Neutropenic Fever and Sepsis: Evaluation and Management

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Abstract

Neutropenia remains the predominant predisposing factor for infection in most cancer patients. Bacterial and fungal infections are common in this setting. Not all neutropenic patients have the same risk of developing severe infection or serious medical complications. Although all patients with neutropenia and fever should receive prompt, empiric antibiotic therapy, low-risk patients can be effectively managed without hospitalization—often with the administration of oral antibiotics. Other patients need hospital-based therapy. The emergence of resistant microorganisms has become a significant problem in neutropenic patients. Frequent epidemiologic surveys to detect the emergence of resistant organisms are recommended. Antibiotic stewardship and Infection Control Programs are important tools in combating resistant organisms.

Keywords

Neutropenic fever · Risk-assessment · Empiric therapy · Outpatient therapy · Antimicrobial stewardship

Contents

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1 Introduction

Neutrophils provide protection against a multitude of bacterial and fungal pathogens. Neutropenia from any cause results in increased frequency and severity of infections caused by these organisms. Bodey and colleagues first described the association between neutropenia and infection in patients with hematologic malignancies in 1966 [1]. They demonstrated that the frequency and severity of infection was directly related to the degree and duration of neutropenia, once the absolute neutrophil count (ANC) dipped below 1,000/mm^3. The currently accepted definition of neutropenia is an ANC of $\leq$500/mm^3. It was traditional to admit all febrile neutropenic patients to the hospital for close monitoring and the administration of broad-spectrum, parenteral, antibiotic therapy for the entire duration of the febrile episode [2]. Our understanding of the syndrome of neutropenic fever has improved substantially in the ensuing years. The availability of truly broad-spectrum antimicrobial agents (extended spectrum cephalosporins, carbapenems) made it possible to administer monotherapy instead of always using two or three agents in combination [3]. The development of accurate risk prediction rules, improvement in infusion therapy and supportive care, and the increasing role played by home health care agencies has enabled clinicians to shift the site of care of febrile neutropenic patients from the hospital to the ambulatory clinic/home, for at least part of the duration of the febrile episode [4, 5]. The development of oral agents such as the fluoroquinolones, with potent activity against important gram-negative pathogens including *Pseudomonas aeruginosa,* has considerably improved the efficacy of infection prevention/prophylaxis for high-risk neutropenic patients. Improved diagnostic techniques have made the documentation of many infections (particularly fungal infections) quicker and more accurate [6, 7]. The frequent use (misuse?) of many antimicrobial agents in this setting has led to reduced susceptibility and/or the development of overt resistance among common bacterial and fungal pathogens [8, 9]. With new drug development almost at a standstill, antimicrobial stewardship and infection control have gained increasing importance in limiting the damage caused by multidrug-resistant organisms [10, 11]. The development of novel antineoplastic agents (e.g., purine analogs, various monoclonal antibodies, temozolamide) has altered the traditional spectrum of infection in patients receiving chemotherapy. These and other issues will continue to provide diagnostic and therapeutic challenges in the years to come.

Table 1 Common causes of infection in neutropenic patients

Gram-positive bacteria	*Fungal*
Coagulase-negative staphylococci	*Candida* species
Staphylococcus aureus	*Aspergillus* species
Enterococcus species	Zygomycetes
Viridans group streptococci	Other opportunistic fungi
Bacillus species	
Corynebacterium species	
Streptococcus pneumoniae	
Beta-hemolytic streptococci (groups A, B, C, G, F)	
Stomatococcus mucilaginosus	
Gram-negative bacteria	
Escherichia coli	
Klebsiella species	
Other *Enterobacteriaceae*	
Pseudomonas aeruginosa	
Pseudomonas (non-*aeruginosa*) species	
Acinetobacter species	
Stenotrophomonas maltophilia	
Anaerobes	
Bacteroides species	
Clostridium species	

2 Epidemiology of Infection

Bacterial infections predominate during the initial phases of a neutropenic episode, whereas fungal infections are more common in patients with prolonged neutropenia. Bacterial and fungal pathogens that frequently cause infections in such patients are listed in Table 1. This list is by no means all inclusive, and it is important to remember that most microorganisms (even those with a low virulence potential) can cause opportunistic infection in neutropenic patients.

Additionally, the epidemiology of infection keeps changing, and institutional differences are not uncommon [12, 13]. Consequently, it is advisable to conduct local surveillance studies, at least in institutions that have been designated Comprehensive Cancer Centers, and treat large numbers of cancer patients [14, 15].

Most recent epidemiologic surveys have documented the predominance of gram-positive bacteria over gram-negative bacteria [14, 16, 17]. The proportion of infections caused by gram-positive bacteria has been reported to be as high as

75–80 % at some centers. These data, however, do not paint a complete picture, since both the European Organization for Research and Treatment of Cancer (EORTC) and the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) focus only on single-organism (monomicrobial) bacteremias [14, 16]. Although this is useful information, bacteremias cause only 20–30 % of infections in neutropenic patients [2, 3]. Other common sites of infection include the respiratory tract, the urinary tract, skin and skin structures, and the gastrointestinal tract [18]. Whereas gram-positive bacteria are the predominant organisms isolated from blood cultures, gram-negative organisms predominate at most other sites (e.g., pneumonias, urinary tract infections, peri-rectal infections, biliary tract infections, neutropenic enterocolitis). Another critical piece of information missing from the EORTC, SCOPE, and other surveys is the proportion of infections that are polymicrobial. Data from the M. D. Anderson Cancer Center indicate that polymicrobial infections have more than doubled in frequency since the early 1980s and currently account for 25–30 % of microbiologically documented infections [17–20]. Additionally, approximately 80 % of polymicrobial infections have a gram-negative component, and approximately 33 % are caused exclusively by multiple species of gram-negative bacilli [19, 21]. When all sites of infection as well as monomicrobial and polymicrobial infections are included in the overall spectrum, a substantially different picture emerges. The proportion of monomicrobial gram-positive infections falls sharply from approximately 80 to <50 % [17, 18]. This can have a significant impact on the choice of agents/regimens used for antimicrobial prophylaxis and for empiric therapy in this setting.

Gram-positive organisms colonizing the skin are isolated frequently. These include coagulase-negative staphylococci (CoNS), *Staphylococcus aureus, Bacillus* species, and *Corynebacterium* species. Gram-positive organisms arising from the oropharynx and upper airways include viridans group *Streptococci* (VGE), *Streptococcus pneumoniae*, and *Stomatococcus mucilaginosus*, whereas the enterococci arise primarily from the lower gastrointestinal tract. Gram-negative organisms are represented most frequently by the Enterobacteriaceae (*Escherichia coli, Klebsiella* species, *Enterobacter* species) and *P. aeruginosa*, with *Acinetobacter* species and *Stenotrophomonas maltophilia* being reported as increasing frequently at some institutions [22–24]. Strict anaerobes are seldom isolated from neutropenic patients (<2 % of all bacterial infections), although *Clostridium difficile*-associated disease is becoming increasingly common [25, 26]. Rapidly growing mycobacteria are uncommon but occasionally cause catheter-related infections in neutropenic patients [27].

Candida species are still the most common fungi isolated from neutropenic patients and cause infections ranging from superficial lesions (thrush, esophagitis, vaginitis) to deep, systemic candidiasis [28]. Most cancer treatment centers have reported a decline in the proportions of infections caused by *Candida albicans* and an increase in the proportion caused by other *Candida* species (*C. tropicalis, C. glabrata, C. krusei*) [29]. *Candida parapsilosis* is the most common species associated with catheter-related candidemia [30]. This epidemiologic shift has been attributed largely to the use of fluconazole prophylaxis, although a similar

pattern has been described in patients who are fluconazole naïve [31, 32]. *Aspergillus* species are second in frequency among fungal pathogens in neutropenic patients [33]. They also cause a range of infections, including localized infections such as sinusitis, cutaneous aspergillosis, aspergilloma (fungus ball), and invasive/disseminated infections frequently involving the lungs and the central nervous system [34].

Many centers have reported an increase in the frequency of infections caused by the Zygomycetes, in part related to the use of voriconazole [35–37]. These infections are often indistinguishable from aspergillosis, with the rhino-cerebral form being particularly devastating [38]. A number of opportunistic fungal pathogens have emerged in recent years including *Fusarium* species, *Trichosporon beigelii, Blastoschizomyces capitus*, and *Scedosporium* species [33].

Viral infections are uncommon in neutropenic patients and are seen more often in patients with impaired cell-mediated immunity. It is important to remember that such patients do develop neutropenia, and viral infections may then need to be considered [2, 18]. Community respiratory viruses (influenza, parainfluenza, respiratory synsitial virus) do pose a significant threat to patients with hematologic malignancies and recipients of stem cell transplantation, particularly in the winter months [39, 40].

3 Initial Assessment of the Neutropenic Patient

One of the basic principles of the management of febrile neutropenic patients is to perform a quick but thorough evaluation before the administration of empiric antibiotic therapy. A complete history and physical examination is essential. Historical information of interest includes details of antineoplastic and immunosuppressive therapy, the use of antimicrobial prophylaxis, previous episodes of infection (or colonization with important pathogens) and their treatment, recent surgical/dental procedures, travel history, and potential exposure to sick contacts. Underlying comorbid conditions such as diabetes mellitus, chronic lung disease, cardiovascular, renal, and hepatic problems should also be noted as they might have an impact on the nature and severity of infection, the risk of complications, and the antimicrobial agents selected for therapy.

The inflammatory response is often blunted in neutropenic patients resulting in a paucity of symptoms and signs. Consequently, the physical examination should focus on detection of subtle signs especially at frequently infected sites such as the skin, oropharynx, gastrointestinal tract, and perineum. Although fever is the most consistent sign of infection in neutropenic patients, some patients may develop a serious infection without mounting a febrile response, particularly if they are receiving corticosteroids or other immunosuppressive agents.

Standard laboratory investigations include blood and urine cultures and cultures from other sites (e.g., respiratory specimens, CSF, wounds) when indicated. In patients with diarrhea, stool cultures are not very informative, but stool specimens for the detection of *Clostridium difficile* toxins should be obtained. Patients with

pulmonary symptoms or an infiltrate might require a bronchoscopy to obtain adequate specimens for microbiologic evaluation, as very few will have a productive cough. Nasal specimens are recommended for detecting the presence of community respiratory viruses, especially in the winter months.

Routine chest radiography is not recommended and should be done only in patients with respiratory signs and symptoms. Computerized tomography of the chest and other areas (sinuses, abdomen, pelvis) should be performed as clinically indicated and is far more informative than routine radiographic imaging. Other standard laboratory tests include complete blood cell and differential counts, a serum electrolyte panel, blood urea nitrogen and serum creatinine levels, and a hepatic panel (serum bilirubin and hepatic enzymes). These investigations should be repeated as clinically indicated.

4 Risk Assessment and Risk-Based Treatment Strategies

It has long been recognized that not all neutropenic patients have the same risk of developing serious infections and/or life-threatening complications. However, our ability to reliably identify low-risk and high-risk subgroups at the onset of a febrile episode was limited. This led to the practice of administering hospital-based empiric antibiotic therapy to all febrile neutropenic patients [2]. Although successful, this strategy was associated with prolonged hospital stay for many patients, leading to increased resource utilization and costs, and exposing patients to some of the iatrogenic hazards of hospitalization, as well as to the more resistant hospital microflora. With a greater understanding of the syndrome of febrile neutropenia, many investigators have developed reliable risk prediction rules. The most widely accepted of these, and the one used to identify low-risk patients for most antibiotic trials worldwide, is the risk index devised by the Multinational Association for Supportive Care in Cancer (MASCC). This risk index was derived (and subsequently validated) by assigning integer weights to seven characteristics to develop an index score—Table 2 [41]. A score of 21 identified low-risk patients with a positive predictive value of 91 %. Higher scores impart greater specificity with a corresponding loss in sensitivity. Separate but similar risk prediction rules have been developed for pediatric oncology patients [42]. Many investigators have developed simple clinical criteria to identify low-risk patients without having to calculate a risk index score [43–45]. This might be a simpler and more practical method of identifying such patients in a busy clinical practice setting.

There is uniform agreement that patients who are not classified as low risk should be hospitalized for the administration of empiric antibiotic therapy and close monitoring [2, 18]. Several different options for the treatment of low-risk patients have recently been evaluated. These include the nature of the empiric regimen (parenteral, sequential, i.e., IV → PO, oral) and the setting of therapy (initial hospitalization followed by early discharge, outpatient management of the entire febrile episode). These options constitute the entire scope of risk-based therapy.

Table 2 The Multinational Association of Supportive Care in Cancer (MASCC). Risk index for the identification of low-risk febrile neutropenic patients

Patient characteristics	Assigned score
Burden of illness	
No symptoms or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic lung disease	4
Solid tumor/no previous fungal infection	4
No dehydration	3
Outpatient status at onset of fever	3
Age <60 years	2

Highest possible score = 26. A score of ≥21 indicates low-risk status [41]. Scores >21 increase specificity with corresponding loss of sensitivity

5 Empiric Antibiotic Therapy in Low-Risk Patients

The various strategies currently in use for the treatment of low-risk febrile neutropenic patients and the antimicrobial regimens used in this setting are listed in Tables 3 and 4. The first reports of oral therapy for documented bacterial infections in neutropenic patients focused on the therapeutic potential of trimethoprim/sulfamethoxazole, with a response rate of 54 % being reported in infections refractory to other regimens [46]. With the development of fluoroquinolones like ciprofloxacin with potent activity against most gram-negatives including *P. aeruginosa*, and moderate activity against many gram-positives, empiric oral therapy became a viable option [47]. With the development of accurate risk prediction rules, an appropriate population for such therapy was better defined [41, 48]. Despite these advances and the emergence of home healthcare agencies capable of safely delivering outpatient antibiotic therapy, many clinicians are still not comfortable with this approach [KR-personal observations]. Many prefer to admit low-risk patients to the hospital for a short (24–48 h) "stabilization" period, followed by early discharge on parenteral or oral antimicrobial agents. This conservative approach has been successfully evaluated in both adults and pediatric patients [49–52]. The results of these trials are summarized in Table 5. Talcott's pilot study produced disappointing results since 30 % of patients required readmission to the hospital for various reasons and 13.3 % developed serious medical complications. Patients with leukemia, some of whom were classified as low-risk patients but had prolonged neutropenia (up to 31 days), were included in this study and probably account for the high readmission rate [49]. Better results were achieved by investigators from Britain who only enrolled patient with solid tumors and lymphomas and excluded patients with hematologic malignancies [50]. Early

Table 3 Treatment options for low-risk, febrile neutropenic patients

• Short (24–48 h) stabilization period in hospital, followed by early discharge on parenteral or oral regimens
• Outpatient (clinic/office/home) treatment of the entire febrile episode (parenteral, sequential, IV → PO, or oral regimen)
• Hospital-based parenteral or oral regimens

Adapted from Refs. [4, 5, 43–45, 62]

Table 4 Frequently used antibiotic regimens in low-risk patients

Parenteral regimens	Oral regimens
Aztreonam + clindamycin	Cefuroxime
Ciprofloxacin + clindamycin	Ciprofloxacin + amoxicillin/clavulanate
Ceftriaxone (±) amikacin	Ciprofloxacin + clindamycin
Ertapenem (±) amikacin	Ciprofloxacin + azithromycin
Ceftazidime or cefepime	Moxifloxacin (±) agents used in combination with ciprofloxacin

Adapted from Refs. [18, 45, 62, 63]

Table 5 Outpatient management of low-risk febrile neutropenic patients after a short hospital stay

Authors	Ref. no	Type of study and patient population	Antibiotic regimens	Response to initial regimen (±) no readmission %
Talcott et al.	[49]	Open-label, pilot study of 30 low-risk patients	IV mezlocillin + gentamicin or IV ceftazidime	53
Innes et al.	[50]	Randomized study comparing oral outpatient therapy ($n = 66$) to parenteral inpatient therapy ($n = 60$) after 24 h of hospitalization	IV gentamicin + piperacillin/tazobactam	90
			versus	
			PO ciprofloxacin + amoxicillin/clavulanate	84.8
Klastersky et al.	[51]	Open-label study of oral, outpatient antibiotics in 79 low-risk patients	Ciprofloxacin + amoxicillin/clavulanate	96
Santolaya et al.	[52]	Prospective, randomized comparisons of hospital-based ($n = 71$) and ambulatory ($n = 78$) antibiotic therapy in low-risk pediatric patients following 24–36 h of hospitalization	IV ceftriaxone + teicoplanin (hospital based treatment)	94
			PO cefuroxime (ambulatory treatment)	95

discharge on oral ciprofloxacin + amoxicillin/clavulanate was associated with a much lower readmission rate (7.6 %). The oral regimen was well tolerated, and there were no deaths among patients enrolled on this study. Investigators from the Institute Jules Bordet (Brussels, Belgium) also used this approach (i.e., early discharge on oral ciprofloxacin + amoxicillin/clavulante) in 79 patients, most of whom had solid tumors [51]. The overall success rate was 96 % with only 3 patients needing readmission. No serious complications or deaths occurred in this cohort of patients. In a similar study conducted in Chile, children presenting with fever and neutropenia were assigned to receive oral cefuroxime 24–36 h after hospitalization if categorized as being low risk [52]. Seventy-four (95 %) of 78 patients treated in this manner had a positive response. These studies demonstrate the adaptability and success of this approach on a global scale.

A significant proportion of patients cared for at a comprehensive cancer center such as the M. D. Anderson Cancer Center come from other nations, are uninsured, or pay out-of-pocket. Even a short hospital stay can have a significant financial impact on these patients and their families. In the early 1980s, approximately 90 patients with solid tumors who developed fever during episodes of chemotherapy-induced neutropenia were treated with oral TMP/SMX + clindamycin or rifampin, having refused hospital admission [K. R. –unpublished data]. Most responded to this therapy with no serious complications or deaths, and considerable cost savings. This experience served as background data for formal trials of outpatient antibiotic therapy at this center. To date, 3 randomized trials at M. D. Anderson Cancer Center (2 in adult patients and 1 in pediatric patients) have evaluated this approach (i.e., outpatient treatment of the entire febrile episode [53–55]. Smaller pilot studies and institutional pathways in place at M. D. Anderson Cancer Center have added to this experience which is summarized in Table 6 [56–59]. Investigators from other institutions have also adopted this approach and reported their findings [60]. These studies demonstrate that both parenteral and oral regimens are safe and effective with response rates ranging from 80 to 95 %. Many patients not responding to the initial regimen did not require hospital admission, as they responded to alternative outpatient regimens. Among the few patients that needed hospitalization, none had serious complications, none required intensive care, and there were no infection-related deaths. A recently published systematic review concluded that “oral antibiotics may safely be offered to neutropenic patients with fever who are at low-risk for mortality” [61].

Outpatient management of febrile neutropenic patients does require institutional infrastructure that some institutions just cannot afford, particularly if they see small numbers of cancer patients—Table 7. Additionally, some medially low-risk patients may not have the psychosocial backup and support to be candidates for outpatient therapy [45, 58]. These patients can be treated in the hospital with the regimens listed in Table 3 [43, 44, 62].

Table 6 Outpatient (parenteral and oral) antibiotic therapy of low-risk, febrile neutropenic patients. Experience from clinical trials and institutional pathways at the M. D. Anderson Cancer Center

Authors	Reference no	Type of study and patient population	Antibiotic regimens	(%) Response to initial regimen
Rubenstein et al.	[53]	Randomized trial of IV versus PO outpatient regimen. 83 episodes, all adult	IV—aztrenonam + clindamycin	95
			PO—ciprofloxacin + clindamycin	88
Rolston et al.	[54]	Randomized trial of IV versus PO outpatient regimens, 179 episodes, all adults	IV aztreonam + clindamycin	87
			PO ciprofloxacin + amoxicillin/clavulanate	90
Mullen et al.	[55]	Randomized trial of IV versus PO regimens in pediatric patients, 75 episodes	IV ceftazidime	94
			PO ciprofloxacin	80
Rolston et al.	[56]	Open label, pilot study of oral quinolone monotherapy in adult, 40 episodes	PO gatifloxacin	95
Rolston et al.	[57]	Open-label, pilot study of oral quinolone monotherapy in adults, 21 episodes	PO moxifloxacin	95
Elting et al.	[58]	529 episodes, adult patients enrolled on institutional outpatient pathways	PO ciprofloxacin + amoxicillin/clavulanate	80
Escalante et al.	[59]	257 episodes, adult patients enrolled on institutional outpatient pathways	IV ceftazidime + clindamycin	80[a]
			PO ciprofloxacin + amoxicillin/clavulanate	

IV intravenous, *PO* oral
[a]Combined response rate for parenteral and oral regimens, as individual response rates were not mentioned

6 Empiric Therapy for Patients Not Categorized as Low Risk

The accepted standard of care for febrile neutropenic patients that do not fall into the low-risk category is the prompt administration of broad-spectrum antibiotic therapy (based on local susceptibility/resistance patterns) with close monitoring

Table 7 Requirements for a successful program of outpatient antibiotic therapy in low-risk febrile neutropenic patients

Institutional support for necessary infrastructure
Dedicated, multidisciplinary teams of healthcare providers, (physicians, nurses, pharmacists, infusion therapists, etc.)
Local epidemiologic/microbiologic detail including current susceptibility/resistance patterns
Adequate monitoring and follow-up
24-h access to healthcare team including "hotline" number
Adequate transport/communication for patients

for response and the development of complications in the hospital [2, 18]. The various treatment options are listed in Table 8 and include combination antibiotic regimens (usually an antipseudomonal beta-lactam + an aminoglycoside, or an agent with gram-positive activity such as vancomycin or linezolid), or monotherapy with a single, broad-spectrum, antipseudomonal beta-lactam [2, 18]. Prior to the emergence of gram-positive organisms as the predominant bacterial pathogens in neutropenic patients, combinations of an aminoglycoside (e.g., gentamicin, amikacin, tobramycin) with an antipseudomonal beta-lactam were the

Table 8 Antibiotic regimens commonly used in febrile neutropenic patients not classified as low risk

Combination regimens with vancomycin[a]
Vancomycin + cefepime or ceftazidime[b]
Piperacillin/tazobactam
Imipenem or meropenem
Aztreonam[c]
Ciprofloxacin (or other quinolone)[d]
Combination regimens without vancomycin
Aminoglycoside + cefepime or ceftazidime[b]
Piperacillin/tazobactam
Imipenem or meropenem
Quinolone[d]
Monotherapy
Cefepime or ceftazidime[b]
Piperacillin/tazobactam
Imipenem or meropenem

[a]Vancomycin is occasionally replaced by linezolid
[b]Ceftazidime not useful at many institutions due to the emergence of resistant pathogens
[c]Aztreonam used primarily in patients with severe beta-lactam allergy
[d]Quinolones should not be used if patients have received prophylaxis with these agents

most frequently used regimens in this setting. Advantages associated with such combinations included broad coverage against most pathogens encountered in such patients, possible synergy resulting in rapid bactericidal activity (an important consideration in neutropenic patients), and the potential for reducing the development of resistant organisms [2, 18, 63]. The disadvantages of such combinations were an increase in adverse events and organ toxicity (oto- or nephrotoxicity), the need to monitor drug levels frequently particularly in patients with renal insufficiency and those receiving other nephrotoxic drugs, and suboptimal activity against many gram-positive pathogens (e.g., MRSA, viridans group streptococci, *Enterococcus* species). With the emergence of resistant gram-positive organisms as frequent pathogens in neutropenic patients, the inclusion of vancomycin (and teicoplanin in other countries) and later linezolid into the initial regimen became commonplace [2, 18, 64, 65]. Several studies, however, have demonstrated that the initial use of a narrow-spectrum gram-positive agent like vancomycin is not associated with superior outcomes when compared to the addition of such agents after isolation of a gram-positive organism [66–68]. These data, and the association of increased and prolonged vancomycin usage with the selection of VRE and staphylococci with reduced susceptibility to vancomycin (VISA), have led to the recommendation by most experts and societies that vancomycin (and similar agents) should only be included in the initial regimen at institutions that have a high rate of isolation of resistant gram-positive pathogens, or in patients with known colonization or a previous infection with such agents [2, 18, 69].

With the development of truly broad-spectrum agents (extended spectrum cephalosporins, carbapenems, piperacillin/tazobactam), empiric monotherapy became an option [70–72]. Many prospective, randomized trials have demonstrated that monotherapy with agents such as ceftazidime, cefepime, imipenem, meropenem, and piperacillin/tazobactam is associated with response rates similar to various comparator combination regimens [73–78]. A recently published systematic review showed that monotherapy was as effective as combination therapy with similar mortality rates, and similar rates of bacterial and fungal superinfection [79]. Monotherapy regimens were also associated with lower rates of treatment failure and fewer adverse events.

The same group has published an analysis linking cefepime monotherapy with a higher all-cause mortality than other agents used for monotherapy, including ceftazidime [80]. These data need to be interpreted with caution. Ceftazidime has limited activity against many gram-positive organisms, and many gram-negative pathogens have developed considerable resistance to it over the years [81, 82]. At least one recent meta-analysis has reported lower response rates with ceftazidime, and this agent has largely been replaced by cefepime in clinical practice [83]. Additionally, the FDA has just completed its own meta-analysis based on additional data beyond those in the aforementioned publication [84]. The FDA has determined that cefepime remains an appropriate therapy for its approved indications (including neutropenic fever). The decision of which cephalosporin to use should be based on local and current susceptibility data and not on studies conducted over two decades

ago [82]. The weight of current data/opinion supports the use of empiric monotherapy for most neutropenic patients with fever [2, 18, 79]. In today's tight economic environment, monotherapy may represent the most cost-effective option. Figure 1 provides an algorithm for the management of febrile neutropenic patients based on risk groups.

7 Evaluation of Response

The median time to defervescence in low-risk patients is 2 days and approximately 5 days in patients not classified as low risk [85–87]. Persistence of fever for 3–5 days in otherwise stable patients does not necessarily indicate failure of the initial regimen, particularly in patients with profound neutropenia. Approximately 70–80 % of patients will respond to the empiric regimen during this initial period [2, 18]. Persistence of fever beyond 3–5 days should lead to a full re-evaluation of the patient including a search for a drainable (abscess) or removable (infected medial device) focus, or development of a secondary or superinfection. A change in the initial regimen is recommended at this stage. This may consist of additional antibacterial agents if there were gaps in the original regimen, or the administration of antifungal or antiviral agents, if indicated [24].

In patients who remain febrile, imaging of various sites (paranasal sinuses, chest, abdomen), Doppler or venous flow studies, and various serologic tests may provide diagnostic clues. Occasionally, more invasive procedures (generally biopsy of various tissues) might be necessary but are often deferred as many neutropenic patients are severely thrombocytopenic as well. A small proportion of patients will have a non-infectious cause of fever, such as tumor fever or drug fever.

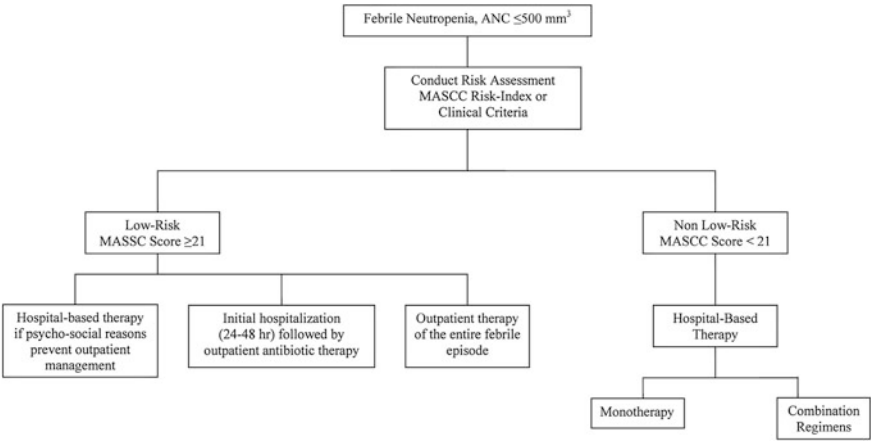

Fig. 1 Algorithm for the management of febrile neutropenic patients (Adapted from Refs. [2, 5, 18, 24, 41, 45])

8 Duration of Therapy

The duration of therapy continues to be vigorously debated. One approach is to continue antibiotic therapy in all patients until the resolution of neutropenia (ANC $> 500/mm^3$ for 2 days) regardless of whether or not an infection was documented during the febrile episode [2, 18]. Another approach is the administration of therapy for approximately 3–4 days after resolution of all signs and symptoms of infection (including microbiologic or radiographic evidence if present initially), with a minimum of 7 days of treatment, regardless of whether or not the patients have persistent neutropenia. The former approach may result in needless administration of antibiotics to many patients, potentially increasing health care costs, toxicity, and the development of bacterial or fungal superinfections. The latter approach requires careful observation of the patient after discontinuation of therapy. The ultimate decision as to when to stop therapy often needs to be individualized and depends on various factors including (1) the patient's risk group, (2) the presence and nature of a documented infection, (bacteremia, pneumonia, urinary tract infection), (3) the nature of the underlying malignancy (solid tumor or hematologic malignancy), (4) the need for additional chemotherapy or immunosuppressive therapy or invasive procedures, and (5) the persistence of neutropenia. Some patients with documented infections and persistent neutropenia might benefit from the administration of hematopoietic growth factors (G-CSF; GM-CSF) and/or granulocyte transfusions, but their use remains controversial [88–90].

9 Antimicrobial Prophylaxis

A detailed discussion on antimicrobial prophylaxis is beyond the scope of this review. As already mentioned, the risk of developing severe infection is not uniform among all cancer patients, but is largely dependent on the underlying disease and the severity and duration of neutropenia. The benefit of antibacterial prophylaxis in reducing documented infections has only been established in patients with neutropenia exceeding 7 days. A recent meta-analysis showed increased survival in patients receiving antibacterial (quinolone) prophylaxis, especially patients with hematologic malignancies [91]. Routine antibacterial prophylaxis should not be given to patients in whom neutropenia is expected to last less than 7 days. This group includes most patients with solid organ malignancies [92]. The main drawback of antibacterial prophylaxis, even when it is clinically indicated, is the emergence of resistant organisms [93]. Consequently, local microbiological monitoring for the emergence of such organisms (primarily *E. coli* and *P. aeruginosa*) is recommended in institutions where prophylaxis is commonplace [94]. Trimethoprim–sulfamethoxazole is the agent of choice for the prevention of *Pneumocystis jivoreci* infection in patients at risk. Alternative agents include dapsone, pentamidine, and atovaquone [95]. Mold-active prophylaxis

(echinocandin, mold-active azole) is recommended in patients at high risk for developing invasive fungal infections, including recipients of allogeneic hematopoietic stem cell transplantation [96–99]. As always, the risks and benefits associated with antifungal prophylaxis need to be weighed before deciding on whether or not to administer prophylaxis [100].

10 Antimicrobial Stewardship

Antimicrobial agents are used with greater frequency and for a larger number of indications (prophylaxis, preemptive therapy, empiric therapy, targeted or specific therapy of a documented infection, and maintenance/suppressive therapy) in cancer patients than in most other patient populations [2]. Although justified, this has created pressures leading to the emergence of resistant organisms [93]. Traditionally, the development of novel antimicrobial agents has been an important tool in battling the problems caused by resistant organisms. However, the development of novel agents is at an all time low, mandating the judicious use of currently available agents—i.e., antimicrobial stewardship. The various strategies for antimicrobial stewardship program are listed in Table 9, and include a multidisciplinary antibiotic stewardship team (MAST), institutional pathways/

Table 9 Recommendations for antimicrobial stewardship

Baseline data/infrastructure
Determine local epidemiology and resistance patterns
Know institutional formulary and prescribing habits
Develop multidisciplinary antimicrobial stewardship team (MAST)
Recommendations for antimicrobial usage
Limit antibacterial prophylaxis
Encourage targeted/specific therapy
Consider formulary restriction and/or preauthorization
Create guidelines and clinical pathways
Consider antimicrobial heterogeneity
Consider de-escalation (streamlining) of empiric regimen
Dose optimization
Parenteral to oral conversion
Optimization of duration of therapy
Other strategies
Prospective audits of antimicrobial usage with feedback to prescribers
Educational activities (grand rounds, in-services)
Strict adherence to infection control policies

guidelines, formulary restrictions or preapproval requirements for certain agents, and de-escalation or streamlining of therapy when appropriate [10]. Antibiotic stewardship programs have been successfully implemented at several institutions (including ours) and in the opinion of this investigator will soon become mandatory at most institutions [11, 101–103].

11 Summary

Neutropenic patients continue to develop serious infections despite significant improvements in the supportive care of cancer patients, and the implementation of preventive and infection control strategies. The spectrum of infection undergoes periodic change with the emergence of newer opportunistic pathogens and/or the development of resistance among well-recognized pathogens. Prompt, empiric antibiotic therapy when a neutropenic patient becomes febrile remains the standard of care. However, not all neutropenic patients have the same risk of developing severe infections and associated complications. Low-risk patients can now be accurately identified at the onset of a febrile episode, and these patients can be treated with a short duration (24–48 h) of hospitalization followed by outpatient therapy, or can be managed entirely as outpatients. Very little change has occurred in the management of moderate-to-high-risk febrile neutropenic patients over the past decade. These patients are best managed in the hospital to facilitate close monitoring for the development of serious medical complications. Antimicrobial stewardship has become an important strategy in the overall management of neutropenic patients, especially since new drug development has declined appreciably. It is hoped that antimicrobial stewardship and strict adherence to infection control policies will reduce the emergence and spread of multidrug-resistant organisms, which are posing serious therapeutic challenges to clinicians caring for these high-risk patients. The development of less myelotoxic/immunosuppressive agents can mitigate this situation considerably, but remains a distant goal.

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