectin (S100A8/S100A9), a protein complex found in neutrophilic cytoplasm, inhibits. *S. aureus* growth via Mn²⁺ and Zn²⁺ chelation. Phagocytosis also enhances neutrophil apoptosis which is necessary for the resolution of the inflammatory response. 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.\(^57\)

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 chemotactin, 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 bacteraemia 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 subset 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 ehrlichiosis. 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).\(^66\) 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 transystampanic 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 burgdorferi*, 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, NpI, 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).
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. 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. In addition, Th17 responses induced by bacteria and fungi result in the secretion of antimicrobial peptides that contribute to mucosal host defense. 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.

B-cell responses lead to the production of antibodies directed against specific antigenic components of a certain pathogen. 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.

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. 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. In addition, 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. 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. 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 been 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 broaden up the question how of is it possible for a host to present with severe infection with a negative blood culture. The presence of bacteria in the bloodstream is a proposed alternative allowing to 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.93 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.94 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 an 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 (caspace 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 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. Heterozygosity 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 very recently been reported to impact on the physical course of bacteremia. This gene encodes for the FcγRIIA receptor of IgG2. This SNP leads to a substitution of arginine with histidine at position 131 of FcγRIIA encoding 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 MBL. 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.

References
1. Bone RC. Septis, the sepsis syndrome, multi-organ failure: a plea for comparable definitions. Ann Intern Med 1991; 114:332-3; PMID:1987879; http://dx.doi.org/10.7326/0003-4819-114-4-332
2. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Pajak JP, Lamont WW, Clark GC, MacFarquhar J, Walton AL, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002; 137:791-7; PMID:12452355; http://dx.doi.org/10.1056/Ann Intern Med 2002; 137:791-7
3. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, Golan Y, Noy A, Schwartz D, Giladi M. Reappraisal of community-acquired bacteremia: a proposal for a new classification for the spectrum of acquisition of bacteremia. Clin Infect Dis 2002; 34:1431-9; PMID:12015688; http://dx.doi.org/10.1086/369809
4. Kanoksil M, Jarapai A, Peacock SJ. Limmathurotsakul D. Epidemiology, microbiology and mortality associated with community-acquired bacteremia in north-east Thailand: a multicenter study. PLoS One 2013; 8:e54714; PMID:23349954; http://dx.doi.org/10.1371/journal.pone.0054714
5. Søgaard M, Nørgaard M, Dethlefsen C, Schønheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. Clin Infect Dis 2011; 52:61-9; PMID:21148521; http://dx.doi.org/10.1093/cid/ciq069
6. Uslan DZ, Crane SJ, Steckelberg JM, Cockerill FR. Evolution over a 15-year period of clinical characteristics and outcomes of critically ill patients with bacteremia. Clin Infect Dis 2011; 52:61-9; PMID:21148521; http://dx.doi.org/10.1093/cid/ciq069
7. Vandevenne M, Delvaux E, Hubert A, Vandenbossche A, Desmette P. Prevalence of bacteremia and seasonal variations in Olmsted County, Minnesota. Arch Intern Med 2007; 167:834-9; PMID:17452548; http://dx.doi.org/10.1001/archinte.167.8.834
8. Laupland KB, Kibsey PC, Gregson DB, Gallbraith JC. Population-based laboratory assessment of the burden of community-onset bloodstream infection in Victoria, Canada. Epidemiol Infect 2013; 141:1748-59; PMID:24227485; http://dx.doi.org/10.1017/S0950268812004028
9. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Chastre J, Bihari D, Suter PM, Opal SM, Takala J, et al. Sepsis in hospitalised patients: the International Sepsis Collaborators. Lancet 2006; 368:1705-12; PMID:17101775; http://dx.doi.org/10.1016/S0140-6736(06)69180-7
10. Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest 2003; 123:1615-24; PMID:12740282; http://dx.doi.org/10.1378/chest.123.5.1615
11. Artero A, Zaragoza R, Camarena JJ, Sancho S, González R, Nogueira JM. Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. J Crit Care 2010; 25:276-81; PMID:20149587; http://dx.doi.org/10.1016/j.jcrc.2009.12.004
12. Skogberg L, Lyrykkinen O, Ruutu P, Ollgren J, Nuortti J. Increase in bloodstream infections in Finland, 1995-2002. Epidemiol Infect 2008; 136:108-14; PMID:17353630; http://dx.doi.org/10.1017/s0950268807008138
13. Opal SM. The host response to endotoxin, anti-inflammatory cytokines, and the management of severe sepsis. Int J Med Microbio 2007; 297:65-77; PMID:17452016; http://dx.doi.org/10.1016/j.ijmm.2007.09.006
14. van der Poll T, Opal SM. Host-pathogen interactions in sepsis. Lancet Infect Dis 2008; 8:32-43; PMID:18863412; http://dx.doi.org/10.1016/S1473-3099(07)07265-7
15. Takeda K, Akira S. Toll-like receptors in innate immunity. Immunol Today 2000; 21:315-9; PMID:10905702; http://dx.doi.org/10.1016/s0167-5699(00)02117-0
16. van der Poll T, Opal SM. Host-pathogen interactions in sepsis. Lancet Infect Dis 2008; 8:32-43; PMID:18863412; http://dx.doi.org/10.1016/S1473-3099(07)07265-7
17. Huttunen R, Aittoniemi J. New concepts in the pathogenesis, diagnosis and treatment of bacteremia and sepsis. Lancet Infect Dis 2008; 8:32-43; PMID:18863412; http://dx.doi.org/10.1016/s1473-3099(07)07265-7
18. Klevens RM, Morrison RA, Nadle J, Petit S, Gemmekhan K, Ray S, Patterson L, Lylykond F, Dumeny G, Townes JM, et al. Active Bacterial Core Surveillance (ABCS) MRSA Investigators. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA 2007; 298:1763-71; PMID:17904281; http://dx.doi.org/10.1001/jama.298.15.1763
19. Diekema DJ, Pfaffer MA, Jones RN, Doern GV, Winokur PL, Gales AC, Sader HS, Kugler K, Beach M. Survey of bloodstream infections due to gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. Clin Infect Dis 1999; 29:595-607; PMID:10530454; http://dx.doi.org/10.1086/388404
20. Genser RJ, Kutzon-Moran D, McAllister SK, Marquillan G, Fosheim GE, Jensen BJ, Killgore G, Tenover FC, Kuehnert MJ. Changes in the prevalence of nasal colonization with Staphylococcus aureus in the United States, 2001-2004. J Infect Dis 2008; 197:1226-34; PMID:18422434; http://dx.doi.org/10.1086/520135
21. Hekker TA, Groenewald AB, Simoons-Smit AM, de Man P, Connell H, MacLaren DM. Role of bacterial virulence factors and host factors in the outcome of Escherichia coli bacteraemia. Eur J Clin Microbiol Infect Dis 2001; 19:312-6; PMID:11583484; http://dx.doi.org/10.1007/s10096/0050483
22. Tallus K, Brauner A, Frykblund B, Munkhammar T, Rabsch W, Reisbrodt R, Burman LG. Host factors versus virulence-associated bacterial characteristics in neonatal and infantile bacteraemia and meningitis caused by Escherichia coli. J Med Microbiol 1992; 36:203-8; PMID:13732632; http://dx.doi.org/10.1099/00922215-36-3-203
23. McGaig LF, McDonald LG, Mandal S, Jernigan DB. Staphylococcus aureus associated skin and soft tissue infections in ambulatory care. Emerg Infect Dis 2006; 12:1715-23; PMID:17283622; http://dx.doi.org/10.3201/eid1211.060190
24. Kupper TS, Fuhrig HC. Immune surveillance in the skin: mechanisms and clinical consequences. Nat Rev Immunol 2004; 4:111-22; Infection Control Hospital Epidemiol 2004; 25:107-12; PMID:15093775; http://dx.doi.org/10.1088/0140-6736(06)16999-1
25. Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinel in health and disease. Nat Rev Immunol 2009; 9:679-31; PMID:19763149

Disclosure of Potential Conflicts of Interest
The authors have no conflict of interest to declare.
53. Kennedy AD, Miller LS. Innate and adaptive immune responses to Staphylococcus aureus skin infections. Semin Immunopathol 2012; 34:261-80; PMID:22057887; http://dx.doi.org/10.1007/s00281-011-0292-6

54. von Köckritz-Blickwede M, Nizet V. Innate immune virulence. Volume 5 Issue 1

55. Cho JS, Xuan C, Miller LS. Lucky number seven: TLR2 and the resolution of infection. Immunol Res 2009; 30:513-21; PMID:19699684; http://dx.doi.org/10.1007/s12026-008-8049-6

56. Ericksen B, Wu Z, Lu W, Lehrer RI. Antibacterial defense against Staphylococcus aureus infection. Science 2009; 327:1098-102; PMID:19805720; http://dx.doi.org/10.1126/science.1152449

57. Leung B, Harris HW. NKT cells in sepsis. Clin Dev Immunol 2012; 87:775-83; PMID:22035368; PMCID:3495693; http://dx.doi.org/10.1155/2011/983491; http://dx.doi.org/10.1083/j.iijid.2010.123

58. Gogos C, Kotsaki A, Pelekanou A, Giannikopoulos G, Vaki I, Maravitsa P, Adams S, Alexiou Z, Andrianopoulos G, Antonopoulou A, et al. Early alterations of the innate and adaptive immune states in sepsis according to the type of underlying infection. Crit Care 2010; 14:R36; PMID:20504341; http://dx.doi.org/10.1186/cc9301

59. Stevenson HL, Crossley EC, Thirumalapura N, van der Veerdrink FL, Gresnigt MS, Kulberg B, van der Meer JW, Joosten LA, Netea MG. TH17 responses and host defense against microorganisms: an overview. BMJ Rev 2009; 42:776-78; PMID:20044948; http://dx.doi.org/10.1136/bmjrev.b22776

60. Zhang N, Bevan MJ. CD8(+) T cells: foot soldiers of the immune system. Immunology 2011; 35:161-8; PMID:21867926; http://dx.doi.org/10.1111/j.1365-2958.2011.03701.x

61. Abbas AK, Lichtman AH. Antigen recognition in the adaptive immune system. Basic Immunology. Philadelphia: Saunders Elsevier 2009:67-87.

62. Bohnsack JF, Brown EJ. The role of the spleen in hepatic bacterial clearance. Am J Respir Crit Care Med 2009; 179:R6; PMID:19374582; http://dx.doi.org/10.1164/rccm.200509-1470OC

63. Zipfel PF, Würzner R, Skerka C. Complement evasion of pathogens: common strategies are shared by diverse organisms. Mol Immunol 2007; 44:3850-7; PMID:17768102; http://dx.doi.org/10.1016/j.molimm.2007.06.149

64. Tseng Y, Wang SW, Kim KS, Wang YH, Yoo Y, Chen CC, Chiang CW, Hsieh PC, Teng CH. Nipl facilitates degradation of Cr4bp on Escherichia coli by blocking classical complement-mediated killing, which results in high-level bacteremia. Infect Immun 2012; 80:1560-78; PMID:22882934; http://dx.doi.org/10.1128/IAI.00320-12

65. van de Veerdrink FL, Gresnigt MS, Kulberg B, van der Meer JW, Joosten LA, Netea MG. TH17 responses and host defense against microorganisms: an overview. BMJ Rev 2009; 42:776-78; PMID:20044948; http://dx.doi.org/10.1136/bmjrev.b22776

66. van de Veerdrink FL, Gresnigt MS, Kulberg B, van der Meer JW, Joosten LA, Netea MG. TH17 responses and host defense against microorganisms: an overview. BMJ Rev 2009; 42:776-78; PMID:20044948; http://dx.doi.org/10.1136/bmjrev.b22776

67. Xu Y, Ma M, Ippolito GC, Schroeder HW Jr., Carroll TN, Gubareva LV. Skin commensals and the resolution of infection. Immunol Res 2012; 43:25-61; PMID:19967641; http://dx.doi.org/10.1007/s12026-008-8049-6
83. Korsaki A, Giamarellos-Bourboulis EJ. Molecular diagnosis of sepsis. Expert Opin Med Diag 2012; 6:209-19; http://dx.doi.org/10.1517/17530059.2012.667799; PMID:23480866

84. Krasnodembskaya A, Samarani G, Song Y, Zhao H, Su X, Lee JW, Gupta N, Petriti M, Marthay MA. Human mesenchymal stem cells reduce mortality and bacteria in gram-negative sepsis in mice in part by enhancing the phagocytic activity of blood mono-ocytes. Am J Physiol Lung Cell Mol Physiol 2012; 302:L1003-15; PMID:22427550; http://dx.doi.org/10.1152/ajplung.00180.2011

85. Giamarellos-Bourboulis EJ, Adamis T, Louartaris G, Sabraco L, Kousoulas V, Mouktaroudi M, Perrea D, Karayannacos PE. Giamarellos H. Immunomodulatory clarithromycin treatment of experimental sepsis and acute pyelonephritis caused by multidrug-resistant Pseudomonas aeruginosa. Antimicrob Agents Chemother 2004; 48:93-9; PMID:14695524; http://dx.doi.org/10.1128/AAC.48.1.93-9.2004

86. Giamarellos-Bourboulis EJ, Mouktaroudi M, Adamis T, Kousoulas V, Baziaka F, Perrea D, Karayannacos PE, Giarmarellos H. n-6 polyunsaturated fatty acids enhance the activities of ceftriaxone and amikacin in experimental sepsis caused by multidrug-resistant Pseudomonas aeruginosa. Antimicrob Agents Chemother 2004; 48:4713-7; PMID:15561848; http://dx.doi.org/10.1128/дж.В48.12.4713-4717.2004

87. Rello J, Lisbon T, Lujan M, Gallego M, Kee C, Kay I, Lopez D, Waterer GW. DNA-Neumococo Study Group. Severity of pneumococcal pneumonia and death in the medical intensive care unit. Crit Care Med 2009; 37:192-201, e1-3; http://dx.doi.org/10.1097/CCM.0b013e3181b42af0

88. Peters RP, de Boer RF, Schuurman T, Gierveld S, Koosstra-Smid M, van Agtmael MA, Vandenbroucke-Grauls CM, Persoons MC, Savelkoul PH. Streptococcus pneumoniae DNA load in blood as a marker of infection in patients with community-acquired pneumonia. J Clin Microbiol 2009; 47:3308-12; PMID:19675218; http://dx.doi.org/10.1128/JCM.01071-09

89. Werto AM, Anderson TP, Murdoch DR. Association between pneumococcal load and disease severity in adults with pneumonia. J Med Microbiol 2012; 61:1129-35; PMID:22499777; http://dx.doi.org/10.1099/jmm.0.044107-0

90. Ho YC, Chang SC, Lin SR, Wang WK. High levels of mecA DNA detected by a quantitative real-time PCR assay are associated with mortality in patients with methicillin-resistant Staphylococcus aureus bacteremia. J Clin Microbiol 2009; 47:1443-51; PMID:19279177; http://dx.doi.org/10.1128/JCM.01197-08

91. Chuang YC, Chang SC, Wang WK. High and increasing Oxa-51 DNA load predict mortality in Acinetobacter baumannii bacteremia: implication for pathogenesis and evaluation of therapy. PLoS One 2010; 5:e14133; PMID:21152436; http://dx.doi.org/10.1371/journal.pone.0014133

92. Teuffel O, Ether MC, Beyene J, Sung L. Association between tumor necrosis factor-alpha promoter -308 A/G polymorphism and susceptibility to sepsis and sepsis mortality: a systematic review and meta-analysis. Crit Care Med 2010; 38:276-82; PMID:19789454; http://dx.doi.org/10.1097/CCM.0b013e3181f24a0

93. Korsaki A, Rafaopiantzas M, Rouxi C, Baziaka F, Kotanidou A, Antonopoulos A, Orfanos SE, Katsenos C, Koukoukas P, Plachouras D, et al. Genetic polymorphisms within tumor necrosis factor gene promoter region: a role for susceptibility to ventilator-associated pneumonia. Cytokine 2012; 59:358-63; PMID:22669212; http://dx.doi.org/10.1016/j.cyto.2012.04.040

94. Henckaerts L, Nielsen KR, Steffensen R, Van Steen K, Marthieu C, Giulietti A, Wouters PJ, Milants I, Vanhorebeek I, Langosch L, et al. Polymorphisms in innate immunity genes predispose to bacteremia and death in the medical intensive care unit. Crit Care Med 2009; 37:192-201, e1-3; http://dx.doi.org/10.1097/CCM.0b013e31819263d8; PMID:1905632

95. Ferwerda B, McCall MB, Alonso S, Giamarellos-Bourboulis EJ, Mouktaroudi M, Izagirre N, Koivunen P, Kotanidou A, Antonopoulou A, Orfanos SE, Karayannacos PE, Giamarellou H. n-6 polyunsaturated fatty acids enhance the activities of ceftazidime and amikacin in experimental sepsis caused by multidrug-resistant Pseudomonas aeruginosa. Antimicrob Agents Chemother 2004; 48:4713-7; PMID:15561848; http://dx.doi.org/10.1128/дж.В48.12.4713-4717.2004

96. Khor CC, Chapman SJ, Vanberg FO, Dunne A, Murphy C, Ling EY, Froodham AJ, Walley AJ, Kyrieleis O, Khan A, et al. A Mal functional variant is associated with protection against invasive pneumo-coecal disease, bacteremia, malaria and tuberculosis. Nat Genet 2007; 39:523-8; PMID:17324885; http://dx.doi.org/10.1038/ng1976

97. Wan QQ, Ye QF, Ma Y, Zhou JD. Genetic association of interleukin-1β (+51C/T) and its recep-tor antagonist (86-bpVNTR) gene polymorphism with susceptibility to bacteremia in kidney transplant recipients. Transplant Proc 2012; 44:3026-8; PMID:23195019; http://dx.doi.org/10.1016/j.jfert. transproc.2012.05.081

98. Solé-Violán J, García-Laorden ML, Marcos-Ramos JA, de Castro FR, Rajas O, Borderías L, Briones ML, Herreza-Ramos E, Blanquer J, Aspa J, et al. The Fcy receptor IIA-H/H131 genotype is associated with bacteremia in pneumococcal community-acquired pneumonia. Crit Care Med 2011; 39:1388-93; PMID:2137643; http://dx.doi.org/10.1097/CCM.0b013e31820eda74

99. Huttunen R, Airtoniemi J, Laine J, Vuento R, Karjalainen J, Rovio AT, Eklund C, Hurme M, Huhala H, Syrjänen J. Gene-environment interaction between MBL2 genotype and smoking, and the risk of gram-positive bacteremia. Scand J Immunol 2008; 68:438-44; PMID:18782274; http://dx.doi.org/10.1111/j.1365-3083.2008.02149.x

100. Henao-Martínez AF, Agler AH, LaFlamme D, Schwartz DA, Yang IV. Polymorphisms in the SUFU gene are associated with organ injury protection and sepsis severity in patients with Enterobacteriaceae bacteremia. Infect Genet Evol 2013; 16:386-91; http://dx.doi.org/10.1016/j.megid.2013.03.025; PMID:23538333