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Original Research Article

Bacterial infections in oncological child

Rădulescu Florin – Mihai[1,2*], Dumitru Irina Magdalena[1]

[1]Doctoral School in Medicine of "Ovidius" University, Constanța - Romania

[2]Emergency Clinical Hospital for Children "Maria Sklodowska Curie", București-Romania

***Corresponding Author's Email: radulescu_florin_mihai@yahoo.com**

Abstract

Bacterial infections present a polymorphic aspect, both from the point of view of the pathogens and the pathological mechanisms involved in the infectious process. Documented data reminds of a prevalence of bacterial infections in oncological children. Analyzing information from medical literature, we are putting forward a systematic presentation of the main oncological conditions, with the type of immunodeficiency specific to each one and the most frequent pathogens encountered in every type in particular. Thus, for example, in acute leukemia and acute lymphoma, in neutropenia, the most frequent infections are caused by gram-positive and gram-negative germs, but when the immunodeficiency is cell-mediated, infections with *L. Monocytogenes and Salmonella* occur, and the presentation continues in detail for every individual class of oncological conditions (acute leukemia and acute lymphoma, chronic lymphocytic leukemia, multiple myeloma, hairy cell leukemia and solid tumors). In the end, we are bringing the current tendency in the emergence of bacterial infections in little oncological patients to your attention. We focused on *viridans streptococci and* gram-negative pathogens, such as *Streptococcus maltophilia, Burkholderia cenocepacia, Achromobacter species, Alcaligenes and Stenotrophomonas maltophilia,* discussing their infections at large. The analysis in question has also taken into consideration two bacterial syndromes: the infection with virulent strains of *Clostridium difficile,* which has emerged in the recent years, with lethal potential upon oncological patients, and *pyomyositis* caused by *Escherichia Coli,* described most often in patients with hematologic malignancies.

Keywords: Infection, Immunosuppression, Oncological Child, Bacteria

INTRODUCTION

Pediatric oncology has experienced a substantial development in the last decades. With an increasing survival rate at 5 years from 58% in mid 70s to 80% in 2020 (Jennifer M. Yeh et al., 2020) this pathology launches new challenges Increasing life expectancy also led to extended periods of immunosuppression to which these patients are exposed. Therefore bacterial infections appeared with wide range of etiologies, with access gates that may vary from venous catheters (Raad,2014) to scraping.

MATERIALS AND METHODS

Examining the relevant literature of the last nearly 30 years, we hereby propose a systematic overview of the

main bacterial infections associated to each type of oncological disorder, as well as the main antibiotics that proved to be efficient in the case of these infections.

RESULTS

Bacterial infections show some different forms of the agent that causes them, the pathogenic mechanisms, and the temporary path of the generated condition. Infections can be produced by both gram-positive or negative bacillus and coccus; these were the first known bacterial agents assumed to cause infections. However, a taxonomy so simple does not account for other pathogens, such as *Mycobacterium* species, spirochetes Treponema, Mycoplasmas, Rickettsia, Chlamydia, and Actinomyces. Each of these organisms presents stereotypical characteristics which describe their interaction with the host body, although there are many exceptions and variations. In the last few years, Archaea, a very widespread and ancient group of prokaryotes, which look almost like bacterias, have been withdrawn from the human body (Koskinen et al., 2017); the extent of these microorganisms' role in human pathology is not determined yet.

The mechanisms through which bacterias cause infections are diversified and summarized in the table 1 below.

There are no applicable mechanisms or universal principles in bacterial infections. There is no even need for the causal organism to be in the human body. For example, food poisoning is usually caused by the ingestion of a preformed toxin belonging to pathogenic species when these grow up on food, not inside the host body. Bacterial infections include interactions between the human body (the host) and involved microorganisms which can range from minutes to decades. Each bacterial infection is unique and reflects the causal agent's virulence and also the susceptibility of the host. For example, the saprophyte flora can cause devastating infection not only to immunocompromised patients but also to oncological children.

The most encountered pathogens, according to the type of cancer

The type of cancer and its status (active or in remission), as well as the intensity of treatment whose target is that cancer, are important factors in determining the risk of infection development. There is much information in medical literature, especially for the patients who receive treatment for acute leukemia and lymphomas; a summary of the dates found in accessed medical compendiums is presented in Table 2.

Acute leukemia and acute lymphoma

Patients diagnosed with leukemia and lymphoma, presenting neutropenia either caused by comorbidities or cytotoxic chemotherapy, are exposed to the risk of developing different types of infections, compared with the non-neutropenic patients. The epidemiology of infections in oncological neutropenic patients suffers some periodical changes and often depends on geographic and institutional factors; although, some tendencies continue to persist. About half of all the neutropenic fever episodes will not have a clinical location or an identified causal pathogen, while 20-30 percent will show the clinical aspect of infections, such as pneumonia and cellulite, but negative microbiological cultures. Only 25-30 percent of all episodes will represent a documented infection microbiologically, in many cases the isolation of the microorganism being made from the blood or the urinary tract or respiratory one, from the skin, soft tissues, or the gastrointestinal tract. A small proportion of the patients could present non-infectious causes of fever, such as tumors or pyogenic drugs. (Freifeld AG et. al., 2011; Rolston KV, 2009). In general, gram-negative bacillus like *E.coli, Klebsiella spp.* and *Pseudomonas aeruginosa* cause the first infections in neutropenic patients. These happen during the first two-three weeks from the initialization of the chemotherapy and are due to the fast decrease in the number of neutrophils. These infections are characterized by acute febrile episodes, which can progress to sepsis if they are not treated quickly (Gupta A, et. al., 2010).

However, in the early 1980s, researchers noted a relative decrease in the amount of bacteremia with Gram-negative bacteria and a significant increase in the infections caused by Gram-positive aerobic bacteria, including staphylococcus and streptococcus. These observations persist in more recent studies, with an estimated 50% of documented infections having been caused by Gram-positive microorganisms. Gram-negative bacteria are considered to be responsible for 20-25% of infections, with the rest of the infections being polybacterial. Isolated anaerobic bacterial infections occur very rarely. Viral and fungal infections occur later in neutropenia (Rolston KV, 2009; Erdem H et al., 2019).

Numerous reasons have been postulated for increasing the incidence of Gram-positive infections (Viscoli C et al., 1988). The use of antibiotic cures both prophylactically and empirically, working on Gram-negative bacteria, decreases the recovery of Gram-negative pathogens and selects infections with Gram-positive bacteria (Karp JE et. al.,1986). An example is the emergence of streptococcal infections in patients receiving fluoroquinolones (Arning M et. al., 1990). The use of intravascular catheters increases the likelihood of developing infections with Gram-positive bacteria, such as staphylococcus that colonize the skin (Karp JE et. al.,1986).

Table 1. Pathological mechanisms involved in bacterial infections

Mechanism	Examples
Pyogenic infection	Pneumococcal pneumonia, staphylococcal abscess
Granulomatous infection	Pulmonary tuberculosis (TB), Brucellosis, Syphilis
Intoxication	Cholera
Poisoning – tissue destruction	*Clostridium perfringens, Corynebacterium diphtheriae*
Immunological mediation	Acute rheumatic fever after pharyngitis caused by *Streptococcus pyogenes*
Neoplasias (cancers)	Stomach adenocarcinoma as a result of *Helicobacter pylori's* persistence

Table 2. Bacterial infections prevalent in cancer patients (Rolston KV, 2009)

Oncological disease	Immunodeficiency	Pathogens and common syndromes
Acute leukemia and acute lymphoma	Neutropenia	Gram-positive: S. aureus, S. epidermidis, streptococcus, enterococcus
		Gram-negative: E. coli, Klebsiella spp., P. aeruginosa
	Cell-mediated	*L. monocytogenes, Salmonella spp., N. asteroides, mycobacteria, L. pneumophila*
Chronic lymphocytic leukemia	Hypogammaglobulinemia	*S. pneumoniae, H. influenzae, N. meningitidis*
Multiple myeloma	Humoral; complement deficiency; late-stage neutropenia	*S. pneumoniae, H. influenae, N. meningitidis, neutropenia-associated bacteria*
"Hairy" cell leukemia	Cell-mediated; late-stage neutropenia	*Salmonella spp., L. monocytogenes, M. kansasii, M. avium, M. chelonei*
Solid tumors	Disturbance of anatomical barriers	Skin: Staphylococcus, streptococcus;
		Oral cavity and nasopharynx: anaerobic bacteria, streptococcus, H. influenzae
		GI tract: Enterobacteriaceae;
		Female genital tract: Enterobacteriaceae, anaerobic Gram-negative bacteria, Enterococcus , Clostridium spp.
	Mechanical obstructions	Urinary, biliary and respiratory infections; vascular obstructions.
	Loss of vomiting	Aspiration pneumonia
	Urinary incontinence	Recurrent urinary tract infections
	Limited mobility	Ulcerations with or without osteomyelitis

Chemotherapeutic regimens that cause oral mucositis predispose to infections with bacteria that colonize the oropharynx, such as alpha-hemolytic streptococci. Although the mortality associated with Gram-positive bacterial infections is lower than in infections with Gram-negative organisms, the morbidity is significant. For example, alpha-hemolytic streptococci have been associated with cases of acute respiratory distress syndrome (ARDS) in patients receiving cytarabine (Arning M et. al.,1990). Moreover, patients who remain neutropenic for extended periods of time are more prone to develop infections with resistant bacteria, such as: Enterococcus spp., *Corynebacterium jeikeium*, *Serratia* spp., Stenotrophomonas (Xanthomonas) maltophilia. These infections are a consequence of prolonged treatment with broad-spectrum antibiotics (Shaukat A et. al., 2005).

There is less data on the type of infections found in non-neutropenic patients. In a study that included patients with leukemia and lymphoma, the most common site of infection was the respiratory tract, followed by blood flow and the genitourinary tract, and the offending organisms were Gram-negative bacillus. Primary blood flow infections were less common than in neutropenic patients; however, when they did occur, that was mostly due to Gram-positive coccus.

Patients with tumors of the central nervous system, either primary or metastatic, present the risk of developing a unique set of infections, based on deficits associated with neurological disorders. In a similar manner, any tumors of the solid organs that invades and interrupts anatomical barriers, may predispose to the development of infections.

Non-neutropenic patients with leukemia or lymphoma often have defects of immediate cellular immunity, either due to the disease itself or due to therapy received. These cellular immunodeficiencies can predispose to infections with a variety of intracellular organisms, after the recovery of neutrophils. Bacterial infections caused by *L. monocytogenes, L. pneumophilia, Salmonella spp., M. tuberculosis, Nocardia spp.* and non-tuberculous mycobacteria can be found in clinical practice. Moreover,

patients who have had splenectomies have an increased risk of infections with *S. pneumoniae, H. influenza* and *N. meningitidis* (Schimpff SC et. al., 1975).

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) represents the cloned expansion of neoplastic B lymphocytes in more than 95% of cases. These B lymphocytes, apparently mature, are found in the peripheral blood. They can also infiltrate the spinal cord, spleen, and lymph nodes. A significant proportion of the globulin produced by patients with CLL is dysfunctional, leading to defects in humoral immunity (Wadhwa and Morrison, 2006). Hypogammaglobulinemia may be profound at these patients, precipitated as the condition progresses and does not heal after chemotherapy, increasing the risk of developing infections with encapsulated bacteria, such as: *S. pneumoniae, H. influenzae, N. meningitidis* and *E. coli* (Morrison, 1998). Moreover, defects mediated immunity cellular activity, complement activity and neutrophils, exist either due to disease or as result of treatment. Therapeutic methods involving alkylating agents, with or without association of corticosteroids, predispose to infections with streptococci, staphylococci, and Gram-negative enteric bacteria. In these patients, infections often occur at sites of mucous membranes, especially in the respiratory tract. Treatments with purine analogues or with the alemtuzumab monoclonal antibody, predispose to infections with opportunist organisms (Tsiodas S et al, 2006).

Multiple myeloma

Like at CLL, patients with multiple myeloma (MM) generally have defects in humoral immunity, MM patients are hypogammaglobulinemia, producing normal immunoglobulins at only 10% of normal speed. Thus, they are prone to infections with encapsulated bacteria, such as S. pneumoniae, H. influenzae, and N. meningitidis.

As the disease progresses, malignant plasma cells proliferate in the spinal cord to such an extent that the spinal cord is unable to produce an adequate number of neutrophils. So, patients with advanced disease can be neutropenic, increasing their risk of development of infections with Gram-negative organisms (Paradisi et al., 2001). In recent years, the appearance of new treatments, such as hematopoietic stem cell and new pharmacological agents such as bortezomib, thalidomide and lenalidomide have improved outcomes for patients with multiple myeloma and turned this condition into a chronic disease. The cumulative immunosuppression resulted increases the risk of infection and broadens the spectrum of potential pathogens at this patient population (Nucci and Anaissie, 2009).

'Hairy' cell leukemia

Chronic B-cell lymphoproliferative disease occurs with cytopenia at most patients. In particular, patients presenting monocytopenia, granulocytopenia and impaired T cell function. These lead to immunodeficiency and predispose patients to a wide variety of infections. In one study, the major risk for the development of severe infections was lymphocytopenia (Damaj G et al., 2009). As it is with other patients, neutropenia predisposes to infections with Gram-positive bacteria. Defects in T cell functions mediated by monocytes and macrophages predispose to other bacterial infections with organisms such as Salmonella and (Listeria et. al., 2003)

Tumors of solid organelles

Patients with solid organ tumors do not have the same risk of developing infections such as patients with hematological malignancies. This fact is largely due to the chemotherapeutic regimens used to treat these conditions which, in the case of patients with solid organ tumors, do not involve deep or long-term neutropenia. Exceptions include patients with carcinomas with small cells at the lungs level, testicular carcinomas, and some sarcomas. Aggressive chemotherapeutic regimens used to treat these conditions can lead to periods of neutropenia ranging from 7-10 days, or more (61). In a similar manner, oncological conditions such as metastatic carcinoma of the breast, prostate, lung, adrenal, thyroid and kidney, presents ability to infiltrate the spinal cord and can produce neutropenia in advanced stages.

Patients with tumors at central nervous system, either primary or metastatic, have a risk of contacting a set of new infections due to the associated neurological deficiency. In a similar manner, any tumor of solid organelles which invades and interrupts the anatomic barrier can lead to the occurrence of infections.

Current tendencies for the emergence of bacterial infections in oncological patients

Viridans streptococcus or gram-positive coccus, which are part of the normal oral flora, is the emerging pathogens causing bacteremia and sepsis to neutropenic patients, especially to those with AML or having suffered from HSCT- hematopoietic stem cell transplantation (Huang et. al., 2007). Many species have been implicated in infections like these, but most of them were *Streptococcus mitis. S. mitis* may be penicillin or fluoroquinolones-resistant from all species (Han XY et al., 2006).

Rhodococcus equi, a gram-positive coccobacillus, is a rare pathogen but is considered the causal agent for infections in patients with defective cell immunity. HIV infection is the most common predisposing factor; however, oncological patients with cell immunodeficiency are at high risk, too. *R. equi* is associated most frequently with cavity pneumonia, which may be confused with a fungal infection or tuberculosis. A study carried out by Harvey and Sunstrum (Harvey and Sunstrum, 1991) shows a 61% survival rate of the patients with cavity pneumonia taking just antibiotics, in comparison with the patients who were under antibiotic therapy, but also had a surgical resection, whose survival rate was 75%. The bacteremia with this pathogen was observed in patients with malignant diseases and 90% of all cases were associated with infections of central catheters (Al et. al., 2012).

Gram-negative pathogens important in the oncological context include Burkholderia cenocepacia, Achromobacter spp, Alcaligenes spp. and S. maltophilia. Colonization and the infection of immunocompromised patients are both increasing, especially in those who receive broad-spectrum antibiotics, particularly carbapenems. S. maltophilia causes pneumonia, urinary tract infection, bacteremia, and wound infections in debilitated patients, being multi-drug resistant (Khardori et. al., 1990). Burkholderia cenocepacia is a Gram-negative pathogen associated with infections patients with cystic fibrosis experience. An epidemic with this causative agent has recently been reported in cancer patients, being associated with central venous catheters (Mann T et. al., 2010). Achromobacter spp and Alcaligenes spp. are Gram-negative bacteria, recently associated with infections in cancer patients. A review of the bacteremia with these causative agents, recorded between 1989 and 2003 at a cancer treatment center, found that 67% of patients with bacteremia had hematologic malignancies and 52% were neutropenic. Achromobacter xylosoxidans was the most common pathogen detected (94%), followed by Achromobacter-denitrificans (4%) and Alcaligenes faecalis (2%). Most patients had infected intravascular catheters, followed by those with pneumonia and urinary tract infections. Most isolates were sensitive to carbapenems and trimethoprim-sulfamethoxazole. The cumulative mortality of these patients was 15% (Aisenberg et al., 2004).

Two bacterial syndromes should be mentioned, in the case of patients with malignant oncological diseases. First, the emergence of a hyper virulent strain of C. difficile in recent years has been associated with the increased rates of severe and recurrent infections, as well as the increased mortality and morbidity. The second syndrome is a pyomyositis with E. coli described more and more often in patients with malignant hematological disorders (Vigil et. al., 2010). Pyomyositis is typically caused by Gram-positive bacteria, and especially S. aureus; however, the review of cases recorded between 2003-2007 at a cancer treatment center revealed 6 cases with E. coli as the causative agent. Out of these patients, all received chemotherapy, five were neutropenic and two died, despite appropriate antibiotic therapy, with carbapenem. It should be noted that they are all isolated with former fluoroquinolone resistant and 55% with broad spectrum beta-lactamase product (Vigil KJ et. al., 2010).

CONCLUSION

Oncological therapy has benefited from a huge development in the last few years (Enhui et al., 2019). Once the chemotherapy and radiotherapy improved, the life expectancy of the oncological patient increased and new challenges appeared (Tseng Y. D et al., 2013). Considering the affection of both the innate immunity and acquired immunity caused by chemotherapy, the problem of bacterial infection in the immunocompromised child is a challenge of pediatric oncology. When we talk about acute leukemia and acute lymphoma, approximately half of the episodes of neutropenic fever do not have a clinical localization or an identified causal pathogen, and 20-30% show clinical signs of infection, but with no microbiological cultures; only 25-30% of the episodes show a microbiologically-documented infection (Mikulska M., 2019). In this context, as previously mentioned, it is of major importance for the clinician to know what are the most common associations between each oncological condition and the pathogenic bacterial agent. The fact that the other forms of malignancy have a similar percentage of bacterial superinfections during immunosuppression makes this correlation between the causal agent and the type of cancer very important in initiating an empirical antibiotherapy with life-saving potential.

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