Hospital-acquired Bacteremia: A Comprehensive Review on Risk Factors, Pathophysiology, Diagnosis and Management

Rakha Prawira Ichsan[a], Agung Dwi Wahyu Widodo[b*]

[b] *agungimunologi@gmail.com*
[a]*Medical Study Program, Faculty of Meidcine, Universitas Airlangga, Surabaya, Indonesia*
[b]*Department of Microbiology, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*

* Corresponding author: agungimunologi@gmail.com

Abstract

This literature review describes several matters related to hospital-acquired bacteremia incidence such as risk factors, pathophysiology, diagnosis and management. Bacteremia, which was defined as a bacterial infection in the bloodstream, often occurs as a complication in patients who were hospitalized. This review describes risk factors that contributes hospitalized patients to be more susceptible to develops hospital - acquired bacteremia during their treatment in inside the hospital. These risk factors could originated from the patients theirselves, such as having a history of comorbidities or from hospital environment such as pathogen spread in the hospital or due to the exposure to medical procedures and devices. Patients who were hospitalized usually experience low immune system, causing bacteria from their original source to spread in the bloodstream due to the failure of the body's defense system to eliminate these bacteria. The primary diagnosis of hospital-acquired bacteremia is proved by positive blood culture after at least 48 hours of admission to the hospital. Management of bacteremia should be based on rapid, appropriate and empirical antibiotic therapy based on the organism causing the bacteremia, history and patient condition.

Keywords: Bacteremia; COVID-19; Tropical Disease;

1. Introduction

Bacteremia is a condition where bacteria present inside the bloodstream. Bacteremia is very dangerous because bacteremia classified as a systemic infection that can develop into sepsis. Sepsis may cause organ failure, hypotension, and has high morbidity and motrality. In the United States, bacteremia ranked tenth as the leading cause of death (Gürol, et al., 2015; Marhaendro, 2008; Zulaikha & Hastuti, 2019). Nosocomial bacteremia is commonly used as indicator of overall nosocomial infection due to their clear definition and clinical relevance. The incidence of hospital-acquired bacteremia in participating hospitals in 2010 was 0.8 per 1.000 patients0days, higher than current estimates in developed countries, including 0.7 per 1,000 patient-days in Canada in 2007-2010. In the United States, the number reached 0.6 per 1.000 patient-days in 2005, and 0.6 per 1.000 patient-days in Estonia between 2004-2005 (Hongsuwan et al., 2014). This comprehensive literature review attempts to dissect the multifaceted interactions in hospital-acquired bacteremia, outlining knowledge in risk factors, pathophysiology, diagnosis and management. Patients who were hospitalized are at risk of experiencing nosocomial infections, one of which is hospital-acquired bacteremia. Several factors that increase patients' risk of experiencing hospital-acquired bacteremia are comorbidities and exposure to medical procedures such as mechanical ventilation, intravascular catheters, hemodialysis and immunosuppressive treatment (Mortensen et al., 2022). Bacteremia happened when bacteria

succeed in evading the body's immune mechanisms at the site of infection or the bloodstream. The special structure of foreign microorganism that enters the body will recognized by the body's immune system. Bacteria that can defeat the immune system will move from their source to the bloodstream, resulting in bacteremia. Structures in bacteria such as pathogen-associated molecular patterns (PAMPs), lipopolysaccharide (LPS), peptidoglycan, flagellin and nucleic acids will be recognized by the body's immune (Christaki & Bourboulis, 2014). Blood culture is the main method used to determine the etiology of bacteremia because this examination is very sensitive and easy (Opota et al., 2015). Bacteremia requires fast and appropriate treatment, especially administering appropriate antibiotics. Treatment of bacteremia varies because it based on the causative organism. The antibiotics given must be empirical and must be based on the patient's history and condition (Smith, 2022; AHRQ, 2019).

2. Review and Content

2.1 Definition and Classification

Bacteremia is the presence of pathogenic bacteria in the bloodstream as proven by positive blood culture results. Clinically, bacteremia is a temporary condition where the body's immune mechanisms are in the process of eliminating bacteria in the bloodstream (Christaki & Bourboulis, 2014). Hospital-acquired bacteremia is a positive blood culture infection acquired after at least 48 hours of admission to the hospital. Hospital-acquired bacteremia also defined as cases where a patient is transferred from a hospital to another hospital where they are hospitalized for 48 hours, and blood cultures collected within 48 hours are positive (Wakabayashi & Iwata, 2021). In the United States, bacteremia was ranked tenth as the leading cause of death. The incidence of bacteremia increases with the number of postoperative complications, use of intravascular catheters and complicated local infections (Lutpiatina, 2015). Bacteremia can be classified as transient, intermittent or persistent. Transient bacteremia lasts for several minutes or hours, and most often occurs due to medical interventions on parts of the body such as dental procedures, gastrointestinal biopsies, percutaneous catheterization of the vascular system, bladder, bile ducts or surgical procedures. Intermittent bacteremia is bacteremia caused by microorganisms that are detected intermittently in the same individual and are in a clearance cycle and often recur. The location of intermittent bacteremia is often infections in closed body cavities, such as intra-abdominal or soft tissue abscesses, liver abscesses, cholangitis and focal infections such as pneumonia, osteomyelitis and spondylodiscitis. Persistent bacteremia occurs in the early stages of systemic bacterial infections and is also characteristic of infective endocarditis or other intravascular infections such as vascular graft infections and mycotic aneurysms. Persistent bacteremia also defined as blood cultures that always give positive results, even after the patient has received anti-infective treatment. This type of bacteremia is usually caused by the bacteria that resistant to prescribed antibiotics or the site of infection cannot be accessed by antibiotics, such as in septic thrombosis (Nielsen, 2015; Opota et al., 2015; Seifert, 2009).

2.2 Etiology and Risk Factor

The most common causes of bacteremia were *Escherichia coli*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Hospital-acquired bacteremia is generally caused by coagulase negative *Staphylococcus*, *Pseudomona*s sp, *Enterococcus* sp, fungi and several types of organisms (polymicrobial bacteremia) (Nielsen, 2015). Bacteremia caused by *E. Coli* could lead to sepsis. *Klebsiella* can cause bacteremia in patients with low immune system. *Serratia* commonly cause bacteremia in hospitalized patients. *Pseudomonas* can develop into fatal sepsis. Many skin and soft tissue infections caused by *S. aureus* also ended up in bacteremia, coupled with the occurrence of methicillin-resistant *S. aureus* (MRSA). (Jawetz et al., 2010; Nielsen, 2015). *S. aureus* and coagulase-negative staphylococci usually originate from catheter-related infections. Unknown source of hospital-acquired bacteremia usually caused by *enterococci*, fungi or polymicrobial. The location of the infected tissue influences risk factors to develop into bacteremia. Infections

of the respiratory tract, urinary tract and intra-abdominal infections are the most common causes of bacteremia. The use of medical devices such as urinary catheters and intravenous catheters increases morbidity and mortality in bacteremia caused by *E. coli*. (Christaki & Bourboulis, 2014). An individual with cardiovascular disorders who used prosthetic device such as a permanent pacemaker or cardioverter-defibrillators increases a person's risk of experiencing bacteremia due to *S. aureus* (Keynan & Rubinstein, 2013). Majority of patients who experienced hospital-acquired bacteremia had comorbid diseases compared to patients who do not experience hospital-acquired bacteremia. These comorbid diseases in particular are diabetes mellitus with complications, hematological cancer and metastatic cancer (Mortensen et al., 2022).

2.4 Pathophysiology

The disease course of bacteremia has several characteristics that related to the genetics of the host. The special structure of a foreign microorganism that enters the body will be recognized by the individual's natural immune system. These structures are pathogen-associated molecular patterns (PAMPs) such as lipoteichoic acid, lipopeptides, lipopolysaccharides (LPS), peptidoglycan, flagellin and nucleic acids. PAMPs will be recognized by receptors on the surface of immune and non-immune cells, namely pattern recognition receptors (PRRs). Toll-like receptors (TLRs) which are part of PRRs have an important role in fighting bacteria. TLR2 and TLR4 will bind bacterial structures such as lipoteichoic acid, peptidoglycan, lipopeptides and lipopolysaccharides. Nod-like receptors (NLRs) such as NLRP3 which are activated via PAMPs will cause oligomerization and aggregation of multiprotein complexes that cause the production of pro-inflammatory cytokines such as IL-1β and antimicrobial peptides. Other PRRs that also play a role in the natural immune system are C-type lectin-receptors (CLRs) and retinoic-acid-inducible-gene I (RIG-I). Ligands that have attached to PRR will activate signaling pathways that cause activation of transcription factors that will modulate gene expression and produce pro-inflammatory cytokines. Activated blood cells will produce TNFα which has pro-inflammatory and procoagulant effects. The pro-inflammatory effect also increases due to other cytokines such as IL-1, IL-2, IL-6, IL-8, and IFN-γ. Microbes most often enter the body through the skin, respiratory tract and digestive tract. S. aureus infection in the skin and soft tissue is caused by keratinocytes which have TLR 1, TLR 2, TLR 6 and NOD2 receptors which recognize and bind lipoptides, lipotechoic acid, peptidoglycan-derived muramyl dipeptide which triggers the production of pro-inflammatory cytokines. Antigen-presenting cells (APC) in the epithelium will capture antigens from bacteria and will be interpreted by T lymphocytes. This protective mechanism will decrease its function in situations of trauma, burns and the use of medical devices, resulting in individuals becoming susceptible to infection. Neutrophils as the first line of defense will migrate from the blood to the site of infection. After phagocytosis, the microorganisms inside the phagosome will be destroyed. Neutrophils play a major role in controlling and clearing extracellular bacteria such as S. aureus. A disturbance in the number of neutrophils due to congenital disease or due to the effects of chemotherapy is a predisposing factor for infections such as gram-negative bacteria or fungi. Tissue macrophages, dendritic cells and natural killer cells (NK cells) also have a role in phagocytosis. When bacteria infect, the complement system is activated. The antigen-antibody complex and C-reactive protein (CRP) will bind to structures on the surface of bacterial cells. This binding will activate the classical complement pathway such as C1, C2, C3 and C4. Cleavage of C3 will produce opsonins which cause pathogens to have the ability to phagocytose, anaphylatoxins and form complexes that attack membranes and lyse target cells. Some pathogen strategies to evade the immune system and attack complex systems are by expressing complement regulator binding proteins, secreting proteases and complement inhibitors. By using this strategy, bacteria can evade the host's immune system and spread in the blood. Bacteremia occurs when the immune system fails to control the spread of bacteria either because the bacteria succeed in evading the immune system or the individual's immune function decreases. Certain genes can increase the risk of experiencing bloodstream infections due to differences in expression of TLR4, NOD2, TNFα, etc. For example, single nucleotide polymorphisms (SNP) at position -511 of IL-1β which has the C allele increases the risk of experiencing bacteremia (Christaki & Bourboulis, 2014).

2.5 Diagnosis

Blood culture is the main method used to determine the etiology of bacteremia because this examination is very sensitive and easy. The volume of blood drawn greatly influences sensitivity. One blood draw usually requires 20 ml of blood in adults and grouped into aerobic bottles or anaerobic bottles. Before antibacterial treatment is carried out, usually 40 ml to 80 ml of blood will be taken to obtain two to four blood cultures, to detect the agent that caused bacteremia. The volume collected affects the sensitivity of the blood culture. The more blood volume taken, the more sensitive the results will be. After the blood culture gives positive results, gram stain will be performed. If microbes are found, the morphotype that appears will be an initial clue to determine the etiology of the infection. The standard incubation time required for bacteria is 5 days. Blood culture gives positive results because the growing microorganisms produce CO_2 which triggers an increase in pH. The increase in pH is then depicted by a color change, fluorescent signal or red-ox variation. However, diagnosis using blood culture has drawbacks, namely the presence of contaminants which can give false positive results. False positives occur when microorganisms that are not actually present in the bloodstream appear during blood sampling. This contamination is often caused by normal skin flora or microorganisms in the surrounding environment such as coagulase-negative *staphylococci* and other microorganisms that have low virulence such as *Micrococcus* spp., *Propionibacterium acnes*, majority of *Bacillus* spp. and *Corynebacterium* spp. However, diagnosis of bloodstream infections using the blood culture method still has high specificity because most of the microbes that prove positive are pathogenic such as *Escherichia coli*, *Staphylococcus aureus* or *Pseudomonas aeruginosa*. To prove that the blood culture results found are true positive, apart from being matched with the patient's clinical signs and symptoms, it is also based on the number of positive blood vials, the place where the sample was taken and the time needed to produce positive results. Transient bacteremia will give positive results due to the presence of microorganisms that remain in the blood for a short time, namely < 30 minutes. The discovery of several positive bottles but taken at different times indicates ongoing bacteremia. A catheter infection will give a positive result if the blood sample taken from the catheter becomes positive > 2 hours, before the results of the sample taken via venipuncture appear (Opota et al., 2015). Apart from blood culture, there are several other supporting examinations. After surgery, if the patient are suspected of having bacteremia, CT imaging will be performed at the surgical site to see or collect abscess samples and also wound cultures in the area suspected to be the origin of the infection. Patients with lung disorders or after receiving intubation treatment will have their sputum sample taken. Patients with venous catheters or hemodialysis catheters will first have the catheter removed and then cultured (Smith, 2022).

2.6 Management

The antibiotics used should have the narrowest spectrum and shortest duration of therapy. On average, antibiotics are used for 7 – 14 days and must be given parenterally. Oral administration is given when the patient has had no fever for at least 48 hours and is in stable condition. In bacteremia due to *Enterobacteriaceae*, as in treatment for gram-negative bacteremia, the optimal duration of antibiotics is 10 – 14 days. However, in patients with a stable hemodynamic condition, no fever and proper source control, 1 week of antibiotic use is said to be sufficient. Extended-spectrum beta lactamase (ESBL) commonly occurs in *E. coli*, *Klebsiella* species and *Proteus* species. The first antibiotic for ESBL bacteremia is carbapenem, apart from that it can be fluoroquinolones and trimethoprim/sulfamethoxazole. For carbapenem-resistant Enterobacteriaceae (CRE), a combination of beta-lactam inhibitors such as ceftazidime/avibactam, meropenem/vaborbactam and imipenem-cilastatin/relebactam are usually used. These agents have proven to work well as sole agents against CRE. In bacteremia caused by *Pseudomonas*, the duration of antibiotic treatment is usually 10 – 14 days. Oral antibiotics that can be used are ciprofloxacin and levofloxacin. If the patient experiences bacteremia caused by *S. aureus*, further examinations such as imaging must be carried out

to determine whether the patient has metastases to the spine. Echocardiography is also important to detect endocarditis due to *S. aureus*. Patients who already have a high risk of experiencing heart complications, such as using prosthetic valves, permanent heart devices, abnormalities in heart conduction or prolonged fever, may require surgical procedures. Blood cultures should be performed routinely to determine clearance of bacteremia. In cases of methicillin-susceptible *S. aureus* (MSSA), therapy can use oxacillin, nafcillin or cefazolin. Meanwhile, methicillin-resistant *S. aureus* (MRSA) can be treated using vancomycin or daptomycin. Daptomycin is used in patients who experience renal toxicity due to vancomycin. The duration of treatment for uncomplicated *S. aureus* bacteremia is 14 days. If you experience complications such as endocarditis or osteomyelitis, the duration of treatment should be 28-42 days (42 days minimum for osteomyelitis and left-sided endocarditis). In patients with endocarditis in prosthetic valves due to *S. aureus*, therapy is added with gentamicin and rifampicin. The duration of treatment for *E. faecalis* and *E. faecium* bacteremia varies depending on the source of the infection causing the bacteremia. Some are transient, namely for 4-5 days, but there are 7 days and 4-6 weeks. The first-line drug for *E. faecalis* is ampicillin. Vancomycin is used as an alternative in patients who have penicillin allergies. However, neither ampicillin nor vancomycin are bactericidal against *E. faecalis*, so combination therapy with gentamicin or ceftriaxone can be used. In vancomycin-resistant *enterococci* (VRE), linezolid and daptomycin can be used. Apart from treating, identifying and controlling the source of infection is also equally important. Source control can be done by removing the tools used on patients who are suspected to be the source of infection and irrigating existing abscesses (Smith, 2022; AHRQ, 2019).

3. Conclusion

In conclusion, this literature review is to describe aspects regarding hospital-acquired bacteremia, which include risk factors, pathophysiology, diagnosis and management. The incidence of hospital-acquired bacteremia and the distribution of sources and pathogens can vary greatly, depending on the level of prevention and control of infection in a hospital. Increased risk factors for a patient who is hospitalized, exposure to medical procedures and empirical antibiotic administration are things that must be considered. in strategies for prevention, early detection and management of bacteremia. With the increasing incidence of bacteremia supported by the increasing incidence of infections in the world, it is hoped that this review will be important for future research, and contribute to interdisciplinary collaboration.

Acknowledgements

The author would like to thank all the parties that involved and gave continuous support in completing this study

References

Agency for Healthcare Research and Quality. 2019. Best Practices in the Diagnosis and Treatment of Bacteremia. [Online] Available at: https://www.ahrq.gov/sites/default/files/wysiwyg/antibiotic-use/best practices/bacteremia-facilitator-guide.pdf

Christaki, E., & Giamarellos-Bourboulis, E. J. 2014. The complex pathogenesis of bacteremia: from antimicrobial clearance mechanisms to the genetic background of the host. Virulence, 5(1), 57–65. Available at: https://doi.org/10.4161/viru.26514

Gürol, G., Çiftci, İ. H., Terizi, H. A., Atasoy, A. R., Ozbek, A., & Köroğlu, M. 2015. Are there standardized cutoff values for neutrophil-lymphocyte ratios in bacteremia or sepsis?. Journal of microbiology and biotechnology, 25(4), 521–525. Available at: https://doi.org/10.4014/jmb.1408.08060

Hastuti, D. S., & Zulaikha, F. 2019. Analisis Praktik Klinik Keperawatan pada An. Az dengan Post Operasi Craniotomy atas Indikasi Space Occupying Lesion (SOL) dengan Intervensi Inovasi Penggunaan 2% Chlorhexidine Gluconate (CHG) sebagai Perawata Sibin Harian untuk Mengurangi Bakteremia pada Anak yang Dirawat di Ruang PICU RSUD A. Wahab Sjahranie Samarinda Tahun 2019. Fakultas Ilmu Kesehatan, Universitas MuhammadiyahKalimantan Timur. Available at: https://dspace.umkt.ac.id/bitstream/handle/463.2017/906/KIAN.pdf?sequence =1&isAllowed=y

Hongsuwan, M., Srisamang, P., Kanoksil, M., Luangasanatip, N., Jatapai, A., Day, N. P., Peacock, S. J., Cooper, B. S., & Limmathurotsakul, D. 2014. Increasing incidence of hospital-acquired and healthcare-associated bacteremia in northeast Thailand: a multicenter surveillance study. PloS one, 9(10), e109324. https://doi.org/10.1371/journal.pone.0109324

Jawetz, Melnick, Adelberg's. 2010. Medical Microbiology. Available at: https://lib.ui.ac.id/detail.jsp?id=136949

Keynan, Y., & Rubinstein, E. 2013. Staphylococcus aureus Bateremia, Risk Factors, Complications, and Management. Critical Care Clinics, 29(3), 547-562. Available at: https://doi.org/10.1016/j.ccc.2013.03.008

Lutpiatina, L. 2015. Pewarnaan Gram Buffy Coat untuk Deteksi Awal Pasien Bakteremia. Medical Laboratory Technology, 1, 38-46. Available at: https://doi.org/10.31964/mltj.v1i1.15

Mortensen, V. H., Søgaard, M., Mygind, L. H., Wolkewitz, M., Kristensen, B., & Schønheyder, H. C. 2022. Incidence and mortality of hospital-acquired bacteraemia: a population-based cohort study applying a multi-state model approach. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 28(6), 879.e9–879.e15. Available at: https://doi.org/10.1016/j.cmi.2021.12.011

Nielsen, S. L. 2015. The Incidence and Prognosis of Patients with Bacteremia. Danish Medical Journal, 62(7), B5128. Available at: https://pubmed.ncbi.nlm.nih.gov/26183054/

Opota, O., Croxatto, A., Prod'hom, G., & Greub, G. 2015. Blood culture-based diagnosis of bacteraemia: state of the art. Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 21(4), 313–322. Available at: https://doi.org/10.1016/j.cmi.2015.01.003

Puthut, M. D. 2008. PERBEDAAN PENGAMBILAN SAMPEL DARAH SECARA BERURUTAN DAN BEDA WAKTU TERHADAP PERTUMBUHAN KUMAN PADA PASIEN BAKTEREMIA. Undergraduate thesis, Faculty of Medicine. Available at: http://eprints.undip.ac.id/24484/

Seifert, H. 2009. The Clinical Importance of Microbiological Findings in the Diagnosis and Management of Bloodstream Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 48 Suppl 4, S238–S245. Available at: https://doi.org/10.1086/598188

Smith, D. A., & Nehring, S. M. 2022. Bacteremia. In StatPearls. StatPearls Publishing. Available at: https://pubmed.ncbi.nlm.nih.gov/28723008/

Wakabayashi, T., & Iwata, H. (2021). Outcome, diagnosis, and microbiological profile comparison of community- and hospital-acquired bacteremia: A retrospective cohort study. Journal of general and family medicine, 22(6), 327–333. Available at: https://doi.org/10.1002/jgf2.453