Febrile neutropenia

Etiology of infection, empirical treatment and prophylaxis

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ABSTRACT

Much has changed in the treatment of patients with fever and neutropenia, including the patterns of microbial flora and drug resistance, and the drugs used. Gram-positive organisms have overshadowed the gram-negative ones as causes of bacteremia. Changes in therapy may include antimicrobials directed against gram-positive bacteria, resistant gram-negative bacteria, or fungi. Due to the high risk for colonization by vancomycin resistant *Enterococci*, vancomycin use is restricted as first line empiric therapy unless the patient is at high-risk for serious gram-positive infection. Prophylactic antibiotic therapy may increase the selection of resistant strains and should be avoided. Therapy with colony stimulating factor is only considered for patients who remain severely neutropenic and have documented infections that do not respond to appropriate antibacterial therapy. Patients stratification for risk of infection-associated morbidity and mortality is essential to facilitate treatment decision.

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Patients with profound neutropenia due to hematologic malignancies or associated treatments are at risk for severe morbidity and for developing fatal bacterial infection. Although the mortality associated with febrile neutropenia has dramatically decreased over the past 3 decades, the overall death rate during or immediately after an episode of febrile neutropenia can be as high as 10% with half of the patients dying directly as result of infection itself. This marked reduction in mortality is due to a series of developments, among them, a pivotal role has been played by the concept of hospital-based empirical therapy with broad-spectrum combinations of antibiotics, aimed primarily against Gram-negative organisms, namely *Pseudomonas aeruginosa* (*P. aeruginosa*). Other factors have also been important to improve the vital prognosis of febrile neutropenia and reduce the complications resulting from it. The use of antibacterial and anti fungal prophylaxis in high-risk patients, as well as the empirical administration of active antifungal agents to non-responding patients and the availability of the granulopoiesis-stimulating agents, has likely helped to diminish the morbidity associated with febrile neutropenia. These interventions have become, to a large degree, the standard procedures.

Evaluation of febrile neutropenic patient. In neutropenic patients, the signs and symptoms of infection are often blunted or absent. Fever is an early warning sign. Current National Comprehensive Cancer Network (NCCN) guidelines[1] recommend that all patients who present with temperature >38^{0}C orally and who have a neutrophil count <500/µL, or <1,000/µL with predicted decline to <500/µL over the following 48 hours, be treated with initial empiric antibiotic therapy. Absence of non-infectious causes of fever such as underlying malignancy, transfusion of blood products,

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or drug reactions (for example cytokines, antimicrobial agents), should be confirmed prior to initiating antibiotic therapy.[2] An initial evaluation of such patients should focus on identifying the causative pathogens, and potential sites of infection (for example catheter site, specific lesions in areas such as the elementary canal, skin and lungs) by thorough medical examination and laboratory and microbiological evaluations. While empiric therapy is usually initiated without microbiologic evidence, pathogen identification should direct secondary treatment modifications. If a central venous access device is in place, some authorities including the new "Infectious Diseases Society of America (IDSA) Guidelines for the Management of Intravascular Catheter-Related Infections"[3] recommend that ≥1 set of blood samples be obtained for culture from the device lumens as well as from peripheral vein. Other investigators believe that culture only of blood sample obtain from a central venous catheter is adequate.[4,5] Complete blood cell counts and determination of the levels of serum creatinine and urea nitrogen are needed to plan supportive care and to monitor for the possible occurrences of drug toxicity.

Patients stratification for risk of infection-associated morbidity and mortality. Stratification for risk of infection-associated morbidity and mortality is essential to facilitate treatment decision.[6] While high-risk patients[7,8] require hospital-based intravenous therapy, low-risk patients may be effectively and safely treated as inpatients and outpatient on a sequential basis. Low risk patients may even be treated on a completely outpatients basis, if risk stratification is accurate and an ambulatory treatment infrastructure is developed. Although there is no universally accepted risk assessment strategy, recent advances have led to the development of clinical criteria and statistically derived risk prediction rules, which are reasonably accurate in distinguishing low-risk from high-risk patients. **Table 1** lists the various risk-groups and associated patient characteristics, while **Table 2** demonstrates the treatment options for different risk groups.

Etiology of infection in the neutropenic patient. In the late 1960's, 1970's and 1980's, aerobic *Gram–negative bacilli,* were the predominant organisms causing infection in the neutropenic patients and were involved in approximately 60-80% of those infections that were microbiologically proven, with *P. aeruginosa* being a leading isolate.[9] In the mid 1980's, Gram-positive organisms overshadowed the gram-negative ones as the bacteria causing infection in the neutropenic patients. A steady increase in the gram-positive infections occurred until presently 60-70% of bacteremia with a single organism identified will be caused by *Gram-positive cocci.*[10,11] Coagulase-negative *Staphylococci* and *Staphylococcus aureus* (*S. aureus)* are the predominant organisms. Why gram-positive organisms overshadowed the gram-negative ones is not absolutely clear. Some probable factors include: aggressive chemotherapeutic regimens that cause severe mucositis, longer duration of neutropenia, the use of long dwelling intravascular catheters, and the use of prophylectic antibacterial agents with relatively weak coverage of gram-positive organisms.[12] New gram positive organisms have become important etiologies of infections in neutropenic patients such as *Viridans Streptococci (V. Streptococci), Enterococcus species, Stomatococcus mucilaginous, Rhodococcus equi, Leuconostoc species,* and *Lactobacillus species*. A matter of concern, is the emergence of high rates of penicillin, and some second and third generation cephalosporins resistance among *V. Streptococci.*[13] It is of interest that a variety of previously unappreciated gram-negative organisms have also been identified as causes of infections in the neutropenic patients. Among these isolates include, *Stenotrophomonas maltophilia, Alcaligenes xylosoxidans,* and *Burkholderia cepacia*.[10] Up to 20% of patients with neutropenia may experience an invasive fungal infection.[14] The most common fungal infections include superficial and invasive infections due to *Candida species* and invasive *Aspergillosis* as well as the emerging pathogens including *Fusarium species (F. species), Trichosporon beigelii,* and *Dematiaceous fungi*.[15] The most common *Candida species* associated with invasive candidiasis in the neutropenic patients is *Candida albicans (C. albicans*), followed by *Candida tropicalis, Candida glabrata (C. glabrata*), and *Candida parapsilosis, Candida krusei* (*C. krusei*) is also an important pathogen among neutropenic patients, though is not a prevalent pathogen in all centers. The increased incidence of *C. krusei* has been almost exclusively in centers where fluconazole has been widely used for prophylaxis.[16] Invasive infections due to *Aspergillus species (Asp. species)* are among the most serious infections complications in neutropenic patients. Risk factors that are strongly associated with invasive aspergillosis include longer duration of neutropenia, use of steroids and other immunosuppressive agents, and chronic graft versus host disease.[17] Infections due to *F. species* have become increasingly common in the neutropenic patients.[18] The most important risk factor is prolonged period of neutropenia, often >3 weeks.[15]

Empiric therapy of febrile neutropenia. The initial empiric therapy of febrile neutropenia has been traditionally aimed at the optimal coverage of infections due to Gram-negative rods, due to their potential for causing fulminant sepsis. The first step in antibiotic selection is to decide whether the patient is a candidate for inpatient or outpatient management, with oral or intravenous antibiotics. Three general schemes of intravenous antibiotic therapy with similar efficacy are considered for the treatment of febrile neutropenic patients. The schemes are: single-drug therapy (monotherapy), 2-drug therapy without vancomycin, and therapy with vancomycin plus one or 2 antibiotics.

Single-drug therapy (monotherapy). A third or fourth generation cephalosporin (ceftazidime or cefepime), or carbapenem (imipenem-cilastatin or

Table 1 - Risk groups in febrile neutropenic patients.[30]

Risk group	Patient characteristics
High-risk	Severe (ANC < 100) and prolonged (> 14 days) neutropenia. Hematological malignancy; allogeneic bone marrow/stem cell transplantation; significant medical co-morbidity or poor performance status; presentation with shock, complex infection (for example pneumonia, meningitis).
Intermediate (moderate) risk	Solid tumors → intensive chemotherapy → autologous hematopoietic stem cell transplantation. Moderate duration of neutropenia (7-14 days). Minimal medical co-morbidity. Clinical or hemodynamic stability.
Low-risk	Solid tumors → conventional chemotherapy. No co-morbidity. Short duration of neutropenia (≤7 days). Clinical and hemodynamic stability. Unexplained fever (FUO) or simple infection (for example urinary tract infection, simple cellulitis).

FUO - fever undetermined the origin,
ANC - absolute neutrophil count

Table 2 - Treatment options based on risk and site of therapy.[30]

Risk group	Treatment options
High-risk	Hospital-based, broad-spectrum, parenteral therapy for duration of febrile episode
Intermediate (moderate) risk	Initial hospital-based parenteral therapy followed by early discharge or a parenteral or oral regimen
Low-risk	Outpatient therapy (parenteral, sequential, or oral) for the entire episode

meropenem) maybe used successfully as monotherapy.[19] The activity of ceftazidime as monotherapy is reduced by extended spectrum-beta-lactamases, and type 1-beta lactamases.[20] Cefepime, imipenem-cilastatin and meropenem, unlike ceftazidime have an excellent activity against *V. Streptococci* and *Pneumococci*. A prospective double-blind study of 411 patients who had cancer showed that the rate of clinical response was higher in febrile neutropenic patients treated with meropenem than it was in those treated with ceftazidime.[19] Piperacillin-tazobactam has also been found to be effective as monotherapy, but its use has not studied as extensively as that of the other agents.[21,22] It should be taken in consideration that the spectrum of these antibiotics used as monotherapy does not cover *Coagulase-negative Staphylococci*, methicillin-resistant *S. aureus* (MRSA), Vancomycin-resistant *Enterococci* (VRE), some strains of penicillin-resistant *Streptococcus pneumoniae*, and *V. Streptococci*. Therefore, addition of other antibiotics may be necessary as the clinical course progressed.

Combination therapy without vancomycin. These includes an aminoglycoside (gentamicin, amikacin, tobramycin) plus an antipseudomonal penicillin (piperacillin-tazobactam, ticarcillin-clavulanic acid); aminoglycoside plus extended-spectrum cephalosporins, such as cefepime or ceftazidime; and or an aminoglycoside plus a carbapenem (imipenem-cilastatin or meropenem). In general, the potential advantages of combination therapy over monotherapy include potential synergy against strains of aerobic *Gram-negative bacilli*; activity against *Anaerobes* especially when beta-lactam or beta-lactamase inhibitor combinations are used, and a possible decrease in the emergence of resistant strains. The major advantages are the lack of activity of these combinations, such as ceftazidime plus aminoglycoside, against some gram-positive bacteria, and the ototoxicity and nephrotoxicity of aminoglycosides.

Should vancomycin be utilized as part of the initial regimen? Clearly, the predominance of *Gram-positive cocci* as the etiologic agents of microbiologically proven infection in neutropenic patients would suggest the use of vancomycin especially at institutions where these gram-positive bacteria are common causes of serious infections, (*V. Streptococci* resistant to penicillin, methicillin-resistant, *S. aureus*, and penicillin-resistant *Pneumococci*). Some studies have shown that vancomycin when used initially may be associated with fewer break-through bacteremias and local infection with *S. aureus*.[23] Subsequent studies suggested that there was no increase in morbidity or mortality overall if vancomycin was held until it was needed, that is, until a gram-positive organism was identified and the patient was not responding to the initial regimen.[24] A significant exception is bacteremia with *V. Streptococci*, which may have higher mortality if not initially treated with vancomycin.[25] If vancomycin is used but no gram-positive infections are identified after appropriate culturing at 48-72 hours, vancomycin should be discontinued.[26] If cultures are positive for gram-positive organisms from initial cultures and the patient is not doing well on the initial antibiotic regimen, vancomycin could be added until the final antibiotic susceptibilities are established.[26] Linezolid, a member of the novel antibiotic class of oxazolidinones, has recently been shown to have similar activity to vancomycin against vancomycin susceptible *Enterococci*, *Staphylococci* and *Streptococci*. It has also been shown to be effective against VRE, and MRSA/methicillin resistant *Staph. epidermidis* (MRSE) invitro.[27] This agent may be a safer alternative to vancomycin and may help prevent increased levels of colonization by VRE. Streptogramins (quinuprestin - dalfoprestin), are also potential candidates for preventing or treating gram-positive infections in cancer patients without using a glycopeptide (vancomycin).

Success of empiric therapy regimen. A review of nearly 100 studies (1990-1995) of various initial empiric regimen among patients with fever and neutropenia found no single regimen to be clearly superior.[26] Although most studies have recommended the use of combination therapy (for example beta-lactams plus aminoglycoside) or double betalactams, no relevant differences have been demonstrated between combination therapy and monotherapy with new extended spectrum antibiotics.[26,28] Monotherapy seems prudent for short duration neutropenia (<1 a week), while combination therapy could prevent breakthrough of resistant infections with long duration neutropenia (>1 a week). Choice of antibiotic is wide and the selection of an initial agent should be based on prior antibiotic regimens, resistant bacterial infections or colonization, duration and severity of current febrile episode and neutropenia, comorbid disease, catheter-site infection, hospital versus community patterns of antibiotic susceptibilities among bacteria most commonly encountered in patient with similar infections.

Treatment of fungal infections in neutropenic patients: an update. The development of antifungal resistance among older established pathogens, and the emergence of new fungal pathogens have led to an emphasis on the development of newer antifungal agents. Echinocandins represent a new class of antifungal drugs. They are cell wall active agents, fungicidal against most *C. species*, and are fungistatic versus most *Asp. species.*[29] They have limited activity against *F. species*, Zygomycetes. Three echinocandins are in development: caspofungin (MK0991), micafungin (FK463), and anidulafungin (LY303366). They are all administered parenterally and can be dosed once daily. Three new triazoles are in various stages of development.[30] These include voriconazole, posaconazole, and ravuconazole. They are derivatives of fluconazole (voriconazole, ravuconazole) and itraconazole (posaconazole). Each of these agents, offers broad spectrum antifungal activity against most strains of *C. species* and *Asp. species*.

Antibiotic prophylaxis for neutropenic patients. The prevention of infection in afebrile neutropenic patients has been the subject of considerable research. Low-risk patients, that is, those without localizing signs of infection and with a short expected duration of neutropenia, are frequently observed and immediately evaluated if any fever occurs. For patients with longer expected duration of neutropenia, antibiotic prophylaxis directed principally against gram-negative pathogens may be considered. Early studies evaluated the role of trimethoprim-sulfamethoxazole (TMP-SMX) for this purpose, but the rise of resistance to TMP-SMZ even among common enteric bacteria such as *Escherichia coli* makes this strategy potentially less useful today. The early quinolones, particularly ciprofloxacin, have been appealing for this purpose due to its powerful broad-spectrum activity against aerobic *Gram-negative bacilli* without antianaerobic activity. However, disadvantages include rise of gram-positive infections in these patients, and the alarming potential for development of resistance to quinolones among *Gram-negative bacilli* in the individual patient and in general.[26] Infectious Diseases Society of America guidelines recommend TMP-SMZ prophylaxis only for patients at risk for *Pneumocystis carinii* pneumonitis, routine quinolone prophylaxis is not recommended except in certain patients with profound and prolonged neutropenia, and then for only short course with awareness of the risk of developing antibiotic resistance.[26] On the other hand, allogeneic bone marrow transplant recipient who remain neutropenic after transplant are at high risk of bacterial, fungal and viral infections and generally require continuous prophylaxis in all 3 categories. Fungal infections are often difficult to diagnose and treat successfully; therefore, antifungal prophylaxis may be appropriate in institutions in which the infections are encountered frequently. Fluconazole has been shown to reduce the frequency of both superficial and systemic infections in patients who undergo bone marrow transplantation.[31-32] However, its efficacy is limited by its lack of activity against *C. krusei*, *C. glabrata* and mold. Increased frequency of colonization with *C. krusei*, and *C. glabrata* has been reported in few institutions in which fluconazole has been used.[33] Routine use of fluconazole or itraconazole for all cases of neutropenia is not recommended. However, in certain circumstances in which the frequency of systemic infections due to *C. albicans* is high and the frequency of systemic infections due to *C. species* and *Asp. species* is low, some physicians may elect to administer antifungal prophylaxis.

Use of colony stimulating factors in treatment of febrile neutropenic patients. Granulocyte-colony stimulating factor (G-CSF), or granulocyte-macrophage colony stimulating factor (GM-CSF), used as part of the treatment of febrile neutropenic patients, consistently shorten the duration of neutropenia, but not the duration of fever, use of antibiotic, or cost of management of the febrile neutropenic episode.[34-36] No study has demonstrated a decrease in infection-related mortality rates. Routine use of hematopoietic growth factor in uncomplicated cases of fever and neutropenia is not recommended by the American Society of Clinical Oncology, and IDSA. Only under certain conditions, when there is an expected long-delay in recovery of the bone marrow, or worsening of the course is predicted. Use of these agents may be indicated. Such conditions include, pneumonia, hypotensive episodes, severe cellulitis or sinusitis, systemic fungal infections, and multiorgan dysfunction secondary to sepsis. Therapy with colony stimulating factors could also be considered for patients who remain severely neutropenic and have documented infections that do not respond to appropriate antimicrobial therapy.

Outpatient therapy for the neutropenic patients. Until recently most patients with fever and neutropenia have been managed in a hospital-based setting in order

to monitor them closely and deal with life-threatening complications, should they occur.[37] There is a uniform agreement that high-risk neutropenic patients (those with hematological malignancies, severe and prolonged neutropenia) need to be treated using standard hospital-based parenteral broad-spectrum, empiric antibiotic therapy for the entire febrile episode.[26] On the other hand, low-risk patients (in whom early discharge after initial stabilization or outpatient therapy are a potential options), are patients with solid tumor receiving conventional chemotherapy, with expected duration of neutropenia ≤7 days, who are clinically stable and present with unexplained fever, or simple infections. These patients are candidates for parenteral outpatient regimen including long acting agent such as ceftriaxone plus once daily amikacin when they present with mucositis, or a combination of quinolone or aztreonam plus an agent with gram-positive activity. Oral regimen, generally include a combination of amoxycillin - clavulanate, clindamycin, or a macrolide.[38] Outpatient therapy is associated with several advantages over standard hospital-based therapy. It is significantly less costly, patients are at less risk for developing a nosocomial infection if they are at home than if they are in the hospital. Enhanced quality of life for patients and increased convenience for family have also been clearly demonstrated. Some potential hazards or disadvantages do exist. The patients are at risk for developing serious complications (septic shock, significant bleeding in thrombocytopenic patients, or seizures) in the outpatient setting, although uncommon, may occur, and delays in management while patients are being transported to the hospital are possible. Noncompliance with oral regimens or infusion-related problems may also occur, but can be minimized with monitoring and follow-up. A successful outpatient therapy requires considerable commitment from all parties involved. Institutional support to create or maintain an adequate infrastructure to deal with substantial numbers of febrile neutropenic patients being treated in the outpatient setting is critical. This includes a dedicated team of health-care providers who are interested and experience in such a program, and 24 hour access to the team. The patients and their families need to be motivated, and compliant, and have adequate communication and transportation facilities. Appropriate antimicrobial therapy based on local epidemiologic and susceptibility or resistant patterns will ensure that outpatient therapy is associated with high response rates.

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