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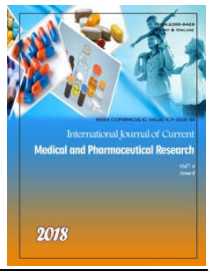

THE PRACTICAL APPROACH OF FEBRILE NEUTROPENIA IN CANCER PATIENTS IN THE EMERGENCY ROOM

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ABSTRACT

The rate of hospitalization of patients in cancer treatment for febrile neutropenia is associated with high rates of morbidity, mortality, and costs associated with high number of patients using chemotherapy from the 50. This is because, most infections are asymptomatic or oligo, rapidly evolving, sometimes with fatal outcomes. This fact requires diagnosis and treatment with empirical antibiotics quickly and effectively, as well as the appropriate follow-up, keeping the patient enlightened, and the health team prepared. To do so, when it comes to the relevance of this theme, the present study aimed at discussing Febrile Neutropenia in this group of patients, through a review of recent scientific literature data, in order to update healthcare professionals about the suspicion, diagnosis, prophylaxis and treatment of this group of patients in the emergency room in emergency and emergency.

INTRODUCTION

The prognosis of patients with neoplasia has become higher after the institution of cytotoxic chemotherapy at the end of the decade of 1950. However, neutropenia associated with this type of treatment has made clear the relationship with risk of infection, because the chemotherapy drugs have direct effects on the mucosal barriers, reducing the innate immunity in addition to the predisposition immune deficiency related to neoplastic condition[1].

Before the use of empirical antibiotic prophylaxis, the mortality from febrile neutropenia in patients on chemotherapy treatment reached 75%. This reduced the number of infections, with improved survival[2]. Consequently, the occurrence of fever in patients during chemotherapy treatment is taken as an oncologic emergency, can be indicative of febrile neutropenia, requiring immediate approach in the emergency room[1].

The infection in these patients is not always clarified, since fever is usually the only clinical sign of infection. Therefore, most of the time, imposing broad-spectrum antibiotics empirically in an attempt to avoid the complications of the disease[2].

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The classification of patients with febrile neutropenia occurs through the index of severity of MASCC (*Multinational Association for Supportive Care of Cancer*), which through assessment criteria, sorts the patient in low, intermediate and high risk. From this point, if indicates treatment with broad-spectrum antibiotics in a hospital environment. However, there is the possibility of oral treatment for patients without the need for hospitalization[3-5].

The present study aimed to discuss about Febrile Neutropenia in this group of patients, through a review of recent scientific literature data, in order to update healthcare professionals on suspicion, diagnosis, prophylaxis and treatment of this group of patients in urgent and emergency care.

Table 1 MASCC[19].

Features	Points
Febrile neutropenia asymptomatic or mild symptoms	5
Absence of hypotension (SBP > 90 mmHg)	5
Absence of Chronic obstructive pulmonary disease	4
Solid tumor or hematologic disease without prior fungal infection	4
Absence of dehydration	3
Febrile neutropenia with moderate or severe symptoms	3
Not hospitalized at the onset of fever	3
Age less than 60 years	2

Caption: SBP: Systolic Blood Pressure

Table 2 Factors for introduction of Vancomycin in the initial schema[27]

Hemodynamic instability
Severe mucositis
Catheter-related infection
Antibiotic prophylaxis with quinolone antibiotics
Prior sensitive germ colonisation only Vancomycin
Culture positive for gram-positive prior to the final determination of the germ

METHODS

This work consists of a literature review in the databases PubMed, Scielo, Scopus, Embase and Web of Science. Data was collected on case reports, cohort studies and literary reviews, using the keywords "*febrile neutropenia, chemotherapy induced febrile neutropenia, infection drug induced, sepsis, immunosuppression, emergency hospital services*". The method used the following guiding question: "*what are the main results and scientific evidence identified in national and international bibliographic production, over the last thirty years, concerning the diagnosis and therapeutic management of febrile neutropenia*?"

Definition

Fever is defined as the oral temperature 38.3° C ≥ or ≥ 38°C since last above 1h. If you used the axillary temperature, one should consider ≥ 37.8°C. However, the use of axillary temperature for definition of fever is not recommended, because it measures body temperature with reduced accuracy. The measurement of core temperature rectally also is discouraged because it increases the risk of bacterial translocation in patients already susceptible to infection[4].

The definition of neutropenia varies according to the source, however, the risk of infection grows significantly, when the absolute neutrophil count is less than 500cells/mL or a fall expected for values below 500 cells/mL in 48h following, being common to use this parameter to set the neutropenia in clinical practice[5].

Etiology

The etiology of infection during neutropenia is not always known. Still, it is recommended the collection of material for microbiological culture (blood and urine). The focus of infection is identified in only 30-50% of patients being the gastrointestinal tract, the skin and the lungs the more involved[4]. Only 10-25% of cases present positive blood cultures[5].

The highest prevalence is gram-positive infectious agents (62-70%), especially *Staphylococcus aureus*, *Staphylococcus epidermidis*, and Enterococci. It is scientifically proven evidence since 1980, being the most common cause in most hospitals, despite the growth in incidence of gram-negative bacteria in recent years, a fact that shows the importance of the knowledge of the flora of each service[5-7]. The gram-positives are related to Methicillin-resistance, however, insidious course, allowing coverage for these strains is established in later time not in admission. The gram-negative bacteria are responsible for more frames and accompanied by severe toxemia, sepsis and septic shock, rapidly evolving and that require initial antibiotic therapy[8]. Fungi and viruses may also be responsible for painting, especially in patients of high immune suppression[5].

Epidemiology

The epidemiological data of febrile neutropenia have undergone changes in the 20th century, once during the decades of 60 and 70, with the advent of cytotoxic chemotherapy; the gram-negative bacteria were prevalent agents. From the years 80, the gram-positives have become the most common infectious agents. This change resulted mainly from the use of central venous catheters, allowing the Gram-positive bacteria from the skin to the bloodstream[9,10].

Thus, most (80%) neutropenia is caused by pathogens present in the bacterial flora of the patient[11]. The main actors identified to cause infections in patients with neutropenia induced by chemotherapy include: gram-positive and *coagulase-negative Staphylococcus*, *Enterococci spp.*, *Streptococcus viridans group* and *Streptococcus pneumoniae*; Gram-negative bacteria such as *Escherichia coli*, *Klebsiella spp*, *Enterobacter spp*, *Pseudomonas aeruginosa*, *Citrobacter spp*. and *Acinetobacter spp*.; other bacteria, including *Clostridium difficile*, anaerobic and Mycobacteria; and fungi, especially *Aspergillus spp*. and *Candida spp*[12].

Despite the abundance of anaerobic bacteria in the native flora of the gastrointestinal tract, these microorganisms are unlikely to cause infection in neutropênicos patients, but contribute to the development of mucosites, sinusitis, perianal cellulitis and periodontal diseases, among others[13].

Among gram-positive agents, the *S. epidermidis* is the most common, accounting for approximately half of the infections caused by this group, however, is far less virulent than the other representatives[13]. Despite the gram-negative bacteria are associated with serious Gram-positive frames such as *s. aureus* (methicillin-resistant), *Streptococcus viridians group* and vancomycin-resistant enterococci (VRE) are associated with lethal infections[14].

Fungal infections are common in patients at high risk and are predisposed for severe neutropenia (neutrophil counts < 100cells/mL), prolonged use of antibiotics and greater number of cycles of chemotherapy administered. This type of infection

can cause neutropenia applicant, and can even occur before the administration of chemotherapy cycle[13].

Polymicrobial infections are infrequent, but evidence shows that your focus is growing so statistically significant[11-13].

Clinical condition

The clinical picture is marked by fever in absolute count of white blood cells less than 500cells/mL or with expected values fall below 500cells/mL in the 48h following, and the diagnosis is essentially clinical/laboratory. Other clinical manifestations associated with are not striking, as there is a sharp reduction of cellular inflammatory response[15]. It is a pathology that requires detailed physical examination and history, with emphasis on signs that may suggest possible infection, do not always practice adopted in emergency services, due to the emergency nature of the calls. However, changes in skin, oral cavity, perineal, eye, lungs, abdomen and catheter insertion sites should be thorough. It is recommended to avoid the digital rectal examination, by the risk of bacterial translocation[13-15].

It is important to recognize that patients present oligo symptomaticneutropenic patients. Thus, erythema, pain or heat, even if of mild intensity, should be considered. Likely cellulite, possibility of meningitis without nuchal rigidity should be suggested and pneumonia without radiological changes. Due to the absence of typical clinical picture, at least half of the patients remain with infection considered hidden[15].

Classification

The febrile neutropenia can be classified into low and high risk, according to the determination of gravity. For this, in addition to other indicators, is used the MASCC score (*Multinational Association of Supportive Care in Cancer*), which includes the following criteria: the intensity of symptoms, blood pressure, lung disease, cancer, dehydration, institutionalization and age, which should be analyzed at the time of admission to emergency room (Table 1)[16-19].

This classification has importance in conducting the clinical management, suggesting the need for hospitalization and the antibiotics to be used. The patient is considered high risk when presents hypotension, pneumonia, abdominal pain of recent onset or neurological changes, neutropenia for more than 7 days or absolute neutrophil count < 100 cells/mm³. According to the MASCC is classified at high risk if you score less than 21[20].

Treatment

The success of the approach to the patient with febrile neutropenia is primarily associated with the time of diagnosis and institution of antimicrobial empirical schema that must be started immediately after the collection of biological material for crops and before any other additional research, and should be maintained until the diagnostic definition or laboratory findings that clarify the diagnosis[21]. That measure is independent of factor favorable change of course of the disease, preventing serious outcomes, such as evolution of the infection to septic shock and death. Thus, it is important that professionals working in the emergency room (ER) know diagnose and drive these cases[22].

This therapy should be instituted in the first 60 minutes after the admission of the patient in the ER, and may not be deferred based on results of additional tests. Thus, it is important to estimate the neutrophil count, even before the result of the WBC. Cancer patients are susceptible to neutropenia, so the hospital triage team must question the febrile patients about the presence of neoplastic condition associated and chemotherapeutic therapies[23-25].

Patients were receiving chemotherapy in six weeks before the emergence of fever should be considered neutropenic, the highassociated risk. As a result, it is important that the oncologist guide the patient with neoplasia and their families to report that condition, as well as the date of the last cycle of chemotherapy, whenever there is a need for medical assistance[22-24].

The additional tests should be used as an attempt to find the focus of current infection. It is recommended that blood collection (two peripheral blood cultures and of all perforated, if present), urine, secretions and body fluids, as well as tracheal aspirate or bronchus alveolar, if possible, for microbiological analysis and culture, in order to identify growth of pathogenic microorganisms; In addition to contents of urine and chest x-ray[20-23].

In the duration of severe neutropenia (neutrophils < 100 cells/mm ³, persisted for more than 7 days), must be performed CT scans of lung and thin cuts of sinuses. The lumbar puncture to collect cerebrospinal fluid can be considered, especially in the presence of neurological changes. The request of galactomanana dosing, serum marker of fungal infection is authorized to persistently febrile patients without clear etiology. Other tests may be ordered to monitor the evolution and prognosis, such as CBC, renal function, liver enzymes and electrolytes, which must be repeated according to clinical evaluation[25].

The initial antimicrobial recommended scheme is broad spectrum with coverage for *Pseudomonas aeruginosa*. There is no scientific evidence to indicate superiority of monotherapy or associated therapy against bacterial resistance or survival, but adverse effects are more commonly reported in patients using more than one antibiotic associated. Regarding the therapeutic conduct, although there are possibility of outpatient treatment, most experts practice hospitalization, since no studies proving the safety of the treatment to outpatient level, especially in Brazil[26-28].

Some authors advocate low-risk patients can complete outpatient level antibiotics if they are afebrile with neutrophils > 500 cells/mm ³ after 72 hours of intravenous therapy[25].

Studies have shown that low-risk patients can be benefited by oral antibiotics without worsening prognosis and can be a way to avoid venous access, reducing entrance doors to pathogenic microorganisms. However, most patients will be subjected to intravenous therapy, especially those at high risk, the severity of the frame or at risk of hemodynamic instability secondary to septic shock[25].

Once chosen the oral therapy with proven efficacy is the association between Ciprofloxacin 500 mg, twice a day, and Amoxicillin-Clavulanate-1,5g/day, although generation quinolones may be used, if the patient has not done prophylaxis with these agents. Intravenous therapy recommended is made with Cefepime, Carbapenems (Meropenem or Imipenem) or Piperacillin-Tazobactam. Some patients have criteria that suggest the early Association of Vancomycin, represented in Table 2. This measure, although

not significantly affect mortality from infections by Gram-positive germs in General, improves the prognosis of patients infected by *Streptococcusviridans*group[26].

Evidence showed that the time of dissolution of the fever is 2-7 days, so it is recommended to observe the patient for 72h as well as the clinical course to assess the need for change or association of other antimicrobials in the initial scheme, except in cases of worsening of the condition or identifying etiologic agent through culture[29].

It is estimated that the first antimicrobial schema present therapeutic failure with persistence of fever by up to 40% of cases. In these cases, one must assess the need of other antimicrobials, with individual choice by most common infectious agents and local sensitivity profile, or by clinical manifestations. If identified infection, therapy should be directed[26].

The evolution of the patient should be accompanied with frequent physical examination and laboratory tests as needed. The antibiotic therapy is guided by the presence of fever, if there are persisting for more than 72h, Vancomycin should be linked; continuing feverish for more than 96h, it is recommended to exchange of Cefepime for a Carbapenems and consider infection in close focus (repeat chest x-ray and/or perform CT scan of sinuses). The painting for more than 120h, it is recommended the addition of antifungals in therapeutic and expert evaluation (Hematologist or Infectologist). Antimicrobial therapy should be maintained until the patient remain afebrile for at least 5 days and have your absolute neutrophil count > 500 cells/mm³ for at least 2 consecutive days[26,30].

Other aspects should be monitored, as adverse effects to medicines used, emergence of complications secondary to infection and the development of antibiotic resistance that may be responsible for the persistence of feverish state[26-29].

Despite all the evidence, there are still doubts about the use of other medications associated with antibiotic therapy, hematopoietic growth factors, in order to reduce the duration of neutropenia, minimizing the risk of complications associated with immunosuppression, however, studies have shown that your use, despite reducing the time of neutropenia, not provided significant clinical change in severe outcomes[29,30].

Based on these arguments, some hematologists using granulocyte colony stimulating factor, in order to re-establish the earliest possible cellular immunity, allowing the next cycle of chemotherapy in smaller time interval. However, the institutions that produce the most used guidelines, IDSA (*Infectious Diseases Society of America*) and ASCO (*American Society of Clinical Oncology*), do not recommend the use of these medicines in routine treatment, because raise the costs and do not guarantee significant benefits. However, if the risk of neutropenia is greater than 20% with the use of chemotherapy, it is recommended the use of prophylactic granulocyte colony-stimulating factor[28].

Prophylaxis

The prophylaxis of febrile neutropenia may be primary, where administering antibiotics during chemotherapy in patients at high risk; or secondary, which is in the use of antibiotics to prevent recurring infections[29].

A meta-analysis of 17 randomized controlled trials that evaluated the prophylaxis with fluoroquinolone versus placebo or no treatment achievement demonstrated a relative risk reduction of 48% in the General causes of mortality and 62% in the mortality causes infection in those patients receiving fluoroquinolone, especially ciprofloxacin[30].

As antifungal prophylaxis is not recommended for patients with solid tumors or lymphoma undergoing conventional chemotherapy with or without concomitant immunotherapies[29-31].

CONCLUSION

The presence of fever in the wearer of neutropenia in chemotherapy treatment remains a challenge in Oncology. It is a fact that the suspicion and diagnosis of febrile neutropenia should be established quickly and effectively, even in the ER, enabling immediate institution of empirical antibiotic therapy, due to possibility of prevent complications and reduce mortality.

In addition, the patient must be classified by the severity index MASCC as low, intermediate and high risk, through pre-established criteria, with the aim of establishing appropriate therapy.

In conclusion, it is important to have well educated patients about the need to seek medical help in the event of fever associated with immunosuppression. It is therefore essential that the presence of a health team ready to suspect and identify the picture, in addition to performing the proper management of the febrile patient neither, for neutral.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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