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REVIEW

Management of Patients With Fever and Neutropenia Through the Arc of Time

A Narrative Review

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The association between fever and neutropenia and the risk for life-threatening infections in patients receiving cytotoxic chemotherapy has been known for 50 years. Indeed, infectious complications have been a leading cause of morbidity and mortality in patients with cancer. This review chronicles the progress in defining and developing approaches to the management of fever and neutropenia through observational and controlled clinical trials done by single institutions, as well as by national and international collaborative groups. The resultant data have led to recommendations and guidelines from professional societies and frame the current principles of management. Recommendations include those guiding new treatment options (from monotherapy to oral antibiotic therapy) and use of prophylactic antimicrobial regimens in high-risk patients. Of note, risk factors have changed with the advent of hematopoietic cytokines (especially granulocyte colony-stimulating factor) in shortening the duration of neutropenia, as well as with the discovery of more targeted cancer treatments that do not result in cytotoxicity, although these are still the exception. Most guiding principles that were developed decades ago—about when to begin empirical treatment after a neutropenic patient becomes febrile, whether and how to modify the initial treatment regimen (especially in patients with protracted neutropenia), and how long to continue antimicrobial therapy—are still used today. This review describes how the treatment principles related to the management of fever and neutropenia have responded to changes in the patients at risk, the microbes responsible, and the tools for their treatment, while still being sustained over the arc of time.

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Since Bodey and colleagues' seminal study in 1966 (1), the medical community has known that fever in a patient with neutropenia (neutrophil count $<0.50 \times 10^9$ cells/L) could signal potentially life-threatening infection and should prompt immediate empirical therapy with broad-spectrum antibiotics (1–3). Although neutropenia is still the quintessential risk factor for infection after cytotoxic chemotherapy, many neutropenic patients also have other disease- or treatment-related perturbations of their host defense matrix—from breaches of physical and mucosal barriers to alterations in the innate, cellular, and humoral immune system—that make them vulnerable to bacterial, viral, fungal, and parasitic infections.

In 2019, we stand at a time of remarkable progress in cancer therapy. Over past decades, treatment advances have increased survival rates for childhood cancer from less than 10% to nearly 90% (4). Improvements in the treatment of many types of adult cancer have also been notable (5). The 1998 discovery that a tyrosine kinase inhibitor provided a selective and effective treatment of chronic myelogenous leukemia led to the first targeted therapy that might avoid the complications of cytotoxic chemotherapy (6, 7). Many other small molecules have been developed for an array of defined molecular targets and are being integrated into regimens for leukemia, lymphoma, and solid tumors. Targeted therapies also include monoclonal antibodies and an expanding repertoire of immunotherapeutic agents (checkpoint inhibitors and chimeric antigen receptor T cells), some of which also alter the host's microbiome and risk for infection (8).

Despite the effect of novel immune-based therapies, cytotoxic chemotherapy (with its associated risk for fever and infection) is still the basis of most cancer treatment regimens. Fortunately, the introduction of hematopoietic cytokines, including granulocyte colony-stimulating factor, can shorten the duration of neutropenia from 6 days to 1 day and can reduce the incidence of infection and its complications, but not mortality, by 50% in high-risk patients (9–11). Granulocyte colony-stimulating factor is currently recommended as primary prophylaxis against neutropenia in patients whose risk is higher than 20%, as well as in patients who are older than 65 years or are receiving intensive chemotherapy regimens. With these advances, risk stratification and empirical antimicrobial treatment of patients receiving cytotoxic chemotherapy has evolved.

In 1990, the International Immunocompromised Host Society published guidelines for the design, analysis, and reporting of clinical trials on the antibiotic management of neutropenic patients (12). This report developed standards for the conduct of such trials, and many of its recommendations remain relevant today. Of note, the report coincided with the first guidelines for antimicrobial therapy in febrile neutropenic patients (13), which were updated in 2002 (14) and 2011 (15). In 2018, the Infectious Diseases Society of America and American Society of Clinical Oncology released recommendations for the outpatient management of fever and neutropenia in lower-risk adults having cancer treatment (generally defined as those with neutropenia <7 days in duration) (16). Table 1 summarizes the evolution of recommendations from 1993 to 2018.

In concert with changes in cancer therapy, advances in the antimicrobial armamentarium and the development of host-modifying agents have led to changes in the management of neutropenic patients, especially those at lower risk (<7 days of neutropenia). Once empirical antibiotic therapy is initiated, when and

how it should be modified when patients remain neutropenic for periods longer than 1 week remains an important issue. Table 2 summarizes recommendations for modifications to antimicrobial therapy in 2018 and compares them to 1993 recommendations.

Observations beginning as early as the 1970s and 1980s showed that nearly 80% of the microorganisms associated with infection in the febrile neutropenic patient arose from endogenous microbial flora (18, 19). These observations forecast the future understanding of the balance between aerobic and anaerobic organisms, the role of selective decontamination, and the role of the microbiome in risk for infection and modulation of host defenses, including risk for graft-versus-host disease. The importance of colonization and alterations in the microbiome was shown in 2017 in a multicenter study of 1118 recipients of allogeneic stem cell transplants and 1625 of autologous hematopoietic stem cell transplants, in whom colonization with resistant gram-negative bacteria was associated with infection by the same bacteria after transplant (18, 20, 21).

In the 1970s, researchers observed a shift in the oral and gastrointestinal microflora from the "normal" gram-positive, anaerobic environment when a patient is first diagnosed with cancer to one dominated by gram-negative organisms after onset of illness and associated therapies that alter the balance of aerobes and anaerobes. Van der Waaij (19) showed that anaerobes are necessary to help balance the proliferation of aerobes on the basis of studies that found significant differences in the log-rank number of aerobes needed to colonize a mouse whose anaerobes were preserved compared with mice whose anaerobes were decreased by antibiotics. The gut is a complex microenvironment where anaerobes inhibit colonization by new aerobes by altering metabolism and nutrient availability and producing inhibitory toxins and fatty acids. The gut microbiome can influence the response to chemotherapy, including stem cell therapy, and modulate the immune system (22, 23). Several studies have shown that the diversity and composition of the gut microbiota is correlated with risk for fever, neutropenia, and infection. For example, Hakim and colleagues (24) showed in children with acute lymphocytic leukemia that an abundance of Proteobacteria before chemotherapy was associated with development of fever and neutropenia. Whether the gastrointestinal microbiota is dominated by Enterobacteriaceae or Streptococcaceae during chemotherapy predicts risk for subsequent infection (24).

Infection in immunocompromised neutropenic patients can be caused by fungi, viruses, and parasites, as well as by bacteria. Important fungi include *Candida, Aspergillus, Mucor, Trichosporon, Fusarium, Scedosporium,* and dematiaceous molds (25–30). Viruses are also important causes of infection in immunocompromised patients and include adenovirus (31, 32); the herpesviruses (herpes simplex virus, cytomegalovirus, varicella-zoster virus, Epstein–Barr virus, and human herpesvirus 6); and respiratory viruses, such as influenza, parainfluenza, respiratory syncytial virus, coronavirus, human metapneumovirus, and rhinovirus.

Key Summary Points

Fever and neutropenia due to cytotoxic cancer chemotherapy can result in risk for life-threatening infections.

Although neutropenia is a quintessential risk factor, patients with cancer also have a panoply of disease- and treatment-related alterations of their innate and acquired immune defenses, rendering them vulnerable to infection with bacteria, viruses, fungi, and protozoa.

Beginning broad-spectrum empirical antibiotic therapy at the first sign of fever in a profoundly neutropenic patient can be life-saving and has been a standard of therapy for nearly 5 decades.

Low-risk neutropenic patients can have shorter durations of treatment, including oral regimens, whereas high-risk patients (>7 d of neutropenia) often require additions and modifications of the initial regimen, as well as more prolonged treatment courses.

The advent of hematopoietic cytokines (granulocyte colony-stimulating factor) and the selected use of prophylactic antimicrobial regimens have altered risk for infectious complications in high-risk patients.

When and Where to Initiate Antibiotics and Which Ones Should be Administered

In the early days of cytotoxic chemotherapy–induced neutropenia, clinicians learned that neutropenic patients must be promptly evaluated and, ideally, start empirical antibiotic therapy within an hour of fever onset. Over decades, researchers have sought strategies to differentiate patients with life-threatening infection from those whose fever might not be of infectious cause and ways to determine which patients require longer versus shorter antibiotic courses, but these questions remain unresolved. Despite advances in culture-independent technologies (for example, inflammatory markers, molecular sequencing techniques and polymerase chain reaction, immunodiagnostics, and imaging [33, 34]), their usefulness in identifying serious infections, including invasive mycoses, remains limited. Although many assays have been developed to diagnose invasive mycoses, sensitivity is limited (galactomannan, 44% to 90%; [1,3]-β-D-glucan, 30% to 100%; and polymerase chain reaction, 84%) (17, 34–37). Further, they can be unreliable when a single sample is measured, although serial sampling has better performance (31–36, 38–41). Of note, many of the assessment tools, such as physical examination and blood cultures, that were pillars of diagnosis 40 to 50 years ago still serve as standard diagnostic tools. Selected imaging studies have proven valuable for diagnosing invasive fungal infections of the lung, sinuses, and brain in patients with prolonged neutropenia (31, 34).

When principles for initial empirical antibiotics for neutropenic fever were first being formulated, no single

antibiotic could provide coverage against the broad array of potential gram-positive and gram-negative aerobes and anaerobes. Thus, combination antibiotic therapy was the rule, generally with a first-generation cephalosporin, an aminoglycoside, and an extended-spectrum penicillin. Because gram-negative bacteria and especially *Pseudomonas aeruginosa* were dominant in the 1960s and 1970s, achieving high bactericidal levels was an important objective (3, 17, 37). With advances in antibiotic therapy, efforts were made to reduce toxicity (primarily by limiting exposure to aminoglycosides and vancomycin) and to avoid emergence of β-lactamase–producing bacteria by combining β-lactam antibiotics with β-lactamase inhibitors. The third- and fourth-generation cephalosporins, followed by the carbapenems and fluoroquinolones, were major advances in the 1980s. At that time, the predominant bacterial pathogens also shifted to gram-positive organisms, especially *Staphylococcus aureus*, Methicillin-resistant *S aureus*, and coagulase-negative staphylococci.

In the late 1980s and 1990s, monotherapy was considered because selected third-generation cephalosporins (such as ceftazidime and cefoperazone) and carbapenems (initially imipenem–cilastatin and now meropenem) provided coverage of the most common gram-negative bacteria (including *Pseudomonas)*. Monotherapy was controversial, and some considered it risky, but randomized clinical trials affirmed its safety and efficacy (42, 43). However, the emergence of extensively drug-resistant and pandrug-resistant gram-negative bacteria (for example, *Acinetobacter* and *Pseudomonas*) and carbapenemase-producing organisms (for example, *Klebsiella*) has decreased the utility of some third-generation cephalosporins (such as ceftazidime) and carbapenems as monotherapy. Additional concerns were related to the OMP36 mutation leading to porin loss; extended-spectrum, β-lactamase–producing Enterobacteriaceae (especially *Escherichia coli* and *Klebsiella*); and the AmpC-E mutation in SPICE microbes (*Serratia*, *Providencia*, *Pseudomonas*, *Proteus*, *Citrobacter*, and *Enterobacter*). Newer antibiotics, such as ceftazidime–avibactam and ceftolozane–tazobactam, overcome some of these limitations and provide activity against β-lactamase–producing microbes (44). Although monotherapy remains a standard approach, the agents used have changed to overcome emerging resistant organisms (15, 42, 43).

Along with the shift to monotherapy, the availably of fluoroquinolones—with their broad-spectrum activity, high bioavailability, and ability to be administered orally—raised the prospect of using regimens that could be administered in an ambulatory setting. Although

Table 1. Evolving Principles for the Management of Fever and Neutropenia Over Time

2018 Recommendations (50 Years After the Initial Studies of Fever and Neutropenia)	**1993 Recommendations (25 Years After the Initial Studies of Fever and Neutropenia)***
A neutropenic patient who becomes febrile should be promptly evaluated and should start receiving empirical antibiotics within an hour of the onset of fever.	Same as current.
Persistently febrile patients with protracted neutropenia require daily evaluation. Patients whose neutropenia or fever has resolved can be evaluated as needed.	Recommended daily evaluation for all patients without assessment of risk factors (which were less defined at that time).
Intravenous, empirical, broad-spectrum, antibiotic therapy should be promptly initiated in neutropenic patients who become febrile. Oral antibiotics, including in an ambulatory setting, can be used in defined low-risk patients (<7 d of neutropenia) after a first dose in a hospital or emergency department setting.	Recommended inpatient intravenous antibiotics for all febrile (a single elevation of oral temperature to >38.5 °C, or 3 elevations to >38 °C during a 24-h period) and neutropenic (neutrophil count <0.50 × 10^9 cells/L) patients.
If the patient has an indwelling intravenous catheter, obtain cultures from each catheter port and lumen, as well as from a peripheral vein. Rotate antibiotic therapy through each lumen of multiple-lumen catheters. Although efforts are made to treat infections without catheter removal, this does become necessary when blood cultures remain positive; with evidence of a tunnel or pocket infection; or with certain microbes, especially *Candida*. See Table 2.	Same as current, even though in 1993, experience with indwelling catheters was nascent and there was an absence of robust data.
Monitor high-risk patients (>7 d of fever and neutropenia) for secondary clinical or microbiological infections. The risk for secondary infections in low-risk patients is very low.	Recommended monitoring all patients closely for secondary infections requiring additions or modifications to the initial antibiotic regimen, regardless of risk.
Continue empirical antibiotic therapy if the patient has prolonged (>1 wk) fever and neutropenia. See below regarding patients who become afebrile or who show signs of hematologic recovery.	Recommended continued antibiotics until the resolution of fever and/or neutropenia.
Add empirical antifungal therapy if a patient with neutropenia remains febrile after 4–7 d of broad-spectrum antibiotic therapy or has recurrent fever while persistently neutropenic.	Same as current, although the starting point for adding empirical antifungal therapy was closer to 7 d in patients with persistent fever and neutropenia.
Multiple studies have shown that antibiotics can be withdrawn with the resolution of fever and/or neutropenia, with patients followed closely.	Recommended discontinuing antibiotic therapy when the neutrophil count increased above 0.50 × 10^9 cells/L in a high-risk patient or was increasing in a low-risk patient.
Although 10–14 d of treatment is adequate in most patients with neutropenia, prolonged therapy is necessary for a patient with a residual focus of infection or invasive mycoses (e.g., hepatosplenic candidiasis).	Same as current.
All those caring for a febrile patient with neutropenia should wash their hands carefully before any contact with the patient. With gels and quality care guidelines, handwashing has improved and remains an essential means to reduce nosocomial infections.	At the time of the 1993 review, handwashing was known to be important but was practiced less than optimally by health care providers, including physicians.

* The Year 25 General Principles were from a review by Pizzo (17).

Table 2. Common Modifications or Additions to Initial Empirical Antibiotic Therapy in Patients With Neutropenia and Fever*

Status or Symptoms	Modifications of Primary Regimen	
	2018 (50 Years After the Initial Studies of Fever and Neutropenia)	**1993 (25 Years After the Initial Studies of Fever and Neutropenia)**
Fever		
Persistent for >1 wk	Add empirical antifungal therapy, with the caveat that some centers recommend commencing antifungal therapy with liposomal amphotericin, voriconazole, or caspofungin after 4 d of fever and neutropenia.	Similar recommendation, although many centers used 7 d of persistent fever and neutropenia as the starting point for empirical antifungal therapy, the choices of which were more limited.
Recurrence after ≥1 wk in patient with persistent neutropenia	Add empirical antifungal therapy, as above. Modifications of the initial antibiotic regimen may also be necessary.	Similar recommendation regarding empirical antifungal therapy.
Persistent or recurrent fever at time of recovery from neutropenia	Evaluate liver and spleen by computed tomography, ultrasound, or magnetic resonance imaging for hepatosplenic candidiasis, and evaluate need for antifungal therapy.	Same as current.
Bloodstream		
Cultures before antibiotic therapy		
Gram-positive organism	Add vancomycin, unless the institution has observed infection with vancomycin-resistant enterococci or staphylococci, in which case linazolid should be used, pending further identification.	Similar recommendation, although choice was limited to vancomycin.
Gram-negative organism	The preferred option is a carbapenem (meropenem), but if the isolates are carbapenemase-producing or extended-spectrum β-lactamase–producing, alternate therapy could be ceftazidime–avibactam or meropenem–vaborbactam.	If the patient was stable and isolate-sensitive, the initial regimen could be maintained, but if *Pseudomonas aeruginosa*, *Enterobacter*, or *Citrobacter* was isolated, an aminoglycoside or an additional β-lactam antibiotic was added.
Organism isolated during antibiotic therapy		
Gram-positive organism	Add vancomycin (or linezolid).	Add vancomycin.
Gram-negative organism	Change to new regimen, such as ceftazidime–avibactam or meropenem–vaborbactam.	Change to new regimen, albeit limited choices (for example, imipenem plus gentamicin or vancomycin, or gentamicin plus piperacillin).
Head, eyes, ears, nose, or throat		
Necrotizing or marginal gingivitis	Add specific antianaerobic agent (clindamycin or metronidazole) to empirical therapy.	Same as current.
Vesicular or ulcerative lesions	Suspect herpes simplex infection. Culture and begin valacyclovir therapy.	Same, except acyclovir was the only option.
Sinus tenderness or nasal ulcerative lesions	Suspect fungal infection with *Aspergillus* or *Mucor*.	Same as current.
Gastrointestinal tract		
Retrosternal burning pain	Suspect *Candida*, herpes simplex, or both. Add antifungal therapy (with an azole [fluconazole, voriconazole, or posaconazole], an echinocandin [caspofungin], or amphotericin, and, if no response, valacyclovir. Bacterial esophagitis is also a possibility. For patients who do not respond within 48 h, endoscopy should be considered.	Same as current, except antifungal and antiviral agents were more limited.
Acute abdominal pain	Suspect typhlitis, as well as appendicitis if pain is in right lower quadrant. Add specific antianaerobic coverage to the empirical regimen or use meropenem or meropenem–vaborbactam and monitor closely for need for surgical intervention (albeit rarely used).	Similar to current recommendations, although there were fewer antibiotic choices and surgical intervention was a more common option.
Perianal tenderness	Similar to the treatment of typhlitis.	Similar to current recommendation.
Respiratory tract		
New focal lesion in patient recovering from neutropenia	Observe carefully, because this may be a consequence of inflammatory response in concert with neutrophil recovery.	Same as current.
New focal lesion in a patient with continuing neutropenia	*Aspergillus* is the chief concern. Perform appropriate cultures and consider biopsy. If patient is not a candidate for procedure, administer voriconazole.	Similar to current, except that antifungal therapy was limited to high-dose amphotericin B (1.5 mg/kg of body weight per day).
New interstitial pneumonia	Attempt diagnosis by examination of induced sputum or bronchoalveolar lavage. If not feasible, begin empirical treatment with trimethoprim–sulfamethoxazole or atovaquone. Consider noninfectious causes and the need for lung biopsy if condition has not improved after 4 d of therapy.	Similar to current recommendations.

Continued on following page

Table 2–Continued

Status or Symptoms	Modifications of Primary Regimen	
	2018 (50 Years After the Initial Studies of Fever and Neutropenia)	**1993 (25 Years After the Initial Studies of Fever and Neutropenia)**
Central venous catheters		
Positive culture for organisms other than *Bacillus* species or *Candida*	Attempt to treat. Rotate antibiotic administration in patients with multiple-lumen catheters.	Same as current.
Positive culture for *Bacillus* species or *Candida*	Remove catheter and treat appropriately, although some advocate attempting to treat *Candida* infections without catheter removal.	Similar to current, but with stronger recommendation to remove catheter for *Candida* infections.
Exit-site infection with mycobacterium or *Aspergillus*	Remove catheter and treat appropriately.	Same as current.
Tunnel infection	Remove catheter and treat appropriately.	Same as current.

* The Year 25 Modifications of the Primary Regimen are based on a review by Pizzo (17).

many clinicians believe that beginning empirical therapy with intravenous antibiotics is important, the combination of ciprofloxacin with amoxicillin–clavulanic acid makes it possible to switch to oral antibiotics administered at home (16, 45–49).

Another advance is use of fluoroquinolones as antibiotic prophylaxis against neutropenic infection. A 2014 meta-analysis (48) of 17 clinical trials enrolling 1453 patients who were having an autologous or allogeneic hematopoietic stem cell transplant (albeit with different preparative regimens and study designs) showed that fluoroquinolone prophylaxis significantly reduced incidence of febrile episodes, including clinically and microbiologically defined infections, without altering all-cause or infection-related mortality. These positive results must be considered against the equally important finding that, with extensive use, resistance to fluoroquinolones has increased to 28%, which could negatively affect the clinical utility of this important class of antibiotics (20, 48). Striking a balance of benefit and harm has led the American Society of Clinical Oncology to recommend that antibiotic prophylaxis be limited to patients who are likely to have severe neutropenia (neutrophil count $<0.100 \times 10^9$ cells/L) for longer than 7 days (16, 45, 47).

When and How Should the Initial Antibiotics be Modified?

With prompt empirical antibiotics at the onset of neutropenic fever, patients whose neutropenia lasts beyond 7 to 10 days (that is, high-risk patients) will become afebrile, remain persistently febrile, manifest no clinical or microbiological signs of infection, or develop confirmed infection. This spectrum of outcomes prompted complex clinical trials of antimicrobial strategies that evaluated such outcomes as "success without the need to modify the initial regimen" and "success with modifications or additions of the initial regimen" (14, 15, 17, 37, 42, 50). In 2002, the International Immunocompromised Host Society and the Multinational Association of Supportive Care in Cancer proposed that a response to an antibiotic regimen without any modifications should be determined at 72 hours of therapy and again at day 5, and that the reasons for regimen modification (if required) should be stated. Reasons for modifying initial empirical therapy include persistent fever (with or without clinical deterioration), a new microbiological finding (with or without clinical deterioration), and evidence of clinical progression of a presumed infection. Therapy might also be modified because of adverse events or intolerance to the study drug (12, 51).

Duration of Antibiotic Therapy in Patients With Unexplained Fever or Defined Infection

Uncertainty surrounds decisions about how long to continue empirical therapy, especially without microbiological or clinical signs of infection and when the patient remains neutropenic with or without persistent fever.

Patients Whose Neutrophils Recover or Who Become Afebrile

Initial studies that randomly assigned patients who were still neutropenic after 7 days of empirical antibiotics without any defined source of infection suggested that continuing antibiotics was advantageous, especially for patients with persistent fever (52, 53). Although continuing empirical antibiotics in such patients has remained standard practice for nearly 4 decades, the approach has evolved for patients who become afebrile while receiving antibiotics or have signs of bone marrow recovery or resolution of neutropenia. In 1993, Buchanan (54) showed that discontinuing empirical antibiotics was generally safe when patients had signs of hematologic recovery, defined as an increasing neutrophil count even if not fully recovered to more than 0.50×10^9 cells/L (50, 54). Several studies have affirmed this approach, including the ANTIBIOSTOP (Early Discontinuation of Empirical Antibacterial Therapy in Febrile Neutropenia) study reported in 2018 (55–57). The debate about continuing or discontinuing therapy was further addressed in a 2017 study that randomly assigned 709 patients, including 157 adults with hematologic cancer and "high-risk" neutropenia (>7 days), to continue or discontinue empirical antibiotic therapy if they were clinically stable and afebrile after

72 hours of treatment (58). The trial found no differences in adverse consequences between the groups, making discontinuation of antibiotics under these circumstances the recommended approach.

Patients Who Remain Febrile and Neutropenic

In contrast to therapy for patients who become afebrile or recover from neutropenia, discontinuing empirical antibiotics is not recommended when patients remain persistently febrile and neutropenic. National Cancer Institute studies reported in 1982 not only showed the benefit of continuing empirical antibiotics but also suggested a benefit of adding empirical antifungal therapy for patients with fever and neutropenia that persisted for 7 or more days (53). These initial observations were supported by a randomized clinical trial in which empirical antifungal therapy started 4 days after empirical antibiotic therapy (59). At the time of these studies, amphotericin B was the only suitable antifungal agent, but subsequent studies demonstrated benefit and lower toxicity from newer classes of antifungal therapy, such as liposomal preparations of amphotericin, and more recently, newer azole antifungals (particularly voriconazole), liposomal amphotericin, and echinocandins like caspofungin.

Although empirical antifungal therapy has been standard management of prolonged fever and neutropenia for more than 35 years, researchers have tried to better define which patients are most likely to benefit. Efforts have included clinical risk criteria coupled with imaging studies and culture-independent diagnostics. Many randomized trials, observational studies, and meta-analyses have provided evidence codified in clinical guidelines (26, 60, 61). Although definitive proof of benefit is lacking, the apparent reduction in morbidity and mortality associated with use of empirical antifungal therapy makes it the default.

In summary, for high-risk patients with persistent fever and neutropenia, continued antibiotic therapy along with empirical antifungal therapy starting 4 to 7 days after initiation of antibiotic therapy is recommended. Continued pursuit of tools to reliably predict and diagnose invasive fungal infections and monitor their management remains a priority.

The Management of Specific Infections

If an infection is identified, management depends on the causative microbes, sensitivity pattern, site, underlying cancer and its treatment, pattern and severity of the host's immunodeficiency, and projected time to recovery (62). Whether focused therapy for an identified infection is appropriate in the setting of immunodeficiency or broader therapy remains a conundrum. An additional topic of debate is whether effective treatment should be accomplished within a defined period (such as 7 to 10 days) or should be continued until neutropenia and all signs of infection resolve.

Early studies suggested that narrowing the spectrum of antimicrobial therapy to target a specific gram-positive or gram-negative organism in a patient who has protracted neutropenia favored use of continuing broad-spectrum therapy (62). However, an argument can be made for narrowing the spectrum of therapy and monitoring the patient closely for new signs of infection. Similar uncertainty pertains to the length of therapy for patients with a defined infection and persistent neutropenia. Also of note, signs of "infection" could seem to worsen with the recovery of the neutrophil count and should not necessarily prompt other changes in therapy. The more worrisome scenario is the patient who seems to be worsening despite optimal antimicrobial therapy, particularly in the setting of prolonged neutropenia.

Granulocyte transfusion is a supportive method with a storied history. Since the early 1970s, some clinicians have recommended donor granulocytes as adjunctive therapy despite limited data supporting the method's efficacy. There are technical difficulties in harvesting sufficient donor granulocytes for transfusion to a profoundly neutropenic patient (58). This limitation has been partly overcome by stimulation of donor granulocytes with either steroids or granulocyte colony-stimulating factor (9–11, 63–66). Despite these technical improvements, the most recent randomized clinical trial did not show statistically significant benefit (67).

Because of their effect on management of neutropenic patients, specific attention has been paid to invasive fungal infections, which are the focus of guidelines from the Infectious Diseases Society of America for *Candida* (2009) and *Aspergillus* (2016) (41, 68). In addition, the European Society of Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology, and the European Conference on Infections in Leukemia issued clinical guidelines for mucormycosis in 2013 (69).

FUTURE DIRECTIONS

Neutropenic fever in patients having cancer therapy has been a focus of investigation over the past 5 decades. In the early days of cancer treatment, infectious complications were a leading cause of death and often limited the delivery of chemotherapy. Although the risk for infection is still notable, infection-related morbidity and mortality have decreased. Many early approaches to the management of febrile neutropenic patients remain relevant today, suggesting that some interventions endure over the arc of time. Given the pace of new knowledge and studies suggesting that new evidence generally renders systematic reviews out of date within 5.5 years of publication (70), that management of neutropenic fever has remained largely consistent is notable.

Future research should build on the longstanding issues that remain unresolved. Seeking cancer treatments that result in less cytotoxicity and immunodeficiency remains a priority, and progress has certainly been made. Strategies to lessen the effect of treatment-related immunosuppression have also seen progress, such as empirical antibiotic regimens, prophylactic antibiotics, and hematopoietic cytokines in high-risk patients. Our understanding of the immune system is increasingly sophisticated, and new ways of modulating it will likely be

identified to lessen treatment-induced immunodeficiency and further alter the relationship among cancer treatment, neutropenia, fever, and infection.

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References

1. **Bodey GP, Buckley M, Sathe YS, Freireich EJ.** Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med. 1966;64:328-40. [PMID: 5216294]
2. **Klastersky J, Zinner SH.** Synergistic combinations of antibiotics in gram-negative bacillary infections. Rev Infect Dis. 1982;4:294-301. [PMID: 7051232]
3. **Love LJ, Schimpff SC, Schiffer CA, Wiernik PH.** Improved prognosis for granulocytopenic patients with gram-negative bacteremia. Am J Med. 1980;68:643-8. [PMID: 7377220]
4. **Hunger SP, Mullighan CG.** Acute lymphoblastic leukemia in children. N Engl J Med. 2015;373:1541-52. [PMID: 26465987] doi:10.1056/NEJMra1400972
5. **DeVita VT Jr, Chu E.** A history of cancer chemotherapy. Cancer Res. 2008;68:8643-53. [PMID: 18974103] doi:10.1158/0008-5472.CAN-07-6611
6. **Longo DL.** Imatinib changed everything [Editorial]. N Engl J Med. 2017;376:982-3. [PMID: 28273011] doi:10.1056/NEJMe1700833
7. **Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al.** Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344:1031-7. [PMID: 11287972]
8. **June CH, Sadelain M.** Chimeric antigen receptor therapy. N Engl J Med. 2018;379:64-73. [PMID: 29972754] doi:10.1056/NEJMra1706169
9. **Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.** Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Ann Intern Med. 2007;147:400-11. [PMID: 17876022]
10. **Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL.** Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer. 2011;11:404. [PMID: 21943360] doi:10.1186/1471-2407-11-404
11. **Truong J, Lee EK, Trudeau ME, Chan KK.** Interpreting febrile neutropenia rates from randomized, controlled trials for consideration of primary prophylaxis in the real world: a systematic review and meta-analysis. Ann Oncol. 2016;27:608-18. [PMID: 26712901] doi:10.1093/annonc/mdv619
12. From the Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. J Infect Dis. 1990;161:397-401. [PMID: 2179421]
13. **Hughes WT, Armstrong D, Bodey GP, Feld R, Mandell GL, Meyers JD, et al.** From the Infectious Diseases Society of America. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis. 1990;161:381-96. [PMID: 2179420]
14. **Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al.** 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002;34:730-51. [PMID: 11850858]
15. **Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al; Infectious Diseases Society of America.** Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56-93. [PMID: 21258094] doi:10.1093/cid/cir073
16. **Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al.** Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. J Clin Oncol. 2018;36:1443-53. [PMID: 29461916] doi:10.1200/JCO.2017.77.6211
17. **Pizzo PA.** Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med. 1993;328:1323-32. [PMID: 8469254]
18. **Girmenia C, Bertaina A, Piciocchi A, Perruccio K, Algarotti A, Busca A, et al; Gruppo Italiano Trapianto di Midollo Osseo (GITMO) and Associazione Microbiologi Clinici Italiani (AMCLI).** Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey. Clin Infect Dis. 2017;65:1884-96. [PMID: 29020286] doi:10.1093/cid/cix690
19. **van der Waaij D.** History of recognition and measurement of colonization resistance of the digestive tract as an introduction to selective gastrointestinal decontamination. Epidemiol Infect. 1992;109:315-26. [PMID: 1468517]
20. **Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, et al.** Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis. 2017;65:1819-28. [PMID: 29020364] doi:10.1093/cid/cix646
21. **Baker TM, Satlin MJ.** The growing threat of multidrug-resistant gram-negative infections in patients with hematologic malignancies. Leuk Lymphoma. 2016;57:2245-58. [PMID: 27339405] doi:10.1080/10428194.2016.1193859
22. **Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA.** The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell. 2018;33:570-80. [PMID: 29634945] doi:10.1016/j.ccell.2018.03.015
23. **Koh AY.** The microbiome in hematopoietic stem cell transplant recipients and cancer patients: opportunities for clinical advances that reduce infection. PLoS Pathog. 2017;13:e1006342. [PMID: 28662165] doi:10.1371/journal.ppat.1006342
24. **Hakim H, Dallas R, Wolf J, Tang L, Schultz-Cherry S, Darling V, et al.** Gut microbiome composition predicts infection risk during chemotherapy in children with acute lymphoblastic leukemia. Clin Infect Dis. 2018;67:541-8. [PMID: 29518185] doi:10.1093/cid/ciy153
25. **Arif S, Perfect JR.** Emergence of the molds other than *Aspergillus* in immunocompromised patients. Clin Chest Med. 2017;38:555-73. [PMID: 28797495] doi:10.1016/j.ccm.2017.04.014
26. **Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al; Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer.** Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis. 2002;34:7-14. [PMID: 11731939]
27. **Farmakiotis D, Kontoyiannis DP.** Mucormycoses. Infect Dis Clin North Am. 2016;30:143-63. [PMID: 26897065] doi:10.1016/j.idc.2015.10.011
28. **Luplertlop N.** *Pseudallescheria/Scedosporium* complex species: from saprobic to pathogenic fungus. J Mycol Med. 2018;28:249-56. [PMID: 29567285] doi:10.1016/j.mycmed.2018.02.015

29. **Polvi EJ, Li X, O'Meara TR, Leach MD, Cowen LE.** Opportunistic yeast pathogens: reservoirs, virulence mechanisms, and therapeutic strategies. Cell Mol Life Sci. 2015;72:2261-87. [PMID: 25700837] doi: 10.1007/s00018-015-1860-z
30. **Walsh TJ, Groll AH.** Emerging fungal pathogens: evolving challenges to immunocompromised patients for the twenty-first century. Transpl Infect Dis. 1999;1:247-61. [PMID: 11428996]
31. **Khanal S, Ghimire P, Dhamoon AS.** The repertoire of adenovirus in human disease: the innocuous to the deadly. Biomedicines. 2018;6. [PMID: 29518985] doi:10.3390/biomedicines6010030
32. **Tebruegge M, Curtis N.** Adenovirus: an overview for pediatric infectious diseases specialists. Pediatr Infect Dis J. 2012;31:626-7. [PMID: 22592487] doi:10.1097/INF.0b013e318250b066
33. **Orlowski HLP, McWilliams S, Mellnick VM, Bhalla S, Lubner MG, Pickhardt PJ, et al.** Imaging spectrum of invasive fungal and fungal-like infections. Radiographics. 2017;37:1119-34. [PMID: 28622118] doi:10.1148/rg.2017160110
34. **Greene RE, Schlamm HT, Oestmann JW, Stark P, Durand C, Lortholary O, et al.** Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis. 2007;44:373-9. [PMID: 17205443]
35. **Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group.** ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect. 2014;20 Suppl 3:5-26. [PMID: 24479848] doi:10.1111/1469-0691.12371
36. **Batzlaff CM, Limper AH.** When to consider the possibility of a fungal infection: an overview of clinical diagnosis and laboratory approaches. Clin Chest Med. 2017;38:385-91. [PMID: 28797483] doi: 10.1016/j.ccm.2017.04.002
37. **Pizzo PA.** Fever in immunocompromised patients. N Engl J Med. 1999;341:893-900. [PMID: 10486422]
38. **Walsh TJ, Merz WG, Lee JW, Schaufele R, Sein T, Whitcomb PO, et al.** Diagnosis and therapeutic monitoring of invasive candidiasis by rapid enzymatic detection of serum D-arabinitol. Am J Med. 1995;99:164-72. [PMID: 7625421]
39. **Walsh TJ, Hathorn JW, Sobel JD, Merz WG, Sanchez V, Maret SM, et al.** Detection of circulating candida enolase by immunoassay in patients with cancer and invasive candidiasis. N Engl J Med. 1991; 324:1026-31. [PMID: 2005939]
40. **Steinbach WJ.** Blood-based diagnosis of invasive fungal infections in immunocompromised/oncology patients. Pediatr Infect Dis J. 2015; 34:1020-2. [PMID: 26083591] doi:10.1097/INF.0000000000000797
41. **Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al; Infectious Diseases Society of America.** Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503-35. [PMID: 19191635] doi:10.1086/596757
42. **Pizzo PA, Hathorn JW, Hiemenz J, Browne M, Commers J, Cotton D, et al.** A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N Engl J Med. 1986;315:552-8. [PMID: 3526155]
43. **Freifeld AG, Walsh T, Marshall D, Gress J, Steinberg SM, Hathorn J, et al.** Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. J Clin Oncol. 1995;13:165-76. [PMID: 7799016]
44. **van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al; Antibacterial Resistance Leadership Group.** Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant enterobacteriaceae. Clin Infect Dis. 2018;66: 163-71. [PMID: 29020404] doi:10.1093/cid/cix783
45. **Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, et al.** Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013;31:794-810. [PMID: 23319691] doi:10.1200/JCO.2012.45.8661
46. **Freifeld AG, Pizzo PA.** The outpatient management of febrile neutropenia in cancer patients. Oncology (Williston Park). 1996;10: 599-606, 611-2; discussion 615-6. [PMID: 8723296]
47. **Freifeld AG, Sepkowitz KA, Martino P, Steven N, Billingham L, Cullen M, et al.** Antibacterial prophylaxis in patients with cancer and neutropenia [Letter]. N Engl J Med. 2006;354:90-4; author reply 90-4. [PMID: 16394310]
48. **Kimura S, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, et al.** Antibiotic prophylaxis in hematopoietic stem cell transplantation. A meta-analysis of randomized controlled trials. J Infect. 2014; 69:13-25. [PMID: 24583063] doi:10.1016/j.jinf.2014.02.013
49. **Pizzo PA, Robichaud KJ, Edwards BK, Schumaker C, Kramer BS, Johnson A.** Oral antibiotic prophylaxis in patients with cancer: a double-blind randomized placebo-controlled trial. J Pediatr. 1983; 102:125-33. [PMID: 6336781]
50. **Aquino VM, Buchanan GR, Tkaczewski I, Mustafa MM.** Safety of early hospital discharge of selected febrile children and adolescents with cancer with prolonged neutropenia. Med Pediatr Oncol. 1997; 28:191-5. [PMID: 9024515]
51. **Feld R, Paesmans M, Freifeld AG, Klastersky J, Pizzo PA, Rolston KV, et al; Immunocompromised Host Society.** Methodology for clinical trials involving patients with cancer who have febrile neutropenia: updated guidelines of the Immunocompromised Host Society/ Multinational Association for Supportive Care in Cancer, with emphasis on outpatient studies. Clin Infect Dis. 2002;35:1463-8. [PMID: 12471564]
52. **Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG, Levine AS, Deisseroth AB, et al.** Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am J Med. 1979;67:194-200. [PMID: 380336]
53. **Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG.** Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med. 1982;72:101-11. [PMID: 7058815]
54. **Buchanan GR.** Approach to treatment of the febrile cancer patient with low-risk neutropenia. Hematol Oncol Clin North Am. 1993; 7:919-35. [PMID: 8226566]
55. **Micol JB, Chahine C, Woerther PL, Ghez D, Netzer F, Dufour C, et al.** Discontinuation of empirical antibiotic therapy in neutropenic acute myeloid leukaemia patients with fever of unknown origin: is it ethical? Clin Microbiol Infect. 2014;20:O453-5. [PMID: 24313354] doi:10.1111/1469-0691.12445
56. **Orasch C, Averbuch D, Mikulska M, Cordonnier C, Livermore DM, Gyssens IC, et al; 4th European Conference on Infections in Leukemia (ECIL-4).** Discontinuation of empirical antibiotic therapy in neutropenic leukaemia patients with fever of unknown origin is ethical [Letter]. Clin Microbiol Infect. 2015;21:e25-7. [PMID: 25658572] doi:10.1016/j.cmi.2014.10.014
57. **Le Clech L, Talarmin JP, Couturier MA, Ianotto JC, Nicol C, Le Calloch R, et al.** Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. Infect Dis (Lond). 2018;50:539-49. [PMID: 29451055] doi:10.1080/23744235.2018.1438649
58. **Aguilar-Guisado M, Espigado I, Martín-Peña A, Gudiol C, Royo-Cebrecos C, Falantes J, et al.** Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol. 2017;4:e573-83. [PMID: 29153975] doi:10.1016/S2352-3026(17)30211-9
59. **Empiric antifungal therapy in febrile granulocytopenic patients.** EORTC international antimicrobial therapy cooperative group. Am J Med. 1989;86:668-72. [PMID: 2658574]
60. **Mellinghoff SC, Panse J, Alakel N, Behre G, Buchheidt D, Christopeit M, et al.** Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). Ann Hematol. 2018;97:197-207. [PMID: 29218389] doi:10.1007/s00277-017-3196-2

61. **Wingard JR.** Empirical antifungal therapy in treating febrile neutropenic patients. Clin Infect Dis. 2004;39 Suppl 1:S38-43. [PMID: 15250019]
62. **Pizzo PA, Commers J, Cotton D, Gress J, Hathorn J, Hiemenz J, et al.** Approaching the controversies in antibacterial management of cancer patients. Am J Med. 1984;76:436-49. [PMID: 6367456]
63. **Liles WC, Huang JE, Llewellyn C, SenGupta D, Price TH, Dale DC.** A comparative trial of granulocyte-colony-stimulating factor and dexamethasone, separately and in combination, for the mobilization of neutrophils in the peripheral blood of normal volunteers. Transfusion. 1997;37:182-7. [PMID: 9051093]
64. **Peters C, Minkov M, Matthes-Martin S, Pötschger U, Witt V, Mann G, et al.** Leucocyte transfusions from rhG-CSF or prednisolone stimulated donors for treatment of severe infections in immunocompromised neutropenic patients. Br J Haematol. 1999;106:689-96. [PMID: 10468857]
65. **Price TH.** Granulocyte transfusion therapy: it's time for an answer [Editorial]. Transfusion. 2006;46:1-5. [PMID: 16398722]
66. **Price TH, Bowden RA, Boeckh M, Bux J, Nelson K, Liles WC, et al.** Phase I/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in hematopoietic stem cell transplantation. Blood. 2000;95:3302-9. [PMID: 10828009]
67. **Price TH, Boeckh M, Harrison RW, McCullough J, Ness PM, Strauss RG, et al.** Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. Blood. 2015;126:2153-61. [PMID: 26333778] doi:10.1182/blood-2015-05-645986
68. **Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al.** Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1-60. [PMID: 27365388] doi:10.1093/cid/ciw326
69. **Chen SC, Sorrell TC, Chang CC, Paige EK, Bryant PA, Slavin MA.** Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care setting, 2014. Intern Med J. 2014;44:1315-32. [PMID: 25482743] doi:10.1111/imj.12597
70. **Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D.** How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007;147:224-33. [PMID: 17638714]

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