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Patients with immune system deficiencies and their predisposition to sepsis - the current state of knowledge

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ABSTRACT

Many diseases compromise the immune status. Some of them are congenital, and environmental factors induce others. As a result, patients are more prone to other diseases that would not match their clinical presentation at first sight. The main categories include primary and secondary immunodeficiency. Inborn errors of immunity (IEI) are a group of congenital diseases characterised by incomplete innate or acquired immunity pathways. Secondary immunodeficiency is the result of the immune system being compromised due to an environmental factor, such as specific viruses. The clinical presentation of immunodeficiency tends to be apparent at first sight as diagnostic criteria include recurrent infections of severity that are incoherent with age-related risk factors. Late diagnosis may lead to conditions such as sepsis due to severe infection. Every specialist has his own points of view on the factors that lead to sepsis, but all of them should keep in mind the possibility that a patient develops sepsis. To see the different points of view, we reviewed the literature on patients with immunodeficiency-related sepsis treated by clinicians of different specialities to find factors leading to such complications.

KEY WORDS: Sepsis, immune system, immunodeficiency, COVID-19, transplantation, immunosuppression.

INTRODUCTION

The definition of sepsis is debatable, although the Third International Consensus Definitions for Sepsis and Septic Shock set the definition of sepsis as “a life-threatening organ dysfunction due to the dysregulated host infection response to infection”. The same definition appears in the 2021 Surviving Sepsis Campaign Guidelines [1]. Sepsis is a major problem throughout the world with a mortality risk of around 40%. One million patients are diagnosed with sepsis each year, mainly caused by bacteria, but also by viruses, fungi, and protozoa [2]. The most common pathogens that cause sepsis are: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenza b*, *Neisseria meningitides*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Acinetobacter baumannii*, *Escherichia coli*, *Salmonella enterica*, *Pseudomonas aeruginosa* and *Proteus mirabilis* [3,4]. For the risks of developing sepsis, in addition to older age, we can point to young age (<1year), the presence of some chronic diseases such as heart failure, cirrhosis, diabetes, but also cancer and congenital immune dysfunction [5].

In the last 20 years, amount of immunosuppressed patients has risen remarkably [6]. Furthermore, immunological disorders are more often identified as mortality prognostic factors in patients with severe sepsis and septic shock [7]. Medical procedures are at an ever higher level leading to improvement in quality of life, however entails the risk of possible side effects. Transplantations are often life-saving operations, but having foreign tissues poses a threat of implant rejection. In this case, immunosuppressive agents are necessary, leading to increased infection risk and closing the vicious circle. Patients with immune system deficiencies are more susceptible to infections caused by common, even harmless pathogens. Consequently, the chance of developing systematic disorders such as sepsis and septic shock increases [8]. Sepsis is the leading cause of death in Intensive Care Units (ICU) [9]. Mortality of septic shock and sepsis during admission to the ICU amounts to 30% [10]. An additional factor that predispose to the development of sepsis and the problems related to its treatment is the increasing resistance of bacterial strains to antibiotics. Tolsma et al. evaluated stay in the ICU due to sepsis or septic shock. Approximately 30% of the patients admitted for these purposes were immunocompetent. The reasons for immunodeficiency were classified into the following groups: AIDS, organ transplant, solid organ tumour without neutropenia, hematologic malignancy without neutropenia, all-cause neutropenia, inflammatory and/or immune disorder, and primary or congenital immunodeficiency. The main causes of immunodeficiency were related to all-cause neutropenia (28%), no neutropenic hematologic malignancy (26.3%), no solid neutropenic tumor (19.6%), and less often AIDS (11.2%).

Furthermore, AIDS, solid tumours without neutropenia, hematologic malignancies without neutropenia, and neutropenia regardless of their cause were distinguished by a higher mortality rate [11]. Due to a different immunological response among immunosuppressed patients, the classic clinical characteristics associated with casual infections and sepsis may be absent. Therefore, diagnosing these groups of patients may be challenging [12].

However, according to chronically immunosuppressed patients, biomarkers such as procalcitonin remain constant in the absence of infection and thus may be useful in the recognition of bacterial infection in immunosuppressed patients who do not present typical symptoms of infection [13]. As the techniques to identify pathogens develop, rapid antimicrobial susceptibility tests are believed to be beneficial especially for patients with immunodeficiencies, as they will allow them to avoid broad-spectrum antibiotic therapy [12]. The objective of our study was to elucidate the significance of the immune system in the development of sepsis, its underlying pathological mechanisms predisposing to the septic phenomenon, the distinctive characteristics of sepsis in patients with immunodeficiencies, and the classification of sepsis based on the aetiology of the pathogenic microorganisms involved.

IMMUNE SYSTEM

The human immune system recognises different types of pathogens in the bloodstream, tissues, and also on the surface of the skin, and reacts to them appropriately. It consists of two main parts: innate and adaptive immunity [14,15]. Innate (general) immunity is responsible for first line of defence against entering germs. It is characterised by immediate or developing within hours against all penetrating pathogens. The general immunity system reacts against any type of pathogen in at the same way in antigen-independent (nonspecific) mechanism. Skin, together with mucous membranes and immune system cells with proteins, maintain body protection and make up the innate immunity system [16]. The skin provides a physical barrier against microbial penetration. Furthermore, substances located on the skin, such as enzymes, acids, and mucus, reduce the settlement of all germs [16]. The crucial role of innate immunity is to accumulate and activate immune cells, especially neutrophils at the site of infection, and to induce inflammation by releasing cytokines and chemokines [14,15]. Tumour necrosis factor, interleukin 1 (IL-1) and interleukin 6 (IL-6) are inflammatory cytokines that are relevant in bacterial infections. The complement system links the functioning of the innate and additive immune system. It consists of a system of 20 glycoproteins whose activation occurs in a three-path cascade: mannan binding lectin pathway,, classical pathway and alternative pathway [14,15]. In response to inflammatory factors, the complement system participates in inactivating pathogens through recognition, opsonisation, and lysis of organisms [14,15,17].

Many cells such as granulocytes (neutrophils, eosinophils, basophils), dendritic cells, natural killer cells (NK), innate lymphoid cells, mast cells and macrophages are integral part of innate immune system. Neutrophils and macrophages, which are also known as scavenger cells, neutralise bacteria through the phagocytosis. Macrophages and dendritic cells are also involved in antigen presentation, which plays an important role in the cooperation between innate and adaptive immunity [18]. The innate immune system recognises foreign pathogens more slowly, but, in contrast to the innate immune system, it is able to develop a memory, resulting in a quicker and much more accurate re-immune response when the same antigens are penetrating [19].

This system is made up of two types of cells: T and B lymphocytes, which specialise in producing antibodies [15]. T lymphocytes are formed in the bone marrow, while the maturation process occurs in the thymus [15,16]. To recognise a specific antigen, T lymphocytes need stimulation of the T-cell receptor (TCR) on their surface by antigen-presenting cells (APC). Antigen-presenting cells through presentation by major histocompatibility complex (MHC): Class I internal peptides and MHC class II peptides stimulate T cells to specialisation into CD8+ T-cells (cytotoxic) and CD4 + T cells (helper). Among CD4+ lymphocytes, three subtypes are distinguished: Th1, which are responsible for CD8+ activation, memory formation among T lymphocytes through IL-2 release, IFN- γ which stimulates macrophages to neutralise bacteria and increases phagocyte performance through cytokine release [15,20,21]. The response of Th2 cells is characterised by the IL-4, IL-5 and IL-13 production, development of B lymphocytes that generate IgE antibodies and stimulating an antiparasite response [15]. These cells also participate in the switching of B- and lymphocytes [22]. Th17 are involved in the production of IL-17, IL-22, and TNF- α [18]. Cytotoxic T cells (CD8 +) remove cells infected with viruses and bacteria and destroy tumor cells with abnormal antigens on the surface [15]. By production of INF- γ and tumour necrosis factor (TNF), effector CD8+ cells lead to cell apoptosis. B lymphocytes play a key role in the humoral response. They appear in the bone marrow, where they also acquire immunological maturity. Lymphocytes B do not require APCs to respond. After activation by a specific antigen, lymphocytes B may differentiate into memory cells or plasma cells. The first may persist in the bloodstream for many years. They memorise antigen during initial infection, express antigen-binding receptors, and after re-exposure with antigen, respond very quickly. Unlike memory cells, immunoglobulins do not persist as long in the bloodstream. In the case of an immune response, its role is to produce a huge amount of immunoglobulins [15].

PATHOLOGY OF IMMUNE SYSTEM

The innate and acquired immune systems can become dysregulated and develop malfunctions that trigger various illnesses. Abnormalities lead to three types of disease resulting from: overreaction of the immune system (hypersensitivity), incorrect reaction against the body (autoimmunity) and decreased ability of the body to fight infections and other diseases (immunodeficiency) [15]. Hypersensitivity is classified in 4 types and arises when the immune system's response is too strong. As a result, an inflammatory reaction arises, and tissues may be harmed. Type I occurs within minutes of reexposure to the antigen. It is developed by combining environmental antigens such as animal dander, food, and house dust mites with previously sensitised tissue mast cells and blood basophils sensitized by the IgE antibody. Exposure to antigen leads to degranulation of inflammatory mediators, including histamine, leukotrienes, and prostaglandins, which cause vasodilation, mucus secretion, smooth muscle contraction, and in most severe hypersensitivity to systemic anaphylaxis. Type II hypersensitivity develops within 2 to 24 hours. It occurs rare and is caused by reactions of antibodies, especially IgM and IgG, against tissues. Antibodies may attach to cells, opsonize them and lead to activation of complement system, aggregation of neutrophils and macrophages, and tissue injury. The most popular example of Type II hypersensitivity is foetal erythroblastosis.

Complexes of antibodies comprising IgG or IgM combined with proteins that can aggregate in tissues and lead to activation of the complement system are the basis of the Type III reaction of hypersensitivity. The outcome of the Type III reaction may be systematic or a limited to a tissue or specific organ. The reaction can develop from a few days, up to months and is exemplified by systemic lupus erythematosus and rheumatoid arthritis.

Type IV is a cell-mediated reaction that does not require antibodies to trigger pathways leading to the immune response. Tissue damage is caused by antigen-sensitive T cells, which destroy cells directly or through delayed-type hypersensitivity. Sometimes neutrophils, eosinophils, and monocytes may also participate in type IV hypersensitivity [15,23]. Autoimmune diseases are the result of the pathological reaction of the immune system against self-body tissues and molecules [15]. Tissue damage may occur by binding autoantibodies to the cell surface resulting in cell lysis. Activation of the complement system or antibody-dependent cytotoxicity are often responsible for this kind of cell destruction [24]. Furthermore, autoreactive T lymphocytes can recognize tissue through linking the T cell receptor (TCR) with MHC I and autoantigen-derived peptides, releasing cytotoxic granules, destroying the cell membrane and secretion of cytokines leading to tissue injury [25]. The prevalence of autoimmune diseases is 3% in the population, with higher incidence in the women's group [26].

Immunodeficiency is a condition in which, due to defects or deficiencies in the immune system in the aspect of lymphocytes, phagocytes, and the complement system, the immune system is ineffective or unable to fight infection that arises [15,27]. Immunodeficiency can be divided into two groups: primary and secondary. Primary immunodeficiencies (PIDs) are considerably rarer and arise from genetic defects. More than 120 genes are responsible for 150 different PID defects in both innate and adaptive immune systems [28]. Secondary immunodeficiency can arise under the influence of various factors such as HIV infections, immunosuppressive treatment, malnutrition, genetic and metabolic diseases and environment-induced stress [29].

THE IMMUNE SYSTEM IN SEPSIS

In certain circumstances, such as sepsis, prolonged exposure to antigens and prolonged inflammation may lead to T cell exhaustion [30]. Boomer et al. showed through a postmortem examination of a sepsis patient that the spleen contained T lymphocytes with a reduced level of pro-inflammatory cytokines such as IFN- γ and TNF- α [31].

Furthermore, circulating T lymphocytes in patients with sepsis have an increased expression of PD-1, which influences the reduced proliferation of these cells and the reduced ability to respond against secondary infections [32]. Of all cells in the immune system, sepsis has the greatest impact on CD4+ T cells [33]. Reduced number of CD4+ T cells during sepsis is a consequence of the higher incidence of programmed cell death [31]. In addition, the production of pro-inflammatory cytokines such as IL-2, IL-12, IFN- γ is reduced [34].

Significant dysfunction is also seen in B lymphocytes [35]. Suzuki et al. revealed that the ratio of exhausted CD21+ B cells compared to normal CD21+ B cells in patients with acute sepsis is significantly higher than in healthy subjects [36]. The innate immune system may also be dysfunctional during sepsis. The number of dendritic cells (DC) is lower in patients with sepsis [37]. Furthermore, DCs derived from a septic patient have a decreased ability to produce inflammatory cytokines [38].

INBORN ERRORS OF IMMUNITY

Inborn Immune Illness Errors (IEI) comprise a genetically, immunopathogenetically, and clinically heterogeneous group of diseases. The recent 2022 update on the classification of the International Union of the Immunological Societies (UIS) distinguishes 485 disease entities. This classification based on clinical phenotypes, immunological workup, and genetic variants includes nine categories: immunodeficiency affecting cellular and humoral immunity, combined immunodeficiency with associated or syndromic characteristics, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocyte number or function, defects in intrinsic and innate immunity, auto inflammatory disorders, complement deficiencies, bone marrow failure [39]. Although the symptomatology of IEI is complex and characterised by different clinical phenotypes including autoimmune, allergic, lymphoproliferative, and malignant disorders, infections remain their main manifestations. IEIs are no longer perceived as infectious diseases, and physicians need to be aware of the various phenotypic characteristics they may encounter in IEI patients, but sepsis, positive family history, and failure to thrive in children are sensitive warning signals of immune deficiencies [40]. Furthermore, certain aetiologies of infections can be characteristic to and suggest a specific defect in the immune system. For example, recurrent viral and fungal infections are typical of T lymph cell impairments and combined immunodeficiency, whereas infections caused by encapsulated bacteria are associated with complement component deficiencies [41]. It is noteworthy that pathogens mostly associated with immunosuppressed patients such as *Pseudomonas aeruginosa* can cause sepsis in hitherto undiagnosed children with IEI who have never suffered from recurrent infections [42].

The most serious IEI are severe combined immunodeficiency disorders (SCID), characterised by abnormal T-cell generation and maturation and also affecting the development and function of other immune cells such as B lymphocyte cells and NK cells [43]. It is a profound defect in the adaptive immune response that poses a high risk of severe generalised infections and neonatal sepsis may be the first manifestation of severe combined immunodeficiency disorders [44].

Severe B-cell deficiency occurs in agammaglobulinemia, which is a defect of maturation of B-cell precursors at their early stage of development in the bone marrow. The subsequent lack of mature B cells in peripheral blood and peripheral immune organs and an almost total lack of antigen-specific antibodies make affected individuals highly susceptible to pyogenic infections and sepsis caused by *Pseudomonas aeruginosa* [45].

Beyond qualitative and quantitative lymphocyte dysfunctions in the IEI mentioned above, deficiencies in the neutrophil compartment can also predispose to severe, not infrequently fatal, bacterial infections and sepsis. Severe congenital neutropenia is a group of immune defects whose pathophysiology is associated with the maldevelopment of neutrophils in the bone marrow. The genetic background for severe neutropenia / agranulocytosis is mutations in genes such as ELANE, HAX1, and G6PC3. Whereas the ELANE mutation has been identified in patients with cyclic neutropenia, sepsis due to bowel perforation has been reported [46]. Chronic granulomatous disease (CGD) is a genetically heterogeneous severe immunodeficiency caused by mutations in NADPH oxidase, thereby affecting the generation of reactive oxygen species and intracellular killing of phagocytosed microbes. Superficial cutaneous and deep-organ abscesses, lymphadenitis, gastrointestinal and urinary tract fistulas, as well as metastatic abscesses in different organs, such as the lung, liver, and brain, as well as osteomyelitis, occur in affected patients. The aetiology of infections in CGD includes Gramme-positive and Gramme-negative bacteria, such as *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, and *Salmonella sp*, intracellular pathogen, *Nocardia*, as well as mycotic infections with *Aspergillus* and *Candida*. This spectrum of pathogens is also observed in CGD-associated sepsis [47].

The next group of IEI showing a high index of sepsis are complement deficiencies. The complement is composed of a system of protein cascade, the activity of which is tightly regulated by numerous activating and inhibiting factors. Although deficiencies of the components C1, C2, and C4 predispose affected individuals to autoimmune diseases, and the defect C3, which is a central component of all complement activation pathways, is associated with recurrent infections, terminal defects C5-C9 defects show a high risk of sepsis. Patients with deficiencies in terminal complement components, aka membrane attack complex (MAC) are particularly vulnerable to sepsis due to meningococcal and pneumococcal infections [48,49].

Bacterial infections can also cause severe diseases and fatalities in IEI belonging to the innate immunodeficiency. This group comprises interleukin-1 receptor activated kinase (IRAK-4) and the myeloid differentiation primary response gene 88 (MyD 88), which are components of the signaling pathways related to toll-like receptors (TLR) that play a role in the recognition of microbial organisms. Immune deficiencies of IRAK-4 and MyD 88 manifest primarily as severe bacterial infections, such as deep organ abscesses, invasive pneumococcal disease, meningitis, osteomyelitis, and sepsis. The invading pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, but *Shigella* and *Clostridium* have also been reported [50,51].

Rare inborn immune deficiencies associated with predisposition to severe bacterial and/or fungal infections are, among others, mannose-binding lectin (MBL) deficiency, leukocyte adhesion deficiency (LAD), interferon-gamma (IFN- γ) and interleukin-12 deficiency, and hyper-immunoglobulin E syndrome caused by a mutation in STAT3 (signal transducer and transcription 3) [49,52,53].

Sepsis can be a warning sign of an inborn error of immunity due to dysfunctional innate or adaptive immune responses that underpin susceptibility to severe infection. Therefore, every patient with an episode of sepsis should be a candidate for immunodiagnostic procedures aimed at identifying a primary immunodeficiency disease [15].

SEPSIS AND TUMORIGENESIS

There is a co-occurrence of cancer and sepsis, with a synergistic effect on mortality - while cancer patients are susceptible to sepsis, sepsis survivors are also susceptible to developing certain cancers [54]. Both are associated with inflammation at some stage of the disease, leading to hospitalization of patients in the intensive care unit [54]. As cancer is responsible for an estimated 10-fold increase in the risk of sepsis compared to non-cancer patients, there are few more factors, including tumour location [55]. Disorders of immune system homeostasis can lead to sepsis and tumor formation [56]. The mechanism between late-onset carcinogenesis and sepsis is not yet well understood [57]. However, certain pathogens are known to induce the activity of the immune system towards the T helper 1 (Th1) and T helper 2 response [58]. The Th1 and Th2 effectors mutually inhibit each other [59], resulting in an altered immune response against cancer cells. Furthermore, the response against extracellular bacteria and fungi, through the T helper 17 mediated response, may increase the risk of cancer [60]. An Australian study showed that the probability of sepsis within one year of diagnosis was higher for men, younger and older patients, those who presented metastatic disease at the moment of diagnosis [61]. Another American study revealed that septic patients and patients suffering from septic shock have the same risk of mortality due to solid tumours compared to hematological tumors. However, patients with hematologic malignancy admitted with sepsis or septic shock have higher rates of bacteremia rates [62].

PULMONARY RISK OF SEPSIS

Lower respiratory tract infection is the most common primary diagnosis in sepsis [63]. Esposito et al. claim that sepsis predispositions are higher in patients over the age of 60 years [3]. Madaline et al. analysed that most patients in their investigation were hospitalised due to pneumonia (58.5%), as the presumed source of infection [64]. Montull et al. suggest that approximately every third patient hospitalised with community-acquired pneumonia (CAP) may develop severe sepsis.

CAP caused by *Streptococcus pneumoniae* or by mixed pathogens increases the risk of sepsis [65]. Hospital acquired pneumonia (HAP) has a higher risk of mortality, because it is caused by pathogens that are more antibiotic resistant. One of the most common bacteria that causes HAP is, according to Wunderink et al., *Staphylococcus aureus* [66]. Bacteremia leading to sepsis is also an uncommon consequence of ventilator-associated pneumonia (VAP). *Acinetobacter baumannii* is associated with bacteremia in VAP in critically ill patients [67]. Kunac et al. detailed other common pathogens found in blood in patients with VAP such as Gramme-positive *Staphylococcus aureus* both Methicillin sensitive and resistant to Methicillin (MSSA and MRSA), and Gramme-negative *Klebsiella pneumoniae*, *Enterobacter spp.* *Escherichia coli* or *Pseudomonas aeruginosa* [68].

Cystic fibrosis (CF) is another condition that can be exposed to septic complications. The lower airways are chronically colonised by pathogens which influence the morbidity and mortality of these patients. According to Surette, the most common bacteria in CF patients are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. There is a group of emerging pathogens in CF, including *Stenotrophomonas maltophilia*, MRSA, *Mycobacterium abscessus*, or *Achromobacter spp.* [69]. The prevalence of *Achromobacter xylosoxidans* in CF patients is still increasing and may be underestimated due to the difficulty in identifying this pathogen. Stobbelaar et al. described the first case of septicaemia caused by *A. xylosoxidans* in a 10-year-old child with CF with severe lung disease [70]. Another bacterium that can be very dangerous to patients with CF, especially those after lung transplantation is *Burkholderia cepacia* [71]. Nash et al. [71] Unfortunately, another opportunistic sepsis caused by bacteria from *Burkholderia* species, *B. gladioli*, ended fatal. Quon et al. described a case of post-lung transplant rhinosinusitis. The patient died 18 months after transplantation [72]. Occupational sepsis caused by microorganisms in CF patients with CF is not a common problem, but the risk of death is increased especially in patients who underwent lung transplantation [73].

CATHETER-RELATED BLOODSTREAM INFECTION

Hospitalisation is strictly associated with catheterisation of the patients, which predisposes to iatrogenic infections iatrogenic sepsis, especially when the central venous catheter was inserted. The pathogens colonising the catheter vary, but some of them have to be distinguished, like: multidrug resistant *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and nonmulti drug resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. According to Pitriga Gramme negative bacteria are more frequent than Gram positive [74]. Leonidou et al. point out that the catheter biofilm contains *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterococcus faecalis* [75]. Velasquez et al. highlighted the procedures to be performed to reduce or prevent catheter-related bloodstream infections, including the appropriate insertion site, aseptic management, and early removal if necessary [76].

CONCOMITANT VIRAL INFECTIONS AND RESULTING SEPTIC COMPLICATIONS

For the purpose of this study, we include the human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) as their chronic course and septic complications are most broadly described in the literature. Despite innovative treatment methods, sepsis in patients suffering from chronic viral infections remains a relevant clinical problem. Treatment requires special caution, considering that the site and cause of bloodstream infection are often not obvious.

Although now rare due to the progress of viral inactivation procedures, patients are still prone to nosocomial infections - especially those who need frequent transfusions, such as hemophiliac. In the mid-1980s, plasma-derived factor concentrates were thought to be the primary source of HIV and HCV [77]. Ten years later, Gilbert et al. examined 10 patients suffering from haemophilia A (factor VIII<1%) and the resulting septic arthritis – 80% were HIV-positive [78].

External risk factors for sepsis included catheter-related infections (n=2), pneumonia (n=2) and joint trauma before hem arthrosis (n=1). The authors emphasised that for clinical practice it is important to consider HIV infection in hemophilic patients, as hem arthrosis may be difficult to distinguish from early joint infection, and misdiagnosing these conditions may lead to sepsis. To avoid such a complication, early aspiration should be performed in any hem arthrosis associated with unusual pain pattern, elevated temperature, or lack of response to appropriate factor replacement [78]. On the other hand, acquired haemophilia A, which affects the elderly population, increases risk of sepsis by immunomodulatory pharmacotherapy [79]. When steroids are not sufficient, cyclophosphamide and rituximab can be used, which further compromises immune status [80].

The spectrum of bacteria that cause osteoarticular sepsis may be much broader when the patient is HIV positive. Interestingly, in such cases, *Streptococcus pneumoniae* plays a dominant role, not *Staphylococcus aureus*. As pneumonia is the leading cause of bacteremia in these patients, the synovium may be a secondary pathway to the joint for these pathogens. Taking this into account, the authors recommend starting patients on broad-spectrum antibiotics such as cloxacillin and ceftriaxone as an empirical first-line therapy, whenever HIV-related osteoarticular sepsis is suspected [81].

Furthermore, HIV infection can increase morbidity in patients with malaria or sepsis by decreasing protein S levels and, therefore, improving coagulation [82]. Simultaneous HIV and sickle cell disease results in an increased rate of hospitalisations for bacterial sepsis, however, at the same time, progression to AIDS might be delayed [83].

As the immune system is compromised on many levels, they are at increased risk of bacterial bloodstream infections – in particular non-typhoid *Salmonella*, *Streptococcus pneumoniae* and *Escherichia coli* [84]. Defects of epithelial barriers, especially the gut during acute infection, predispose to nontyphoid *Salmonella* bacteremia [85]. Furthermore, translocation of microbial metabolites disrupts immunity homeostasis [86]. Insufficient macrophage phagocytosis and impairment of proinflammatory cytokines in alveolar macrophages would explain the susceptibility to invasive pneumococcal infection in patients affected by HIV [84]. HIV infection is a well-known risk factor for postoperative sepsis, therefore special perioperative caution should be maintained [87]. Low CD4 cell counts, hypoalbuminemia, wound infection, and major surgical procedures risk up to 40% [88]. Preparing HIV-positive patients pharmacologically and nutritionally prior to operation and implementing less invasive surgical methods improve outcomes and prevent postoperative sepsis [87,88]. Interestingly, some viruses can compromise patients perioperative even more than HIV. Kildow et al. found that patients with hepatitis C virus or hepatitis B virus had an increased risk of sepsis after total joint arthroplasty compared to the HIV-positive cohort.

The combination of HIV and hepatitis B or C would further increase this ratio [89]. Eventually, coexisting HIV infection would alter outcomes after subsequent liver transplantation, as HIV infection aggravates HCV recurrence, therefore fastening the progression of fibrosis [90].

It is important to forget that relatively benign localised infection may be easily exacerbated in patients whose immune system was compromised. Yakobi et al. reviewed cases of intracranial sepsis in patients positive for HIV or tuberculosis. As ear discharge was the most common symptom, the authors highlight that apparently mild conditions such as otitis media should not be neglected in patients suspected of chronic immunocompromising infection [91].

SEPSIS AND COVID-19

The Covid-19 pandemic discovered a significant problem regarding severe infection and proper care for ill patients. It outperformed sepsis as the most common cause of emergency admission to hospitals and intensive care units. It triggered the comparison of these two disorders to show their similarities and differences. Kocak Tufan et al. focused on the similarities between sepsis and severe Covid-19, starting with the similar high level of cytokines and chemokine in both diseases and ending with the claim that both disorders can lead to multiple organ failure. However, they point out that sepsis is mainly caused rapidly and secondarily by bacteria, less often by fungal and viral infection. It occurs mainly in the lungs (64%), abdomen (20%) and bloodstream (15%), while Covid-19 is a viral infection that can show delayed onset [92]. Therefore, Lopez-Collazo et al. pointed out the similarity to the inflammatory reaction's mechanism of Covid-19, which contains the production of multiple factors related to the coagulation cascade and can result in thrombosis and DIC, which can also be seen in sepsis [93]. Bouck et al. confirmed that both are associated with abnormalities of coagulation and fibrinolytic activity but in different ones. The authors compared the plasma of Covid-19 patients (46), healthy donors (53), and sepsis patients (18). The resemblance between Covid-19 and sepsis was shown to be that both groups of patients had elevated fibrinogen, D-dimer, soluble thrombomodulin, and plasmin-antiplasmin complexes. Furthermore, patients with SARS-CoV-2 infection had a higher potential for thrombin generation despite prophylactic anticoagulation, and their plasma also had a higher endogenous plasmin potential, while patients with sepsis showed delayed plasmin generation [94].

According to the Centres for Disease Control and Prevention (CDC), people with immune deficiencies are more prone to suffering from severe Covid-19. Although Leschikova et al. reported that in their studies among five patients with primary immune deficiencies the symptoms of Covid-19 were mild to moderate and none of them developed a critical form of the disease [95]. Delevari et al. point out that patients with the immune deficiency are more aware of the importance of self- and tight isolation compared to other immunocompetent ones, and that may be the reason [96]. Furthermore, Vergidis et al. indicates also indicate increased awareness of the additional protection measures such as masks, social distancing and appropriate hygiene in patients [97].

SOLID ORGAN TRANSPLANTATION AND POSTTRANSPLANT INFECTION RISKS

Solid organ transplants (SOT) are conducted as a standard of care for some decades, however, as with any medical intervention, they carry a lot of potential risks for the recipient [98,99]. Immunosuppression, which is inherent in the treatment of patients with SOT, allows the host to accept

foreign substances, by inhibiting the efficacy of the immune response [100]. The immune response depends on the origin of the graft [100]. Different targets for available drugs improves the therapy, however, each agent has its side-effects [100]. The mechanism of action is complex, but their impact on the immune system includes a decrease of the production of cytokines and a decrease in CD4 + T cell circulation of CD4+ T-cells [100–102]. Azathioprine and mycophenolic acid belong to antimetabolites and they act by impairing DNA synthesis [100,101].

The first drug stops DNA replication by incorporation of its 'false' metabolites into replicating DNA[101]. The other inhibits the synthesis of guanosine nucleotides by inhibiting inosine monophosphate dehydrogenase [101]. Calcineurin inhibitors inhibit cytokine production, as well as T-cell activation and proliferation [101,102]. They bind to immunophilins and prevent the dephosphorylation of NFAT (activated T lymphocytes) resulting in the failure of T-cell activation [102].

Other immunosuppressive agents are used depending on the regimen. Diagnosing infections in SOT patients is complicated. Difficulties in early recognition of the condition include reduced infection signs, leading to inhibition of sepsis identification [99,103,104]. Therefore, sepsis should be suspected earlier when taking care of these patients [12,99]. The risk factors in this group consist of factors derived from donor and recipient derived before and after transplant [98]. Pretransplant risk factors include for example, underlying diseases, age or acquired pathogens from donors [98]. Intraoperative factors, such as the choice of the appropriate surgical method and the duration of surgery itself, which is affected by other intraoperative factors such as loss of blood or body fluids, correlate with the mean number of episodes of infection[105].

Postoperative immunosuppressive therapy, although continuously upgraded, puts SOT recipients at risk for opportunistic infections throughout the whole post-transplant course [98]. The posttransplant period is often divided into three main periods [99]. The first period lasts 30 days after the procedure and is characterised by pre-existing donor and recipient-derived infections or complications of surgeries, not with opportunistic infections, although the full immunosuppressive effect is not yet present [98,102,104]. This period includes the highest probability of Gram-negative bacterial bloodstream infections [106]. In the intermediate period that lasts 1-6 months post-transplantation immunosuppressive therapies play a more important role in possible infections, enhancing the probability of opportunistic infections [99,102].

Here, among others, preventive strategies for CMV and EBV are required [98]. Community-acquired infections remain the main threat to SOT recipients in the third post-transplant period which is more than 6 months after transplantation, but the risk varies according to immunosuppressive agents and exposures [98,99,102,104]. Preventive pretransplant strategies such as vaccination, universal prophylaxis and preemptive therapy are complicated, however they are necessary and are pointed to be extremely important in reducing posttransplant infections risks [104,107].

CONCLUSIONS

Due to the frequency of sepsis occurrence and the sequelae of the process, sepsis is a significant problem in clinical practise. Confirmation of sepsis in patients with immune deficiencies requires special attention, as they are more vulnerable to infections and the classic symptoms of sepsis may not be visible. The onset of sepsis may indicate congenital or acquired immune system impairments that were previously undiagnosed. A rational approach to the topic of infections and possibly their prevention during the pre- and post-transplant period is needed.

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