

## CURRENT MANAGEMENT OF THE FEBRILE NEUTROPENIC PATIENT

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Neutropenia is the most common factor predisposing cancer patients to infection, and is associated with a specific spectrum of infection (although periodic epidemiologic changes do occur) (1-3). Neutropenia is often superimposed on other risk factors, such as impaired cellular or humoral immunity mucosal and/or integumentary damage, and the use of external medical devices (eg. catheters) all of which influence the spectrum of infection as well. Approximately 50 percent of patients with fever and neutropenia have episodes of unexplained fever (Table 1). Currently gram-positive organisms cause approximately 40-55 percent of documented infections. The most common organisms isolated include coagulase-negative staphylococci, *Staphylococcus aureus* (including MRSA), *Enterococcus* species (including VRE), and viridans group (alpha-hemolytic) streptococci (4). Gram-negative bacilli are isolated less frequently, particularly in patients receiving quinolone prophylaxis, and account for 20-25 percent of documented infections. The most commonly isolated organisms include the *Enterobacteriaceae* (particularly *Escherichia coli*, and *Klebsiella* species), and non fermentative gram-negative bacilli such as *Pseudomonas aeruginosa*, other *Pseudomonas* species, *Acinetobacter* species and *Stenotrophomonas maltophilia* (5). Anaerobic infections are distinctly uncommon. However, polymicrobial infections have increased in frequency over the years and now account for 20-25 percent of documented infections (6). These are generally tissue infections such as pneumonia, neutropenic enterocolitis, and perirectal infections. Up to 80 percent of these infections have a gram-negative component, and approximately one third are caused by multiple species of gram-negative bacilli.

*Pseudomonas aeruginosa* is isolated from 40-50 percent of polymicrobial infections.

Fungal infections occur in patients with persistent neutropenia. Established fungal pathogens include *Candida albicans* and *Aspergillus fumigatus*. The spectrum of fungal infections is changing (7). Other *Candida* species (*C. tropicalis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*), *Aspergillus terreus*, the Zygomycetes, *Fusarium* species, and *Scedosporium apiospermum* have all emerged as significant pathogens in recent years. Many of these organisms are resistant, or less susceptible to standard antifungal agents.

It is important to be aware of local epidemiology and susceptibility/resistance patterns, since these can differ from institution to institution. Specific choices for antimicrobial prophylaxis, empiric therapy, and targeted therapy should be guided by such local data (8).

Febrile neutropenic patients have traditionally been managed in the hospital and receive broad-spectrum, parenteral antibiotic therapy empirically. Recent advances have made it possible to identify a "low-risk" subset using clinical criteria and/or statistically derived risk prediction rules (9-11). Low-risk patients can be treated in the outpatient/clinic setting with parenteral and/or oral antibiotic regimens – Table 2 (11).

TABLE 1. Nature of Febrile Episodes in Neutropenic Patients

Type of Episode	% Frequency
Unexplained Fever	45-50
Documented Infection	40-50
Microbiologically documented	40-50
Clinically documented	40-50

TABLE 2. Common Outpatient Regimens in Low-Risk Febrile Neutropenic Patients

Parenteral	aztreonam + clindamycin ceftriaxone + amikacin ceftazidime (?) cefepime
Oral	ciprofloxacin + amoxicillin / clavulanate ciprofloxacin + clindamycin or macrolide gatifloxacin †

(?) ceftazidime usage based on current resistant patterns

† only pilot data available

Patients not identified as “low-risk” receive hospital based therapy. Two types of empiric regimen are common: a) combination regimens, b) monotherapy. Various choices are listed in Table 3.

TABLE 3. Antibiotic Regimens in Febrile Neutropenic Patients

Combination Regimens (without vancomycin)	
Aminoglycoside (eg. amikacin)	+ cephalosporin (eg. cefepime) + penicillin (eg. piperacillin/tazobactam) + carbapenems (eg. imipenem/meropenem)
Combination Regimens (with vancomycin)	
Vancomycin	+ extended spectrum cephalosporin + antipseudomonal penicillin + aztreonam or a quinolone
Monotherapy	
Extended spectrum cephalosporin (cefepime) Carbapenem (imipenem or meropenem) Piperacillin/tazobactam	

Vancomycin should be used sparingly and should be discontinued if cultures do not isolate a resistant gram-positive organisms (8). Linezolid, daptomycin, or quinupristin/dalfopristin should not be used empirically unless a patient is known to be colonized with VRE.

The response to the initial regimen is generally in the 75-85 percent range. Modifications are made, based on the nature of the initial regimen, and microbiological data (if cultures become positive). The most common modifications include strengthening antibacterial coverage (vancomycin, aminoglycoside, quinolone, anaerobic agent) particularly if monotherapy was used initially. Empiric antifungal therapy is generally added on day 3-5, especially in patients with hematologic malignancies, HSCT recipients, or in patients known to have had a previous fungal infection or colonization.

Duration of therapy depends on the nature of the febrile episode. In patients with unexplained fever, therapy can be discontinued after 6-7 days, if patients have been afebrile for 72 hours. In patients with documented infections most experts recommend continuing therapy until signs/symptoms of infection have

resolved and there is evidence of hematologic recovery as well ( $ANC > 500/mm^3 \times 2$  consecutive days) (8).

Colony stimulating factors (G-CSF, GM-CSF) and WBC transfusions are not recommended for routine use but might be useful in neutropenic patients with refractory infections. Human activated protein C (drotrecogin alfa) reduces mortality in patients with severe sepsis, but it has not been fully evaluated in neutropenic patients. Routine antibacterial, antifungal, or antiviral prophylaxis is not recommended. High-risk patients might benefit from antibacterial prophylaxis (usually with a fluoroquinolone), and antifungal prophylaxis (with an azole or a polyene agent). Prophylaxis with trimethoprim/sulfamethoxazole or an alternative agent is recommended for all patients at risk for *Pneumocystis jiroveci* infection. All prophylaxis should be given for the shortest at-risk duration, as possible.

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