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Neutropenia – there are always two sides to a story

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Abstract
Neutropenia is uncommon but a very challenging problem in medicine. It remains a well-known risk factor for the development of infection while conversely neutropenia can be caused by infection or its treatment. The issue is discussed in the paper with respect to different patient populations, medical intervention, and life situations.

Keywords:
neutropenia, neutropenic fever, infectious-induced neutropenia

Introduction

Neutropenia is defined as a decrease in circulating neutrophils (absolute neutrophil count), in persons and the normal level of adults is <1.5 G/L, and is classified as mild when level is 1–1.5, moderate when 0.5–1.0, and severe when <0.5. Differential diagnosis of neutropenia is a difficult interdisciplinary problem with congenital and acquired causes along with the impact of comorbidities, infections, and medications. Neutropenia coexisting with thrombocytopenia and anemia is a manifestation of bone marrow damage (aplastic anemia, myelodysplastic syndrome, and chemoradiotherapy), bone marrow infiltration (acute leukemia) or deficiency (megaloblastic anemia). Isolated neutropenia is a common hematological finding, usually based on a timeframe of 3 months and may be divided into acute and chronic forms. It can be diagnosed as an inherited/congenital disorder or an acquired condition. Most inherited neutropenia cases are diagnosed before the age of 10 years. Among the inherited causes of neutropenia, including benign ethnic neutropenia (mainly in individuals of African descent), familiar neutropenia, and other congenital neutropenia with or without somatic findings such as premature graying of hair, cardiac or urogenital abnormalities (G6PC3 mutation), and skeletal abnormalities (Shwachman-Diamond syndrome), the most common is cyclic congenital neutropenia. It is often caused by an ELANE mutation which should be considered in patients with episodic, recurrent aphthous ulcers and confirmed by performing a complete blood count at least twice a week up to six weeks. Other genetic causes of neutropenia include *WAS*, *SBDS*, and *HAX1*. On the other hand, the presentation of chronic idiopathic neutropenia or idiopathic neutropenia may be asymptomatic or may lead to recurrent infections with fever, gingivitis or aphthous ulcers. Neutropenia is often found in the course of rheumatologic disorders such as rheumatoid arthritis, including Felty syndrome, systemic lupus erythematosus, and Sjögren syndrome, and should be excluded in differential diagnosis [1, 2]. Above all, an underappreciated cause of neutropenia is infections, thus neutropenia can be a complication of viral, bacterial, and parasitic infections. There are several mechanisms leading to neutropenia in the course of infections including impaired proliferation and differentiation in the bone marrow, incorrect distribution of circulating granulocytes and their adhesion to the vascular endothelium, excessive sequestration of circulating granulocytes in the spleen and/or their destruction in the course of immune processes, nutritional deficiencies or the pharmacotherapy used. Neutropenia in the course of infections is most often transient, lasts <3 months and is usually unnoticeable. This is often the case with the course of viral infections and, less often, it is associated with acute bacterial infections (sepsis) or less severe bacterial and protozoal infections [3, 4].

Infectious complications during neutropenia

Infections during neutropenia are life threatening. The risk of their occurrence increases in the severe form cases with a neutrophil count below 0.5 G/L lasting more than 7 days. Such condition is usually seen in patients undergoing intensive antineoplastic treatment (e.g., chemotherapy for acute myeloid leukemia or treatment with hematopoietic cell transplantation) and accompanied by thrombocytopenia and anemia (pancytopenia). The Multinational Association for Supportive Care in Cancer (MASCC) scale, taking into account clinical symptoms and the presence of comorbidities, allows for the identification of patients with high (number of points <21) and low risks of infectious complications (Tab. I).

In the course of neutropenia, bacterial infections are the most common, less frequently fungal and viral infections are seen. Bacteria are responsible for blood stream infections mainly, occurring in 13–60% of patients with mortality reaching 12–42%. About 50% of bacterial infections during neutropenia are caused by Gram-positive ones, especially methicillin-resistant coagulase-negative staphylococci, but also by *Streptococcus* sp. An increasing threat in recent years is the increase of infections caused by resistant pathogens:

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Table I. MASCC scale

Characteristic	Weight
Burden of febrile neutropenia symptoms No or mild symptoms Moderate symptoms Severe	 5 3 0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematological malignancy without previous fungal infection	4
No dehydration	3
Outpatient status	3
Age <60 years	2

High risk for poor outcome: <21 points

vancomycin-resistant enterococci (VRE) and staphylococci (vancomycin-intermediate *Staphylococcus aureus* [VISA]; hetero-resistant *Staphylococcus aureus* [hVISA]). Infections with Gram-negative bacteria, especially those of resistant pathogens, are among the most serious complications associated with high mortality rate of around 50%. *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* sp., and *Acinetobacter* sp. are the most common causes of infections.

Infections during neutropenia spread quickly, posing a direct threat to life, therefore the immediate implementation of empirical antibiotic therapy is obligatory, without waiting for identification of the pathogen and its susceptibility determination. The principle of treatment is the intravenous administration of broad-spectrum antibiotics against both Gram-positive and Gram-negative bacteria, and its modification depending on response to therapy, clinical condition, and microbiological test results. The choice of empirical treatment should be based on the frequency and sensitivity of the pathogens present in a given ward, as well as the experience of the center. Currently, two empirical strategies are employed: escalation therapy, consisting of modification depending on the clinical condition and results of microbiological tests, or de-escalation, based on application from the beginning of combination antibiotic therapy including antibiotics against resistant pathogens. In patients with a confirmed bacterial infection, especially resistant pathogens, targeted and narrowed therapy should be implemented. It is emphasized that the targeted therapy should be based on the bacterial sensitivity in vitro, the confirmed efficacy of the antibiotic in the treatment of infections caused by a given pathogen, the pharmacokinetic and pharmacodynamic data, and also individual analysis of the risks and benefits of the treatment used [5, 6].

Persistent or recurrent neutropenic fever despite the administration of broad spectrum of antibiotics may suggest invasive fungal infection. The most common fungal pathogens responsible for neutropenic infection is *Aspergillus* sp. followed by *Mucorales*. *Candida* sp. infections, which are currently rare, diagnosed in approximately 5% of patients as a blood stream infection, however, mortality in their course may exceed 20%. The strategy of antifungal therapy during neutropenia includes empirical therapy, pre-emptive treatment, and treatment for confirmed mycosis defined and described by European Conference on Infections in Leukemia (ECIL) [7, 8, 9].

Infection-induced neutropenia

Bacterial infections as a cause of neutropenia

Although leukocytosis is usually observed due to bacterial infections with an increase in the number of bands (shift of maturation to the left), in some bacterial infections symptoms such as typhoid fever, bacterial dysentery, brucellosis, tularemia or tuberculosis, and a decrease in the number of granulocytes are observed [10, 11].

Sustained fever with abdominal symptoms after returning from endemic areas may indicate typhoid fever. Typhoid fever is a disease among tropical diseases responsible for up to 20–30% of admissions with leukopenia and neutropenia to the intensive care units and other complications in Africa, Asia, and South Africa [12, 13, 14]. Bone marrow evaluation often shows granulocytic hyperplasia with hemaphagocytosis, whose severity correlates with peripheral blood cytopenia followed by hemaphagocytosis [15]. The pathomechanism of neutropenia in typhoid fever is complex and includes the presence of endotoxins, cytokines including tumor necrosis factor (TNF), interleukin 6 (IL-6), and interferon γ (IFN-γ) contributing to increased hemophagocytosis. All these inflammatory mediators lead to upregulation of endothelial adhesion molecules and a shift of peripheral granulocytes to endothelium [16, 17]. Cases of typhoid fever imported because of travelers from India and Nepal are also published in Polish literature [18].

In the course of shigella enteritis, abnormalities in the granulopoeitic system, ranging from leukopenia to leukocytosis, are also observed, with a shift to less mature band forms in the peripheral blood. The mechanism of these disorders is unknown. A shigella infection can lead to serious systemic complications, including septicemia, hemolytic uremic syndrome or a leukemoid reaction. The occurrence of neutropenia, in both adults and children, is an unfavorable prognostic factor [19].

The incidence of neutropenia will be up to 30% for adults and children with brucellosis, and almost 20% of patients have pancytopenia [20, 21]. The spleen size is related to the severity of hemophagocytosis and the development of non-serous granulomas in the bone marrow [22]. In an assessment of the leukocyte immunophenotype in patients with brucellosis, shifts to the left in the granulocytic lineage and disturbances in the activation of T and B lymphocytes and monocytes are found [23].

Neutropenia is occasionally observed in the course of tularemia, zoonosis shows the involvement of ulcer-glandular lymph node and sometimes pneumonia. In rare situations, it can be life-threatening in immunocompromised patients, including patients after allogeneic hematopoietic stem cell transplantation [24]. The effect of these bacteria on neutrophil and macrophage functions is well known. It has been shown that these bacteria can change their overall response to antigens, induce disorders in neutrophil recruitment mechanisms, disorders in opsonization and phagocytosis and cause inhibition of neutrophil defense mechanisms [25].

Neutropenia is observed in the most of severe cases of disseminated miliary tuberculosis with pancytopenia and is estimated to be around 5% of all patients. Furthermore, it may lead to lymphopenia in almost 87% of cases, leukopenia in approximately 15% of patients, and thrombocytopenia in 23% of cases [26, 27].

Rickettsia infections can also lead to neutropenia including rickettsialpox, human granulocytic anaplasmosis, and Rocky Mountain spotted fever [28]. Rickettsiae occur mainly in Africa, the Mediterranean, and southern Europe, as well as in the United States and Canada [29, 30, 31]. One of the rickettsia infections, Anaplasma phagocytophilum, often diagnosed in Poland and other European countries, may lead to leukopenia with neutropenia, thrombocytopenia, and increased hepatic transaminase activities at early presentation of the disease [32–36].

Parasitic infections as a cause of neutropenia

The occurrence of neutropenia is mainly observed in the course of two parasitic infections, malaria and leishmaniasis. Both diseases occur in endemic regions. Leishmania flagellate infections occur in the Mediterranean, East Africa, and South America, while malaria is endemic to Africa, India, and Southeast Asia. In Poland, these diseases occur occasionally, usually, imported from endemic regions, but diagnosing them is a serious problem. The most dangerous form of the disease is visceral leishmaniasis caused mainly by *Leishmania donovani*, which leads to fever, hepatosplenomegaly, and neutropenia in the course of pancytopenia. Large studies have shown that the incidence of leukopenia reaches 75% of visceral leishmaniasis cases. It is believed that hypersplenism is the main cause of its development [37, 38]. The presence of myeloid hyperplasia, an increased number of lymphocytes, plasma cells and megakaryocytes, hemophagocytosis (phagocytosis of erythrocytes, leukocytes, and platelets occur in 46% of cases), ineffective erythropoiesis, and granulomas can be found in the course of visceral leishmaniasis. The severity of the hematological changes depends on the duration of the disease and the size of the spleen, not on the number of parasitized mononuclear cells [38]. Severe neutropenia in celiac leishmaniasis is prognostically unfavorable factor [39].

Malaria is a tropical disease caused by a protozoan of the genus Plasmodium (out of 120 *Plasmodium* sp., the six species of malaria parasites including *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale wallickeri*, *Plasmodium ovale curtisi*, *Plasmodium malariae*, and *Plasmodium knowlesi* are pathogenic for humans), transmitted by a vector – Anopheles mosquito, and the disease occurs in 91 countries around the world [40, 41, 42]. The incidence of neutropenia at diagnosis is seen in 7% of malaria cases caused by *Plasmodium falciparum* and increases in the first 7 days of treatment. In one-third of all neutropenia cases, the number of granulocytes falls below 0.5 G/L. The risk of neutropenia increases with the observation time, along with higher levels of baseline parasitemia, althoguh it is independent of the final treatment result and is lower in the elderly and during combination therapy with artemisinin [43]. The pathomechanism of neutropenia in the course of malaria is complex, including an increase in the number of sporozoites in peripheral blood, disturbances in the distribution of granulocytes with its marginalization, and a decrease in both the number of mature granulocytes and myeloid reserve by premature release of immature forms from the bone marrow [44].

Viral infections as a cause of neutropenia

In the majority of cases, in children and young adults, mild to moderate neutropenia is thought to be due to transient myelosuppression caused by various viral infections [45]. Neutropenia is observed in patients infected with Herpes viruses (EBV, CMV, HHV6, and HSV), respiratory tract viruses (RSV, influenza A and B, and parainfluenza), and hepatitis viruses, as well as other viral exanthematous diseases, including chickenpox, rubella, and measles. Neutropenia often occurs during the first few days of the viral disease and lasts for 3–8 days [45].

The Epstein–Barr virus (EBV) infection is common and affects more than 80% of the world's population [31]. It is most common in children, while in young adults it may cause an acute infection with fever, pharyngitis, lymphadenopathy, and splenomegaly. The EBV virus infects B lymphocytes, and in a peripheral blood smear lymphocytosis with atypical lymphocytes is detected along with antibodies to erythrocytes, neutrophils, and EBV [46, 47]. The presence of anti-neutrophil antibodies and their transient aggregation leads to neutropenia [46, 48]. Rare hematological complications of acute infection include hemolytic anemia and thrombocytopenia, which occur in <1% of cases [49]. After infection, the virus remains in the body in a persistent form. EBV has been shown to have oncogenic potential, especially in endemic forms of Burkitt's lymphoma, it also plays a role in the pathogenesis of Hodgkin's lymphoma, epithelial and gastric cancers, and the development of post-transplant lymphoproliferative disease (PTLD) in both organ transplant recipients and hematopoietic cell recipients (HCT) [49].

Cytomegalovirus (CMV) infection is also a common infection, it can cause fever, sore throat, lymphadenopathy, splenomegaly, and myalgia in adolescents and young adults. Transient mild neutropenia and thrombocytopenia may occur in its course [50]. After infection, the virus remains in the body in a persistent form. CMV infection is one of the main causes of morbidity and mortality in immunocompromised individuals, including AIDS patients and HCT recipients and after solid organ transplantation. In this group of patients, the most common hematological disorders include neutropenia and thrombocytopenia, but the infection may lead to secondary transplant rejection [50]. The average frequency of CMV reactivation after HCT was estimated to be, 37% after allogeneic transplantation, 30% in solid organ transplant recipients, 20% during active replication in HIV infected patients, and

3.3% during antiretroviral therapy. The highest risk of CMV infection and CMV disease was demonstrated in seropositive HCT recipients [51]. Neutropenia also increases with ganciclovir, used to treat CMV infections and diseases.

Hepatitis A rarely leads to transient neutropenia, most often occurs in the second week of infection, but in some cases, agranulocytosis occurs [52, 53]. However, mild to moderate neutropenia is often diagnosed in the course of chronic hepatitis C (HCV) [54]. The development of neutropenia occurs as a result of the inhibitory effect of the virus on myelopoiesis, hypersplenism, and autoimmune processes [54, 55]. Neutropenia can also occur in patients with chronic hepatitis B, usually its severity is related with the development of liver cirrhosis and hypersplenism [56, 57].

Primary infection with herpes virus-6, which causes sudden erythema in children (also called three-day fever), is especially dangerous in recipients of solid organs and hematopoietic cells and can lead to neutropenia, often during the course of severe pancytopenia [58, 59]. The infection is often accompanied by skin lesions such as roseola infantum and neurological disorders.

Leukopenia with mild neutropenia and lymphopenia is commonly found in the course of viral rash diseases such as measles, rubella, and chickenpox. In the course of measles, leukocytosis is usually observed during the incubation period, followed by a sharp decrease in the number of granulocytes with the lowest value during the time of skin lesions [60, 61]. Impaired neutrophil chemotaxis and phagocytosis are also observed, which leads to secondary impairment of immunity [62, 63, 64]. The measles vaccine contains a live, attenuated measles virus which may cause transient mild neutropenia between days 3 and 16 [65].

In the course of rubella, neutropenia occurs in about 50% of cases and disappears slowly within six weeks [66]. In isolated cases, severe neutropenia is observed in chickenpox, which usually causes leukocytosis and neutrophilia [67].

Neutropenia often occurs in patients with human immunodeficiency virus (HIV) infection. The causes of neutropenia in the course of this infection are complex and include the toxic effect of the virus on hematopoiesis, the effect of infections secondary to HIV infection, and the use of myelotoxic agents in its treatment. Increased incidence and the severity of neutropenia are particularly marked in the advanced stages of HIV. In addition, reduced neutrophil counts in the blood are closely related to CD4+ cell loss and inversely related with HIV viremia [68, 69, 70]. Opportunistic infections in HIV that can induce or exacerbate myelosuppression and neutropenia are numerous and include Mycobacterium avium Complex, Mycobacterium tuberculosis, Cryptococcus *neoformans*, *Candida albicans*, *Pneumocystis jiroveci*, *Toxoplasma gondii*, and infection with hepatitis B virus infection. Some of these infections show increased destruction of granulocytes in the peripheral blood or their sequestration in the enlarged spleen [69].

Another example of neutropenia, which is seen in travelers especially in endemic areas and considered in differential diagnosis of fever, is acute Dengue virus infection (benign neutropenia occurs in 76–100% of cases) [71–74]. Neutropenia may also occur in the course of yellow fever and other viral infections [75–78]. It is believed that the main cause of leukopenia or neutropenia is the direct effect on the bone marrow by viruses.

Antibiotic-induced neutropenia

The occurrence of neutropenia may not only be caused by infections, but may also be induced by the anti-infective treatment used. The incidence of treatment-induced neutropenia is estimated around 4 cases per 10,000 hospitalized patients [79]. Among the undesirable effects, regardless of the route of administration (oral or parenteral), the incidence of neutropenia is 6% [80]. One of the most common causes of neutropenia is the use of antibiotic therapy, particularly beta-lactams, sulfamethoxazole with trimethoprim and vancomycin [81]. With antibiotic-induced neutropenia immediate discontinuation of treatment is indicated. In most cases, neutropenia resolves spontaneously.

Infection-induced neutropenia in children

It is believed that in both transient and chronic neutropenia in children, it is possible to identify infectious causes in more than 50% of cases [82, 83]. In 85% of children, neutropenia is diagnosed accidently [84] and resolves spontaneously. Acute transient neutropenia most often occurs after viral infections. It can start a few days before the infection starts and usually lasts until the end of the viremia. Viral infections, including chickenpox, measles, rubella, hepatitis A and B, influenza, cytomegalovirus, EBV, parvovirus B19, adenovirus, and coxsackie lead to neutropenia, resulting in reduced production and increased destruction of granulocytes. Neutropenia in children can also be observed due to bacterial infections, including *Staphylococcus aureus*, and in the course of brucellosis, rickettsiosis, and tuberculosis [85].

Hemophagocytic syndrome secondary to infections

Hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) secondary to infections should be considered when interpreting neutropenia reports/results in the course of some infections. Cytopenia and splenomegaly are the result of macrophage activation in response to many stimuli including numerous viral, bacterial, parasitic, and fungal infections. It is believed that this reaction can be triggered by viruses, in particular EBV, cytomegalovirus, HIV, and H1N1 influenza virus [86, 87]. There are also reports indicating the role of parvovirus, herpes simplex virus, varicella-zoster virus, disseminated adenovirus, measles virus, and human herpes virus 8 [88–93]. HLH can also occur in infections caused by bacteria include visceral leishmaniasis, atypical/tuberculous mycobacteria, histoplasmosis, ehrlichia, bartonella, and Brucella species [89]. It is believed that HLH-like syndrome can be triggered by SARS-CoV-2 [94, 95].

Travel-induced infections and neutropenia

A history of traveling, especially in some endemic areas of diseases, should be considered in differential diagnosis of neutropenia. Selected issues characterizing neutropenia in the course of bacterial infections including geographical distribution, source and transmission, along with recommendations for travelers are presented in table II. Travel-related pandemic/endemic viral diseases leading to neutropenia are shown in table III.

Table II. Selected issues characterized by neutropenia in the course of bacterial infections including geographical distribution, source, and transmission with recommendations for travelers

Type	Etiopathogenesis	Frequency of neutropenia	Geographical distribution	Source and transmission	Recommendations for travelers
Salmonellosis	*Salmonella enterica*, *Salmonella typhi*	25–50%	Still endemic in India and Pakistan, Africa, Far East Asia, the Middle East and South and Central America	*Salmonella* bacteria are widely distributed in domestic and wild animals. They are prevalent in food animals such as poultry, pigs, and cattle; and in pets, including cats, dogs, birds, and reptiles such as turtles	Ensure food is properly cooked and still hot when served. Avoid raw milk and products made from raw milk. Drink only pasteurized or boiled milk. Avoid ice unless it is made from safe water. Wash hands thoroughly and frequently using soap, in particular after contact with pets or farm animals, or after having been to the toilet. Wash fruits and vegetables carefully, particularly if they are eaten raw. If possible, vegetables and fruits should be peeled
Shigellosis	*Shigella*: *S. dysenteriae, S. flexneri, S. boydii*, and *S. sonnei*	Variable occurrence	The highest for people traveling to Africa, followed by Central America, South America, and Asia	*Shigella* is transmitted via the fecal–oral route, including through direct person-to-person or sexual contact or indirectly through contaminated food, water, or fomites	No vaccines are available. Frequent handwashing, strict adherence to standard food and water safety precautions and minimizing fecal–oral exposure during sexual activity
Brucellosis	*Brucella melitensis, Brucella suis, Brucella abortus, Brucella canis*	20–30%	Worldwide, in animals, most common in developing countries, South America, central Asia, the Mediterranean and the Middle East	Primarily a disease of animals. Infection in people is acquired from cattle (*Brucella abortus*), dogs (*B. canis*), pigs (*B. suis*), or sheep and goats (*B. melitensis*), usually by direct contact with infected animals or by consumption of unpasteurized (raw) milk or cheese	Avoid consumption of unpasteurized milk and milk products and direct contact with animals, particularly cattle, goats, and sheep
Tularemia	*Francisella tularensis*	Rare	The northern hemisphere – North America, Russia, Europe, and Japan	Primarily a disease of a wide variety of wild mammals and birds. Humans become infected mainly through the bite of arthropods, particularly ticks and mosquitoes, and through the skin, conjunctival sac or oropharyngeal mucosa, by direct contact with infected animals or animal materials and by ingestion of contaminated food or water or inhalation of contaminated dust or aerosols	The use of insect repellents, wearing appropriate clothing during a stay in the forest (long legs and sleeves), quick removal of ticks, avoiding consumption of untreated water from natural water bodies, proper heat treatment of meat before consumption, not touching sick or dead animals, using gloves when touching rabbits, muskrats, prairie dogs and other animals, using masks in situations where there is a risk of inhalation of bacteria into the respiratory system (e.g. when cleaning places where rodents may stay)
Tuberculosis	*Mycobacterium tuberculosis*	5% of disseminated millary tuberculosis	Mainly in Third World countries, in highly developed countries due to a decrease in immunity in the course of immunosuppressive treatment, addiction or HIV infection	Spread through the air when people who have active TB in their lungs cough, spit, speak, or sneeze	Tuberculosis prevention and control efforts rely primarily on the vaccination of infants and the detection and appropriate treatment of active cases

Table III. Travel-related pandemic/endemic viral disease leading to neutropenia

Pandemic, endemic disease	Neutropenia frequency	Geographical distribution	Source and transmission
Chikungunya	4% of hospital admission	Tanzania, Brazil, Puerto Rico, and Bangladesh	Mosquito-borne viral disease
Crimean-Congo hemorrhagic fever	>50%	Africa, the Balkans, the Middle East, and Asia	Spreads to humans either by tick-bites, or through contact with viremic animal tissues
Ebola virus disease	In case fatality	Central Africa, near tropical rainforests, Guinea, Sierra Leone, and Liberia	Transmitted to people from wild animals (such as fruit bats, porcupines and non-human primates) and then spreads in the human population through direct contact with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids
Dengue fever virus	In severe cases	Africa	Mosquito-borne viral infection
Colorado tick fever virus	Major finding	The western United States	Transmitted by ticks
Yellow fever	First week	Tropical areas of Africa and Central and South America	Transmitted to humans by the bites of infected *aedes and haemagogus mosquitoes*
Phlebotomus fever virus pappataci	Protracted neutropenia	In the subtropical zone of the Eastern Hemisphere, particularly in Southern Europe, North Africa, the Balkans, Eastern Mediterranean, Iraq, Iran, Pakistan, Afghanistan, and India	A vector-borne febrile arboviral infection caused by the bite of the sandfly

Infection-induced neutropenia in transplant recipients

In the setting of HCT recipients, recurrent neutropenia is a common observation even after hematological reconstitution. This condition is usually transient and related to the viral infections described above: CMV, EBV, HHV-6, and Herpes simplex [96, 97, 98]. In specific situations, the Zika infection may also be considered [99]. Additionally, severe bacterial infection may cause neutropenia, especially in the course of septic shock. In differential diagnosis the formation of antibodies directed against granulocytes in autoimmune neutropenia after HCT should be included [96, 100]. Although autoimmune neutropenia most often occurs in the early post-transplant period, cases of late-occurring neutropenia with identified antibodies against human neutrophil antigens (usually type 2 and type 1a) following upper respiratory tract viral infections are also reported in the literature [101].

Summary

Neutropenia remains an important interdisciplinary issue, which requires special attention. One should emphasize on complex causes of infection-induced neutropenia and risk of infections in the course of severe neutropenia. So for travelers or immunocompromised patients in these clinical situations, proper diagnosis and treatment of this condition help to avoid complications and may improve the outcomes.

Authors' contributions

JRM, LG – conceived the idea for this manuscript and wrote the paper. All authors – edited and approved the final version of the manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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