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REVIEW ARTICLE

Intensive care therapy for cancer patients

Roberto Sapolnik*

Abstract

Objective: To review the most important aspects of the clinical presentation and treatment of children with cancer in intensive care units.

Sources of data: Medline (1970 to 2003); search terms: children, cancer, oncology, intensive care, complications. General and pediatric oncology textbooks.

Summary of the findings: Practically all organs may be affected by cancer or by its treatment. The main complications include infections, hematological problems and electrolyte/ metabolic disturbances. Intensive care therapy is necessary to correct organic dysfunctions (cardiovascular, respiratory, renal, gastrointestinal, and neurologic). Nutritional and emotional support, as well as pain control are fundamental aspects for recovery in children. The intensivist should be alert to interrupt intensive care measures if required.

Conclusions: Many studies show that the use of intensive care therapy in children with cancer is not futile, with a reduction in mortality and improvement in the quality of life of these children in the medium and long terms.

J Pediatr (Rio J) 2003;79(Suppl 2):S231-S42: Cancer, children, intensive care, complication, infection, organic dysfunction.

Introduction

Neoplasms are the second most common cause of death in children aged between 1 and 15 years throughout most of the world, being outrivaled only by accident-related traumas.[1] Leukemia is the most frequent type of childhood cancer, followed (in decreasing order) by brain tumor, lymphomas, sarcoma, and ectodermal tumors. Tremendous development has been made in cancer treatment in the last twenty years, especially with the advent of new chemotherapy drugs, radiotherapy and bone marrow transplant. However, these new therapies may cause several side effects and compromise almost all the organic functions. Cancer itself may cause clinical complications with immediate life threat, such as spontaneous tumor lysis syndrome or tumor compression causing renal insufficiency or intestinal obstruction. Children with cancer often require pediatric intensive care; and thanks to such care, many of them have been able to overcome the most acute phase of the disease.[2] In

* Coordinator of the Pediatric ICU, Hospital São Rafael, Salvador, Brazil; physician, Pediatric ICU, Hospital Aliança, Salvador, Brazil; head of the Department of Pediatrics, Society for Intensive Therapy, State of Bahia, Brazil.

order to restore bodily functions, mechanical ventilation, broad-spectrum antibiotics, peritoneal dialysis, and hemodialysis, among other sophisticated treatments, can be used. Intensive care resources can be used in procedures that require sedation and analgesia with continuous cardiorespiratory monitoring. Intensive care is necessary, even in incurable cases, in order to relieve immediate symptoms and improve the quality of life.[3]

We are going to discuss the main clinical situations and aspects of intensive care that may be applied to children with cancer. The issues were divided into topics, but it is fundamental that we have an integrated approach to children with cancer admitted to the ICU through drug therapy and nursing care, physical therapy, nutrition, as well as psychological and emotional support for the patients and their families.

Immunity and infection

Among the indications for intensive care, infectious complications such as localized disease, dissemination with sepsis and septic shock are a common reason for the admission of children with cancer to the ICU. Moreover, infection is the main cause of death in those children who do not die of the cancer itself.[2] Several factors increase the susceptibility of cancer patients.[4] Bone marrow infiltration by lymphomas and leukemias compromises the production and function of neutrophils and lymphocytes, thus affecting humoral and cellular immunity. The risk of infection is high when the neutrophil count falls below 500 cells/mm^3, and there is an imminent risk of bacteremia and sepsis with a count below 100 cells/mm^3. Chemotherapy drugs and corticoids also reduce the bone marrow production of cells. In addition, these drugs damage the integrity of the skin tegument, and of the respiratory and gastrointestinal tracts, facilitating the penetration of microorganisms into the host. Besides these factors, invasive procedures (e.g.: insertion of tubes or catheters, punctures, and prolonged parenteral nutrition) affect even more the integrity of the mechanical barriers of the body's defense system.

Different bacteria, fungi, viruses and parasites are responsible for the infectious process.[5] In the first week of agranulocytosis, aerobic gram-positive and gram-negative bacteria (*Staphylococcus aureus, S. epidermis, streptococci, enterococci, enterobacteria* and *Pseudomonas aeruginosa*) are more common. After the second and third week, fungi, especially Candida species (*albicans, tropicalis, parapsilosis, krusei*), and parasites such as *Pneumocystis carinii*, are more common. Infections caused by the herpes, cytomegalovirus, adenovirus, varicella-zoster, and syncytial respiratory viruses are associated with a decrease in cellular immunity and transfusion of blood derivatives. The mycobacteria are less frequent in children and there are few cases reported in the literature.[6]

The diagnosis of infection may be difficult in cancer patients, not only because of the wide variety of microbial agents, but also because of peculiarities about the clinical presentation of the disease. Due to agranulocytosis, the disease can establish itself without forming an apparent focus of infection, such as pneumonias without radiologic findings or abscesses with no signs of infection.[7] Moreover, the white cell count is not so specific due to alterations caused by the disease and chemotherapy. Fever may be the only sign of infection; however, the fever can be caused by drugs, catheterization or by the cancer itself. Regular bacterial culture, as well as serologic tests and indirect diagnostic methods, is extremely important to the identification of the etiologic agent (protein C polymerase -PCR). The specificity of acute-phase proteins, such as C-reactive protein, is low. New tests, such as those that detect elevated serum levels of interleukin 1 and 6, have been positively correlated with presence of infection, but they have been used only in research so far.[8]

Broad-spectrum antibiotic therapy should be immediately initiated. New antimicrobial treatments have been recently proposed for the management of febrile neutropenic patients even when the infectious agent remains unknown. Bacteremia, caused mainly by gram-positive bacteria (*S. epidermides, streptococci, enterococci*) and by aerobic gram-negative bacteria (*Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli*), often affects 10% to 20% of febrile patients.[9] Figure 1 shows the new protocol of the American Academy of Oncology for antibiotic therapy in febrile neutropenic patients[10]; however each case should be assessed on an individual basis, considering the most probable agents, respecting the profile of sensitivity and resistance of each institution and community.

Low-risk patients can be treated at the outpatient clinic with monotherapy using third-generation cephalosporin (ceftazidime or cefepime) or carbapenem agents (imipenem-cilastatin, meropenem, azactam) (Tabela 1). Although some studies have demonstrated that quinolones are little toxic to children, there is no recommendation for oral antibiotic monotherapy in pediatric patients.[12] The two-drug scheme with addition of an aminoglycoside is justifiable due to the characteristics of the local flora, lesser induction of beta-lactamase producers, and anti-Pseudomonas activity. These associations do not provide coverage of some gram-positive bacteria, such as *Streptococcus pneumoniae*, methicillin-resistant *staphylococci* and *Enterococcus faecallis*. In this case, it is necessary to add vancomycin or teicoplanin.

Usually, cancer patients with infection admitted to the ICU do not respond to the initial treatment and show signs of disseminated infection. Children who respond properly to the treatment show some improvement within 48 hours. The major causes of failure of initial antibiotic therapy are: nonbacterial infection (virus, fungi, parasites), bacteria that are resistant to the initial treatment or that show delayed response, development of new infections, inadequate serum

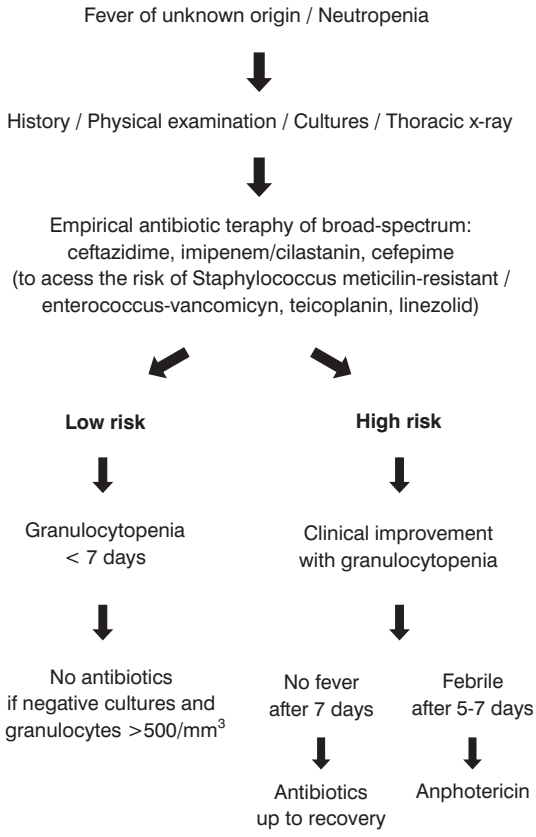

Figure 1 - Protocol for antibiotic therapy in febrile neutropenic patients. Modified by Pizzo, A.P.[4]

level, infection in an avascular region (tubes and catheters) or abscesses.[10] Patients should be re-evaluated, with new cultures, imaging exams (x-ray, ultrasound, CT-scan), inspection of tubes and catheters, and if clinical deterioration occurs, the antimicrobial treatment should be changed and prolonged. The possibility of infection caused by methicillin-resistant *staphylococci* (catheter infection, cellulitis), penicillin/cephalosporin-resistant *pneumococcus* and vancomycin-resistant *Enterococcus faecalis*, gram-negative beta-lactamase producers may require the use of tobramycin and piperacillin, ticarcillin, ciprofloxacin and polymyxin B. The use of new anti-*staphylococcal* drugs, such as linezolid, in oncology, has not been approved by the FDA due to the risk of myelosuppression.[13] Teicoplanin does not offer any clear advantage over vancomycin.[14] If the signs of infection persist and the clinical status worsens after five days, the introduction of an antifungal agent should be considered. In severe cases, the treatment can be initiated up to 48 hours after the introduction of the new antimicrobial therapy. Amphotericin is the drug of choice.[15] The liposomal formulation should be reserved for renal insufficiency cases. This drug can be utilized in itraconazole -sensitive (fluconazole) and in localized infections (fungal cystitis).[16] Aspergillosis responds only to amphotericin. Less common agents, such as atypical bacteria (*Mycoplasma pneumoniae*, typical and atypical *mycobacteria*, *Legionella*), as well as viruses and parasites (*Pneumocystis carinii*), should be investigated if the introduction of vancomycin, beta-lactamase inhibitors, and the association of an antifungal drug do not work.

In infections with a clearly defined focus, antibiotic therapy can be better balanced.[4] Catheter-related infections are often caused by gram-positive bacteria, especially coagulase-negative *staphylococcus* (*S. epidermides*), and are sometimes methicillin-resistant due to frequent hospitalizations and acquisition of nosocomial pathogens. Pneumonias are caused not only by community-acquired bacteria (*pneumococci, Haemophilus influenza, Staphylococcus aureus*), but also by nosocomial agents such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and commensal agents such as *Pneumocystis carinii*. Respiratory viruses (*influenza, syncytial respiratory virus*) can also cause severe pneumonia. Otitis and sinusitis caused by unusual pathogens, such as *P. aeruginosa* and *S. aureus*, or even by fungi and viruses (*herpes virus*), may occur in the upper airways (ear, nose, throat). Gastrointestinal infections (mucositis, colitis, perirectal abscess) are usually caused by anaerobic gram-negative pathogens and *Enterococcus faecalis*. Hepatites can be caused by viruses (CMV, viruses B, C, non-A and non-B), but also by fungi and parasites (giardiasis, strongyloids). The central nervous system can be affected by community-acquired bacteria (*pneumococci, meningococci*), hematogenic dissemination or by the presence of CSF shunt catheter in cases of intracranial tumors. Viruses can also cause severe meningitis and encephalitis. Urinary tract infections are attributable to

Table 1 - Low risk factors for severe infection in neutropenic patients[11]

Neutrophils count > 100 cells/mm^3
Monocytes count > 100 cells/mm^3
Normal thoracic x-ray
Normal hepatic and renal functions
Neutropenia < 7 days
Neutropenia remission < 10 days
No catheter infection
Evidence of marrow recovery
Remission of oncologic disease
Temperature < 39 ºC
No neurologic alteration
General good health
No abdominal pain
No comorbidities: shock, hipoxia, pneumonia or invasive infection, vomiting and diarrhea

the presence of bladder catheter or to the mechanical obstruction provoked by the tumor, and are often caused by gram-negative pathogens, *staphylococci* and sometimes fungi. Skin infections (cellulitis and abscesses) are usually caused by staphylococci and gram-negative bacteria. Catheter infections include endocarditis, caused by gram-positive or gram-negative bacteria.

Table 2 shows the antimicrobials most widely used in cancer patients and their maximum dose.[4] Each clinical situation should be assessed separately in view of the clinical and epidemiological characteristics and the initial response to the treatment.

In addition to antimicrobial therapy, there is a recent concern with the improvement of patient's immunity. The granulocyte colony-stimulating factor is broadly used for this purpose.[17] This drug acts on the bone marrow precursor cells, increasing the number of granulocytes and neutrophils. An adverse effect is, however, the stimulation of neoplastic cells. Today, the recommendation of the American Academy of Oncology is that this drug should be used for severe and life-threatening leukopenia (sepsis and septic shock). The prophylactic use for the prevention of granulocytopenia did not prove efficacious. Another alternative would be

Table 2 - Antimicrobials most widely used in cancer patients

Antibiotic class	**Agent**	**Spectrum of action**	**Dose**
Cephalosporin 3rd generation	Ceftazidime, cefepime	Gram –, some gram +	100 mg/kg
Carbapenem	Imipenem, carbapenem and anaerobic agents	Gram –, gram +	50 mg/kg
Modified penicillin	Piperacillin, azlocillin, mezlocillin	Gram – (*P. Aeruginosa*) anaeróbios	300 mg/kg
Monobactamic	Azactam	Gram – (*Pseudomonas*)	100-150 mg/kg
Glycopeptide	Vancomycin	Gram + (*Estafilococcus, Streptococcus, Enterococcus*)	20-40 mg/kg
Antifungal class	**Spectrum of action**		**Dose**
Anfotericine B	*Candides* (Albicans, Parapsilosis, Kruseii), Aspergilus, Criptococcus, Histoplasma		0.5-1.5 mg/kg
Azoles: Ketoconazole	*C. Albicans*		5-10 mg/kg
Fluconazole, Itraconazole	*C. Albicans, Cryptococcus*		100-400 mg/dia
Antiviral			
Acyclovir	Herpes, Zoster varicella		250 mg/m^2
Ganciclovir	Herpes, Varicella, Cytomegalovirus		5 mg/kg
Foscarnet	Herpes, Varicella, ganciclovir-resistant cytomegalovirus		60 mg/kg
Ribavirin	Respiratory syncytial		
Antiparasital			
Anti-*P. Carinii*	Trimetropim-Sulphamethoxazole		20 mg/kg Trimetropim/ 100 mg/kg Sulpham
	Pentamidine		4 mg/kg
Anti-helmintic			
Thiabendazole	*Strongiloides estercoralis*		50 mg/kg
Mebendazole	Ascaris, Enterobios		300 mg/day
Anti-*Giardia*	Metronidazol		30-40 mg/kg/day

Modified from Pizzo, A.P.[4]

granulocyte transfusion, which is scarcely available in most medical centers and is associated with several adverse reactions. Theoretically, the use of immunoglobulins could be useful, but the clinical results are controversial. Corticoid therapy, hemofiltration, and plasmapheresis have not shown to reduce mortality.[18]

Hemostatic disorders

Hemorrhagic disorders and thrombosis are frequently observed in children with cancer.[19] Bleeding is more frequently seen in leukemias, and less common in solid tumors. Thrombotic disorders are found in up to 50% of autopsied patients. At all stages of coagulation, we may observe quantitative disorders (thrombocytopenia) and qualitative platelet disorders (von Willebrand disease, uremia); increase in coagulation factors V, VII, IX, XI and in fibrinogen; increase in fibrin degradation products due to consumption coagulopathy; reduction in vitamin K-dependent factors; increase in the thrombin-antithrombin complex; changes in fibrinolysis; and decrease in the production of anticoagulants (antithrombin III, protein C and S) by the liver.[20] In addition, catheterization and complications such as sepsis and systemic inflammatory response can increase the risk of thromboembolism. Tumor invasion can also cause localized bleeding, which is sometimes difficult to control and results in hypovolemic shock due to substantial blood loss.

Thrombocytopenia

A wide range of factors may cause thrombocytopenia in children with cancer, including bone marrow invasion, chemotherapy, radiotherapy, sepsis, and disseminated intravascular coagulation.[21] The major clinical signs are mucosal bleeding, petechiae, ecchymosis, epistaxis, and gastrointestinal and genitourinary bleeding. Spontaneous bleeding does not usually occur unless platelet count falls below 20,000/mm^3. Some studies report safe levels of 5,000-10,000/mm^3 in leukemic patients on chemotherapy. Table 3 shows the main indications for platelet transfusion and the thresholds used in each clinical situation.

An adequate platelet count with abnormal platelet function may occur due to von Willebrand disease in patients with leukemias, lymphomas and solid tumors (e.g.: neuroblastomas) and is associated with autoimmune response.[23] The clinical signs resemble that of an inherited disease, with mucosal, gastrointestinal and surgical wound bleeding. Patients show prolonged aPTT with normal bleeding time. The treatment consists of desmopressin acetate (DDAVP), transfusion of von Willebrand factor and use of immunoglobulin. Uremia as a result of acute or chronic renal insufficiency can also cause platelet dysfunction and bleeding, which may be mitigated by dialysis.

Although the production of coagulation factors is often high due to carcinogenic stimulus, that of vitamin K-dependent factors (II, V, IX and X) might be reduced because of malnutrition, liver infiltration, use of anticoagulants and antibiotic therapy. The treatment consists of plasma transfusion (10-15 ml/kg), vitamin K (5-10 mg) and cryoprecipitate (1 U/5kg), which is rich in von Willebrand factor, fibrinogen, fibronectin and factor XIII.[24]

Thrombosis

Thrombotic disorders may manifest themselves as deep vein thrombosis, pulmonary thromboembolism, thrombotic thrombocytopenia purpura and hemolytic uremic syndrome, and disseminated intravascular coagulation.[25]. In addition

Table 3 - Indications for platelet transfusion

Transfusion indication	Threshold
Mucocutaneous/gastrointestinal bleeding	> 50,000/mm^3
Leukemias:	
Chemotherapy induction	> 20,000/mm^3
Acute leukemia acute	> 5,000-10,000/mm^3
Prophylaxis:	
Asymptomatic	> 5,000/mm^3
Large surgery	> 50,000/mm^3
Invasive procedure:	
Small procedure	> 50,000/mm^3
Large procedure	> 20,000/mm^3

Modified from DeSancho M.T.[22]

to the production of thrombogenic substances by the neoplasm and of thrombolytic factors, several chemotherapy drugs such as cyclophosphamide, cisplatin, 5-fluorouracil and methotrexate increase the risk of thromboembolism. The commonly involved sites are the ileofemoral region and the site of central catheter insertion (superior vena cava, right atrium).[26] The diagnosis is established by imaging exams, especially Doppler ultrasound and laboratory investigation of fibrin degradation products (D-dimers). The treatment consists of the administration of intravenous heparin or low molecular weight heparin. The use of thrombolytic agents (streptokinase, urokinase, plasminogen activator) is associated with significant bleeding and should normally be avoided. Thrombotic thrombocytopenia purpura and hemolytic uremic syndrome are rare, but lymphomas may occur, including non-Hodgkin's lymphoma.[27] They are characterized by the presence of hemolytic anemia, thrombocytopenia, reticulocytosis, increase in lactic dehydrogenase and schizocytosis in peripheral blood. The treatment consists of plasmapheresis, immunoglobulins, corticoid therapy and splenectomy. Platelet transfusion should be avoided due to the increase in thrombus formation. Disseminated intravascular coagulation might occur especially in children with leukemia, and is associated with high production of plasmin.[28] It is characterized by generalized bleeding and signs of poor organ perfusion. The treatment consists of platelet and fibrinogen transfusion. The use of plasma for replacement of coagulation factors is controversial due to the promotion of thrombosis. Transretinoic acid is used in promyelocytic leukemia. Heparin may be used in cases of compromised organ perfusion (limb ischemia, renal insufficiency).

Superior vena cava syndrome

The drainage of the superior vena cava may be compromised especially in lymphomas of the cervical and mediastinal region. Mediastinal masses can also compress the trachea and upper airways causing respiratory insufficiency.[29] The patient presents facial edema with venous engorgement and sometimes neurological symptoms (stupor and seizures). The chest X-ray shows mediastinal enlargement and deviation of structures, especially of the trachea. The increase of the hydrostatic pressure produces transudates and pleural and pericardial effusion, which sometimes require drainage and thoracentesis. When the patient has cervical and dorsal pain and signs of neurological deficit, bone marrow compression should be considered, and decompression should be performed immediately for maintenance of the neurological function. The focus of the treatment is on the neoplastic disease. In cases of lymphomas, tumor reduction often occurs within 48 hours after the implementation of prednisone therapy. If the signs and symptoms are associated with remarkable vena cava thrombosis, heparinization and the use of thrombolytic agents are indicated.

Hyperleukocytosis

Up to 20% of children recently diagnosed with leukemia may have a leukocyte count greater than 100,000/mm^3. These children are at risk for spontaneous tumor lysis syndrome and for complications related to the formation of cell aggregates in microcirculation. Pulmonary involvement causes dyspnea, hypoxemia and acidosis,[30] also with reduction of brain perfusion, causing varying degrees of coma and intracranial hemorrhage. The treatment includes hyperhydration two or four times the baseline water requirement. Platelet transfusion and the use of diuretics should be avoided as they increase blood osmolarity. Exchange transfusion or plasmapheresis is indicated when leukocyte count exceeds 100,000/mm^3 in non-lymphocytic leukemias (larger myeloblasts), and 200,000-300.000/mm^3 in lymphocytic leukemias.

Water and electrolytic disorders

Children with cancer often have water and electrolyte homeostasis.[31] Fluid accumulation is usually associated with heart failure (cardiotoxicity of chemotherapy drugs), malnutrition and hypoalbuminemia, and renal insufficiency. The treatment may include cardiotonic drugs, diuretics, albumin transfusion and even renal replacement therapy, in view of the pathophysiological mechanism involved. The major electrolytic disorders found in children with cancer are described below:

Hyponatremia

Cancer patients often have hyponatremia associated with the reduction of circulating blood volume (hypovolemic hyponatremia). The most common causes are hemorrhage, third space loss, and gastrointestinal loss. It might also result from renal loss due to the use of diuretics or to tubular injury provoked by drugs such as cisplatin and ifosfamide.[32] In addition, fluid retention caused by heart failure and hypoalbuminemia may lead to dilutional hyponatremia, as well as in some types of neoplasms (lymphomas and leukemias) due to the development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[33] Cyclophosphamide may also be related to SIADH. In intracranial tumors, the release of brain natriuretic peptides may lead to the cerebral salt-wasting syndrome, with occasionally fatal hypovolemia and hyponatremia. The symptoms of hyponatremia result from cerebral edema and develop from mild drowsiness to seizures and deep coma. The treatment depends on the pathophysiological mechanism involved, and the correction should not exceed 8 mosm/l/24 hours, in order to avoid the development of central pontine myelinolysis.

Hypernatremia

Hypernatremia occurs when the salt content is extremely higher than that of body water. It may occur when thirst mechanisms are compromised, but it is commonly related to

inadequate fluid replacement in hypovolemic patients. It may also result from the excess administration of sodium bicarbonate and parenteral nutrition.[31] In surgeries for removal of craniopharyngiomas there might be *diabetes insipidus* if part of the pituitary gland is not preserved, which could produce severe and hard-to-control cases.[34] Clinical signs are also associated with the movement of water through the brain, which could cause intracranial hemorrhage due to the rupture of veins of the dura mater and venous sinus. Exogenous desmopressin (DDAVP) should be used and sodium correction should not exceed 10 mosm/l/24 hour.

Hypokalemia

Hypokalemia results from body potassium loss or transcellular shift. The losses occur due to diarrhea (radiation enteritis, chemotherapy drugs) and vomiting, with increase of renal excretion provoked by hypochloremia. Drugs such as cisplatin, ifosfamide, and amphotericin can increase renal potassium loss.[36] Transcellular shifts are less common and are related to the use of ß2-sympathomimetic drugs and insulin. The symptoms are related to the electrical transmission system (bradycardia, arrhythmia), paralytic ileus and loss of muscle strength. The treatment consists of potassium replacement, without exceeding 20 mEq/hour or 0.5 mEq/Kg/hour, with continuous electrocardiographic monitoring.

Hyperkalemia

Initially, it is important to check whether the increase in potassium levels is real, since hemolysis during blood sample collection, hyperleukocytosis and thrombocytosis can result in false assessments of *in vitro* serum potassium.[35] Actual increases are associated with reduced excretion of potassium due to renal insufficiency or use of drugs that lower tubular excretion (angiotensin inhibitors); or due to the transcellular shift of potassium caused by plasma hypertonicity. In the tumor lysis syndrome, the release of potassium may exceed the capacity of the kidneys to eliminate it, resulting in severe hyperkalemia. Clinical signs include loss of muscle strength and cardiac arrhythmia. In emergencies with abnormal electrocardiogram, calcium gluconate, a polarizing solution with insulin, ß2-adrenergics and sodium bicarbonate may be utilized. The increase in potassium elimination by the body can be attained by the administration of diuretics, exchange enzymes (Kayexalate) and renal replacement therapy.[37]

Hypocalcemia

As 40% of the calcium is bound to albumin most hypocalcemias are indeed hypoalbuminemias, and the ionizable serum calcium is normal. Deficiencies due to hypoparathyroidism in pediatric patients are not so common. Quite frequently, hypocalcemia is related to the tumor lysis syndrome by the precipitation caused by organic acids and hyperphosphatemia.[38] The citrate used in transfusions can also reduce calcium levels. Clinical signs include paresthesias, cramps, tetany, laryngospasm and seizures, and could evolve into ventricular fibrilation. In severe cases, the treatment consists of intravenous infusion of calcium gluconate. Hypocalcemia should be treated prior to the correction of acidosis.

Hypercalcemia

Hypercalcemia is usually related to the production of proteins analogous to the parathyroid hormone by tumor cells, or by osteolysis due to bone metastases. In Hodgkin's and non-Hodgkin's lymphomas hypercalcemia occurs due to the production of calcitriol with an increase in intestinal absorption.[39] Clinical signs include nausea, obstipation, loss of muscle strength, seizures and coma. Severe hypercalcemia may lead to cardiac blockade and arrest. The treatment consists of volumetric expansion, diuretics and drugs that inhibit bone reabsorption (etidronate, pamidronate). Cancer treatment can also reduce serum calcium levels.

Hypomagnesemia

Decreases in magnesium levels are related to gastrointestinal losses caused by diarrhea and steatorrhea, and by the increase in renal excretion due to the use of diuretics and hyperhydration. Nephrotoxic drugs such as ifosfamide, cisplatin, amphotericin and aminoglycosides also increase renal magnesium elimination.[40] Clinical signs are nonspecific, as they are usually associated with concomitant hypocalcemia and hypokalemia. Paresthesias, cramps, seizures, fibrilation and cardiac arrest might occur. Parenteral correction should not exceed 1-2 mEq/Kg in 8 to 24 hours.

Hypermagnesemia

Hypermagnesemia is rare and is often associated with exogenous administration.[40] Clinical signs include abnormal level of consciousness, hypotension and arrhythmias. The treatment consists in reducing magnesium supply, and in severe cases, antagonism with calcium gluconate and dialysis.

Hypophosphatemia

The decrease in body phosphorus levels results from malnutrition, intestinal malabsorption, increase in renal elimination and transcellular shift. Nephrotoxic drugs and diuretics increase renal phosphorus elimination.[41] In leukemias, hyperleukocytosis may lead to exaggerated cellular absorption with reduction of the serum phosphorus level. Respiratory alkalosis also increases transcellular shift. Clinical signs are loss of muscle strength, adynamic ileus, respiratory failure and cardiac dysfunction. Encephalopathy and coma might occur. In mild cases, the problem is corrected with oral supplementation of

phosphorus, and in severe cases, parenteral administration of 2-2.5 mg/kg in 6 hours may be used.

Hyperphosphatemia

Increase in phosphorus levels may occur due to higher exogenous administration, but it is more frequent because of cellular release in the tumor lysis syndrome. It may also be caused by renal insufficiency with glomerular filtration below 25 ml/minute.[41] Hypocalcemia and tetany occur in rapid increases of phosphorus levels. When the calcium-phosphorus product exceeds 70 the risk of precipitation and ectopic calcification increases. The treatment consists of volumetric expansion, use of diuretics and dialysis. The oral administration of aluminum hydroxide reduces the magnesium level more gradually.

Tumor lysis syndrome

The tumor lysis syndrome results from the destruction of neoplastic cells. It is more commonly observed in diseases such as leukemias and lymphomas.[43] It may develop spontaneously before the onset of chemotherapy, and it distinguishes itself from the secondary form by the absence of hyperphosphatemia. Cell lysis produces a constellation of electrolytic and metabolic disorders, which may exceed the renal elimination capacity or cause obstruction in renal tubules due to uric acid and calcium precipitation; in addition, the uric acid: creatinine ratio is often above 1.0.[44] Hyperuricemia, hyperphosphatemia, hyperkalemia and hypocalcemia usually occur after the destruction of cells by chemotherapy. Sometimes the process may lead to the systemic inflammatory response syndrome, with hemodynamic disorders (hypotension) and coagulopathies, including disseminated intravascular coagulation. Despite the severity of metabolic disorders and organic dysfunction, the development of tumor lysis syndrome after the onset of chemotherapy means that the neoplasm is responsive to the treatment. Some signs are suggestive of high risk for the syndrome: extremely high lactic dehydrogenase, large tumor masses, and hyperleukocytosis. The initial treatment consists of hyperhydration usually with 150-200% of the baseline water intake (3 l/m^2/day) and stimulation with loop diuretics (furosemide). Pretreatment with allopurinol helps normalize the levels of uric acid by preventing the conversion of hypoxanthine into xanthine.[45] New drugs, such as urate oxidase, have shown to be efficient in reducing hyperuricemia. Alkalinization of the urine by the use of sodium bicarbonate is no longer recommended as it increases calcium precipitation. If the patient develops renal insufficiency or severe electrolytic disorders, dialysis should be used, preferably hemodialysis or hemofiltration. Peritoneal dialysis is not so efficient in eliminating uric acid and phosphate.

Metabolic disorders

Metabolic alkalosis may occur due to excessive vomiting and use of a nasogastric tube because of hydrogen chloride loss. The use of diuretics also increases the renal excretion of hydrogen with greater bicarbonate reabsorption. The treatment consists of the correction of the underlying cause, but the use of hydrochloric acid may be necessary.[46] A common cause of alkalosis in intensive care is the rapid correction of respiratory acidosis by means of mechanical ventilation. The kidney cannot keep up with the artificial rate of ventilatory correction, and retains bicarbonate in response to initial acidosis.

Metabolic acidosis can occur with a normal or abnormal *anion gap*. In patients with intestinal resection and stomal fluid loss (jejunostomy, ileostomy), bicarbonate loss may be remarkable, giving rise to severe acidosis. Patients with low renal capacity of acid elimination may develop metabolic acidosis as well. Drugs such as ifosfamide, cisplatin and amphotericin B reduce the tubular capacity of bicarbonate reabsorption and hydrogen excretion.[47] Acidosis also occurs in states of shock and poor organ perfusion. Acidosis without elevation of lactate levels or hypoperfusion can occur, with no known cause, in some types of leukemias and Hodgkin's disease. The treatment depends on the underlying pathophysiological event, and correction with bicarbonate is indicated when pH falls below 7.1.[46]

Toxicity of chemotherapy drugs

Several chemotherapy drugs can cause cardiotoxicity, nephrotoxicity, and bone marrow depression, in addition to a wide range of other side effects that compromise various organic functions. Table 4 lists the drugs most commonly used to treat children, and the toxic effects of these drugs.

Bone marrow transplant

From the first report of bone marrow transplant in 1939 to the present time, several advancements have been made regarding the replacement of hematopoietic cells, in addition to the increase in clinical indications of bone marrow transplant for nonneoplastic diseases (aplastic anemia, hemoglobinopathies, inborn errors of metabolism).[49] Several clinical complications affect patients in the immediate post-transplant period (30 days), and also at a later time (30-100 days); up to 40% of the patients require intensive care. Infections are the major complications due to pretransplant bone marrow ablation. At the initial stage, the most commonly observed pathogens include bacteria, fungi, and the *herpes virus*. After the second week, the leukocyte count rises, and infections caused by *Candida, Aspergillus* and cytomegalovirus are frequent. Reverse laminar flow is no longer recommended; in this case, proper handwashing proved equally efficient in preventing infections.

Table 4 - Drugs most commonly used to treat children and their toxic effects

Drugs	Adverse effect
Mustard and derivates	Myelosuppression, phlebitis
Cyclophosphamide	Myelosuppression, hemorrhagic cystitis
Iphosphamide	Myelosuppression, neurotoxicity, nephrotoxicity
Cisplatin	Myelosuppression, renal dysfunction
Carboplatin	Renal dysfunction
Cytarabine	Myelosuppression, neurotoxicity
Fluoruracil	Myelosuppression, mucosity
Hydroxiurea	Myelosuppression
Metrotexate	Myelosuppression, mucosity, hepatotoxicity, neurotoxicity, nephrotoxicity
Actinomycin	Myelosuppression, mucosity
Bleomycin	Fever, chill, lung fibrosis
Daunorubicin	Myelosuppression, cardiotoxicity
Vincristine	Neurotoxicity, ileus, pain
Vinblastine	Myelosuppression, neurotoxicity
L- Asparaginase	Pancreatitis, bleeding and thrombosis

Modified from Farrow C.A. et al.[48]

Noninfectious respiratory complications can also interfere with the course of evolution after bone marrow transplant. Pulmonary hemorrhage, idiopathic pulmonary syndrome, pleural effusion, pulmonary vascular disease and complications related to the upper airways (mucositis, bleedings) may result in severe respiratory insufficiency. The prognosis worsens considerably when the patient needs mechanical ventilation. Gastrointestinal (veno-occlusive hepatic insufficiency, gastric bleeding), neurological (metabolic encephalopathy, hemorrhages), and cardiac disorders (drug toxicity, pericardial effusion), in addition to coagulopathies and renal insufficiency are the most common complications in transplant recipients that might need intensive care.[50]

Nutritional support

Children with cancer often show signs of malnutrition, sometimes of severe malnutrition. Cancer cachexia is widely known and results from a series of factors, such as tumor growth, release of cytokines with development of hypercatabolic state, muscle loss, and organic dysfunction.[51] The baseline metabolic rate is elevated and there are problems with all energy intake pathways. There may be glucose intolerance, in addition to hypoglycemic bouts. Protein catabolism is enhanced with the use of muscle proteins. The increase in lipolysis leads to hypertriglyceridemia. Moreover, chemotherapy drugs cause a wide range of effects on the gastrointestinal tract compromising the intake and uptake of nutrients. Nausea, vomiting, diarrhea, mucositis and colitis can prevent the use of the enteral route for nutrient intake. The negative consequences of malnutrition to organic functions in cancer patients are devastating. Humoral and cellular immunity are compromised, the healing of surgical wounds takes longer, and there is less tolerance to chemotherapy and radiotherapy, which increases morbidity and mortality, regardless of the type of cancer.

The therapeutic approach begins with the assessment of the nutritional status. There are several aspects that hinder the assessment of the nutritional status of cancer patients in the ICU. The measurement of body weight is influenced by fluid accumulation (edema). Laboratory tests such as albumin, lymphocyte count, creatinine/ body mass index can also be influenced due to clinical disorders that are not related to the nutritional status.[52] Determining the risk for malnutrition is crucial, and the results are better the earlier the intervention. After hemodynamic stabilization the diet should be preferably via the enteral route, unless there are contraindications (adynamic ileus, active gastric bleeding, shock). The use of the enteral route reduces bacterial translocation and helps maintain the integrity of the intestinal mucosa.[53] The use of hypercaloric diets, which should take age group characteristics into account, focuses on the organic dysfunctions that may be present (renal, respiratory, and

hepatic insufficiencies). Parenteral nutrition is indicated when it is not possible to use the enteral route or as caloric support while enteral nutrition is initiated. Well-nourished patients need no nutritional support if food intake is reestablished in less than seven days. Calorie requirements of pediatric patients are calculated through the modified Harris Benedict formula, but these formulas often overestimate these requirements. 60% to 70% of the calories are supplied as carbohydrates, but in patients with respiratory insufficiency with an increase in carbon dioxide, the supply should be reduced to 40%-50%. 40% of the calories are supplied in the form of fats, and triglyceride levels should be maintained below 250 mg/dl.[54] Hypertriglyceridemia increases the risk of thrombosis and reduces the phagocytic activity of leukocytes. 10% to 15% of calories are supplied in the form of proteins, but they could be reduced due to uremia; or even increased at the stage of nutritional recovery and intense anabolism. Under greater stress, the nitrogen/non-protein calorie ratio should range between 1:100 and 1:150. The use of amino acids (glutamine, arginine) with immunomodulatory activity is controversial. One should pay special attention to the deficiency of vitamins and trace elements (vitamin A, C, zinc), essential substances for the recovery of body defenses.

Emotional support, treatment withdrawal and alleviation of pain

One of the most important aspects during intensive care is the emotional and psychological support for children and their families, as well as the attention given to the alleviation of pain. Older children with higher cognitive capacity should be informed about their disease openly and in a way that they can easily understand. An opportunity to talk about and express their feelings of fear and anxiety increases the trust between physicians, patients and family. The interaction between intensivist and oncologist is fundamental so that a better assessment of admission, complex treatments (mechanical ventilation, dialysis) and policies regarding intensive care withdrawal can be established. Decisions are taken in conjunction with the family, respecting the basic principles of autonomy, beneficence and nonmaleficence.[55] In case of younger children, parents are supposed to take decisions on their behalf, but the situation is complicated in case of adolescents. Ethical principles, as well as spiritual and religious principles of the family should be respected. Prognostic indicators can be used to aid in the decision-making process. The pediatric risk of mortality (PRISM) usually underestimates the chances of survival of children with cancer admitted to the ICU. A new version (PRISM III) seems to yield more reliable results. Intensive care units that treat children with cancer should include experienced psychologists.

Proper pain management is an important part of the treatment not only in humanitarian terms, but also because of all the deleterious consequences that the pain stimulus causes on the hormonal, cardiovascular and immune systems, compromising even more the homeostasis of organic functions.[56] Mild pain should be treated with simple analgesics (dipyrone, acetaminophen). The use of nonhormonal anti-inflammatory drugs should be reserved for patients at low risk for gastrointestinal bleeding. Moderate pain is treated with a combination of analgesics (acetaminophen) and codeine, or even with morphine and its derivatives. The drug of choice for the treatment of intense pain is morphine and its derivatives, which can be used as continuous infusion. Despite the restrictions on its use in children younger than six years, propofol has been used at several centers for analgesia of procedural pain (lumbar puncture). Analgesia should be efficient and the risk of cardiovascular and respiratory depression should not prevent the use of proper doses for pain relief. Patients should be continually monitored, and respiratory support and vasoactive drugs should be introduced if necessary.

Conclusion

Intensive care support in children with cancer is essential for their recovery. Even when the prognosis is defined the treatments can be used for pain relief and improvement of the quality of life. The interaction between the intensive care team and oncologists, with improved knowledge of pathophysiological events related to the disease and treatment, has allowed for the solution of extremely life-threatening situations. Above all, intensive care in children with cancer has been a key step for the improvement of survival of children, with an increasing number of reports on the cure of neoplastic diseases.

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Corresponding author:
Roberto Sapolnik
Rua do Barro Vermelho, 299/402
CEP 41940-310 – Salvador, BA, Brazil
E-mail: sapolnik@uol.com.br