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New guidelines for the clinical management of febrile neutropenia and sepsis in pediatric oncology patients

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Abstract

Objectives: To provide a foundation for the diagnostic, prophylactic and therapeutic management of febrile neutropenia and sepsis in children with oncological diseases, with special attention to new protocols and guidelines.

Sources: A review of the scientific literature utilizing an electronic bibliographic search on MEDLINE, Medscape, SciELO, Google, Cochrane and PubMED using the keywords febrile, neutropenic, cancer, children, sepsis, intensive, care. Articles published between 1987 and 2007 were selected, with preference given to review articles, protocols, systematic reviews, epidemiological studies, task force recommendations and phase III clinical trials. Consensus documents published by the Infectious Diseases Society of America, the Center for Diseases Control and the Infectious Diseases Working Party of the German Society of Hematology and Oncology, in addition to the recommendations of the World Federation of Pediatric Intensive and Critical Care Societies and Society of Critical Care Medicine, were also reviewed.

Summary of the findings: The use of aggressive chemotherapy regimens, bone marrow transplantation and intensive care resources have increased the survival rates of children with cancer and also their infectious morbidity, with septic complications as the principal cause of mortality. Several risk factors have been identified, such as neutropenia, oncology type, clinical signs and inflammatory response markers (polymerase chain reaction, procalcitonin) and also increased resistance to antimicrobials and antifungal agents. Protocols for risk classification, diagnosis and treatment should be established at each service, taking into account the microbiological flora of each population. Pediatric intensive care has increased the short and long-term survival of these patients.

Conclusions: Oncology patients are particularly vulnerable to infectious complications. Early identification and treatment are fundamental to improving survival rates.

J Pediatr (Rio J). 2007;83(2 Suppl):S54-63: Febrile neutropenia, infection, sepsis, intensive care, child, cancer.

Introduction

Over the last 10 years a large number of publications have attempted to provide safe and consolidated guidelines for the diagnosis and treatment of pediatric oncology patients with febrile neutropenia, infection, sepsis, septic shock and organ and system dysfunction.[1,2] They are justified by their importance, since these conditions constitute the principal cause of mortality in children with cancer, and the primary reason for indicating intensive care, both among those who are cured and those who die as a result of oncological diseases.[3]

The approach taken by the majority of protocols generally focuses on adult patients and does not dwell on questions that involve the pediatric population specifically.[4,5] In order to be

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safe, clinical management of febrile neutropenia, infection and sepsis in pediatric oncology must take into account specific issues that involve this population. This review aims to provide a basis for the etiology, diagnosis and prophylactic and therapeutic approach to febrile neutropenia and infection and to the diagnosis and treatment of sepsis in children with varying types of cancer.

Epidemiological studies demonstrate a high prevalence of sepsis among these children, with 12.8% of cases of sepsis in children aged 1-9 years affecting children with cancer, with an even higher incidence (17.4%) among those aged 10-19 years. Furthermore, while lethality is 10% in the general population, among cancer patients this number reaches 16%. There appears to be a clear difference in children who undergo bone marrow transplant, a group with a much higher mortality rate in the majority of case series.[6] Additionally, among patients with lymphoma/leukemia, there is an increased predisposition towards development of septic conditions, when compared with solid tumors, perhaps because of the use of more aggressive myeloablative therapy.

In addition to the type of cancer, the disease stage and the treatment given have an influence on the predisposition towards sepsis. Children on intensive chemotherapy protocols have a six times greater chance of developing sepsis than more conservative protocols. In a previous study, involvement of the bone marrow increased the odds ratio for sepsis to 2.4 (95%CI 1.3-4.6).[7]

Circulatory shock is clearly a factor for poor prognosis among these children. Other clinical signs, such as positive blood cultures, temperature > 39 ºC and extended capillary refill time, are also indicative of the need to employ intensive care resources.[8] The intensity of neutropenia and its duration have been demonstrated in many studies as predictive of the development of infectious complications and sepsis, deserving specific protocol led management.

Some years ago, the indication of intensive care for child cancer patients was greeted with skepticism and pessimism, with questions being asked of the validity of intensive, sophisticated and expensive treatments, with mortality rates of up to 85%. Almost a decade ago, improved survival was demonstrated in children with sepsis and cancer. In an evaluation of 206 admissions over a 9-year period, the author demonstrated a mortality rate of 29%, while, among patients with septic shock, put on mechanical ventilation and vasoactive drugs, the survival rate was 54%.[8] For patients in septic shock, mortality was 43%, and rates of organ dysfunction were 36, 66 and 83% for the presence of two, three or four dysfunctional organs, respectively. Mortality was significantly greater among bone marrow transplantation patients (46%; $p < 0.05$). After 3.5 years' follow-up, 45% of the children were free of oncological disease, without neurological sequelae, 2% still had cancer and 4% were disease-free but had clinical sequelae. The authors[8] argued that the positive results were the result of better integration between oncologists and intensive care specialists, with early prescription of advanced support prior to the various organic dysfunctions setting in. Recently, Fisher et al.[8] studied 446 admissions of children with cancer to a pediatric intensive care unit (ICU) over a 13-year period (1990-2002). The global mortality rate was 17%, being 30% for children receiving bone marrow transplantation and 12% for all other patients. Mortality was 64% among the 106 admissions for which mechanical ventilation and vasoactive drugs were used, and in these patients, survival beyond 6 months was 71%. Mortality was greater among patients with blood cultures positive for fungi (OR = 10.7; $p = 0.03$), receiving bone marrow transplantation (OR = 2.9; $p = 0.03$), use of multiple inotropics (OR = 4.1; $p = 0.01$) and with a PRISM severity score (OR = 1.1; $p = 0.04$).

Definitions

Fever

In the context of neutropenia, fever is understood to mean a single oral temperature measurement ≥ 38.3 °C, or a temperature ≥ 38 °C for 1 hour continuously or at two times with a minimum interval of 12 hours.[1,2] It is worth pointing out that, while infectious and non-infectious causes of fever can occur together, when dealing with neutropenic patients non-infectious etiologies of fever should be considered, such as those resulting from the use of blood products, granulocyte colony stimulating factors, active tumoral disease or medications.

Neutropenia

This describes a total neutrophil count < 500/µL or < 1,000/µL, with decline predicted over the next 2 days.[1,2] The severity of neutropenia in terms of the risk of infection is related to the total number of neutrophils, with greatest risk of infection considered to affect those who have a global count ≤ 100 neutrophil/µL.[1]

Sepsis

Temperature > 38 ºC or < 36 ºC accompanied by one or more of the following findings: tachycardia (heart rate > 95th percentile for age); tachypnea (respiratory rate > 95th percentile for age) or hypocapnia (PaCO < 32 mmHg). It is defined as severe sepsis when associated with signs of poor organic perfusion (oligoanuria, altered level of conscience, hypoxemia), metabolic acidosis or hyperlactatemia. Septic shock occurs when hypotension persists, despite volumetric resuscitation, with a need for vasoactive amines (dopamine, dobutamine, adrenaline, noradrenaline). Finally, organ and system dysfunction occurs when therapeutic intervention is

needed to maintain the organ/system (oxygen therapy and mechanical ventilation, vasoactive drugs, blood products, dialysis methods.

Classification of the risk of the neutropenia

Clinical assessment of febrile neutropenia in children should initially consider epidemiological data and the degree of risk of infection. Specific epidemiological data that should be considered with respect to the pediatric population include: contact with children carrying common childhood infections, seasonal outbreaks, travel, exposure to pets, recent use of immunobiologicals, such as vaccines containing attenuated live microorganisms, etc. The classification of febrile neutropenia in terms of the risk of infection can be of aid when choosing the antimicrobial therapy to be employed, in defining the route of administration, the possibility of outpatients treatment and the probable etiology. There are special issues that need to be considered when employing any criteria of risk pediatrics. One of these is the underlying disease, since some authors recommend that patients with neutropenia secondary to treatment for hematological neoplasms should never be considered as low risk. Another important issue is that, with these patients, risks classifications should be re-assessed after 12 to 24 hours, since it is possible for scores to change, both for better and for worse, as the febrile neutropenia runs its course[1] (Table 1).

Some pediatric studies have aimed to determine certain variables of risk of infection during a febrile neutropenia episode. In 1996, Rackoff et al.[4] defined temperature < 39 °C and total monocyte counts ≥ 100/mm^3 were predictive of low risk. Later, in 2000, Klaasen et al. added normal total leukocyte and chest X-ray and no comorbidities as criteria for low risk of infection.[9] More recently, in 2005, the Infectology Committee of the National Pediatric Antineoplastic Drugs Program (PINDA) of Chile managed to develop risk models applicable to pediatrics, by means of multicenter studies.[5] On initial presentation, at the point of admission, five variables exhibited a relationship with increased risk of infection, as shown in Table 2: polymerase chain reaction (PCR) ≥ 90 mg/L, arterial hypotension, relapsed leukemia, platelet count < 50,000/mm^3 and an interval < 7 days between the end of the last chemotherapy cycle and onset of fever. These variables exhibited sensitivity, specificity, positive predictive value and negative predictive value of 92, 76, 82 and 90%, respectively. The research identified variables that are easy to acquire and can be used the first time the patient is seen with no need for an advanced technological Arsenal (Table 2).

Diagnostic approach

During the initial diagnostic approach to these patients, clinical workup should be systematically applied in a complete manner, giving special attention to scheme, mucosa and hair and nails, the genital, anal and oral areas, locations where catheters have been inserted, marrow puncture sites and the site of surgery, when present. During this assessment, it is of fundamental importance to know that the classic inflammatory signs of temperature, edema, erythema and suppuration may be reduced and, very often, it may only be the presence of discreet to moderate pain that indicates possibility of infection. This fact is especially important in infections related to catheters and at the sites of surgery. For the same reason, one should not expect respiratory investigations to demonstrate an abundance of adventitial sounds indicative of secretion or rich radiological findings on chest X-ray. Very often dyspnea is the only symptom of respiratory infection in these patients during

Table 1- Risk groups as defined by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)[1]

Group	Definition
Low risk	Duration of neutropenia ≤ 5 days, in the absence of any factor listed in Table 2
Intermediate risk	Duration of neutropenia between 6 and 9 days
High risk	Duration of neutropenia ≥ 10 days

neutropenia. Similarly, we may observe that urinary sedimentation has little pyuria despite a urinary tract infection or discrete meningism and we might observe cerebrospinal fluid with low pleocytosis in the presence of meningitis.[2] special attention should be given to the skin of neutropenic patients, especially pediatric ones. Atypical manifestations of fungal, bacterial and viral infections may be present and can only be elucidated with respect to etiology with early supplementary and, sometimes, minimally invasive propaedeutic such as skin biopsy. Microorganisms such as *Pseudomonas aeruginosa*, viruses of the *Herpesviridae* family, opportunist fungi such as *Fusarium* and *Histoplasma* and atypical mycobacteria should be considered in cases with skin involvement.[10]

Febrile neutropenia frequently presents with signs of the hemodynamic repercussion of infection already apparent and as such is a medical emergency due to the risk of dissemination and refractory septic shock.

Supplementary worker with these patients can be of limited aid for gauging the dying mentions of the infection according to the factors mentioned earlier, and its principal role is in the definition of the etiology of infection. While we know that bacterial etiology predominates and that, in the majority of cases, the bacteria originate in the gastrointestinal tract, exiting via the mechanism of translocation, reaching the bloodstream, many other microorganisms can also be responsible for fever during neutropenia, especially in high risk patients or those who have been subjected to invasive procedures. Therefore, microbiological investigation should be prioritized even in cases where outpatients follow-up is the option. The recommended microbiological investigation should include tests for bacteria and fungi and, in the case of secretion cultures, the possibility of atypical mycobacteria should also be considered.

Blood culture

Preferably, two samples should be taken from a peripheral vein, with a 20-minute interval and from two different sites. When a central venous catheter (CVC) is in place, a sample should be taken from it, and another from a peripheral vein. In these cases, bacterial growth observed in the CVC sample 2 hours or more before it occurs in the other sample suggests that the catheter is the site of infection.[11]

Urine culture

Indicated in the presence of urinary symptoms[2] or in cases where neoplasms are located in urinary or renal areas.

Cultures of wound secretions

By puncture (preferable) or swab, they should be taken when present from the site of catheter insertion, the site of surgery or mucocutaneous injuries.[2]

Surveillance cultures

These are not systematically indicated, except in cases where there is a suspicion of colonization by multi-resistant microorganisms. In such cases, the indication is to take a nasal swab and a skinfold swab sore in order to identify oxacillin resistant *Staphylococcus aureus* (MRSA) and an anal swab to detect gram-negative beta-lactamase producers or fermenters. It should be stressed, however, that these cultures should not use to determine therapeutic regimens,

Table 2 - Variables associated with the risk of invasive bacterial infection in children with febrile neutropenia[5]

Variable	RR	95%CI
Serum PCR ≥ 90 mg/L	4.2	3.6-4.8
Arterial hypotension	2.7	2.3-3.2
Relapsed leukemia	1.8	1.7-2.3
Platelets < 50,000/mm^3	1.7	1.4-2.2
< 7 days between last chemotherapy and onset of fever	1.3	1.1-1.6

95%CI = 95% confidence interval; PCR = polymerase chain reaction; RR = relative risk.

since colonization is not affected by antibiotic therapy and is an important factor inducing resistance. Only in cases of infections that are clinically manifest, should antibiotic therapy be used against the colonization.[12]

Testing cerebrospinal fluid is not routinely indicated, only in cases where symptomology is related to central nervous system (CNS) involvement.

General tests, such as assays of serum urea, creatinine, transaminases, bilirubins and electrolytes, should be performed periodically during neutropenia, especially to monitor the toxicity of drugs and hydration. In general protocols for sepsis, glucemia has been described as a marker of prognosis and should also be considered in these patients.[13]

Nonspecific inflammatory tests, such as erythrocyte sedimentation rate, PCR and, now, procalcitonin,[14] can be non-specific predictors of infection, and their utility lies solely in their high sensitivity cleanup. Their use, therefore, does not generally aid in arriving at a decision on therapeutic management.[5]

Other tests to predict the level of tissue oxygenation, such as lactate and hemogasometry, may be considered depending on the severity of clinical status.

Chest X-ray

Previously chest X-rays were used as criteria of severity in children with febrile neutropenia, however, their value was called into question in recent work by Renoult et al.[15] in that study, pneumonia was the cause of fever in 5% of neutropenic febrile children, and at just 1% of pneumonias exhibited an absence of respiratory symptoms. This being so, chest X-rays on admission can safely be reserved for patients with respiratory abnormalities. Added to that finding is the factor that, as neutrophils are reduced, the inflammatory infiltrate capable of generating radiological images of consolidation are scarcer, which could reduce the sensitivity of the test. However, it is still worth pointing out, that abnormal x-ray findings are a strong indication of pulmonary involvement in this group of patients.

Other supplementary tests should be requested in accordance with the clinical status presented and should focus on elucidating etiology of the infectious agent involved the basic empirical therapy. Radiological tests of greater accuracy, such as ultrasound, echocardiogram, computerized tomography, magnetic resonance imaging and positron emission tomography in a relevant in this context and should be directed at the probable focus of infection (skin, soft parts, abdomen, sinuses, CNS, lungs, etc.) Other tests that, more than anything else, favor diagnostic elucidation are serology, antigenemia and molecular biology tests, such as PCR. It is worth remembering that, in this group of patients, humoral immunological alterations may be present, depending on the underlying disease, and these may affect serological test results, to the extent that detection of antigens by immunoenzymatic techniques or by molecular biology may be the principal means of diagnosis, especially in the case of viral or fungal agents. Notwithstanding, it should be clear that investigations to determine etiology should not compromise starting appropriate treatment early, particularly in cases classified as at high risk of infection.[1,2,15]

Etiology

The majority episodes of febrile neutropenia are treated empirically without identifying the site or etiologic agent, as fever of indeterminate origin.[16] in the remaining cases of documented infection, a variety of variables are involved in etiology. Factors such as recent hospital stays, previous use of prophylactic or therapeutic antimicrobials, underlying disease, intensity and duration of neutropenia, sustained use of central venous catheters or other invasive devices should all be considered when deciding on initial empirical treatment. The most frequently involved sites are pulmonary infections, infections of the bloodstream related to catheters, skin and soft parts infections, among others.

In general, bacterial agents are predominantly responsible for infection during febrile neutropenia. Of these, enterobacteria are prominent, reaching the bloodstream by the classic mechanism of translocation, and gram-positive bacteria, whose increase in incidence has resulted from the progressive use of invasive devices, especially long duration use of catheters and wide spectrum antimicrobials.[2] The predominance of gram-negative organisms that was observed up to the end of the 1990s, has given way to a panorama in which both gram-negative and gram-positive bacteria are equally responsible for the etiology of febrile neutropenia, even tending to the predominance of gram-positive bacteria, as observed in studies at several different centers. The most recent guideline of the Infectious Diseases Society of America (IDSA), states that gram-positive bacteria are responsible for 60 to 70% of microbiologically confirmed cases of febrile neutropenia. Special prominence is given to coagulase-negative staphylococci, vancomycin resistant enterococci and *Corynebacterium* spp. Other bacteria, such as *S. aureus*, pneumococcus and streptococcus *viridans*, can cause severe infections in these patients. With respect to these last, many studies have demonstrated an increase in their incidence, primarily in patients with severe mucositis and/or on prophylactic quinolones.[16] Gram-negative bacteria of significance included *P. aeruginosa* and enterobacteria, especially *Klebsiella* spp. and *E. coli*, many of which, depending on local epidemiology, are extended-spectrum beta-lactamase (ESBL) producers. One Chilean study,

carried out specifically with children with cancer between 1994 and 1998, isolated 707 strains with gram-positive cocci predominating: *S. coagulase* negative (43%) and *S. aureus* (16%), followed by *Enterobacteriaceae* (20%); gram-negative non-fermenting bacilli, primordially *P. aeruginosa* and *Acinetobacter* sp. (6%); gram-positive non-staphylococcus cocci: *Enterococcus* sp. and *Streptococcus* sp. (5%). More recent patient samples, studied at three pediatric hospitals in Santiago also demonstrate a predominance of gram-positive cocci.[5] Guidelines from European countries, such as those produced by the German group, show the same tendency,[17] and studies carried out in Oriental countries reveal the same tendency to a progressive increase in the incidence of gram-positive organisms as the predominant etiology in microbiologically confirmed cases.[18-20]

In Brazil, a study carried out with febrile neutropenic patients with chronic lymphoid leukemia revealed that the most common pathogens were capsulated germs (*Streptococcus pneumonia, Haemophilus influenzae), S. aureus* and gram-negative enteric bacteria.[21]

Other etiologic agents, such as fungi and mycobacteria, may affect, with lower frequency, febrile neutropenic patients and are normally related to more severe and prolonged episodes of neutropenia (neutrophil < 500/µL and neutropenia for more than 10 days), to previous and prolonged wide spectrum antimicrobial use or antifungal prophylaxis and bone marrow or hematopoietic stem cell transplantation.[21] In these patients, fever that persists even when adequate empirical antibiotic therapy is started and the presence of pulmonary infiltrates refractory to treatment should be considered as indicative of the need for antifungal therapy. Fungi can be responsible for 30-40% of confirmed infectious agents after the fifth day of neutropenia. The most often involved fungi are *Candida albicans* and *Aspergillus* spp. Nevertheless, a growing number of non-*albicans* candida species has been documented.[18,22]

Therapeutic approach

Therapeutic management of febrile neutropenic patients should aim at a multifactor approach. This should include everything from adequate antibiotic therapy to the use of factors that implement immunity and help to control damage related to the underlying pathology, to chemotherapy or sepsis, such as thrombocytopenia, hemorrhagic phenomena and circulatory shock.

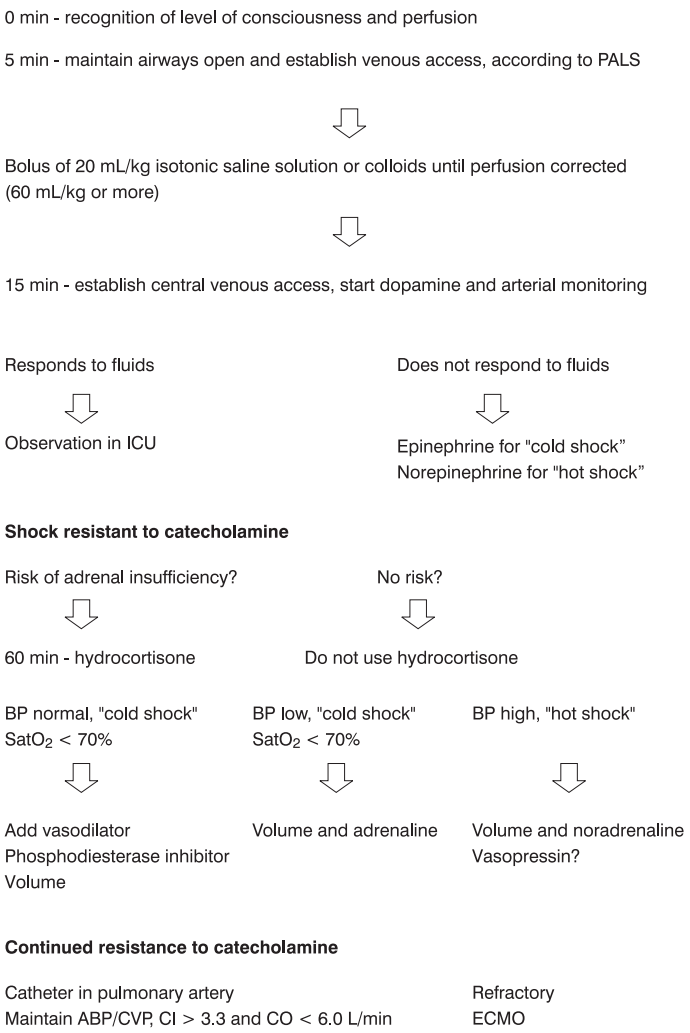
Antimicrobial therapy

Antimicrobial therapy should be based on the clinical characteristics of febrile neutropenic patients, the local epidemiology and concomitant diseases. The therapy chosen should act both to implement immunity and to control the microbiological agents involved in the febrile episode. This being so, although the guidelines of a number of medical associations provide a basis, a knowledge of the local microbiological flora, and of its phenotypical characteristics of sensitivity or resistance to antimicrobials, is of fundamental importance.

The IDSA classifies patients as low or high risk, before suggesting that antimicrobial agents be used empirically. For low risk patients, the empirical therapy can be oral, as long as it includes drugs with an activity against members of the *Enterobacteriaceae*, *P. aeruginosa* and group B *Streptococcus* families. A satisfactory combination for this spectrum is a quinolone with an antipseudomonal action, such as ciprofloxacin, and a beta-lactam, such as amoxycillin /pleocytosis, both with oral presentations, although, in the case of the quinolone, account should be taken of restrictions for very young age groups.[23] When the decision is taken to employ intravenous therapy, low risk patients can be treated with a fourth generation cephalosporin (cefepime), a penicillin with an antipseudomonal action (piperacillin /tazobactam) or even a carbapenems (imipenem or meropenem), depending upon the microbiological flora to which the patient is exposed.[2,17,18] When the patient's clinical and epidemiological factors suggest there is a probability of infection with *S. aureus* or coagulase-negative staphylococcus, a combination of de drugs with a spectrum against oxacillin-resistant staphylococcus should be used, including a glycopeptide (vancomycin or teicoplanin) or an oxazolidinone (linezolid).[24] When choosing these drugs, the most likely site of infection must be considered and also serum characteristics, minimum inhibitory concentration, tissue concentration and toxicity.

In high risk patients, oral therapy is not recommended, but the remaining recommendations are transposable. For all groups of patients, the empirical association of aminoglycoside does not demonstrate improved survival and is known to increase toxicity and should therefore be avoided.[2]

In all cases, the recommendation remains to reassess empirical therapy after 48-72 hours, or even earlier, depending on the severity of the case. Once this period has elapsed, therapy should be stepped up, associating the glycopeptide or oxazolidinone (if these have not yet been introduced). After 5 to 7 days, ion cases where fever persist, it is recommended that adequate antifungal treatment be instigated. When choosing the antifungal agent, the need to know which drugs have been used for prophylaxis, the local epidemiology and the sensitivity profile, especially with relation to species of *Candida* spp. are once more of importance. In our country, patients who have not previously been given fluconazole and with no risk factors for infection by filamentous fungi, have this agent as a safe alternative.[25]



CO = cardiac output; ECMO = extracorporeal membrane oxygenation; CI = cardiac index; BP = arterial blood pressure; PALS = Pediatric Advanced Life Support; ABP = average arterial blood pressure; CVP = central venous pressure; $SatO_2$ = oxygen saturation; ICU = intensive care unit.

Figure 1 - Algorithm for the therapeutic management of septic shock

Other therapeutic options with a wider spectrum and an action against strains resistant to fluconazole, include amphotericin B, echinocandins (caspofungin) and new azoles (voriconazole or posaconazole).[22,25,26] In relation to amphotericin B, whenever possible, preference should be given to lipid formulae, both because of their lower toxicity and because the original amphotericin B desoxycholate is no longer on the pharmaceutical market.

Whatever the method for stepping up treatment, the attempts to identify the etiologic agent must be sustained, by means of microbiological, serological and molecular biology tests. Furthermore, once the agent is diagnosed, treatment should be stepped down and, wherever the patient's status allows, only those drugs used to treat the agent identified should be maintained.

More recently, in addition to the antimicrobial treatment, attempts are now made to improve patients' immunity. The drug most often used for this is granulocyte stimulating factor.[27] This substance acts on bone marrow stem cells, increasing the population of granulocytes and neutrophils. The problem with this would be stimulation of neoplastic cells. The current recommendation of the Children's Oncology Group is to use this medication for severe leucopenia where there is risk of death (sepsis and septic shock).[2] Prophylactic use in order to prevent granulocytopenia has not proved effective. One alternative would be granulocyte transfusion, which is unavailable at the majority of services and is associated with a series of adverse reactions. Theoretically, the use of immunoglobulins could be useful, but clinical

results are discordant. Corticoid therapy, hemofiltration and plasmapheresis have not demonstrated reduced mortality.[28]

Management of septic shock

Children with oncological disease should be given the therapeutic conduct for septic shock recommended by the recent septic shock task force guidelines,[29] as defined in the algorithm below.

Management of blood hemostasis disturbances

Hemorrhagic disturbances and thrombosis are common complications in children with cancer when in infectious or septic states.[30] Bleeding is more common with leukemia, and less so with solid tumors. Thrombotic phenomena may be observed in up to 50% of patients at autopsy. There are abnormalities in almost all phases of coagulation, with quantitative (thrombocytopenia) and qualitative (von Willebrand, uremia) changes in platelets; increase in coagulation factors V, VII, IX, XI and fibrinogen; increase in fibrin degradation products, due to consumptive coagulopathy; reduction in vitamin-K-dependent factors; increase in thrombin-antithrombin complex; altered fibrinolysis; and reduced hepatic anticoagulant production (antithrombin III, protein C and S).[31] Furthermore, the presence of catheters and complications, such as sepsis and systemic inflammatory response, can increase the risk of thromboembolism. Tumoral invasion can also cause localized bleeding, sometimes difficult to control, leading to hypovolemic shock as a result of the significant blood loss.

Although production of coagulation factors is usually elevated due to the carcinogenic stimulation, vitamin-K-dependent factors (II, V, IX and X) may be reduced as a result of malnutrition, hepatic infiltration or use of anticoagulants and antibiotic therapy. Treatment is with plasma transfusion (10-15 mL/kg), vitamin K (5-10 mg) and cryoprecipitate (1 U/5 kg), which is rich in von Willebrand factor, fibrinogen, fibronectin and factor XIII24, prothrombin complex and factor VII.

Management of thrombocytopenia

Several factors may be responsible for the development of thrombocytopenia in children with cancer, such as invasion of the bone marrow, chemotherapy, radiation, sepsis and disseminated intravascular coagulation.[32] The principal clinical manifestation is bleeding from mucosas, petechiae, ecchymosis, epistaxis, gastrointestinal and urogenital bleeding. Usually spontaneous bleeding does not occur, unless platelets fall below 20,000/mm^3. Some studies have reported that levels of 5,000-10,000/mm^3 are safe in leukemia patients receiving chemotherapy. Table 3 lists the principal indications for platelet transfusions and the cutoffs employed in each clinical situation.

Adequate platelet counts, but with abnormal function, may occur if von Willebrand disease develops in patients with leukemia, lymphomas and solid tumors, such as neuroblastomas, and are related to an autoimmune reaction.[34] The clinical manifestation is similar to with hereditary disease, with bleeding of mucosas, gastrointestinal tract and surgical wounds. The patient presents with

Table 3 - Indications for platelet transfusion

Indication for transfusion	Cutoff
Mucocutaneous/gastrointestinal bleeding	> 50,000/mm^3
Leukemia	
Chemotherapy induction	> 20,000/mm^3
Leukemia acute	> 5,000-10,000/mm^3
Prophylaxis-asymptomatic	> 5,000/mm^3
Extensive surgery	> 50,000/mm^3
Invasive procedure	
Small scale	> 50,000/mm^3
Large scale	> 20,000/mm^3

Source: Adaptation of DeSancho MT et al.[33]

extended activated partial thromboplastin time (TTPA) with normal bleeding time. Treatment is with desmopressin (DDAVP), transfusion of von Willebrand factor and immunoglobulins. Uremia due to acute or chronic renal insufficiency may also be a cause of platelet dysfunction and bleeding, and dialysis may improve the situation.

References

1. Maschmeyer G, Ostermann H, Wendt S, Richter G. Guidelines of the infectious diseases working party of the German Society of Hematology and Oncology. Ann Hematol. 2003;82 Suppl 2:S105-17.
2. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002;34:730-51.
3. Tamburro R. Pediatric cancer patients in clinical trials of sepse: factors that predispose to sepsis and stratify outcome. Pediatr Crit Care Med. 2005;6:1234-40.
4. Rackoff W, Gonin R, Robinson C, Kreissman S, Breitfeld P. Predicting the risk of bacteremia in children with fever and neutropenia. J Clin Oncol. 1996;14:919-24.
5. Santolaya ME, Rabagliati R, Bidart T, Paya E, Guzman AM, Morales R, et al. Consenso manejo racional del paciente con cáncer, neutropenia y fiebre: rational approach towards the patient with cancer, fever and neutropenia. Rev Chilena Infectol. 2005;22 Supl 2:S79-S113.
6. Hallahan AR, Shaw PJ, Rowell G, O'Connell A, Schell D, Gillis J. Improved outcome of children with malignance admitted to a pediatric intensive care unit. Crit Care Med. 2000;28:3718-21.
7. Price KJ, Thall PF, Kish SK, Shannon VR, Andersson BS. Prognostic indicators of blood and marrow transplant patients admitted to the intensive care unit. Am J Respir Crit Care Med. 1998;158:876-84.
8. Fiser TG, West NK, Bush AJ, Sillos EM, Schmidt JE, Tamburro RF. Outcome of severe sepsis in oncology patients. Pediatr Crit Care Med. 2005;6:531-6.
9. Klaassen RJ, Goodman TR, Pham B, Doyle JJ. "Low-risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. J Clin Oncol. 2000;18:1012-9.
10. Lopez FA, Sanders CV. Recognizing cutaneous signs of infection in immunocompromised patients. Abstr Hematol Oncol. 2003;6:19-26.
11. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, Harris JS, et al. Guidelines for the management of intravascular catheter-related infection. Clin Infect Dis. 2001;32:1249-72.
12. Naoum FA, Martins LTV, Castro NS, Barros JC, Chiattone CS. Perfil microbiológico dos pacientes nos primeiros trinta dias pós transplante de medula óssea do Serviço de Transplantes da Santa Casa de São Paulo. Rev Bras Hematol Hemoter. 2002;24:91-6.
13. Vincent JL. Give your patient a fast hug (at least) once a day. Crit Care Med. 2005;33:1225-9.
14. Kitanovski L, Jazbec J, Hojker S, Gubina M, Derganc M. Diagnostic accuracy of procalcitonin and interleukin-6 values for predicting bacteremia and clinical sepsis in febrile neutropenic children with cancer. Eur J Clin Microbiol Infect Dis. 2006;25:413-5.
15. Renoult E, Buteau C, Turgeon N, Moghrabi A, Duval M, Tapiero B. Is routine chest radiography necessary for the initial evaluation of fever in neutropenic children with cancer? Pediatr Blood Cancer. 2004;43:224-8.
16. Danilatou V, Mantadakis E, Galanakis E, Christidou A, Stiakaki E, Kalmanti M. Three cases of viridans group streptococcal bacteremia in children with febrile neutropenia and literature review. Scand J Infect Dis. 2003;35:873-6.
17. Link H, Böhme A, Cornely OA, Höffken K, Kellner O, Kern WV, et al. Antimicrobial therapy of unexplained fever in neutropenic patients. Ann Hematol. 2003;82 Suppl 2:S105-17.
18. Greenberg D, Moser A, Yagupsky P, Peled N, Hofman Y, Kapelushnik J, Leibovitz E. Microbiological spectrum and susceptibility patterns of pathogens causing bacteraemia in paediatric febrile neutropenic oncology patients: comparison between two consecutive time periods with use of different antibiotic treatment protocols. Int J Antimicrob Agents. 2005;25:469-73.
19. Lai HP, Hsueh PR, Chen YC, Lee PI, Lu CY, Lu MY, et al. Bacteremia in hematological and oncological children with febrile neutropenia: experience in a tertiary medical center in Taiwan. J Microbiol Immunol Infect. 2003;36:197-202.
20. Celkan T, Ozkan A, Apak H, Diren S, Can G, Yuksel L, et al. Bacteremia in childhood cancer. J Trop Pediatr. 2002;48:373-7.
21. Garnica M, Nucci M Epidemiology, treatment and prophylaxis of infections in chronic lymphocytic leukemia. Rev Bras Hematol Hemoter. 2005;27:290-300.
22. Ruhnke M, Böhme A, Buchheidt D, Donhuijsen K, Einsele H, Enzensberger R, et al. Diagnosis of invasive fungal infections in hematoloy and oncology. Guidelines of the Infectious Diseases Working Party (AGIHO) of the Germany Society of Hematology and Oncology (DGHO). Ann Hematol. 2003;82 Suppl 2:S141-8.
23. Lucas KG, Brown AE, Armstrong D, Chapman D, Heller G. The identification of febrile, neutropenic children with neoplasic disease low risk of bacteremia and complications of sepsis. Cancer. 1996;77:791-9.
24. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis. 2006;42:597-607.
25. Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. Am J Med. 2000;108:282-9.
26. Segal BH, Almyroudis NG, Battiwalla M, Herbrecht R, Perfect JR, Walsh TJ, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis. 2007;44:402-9.
27. Liang DC, Chen SH, Lean SF. Role of granulocyte colonystimulating factor as adjunct therapy for septicemia in children with acute leukemia. Am J Hematol. 1995;48:76-81.
28. Sachdeva RC, Jefferson LS, Coss-Bu J, Brody BA. Resource consumption and the extent of futile care in a pediatric intensive care setting. J Pediatr. 1996;128:742-7.
29. Carcillo J. What's new in the pediatric intensive care medicine. Pediatr Crit Care Med. 2006;34:S183-190.

30. Goad KE, Gralnick HR. Coagulation disorders in cancer. Hematol Oncol Clin North Am. 1996;10:457.

31. Pizzo PA. Infectious complications in the pediatric cancer patient. In: Pizzo PA, Poplack DA, editores. Principles and practice of pediatric oncology. 3rd ed. Philadelphia: Lippincott-Raven; 1997. p. 1069-114.

32. Johnson MJ. Bleeding, clotting, and cancer. Clin Oncol (R Coll Radiol). 1997;9:294-301.

33. DeSancho MT, Rand JH. Bleeding and thrombotic complications in critically ill patiensts with cancer. Crit Care Clin. 2001:17:599-622.

34. Veyradier A, Jenkins CS, Fressinaud E, Meyer D. Acquired von Willebrand syndrome: from pathophysiology to management. Thromb Haemost. 2000;84:175-82.

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