Infections in Oncology

Early Empiric Antibiotic Therapy for Febrile Neutropenia Patients at Low Risk

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Introduction

The association of neutropenia and infection in patients with neoplastic disorders who were receiving myelosuppressive chemotherapy was established more than three decades ago.[1] Infection continues to be a leading cause of morbidity and mortality in such patients.[2] Patients with short-lived neutropenia (up to 10 days) have a lower risk of developing infections and respond better to empiric antimicrobial therapy when infection does develop compared with patients having profound and prolonged neutropenia (longer than 14 days).[3]

Until recently, febrile neutropenic patients were hospitalized for the administration of empiric, broad-spectrum intravenous antibiotic therapy.[4] In recent years, the concept of risk assessment during the initial phases of a febrile episode has been introduced and evaluated.[5,6] It is now possible to identify and classify febrile neutropenic patients into subsets with varying degrees of risk. Factors that are considered in the classification of these patients include the presence of concurrent comorbidities, the disease status of the underlying malignancy, and other clinical characteristics.

Therefore, the standard practice of hospitalizing low-risk patients for antibiotic therapy has been questioned, and newer therapeutic modalities - and the settings in which these therapies are delivered - are being evaluated.

Risk Assessment in Febrile Neutropenic Patients

A study from the National Cancer Institute[3] examined the influence of the duration of neutropenia on the response to empiric antimicrobial therapy in patients with fever of undetermined origin (FUO). Response rates to initial antimicrobial therapy were 95% in patients with neutropenia lasting seven or fewer days compared with 32% in patients with more than 14 days of neutropenia ($P=0.001$). Also, many trials of empiric antibiotic therapy in febrile neutropenic patients have demonstrated better response rates in patients with documented infections in whom recovery from neutropenia occurs compared with those with persistent neutropenia.[7,8] Patients with hematologic malignancies and recipients of bone marrow transplantation are at greatest risk, because the duration of severe neutropenia often exceeds 14 days in such patients. In contrast, most patients with solid tumors have neutropenia lasting up to 10 days and a much lower risk (with a few exceptions, such as testicular carcinoma, small-cell lung carcinoma, some lymphomas, and sarcomas). The depth of neutropenia also correlates with an increased frequency of infectious complications, with more bacteremias and pneumonias occurring at fewer than 100 cells/mm$^3$.[1] However, the duration of neutropenia or, perhaps more accurately, the rate at which the granulocyte count returns may have an overriding importance in determining the complexity of a patient's clinical course following the onset of fever.[9,10] Other factors that increase the risk include damage to the gastrointestinal mucosa by chemotherapeutic regimens or damage to the skin by invasive procedures such as the placement of vascular access devices or bone marrow aspiration/biopsies.[4] In addition, patients with neoplastic disorders are often debilitated and in poor nutritional balance.

Although risk varies substantially in subsets of febrile neutropenic patients, the ability to predict risk early during the course of a febrile episode has been limited. Talcott et al[5] initially developed a prediction model to identify low-risk patients with fever and neutropenia in a retrospective study of 261 patients. This model, which was subsequently validated in a prospective study of 444 cancer patients with fever and neutropenia,[6] accurately identified the medical risk of these patients by using only the clinical information available on the first day of their course. The patients were categorized by risk into four groups. Group 1 consisted of high-risk patients who were hospitalized when their febrile neutropenic episodes developed, including patients with hematologic disorders and recipients of bone marrow transplantation with substantial morbidity and an overall mortality rate of 13%. Group 2 included outpatients with concurrent comorbidity (eg, hypertension, altered mentation, respiratory failure, uncontrolled bleeding, dehydration, hypercalcemia, and cord compression). Serious complications occurred in approximately 40% of these patients, and the overall mortality was 12%, making this group of patients high-risk as well. Group 3 consisted of patients who developed fever and neutropenia as outpatients and had no concurrent comorbidity, but had progressive uncontrolled cancer. Serious complications occurred in 25% of these patients and 18% died. Group 4 consisted of clinically stable outpatients with responsive tumors and no concurrent comorbidity who rarely developed serious complications (3%) and in whom no mortality occurred ($P=0.0001$ for Group 4 vs Groups 1 through 3). These are considered "low-risk" patients, and they constitute approximately 40% of febrile neutropenic patients treated at referral cancer centers such as the Dana-Farber Cancer Institute and the M.D. Anderson Cancer Center.

Home Antibiotic Therapy Following Early Discharge

Talcott et al[11] performed a pilot study of low-risk febrile neutropenic patients (Group 4) who were discharged early to home antibiotic therapy after initial hospitalization for 48 hours. In order to further reduce risk, Group 4 patients who had significant infections (bacteremia, pneumonia, urinary tract infection) or were 65 years of age or older were excluded. Eligible patients received standard, broad-spectrum intravenous antibiotics in the hospital. The initial regimens used were either mezlocillin plus gentamicin or ceftazidime as a single agent with therapeutic alterations made as needed by the patients' primary physicians. After two days of in-hospital observation, stable patients were enrolled in the home antibiotic program. Antibiotics were delivered to the patients' homes and stored in refrigerators until one to four hours prior to infusion. Central venous catheters were used for the infusion of antibiotics in 23 patients, while seven patients had peripheral venous access only. Patients or their home companions were instructed to change infusion pump cassettes and/or attach antibiotic bags. Patients were examined daily at home by a nurse for new signs and symptoms of infection and for the development of adverse effects. Patients were readmitted at the discretion of treating physicians or when a complication
occurred. Patients who remained on the study underwent laboratory evaluation according to a written protocol and were examined in clinic by a physician at two to four days after discharge and weekly thereafter. The mean duration of neutropenia among the 30 patients treated in this manner was six days; however, five patients had neutropenia of 13 to 36 days' duration. Only five (18%) had clinically documented infections (four had cellulitis and one had a suspected dental abscess). Patients were treated at home for a median of 3.5 days (range 1-24 days). Only 16 (53%) responded to the original antibiotic regimen. Four developed serious medical complications (hypotension, acute renal failure, disseminated fungal infection, coagulase-negative staphylococcal bacteremia) and required prolonged hospitalization after readmission. Five were readmitted for persistent fever, and five received additional antibiotics at home. Quality of life improved during the patients' home therapy, and favorable attitudes towards home care persisted after treatment. Daily medical charges were reduced by 44% for patients receiving home antibiotics compared with patients receiving hospital-based therapy. Although no patients died, the high rate of readmission (30%) and alteration of the original regimen raised questions about the practical applications of the prediction model. An overrepresentation of patients with acute leukemia and/or persistent neutropenia of more than seven days may account for the results of this pilot study. Consideration of the expected duration of severe neutropenia, as well as the underlying neoplasm (leukemia or other hematologic malignancy or solid tumor), might further refine the prediction model and lead to better patient selection and thus a higher response rate.

### Hospital-Based Oral Antibiotic Therapy

In a departure from the standard practice of administering parenteral antibiotics in febrile neutropenic patients, Malik and colleagues[12] reported on the use of oral ofloxacin as a single agent in this setting. In a prospective, randomized trial, they compared ofloxacin (400 mg orally twice a day) to standard parenteral regimens (amikacin plus carbencillin, cloxacillin, or piperacillin) in use at their institution for febrile neutropenic patients who could tolerate an oral regimen. Risk stratification was not performed, and the study was open to all patients treated by the oncology service. Approximately 68% of patients had leukemia, lymphoma, or aplastic anemia as the underlying disease, and the mean duration of neutropenia was nine days. The response rates (without alteration of the original regimen) for oral ofloxacin and the parenteral regimens were identical (53%), and the overall response rate (with and without modification of the original regimen) was 77% in patients initially randomized to receive oral ofloxacin compared with 73% in patients who received parenteral therapy. Responses in patients with documented infections were lower than in patients with FUO. Four patients (7%) randomized to the oral arm died, and six patients (10%) randomized to parenteral therapy died. Prior to this trial, limited data existed on the use of oral antibiotics. The equal efficacy of either orally or intravenously administered antibiotic therapy has significant implications for the management of febrile neutropenic patients, particularly in countries with limited medical resources. Also, with appropriate risk stratification and the selection of better oral regimens, response rates are expected to be higher than those achieved in this study.

A large, randomized, double-blind trial of oral ciprofloxacin plus amoxicillin/clavulanate vs intravenous ceftazidime therapy in hospitalized, low-risk patients with fever and neutropenia currently is ongoing at the NCI and is anticipated to provide additional objective data about the relative use of oral therapy in this population.

### Outpatient Antibiotic Therapy

Several recent trials have demonstrated the efficacy of outpatient antibiotic therapy in febrile patients with neutropenia. In a multicenter trial conducted in France,[13] 68 episodes of fever and neutropenia were treated with oral pefloxacin (400 mg twice daily) and amoxicillin/clavulanate (500/125 mg three times per day). These were patients with various lymphomas in whom neutropenia was expected to last fewer than seven days. Patients self-administered these drugs on first becoming febrile without examination by a physician and without initial laboratory evaluation, but they were required to contact the study centers if they were still febrile or otherwise symptomatically after 72 hours of antibiotic therapy. This approach was successful in 59 episodes (87%). Among the nine failures, eight responded to hospital-based therapy. One patient with methicillin-susceptible Staphylococcus aureus bacteremia died despite therapy with vancomycin plus amikacin. The average duration of neutropenia in these patients was five days. This study demonstrated that broad-spectrum, oral antibiotic therapy in patients with relatively short-lived neutropenia (likely a low-risk group) was associated with a higher response than that of patients in studies where such selections and exclusions were not made. This trial also demonstrated that such therapy could be given in an ambulatory/home setting and that an exhaustive laboratory evaluation was not necessary in many febrile neutropenic patients. These factors have important implications on the overall costs associated with the management of febrile neutropenic patients.

In a similar study, Malik et al.[14] evaluated the efficacy of self-administered oral ofloxacin (400 mg twice daily) for the treatment of chemotherapy-induced, low-risk febrile neutropenic patients with nonhematologic malignancies and an expected duration of neutropenia of less than one week. These patients either lived too far away from the oncology center or could not afford hospital-based therapy. As in the previously described French study,[13] patients instituted oral antibiotic therapy without initial contact with a physician or laboratory evaluation. Of the 111 febrile episodes, 92 (83%) responded to oral ofloxacin, and hospitalization of these patients was not necessary. Of the 19 patients who did not respond to ofloxacin, two died before they could reach a hospital, and one died in the hospital after prolonged neutropenia and fever. This study showed an overall response rate to antibiotic therapy of 97%, thereby providing further evidence that patients with short-lived neutropenia have only a small risk of developing serious complications or dying during a febrile episode and can be managed with oral antibiotic therapy in a relatively unsophisticated outpatient setting.

Two studies have been conducted at the University of Texas M.D. Anderson Cancer Center using oral and intravenous antibiotic administration.[10,15] The hypothesis that low-risk febrile neutropenic patients with cancer could be identified and treated safely and effectively in the ambulatory setting was tested in a randomized clinical trial. Low-risk febrile neutropenic patients were defined as those with fever that developed outside the hospital, with no significant comorbidity otherwise requiring hospitalization (eg, hypotension acidosis/respiratory distress, severe electrolyte abnormalities), and with normal liver and renal function. Psychosocial criteria for eligibility for outpatient therapy also included a history of compliance with medical therapy, a telephone in the local residence (which had to be within a 30-mile radius of the cancer center), and a willing caregiver to assist with following the treatment protocol.

Patients underwent a complete blood and laboratory examination, appropriate cultures, a chest radiograph, and a standard evaluation to determine the focus of infection (if any). Eligible patients were randomized to oral therapy with 750 mg of ciprofloxacin plus 600 mg of clindamycin every eight hours or to intravenous antibiotics consisting of 2 g of aztreonam plus 600 mg of clindamycin every eight hours.

Patients received their first dose of antibiotics in the emergency department of the Ambulatory Treatment Center, were observed for four to six hours, and were discharged to home. For patients randomized to the intravenous regimen, a nurse from a local home infusion therapy company connected the pre-existing central venous catheter to two infusion pumps (Cadd+, Pharmacia-Deltic, Minneapolis, Minn), each containing a 24-hour supply of antibiotic programmed to deliver the appropriate dose every eight hours. All patients returned to the clinic the following day for evaluation of response to therapy and toxicity, and they were seen daily either at home by the home infusion therapy nurse (who also performed standardized assessments of the patients on oral antibiotics) or in the clinic by one of the physician investigators.[10]

This trial evaluated 83 episodes - 40 on the oral regimen and 43 on the intravenous regimen. When enrolled in the study, 26% of patients had hematologic malignancies and 93% were moderately or severely neutropenic (<500 neutro-phil/mm3). Infections were documented in 39%, of which 88% were microbiologically documented (eg, bacteremias, urinary tract infections, and other skin/solid tissue infections). If otherwise eligible, patients older than 65 years of age were not excluded. Response rates for both regimens were much higher than those obtained in the study by Talcott et al. The response rates for the intravenous and oral regimens were 95% and
88% (P=0.19), respectively, giving a combined response rate of 92% for outpatient antibiotic therapy. The oral regimen was associated with renal toxicity; combining safety and efficacy, the intravenous regimen was superior. Of the 83 episodes, only six required admission to the hospital, three for management of renal toxicity and three for treatment of persistent fever. No infection-related complications (eg, septic shock) or deaths occurred on this trial. Although patients with solid tumors may have been overrepresented in this trial compared with the pilot study of Talcott and associates,[11] the high response rates of both initial regimens and the low rate of readmission (7%) substantiates the practical application of this model of eligibility for outpatient management.

These results have been replicated in a recently completed randomized clinical trial (ASCORP-II).[15] The intravenous regimen was retained, but the oral regimen was changed to 500 mg of ciprofloxacin plus 500 mg of amoxicillin/clavulanate every eight hours. Using the same eligibility criteria, 179 patients were randomized to either outpatient intravenous antibiotics (91 patients) or outpatient oral antibiotic therapy (88 patients). The median age of the patients in each group was 46 years, and the majority had solid tumors, primarily sarcoma and breast cancer. At the time of study entry, 89% of the patients on the intravenous regimen had a neutrophil count of 500 per mm\(^3\) or less compared with 86% for the oral regimen. The response rate for all episodes was 87% for the intravenous regimen and 90% for the oral regimen (P<0.05). No major toxicity was associated with either regimen, and no patients developed septic shock or died from their infections. >

Inpatient Parenteral to Outpatient Oral Therapy

According to P. Pizzo, MD, a study at the National Cancer Institute randomized febrile neutropenic patients who defervesced within 72 hours after administration of parenteral, broad-spectrum antibiotic monotherapy (either ceftazidime or imipenem/cilastatin) to either continue parenteral antibiotics or complete the course with oral ciprofloxacin at 25 mg/kg per day in three divided doses (at a maximum dose of 500 mg every eight hours). Patients who were persistently granulocytopenic and had either FUO or a clinically or microbiologically defined infection were eligible if they were able to take medicine by mouth, had no evidence of organ failure, and were hemodynamically stable. Also included were patients who had recovered their granulocyte counts to more than 500/mm\(^3\) but who were to complete a 10- to 14-day course of therapy for a documented infection. Solid tumors accounted for approximately half of the underlying disease in randomized patients, and the mean duration of neutropenia following the 72-hour evaluation period was approximately 10 days in both groups (range 1-37 days). Two thirds of patients had FUO in both groups, although documented infections included five bacteremias and one pneumonia among ciprofloxacin recipients, but only one bacteremia and no pneumonias in those who continued intravenous therapy. Of 27 evaluable episodes that were randomized to continue parenteral antibiotic, 24 (89%) were successfully treated without modifications, and 22 of 29 patient episodes (76%) in the oral treatment group completed therapy outside of the hospital, also without changes after switching to ciprofloxacin. Seven patients who had been discharged on ciprofloxacin required readmission to the hospital for recurrent fever at a mean of three days after discharge. Six of the seven readmitted patients had no identified source for recurrent fever, and one had a pharyngitis with negative culture for group A streptococcus. All patients responded to the reinstitution of their original parenteral antibiotic therapy with no major complications or deaths.

The high rate of recurrent fever (24%) in the oral ciprofloxacin group may have been due to the fact that patients were not selected for short-duration neutropenia and that many had low granulocyte counts for prolonged periods. It also is possible that occult Gram-positive infections accounted for recurrent fever, since ciprofloxacin has weak activity against these organisms, particularly the streptococci.

A Canadian group has explored a similar "switch" strategy in febrile neutropenic children who defervesced on parenteral antibiotics after 72 hours.[16] Patients who had negative blood cultures, were hemodynamically stable, and remained granulocytopenic were treated with the oral combination of cefixime (8 mg/kg per day as a single daily dose) and cloxacillin (100 mg/kg per day in four divided doses). Of 23 patients treated, the first 12 were observed on oral therapy in the hospital, and the remaining 11 patients were followed as outpatients until resolution of granulocytopenia. Median time from the switch to oral therapy until recovery of the absolute neutrophil count was three days (range 1-10 days). Three patients (13%) had recurrent fever with negative cultures, and all survived with inpatient treatment.

Similarly, Bash et al[17] permitted a switch to oral therapy (unspecified regimen) and discharge in 30 persistently neutropenic children with localized infections who defervesced on initial intravenous antibiotics, as long as they showed definitive signs of impending marrow recovery, eg, increasing neutrophil, leukocyte, and/or platelet counts. Five (16%) of these children required readmission for recurrent fever, but all were stable and responded to the reinstitution of parenteral therapy.
While limited in size and detail, these studies suggest that there is a role for the strategy of switching from an initial course of intravenously administered empirical antibiotics to an oral regimen in selected febrile neutropenic patients. Although low-risk patients can be safely managed with initial outpatient oral therapy, sequential intravenous to oral therapy may offer a more comfortable management plan for some patients and physicians. Several days of in-house observation provides an opportunity to stabilize and assess patients and permits ample time to identify those who are at low risk for subsequent complications. It also allows for intravenous therapy during the critical period following onset of fever, when some patients may have nausea or mucositis that limits oral intake or may have rapid hemodynamic changes associated with dehydration or sepsis. Early discharge after this initial observation period and prior to recovery of the absolute neutrophil count would still decrease the costs and risks associated with a more prolonged hospitalization.

Future Considerations

Refinement of the Risk Model

The results of clinical trials using intravenous and oral antibiotics demonstrate a range of response rates for low-risk febrile neutropenic patients from 53% to 95%. The lower response rates seen in studies conducted by Talcott[11] and Malik[12] may be the result of an overrepresentation of patients with hematologic malignancies or those who had undergone bone marrow transplantation. The studies conducted at M.D. Anderson Cancer Center and by Malik et al[18] with a population primarily of solid tumor patients or those with an expected duration of neutropenia of seven days of less were associated with more favorable response rates in the range of 83% to 95%.

The differences in response rates among the trials suggest that refinement of the risk model by incorporating other variables, such as severity of illness, underlying disease (hematologic malignancy vs solid tumor), and expected duration of neutropenia (<7 days, 7 to 14 days, >14 days), may allow for better selection of low-risk patients who can benefit from outpatient therapy. Separate models may be needed for patients with solid tumors, for patients undergoing high-dose chemotherapy with stem cell support, and for patients with leukemia and other hematologic malignancies. This issue currently is being examined in a multinational study as part of the Infectious Disease Subcommittee for the Multinational Association Supportive Care in Cancer.

Role of Growth Factors

Most of the studies conducted in low-risk patients have not examined the role of growth factors. Preliminary analysis of the ASCORP-II trial suggests that the oral regimen was associated with a higher response rate when patients were on a growth factor compared with those who did not receive a growth factor as part of their chemotherapy regimen, although the difference did not reach statistical significance.

Benefit has been shown when growth factors are used in moderate- and high-risk settings such as high-dose chemotherapy and stem cell support, as reported by Gilbert et al[19] in facilitating an outpatient management strategy for a group of patients who otherwise would require hospitalization.

It is unlikely that growth factors will prove to be cost effective if used routinely in an attempt to prevent febrile neutropenia in low-risk patients who are expected to have short durations of neutropenia. Existing data indicate that prophylactic growth factor administration is clinically useful and cost effective if a high incidence of febrile neutropenia (more than 40%) is anticipated for a given chemotherapy regimen.[20] Generally, only intensive regimens are likely to yield such a high incidence of fever during neutropenia. For less myelotoxic regimens, prophylactic growth factors are best reserved for patients who may be considered high risk on the basis of disease-related or underlying host factors.
Although growth factors can reduce the occurrence of fever during neutropenia in some situations, there is no evidence that they affect infectious mortality, response rates to antibiotics, or overall survival.

It also has been suggested that growth factors be used concomitantly with antibiotics to treat fever and neutropenia. Prior work indicates that days of hospitalization may be marginally reduced and suggests that the routine use of growth factors leads to less consumption of inpatient resource utilization, thereby partially offsetting the cost of the cytokine.[21] However, since low-risk patients do not need to be routinely hospitalized, duration of hospitalization is an artificial endpoint that probably has less relevance in the low-risk setting.[22] With initial responses to antibiotics (even oral agents) being in the range of 83% to 87% and ultimate response rates being almost 100%, the addition of costly adjuncts such as growth factors provides little benefit. Well-designed clinical trials that include a detailed economic analysis are needed to further examine this issue. Hematopoietic growth factors will probably be useful in moderate- and high-risk patients who have tissue-based or complex infections. These patients traditionally are hospitalized for management with broad-spectrum intravenous antibiotics and can be targeted for specific strategies using cytokines and antibiotics to decrease inpatient resource utilization.

Oral Antibiotic Regimens

It is not yet clear which is the safest and most reliable oral regimen for outpatient use, either for initiation or for completion of an empirical antibiotic regimen. Oral quinolone-containing regimens have been associated with side effects (eg, diarrhea and renal insufficiency) and gaps in antimicrobial spectrum. For example, ofloxacin has poor activity against *Pseudomonas aeruginosa* but is an acceptable agent in a febrile neutropenic population in which the incidence of *P. aeruginosa* infections was low. Conversely, ciprofloxacin has good antipseudomonal activity but is less active against Gram-positive organisms; it has been used successfully in combination with agents such as clindamycin or amoxicillin/clavulanate for empirical coverage of fever and neutropenia. However, side effects limit the use of these adjunctive agents.[10,23] The drawbacks associated with oral regimens might be minimized by careful patient selection, adequate oral hydration, and combination therapy to broaden the antimicrobial spectrum. To date, the most effective regimen studied in adults with the least amount of toxicity has been ciprofloxacin plus amoxicillin/clavulanate.[15] The choices for oral regimens will expand as new potent, broad-spectrum and orally bioavailable antibiotics are developed. It will be important to identify which of the new or currently available agents is most appropriate to treat infectious processes in the febrile neutropenic patient.

Conclusions

Although some patients with febrile neutropenic episodes can benefit from outpatient antibiotic therapy, not all low-risk patients are treated in this fashion. Many real and perceived disadvantages and barriers for patients, health care providers, and caregivers impede implementation of ambulatory management of febrile neutropenic patients. Advantages include greater convenience for the patient, the family and/or the caregiver; an improved quality of life for the patient; fewer superinfections; and lower cost. Disadvantages include loss of time at work caring for the patient; added stress and decreased quality of life for the caregiver; a potential risk of developing serious complications at home; and the risk of noncompliance and a false sense of security or inadequate monitoring for response to therapy/toxicity.

For many patients and physicians, outpatient oral antibiotics may be preferred, whereas more conservative approaches might be needed for others in order to feel comfortable with treating this population on an outpatient basis. Use of outpatient oral antibiotics may be the preferred strategy for patient populations with no nausea, a history of excellent compliance, the capability to understand risks and alternatives and the willingness to keep scheduled follow-up clinic visits. Outpatient IV antibiotics in conjunction with home care services may be the preferred strategy for patient populations with severe mucositis, pre-existing central venous access, and a high comfort level with infusion devices. Use of inpatient, short-term IV antibiotics followed by oral
antibiotic therapy may be the preferred strategy for patient populations that live too far away to comply with daily follow-up, have no caregiver or limited performance status, or if there are concerns about comorbidity or accuracy or risk assessment. Use of inpatient oral antibiotics may be the best choice for patients who live too far away for daily follow-up. These treatment alternatives give physicians and patients several options to consider when planning treatment strategies for febrile neutropenia.

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References


