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Bloodstream infections

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Abstract

Vascular bed infections (BSI) are a significant clinical problem. They are characterized by a high mortality rate, which is both a diagnostic and therapeutic challenge. The aim of the study is to discuss in detail the etiology, epidemiology and classification of bloodstream infections, as well as their impact on inpatients and outpatients. Vascular bed infections can be classified as nosocomial or community-derived, and the incidence varies depending on the age group and the patient's contact with the medical community. In particular, older patients and immunocompromised patients are at higher risk of developing BSI, which is associated with a higher risk of severe complications such as sepsis and septic shock. Blood cultures are primarily used in diagnostics, but new technologies such as MALDI-TOF can speed up the process. Treatment is based on early initiation of antibiotic therapy, which should be adapted to the sensitivity of the pathogens and the source of infection. The paper also highlights the importance of monitoring bacterial resistance and adapting therapies to the changing epidemiological profile. The conclusions of the study are aimed at increasing the effectiveness of diagnosis and treatment of vascular bed infections, which is crucial in improving patients' health outcomes.

Aim of the Study: The aim of the study is to understand issues related to the epidemiology, etiology, classification and diagnosis of bloodstream infections (BSI), as well as their impact on the health of patients. In addition, the aim of the analysis is to assess the impact of bacterial resistance in relation to treatment and new therapeutic methods. The aim of the study is also to provide information that can support actions to prevent vascular bed infections.

Material and Methods: The materials used for the analysis include selected teaching hospitals and patients over 18 years of age who have been confirmed to have a positive blood culture infection. The material for the study was collected under aseptic conditions, and the pathogens

were identified using MALDI-ToF and PCR methods. The study used descriptive and multivariate analysis to assess prevalence and risk factors.

Conclusions: Vascular infections are a serious clinical problem, especially in hospitalized patients, especially in intensive care units. Among the important risk factors, we can distinguish the presence of vascular catheters, age and comorbidities. Appropriate diagnostic methods, such as MALDI-ToF and PCR, allow pathogens to be identified more quickly. The observed increase in bacterial resistance to the antibiotics used draws particular attention to the need to monitor resistance patterns and the use of targeted antibiotic therapy.

Key words: vascular access infections, bloodstream infections (BSI), sepsis, antibiotic therapy, antimicrobial resistance, vascular catheters, healthcare-associated infections (HAI), blood culture, septic shock.

Glossary of Abbreviations: BSI – Bloodstream Infections; HAI – Healthcare-Associated Infections; ECDC – European Centre for Disease Prevention and Control; C-CVC – Central Vascular Catheter; C-PVC – Peripheral Vascular Catheter; HSCT – Hematopoietic Stem Cell Transplantation; CNS – Coagulase-Negative Staphylococci; CAP – Community-Acquired Pneumonia; HCAP – Healthcare-Associated Pneumonia; ESBL – Extended-Spectrum Beta-Lactamases; MRSA – Methicillin-Resistant Staphylococcus Aureus

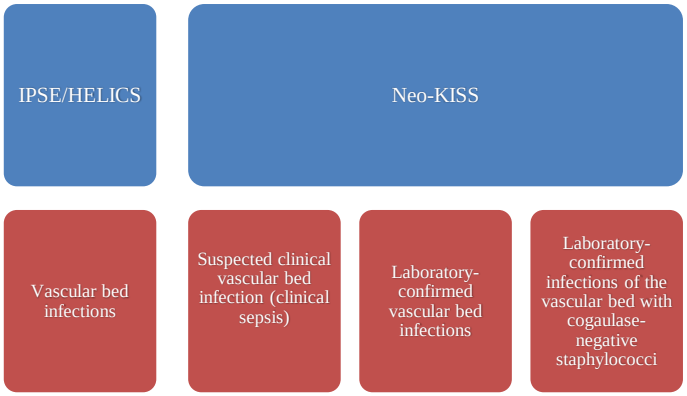
Definition

Vascular bed infections, also known as bloodstream infections (BSI), are infectious diseases caused by living microorganisms such as bacteria or fungi in the bloodstream (confirmed by at least one positive blood culture for one or more microorganisms) that have the ability to cause or have caused an inflammatory response characteristic of the body, which has been diagnosed on the basis of clinical changes and laboratory parameters and hemodynamic (Viscoli 2016, Laupland and Church 2014). Moreover, the definitions describing vascular bed infections (BSI) and sepsis are two sides of the same phenomenon, where sepsis is classified as an infectious syndrome caused by an infectious disease, while BSI is sepsis caused by bacteria or fungi circulating in the circulatory system (Viscoli 2016). In addition, sepsis is associated

with a severe clinical condition of the patient and poses a direct threat to his life. In some cases, it is possible to progress to severe sepsis, which is characterized by high mortality of up to 50%, or to septic shock (Laupland and Church 2014, Kędzia and Podgórska 2018, Mayr et al. 2013).

In addition, vascular bed infections belong to the group of healthcare-associated infections (HAIs). This definition is mainly based on the definition used by IPSE/HELICS (Improving Patient Safety in Europe) and has been supplemented with the definitions of the Neo-KISS system in the case of neonatal infections (National Antibiotic Protection Program 2016).

Figure 1. IPSE/HELICS case definitions and neonatal definitions established by the KISS network (National Antibiotic Protection Program 2016).



Division

Bloodstream infections can be divided into two categories – nosocomial BSI and community-acquired BSI (Viscoli 2016, Laupland and Church 2014). There are a number of diagnostic and classification criteria for diagnosing vascular bed infection and assigning this entity to the appropriate group. However, the definitions used for bloodstream infections, and especially for community-acquired BSI, are not consistently used.

Hospital-acquired vascular bed infection is a blood infection that is identified for the first time (culture collection) in a patient after 2 or more days of stay in a healthcare facility (≥ 48 hours) or within 2 days (< 48 hours) of discharge from hospital (Laupland and Church 2014).

Community-acquired vascular bed infection is a blood infection that is diagnosed in an outpatient patient or identified for the first time (culture collection) in the patient within 2 days (< 48 hours) of admission to the hospital (Laupland and Church 2014). In addition, community-acquired infections can be classified as healthcare-related if the patient has previously been

involved in the diagnostic and therapeutic process or as related to the environment (Viscoli 2016).

Epidemiology

BSI infections are one of the most severe forms of infection, which occurs in hospitalized patients and is associated with high mortality (Podgórska and Kędzia 2018, Bassetti et al. 2016, Yahay et al. 2016). The global epidemiology of vascular bed infections is difficult to estimate due to the different methodology used during the research (for example, depending on the hospital, the results were presented in the form of morbidity or prevalence). Additionally, the studies included diverse patient populations and types of hospitals and departments. The prevalence of BSI varies significantly between different groups of patients, especially among patients affected by pathological conditions or pharmacologically treated with a predisposition to infection. In this community, the incidence correlates with the underlying disease, country, type of hospital, type of ward and length of hospitalization (Bassetti et al. 2016, Gustinetti and Mikulska 2016, Yahay et al. 2016).

Research by the European Centre for Disease Prevention and Control (ECDC) shows that the prevalence of at least one HAI among patients in European hospitals is 6%, with a range ranging from 2.3% to 10.8%. About 10% of cases are vascular bed infections (European Centre for Disease Prevention and Control 2019). Most episodes of blood infections result from the patient's stay in a hospital ward and other available forms of medical care. It is also worth noting that the occurrence of healthcare-associated vascular bed infections is more likely in elderly patients with comorbidities (Viscoli 2016, Yahay et al. 2016).

Intensive care units and transplant wards have the highest percentage of vascular bed infections (Podgórska and Kędzia 2018). In the 2019 ECDC report, BSI was found in 3.7% of patients staying in intensive care units for more than two days. These infections occurred in association with a catheter (36.5%) and secondary to another infection (35%). Infection of unknown origin affected about 20% of patients (European Centre for Disease Prevention and Control 2019). The incidence of BSI after hematopoietic cell transplantation (HSCT) reaches as much as 30% of the population (Mikulska et al. 2012). In addition, the number of cases of vascular bed infections is constantly increasing, which is caused by a higher frequency in the use of invasive treatment and diagnostic techniques (Podgórska and Kędzia 2018).

Vascular bed infections are not exclusively associated with the patient's hospitalization, but can be of community-acquired origin. The epidemiology of blood infections of this nature has changed in recent decades. According to the latest data, the annual incidence of BSI ranges

from 40 to 154/100,000 of the population, but this value is very different from the actual number of people who will develop the disease (Viscoli 2016, European Centre for Disease Prevention and Control 2019, European Centre for Disease Prevention and Control 2013). The incidence of out-of-hospital blood infections is comparable in size to the number of people affected by acute myocardial infarction, stroke and serious trauma (Laupland and Church 2014).

Sources of bacteremia
Central vascular catheter (C-CVC)
Peripheral vascular catheter (C-PVC)
Secondary to pneumonia (S-PUL)
Secondary to urinary tract infection (S-UTI)
Secondary to gastrointestinal infection (S-DIG)
Secondary to surgical site infection (S-SSI)
Secondary to skin and subcutaneous tissue infections (S-SST)
Secondary to infection elsewhere (S-OTH)
Bacteremia of unknown origin (UO)
Unknown (UNK)

Classification

According to the National Antibiotic Protection Program, BSI infections are classified according to the source of bacteremia (European Centre for Disease Prevention and Control 2019). Of the vascular bed infections listed below, the most important role is played by those where the source of bacteria is the central vascular catheter
(C-CVC) and the peripheral vascular catheter (C-PVC), as the most common causes of this type of infection (Podgórska and Kędzia 2018).

Figure 2. Classification of vascular bed infections – the source of bacteremia (European Centre for Disease Prevention and Control 2019).

Etiological factors

In vascular bed infections, there are 3 groups of patients in whom various microorganisms are responsible for the occurrence of the infection: (1) patients with norma immunity with intact defense, (2) patients with impaired immunity due to physiological condition (children, the elderly), (3) patients affected by pathological conditions or treated pharmacologically with a predisposition to infection (Viscoli 2016).

Among patients with normal immunity with intact defense of etiological factors that are responsible for blood infection are *Neisseria meningitidis*, *Staphylococcus aureus* and bacteria of the genus *Streptococcus* (m.in. *S. viridans* and *S. pneumoniae*) and *Salmonella* (Viscoli 2016, Kraker et al. 2013). These are mostly community-acquired infections, although they can sometimes be diagnosed a few hours after admission to hospital. Bacteremias in these patients are secondary infections associated with infective endocarditis in children, adolescents and young adults (*S. viridans*) and post-influenza infections (*S. pneumoniae* and *S. aureus*) (Viscoli 2016).

In children and the elderly – patients with an impaired immune response due to age – vascular bed infections are caused by bacteria of the genera *Listeria*, *Streptococcus* (m.in. *S. pneumoniae type B*), *Escherichia* (m.in. *E. coli*), *Klebsiella*, *Pseudomonas* (m.in. *P. aeruginosa*) and *Staphylococcus* and *Candida fungi* (Viscoli 2016, Kraker et al. 2013).

In the group of patients affected by pathological conditions or treated pharmacologically with a tendency to develop infections, BSI infection can be caused by a significant proportion of pathogens – most of the occurring gram-negative to gram-positive bacteria and fungi (Viscoli 2016, Kraker et al. 2013). In addition, these are infections both nosocomial and community-acquired infections. Such a wide range of pathogens causing bloodstream infections correlates with patients belonging to this group. Among them, we distinguish people with acquired or congenital immunodeficiency and those affected by lifestyle diseases, such as diabetes and cancer, which pose an increased risk of infectious complications (Viscoli 2016, Gustinetti and Mikulska 2016, Yahay et al. 2016, Taramasso et al. 2016). This population also includes patients in whom we diagnose infections resulting from medical care (Podgórska and Kędzia 2018).

It is worth noting that coagulase-negative staphylococci (CNS), and in particular *S. epidermidis*, are among the leading factors that promote vascular bed infections due to the use of peripheral and central vascular catheters. This is due to the ability of these bacteria to form a biofilm on the internal and external vascular accesses. The presence of CNS was found in 8-40% of cases of removed punctures (Podgórska and Kędzia 2018).

Risk factors

Risk factors for vascular bed infection include, above all, hospitalization and vascular catheters, which are currently an indispensable element of treatment and diagnostic procedures (Podgórska and Kędzia 2018, Bassetti et al. 2016). With their use, it is possible to administer medication to the patient, replenish fluids and electrolytes, parenteral nutrition and blood

transfusion. In addition, vascular catheters are used during diagnostic tests and hemodialysis. The risk of infection increases with the time the catheter is maintained in the vascular bed (Podgórska and Kędzia 2018).

Another element that contributes to the development of BSI is the patient's age. In particular, healthcare-associated bloodstream infections affect older people with comorbidities (Yahay et al. 2016). Vascular bed infections in this group of patients are characterized by a different distribution of pathogens than in other communities (higher percentage of *S. aureus* and *P. aeruginosa* and lower percentage of *S. pneumoniae* and *E. coli*) and higher mortality and bacterial resistance to antimicrobials (Viscoli 2016, Kraker et al. 2013).

In addition, lifestyle diseases, such as cancer and diabetes, promote the formation of vascular bed infections. The same applies to people with congenital or acquired immunodeficiency who have a single defect or numerous abnormalities in the body's defense mechanisms, predisposing to severe infections caused by opportunistic pathogens (Gustinetti and Mikulska 2016, Taramasso et al. 2016).

Diagnostic criteria

There are many considerations, both diagnostic and classifying, regarding the confirmation of the occurrence of a BSI episode. BSI is generally considered to be present when a pathogen is cultured from the blood of an infected patient. For this reason, regardless of the type of BSI definition, a positive blood culture for at least one pathogenic agent is required. However, it should be remembered that obtaining a positive blood culture is not synonymous with a blood infection. Positive blood culture results can occur in three main, differentiated situations. In the case of sample contamination, a true positive result without a picture of concomitant disease and a true positive result accompanied by clinical symptoms (Laupland and Church 2014).

Contamination, bacteremia and fungemia

Contamination occurs when a positive culture result is caused by the presence of physiologically absent organisms in the bloodstream with which the sample has been infected due to non-compliance with sterile rules for collecting, storing or transporting blood for culture. The terms "bacteremia" and "fungemia" refer to the presence of live bacteria or fungi in the blood. They are used for naming positive blood cultures in which contamination has been excluded. The term "bacteremia" is often used interchangeably with BSI. However, these terms are not synonymous and there are two factors that distinguish them. BSI applies to both bacterial

and fungal infections, so it is a more broad term. In addition, the term bloodstream infection means that a positive culture result is accompanied by clinical symptoms, while bacteremia may be asymptomatic (Laupland and Church 2014).

Blood culture

There are numerous, different protocols and laboratory procedures that apply to blood cultures. A significant number of modern laboratories use fully automated incubation and detection systems because they are more efficient, carry a lower risk of sample contamination and require a shorter incubation time than manual methods (Cockerill et al. 2004, Zadroga et al. 2013, Walker et al. 1986).

Documenting a positive blood culture is an obligatory element in the diagnosis of BSI. A prepared culture kit (at least one bottle), which is filled with broth medium, should be filled immediately with an appropriate amount of blood. Blood must be collected under aseptic conditions, preferably through a venous puncture (DesJardin et al. 1999). It is also possible to collect blood through a permanent intravascular catheter, but it is recommended that at least one set of cultures be collected from the peripheral vein (Leisure et al. 1990)

Adding an anaerobic bottle to research kits makes it possible to detect anaerobic bacteria, increases the chance of growing relatively anaerobic bacteria and shortens the time of appearance of some fussy organisms (Pohlman et al. 1995).

Sample volume

The volume of blood collected for culture is of great importance, it is related to the probability of detecting bacteremia in the patient. Some medical conditions, such as septic thrombophlebitis or endocarditis, are accompanied by constant bacteremia. In this case, a consistently high level of pathogens is maintained in the bloodstream, which will result in positive cultures even if a small volume of blood is collected for testing. However, in almost all infections, the level of bacteria present in the bloodstream is lower, so it is necessary to take a larger sample volume to increase the probability of detecting microbes (Lee et al. 2007).

Number of samples

A fundamental factor influencing the authenticity of the results of cultures is their number and sample volume. According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, it is recommended to collect two sets, which include an oxygen and anaerobic bottle with a capacity of 10 ml each (a total of 4 bottles, which corresponds to taking

40 ml of blood from the patient) (Lee et al. 2007). On the other hand, the National Antibiotic Protection Program recommends performing 2-3 blood cultures in an adult patient (2-3 sets containing an oxygen and anaerobic tube), and 1-2 cultures in children (National Antibiotic Protection Program 2015). The number of cultures performed increases the detection of bacteremia. In the case of two cultures, the detection rate varies between 90-95%, while the addition of a third set increases the probability of detecting bacteremia to 95-99%. The number of cultures performed is also important in terms of the organisms detected in the culture. According to research, in the case of *Staphylococcus aureus*, bacteremia is confirmed in 90% of cases at the first sample. In contrast, in the case of *Pseudomonas aeruginosa* and *Candida albicans*, only 60% of bacteremia and candidaemia could be detected in one blood culture. Similar data are found in the case of multimicrobial infections. In this case, 67% of all microorganisms were isolated in the first sample, and most of them were detected only in the third sample (99.1%) (Lee et al. 2007).

The number of positive blood cultures can also be used as an indicator to differentiate contamination from bacteremia. Most studies on this topic focus on nosocomial coagulase-negative staphylococcus infections. Based on their results, it was determined that a positive result in one farm indicates contamination in 75-95% of cases. In patients who actually have bacteremia, the probability of growing the same pathogenic agent in the second trial is high (over 75%) (Weinstein et al. 1983). However, in the case of contamination, the result of the second culture is usually negative (Hall and Lyman 2006).

Differentiation of BSI

Once sample contamination has been ruled out, it is important to determine whether bacteremia or fungemia is related to the infection (i.e., BSI). For this purpose, however, there is no universally accepted "gold standard" for differentiating these units. In most situations, co-occurrence of microbiological, clinical and laboratory factors is necessary (Hall and Lyman 2006).

In most cases, microbial isolation from an aseptically obtained and processed blood sample indicates BSI. However, there are many commensal organisms on the skin that can grow in blood cultures, where in most cases they are contaminants (false positives). These organisms include coagulase-negative staphylococci (CNS), *Bacillus spp. (*except *Bacillus anthracis), Micrococcus spp., Corynebacterium spp. (without Corynebacterium jejkieum) and Propanibacterium acnes*. Among immunocompetent patients who do not have a permanent prosthetic device, e.g. a vascular catheter, the above pathogens are rare but possible causes of

non-hospital onset BSI. Particular caution should be exercised in the case of streptococci from the *Viridans* group. These bacteria are rarely contaminants in blood cultures, but their presence in the absence of symptoms of infection may indicate transient bacteremia originating from the upper gastrointestinal tract or teeth. Particular care should also be taken with mushrooms. If the patient does not have significant immunodeficiencies, the isolation in the mold culture is usually due to environmental pollution. On the other hand, the appearance of yeast or dimorphic fungi in culture always indicates fungemia or BSI (Hall and Lyman 2006, Chu et al. 2008).

Sometimes a positive blood culture result may indicate transient bacteremia that is not related to infection. In this case, live microbes are present in the bloodstream, but they are not associated with the infection, so it is not BSI. There are many different causes of transient bacteremia. The most common are interventions within colonized or contaminated mucous membranes, e.g. dental procedures (Maharaj et al. 2012), endoscopic gastrointestinal procedures (Levy et al. 2007). and invasive respiratory procedures (Konstantinou et al. 2008). Transrectal prostate biopsy is also associated with transient bacteremia, 20% of which are associated with bacteremia, which may develop into BSI (Zani et al. 2011).

If BSI is confirmed, it is important to document the clinical and/or microbiological focus of infection. This is usually done by isolating the same pathogen from a physiologically sterile site of the body (cerebrospinal, pleural or synovial fluid, or a sample obtained from deep tissue aspiration) as in a blood culture. However, it may not be possible to determine the focus of infection in some cases, or the primary focus does not exist (as in primary BSI). In such a situation, other parameters such as fever or white blood cell count are used to differentiate BSI (Elzi et al. 2012).

New methods in the diagnosis of BSI

As already mentioned, the standard in the diagnosis of BSI is a positive blood culture. However, diagnostics based on blood culture is not effective in the case of infection caused by non-cultured microorganisms or after the introduction of antibiotic therapy. In addition, the whole procedure is quite time-consuming and imperfect at a time when treatment should be introduced as soon as possible. On the other hand, making an appropriate diagnosis is necessary in order to choose the correct treatment. Therefore, new procedures for BSI diagnostics are constantly being developed, using the MALDI-ToF and PCR techniques (Viscoli 2016).

The MALDI-ToF method is a new, extremely effective tool for identifying microorganisms. The growing interest in this method is due to its high accuracy, short time of obtaining analysis results and relatively low costs (Gnat et al. 2020). The use of the MALDI-

ToF technique in BSI diagnostics seems very promising. This technique allows the analysis to be carried out directly from the blood culture bottles and significantly reduces the duration of the entire procedure. Standard culture and identification take about 18-24 hours (for fast-growing bacteria), while MALDI-ToF MS is able to provide a result even within an hour. This is possible thanks to the use of purified bacterial granules obtained from culture bottles (Nomura et al. 2020).

Disclosure:

Author's contribution:

Conceptualization: Kinga Rogowska-Borettini, Aleksandra Romanowska, Weronika Biaduń-Mućko; Methodology: Weronika Biaduń-Mućko, Kinga Rogowska-Borettini; Software: Paweł Arkadiusz Malmur, Aleksandra Romanowska , Maria Wysieńska; Check: Adam Rybak, Kinga Rogowska-Borettini, Piotr Jóźwiak; Formal analysis: Paweł Arkadiusz Malmur, Adam Rybak, Aleksandra Romanowska; Investigation: Kinga Rogowska-Borettini, Paweł Arkadiusz Malmur, Piotr Jóźwiak; Resources: Kinga Rogowska-Borettini; Data curation: Paweł Arkadiusz Malmur; Writing - rough preparation: Weronika Biaduń-Mućko, Aleksandra Romanowska, Maria Wysieńska; Writing - review and editing: Kinga Rogowska-Borettini, Maria Wysieńska, Piotr Jóźwiak; Visualization: Adam Rybak, Paweł Arkadiusz Malmur; Supervision: Kinga Rogowska-Borettini; Project administration: Piotr Jóźwiak, Adam Rybak, Paweł Arkadiusz Malmur, Weronika Biaduń-Mućko.

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