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Febrile Neutropenia in Pediatrics with Cancer: Review Article

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ABSTRACT

Background: It is known as febrile neutropenia (FN) if a patient suffering from neutropenia also exhibits fever. This is the most common life-threatening complication of cancer treatment and is considered an emergency by oncologists. The condition of neutropenia is caused by damage to the bone marrow caused by cancer, chemotherapy, or radiotherapy. Infections caused by bacteria, fungi, and viruses result from the damage caused by chemotherapy and radiation to the host's barriers.

Objective: Review of literature about febrile neutropenia in pediatrics with cancer

Methods: We searched PubMed, Google Scholar, and Science Direct for relevant articles on Febrile neutropenia and Cancer. Only the most recent or thorough study was taken into account between June 2010 and July 2022. Documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research.

Conclusion: When planning treatment, it is important to take into account the patient's past medical history, including any illnesses, chemotherapy, medications, infections (particularly those caused by antibiotic-resistant bacteria), and allergic reactions. It may be necessary to evaluate any pain or discomfort as possible symptoms of infection. Age, co-morbidities, cancer type, and the use of myelosuppressive chemotherapeutic drugs are all major contributors to the emergence of febrile neutropenia.

Keywords: Febrile neutropenia, Pediatrics with cancer.

INTRODUCTION

No one, universally accepted definition of febrile neutropenia exists at this time. A person is considered to have febrile neutropenia if they have a temperature of 38.3 degrees Celsius or higher, or if they have two separate readings of 38 degrees Celsius or higher that are at least an hour apart, and their absolute neutrophil count (ANC) is below 500 cells/mm^3 or is expected to drop below 500 cells/mm^3 within the next 48 hours [(1)].

The susceptibility to the illnesses increases as the neutrophil count falls below 1000/µl, and patients with a neutrophil level of 500/C are regarded to be at an increased risk for bacterial and fungal infections. The risk of life-threatening infection is proportional to the length and severity of neutropenia. Risk increases from about 15% for neutrophil levels between 1000 and 500/µl to 20-35% for numbers between 100 and 500/µl to as high as 50% for counts below 100/µl [(2)].

Epidemiology

When it comes to paediatric oncology, FN is one of the most lethal infection complications that can arise from cytotoxic chemotherapy. During their neutropenic phase, around a third of children who were treated for cancer or who received hematopoietic stem cell transplantation (HSCT) developed FN. Fever problems occur at a different rate and occur less frequently at higher intensities of care. Primary febrile episodes during neutropenic periods were more common after autologous HSCT (58%), intensive treatment for acute leukaemia (AL) or non-Hodgkin lymphoma (NHL), and allogeneic HSCT (44%), but they were less common during maintenance chemotherapy for AL (9%) [(3)].

Infections in the bloodstream are the leading cause of FN (BSIs). Neutropenia is related with bloodstream infections (BSIs) in 84% of AL patients, compared to 47% of solid tumor patients and 55% of bone marrow transplant recipients, according to a major national survey [(4)]. Other disorders, such as viral or fungal infections, medication or transfusion responses, or mucositis, may also cause fever as a symptom [(5)].

Pathophysiology:

Although cytotoxic medication is the most prevalent cause of neutropenia, a cancer's direct involvement with hematopoiesis (as in leukaemia) or the bone marrow's metastatic replacement of healthy tissue can also cause a considerable decrease in ANC. A pathological infection, caused by pathogenic microorganisms in 33% of instances, is generally present when neutropenia is accompanied by a rise in body temperature. The severity and duration of FN both increase the likelihood of complications. Increases in alkaline phosphatase, bilirubin, or aspartate aminotransferase levels, a low glomerular filtration rate, cardiovascular comorbidities, and the rate at which the ANC is declining are all risk factors [(6)].

Risk factors of infection in hematological malignancies patients:

Patients with haematological malignancies have a high risk of infection due to a number of factors. There is a complicated interplay between the pathogen and its virulence and the degree of impairment of the host's defensive mechanisms that determines the risk of development and the severity of infections [(7)].

A) Disease-associated Factors: As a result of aberrant maturation and dysregulated proliferative immature

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cells, neutropenia and reduced granulocyte function are hallmarks of acute leukemia [8].

It is generally known that a reduction in the number of immune cells circulating in the bloodstream increases an organism's vulnerability to invasive infections. In addition, immature myeloid cells can stifle an immune response to an antigen by a T cell**.** Most patients will have an immunoglobulin deficiency because the disease and its treatment compromise the humoral immune system. The immunoglobulins most commonly impacted are IgG and IgM, and patients who have achieved complete remission may still exhibit humoral deficiency immunity [7]**.**

B) Patient-related Factors:

I. **Age and presence of underlying comorbid conditions:** Infectious problems after therapy for acute leukaemia are more likely to occur in older patients [9]**.**

II. **The natural function of the immune system:** Age-related decreases in B-cell and T-cell function are inevitable**.** In individuals with acute leukaemia, death is frequently the result of infectious complications. Older patients and those with other medical conditions are at a higher risk for being admitted to the intensive care unit (ICU) [9]**.**

III. **Nutritional state and weight loss:** Recent years have also seen an uptick in nutrition research, with undernourishment being recognized as a key risk factor for life-threatening viral diseases [10]**.**
Leukemia therapy frequently causes nutritional issues due to common side effects such as nausea and vomiting. Consequently, poor nutritional intake raises the risk of serious infections, and decreased food intake and weight loss are common treatment-related side effects [7]**.**

IV. **Splenic function:** The bacterial pathogens Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitides are the most common causes of fulminant sepsis in asplenic and splenomegaly patients [11]**.**
Overwhelming post-splenectomy infection (OPSI) appears to be less common following a splenectomy for trauma as opposed to one for hematologic illness. Patients who have undergone splenectomy to treat hypersplenism caused by hematologic illnesses are immunocompromised, putting them at high risk for developing a life-threatening infection [12]**.**

V. **Patient's response to chemotherapy:** The likelihood of a patient developing neutropenic problems after chemotherapy depends on their initial hematologic response to the treatment. This has the benefit of being a functional evaluation of how the patient's bone marrow has responded to treatment. Early treatment cycles can identify high-risk patients, allowing for subsequent dose adjustments or prophylactic growth factors to reduce risk [13]**.**

C) Treatment-related factors:

I. **Mucositis:** The mucosal barrier is the body's initial line of defense against invaders. Mucosal barrier damage is a side effect of cytotoxic therapy and radiotherapy [7]**.** Inhabitant bacteria may acquire bloodstream infections as a result of the barrier breakdown [14]**.**

II. **Chemotherapy-induced neutropenia:** The hematopoietic system is downregulated by cytotoxic chemotherapy, which compromises host defenses and lowers the maximum tolerated dose. Chemotherapy for cancer often causes a severe side effect known as neutropenia. The disturbance of the immune defense mechanisms caused by the loss of neutrophils increases the incidence of infections. Febrile neutropenia is a state of fever caused by an infection [15]**.**

III. **Hematopoietic stem cell transplantation:** The conditioning regimen used to prepare the patient for HSPC infusion is essential to HSCT since it helps eliminate the patient's disease and prevents rejection of the transplanted graft. Both myeloablative and non-myeloablative conditioning methods exist, with the former involving the destruction (ablation) of the recipient's BM by the administration of heavy doses of chemotherapy and/or whole-body irradiation [16]**.**
In Another factor that raises HSCT recipients' susceptibility to serious infection problems is their exposure to many antibiotics for either therapeutic or preventative purposes, which disrupts the gut microbiota makeup [17]**.**

IV. **Immunomodulatory agents and infectious risk**:

a. **Corticosteroids:** Corticosteroid patients are more susceptible to bacterial and fungal infections because their phagocytic function and cell-mediated immunity are compromised [18]**.**
In cancer chemotherapy, several corticosteroids serve as antiemetic, anticancer, and complication medicines. Corticosteroids have an anti-inflammatory action, which causes a reduction in body temperature. The anti-inflammatory effects of corticosteroids are mentioned in the NCCN guidelines, which may reduce fever responses and local indications of infection [19]**.**

b. **Monoclonal antibodies:** Even healthy cells that express the target of a monoclonal antibody will be eliminated from the body. Humoral immunosuppression and B-cell depletion are two side effects of rituximab treatment. Depending on the host, this may increase susceptibility to specific illnesses [20]**.**
Reactivation of hepatitis B virus has been linked to Rituximab treatment, especially when combined with cyclophosphamide, Doxorubicin, Vincristine, and Prednisone [21]**.**

c. **Alemtuzumab:** The anti-CD52 monoclonal antibody alemtuzumab has been shown to be effective in treating CLL and multiple sclerosis. Serious immunological abnormalities (including B, T, and natural killer [NK] cells) are produced, and these flaws can last for as long as 9 months after treatment has stopped. Higher rates of hepatitis B and C virus reactivation as well as opportunistic infections have been linked to drug use (PJP, CMV disease, mycobacterial infections, herpesvirus infections)**.**

d. **Venetoclax:** Tumor cells overexpress BCL-2, an antiapoptotic protein, making this a highly specific and effective oral inhibitor of that protein. AML and CLL patients with unfavourable cytogenetics are candidates for treatment with this drug, either as a monotherapy or in combination with anti-CD20 monoclonal antibodies [(21)]**.**

Venetoclax causes cytopenia, which contributes to its immunosuppressive impact. Forty to fifty percent of patients in the most important trials experienced neutropenia, and fifteen percent of those with grade 3 or 4 neutropenia developed a life-threatening infection. Seventy-two percent of 350 CLL patients in a safety study of three early-stage studies experienced infections of any grade, the most common of which were respiratory infections and fever with neutropenia [(22)].

PI3K inhibitors: Many lymphoproliferative disorders have an overexpression of the PI3K signaling pathway, which is inhibited by PI3K inhibitors such idelalisib, rigosertib, and duvelisib when taken orally [(21)]**.** Colitis, hepatitis, and pneumonitis are all examples of immune-related adverse effects that might increase the risk of infection if not treated with high-dose glucocorticoids [(23)]**.** Up to 3.5% of unprotected patients have been found to develop PJP. 2.4% of patients experienced cytomegalovirus (CMV) reactivation during the first 6 months of treatment in pivotal studies, and this number increased further when idelalisib was used in conjunction with bendamustine (6.3%) [(21)]**.**

e. **Tumor necrosis factor (TNF)-α inhibitors:** The cytokine tumour necrosis factor alpha is essential for the proper functioning of macrophages, phagosomes, and the development and upkeep of granulomas. The risk of infection, especially granulomatous illnesses like tuberculosis and histoplasmosis, is raised by blocking TNF alpha [(24)]**.**

f. **Purine analogues:** Due of the potential for medullar suppression from azathioprine and 6-mercaptopurine, regular blood counts are required for individuals on these medications [(25)]**.**

V. Radiation therapy:

Radiation causes harm to stem cells, which becomes apparent when tissues die off as a result of normal cell turnover but are not adequately replaced by stem cells. This causes the protective barrier to be compromised, most often at the skin, oral mucosa, and gastrointestinal (GI) levels [(26)]**.** Prolonged marrow depression and neutropenia are possible side effects of total body irradiation, and the suppression of cellular immune function that ensues can last for months or even years [(27)]**.**

Spectrum of pathogens causing infection in neutropenic patients:

Patients who are neutropenic are susceptible to many different kinds of infections.

Bacterial pathogens:

The aetiology of microbially-related FN events has shifted during the past few decades. Gram-negative bacteria (GNB), especially Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa, were the leading causes of bacteremia in febrile neutropenia in the 1960s and 1970s. In the 1980s, the use of central line catheters, the development of fluoroquinolone prophylaxis, and the use of intense chemotherapy led to an increase in bacteremia caused by Gram-positive cocci, resulting in severe mucositis [(28)]**.**

Microbiologically confirmed infections in neutropenic individuals are most commonly caused by Gram-positive cocci, according to several global epidemiologic surveys conducted on both adult and paediatric patients [(28)]**.**

The proportion of infections caused by Gram-positive organisms has been reported to be as high as 75–80 % at some cancer treatment centers. Most cases of bacteremia are brought on by Gram-positive bacteria that live on the skin normally. Gram-negative organisms predominate in infections of the lung, intestine, and urinary system. The apparent predominance of Gram-positive organisms diminishes when all sites of infection and mono microbial as well as poly microbial infections are evaluated, with Gram-negative species being equally as numerous [(29)]**.**

Some hospitals have also seen an increase in the number of Gram-negative bacteria found in patients with bacteremia. The widespread adoption of fluoroquinolone prophylaxis, which led to the growth of drug-resistant Gram-negative bacteria, appears to be the fundamental cause of this trend's reversal. Although anaerobic coverage is standard practice, especially for infections of the intestine, it is unknown why anaerobes are not routinely isolated from neutropenic patients [(30)]**.**

Clinical patterns of infection in neutropenic fever:

While fever is the most common and sometimes sole symptom of infection in neutropenic patients, approximately 20-25% of febrile episodes in this

population are really traced to a single etiologic agent [29].

About 45-50% of patients are classified as having "episodes of unexplained fever," meaning that there is neither clinical indication of infection nor positive microbiological verification of infection. Twenty-five to twenty-five percent of patients had obvious sites of infection (such as pneumonia, enterocolitis, or cellulitis) but negative cultures. Twenty-five to twenty-seven percent of patients with neutropenic fever have infections that can be confirmed by microbiology [29].

Patients with neutropenia typically get infections in the following places: The most common types of infection are those of the respiratory system, followed by bacteremia (including CLABSI, or central line associated bloodstream infection), the urinary system, the skin and its structures, and the gastrointestinal system. The central nervous system, bones, joints, and end organs including the liver and spleen are among the less common but clinically significant locations [29].

1. Respiratory tract infections: Sinusitis, coryza, and rhinorrhea are examples of upper respiratory symptoms that typically precede the involvement of the lower respiratory tract but can also be absent. Upper respiratory tract infection, renal parenchymal disease, hemorrhagic cystitis, hepatitis, small and large bowel disease, and encephalitis are all possible manifestations of adenovirus in immunocompromised patients, from asymptomatic peeling to fatal multisystem disease with pneumonia and hepatitis**.** There may be no outward manifestations of pneumonia or pulmonary infiltrates on chest radiographs of a severely neutropenic patient with a pulmonary infection. Patients with pneumonia are more likely to be colonised by or infected with microorganisms resistant to multiple antimicrobials [31].

2. Bacteremia: In the neutropenic patient, bacteremia and pneumonia are the most often observed microbiologically documented illnesses. About a third of febrile neutropenic patients are recorded to have bacteremia, a common and potentially life-threatening consequence in patients with haematological diseases and therapy-induced neutropenia**.** Multi-organ failure from a systemic infection was the major cause of death in patients with fever and neutropenia. Patients with SIRS (including two or more of the following criteria: temperature of 38 degrees Celsius or lower, heart rate 90 beats per minute or higher, respiratory rate 20 breaths per minute or lower, partial pressure of carbon dioxide 32 mm Hg or higher) and clinical suspicion of infection were diagnosed with sepsis [32].

3. Central venous catheter infection: Infection risk varies according to the type of device, how long it remains in place, and how severely the patient's immune system has been compromised. Infection is most likely to occur with a non-tunneled catheter, followed by a PICC, a tunneled catheter, and an implanted port. Infection is a concern while using multilumen catheters. Local indications of infection including erythema and discomfort are inconsistent and, even if present, may not be reliable indicators of catheter infection even in impaired patients, making clinical diagnosis challenging [33].

4. Skin Lesions and Soft Tissue Infection: Immunocompromised people frequently get skin infections. Patients with neutropenia are more likely to contract infections caused by fungi, bacteria, and viruses. Primary cutaneous infections and cutaneous symptoms of a disseminated illness are the two most common types of skin infections [34].

i. Ecthyma gangrenosum (EG):

A painful blackish grey necrotic region (eschar) is surrounded by an erythematous halo, which develops from an initial area of erythema and edoema that progresses to hemorrhagic bullae that burst. In the span of 12-24 hours, its diameter can expand to several centimeters. The necrosis could reach the muscle layer. Ecthyma gangrenosum most frequently occurs in the gluteal region, perineal region, axillary region, and extremities. Pseudomonas aeruginosa is the offending microbe in this case. Patients with neutropenia often present with a widespread soft tissue infection that spreads throughout the fascia and muscle. Bacteremia caused by Clostridium septicum [34].

ii. Spontaneous myonecrosis (gas gangrene):

Clinically, it manifests as a sudden, unbearable pain in the affected area, most often the leg but also the abdomen. The swelling worsens rapidly, is accompanied by a purple or bronze colouring, and is accompanied by the rapid development of blisters (which are typically hemorrhagic) [34].

iii. Spreading cellulitis:

Patients with neutropenia often develop a life-threatening infection called clostridial septicemia. The skin discolours somewhat purple, most frequently on the flank or abdominal wall. After a few hours, the lesion will have significantly grown, and more lesions will have appeared in other regions. The lesions darken to brown or black, develop blisters, and crepitate as the condition worsens [34].

5. Abdominal infection: Patients with impaired immune systems are more likely to develop neutropenic colitis, a potentially fatal illness. Neutropenic enterocolitis (NE) is a disease that was first identified in children with leukaemia. Intestinal mucosal damage, neutropenia, and a compromised immune system appear to be the primary causes of illness development. Patients with neutrophil counts of less than 500 µl are more likely to develop NE**.** Abdominal pain, diarrhoea, and fever are the hallmarks of NE. Common side effects include sickness, diarrhoea, and bloating. Pain in the abdomen can be either limited to the lower right quadrant or widespread. Palpation reveals tender areas. One patient with NE who presented with ascites and abdominal distension was diagnosed with abdominal compartment syndrome. Melena and hematochezia are

uncommon presentational forms. Necrosis and intestinal perforation may be suspected when peritoneal symptoms, shock, and fast clinical deterioration are present [(35)].

CONCLUSION

When planning treatment, it is important to take into account the patient's past medical history, including any illnesses, chemotherapy, medications, infections (particularly those caused by antibiotic-resistant bacteria), and allergic reactions. It may be necessary to evaluate any pain or discomfort as possible symptoms of infection. Age, co-morbidities, cancer type, and the use of myelosuppressive chemotherapeutic drugs are all major contributors to the emergence of febrile neutropenia.

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