Trainee Section

The Febrile Patient with Neutropenia

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Abstract

Fever in a neutropenic patient is an acute medical emergency. This article considers the diagnosis, investigation and management of neutropenic sepsis, along with the clinical challenges that an acute physician may face when treating patients presenting with this condition.

Keywords

Fever, Neutropenia, Sepsis, Chemotherapy, Cancer.

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Introduction

Fever in a neutropenic patient needs to be considered an acute medical emergency. Neutropenic sepsis is a potentially fatal complication of cancer therapies, particularly chemotherapy. Neutropenic sepsis is defined as a temperature > 38°C and a neutrophil count <0.5 x 10^9/L. Fever during chemotherapy induced neutropenia may be the only indication of severe infection as other signs and symptoms may be suppressed.[1] Acute physicians need to be aware of the infection risks, diagnostic approaches and initial management strategies of patients presenting with fever who are at risk of neutropenia.

A National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report found shortcomings in the management of patients with neutropenic sepsis leading to avoidable deaths.[2] Algorithms for the management have been created and adapted as diagnostic and management techniques improve. The National Institute for Health and Clinical Evidence (NICE) has recently produced a guideline "Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients".[3]

Pathophysiology

There are a number of contributory factors leading to the development of neutropenic sepsis including the direct effects of the chemotherapy on mucosal barriers and the immunocompromise related to the underlying malignancy.[1] Chemotherapy-induced mucositis occurs throughout the gastro-intestinal system and seeding of the bloodstream from endogenous flora in the GI tract causes the majority of febrile neutropenic episodes.

An infectious source is only found in approximately 30% of patients with neutropenic sepsis.[4] The risk for certain types of infection is increased by the type of malignancy. For example, patients with functional asplenia are more at risk of developing sepsis from encapsulated organisms, such as Streptococcus Pneumoniae and Haemophilus Influenzae. Table 1 shows the pathogens commonly isolated in patients with neutropenic sepsis.

Fungal and viral pathogens are also common in this cohort of patients. Fungal infections are typically seen in patients with prolonged neutropenia.[5]

Typical Case History

A 64 year old lady with inoperable pancreatic carcinoma presented 4 days following her 1st cycle of chemotherapy (gemcitabine and capecitabine). She complains of 1 day history of rigors and diarrhoea. Initial observations find a fever of 39.1°C, a blood pressure of 80/40mmHg and a pulse rate of 110bpm.

What are the key components of the history and examination?

All patients with suspected neutropenic sepsis should have a thorough history and examination performed. A detailed history should include eliciting any symptoms suggestive for the focus of infection, recent exposures to infection, previous infections and confirmation of antimicrobial prophylaxis. Obtaining the patient's understanding of their diagnosis and prognosis is important.

A thorough examination is required especially as signs of inflammation can be extremely subtle or absent in neutropenic patients.[1,6] The skin and mucous membranes should be examined carefully for erythema, cellulitis, warmth, rashes and ulcers. Any tunnelled lines or recent line insertion sites should be thoroughly examined for signs of infection. Any tunnelled lines or intravenous catheters should be assessed for patency as any difficulty with withdrawing blood or infusion administration may

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Table 1. Pathogens commonly isolated in patients with neutropenic sepsis.[1]

Gram-Positive Bacteria
Coagulase-negative staphylococci
Staphylococcus Aureus – including MRSA
Enterococcus Species – including VRE (Vancomycin-resistant enterococcus)
Viridans group streptococci
Streptococcus pneumoniae
Streptococcus pyogenes
Gram-Negative Bacteria
Escherichia coli
Klebsiella species
Enterobacter species
Pseudomonas aeruginosa
Citrobacter species
Acinebacter species
Strenotrophomonas maltophila
Other bacteria
Clostridium difficile
Anaerobes
Mycobacteria
Fungi
Aspergillus
Candida species

indicate an infected clot even if the entrance site appears to have no abnormality.

What initial investigations should be performed?

All patients presenting with fever post chemotherapy should have a full blood count (FBC), urea and electrolytes (U&Es), liver function tests (including serum albumin), C-reactive protein (CRP) and lactate performed.

At least 2 sets of blood cultures should be performed from separate venepuncture sites.[1,7-8] If the patient has a tunnelled line or central venous line in situ, a set of blood cultures should be obtained from each lumen of the line and peripherally at the same time.

Culture specimens should be obtained from other sites as clinically indicated. Sputum cultures should be sent if the patient has a productive cough. Stool cultures should be sent and evaluated for Clostridium Difficile Toxin assay. Urine culture should be sent if the patient has symptoms of a urinary tract infection or a positive urinalysis. A chest x-ray is not recommended to be performed routinely and is limited to those with respiratory symptoms.[3]

Cerebro-spinal fluid (CSF) should be sent in those with symptoms suggestive of central nervous system infection. Many patients with malignancy and post-chemotherapy are either thrombocytopenic or coagulopathic. It is important to correct coagulopathy or transfuse platelets prior to performing lumbar puncture in this situation.

What are the key goals of initial treatment?

Suspected neutropenic sepsis is an acute medical emergency and empirical antibiotic therapy should be administered immediately.[1,3,6,9-11] The goal of empirical therapy is to cover the most likely pathogens that will cause life-threatening infections in neutropenic patients. Initial antibiotic selection should be guided by the patient's history, allergies and local antimicrobial policy.[10]

The NICE guidance suggests beta lactam monotherapy with piperacillin-tazobactam as the initial antimicrobial of choice unless there are local microbiological contraindications.[3] Aminoglycosides are not recommended for monotherapy or in dual therapy.[1,3,12] A meta-analysis comparing beta-lactam monotherapy against beta-lactam plus aminoglycoside found similar rates of survival but greater rates of morbidity and adverse events in the dual therapy group.[12]

In patients who have a history of immediate-type hypersensitivity reactions to penicillin beta-lactams and carbapenems should be avoided. Alternative empirical antibiotic choice includes fluoroquinolones but local antimicrobial guidelines should be consulted.

Vancomycin is not recommended as part of the standard initial empirical antimicrobial regimen.[1] However, it should be considered in patients with evidence of line infection, soft tissue infection or severe mucositis.[1]

Alongside the specific empirical antimicrobial therapy patients with neutropenic sepsis require the same early goal-directed therapy as those with non-neutropenic sepsis, ensuring adequate end-organ perfusion with oxygen therapy and aggressive fluid resuscitation.[13]

Impeccable hand hygiene, as the most effective method of preventing the transmission of hospital infections, standard barrier precautions and isolation in a side room are important to prevent neutropenic patients acquiring further infections.

Can I predict if my patient is high or low risk?

Categorising febrile neutropenic patients into high risk and low risk groups for the development of severe infection has become an important process in the management of this cohort of patients. This assessment aids in the decision making process with regards to route of antimicrobial therapy (oral versus intravenous), need for inpatient admission and duration of antimicrobial therapy.[1]

Factors used to discriminate between these groups include the presenting clinical condition, the type of underlying malignancy and pre-existing medical co-morbidities.[1,9] Patients are considered to be high-risk if they have significant neutropenia

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which is predicted to last more than 1 week. Patients should also be categorized as high risk if they have:-

- Haemodynamic instability
- Gastrointestinal disturbances, such as abdominal pain, diarrhoea or vomiting
- Acute neurological symptoms such as delirium
- Respiratory compromise either due to chronic lung disease or acute hypoxia
- Evidence of renal or hepatic insufficiency.

All patients with any of these features should be admitted for inpatient intravenous antimicrobial therapy. "Low-risk" patients with few co-morbidities and none of these features may be appropriate for outpatient treatment with oral antibiotics.[1,9,14] Figure 1 shows an algorithm for the management of patients presenting with fever and neutropenia.

The Multinational Association for Supportive Care in Cancer (MASCC) score (see Table 2) is a formal scoring system for assessing for identifying patients at low and high risk of severe infection and complications.[9] High risk patients have a score >21 require inpatient care where as those with a score of 21 or less may be appropriate for outpatient care.[9,14]

Case progression

The patient is admitted to hospital and treated with intravenous fluids and intravenous piperacillin-tazobactam 4.5g TDS. Her full blood count shows pancytopenia including neutropenia (White Cell Count = 0.9 x 10^9/L, Neutrophil count = 0.2 x 10^9/L, Haemoglobin=9.1g/dL and platelet count 90 x 10^9/L). 24 hours following admission she continues to spike fevers and have diarrhoea. Her haemodynamic parameters have improved with BP=110/50mmHg and Pulse = 90bpm. She does not yet have any positive microbiological cultures.

Table 2. Multinational Association for Supportive Care in Cancer Risk Score.

Characteristic	Score
Burden of illness (febrile neutropenia) No or mild symptoms Moderate symptoms Severe symptoms or moribund	 5 3 0
No hypotension (Systolic blood pressure >90mmHg	5
No chronic obstructive pulmonary disease	4
Solid tumour or haematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age <60 years	2

When should a change in antimicrobial regimen be considered?

Changes to the initial empirical antimicrobial treatment should be guided by the clinical picture and microbiological results.[1,3,6] Patients being treated

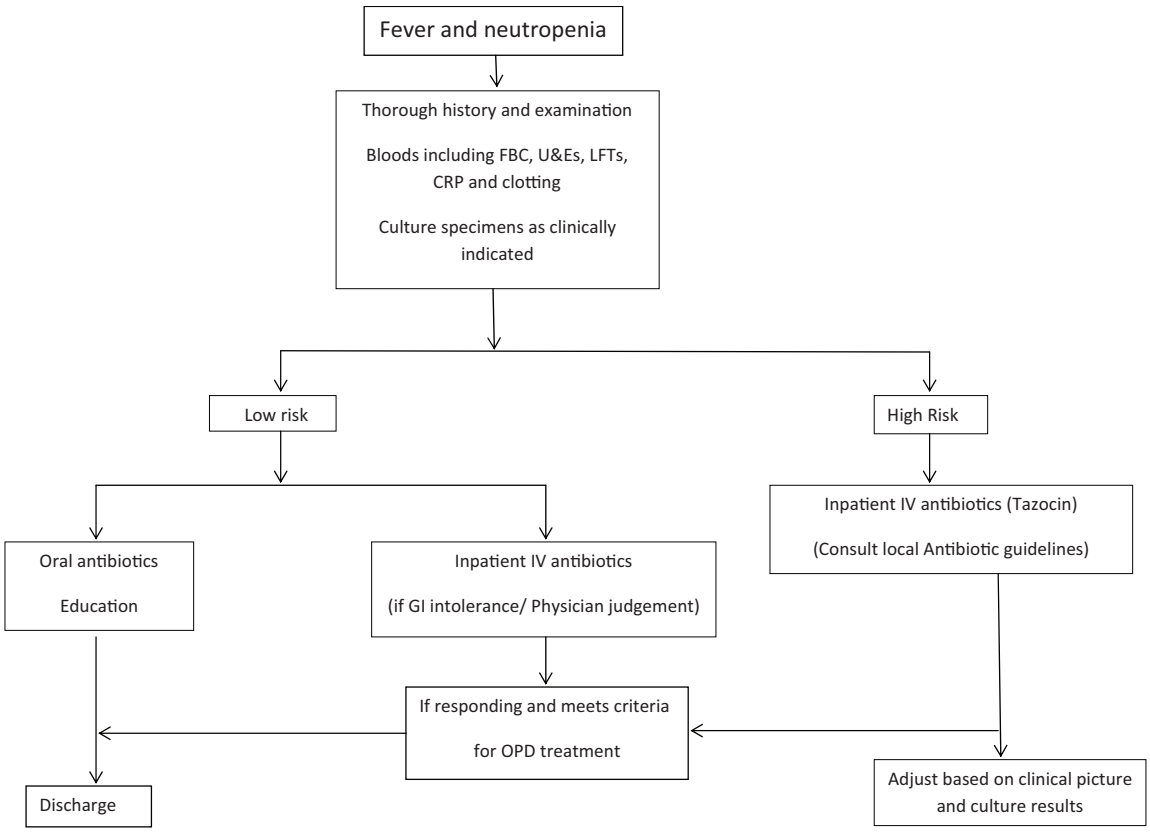

Figure 1. Algorithm for the management and treatment of patients presenting with fever and neutropenia.

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for neutropenic sepsis should be monitored closely and examined daily for signs of infection.

Patients with unexplained fever who are otherwise improving clinically should be maintained on their empirical antimicrobial therapy.[3] If the patient continues to have fevers after 3 days of treatment the patient's septic screen should be repeated with further blood cultures and imaging based on the patient's symptoms and clinical findings.

Addition of further antimicrobial agents may be indicated if there are clinical suspicions of specific organisms – for example oral metronidazole if the patient has abdominal pain and diarrhoea to cover Clostridium Difficile[15] or consideration of vancomycin in patients known to have Methicillin-Resistant Staphylococcus Aureus (MRSA).[16]

Haemodynamically unstable neutropenic patients with continued fevers without a clear focus of sepsis should have their antimicrobial regimen broadened to ensure coverage of drug-resistant gram-negative and gram-positive organisms and anaerobes.[1] Empirical anti-fungal cover should be considered after 4 days of treatment if the patient continues to spike fevers and no focus of infection has been identified.[17]

Should I prescribe G-CSF for the patient?

Granulocyte colony stimulating factors (G-CSF), such as filgrastim, are not currently recommended as adjuncts to therapy in patients with neutropenic sepsis.[1,18,19] Although, they have been shown to reduce the duration of neutropenia and fever they have not been associated with any improved mortality outcomes.[19]

When should I remove the patient's tunnelled line if it is the source of sepsis?

The NICE guidance states that central venous lines should not be removed as part of the initial empiric management of neutropenic sepsis.[3] Blood cultures should be taken from all lumens of tunnelled lines as part of the initial assessment.

Removal of the tunnelled line is recommended in most line infections with the exception of those caused by Coagulase Negative Staphylococci.[20] In patients with Staphylococcus Aureus, gram-negative bacilli and Candida-related line infections antimicrobial therapy is recommended for 2 weeks in addition to line removal.[20] Prolonged treatment for 4-6 weeks is recommended for patients who continue to spike fevers 72 hours after removal of the line or in those with evidence of deeper infection, such as endocarditis.[21]

Case progression

4 days after admission the patient feels much better and is keen to go home. Her diarrhoea has settled and she has been afebrile for 48 hours. She is haemodynamically stable. Her repeat full blood count shows WCC=3.4, Neutrophils = 1.6, Hb = 10.2 and Platelets = 140. No positive microbiology was identified.

How long should antimicrobial therapy be continued?

In patients with confirmed bacteraemia the duration of antimicrobial therapy should be tailored to the individual organism but typically require 10-14 days of treatment.[1] However, antibiotic therapy should be continued until the neutrophil count is >0.5 x 10^9/L.

If no source of infection is identified, the timing of discontinuing antibiotics is based on the clinical picture. If the patient is afebrile for 48 hours and their neutrophil count has recovered it is appropriate to stop antimicrobial therapy.[1]

Patients should be switched from intravenous therapy to oral treatment after 48 hours if their risk of developing further complications is low.[3] NICE recommends discharging patients having empirical antibiotics whose risk of developing septic complications is low based on the MASCC score.[3]

Are there any other considerations required before discharge?

NICE recommends that all patients undergoing anti-cancer treatment should have access to a 24 hour Specialist Oncology telephone helpline.[3] It is also important that patient's feel supported, know the signs and symptoms that should trigger them seeking medical assessment and where they should present in an emergency.

Prophylaxis with a quinolone should be offered to all patients with acute leukaemias, stem cell transplants or solid tumours whilst they are neutropenic.[1,3] Antifungal and antiviral prophylaxis is only recommended for high risk patients.

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