

## Editorial

# Infection in Neutropenic Patients.

Fever in a neutropenic patient should be considered a medical emergency. Prior to the era of empiric antibiotic therapy infection accounted for almost 75 percent of the mortality related to chemotherapy. With the availability of broad-spectrum antibiotics, more aggressive chemotherapeutic regimens have been used. Although initially designed for patients undergoing chemotherapy for leukemia or lymphoma, empiric antibiotics are now initiated in all febrile patients with chemotherapy or drug-induced neutropenia. Beside the primary disease which may be associated with neutropenia, the treatment is often complicated by damage to the integument of the mouth and gastrointestinal tract, which predisposes them to episodes of infection. Despite advancement in diagnosis, better understanding of the aetiopathogenesis and introduction of new antimicrobial agents, infection continues to be a major problem in neutropenic patients.

Fever in a neutropenic patient is usually defined as a single temperature of  $> 38\text{C}$  ( $101\text{F}$ ), of a sustained temperature  $> 38\text{C}$  ( $100.4$ ) for more than one hour. However, on occasion a neutropenic patient may not present with fever despite the presence of infection. This can occur more commonly in elderly patients or those receiving corticosteroids. Neutropenic patients may present with hypothermia, hypotension, or clinical deterioration as the initial signs of occult infection. Consequently, there should be a low threshold for starting empiric antibiotic, especially if there are signs of clinical deterioration, even in the absence of fever. The definition of neutropenia varies from institution to institution but is usually defined as an absolute neutrophil count (ANC)  $< 500$  cells/microL or  $< 1000$  cells/microL with a predicted nadir of 500 cells/microL mechanism. Factors that are responsible for compromised host defense system could be due to the underlying disease (e.g. myelodysplastic syndrome, aplastic anemia, leukemia), the therapy of the hematological malignancy or a breach in the normal physical barrier (mucositis, indwelling/intravenous catheters). Absolute neutropenia remains the single most important factor for infection; other risk factors for occult infection have been identified as: (a) rapid decline in ANC; (b) prolonged duration of neutropenia ( $> 7$  to 10 days); (c) cancer not in remission; (d) comorbid illnesses requiring hospitalization; (e) use of peripheral lines and central venous catheters; (f) use of monoclonal antibodies against cellular receptors.

The risk of infection correlates closely with the degree and duration of neutropenia; it is highest when neutropenia is prolonged (more than 7 to 10 days) and profound (ANC of less than 100/cumm) and when ANC falls sharply as the result of antecedent chemotherapy. Bodey et al in 1966 demonstrated for the first time that the risk of infection was 14% if the ANC fell to less than 500/cumm but rose to 24% to 60% if the ANC fell less than 100/cumm. The risk of infection is almost 100% with prolonged neutropenia of greater than 5 weeks.

Contributory factors to the pathogenesis of neutropenia include *direct effects* of chemotherapy on mucosal barriers and immune deficiency related to the underlying malignancy. *Chemotherapy-induced mucositis* occurs throughout the alimentary system, and seeding of the bloodstream from endogenous flora in the GI tract is believed to explain a majority of febrile neutropenic episodes. *Obstruction* of the lymphatic, biliary tract, bronchial, gastrointestinal or urinary tracts by tumors or as a result of surgical procedures is also a common cause of infection. Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy also place patients at higher risk for infections. In one study, patients who developed severe infection or died, had a significant in phagocytic activity of neutrophils compared to those with only a mild infection, suggesting that neutrophils might be preactivated and have reduced function prior to the initiation of chemotherapy. Furthermore, the administration of chemotherapy not only decreases the number of neutrophils,

but also results in chemotactic and phagocytic defects as well. More than 80% of infections in immunocompromised episodes are acquired from colonizing microbial flora and approximately 50% of these are hospital acquired. The composition of the resident flora varies between institutions as a result of different pattern of microbial distribution and antibiotic usage. The microbes causing neutropenic fevers have changed constantly over the past few decades. Gram-negative bacilli, particularly *P. aeruginosa* were the most commonly identified pathogens until the 1980s. In a survey of 49 hospitals in the United States in 1995 and 2000, gram-positive organisms accounted for 62 and 76 percent respectively of all bloodstream infection. A number of factors may account for the trend toward gram-positive infection, including the introduction of long-term indwelling lines (Hickman-Broviac, Portacaths, etc) the empiric antibiotic regimens that were designed to cover *p. aeruginosa*, the use of prophylactic antimicrobials that are primarily active against gram-negative pathogens (eg, fluoroquinolones), and never chemotherapeutic regimens.

Bacteremia is shown to be the most common microbiologically documented infections followed by pneumonia in the immunocompromised hosts. Fungal infections are also increasing being recognized. Abdominal infections are important causes of morbidity and mortality in neutropenic episodes. These are life-threatening complications in such episodes. Neutropenic enterocolitis (NEC) also referred to as typhilitis in the early 1970s is the most common clinical entity amongst these, whereas splenic or hepatic candidiasis cholecystitis, hepatitis and others are less commonly seen. NEC is associated with a very high mortality of up to 50%

Management of patients with febrile neutropenic fever is complex and involves careful consideration of multiple factors. At least one half of neutropenic patients who become febrile have a documented or occult infection. The microbiology of infection has shifted, with more gram positive infection, increasing drug resistance, and previously less common organisms being seen more frequently. Risk assessment is needed to determine whether inpatient or outpatient treatment is indicated and whether intravenous or oral antibiotics can be used. Empiric immunotherapy with a third or fourth generation cephalosporin or carbapenam is as effective as combination therapy and vancomycin can be used when certain criteria are met. Fungal infection should be considered during episodes of prolonged febrile neutropenia despite broad-spectrum antibiotics. Newer antifungal agents are now available, which are effective and less toxic than Amphotericin. Antibiotic prophylaxis for afebrile neutropenic patients and use of colony-stimulating factors during episodes of febrile neutropenia are not recommended routinely, because of lack of data demonstrating consistent reduction in mortality.

Many of the concepts of managing febrile neutropenia patients remain unchanged, but recent problems faced by clinicians, such as increased drug resistance and shifts in pathogens, provide new challenges, and further research and drug development are needed to ensure adequate treatment.

## RECOMMENDED READING

1. **Kannagara S.** Management of febrile neutropenia. *commun oncol* 2006;3:585-591.
2. **Viscoli C, Castagnola E.** Treatment of febrile neutropenia: what is new? *Current Opinion Infect Dis* 2002; 15:377-3382.
3. **Wisplinghoff H, Wenzel RP, Edmond MB.** Current trends in the epidemiology of nosocomial blood stream infection in patients with haematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis* 2003; 36:1103-1110.

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