



The Neutropenic Patient with Fever

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Introduction

Advances in chemotherapy treatments have had a significant impact on the survival of cancer patients, but they can alter the normal flora and the indemnity of natural barriers. This favors the entry of germs that are normally colonizers, making them infectious for the susceptible host. In turn, these treatments, acting on rapidly replicating cells, such as blood cells and those of the digestive tract, produce a decrease in polymorphonuclear cells with which cancer patients are more susceptible to infections.

The immunocompromised patient already has some type of alteration in either phagocytosis or humoral or cellular immunity that increases the risk of infectious complications. The duration of the alteration of the immune defenses plays an important role in the type of infectious complications that can occur. At least half of febrile neutropenic patients have an occult infection, and one fifth of patients with <100 cells / mm^3 have bacteremia.

Definitions

FEVER is defined as a single record of oral temperature $\geq 38^\circ\text{C}$ or a record of $\geq 38^\circ\text{C}$ of axillary temperature for ≥ 1 hour duration.

NEUTROPENIA is defined as <500 neutrophils / mm^3 , or <1000 neutrophils / mm^3 with an expected decrease to <500 cells. / Mm^3 , or a 25% drop in neutrophils in 24 hours.

Risk of Infection

The risk of infection depends on the interaction between factors related to the host, the environment and the type of treatment instituted.

Factors related to the risk of infection

Related to the host

- A. Age: higher risk in children and adults over 60 years old
- B. Acute leukemias: increased risk
- C. Organ dysfunction: damage to the following organs favors the entry of germs
 - i. Mucositis
 - ii. Renal insufficiency
 - iii. Liver failure
 - iv. Skin lesions
 - v. Others
- D. Immunosuppressive diseases: alter immune mechanisms making infection control difficult
 - i. Lymphoma
 - ii. Myeloma
 - iii. Splenectomy
 - iv. Autoimmune diseases
 - v. Immunomodulatory virus (HIV)

Related to the environment: higher microbial load, higher risk of infection

- a. Previous colonization
 - i. Bacterial
 - ii. Fungal
 - iii. High exposure to contaminated elements
 - iv. Water

- v. Food
- vi. Objects
- vii. Air

Related to the treatment received

- a. Prolonged neutropenia
- b. Cellular immunosuppression
- c. Bone marrow transplant (BM)
- d. Antimicrobial prophylaxis

Causes of fever (Etiology)

Often the only manifestation of serious infection in neutropenic patients is the presence of fever. Fever does not have a characteristic pattern, it can even sometimes be absent in the context of generalized infection, either due to severe immune depression or due to the use of drugs such as corticosteroids or NSAIDs.

During the period of neutropenia, more than 60% of fever episodes can be attributed to an infection. The infectious etiology depends on the cause and the depth of the neutropenia. In 20 to 25% they are bacteremic causes, 15 to 20% present evidence of an infectious focus, but in 40 to 60% the patients have fever of unknown origin.

The microorganisms involved in the episodes of bacteremia varied in prevalence over the years, being currently more frequent due to gram-positive bacteria. This can be explained by the continuous evolution of antibiotic use, changes in bacterial resistance patterns, use of antibiotics prophylactically, and changes in medical practice (use of intravenous devices, etc.). Some of these gram-positive bacteria may be resistant to methicillin and sensitive to vancomycin, teicoplanin, linezolid, or quinupristin-dalfopristin. These in general produce more indolent clinical pictures (for example, infections by vancomycin-resistant enterococci -EVR-, coagulase-negative staphylococci, or *Corynebacterium jeikeium*) in which the delay in a few days in the specific treatment may not impact on the evolution, although it can delay hospitalization. Other gram-positive bacteria (such as *S. aureus*, *Streptococcus viridans*, and pneumococcus) can cause fulminant infections that, if not treated early, end with serious complications and even death.

The gram-negative bacteria that cause bacteremia vary according to the epidemiology of each institution. The most frequent are Enterobacteriaceae (*E. coli*, *P. aeruginosa*, *Klebsiella* sp., *Enterobacter* sp., *Proteus* sp., *Acinetobacter* sp., etc.).

Although fungal infections in general are superinfections, some fungi such as *Candida* sp. they can sometimes cause primary infections. Others less frequent and that are related to prolonged neutropenias are *Aspergillus* sp., *Cryptococcus* sp., *Trichosporum* sp., etc. High-risk patients or those undergoing OM transplantation as well as HIV patients can also suffer from viral infections, for example by CMV, EBV, hepatitis B and C, adenovirus, respiratory

syncytial virus, parainfluenza virus, herpes simplex, VZV, etc. Other microorganisms that may be associated with causes of fever are *Pneumocystis carinii*, toxoplasma, *Mycobacterium tuberculosis*.

However, there are other causes of fever of non-infectious origin such as progression of the underlying disease, fever related to transfusions, some drugs or allergies.

Pretreatment evaluation

Infection in the febrile neutropenic patient is an infectious emergency given the high mortality rate. Considering the high probability of the absence of symptoms or signs of infection and the high mortality in neutropenic patients, the mere presence of fever warrants rapid therapeutic action (IED). A thorough physical examination should be performed looking for symptoms such as pain or inflammatory signs in the periodontal, pharyngeal, lower esophagus, lungs, perineum including the anus, back of the eye, skin, catheter insertion sites, or spinal puncture (if performed), and the periungual region. Then, a sample should be taken for culture for bacteria and fungi from blood (through each branch of the catheter and from peripheral blood), urine culture (especially if it refers to symptoms or if the sediment is abnormal or if it has a probe placed bladder; pericatheter discharge if present), stool culture if necessary. For epidemiological reasons, you can search for colonization in the nostrils (*S. aureus*, penicillin-resistant pneumococcus or *Aspergillus* sp.), And rectally (*P. aeruginosa* or other multi-resistant gram-negative bacillus, EVR, *Candida tropicalis*). Imaging methods such as plain radiography or chest CT and abdominal or renal ultrasound are also recommended if there are any symptoms.

It is also necessary to perform a complete blood count, hepatogram, ionogram, urea and creatinine at least every three days, and more frequently if nephrotoxic drugs such as amphotericin B are used.

Initial empirical treatment (ITE)

In a febrile neutropenic patient, a treatment that meets the following criteria should be implemented:

- i. Immediate start
 - ii. Antibiotics
 - a. broad spectrum
 - b. bactericides
 - c. in maximum doses
 - iii. Consider the variables described below for the best choice:
 - a. Local epidemiology
 - b. Local resistance profile
 - c. Presence of clinical focus
 - d. Previous administration of ATB

- e. Previous hospitalization
- f. Hemodynamic status
- g. Other immune defects
- h. Allergies, organic damage

The main reason for rapidly starting empirical treatment is the high risk of infection-related mortality in neutropenic patients, especially when caused by gram-negative bacilli. Not all patients share the same risks. Therefore, the patient's risk must be categorized

Since the 1980s, different risk scores have been proposed considering clinical criteria (Talcott in 1988, Freifeld in 1997). In 2000, the MASCC study (Multinational Association for Solidarity Care in Cancer Risk Index) evaluated 1,139 patients in 15 countries. In this study, a series of clinical variables is considered, assigning a score to each of them. If the sum of the scores is ≥ 21 , the patient is considered low risk, which has a positive predictive value of 91% (E = 68%, S = 71%).

Low risk related factors:

- a. PMN count > 100 cells / mm³
- b. absolute monocyte count > 100 cells / mm³
- c. Normal chest X-ray
- d. normal kidney and liver function
- e. duration of neutropenia < 7 days
- f. resolution of expected neutropenia in < 10 days
- g. not associated with a catheter
- h. early evidence of spinal recovery
- i. Malignant disease in remission
- j. T^o < 39°C
- k. No alteration of the neurological or mental state
- l. No abdominal pain
- m. There are no comorbid complications

In low-risk patients, oral antibiotic treatment may be indicated, either on an outpatient basis or in hospital. In the case of outpatient treatment, the possibility of strict surveillance and the availability of a quick consultation to the health establishment should be ensured, if necessary, 24 hours a day, 7 days a week. If the need for intravenous treatment is considered, it can also be hospitalized or can be treated on an outpatient basis.

Another point to take into account when choosing the TEI is whether or not it is indicated to associate vancomycin. The indications for vancomycin in treatment are:

- a. The state of shock
- b. Catheter-related infection + high incidence of MRSA

- c. Suspicion of sepsis due to *S. viridans*
- d. Documentation of MRSA and *S. viridans* resistant to penicillin
- e. Bacteremia due to gram-positive cocci documented in cultures, without response to initial treatment

Monotherapy versus combination Therapy

Several studies demonstrate the efficacy of monotherapy with carbapenems, piperacillin / tazobactam, cefepime or ceftazidime as monotherapy for hemodynamically stable patients with neutrophils > 500 cells / mm³.

In high-risk patients, with severe neutropenia or those lasting more than 6 days, or with hemodynamic instability, the addition of aminoglycosides is recommended.

In centers where there is a high prevalence of germs resistant to ceftazidime, its use as monotherapy is not recommended.

On the 3rd day the patient will be reevaluated:

- a. The presence of fever
- b. Search for the presence of an infectious focus
- c. Crop results
- d. Clinical / hemodynamic stability
- e. The persistence of neutropenia
- f. The presence of mucositis Indications for the initiation of empirical Amphotericin B
- g. The persistence of fever > 5-7 days
- h. Recurrence of fever > 7 days
- i. Recurrent or persistent fever at the start of neutropenia
- j. Suspicion of sinusitis
- k. Nasal ulcer
- l. New or persistent pulmonary infiltrate despite treatment
- m. Esophagitis

General Preventive Measures

Considering that the neutropenic patient is at risk of infection, preventive measures should be implemented to reduce this risk.

The measures to be taken are:

- i. Proper hand washing: it is the most important and effective measure to prevent the transmission of infections. It should be carried out preferably with antiseptic soap or alcohol-gel, before entering the room and before leaving it, and each time contact with the patient must be made
- ii. Single room: it is preferable if possible and visits should be limited

- iii. Antisepsis to reduce skin-mucosa colonization: daily baths, oral cleaning with antiseptic solutions (chlorhexidine swish) or gentle brushing
- iv. Proper handling of catheters: use sterile gloves and a chemise for handling
- v. Properly isolate from areas under construction: During construction or remodeling, microorganisms such as *Aspergillus* spread.
- vi. HEPA filters / laminar flow for high risk patients
- vii. Avoid plants, water reservoirs, non-washable inanimate contaminated elements, since they can act as a reservoir for germs
- viii. Avoid raw foods (fruits and vegetables), pepper and mate

Antibiotic Prophylaxis in Neutropenic Patients

Some studies have shown a decrease in febrile episodes in neutropenic patients when decontamination of the digestive tract germs was used with the use of antibiotics such as ciprofloxacin and TMS. None were able to verify that these maneuvers decrease mortality. On the other hand, it generates antibiotic pressure and selects resistant germs.

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