

## **What are febrile neutropenia and neutropenic sepsis? – by Bethany Maynard**

Febrile neutropenia and neutropenic sepsis are concepts everyone working in emergency and oncology settings are familiar with: patients presenting with either an isolated temperature  $>38.3$  or a sustained temperature of  $38.0$  for 1 hour or more, in the context of an absolute neutrophil count (ANC)  $<0.5 \times 10^9/L$ .

Often, the difficulty can be in detecting it, particularly in clinical areas less accustomed to the signs and nuances of febrile neutropenia. With a more-or-less complete eradication of their immune system, patients don't always present with classical signs of infection: productive cough, urinary symptoms, pain, erythema... How do you know the patient post-chemotherapy who happens to be feeling fatigued is actually presenting with febrile neutropenia? How do you identify the source of infection?

In contrast to this, is the patient who presents with neutropenic sepsis. Sepsis is defined as the immune system's overreaction to infection resulting in it damaging the body's own organs and tissues. Even from the 'end of bed' review it is glaringly obvious the patient is significantly unwell: ashen, hypotensive, tachycardic, raised respiratory rate and increased respiratory effort, reduced urine output; these are a few of the symptoms which may demonstrate a patient in need of intensive treatment and support. It is crucial these patients receive close monitoring and intensive treatment with IV fluids, IV antibiotics, steroids and potentially intensive care input for organ support. Sepsis can rapidly develop into severe sepsis to septic shock and is a life-threatening emergency.

### **Causes of Neutropenia**

Neutropenia is caused by decreased neutrophil production or increased neutrophil destruction. Chemotherapy is one of the most common causes of increased neutrophil destruction through the body's inability to differentiate between cancer and healthy cells.

Destruction of neutrophils can also be caused by autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis, as well as active infection – sepsis, hepatitis, tuberculosis. Decreased neutrophil production is generally caused by bone marrow dysfunction and is driven by aplastic anaemia or myelofibrosis. It can also occur prior to starting chemotherapy or at progression of disease if there is significant bone marrow involvement from the cancer. While in general, patients presenting to emergency areas will be because of fever following chemotherapy, a lack of recent systemic anti-cancer treatment cannot be assumed to be risk free.

Neutropenia can be classified as mild, moderate or severe based on the ANC;  $1-1.5 \times 10^9/L$ ,  $0.5-1 \times 10^9/L$ ,  $<0.5 \times 10^9/L$  respectively. The severity of neutropenia can impact the management of patients. For example, through the use of IV or oral antibiotics or the use of growth factors such as G-CSF to promote bone marrow production of neutrophils.

### **Identification of Neutropenic Infection**

The key element is the fact that the patient presented with a fever. Even if they are afebrile on arrival at hospital, an episode of pyrexia in the context of cancer demands the neutropenic sepsis pathway. As a result of immunosuppression, patients are unable to activate the normal inflammatory processes resulting from infection, so a cause of temperature is not always apparent. By completing the septic screen– chest x-ray, blood cultures (and FBC, CRP, U+E), urine culture, sputum culture, ECG – you are increasing the

chances of identifying a source of infection. However, in a large number of cases, a cause is not found.

### **Treatment of Infection in Neutropenic Patients**

Every person who works in an oncology or the emergency environment should be aware that the most important and crucial element of treatment of febrile neutropenia is IV antibiotics within 1 hour of presentation. Septic screen and antibiotics. With every hour that the administration of antibiotics is delayed the patient's risk of mortality increases by 7%. As a causative organism is found in only approximately a third of neutropenic infections broad-spectrum antibiotics are the gold standard, with an aim of treating the wide range of likely pathogens. Although infection with Gram-positive bacteria is more common, Gram-negative infections are associated with increased morbidity and mortality. Therefore, anti-pseudomonal beta-lactams are the antibiotic group of choice. In the UK, this means Piperacillin-Tazobactam or Ceftazidime for penicillin-allergic patients.

For the more unwell patients, those demonstrating signs of acute illness, multi-antibiotic treatment, for example including Gentamicin, is often required, as well as IV fluids for initial blood pressure support.

For those patients whose fever persists for >4-7 days, the use of antifungal medications and investigations for a fungal source of infection should be considered.

There is a smaller group of patients, those who present with a fever but are otherwise stable, who could be considered for outpatient treatment with oral antibiotics. The American Society of Clinical Oncology (ASCO) recommends the use of the Multinational Association for Supportive Care in Cancer (MASCC) risk assessment tool to identify patients who would be at low risk of complications from febrile neutropenia. This includes assessing co-morbidities, disease burden and age, among other factors to ascertain their likelihood of deterioration. Those who score 21 or higher are deemed to be low risk and would be suitable for outpatient treatment, whereas a score of 20 or lower is indicative of high-risk for morbidity and mortality.

Despite being a recommended course of treatment for low-risk patients, it is very rare that patients are treated in the community. Whether this is due to the potential risk, lack of infrastructure or patient reluctance, certainly in the UK it is a little-used treatment pathway.

### **Overview**

Febrile neutropenia is a common, potentially life threatening complication of chemotherapy. It requires prompt investigation and treatment to minimise the patient's risk of morbidity and mortality. Every patient who presents with a fever should be treated as if they have febrile neutropenia until it is confirmed or ruled out.