Current Treatments for Infection in Neutropenic Patients With Hematologic Malignancy

By John N. Greene, MD [2], David C. Linch, MD [3], and Carole B. Miller, MD [4]

Neutropenic patients with cancer are a heterogeneous group of patients who carry a variable risk for infection. When such patients present with fever, appropriate empiric antibiotic therapy is initiated and continued until...

**Introduction**

Patients with profound neutropenia due to hematologic malignancies or associated treatment(s) are at risk for severe morbidity and for developing fatal bacterial infection. When patients with neutropenia also present with fever—an early sign of infection among these patients—it is a standard of care to initiate empiric antibiotics.

Such treatment is generally administered to prevent the rapid progression of infection that may result in septic shock or death. However, the overuse of antimicrobials over time may result in antimicrobial resistance and development of cross-resistance among pathogens. Given the benefits of antibiotic treatment, are we reducing the incidence of serious infections in the setting of febrile neutropenia? Conversely, given the drawbacks of inappropriate antimicrobial therapy, are there instances of excessive use of antimicrobials in treatment? Can we minimize the use of antibiotics without compromising the health and well-being of our patients? These are important questions to answer, particularly as we encounter changing patterns of bacterial infection and antibiotic resistance.

The purpose of this article is to examine the characteristics that define those patients requiring antimicrobial therapy. Current therapeutic practices will be reviewed, as well as measures that can improve patient outcome. An evaluation of risk for serious bacterial infection will be examined as a refinement of treatment strategy for febrile neutropenia.

**Target Population for Empiric Antimicrobial Therapy**

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 recommend that all patients who present with a temperature greater than 38°C orally and who have a neutrophil count < 500/µL, or < 1,000/µL with a predicted decline to < 500/µL over the following 48 hours, be treated with initial empiric antibiotic therapy. Absence of noninfectious causes of fever, such as underlying malignancy, transfusion of blood products, or drug reactions (eg, cytokines, antimicrobial agents), should be confirmed prior to initiating antibiotic therapy.

An initial evaluation of such patients should focus on identifying the causative pathogen(s) and potential sites of infection (eg, catheter site; specific lesions in areas such as the alimentary canal, skin, and lungs) by thorough medical examination and laboratory and microbiological evaluations. While empiric therapy is usually initiated without microbiological evidence, pathogen identification should direct secondary treatment modifications. Patient stratification for risk of infection-associated morbidity and mortality is essential to facilitate treatment decisions.

While high-risk patients [4,5] require hospital-based intravenous (IV) therapy, low-risk patients may be effectively and safely treated as inpatients and outpatients on a sequential basis. Low-risk patients may even be treated on a completely outpatient basis, if risk stratification is accurate and an ambulatory treatment infrastructure is developed.

**Current Treatment Approaches**

The choice of antibiotic, mode of administration, and duration of treatment varies from patient to patient, with empiric parenteral, broad-spectrum antimicrobial drugs being indicated for patients...
who are febrile and neutropenic and considered at high risk. Low-risk subgroups may be administered as intravenous (IV) therapy, oral therapy, or sequential IV/oral therapy.[1] Other treatment variables include the number of antibiotics (monotherapy vs combination therapy), dosage, and duration of treatment.

Choice of antibiotics is wide and the selection of an initial agent should be based on the patient’s history. This includes a history of prior antibiotic regimens, resistant bacterial infections/colonization, duration and severity of current febrile episode and neutropenia, comorbid disease, catheter-site infection, drug allergies, and geographic (institutional and community) patterns of antibiotic susceptibilities among bacteria most commonly encountered in patients with similar infections. Current recommendations of the NCCN for initial therapy of fever and neutropenia are summarized in Table 1.[1]

### Success of Empiric Therapy Regimens

A review of nearly 100 studies (1990-1995) of various initial empiric regimens among patients with fever and neutropenia found no single regimen to be clearly superior.[6] Although most studies have recommended the use of combination therapy (eg, β -lactam plus aminoglycoside or double β-lactams), no relevant differences have been demonstrated between combination therapy and monotherapy with newer extended-spectrum antibiotics.[6-8] Monotherapy seems prudent for short duration neutropenia (less than 1 week), while combination therapy could prevent breakthrough of resistant infections with long duration neutropenia (greater than 1 week). Response rates to treatment with β-lactams, with or without aminoglycosides, have varied between 50% and 60%.[2]

One of the major problems associated with comparison studies is the difficulty in interpretation caused by variability in study designs and efficacy or outcome measures.[9,10] Furthermore, many patients with neutropenia have complex medical profiles, leading to increased physician concern and a tendency to modify regimens during the treatment course of febrile episodes. Such modifications generally are made in a setting of inadequate diagnostic information. It has been estimated that empiric regimens may be modified in 40% to 60% of cases.[7]

Data from a series of French studies conducted between 1987 and 1992, involving 591 evaluable febrile episodes, indicate that the mortality rate among patients with neutropenia and fever has not improved despite improved control of gram-positive and gram-negative microorganisms.[11] This outcome has been attributed to an increase in disseminated fungal infections, thereby resulting in the addition of antifungal agents to some treatment regimens. Thus, while empiric therapy is sufficient in controlling infections for many patients, others need additional antibiotics or antifungal agents for fever resolution.

### The Limited Role of Vancomycin/Teicoplanin in Empiric Therapy

It has been greatly debated whether a glycopeptide antibiotic, such as vancomycin or teicoplanin (Targocid), should be added to standard empiric therapy. Initial advocacy for the up-front addition of vancomycin was based on the detection of superinfections during β-lactam monotherapy[12] and the efficacy of vancomycin addition in preventing such superinfections.[13]

A study by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute (NCI-C), Canada, has shown that vancomycin is not an essential component of initial empiric therapy for fever in granulocytopenic cancer patients.[14]

Widespread use of vancomycin has resulted in the emergence of glycopeptide resistance in enterococci, and therefore, initial therapy with vancomycin should be restricted to select groups of patients who may be at a high risk for serious gram-positive infections.[1]

Patients at high risk for serious infections, and in whom vancomycin use is justified, include those with skin or venous-access infections that are clinically apparent and serious, and those subjected to intensive mucositis-producing chemotherapy. Also at high risk are patients colonized with antibiotic-resistant gram-positive pathogens.[1] Patients with prior quinolone prophylaxis are also at high risk for bacteremia due to viridans streptococci.

Patients with gram-positive blood cultures, known colonization with penicillin, or cephalosporin-resistant pneumococci or methicillin-resistant Staphylococcus aureus (MRSA), and those patients with hypotension or septic shock (even in the absence of identified pathogen) may be considered as candidates for empiric vancomycin therapy.[1]

**Restricting the Use of Vancomycin**

It is well known that microbial colonization is a prerequisite to infection and superinfection (infection occurring during antibiotic therapy or developing within 1 week of discontinuation of antibiotics). However, the relationship is not universal and not all
colonizing organisms require treatment or suppression. Choice of treatment regimen, site of treatment, and duration of treatment is dependent on multiple patient and pathogen characteristics. For example, colonization of the upper respiratory tract with *Aspergillus* or the gastrointestinal tract with VRE would prompt immediate pathogen-directed treatment. Treatment would last until resolution of neutropenia. Once these infections are established, prolonged therapy, high morbidity and mortality, and longer hospital stays are commonly seen.

**Study of the Prophylactic Use of Antibiotics to Minimize Infections**

The prophylactic use of antibiotics as a means to minimize infections for patients with neutropenia has been extensively studied. Beta-lactams, trimethoprim/sulfamethoxazole, quinolones, and glycopeptides have been used in this regard, and experience indicates that prophylaxis with antibiotics is only useful in a very select population, who are at high risk for infection and experience prolonged and profound neutropenia. This group includes patients who received high-dose chemotherapy for leukemia or following allogeneic and some autologous stem-cell or bone marrow transplantation.

However, use of prophylactic antibacterial agents may enhance resistance and is unnecessary in most patients.[19,20] Superinfections among neutropenic cancer patients have been shown to be more likely with quinol-one prophylaxis.[21] The addition of ampicillin prophylaxis to quinolone has been shown not to decrease the incidence of viridans group streptococcal infections, but to only select for β-lactam resistance.[22] Penicillin-resistant viridans streptococci increased from 0% to over 40% in one cancer center concomitant with quinolone and penicillin prophylaxis,[23] indicating a possible relationship between antibiotic use and resistance development.

Among bone marrow transplant patients, vancomycin prophylaxis has been shown to reduce the incidence of bloodstream infections, but not deaths when compared to placebo.[24] Ciprofloxacin prophylaxis also increases fluoroquinolone resistance among *Escherichia coli*, with no effect on patient outcome.[25] Thus, antibiotic prophylaxis for control of bacterial infections should be limited.

**Steps to Prevent Infection and Microbial Resistance**

Reduction in use of some antibiotics can reduce selection for resistant strains. For example, VRE incidence has been reduced with the elimination of ceftazidime (Fortaz, Tazidime, Tazicef) from treatment regimens.[26] Nonpharmacologic steps should be employed to prevent nosocomial transmission of potential pathogens. These steps should form an integral part of infection control. Such measures include the institution of adequate policies regarding handwashing, barrier isolation, and catheter care. Surveillance rectal swab cultures may help identify and monitor bacterial profiles, particularly VRE, and can be considered for some high-risk patient populations.[27] When VRE is present, attempts may be made to eliminate intestinal carriage with enteral antimicrobials that may not be systemically absorbed.

**Conclusions**

Despite the numerous trials that underscore the benefits of antibacterial drugs in febrile and/or neutropenic patients, questions remain about what constitutes the most effective and safest treatment. Current empiric therapy is most often a combination of a β-lactam and an aminoglycoside or broad-spectrum monotherapy.[1] Patients with bloodstream infections due to known resistant organisms will need individualized treatment. Combination therapy should be considered for those with serious gram-negative infections and profound and prolonged neutropenia. Prevention or reduction of infection can be accomplished by hospital practices that limit the spread of infection among patients, and with risk-based treatment decisions that are individualized to each patient. Education of patient care providers should highlight the increasing prevalence of gram-positive organisms. Use of newer classes of antibiotics with new mechanisms of action may help in circumventing established resistance mechanisms.

Prophylactic antimicrobial treatment is controversial and should at least be limited to high-risk patients. Prompt administration of empiric antimicrobials directed against gram-negative pathogens is of utmost importance in febrile patients with neutropenia. Although gram-positive organisms are of low virulence, newer strategies for prevention and treatment are needed.
References:


Source URL:
http://www.physicianspractice.com/review-article/current-treatments-infection-neutropenic-patients-hematologic-malignancy

Links: