Risk prediction in patients with neutropenia and fever in a reliable and timely manner has only become possible in the last decade. Patients have been categorized as high risk or low risk based on certain presenting features.

**Introduction**

Historically, fever in neutropenic patients has been considered a medical emergency that requires hospitalization and the parenteral administration of broad-spectrum antibiotics until resolution of symptoms. Identification of patients who are at low risk for serious sequelae (eg, sepsis, death) allows caregivers to consider ambulatory treatment, including both outpatient oral antibiotic treatment and at-home administration of intravenous antibiotics. Consequently, even though definitive evidence supporting this approach is still lacking, increasing numbers of low-risk patients with fever and neutropenia are being placed in these settings.

Potential advantages of ambulatory treatment are self-evident: lower costs, less exposure to nosocomial pathogens, and improved quality of life. Such treatment, however, requires the accurate identification of low-risk patients, an appropriate infrastructure for implementing these options, and easy access to emergency treatment should the patient’s condition deteriorate.

The purpose of this article is to review the components of evaluation and treatment that make ambulatory antimicrobial therapy feasible and successful in patients with fever and neutropenia, to review the effective use of ambulatory care in such patients, and to compare the advantages of ambulatory antimicrobial therapy with its potential risks and drawbacks.

**Identifying Appropriate Patients for Outpatient Care**

Over the last decade, research has made it possible to reliably identify a subset of patients in whom serious complications of infection are unlikely to occur. These low-risk patients might be appropriate for outpatient therapy. Features that delineate high-risk vs low-risk patients are not universally accepted, but several characteristics have been suggested as indicators of relative risk. These include status at the time of presentation (inpatient vs outpatient), acute medical comorbidity, control of cancer, type of underlying neoplasm, type of treatment, predicted duration of neutropenia, and presentation of infections (eg, pneumonia).

In 1988, a decision rule for stratifying patients was published, wherein the first substantial progress was made in clarifying which features were most likely to stratify for low-risk patients. Relevant features for this stratification were derived from a retrospective analysis of 261 medical records obtained from 184 cancer patients with febrile neutropenia, among whom four risk groups were identified based on outcome (infection-related morbidity and mortality). Validity of this risk-assessment model was subsequently demonstrated in a prospective study of 444 patients.

**Groups of Patients Identified at Risk**

The first of the four defined risk groups included bone marrow transplant recipients with hematologic malignancies and other patients who developed fever and neutropenia during their hospitalization. Patients in this group had the highest risk for complications, including high morbidity and mortality. The second high-risk group included outpatients with comorbid conditions, such as hypotension, altered mental status, respiratory failure, bleeding, dehydration, abdominal pain, and spinal cord compression; morbidity and mortality were high in this group as well. The third group included outpatients with uncontrolled cancer, but without comorbidity; as in the previous two groups, serious complications and mortality were seen. This group, as well, was associated with serious complications and mortality. The fourth group was composed of clinically...
stable outpatients without comorbidity, most of whom had solid tumors and were receiving conventional chemotherapy. These patients approximately 40% of those with fever and neutropenia and 60% to 70% of outpatients reported a low rate of serious complications and no mortality. Among the conclusions drawn from these studies were 1) a low-risk subpopulation indeed could be identified, and 2) patients in this study were at a low enough risk to study their management with a less intensive regimen than the standard inpatient, parenteral treatment. A pilot study by the same group tested this latter idea, as have other investigators, with the growing consensus that risk assessment is possible and that outpatient treatment, either completely or in the form of early discharge, is feasible.

Definition of Low-Risk Patients
Low-risk patients can be loosely defined as being clinically stable, having controlled malignancies, and presenting with no significant acute comorbidity. The term, significant, is, of course, a clinical judgment, but here indicates any condition suggesting clinical instability or requiring hospitalization with or without neutropenia. Another significant predictor of risk in these patients is the degree and duration of neutropenia. For instance, a study from the National Cancer Institute (NCI) revealed that 95% of patients with neutropenia lasting seven days or less responded to the initial antibiotic therapy, whereas only 32% of patients with greater than 15 days of neutropenia responded to treatment. Furthermore, the overall risk of medical complications was lower for patients whose neutropenia resolved in less than seven days.

Degree of neutropenia also contributes to risk, with increasing severity correlating with increased frequency of infectious complications. Because patients with solid tumors are more likely to have short-duration neutropenia, these patients may, in general, have a lower risk of complications than patients with hematologic malignancies. Some patients with leukemia in remission who are intensively treated patients may also have low-risk presentations. Although the duration and degree of neutropenia may be difficult to anticipate, both may be influenced by the intensity of the patient’s previous chemotherapy and the patient’s estimated bone marrow reserve.

Although this type of underlying neoplasm is associated with risk, in part because of the intensity of chemotherapy, not all patients with hematologic malignancies belong in this high-risk category. Talcott’s original risk assessment scheme included patients with acute leukemia in remission among low-risk patients. Several studies have upheld the validity of this assessment, such as those conducted by the Ambulatory and Supportive Care Oncology Research Program (ASCORP) at the M. D. Anderson Cancer Center in Houston, Texas, which included patients with controlled leukemia, as well as those with solid tumors. One such study showed that while patients with solid tumors had a significantly better response rate (91%), patients with hematologic malignancies still responded well to therapy, at a rate of 60% (P = .002). Low-risk presentations, while occurring more frequently in patients with solid tumors, do occur among patients with aggressively treated hematologic malignancies.

When fatal infections occur during episodes of fever and neutropenia, they usually occur in the terminal phase of disease and are due to untreatable cancer, not inadequate supportive care. Increasing use of prophylactic antibiotics and hematopoietic growth factors for infection prevention has resulted in an increase in the proportion of patients with unexplained fever compared with those with documented infections. However, evidence purports that some patients who initially appear to have unexplained fever later develop documented infections in the course of the febrile episode and have a higher complication rate. This underscores the need for frequent monitoring of neutropenic patients with fever.

In patients with fever and neutropenia, infections caused by gram-positive pathogens have been
associated with substantially less morbidity and mortality than those caused by gram-negative pathogens. Until the mid 1980s, gram-negative bacilli were isolated from 65% to 80% of documented infections in such patients, with response rates ranging from 50% to 80%, depending on the organism and/or site of infection. Gram-positive organisms were isolated from 10% to 20% of such patients and were associated with response rates of greater than 95%.

Epidemiologic Changes Impact Risk
During the past 15 years, substantial, documented epidemiologic changes have shown a dramatic increase in gram-positive infections (40% to 60%) and a corresponding decline in gram-negative infections. This is largely due to the use of prophylactic antibiotics directed against enteric gram-negative bacteria, and to the use of vascular access devices that break the skin barrier. Both of these factors\[\text{in}\]creases in the proportion of unexplained fever and gram-positive infections\[\text{might}\]be viewed as positive developments, since the morbidity and mortality in such patients have been reduced substantially.

Specific organisms might be associated with particularly aggressive or virulent infections. Examples among gram-positive bacteria include viridans streptococci, Listeria monocytogenes, or pneumococci, which can all cause overwhelming infections. Additionally, organisms, such as vancomycin-resistant enterococci (VRE) and staphylococci with reduced susceptibility to glycopeptides (glycopeptide intermediate Staphylococcus aureus [GISA]), limit therapeutic options. Similarly, among gram-negative pathogens, Pseudomonas aeruginosa, Acinetobacter species, and Stenotrophomonas maltophilia might be particularly problematic. Fortunately, these organisms are seldom isolated from \text{low-risk} patients, as previously defined.

It must be emphasized that risk assessment is a dynamic process that should be performed when the patient is initially evaluated and daily thereafter. When performed with due diligence, such assessments result in reliable risk prediction and can direct treatment strategies.

The Ambulatory Approach in Practice
Once low-risk patients have been identified, several approaches to ambulatory therapy are available. Antibiotics may begin in the hospital or in the clinic, with intravenous or oral antibiotics commencing as initial empiric therapy. In general, oral therapy should not be administered when nausea, vomiting, or mucositis are present. Discharge to home treatment may include the same regimens that were administered in the hospital, yet, on a more convenient regimen (once-daily intravenous infusion), or, as reported in pediatric patients, without any further antibiotic therapy.\[2\] The patients must be afebrile, stable, and show evidence of impending marrow recovery.

These therapies also can be greatly enhanced by the use of broad-spectrum, long half-life antibiotics (such as oral quinolones) and improvements in vascular-access devices. Advantages of ambulatory therapy include cost savings, higher quality of life, and less potential to acquire dangerous nosocomial pathogens.\[2\]

Early Discharge
Early discharge is one possible alternative to inpatient treatment. Low-risk patients who begin therapy in the hospital can continue therapy on an outpatient basis, potentially reducing costs and improving quality of life.

In one study,\[5\] patients were treated with antibiotics during 2 days of inpatient observation, and then evaluated for outpatient intravenous antibiotic treatment. Of the 30 low-risk patients accepted for the outpatient study, nearly half had neutropenia lasting longer than 7 days, with a median granulocyte level of 7/mm³. A total of five patients were readmitted briefly and without complication due to recurrent or prolonged fever, and four patients were readmitted for potentially serious conditions such as transient hypotension.

These results indicate that even severely neutropenic patients who meet carefully assessed criteria could be managed as outpatients. However, the high readmission rate is surprising, in part, because many eligible patients chose a brief extra inpatient stay over the novel\[and perhaps daunting\]alternative of intensive, home-based antibiotic therapy. Those eligible to enroll (but who did not) had less than half the duration of febrile neutropenia than those enrollees. Nevertheless, patients reported improved quality of life with home-based treatment, and there was evidence that enrolled patients had reduced costs over eligible patients who were not enrolled in the study. Thus, early discharge followed by at-home care may offer advantages, yet these advantages can only be accrued with proper patient and drug selection.

Early Discharge Combined With Antibiotics
Another option in the care of the patient with fever and neutropenia is to combine early discharge with oral antibiotics. Several studies have examined the conversion from inpatient intravenous therapy to outpatient oral therapy. For example, in a trial conducted by the National Cancer Institute (NCI), patients who received parenteral antibiotics and experienced defervescence within 72 hours were randomized into two groups: continuation of intravenous therapy or outpatient oral antibiotic use.[3,4,5,18] In the parenteral group, 89% of febrile episodes were treated successfully without antibiotic modifications, compared to 76% in the oral treatment group. Other studies have reported similar results, suggesting a role for sequential therapy with early discharge. [6,7]

**Outpatient Treatment**

Several small, randomized trials have shown that both oral and intravenous antibiotics are effective in the ambulatory treatment of low-risk febrile neutropenia. However, these trials were not powered to assess medical risk of home care. These studies have contributed to the formation of alternate criteria for low-risk assessment, and to the proper application of available medications. As a body of evidence, they suggest key requirements for outpatient management of fever and neutropenia in low-risk patients.

Patients may be treated either in the clinic, home, or hospital setting with traditional intravenous antibiotics, sequential intravenous/oral therapy, or oral combination therapy alone (eg, ciprofloxacin [Cipro] plus amoxicillin-clavulanate [Augmentin]).[17] Sundararajan and colleagues[19] at the M. D. Anderson Cancer Center published a pair of studies in the early 1990s, which were the first to use low-risk criteria to identify patient subgroups for initial outpatient therapy. These randomized trials were designed to compare combination therapies for outpatient management. The first study compared oral ciprofloxacin plus clindamycin (Cleocin, Veocin) to intravenous aztreonam plus clindamycin in 83 episodes of low-risk neutropenic fever.[11] Treatment response rates were 88% for the oral combination and 95% for the intravenous combination. Due to four cases of acute renal failure on the ciprofloxacin-containing regimen, however, this study was halted.

**Oral vs Intravenous Therapy in Ambulatory Treatment**

A follow-up study substituted amoxicillin-clavulanate for clindamycin and used a lower dose of ciprofloxacin than the previous trial. The two regimens were then compared to intravenous aztreonam (Azactam) plus clindamycin. The response rate was 87% for the intravenous method and 90% for the oral regimen.[19] Of the 17 patients requiring hospitalization (seven for oral and 10 for intravenous), none required admission to the intensive care unit, and there were no infection-related deaths. Furthermore, there was no renal toxicity and only mild toxicity—gastrointestinal side effects from oral administration.

Although these studies demonstrate that intravenous therapy is very effective in the home setting, oral antibiotics provide the most convenient form of therapy for outpatients. Oral trimethoprim-sulfamethoxazole (Bactrim, Septra) was initially useful as a prophylactic regimen in the early 1980s. However, the more recent development of synthetic quinolones (eg, ciprofloxacin, ofloxacin, gatifloxacin, and moxifloxacin) has greatly widened the applicability of oral therapy.[2] Newer quinolones are active against many gram-positive and most gram-negative organisms, although the development of resistance among some clinically relevant organisms is of concern.

A study conducted at the M. D. Anderson Cancer Center comparing outpatient oral ciprofloxacin to outpatient intravenous ceftazidime (Fortaz, Tazicef) in children showed an overall 86% success rate for the outpatient treatments, with no significant difference between the two groups in the percentage of patients able to complete therapy entirely as outpatients.[10] Similar conclusions were reached by Malik and colleagues.[9, 20] Following an initial report of an equivalent efficacy and survival rate among hospitalized patients treated with oral ofloxacin and those on standard parenteral combination therapy,[20] a second study randomized patients to inpatient or outpatient therapy consisting of oral ofloxacin twice daily.[9] Overall success of treatment was 98% for inpatients cases and 96% for outpatient cases (which included modification of treatment in 20% of inpatient cases and 19% in outpatient cases). Mortality rates were 2% in inpatients and 4% in outpatients. It should be noted, however, that 21% of the outpatients required hospitalization to help manage their infections.

**Advantages of Ambulatory Treatment**

Together, these studies demonstrate the efficacy of oral and intravenous antibiotics for the ambulatory treatment of low-risk febrile neutropenia. They present a range of options for inpatient treatment of higher-risk patients, initial inpatient treatment followed by outpatient treatment of
some low-risk patients, or complete outpatient treatment of other low-risk patients. Advantages of outpatient treatment have been shown by several studies, and include increased patient satisfaction and quality of life, lower potential for nosocomial infections, and reduced costs, particularly with oral-based approaches.[1,2,5] All of these advantages affect both individual patients and the healthcare system in general. From the patient’s perspective, increased quality of life and the potential for reduced expenses may be particularly attractive in light of the chronic nature of their disease and the multiple hospitalizations they may have had to tolerate with the standard, hospital-based approach.

Potential Drawbacks of Ambulatory Treatment

Although ambulatory treatment of febrile neutropenia offers great advantages for low-risk patients, there are some potential drawbacks (Table 1). Risk assessment can be difficult, perhaps leading to the inappropriate inclusion or exclusion of patients. However, trials in which patients were carefully selected have been successful in identifying patients who are unlikely to suffer any serious consequence of ambulatory treatment.[2] Additional trials that seek to validate these studies are needed.

Other drawbacks of treatment in the outpatient setting include logistic concerns that have potentially significant clinical repercussions. For example, removal of these relatively ill patients from the whole-care setting can make the diagnosis of concomitant problems more difficult and delay treatment. Cancer patients, even those at low risk, are subject to a range of infections and noninfectious complications. Therefore, when deliberating upon outpatient treatment, transportation time to a care center must be considered.

The necessity of an essential infrastructure is another logistic and economic concern. At present, many institutions may not be able to accommodate patients managed in an outpatient setting. To be prepared for emergency admission of patients who are treated in an outpatient setting, not only must emergency response transportation to nearby emergency facilities be available 24 hours a day, so must inpatient facilities, knowledgeable staff, and access to medications. Even the treatment of uncomplicated outpatients requires coordination with the treatment center to deliver required medication (if taken at home) and to conduct periodic examinations.

Because of these drawbacks, some physicians are reluctant to adopt a new treatment approach for patients whose disease has traditionally meant hospitalization. This can be a local or a regional phenomenon. In Europe, for instance, there have been few large clinical trials involving ambulatory treatment of febrile neutropenia, mainly because the reimbursement status does not encourage outpatient treatment. Additional randomized clinical trials, if successful, will support the establishment of outpatient-based treatments.[21] Increasing evidence indicating that the hospital environment is not necessarily a safe environment provides impetus to the evaluation of ambulatory treatment.

Conclusions

Among cancer patients with febrile neutropenia, there exists a subgroup of patients, both adult and pediatric, who are at low risk for serious infectious complications and who may be treated effectively and safely in an outpatient setting. The most crucial aspect of this treatment is proper assessment of risk. Figure 1 summarizes both the criteria that have been most consistently implicated as useful risk-assessment tools, as well as the treatment approaches recommended for each risk category. Additional characteristics that are considered to preclude a low-risk designation include advanced patient age and serum creatinine < 2.0 mg/dL or liver function study values three times higher than normal.[17]

Proper implementation of outpatient therapy requires that patients hold 24-hour access to emergency medical services and make periodic telephone or in-person contact with care providers. Under these conditions, the ambulatory approach can offer a low-risk alternative to exclusively inpatient-based treatment. While outpatient therapy is associated with some level of risk, hospitalization does not guarantee a risk-free environment. In fact, in the hospital, patients stand some risk of acquiring nosocomial pathogens. They also lack a degree of psychological support that some find beneficial in the home environment. Moderate-risk patients may be considered for initial hospitalization and stabilization of the febrile condition, followed by early discharge and completion of antibiotic courses as an outpatient.

Availability of new, oral, broad-spectrum antibiotics with low microbial resistance patterns is greatly enhancing the feasibility of ambulatory treatment. The future, no doubt, holds greater promise in the assessment of risk, greater understanding of cancer and its treatment, and the development of
improved antibiotic agents, all of which will contribute to the design of excellent ambulatory management.

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