# Fifteen Minute Consultation: Fever in children being treated for cancer

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## Abstract

Fever is a common symptom in children receiving treatment for cancer. Clinicians and families are most concerned about febrile neutropenia, though non-neutropenic fever often causes more challenging treatment dilemmas. This article provides a structured approach to the initial assessment, examination, investigation and risk assessment of children with fever during treatment for childhood cancer. Non-neutropenic fever in children with cancer is not well researched. There are no systematic reviews of its management and no NICE (or other international) guidance about what to do. Features to consider when managing non-neutropenic fever are discussed. Febrile neutropenia, meanwhile, is an oncological emergency and requires management using standard sepsis principles including administration of broad spectrum antibiotics. Relevant NICE guidance provides a clear structure for treatment. Ongoing management depends upon the response to initial treatment.

## Introduction

Fever is a common symptom in children receiving treatment for cancer. Clinicians and families are most concerned about febrile neutropenia, although non-neutropenic fever often causes more challenging treatment dilemmas. It is particularly important to be able to separate these two conditions in your mind. Although the approach to the child is the same in both, the management may be somewhat different.

Febrile neutropenia describes the presence of fever in a child with a low neutrophil count. In children, febrile neutropenia is most commonly seen as a result of treatment for malignancy. Fever with unexpected neutropenia can also be found, and should prompt further investigation (see these articles by James and Kinsey, and Knight).[1,2] This article will not discuss the management of fever in children who have neutropenia of a cause other than anti-cancer treatment.

There are a number of factors, along with neutropenia, that are thought to increase the risk of infection for children with cancer. In particular, treatment can reduce mucosal barrier protection by causing mucositis or typhlitis (neutropenic colitis), thus increasing the risk of translocation of bacteria across the gut wall. The skin barrier is often breached by central venous lines or other medical devices. Frequent antibiotics mean the normal body flora is disrupted. Anti-cancer treatment can also affect other aspects of the immune system, including immune cellular function and gamma globulins.[3,4]

The commonest documented causative organisms in children with cancer can be grouped into Gram negative (such as *E coli*, coliforms and *Pseudomonas spp*.) and Gram positive organisms (such as Coagulase-negative staphylococci, *S. aureus*, viridans-group streptococci and enterococci).[5,6] Remember that viral and fungal infection can also cause or complicate febrile illnesses in this population so do consider these when reviewing your patient. [5,6]

In 2012, NICE produced guidance on the management of neutropenic sepsis, CG151.[7] Much of this article will follow this guidance and provide discussion around some of the key points. An example case is provided in Box 1.

Some guiding principles

Febrile neutropenia is the commonest complication of treatment for childhood cancer.[8] It occurs at a rate of 0.75 episodes per 30 days of neutropenia.[9] Around 3% of children with cancer will die of an infection during their treatment.[8,10] Febrile neutropenia can also be associated with complications such as hypotension and renal dysfunction, as well as delays in further treatment.[11,12] However, many episodes of febrile neutropenia have no significant complications, with up to 50% having no definable infection.[12,13]

Febrile neutropenia is defined within the NICE guideline as the presence of a temperature >38°C in a child with a neutrophil count of 0.5x109/L or lower **or** other symptoms or signs of sepsis.[7] There is some debate within the paediatric haematology and oncology community about this definition, and the quality of evidence for this recommendation is poor.[7] Essentially the task is to balance the risk of setting more stringent definitions, with a risk of children who have serious infections not being treated as such (a poor negative predictive value), against setting less stringent definitions, and therefore overtreating children who do not have a serious infection (poor positive predictive value).[7] The NICE definition seeks to reach this balance, based on the evidence available. Be sure to check what the definition for febrile neutropenia is in your centre, and follow local guidelines where they differ from NICE.

You may not know if a child is neutropenic at presentation, as they may not have had a full blood count performed recently, and because neutrophil counts can change rapidly. The nadir of neutrophils is usually seen at 7-10 days following a course of cytotoxic chemotherapy. In a child at risk, it is best to presume that they are neutropenic whilst awaiting the full blood count and therefore to perform investigations and administer antibiotics immediately. You may then choose not to continue the antibiotic course once the neutrophil count is available to you. For example, a child may be started on antibiotics overnight but with further information available the following morning, they are non-neutropenic and have a clear focus. In this setting, you may choose to switch to appropriate oral antibiotics and manage the child as an outpatient.

Given that children with cancer are at increased risk of life threatening infection, whether they are neutropenic or not, if the child is unwell consider the possibility of sepsis early and manage as febrile neutropenia, even if they do not have a fever.

Similarly, if the child is febrile and unwell, particularly if they have a central line, do not consider the absence of neutropenia reassuring but instead manage as any other child with suspected severe infection. Be aware that Central Line Associated Blood Stream Infections (CLABSIs) are also a risk in many patients under the care of paediatric haematology and oncology services and have a low threshold for investigation and management of this.

## Initial Assessment

All children who are receiving treatment for childhood cancer should receive education regarding the risks of infection, including febrile neutropenia, and the appropriate action to take should a child become febrile or unwell. If you are contacted by a family and informed that the child is febrile, they should be advised to come immediately to the hospital and should be assessed as soon as they arrive. Some children may be too unwell to come to hospital by their own transport – assess them for this and advise to call for an ambulance if necessary. Febrile neutropenia is an oncological emergency and these patients should be managed as such.[7]

The initial assessment of a child with cancer presenting with a fever involves an ABCD approach looking for life-threatening infection and managing this according to APLS principles.

If the child is haemodynamically stable, it is important to obtain a clinical history, including key points to help assess the child’s risk of septic complications, to identify any focus of infection and to evaluate the chance of infection with resistant organisms. Remember to ask about:

* What malignancy the child is being treated for, what chemotherapy or radiotherapy they have received recently and how long ago this was
* The symptoms they have had during this period of illness, particularly upper and lower respiratory tract symptoms, loose stools or urinary tract symptoms
* Any symptoms of fungal infection including haemoptysis, chest pain, sinus pain, dental pain, or skin lesions
* Whether the child has a central line, and if so, when this was last accessed
* If there have been any infectious contacts, particularly with chickenpox, measles or other viruses
* Any recent travel, including contact with healthcare services
* If this is not the child’s first episode of fever whilst on cancer treatment, ask about previous episodes, whether they were neutropenic, and what happened to the child, including any ICU admissions
* Identify any recent positive microbiological tests and antibiotic resistance patterns for any organisms identified
* Consider any recent antimicrobial exposure, including both prophylaxis and treatment courses

## Examination

Within the examination of children with cancer when they have a fever, it is important to look for signs of sepsis, as well as a focus for the infection. Children with neutropenia are less likely to develop abscesses or other signs of significant bacterial infection so it is essential to examine them carefully and to be aware that these features may develop later in the illness as the neutrophil count recovers and the child becomes able to produce pus. Abdominal signs in particular can be masked by neutropenia and therefore it is important to have a low threshold for the investigation and treatment of abdominal symptoms or signs.

Remember to explicitly examine the ears, nose and throat, the perianal area and the child’s central line exit site and tunnel. Document whether the child has any mucositis or any skin lesions. Bear in mind that common viral exanthems, such as chickenpox, can present in an atypical way in immunosuppressed children.

## Investigations

The key investigations to be performed at presentation with a fever are detailed in Box 2.[7] The majority of these are standard investigations for suspected sepsis in any child, though lactate is often forgotten.

Paired peripheral blood cultures are recommended for two distinct reasons. First in over 10% of bacteraemia in children with central lines, peripheral cultures are the only positive microbiological investigation.[7] Second, the information provided by the differential time to positivity can help to identify if an infection is related to the central line itself, and thus allow recognition of CLABSIs.[14] However, it should be noted that some families and clinicians feel that peripheral blood cultures should not be performed due to the distress that they can cause. Check and follow your centre’s guidelines for this.

Other investigations should be performed as necessary dependent on the examination and may include chest X-ray, urinalysis, fungal antigens (such as Beta-D-glucan or galactomannan aspergillus tests), bacterial swabs of the skin or line site, or viral swabs of respiratory secretions.

## Management of non-neutropenic fever

This is one of the most challenging aspects of caring for children with cancer when they get a fever. Febrile neutropenia is relatively well researched and has clear guidelines to follow. Non-neutropenic fever in children with cancer is not well researched. There are no systematic reviews of its management and no NICE (or other international) guidance about what to do. Most non-neutropenic fever is managed by expert opinion and thus close liaison with your local Principal Treatment Centre (PTC) is essential.

Generally there are a few key factors to consider:

* If the child is septic, they should be managed according to local sepsis protocols, usually using the antibiotics chosen for febrile neutropenia given that the organisms involved are similar.
* Consider whether the child has a central venous access device *in situ* and have a low threshold for managing them according to the local policy for treating CLABSI if you suspect this might be the case.
* If the child has had a bone marrow transplant (or other stem cell therapy) in the last 6 months, they should be considered functionally neutropenic and managed as febrile neutropenic regardless of their neutrophil count at presentation.
* As in all children with a fever, you should attempt to identify the focus. If you find a focus, and the child is not neutropenic or expected to become neutropenic, then the management of the child should be according to the source of the infection (eg. antibiotics for acute otitis media, or supportive care for the common cold). If the child has a flu-like illness, consider starting oseltamivir (or other anti-influenza agent). It may not be necessary for this child to stay in the hospital.
* If the child does not have a clear focus, then you should have a low threshold for further investigation and treatment of infection. Although the risk of significant bacterial infection is low, it is still likely to be higher than that of a child who is not receiving treatment for cancer, and therefore caution is advised.
* If you are not sure how to manage a child with cancer with non-neutropenic fever, the safest approach is to treat as febrile neutropenia whilst you await advice from the child’s PTC.

Again, as with all other children with fever, if you are discharging a child with cancer from the hospital, be sure to give a clear safety net, including the anticipated course of the illness, signs of worsening infection and triggers for returning to the hospital.

## Febrile neutropenia risk assessment

If a febrile child with cancer is confirmed to be neutropenic, risk stratification allows a targeted approach to care – including increased treatment for those at high risk of complications and particularly reducing treatment in those where the risk is low. There are many different risk stratification tools described in the literature, with the NICE guidelines suggesting use of the modified Alexander rule for children (see Box 3).[13,15] Check if a risk stratification tool is used in your local unit and consider how this is implemented for patients in your area.

Remember also to assess the risk of fungal infection according to local guidelines. The revised EORTC definitions of fungal infection, including defining proven, probable and possible infection can be helpful in considering the likelihood of fungal infection.[16]

## Management of febrile neutropenia

It is essential first to manage any signs of respiratory or cardiovascular instability, as in other children with sepsis. Be aware that children with neutropenic sepsis can deteriorate rapidly and therefore have a low threshold for escalation of care. APLS principles can generally be applied, unadjusted, in children with neutropenia.

The next most important step for the treatment of febrile neutropenia is the early administration of broad-spectrum antibiotics. The National Peer Review Programme Manual for Cancer Services recommends a one hour target for administration of antibiotics.[17]

A large network meta-analysis showed that single agent piperacillin-tazobactam was more effective in terms of reduced mortality compared to meropenem mono-therapy or piperacillin-tazobactam with an aminoglycoside.[7] Therefore, the antibiotic of choice in febrile neutropenia is piperacillin-tazobactam, unless there are patient-specific or local microbiological considerations (eg. penicillin allergy, previous infective organisms in this patient including consideration of acquired or intrinsic resistance, or high local resistance patterns).

In children with suspected CLABSI, it may be necessary to consider adding additional glycopeptide cover (eg vancomycin) according to local guidance, as well as to consider line removal in the unstable or deteriorating patient, or in the presence of certain organisms, following involvement of microbiology and/or infectious disease specialists.

Follow local guidance regarding anti-fungal therapy – this may be indicated early in very high risk individuals (eg after haematopoietic stem cell transplant), or those with signs of fungal disease (including haemoptysis, chest pain, sinus pain, dental pain or skin lesions). Our recent review of international guidelines has shown that these are varied in quality and recommendations – thus no single national or international guideline can be recommended.[18]

Remember to consider revising the child’s chemotherapy if this is count dependent. For example, children who are on the UKALL 2011 trial and receiving maintenance treatment should stop both methotrexate and mercaptopurine if their neutrophil count is <0.5 x109/L – that is, if they have febrile neutropenia. These medications can be recommenced once the neutrophil count has recovered.

Finally, consider whether the child needs to be isolated from other children to prevent transmission of infection to other patients, or from other patients. Isolation practices for neutropenic patients are often more stringent than for other children due to their increased risks of infection. Consider the air flow of the room (positive, neutral or negative pressure rooms) and the necessary personal protective equipment (PPE).

Whilst in hospital, children with febrile neutropenia should have at least daily clinical assessment and risk stratification performed.[7] Many children with febrile neutropenia will continue to spike temperatures for some time. There is no need to switch antibiotics if a patient’s fever fails to settle, unless they are clinically deteriorating or there is a microbiological indication for a change.[7] In children where the blood culture becomes positive for coagulase-negative staphylococci it is important to assess the risk of CLABSI and manage this as appropriate. Remember to also evaluate for non-bacterial infections, including fungi and viruses, as well as for non-infectious causes of fever, including relapsed disease.

Research has shown that it is safe to discontinue antibiotics and discharge patients if they are afebrile, with no other signs of infection, regardless of neutrophil count.[12,19,20] The only significant exceptions to this are those children with certain haematological malignancies, eg AML or infant ALL, who may have their antibiotics stopped but remain in hospital until resolution of neutropenia.

In the future it may be possible to reduce the duration of admission to hospital for children with low risk febrile neutropenia – watch out for future research studies and be sure to offer these to families of children eligible to participate.

## Key messages

* Children with a fever on cancer treatment are at risk of significant infection, including febrile neutropenia.
* Febrile neutropenia is defined as a temperature >38°C in a child with a neutrophil count of 0.5x109/L or lower **or** other symptoms or signs of sepsis.
* Febrile neutropenia is an oncological emergency and antibiotics should be started within one hour of presentation (just as in any child with suspected sepsis).
* Investigations should include FBC, U+Es, LFTs, CRP, lactate, and paired central and peripheral blood cultures
* The management of non-neutropenic fever in children with cancer is poorly researched and there are no national guidelines. Important factors to consider in this situation are discussed.

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**Box 2 – Key investigations at presentation**

* Full blood count
* U+Es
* Liver function tests
* CRP
* Lactate
* Paired central and peripheral blood cultures (in patients with central lines)
* Urinalysis in all children under 5 years old
* Chest X-ray (only if clinically indicated)

**Box 1 - Case**

James is a 4-year-old boy with rhabdomyosarcoma who is nine days into his fourth course of IVA (Ifosfamide, Vincristine, and Actinomycin D) chemotherapy. His mother telephones the ward to say his temperature is 38.5°C and asks what she should do. You ask further questions about his condition and confirm an ambulance is not required. You tell them to come straight to the hospital.

On arrival, you assess James. You find he is slightly tachycardic and still has a temperature but does not require immediate resuscitation. You take a history, which includes coryza for the past 48 hours and today being not quite himself. Otherwise, he has no other symptoms. When you examine James you find no abnormal signs other than his coryza and a slightly red throat.

Recognising that James is likely to be neutropenic, you perform the investigations listed in Box 2, as well as a viral swab for respiratory secretions, assess him as likely to have low risk febrile neutropenia (according to the modified Alexander rule) and immediately administer piperacillin/tazobactam. His full blood count later reveals a neutrophil count of 0.06x109/L. He remains in hospital, source isolated in a negative-pressure side room with respiratory PPE, and continues his antibiotics.

Over the next 48 hours his temperature settles. His central and peripheral blood cultures remain negative, but his secretions are positive for rhinovirus. James seems back to his normal self. You stop his antibiotics and send him home, with advice to call the ward if he develops a further temperature or becomes more unwell.

**Box 3 – Modified Alexander Rule**

Risk factors which exclude from low risk protocol:

**Admission and 48 hour assessment**

* Age <1 year
* Associated medical conditions requiring hospitalisation
  + Shock or compensated shock
  + Haemorrhage
  + Dehydration
  + Metabolic instability
  + Altered mental status
  + Pneumonitis
  + Mucositis (unable to tolerate oral fluids or requiring IV analgesia)
  + Respiratory distress/compromise
  + Perirectal or other soft tissue abscess
  + Rigors
  + Irritability/meningism
  + Organ failure
* Cancer associated co-morbidities
  + ALL at diagnosis/relapse <28d
  + ALL not in remission >28d
  + AML
  + Infant ALL
  + Intensive B-NHL protocols
  + Haemopoietic stem cell transplant
  + Sequential high dose chemotherapy with PBSC rescue
* History
  + Intensive care admission during last FN episode
  + Non-adherence (social concerns or patient)
  + Inability to tolerate oral antibiotics

48 hour assessment only

* Positive blood culture result at 48 hours
* ANC <0.1 x109/L at 48 hours
* Child not clinically well at 48 hours

ALL – aculte lymphoblastic leukaemia, AML – acute myeloid leukaemia, B-HNL – B cell non-Hodgkins lymphoma, BMT – bone marrow transplant, PBSC – peripheral blood stem cells, ANC – absolute neutrophil count