Febrile Neutropenia

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Abstract

The early and proper administration of antibiotic therapy in febrile neutropenic patients became well established in the 1970s, because of the high mortality that was seen when antibiotics were withheld until the presence of infection could be proven. Since then, there has been a trend in decrease in morbidity and mortality with a more directed systematic approach. A careful initial evaluation of the febrile neutropenic patient, an understanding of the potential organisms responsible for infection, risk assessment to guide therapy, and appropriate use of antibiotics are vital in the management of these patients. This review article essentially highlights many of the concepts of managing febrile neutropenic patients including the pathogenesis, diagnosis, risk assessment and antibiotic therapy.

INTRODUCTION

Fever is a common manifestation of infection for most severe neutropenic patients. It is a medical emergency. Prior to the era of empiric antibiotic therapy, infections accounted for almost 75% of the mortality related to chemotherapy.[1] Mortality correlates with the duration and severity of neutropenia and the time elapsed until the first dose of antibiotics is administered for neutropenic fever.[2]

PATHOGENESIS

The breakdown of mucosal barriers secondary to the administered chemotherapy and immune deficits related to the underlying malignancy significantly contribute to the pathogenesis of febrile neutropenia.[13]

A majority of these episodes can be explained by chemotherapy-induced mucositis and seeding of the bloodstream from endogenous flora in the GI tract. Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy also place patients at higher risk for infections. More importantly, the chemotherapy not only causes neutropenia, but also results in chemotactic and phagocytic defects as well.[345]

The risk for specific types of infections is influenced by the nature of the underlying malignancy and its associated humoral or cellular immune deficits. These need to be considered in addition to the presenting neutropenia.

Abnormal antibody production or clearing of immune complexes in multiple myeloma, chronic lymphocytic leukemia (CLL) and splenectomized (including functional asplenia) patients, results in an increased risk of sepsis from encapsulated organisms, including Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, and Capnocytophaga canimorsus.[3]

The T cell defects associated with Hodgkin lymphoma result in an increased risk of infection with intracellular pathogens such as Listeria monocytogenes, Salmonella, Cryptococcus neoformans, and Mycobacterium tuberculosis.[3456]

DEFINITIONS

The Infectious Diseases Society of America (IDSA) has suggested that a single oral temperature of >38.3°C (101°F) in the absence of other obvious environmental causes would be a reasonably safe working definition for an infection-related fever in neutropenic patients.[6]

Some studies suggest that initial oral temperature of >39 degrees C (102.2 degrees F), shaking chills, clinical shock, initial Absolute Neutrophil Count (ANC) of $<0.1 \times 10^9$/L, and initial platelet count of $<10 \times 10^9$/L are to some degree predictive of gram-negative bacteremia.[7]

DIAGNOSIS

The diagnosis of a febrile state in a neutropenic patient requires a complete but directed clinical history and physical examination designed to identify potentially infected foci for which those patients are at special risk.

Important historical facts may be obtained from the patient, from significant others, and from the patient's medical record. The physician must verify that the patient is neutropenic, the degree of neutropenia, and when the patient is a recipient of cytotoxic therapy, the day of the chemotherapy cycle as well as expected nadir and duration of the chemotherapy.[12345678]

The initial clinical evaluation should always include questions pertaining to the temporal association of the febrile episode to the administration of blood products, to a history of fever associated with the underlying disease, to the administration of chemotherapeutic agents or amphotericin B, to the presence of thrombophlebitis, and to the possible association of the febrile episode with thromboembolic or hemorrhagic events.[1]

PHYSICAL EXAMINATION

The physical signs of inflammation and infection are influenced by the ANC. The incidence and magnitude of localizing findings such as exudate, fluctuance, ulceration, or fissure formation are reduced in a direct relationship to the ANC.[19]

Table 1 lists the pertinent historical and physical clues to be sought in the clinical evaluation of a febrile neutropenic patient.

Examination of the head and neck area should include eyeground examination to look for retinal ‘cotton-wool’ exudates suggestive of disseminated Candidiasis.[10] Anterior nasal mucosal ulcerations might suggest the presence of Aspergillus species. Presence of vesicular and crusted lesions in the external nares would suggest HSV infection. Bacterial sinusitis could typically present with nasal stuffiness and tenderness over the maxillary sinuses.

A thorough oropharyngeal examination is imperative with particular attention to dentition and gingival surfaces.[1410] Painful mucosal ulcers are typical of HSV. Progression of this lesion with local tissue necrosis suggests polymicrobic infection due to anaerobic bacteria (eg. Fusobacterium nucleatum, Bacteroides melaninogenicus, and peptostreptococci). Oral thrush or pseudomembranous pharyngitis evolves from an overgrowth of opportunistic yeasts such as Candida species.[11]

On chest examination, the typical signs of pulmonary consolidation may be muted or absent in neutropenic patients; however, localized crepitation on auscultation often precedes the appearance of pulmonary infiltrates radiologically, and thus often represents the earliest clue (and often the only clue) to a developing pneumonia in a neutropenic patient.[312] Purulent sputum is similarly reduced in incidence and amount.

Therefore the symptoms of the neutropenic patient with a developing pneumonia may manifest only as febrile illness associated with an increased respiratory rate and a few localized crepitations, with or without an associated cough or radiologic changes.

The symptoms and signs of an intra-abdominal infection may be obvious or muted, focal or diffuse. The most important finding is focal tenderness. For example, tenderness in the right lower quadrant might suggest neutropenic enterocolitis (typhlitis); right upper quadrant tenderness might suggest a biliary tract focus or hepatomegaly; epigastric pain suggests an upper GI focus; and left lower quadrant tenderness suggests colitis or diverticular disease.[1234567] It is important to examine the perianal tissues for signs of excoriation, local erythema, swelling, tenderness, fissure formation, or hemorrhoidal tissues, since this area is frequently the site of major life-threatening infection in neutropenic patients.

Digital examination of the rectum is not recommended in neutropenic patients because of the additional risk of tissue damage, bleeding, and infection.[7891011121314]

A thorough examination of the skin is important, especially in areas associated with indwelling vascular access devices. Particular attention should be paid to the venous insertion, tunnel, and exit sites associated with central venous catheters.

Skin rashes are a common phenomenon among neutropenic patients. The differential diagnosis must include both infectious and noninfectious causes. Among the former group are focal ulcerative and necrotic lesions caused by metastatic pyogenic bacterial infection such as that associated with bacteremic P. aeruginosa or Staphylococcus aureus (infections causing ecthyma gangrenosum), or by disseminated angioinvasive filamentous fungi such as that due to Aspergillus species, Pseudallescheria boydii or Fusarium species (Fig. 1). Pustular erythematous lesions diffusely distributed over the skin surface suggest the possibility of disseminated fungal infection such as that caused by Candida tropicalis. Vesicular skin lesions suggest the possibility of infection due to HSV or Varicella zoster

virus.[1]

The list of possible noninfectious causes of skin rash is long. The three most important considerations are hemorrhagic petechial or ecchymotic rashes associated with profound thrombocytopenia; hypersensitivity rashes associated with specific drugs such as -lactam antibacterial drugs, allopurinol, or trimethoprim-sulfamethoxazole (TMP-SMX); and specific chemotherapy regimen–related rash syndromes (e.g., the exfoliative palmar/plantar syndrome associated with high-dose cytarabine; Fig. 2. These skin rash syndromes may coexist simultaneously.

{image:1}

LABORATORY STUDIES

Laboratory evaluations should include a complete blood cell count with differential, transaminases, bilirubin, amylase, electrolytes, and cultures. Lumbar puncture is not necessary routinely but should be performed in patients who have a change in mental status.

{image:2}

In interpreting laboratory results in neutropenic patients, it is important to recognize that the absence of neutrophils cannot be used to exclude the possibility of infection. Therefore, absence of a cerebrospinal fluid pleocytosis, pyuria, or PMNs on sputum Gram's stain does not rule out infection.

Specimens for the microbiology laboratory should include two or more blood cultures (some prefer culturing each intravenous port and at least one peripheral blood culture with quantitative measures), sputum Gram's stain and culture, and urine Gram's stain and culture.

Blood cultures should be repeated for persistent fevers or rigors.

Documenting that an intravenous catheter is the infectious source can be difficult and requires blood cultures taken peripherally and through the central access.

Sometimes a more invasive approach including bronchoscopy or open lung biopsy may need to be pursued in order to make a microbiologic diagnosis in patients who cannot produce sputum. This is may be particularly important for patients with infiltrates on chest radiographs or chest CT who continue to worsen despite 24 to 48 hours of empiric antibiotic therapy.[13]

RADIOLOGY

An initial chest x-ray should be done on admission, even if the patient is asymptomatic.

Chest radiographs should be repeated for increasing or persistent pulmonary symptoms, cough, or shortness of breath. Chest x-ray findings are often minimal or absent even in patients with pneumonia. Radiographic findings may develop (“blossom”) along with an increase in symptoms as the neutropenia begins to resolve.

Although CT scanning has not been shown to change clinical outcomes, a clinician should have a low threshold for ordering a CT in patients with pulmonary symptoms to help guide the selection and duration of treatment, and to assess for radiographic evidence of invasive fungal disease especially Aspergillus.[10][11][12][13]

OTHER DIAGNOSTIC STUDIES

If localizing signs or symptoms are present, other tests should be carried out for further investigation, such as radiological imaging of the CNS, sinuses, chest, abdomen, or pelvis, skin biopsy for culture, direct fluorescent antibody (DFA) testing for HSV or VZV, stool for culture, Clostridium difficile toxin, or ova and parasites.

RISK ASSESSMENT

Neutropenia-related febrile episodes are heterogeneous with respect to the cause of neutropenia, the duration of neutropenia, the risks of developing fever, the cause of fever, and the cause of infection.[10][11][12][13][14][15] Accordingly, the practice standard has been to hospitalize all febrile neutropenic patients for assessment, administration of empiric broad-spectrum intravenous antimicrobial therapy, and monitoring for and management of complications. Such complications include management of hemodynamic instability and hypotension; respiratory insufficiency requiring oxygen administration; control of pain, nausea, vomiting, and dehydration; investigation and management of confusion, delirium, and altered mental status; hemorrhage requiring blood product transfusion; cardiac dysrhythmia requiring monitoring; changes in metabolic function requiring intervention; and death.[16] Risk assessment can be performed using simple clinical criteria and these are outlined in Table 1.

{image:3}

MANAGEMENT

Broad spectrum antibiotics should be given as soon as

possible and at full doses (adjusted for hepatic and/or renal function). The following are the general treatment principles:

- Antibiotics are usually administered empirically, but should always include appropriate coverage for suspected or known infection.16
- Initial antibiotic selection should be guided by the patient's history, allergies, symptoms, signs, recent antibiotic use and culture data, and awareness of institutional nosocomial infection patterns.161718
- Ideally, antibiotics should be bactericidal and should be administered through alternate ports of any indwelling intravenous line.
- Clinical response and culture results should be closely monitored, and therapy should be adjusted in a timely fashion.1

EMPIRIC THERAPY

Antibiotic Selection- The following guidelines in Table 2A and 2B are adapted from the IDSA Executive Summary.[7891011121314151617181920212223242526272 8]

{image:4}

{image:5}

Low risk patients- It has become common practice to treat low-risk patients with oral outpatient antibiotic regimens. Most oral regimens are quinolone-based combinations, although newer broad-spectrum quinolones are being evaluated for monotherapy.[2728]

Addition of antifungal therapy- The incidence of fungal infections (especially Candida or Aspergillus) increases after more than 7 days of persistent febrile neutropenia. When reassessment after 5 to 7 days in these patients does not yield a cause for persistent fever, antifungal therapy is added.[23]

The guidelines recommend amphotericin B with or without changing the antibiotics as one option. Another option is voriconazole and caspofungin.[212223] Two factors limit the use of itraconazole it is not used in patients with an estimated creatinine clearance below 30ml/min and in hepatic failure.[24] It has a number of drug interactions with quinidine, statins and cyclosporine. It can also exacerbate congestive heart failure secondary to its negative inotropic effects.

Catheter removal- This is recommended in patients with catheter-related candidemia or bacteremia in which any one of the following responsible: S. aureus, Pseudomonas, fast growing atypical mycobacteria, Stenotrophomonas species, Bacillus species, or C. jeikeium.[2526]

SUMMARY

Febrile neutropenia is a medical emergency that requires immediate administration of broad spectrum antibiotics. Profound neutropenia has been associated with an increased mortality and this is mostly in part secondary to the direct effects of chemotherapy on mucosal barriers and malignancy-related immunodeficiencies.

It is imperative to do a general physical exam daily. Risk assessment is a significant part of the initial evaluation.

Initial therapy typically should comprise of cefepime or carbapenem. In more hemodynamically unstable patients, aminoglycosides are usually added for better gram-negative coverage except for those with renal failure, in whom fluoroquinolone or aztreonam would be utilized.

Presence of hypotension, mucositis, skin or catheter site infection, history of MRSA colonization, recent quinolone prophylaxis or overall clinical deterioration are indications for addition of vancomycin or linezolid.[25]

Duration of therapy is usually dependent on the particular pathogen and site of infection. If the source is not known antibiotic therapy is continued until there is resolution of fever and ANC is >500/microL. If the same patient becomes afebrile but remains neutropenic, therapy should be continued for a total of 14 days with judicious follow-up after cessation. If the source is known, guidelines recommend switching to oral antibiotics for completion of course.[1234567]

Empiric antifungal therapy is recommended in a patient with persistent febrile neutropenia for 5 to 7 days without an obvious site of infection. Choices include amphotericin B, voriconazole and caspofungin.[212223]

The recognition of a low-risk subset has simplified management i.e., oral outpatient therapy of such patients. Conversely, the numbers of high-risk patients has actually increased as a result of widespread use of intensive chemotherapy and or peripheral blood stem cell transplantation, producing severe and prolonged myelosuppression.[262728] These patients still need immediate and a more directed approach to therapy in a hospital-based setting and this shall lead to decreased morbidity and

mortality.

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