PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on “Febrile Neutropenia.” These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Febrile Neutropenia

Developed by Chris Novak, and Dr. Bev Wilson for PedsCases.com.
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Intro

Hi everyone, my name is Dr. Chris Novak. I’m a pediatric resident at the Stollery Children’s Hospital at the University of Alberta. Today’s podcast is designed to give an organized approach to febrile neutropenia in children. This podcast was developed with Dr. Bev Wilson, a pediatric oncologist and Professor at the University of Alberta and in Edmonton, Alberta.

Let’s start with a clinical case.

You are on an emergency medicine rotation in a peripheral hospital. You sign up to see Hakim, a 4-year-old male with a fever, measured 38.9ºC at triage. Upon entering the room Hakim’s parents quickly tell you that he is being treated with outpatient chemotherapy for acute lymphoblastic leukemia, and that his oncology team told the family to go to emergency immediately if he develops a fever. You recognize that Hakim is at risk for febrile neutropenia. What do you need to consider when assessing this patient? What time-sensitive investigations and therapies need to be initiated?

We will come back to the case of Hakim as an example as we go through the podcast.

In the neutropenic patient, a fever can be an ominous sign of a serious infection. With more and more children on immunosuppressive therapy for cancer, autoimmune disease and transplants, febrile neutropenia can present in emergency departments anywhere, and rapid recognition, investigation and therapy can significantly reduce the risk of morbidity and mortality. While much of pediatric hematology and oncology is the realm of subspecialists, febrile neutropenia is a presentation every doctor should know about.

After listening to this podcast the learner should be able to:

1) Define febrile neutropenia.
2) List the common causes of neutropenia in children.

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3) Develop a differential diagnosis for the etiology of fever in the neutropenic patient.
4) List the appropriate investigations and recognize appropriate empiric therapy for patients with febrile neutropenia.

Definitions

Let's start with some definitions.

Neutrophils are a type of white blood cell and a critical part of the innate immune system. Neutrophils attack and destroy foreign pathogens, particularly bacteria and they are usually the first cells to arrive at the site of an infection. Neutropenia is defined as a state of low neutrophils. Precise cutoffs vary, but for our purposes an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/L represents severe neutropenia. With insufficient neutrophils, patients have decreased ability to fight off pathogens and are at a high risk of serious bacterial infection.

Fever in a neutropenic patient is defined as a single oral/axillary temperature of >38.3^{o}C, a temperature >38^{o}C lasting longer than one hour or two temperatures >38^{o}C within twelve hours. Measurement of rectal temperatures should be avoided in these patients due a risk of causing mucosal damage and introducing bacteria into the bloodstream.

Differential Diagnosis

In developing a differential diagnosis for febrile neutropenia, you need to consider two important questions:

1) Why is my patient neutropenic?
2) Why does my patient have a fever?

First "Why is my patient neutropenic?" In the acute setting, the question of why a child has neutropenia is less important than knowing how to manage febrile neutropenia. The differential diagnosis of neutropenia is broad and complex, so this is just a brief introduction. Neutropenia can be classified as acquired or congenital. Acquired neutropenia is much more common and can be caused by either increased destruction or decreased production of neutrophils. Neutrophils can be destroyed by Infection, hypersensitivity reactions to medications, and autoimmune processes. Medications which are frequently associated with neutropenia include immune-regulating medications such as methotrexate, sulfa drugs such as TMP-SMX, and anti-seizure medications including carbamazepine, phenytoin and phenobarbital. Next, Neutrophil production can be suppressed by bone marrow suppression from malignancy, vitamin B12/folate deficiency, aplastic anemia or chemotherapy. Patients on chemotherapy are at an especially high risk of serious infection. Chemotherapy agents can compromise the integrity of skin and mucous membranes, and increase the risk of bacteria entering the bloodstream. Due to the higher risk of complications, treatment recommendations

may be more aggressive for chemotherapy-induced neutropenia than other patients with febrile neutropenia. Congenital causes of neutropenia are rare genetic disorders that lead to chronic or recurrent neutropenia. These include cyclic neutropenia, some inborn errors of metabolism, bone marrow failure syndromes and a number of congenital neutropenia syndromes such as Shwachman-Diamond Syndrome, and Chediak-Higashi syndrome. Overall, congenital causes of neutropenia are rare, but should be considered in patients with recurrent or prolonged neutropenia.

Second question, "why does my patient have a fever?" The etiology of a fever in a neutropenic patient may be non-infectious, viral, bacterial, or less commonly, fungal. It may be a fever with a clear focus such as pneumonia, cellulitis or mucositis, or a fever without a focus. Despite a broad differential, the diagnosis you cannot miss is bacterial sepsis, as this is associated with significant mortality. In the 1970s, widespread recognition and empiric therapy for bacterial sepsis in patients with fever and neutropenia led to huge reductions in mortality in cancer patients. Estimates vary significantly based on the cause of neutropenia, but in cancer patients between 20-50% of cases of febrile neutropenia have positive blood cultures. Common pathogens include gram-positive organisms like coagulase-negative staph, strep viridans, and staph aureus, or gram-negative organisms like E. coli, Klebsiella and Pseudomonas.

History and Physical

Ok, now let's move on to the initial assessment. At first you may not know that a febrile patient has neutropenia. You should suspect neutropenia in a patient with a diagnosis of cancer or recent chemotherapy, congenital neutropenia, in a child with recurrent infections, or in a patient with severe gingivitis or oral ulcers. However, frequently, neutropenia will be an incidental finding on bloodwork.

On history, you should do a head-to-toe review of systems for infectious symptoms including headache, oral ulcers, sore throat, cough, chest pain, abdominal pain, vomiting, diarrhea, dysuria, rashes and joint pain. Ask about any sick contacts, and non-infectious causes of fever such as drug fever or rheumatologic conditions. Review the patient's past medical history, including any previous infections, or episodes of neutropenia. Check if the child has any indwelling lines or vascular access devices, or if they have been previously colonized with MRSA. Review medications and immunization history. Check if any medications can cause neutropenia, or if they took any antipyretic meds that might suppress a fever like Ibuprofen or Acetaminophen. In cancer patients, find out when was their most recent round of chemotherapy.

You should complete a detailed head-to-toe physical exam looking for any focus of infection. First, always check the vitals and assess if the patient is stable! Immunocompromised patients can decompensate quickly, so signs such as tachycardia, tachypnea, or especially hypotension, could warrant immediate resuscitation. In the head and neck look for sinus tenderness, assess the mouth for pharyngitis, gingivitis and ulcers, palpate for cervical lymphadenopathy, and assess for meningismus. Listen to the lungs for crackles, or reduced air entry. Palpate the

abdomen for tenderness. Complete a detailed examination of the skin including the perianal, genital regions and any vascular access sites.

It is important to note that in neutropenic or other immunocompromised patients, symptoms of infection may be less pronounced that you may expect. You are less likely to see swelling, erythema, purulence and lymphadenopathy associated with the infection. In an immunocompromised state the body can't mount as big of an inflammatory response, and therefore serious infections may appear to be more mild than they truly are.

Investigations

After completing your history and physical, all patients require investigations.

A CBC with differential is necessary to confirm the diagnosis of neutropenia. Other basic investigations should include Electolytes, Creatinine, Urea, CRP, and a Type and Screen as the patient may need transfusion if they are pancytopenic.

All patients with suspected neutropenia should have blood cultures drawn before starting antibiotics. Aerobic and anaerobic blood cultures should be drawn from each lumen of any central venous catheter. Many children receiving chemotherapy will have a central venous catheter, and line sepsis is a common problem, so it's important to check each site of access. You can consider peripheral blood cultures, however, at our center, these are not routinely collected. Peripheral blood cultures involving poking the child an additional time, and have higher rates of contamination, however they may help in differentiating line sepsis from other causes. Urinary tract infections are a common cause of fever without a focus, so in children where a clean-catch specimen is possible we recommend collecting a urinalysis and urine culture. In infants and younger children where this is not possible, DO NOT collect a catheter urine specimen as there is a risk of disrupting the mucosa and introducing bacteria into the bloodstream.

Other investigations should be guided by your history and physical, to assess for any identified focus of infection. These include nasopharyngeal viral swabs, throat swab, chest X-ray, abdominal X-ray, ultrasounds, stool cultures, and cultures of any soft tissue infections.

Management

Management of febrile neutropenia should be guided in consultation with specialist colleagues in Pediatric Hematology/Oncology. Essentially all cancer patients are associated with a local pediatric tertiary care center and will have an on-call physician or nurse practitioner available 24/7 for emergencies. Don't be afraid to call for help when dealing with these complex patients.

Patients with febrile neutropenia can be divided into high and low risk groups. High risk patients are defined as patients with signs of septic shock, signs of severe infection,

infants, patients on chemotherapy or certain diagnoses such as some types of leukemia and lymphoma or Down Syndrome. Essentially, they look sick, or have a diagnosis that carries a higher risk of bacteremia. High risk patients require prompt administration of IV antibiotics to cover bacteremia, with a goal time to antibiotics of less than one hour from presentation. Combination therapy with a beta-lactam and an aminoglycoside is recommended to provide increased coverage of the wide range of pathogens including resistant strains. In Alberta, the recommendation is to administer Piperacillin-Tazobactam along with one dose of Tobramycin while waiting for culture and sensitivity results. Vancomycin can be added in select patients to cover staph aureus including MRSA. Criteria for adding vancomycin include central line infections, skin or soft tissue infections, known MRSA colonization, gram-positive cocci on gram stain, or any patient who is hemodynamically unstable.

An evolving area of research is careful selection of low risk patients who are eligible for outpatient oral antibiotics with close follow-up. Low risk patients are defined as being clinically stable, with no comorbidities, with an expected duration of neutropenia of less than 7 days, however this decision is probably best left to Hematology/Oncology. An example of this would be an otherwise healthy child, with a viral URTI where neutropenia was picked up as an incidental finding on bloodwork. In the event that specialist consultation is not available, you would not be faulted for starting empiric IV antibiotics, however it is worth knowing that not all patients with febrile neutropenia require admission.

Once admitted, high risk patients should have a daily CBC with differential and blood cultures until the fever resolves and neutrophil counts recover. Empiric antibiotics should be continued for at least 48 hours until culture results are back, and then therapy can be tailored based on culture and sensitivity. Antibiotics are generally continued until blood cultures are negative, fever resolves and neutrophil counts recover. Further details of inpatient management are beyond the scope of this podcast.

Conclusion

Now let's return to our clinical case.

Hakim is a 4-year-old male undergoing treatment for ALL, presenting with fever. Realizing the high risk for febrile neutropenia, you quickly order a CBC with differential, Lytes, Creatinine, Urea, CRP, and blood cultures. On history, Hakim has had fever for the past 4 hours, but has no focal symptoms of infection. He received his last dose of chemotherapy one week ago. He has an implantable vascular access device (IVAD) and is on prophylactic TMP-SMX. His last CBC showed normal counts, but he has had neutropenia before. On physical exam you cannot find any focus of infection, so you do not order any additional investigations. You contact the pediatric oncologist on call and they agree to start empiric therapy with IV Piperacillin-Tazobactam and Tobramycin, and arrange transport to the nearest pediatric oncology center.

Before we leave, lets finish with a few key take home points:

1) Febrile neutropenia is defined as a patient with an ANC < 0.5 and a temperature >38.3^{o}C, a temperature >38^{o}C lasting longer than one hour or two temperatures >38^{o}C within twelve hours.
2) Neutropenia in children can be congenital or acquired. Children on chemotherapy are at higher risk of infection due to compromised mucous membranes.
3) Patients with febrile neutropenia are at a significant risk of bacteremia and sepsis.
4) All patients with febrile neutropenia require a CBC with differential and blood cultures prior to starting antibiotics. Other investigations should be guided by your history and physical.
5) High risk patients with febrile neutropenia require empiric dual coverage with IV antibiotics. A good regimen is Piperacillin-Tazobactam, Tobramycin +/- Vancomycin.

That concludes our presentation. Thanks for listening to PedsCases podcasts!

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