Febrile neutropenia in haematological malignancies

Sharma A, Lokeshwar N

Department of Medical Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Fever is the principle sign of infection in neutropenic patient and frequently may be the only evidence of infection. The pattern of fever in neutropenia is non-specific and not pathognomonic of any type of infections or non-infectious process and can be suppressed by the antipyretic effects of drugs such as corticosteroids. Neutropenia, resulting from cytotoxic chemotherapy is the most common risk factor for severe infections in hematological malignancies. The duration of neutropenia also contributes significantly to the risk of serious infections. This risk is significantly greater a lower neutrophil counts, such that 100% patients with ANC <100 cells/μl lasting 3 weeks or more develop documented infections. The prompt initiation of empirical antibiotics in febrile neutropenia has been the most important advance in the management of the immunocompromised host. The initial empirical antibiotic regimen started at presentation of the febrile episode frequently requires modifications especially in high-risk febrile neutropenia. Neutropenic patients who remain febrile despite 4-7 days of broad spectrum antibacterial therapy are at a high risk of invasive fungal infection. Empirical antifungal therapy with Amphotericin B in persistently febrile neutropenic patients and other high risk patients has shown to reduce the risk of invasive fungal infection by 50-80% and the risk of fungal infection related mortality by 23-45% in 1980's. The IDSA has recommended that amphotericin B at 0.5-0.7 mg/kg/day be administered till marrow recovery. This approach is limited however by the adverse effects caused by drug infusion (fever, chills, myalgias, nausea, hypotension and bronchospasm). Lipid formulations which improve the therapeutic ratio of the traditional formulation are available. The safety and efficacy of these formulations is well established. These formulations have comparable efficacy and are less nephrotoxic than conventional amphotericin B.A lipid formulation of amphotericin B is appropriate as initial empirical therapy or as definitive therapy for proven mycosis in high risk patients receiving concomitant nephrotoxic drugs (cyclosporine), those with pre-existing renal impairment and those with protracted neutropenia during which dose limiting toxicity may occur.

Correspondence:
Atul Sharma
E-mail: atul1@hotmail.com

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Fever is the principal sign of infection in neutropenic patient and frequently may be the only evidence of infection. The pattern of fever in presence of neutropenia is nonspecific and not pathognomonic of any type of infections or noninfectious process and can be suppressed by the antipyretic effects of drugs such as corticosteroids.

Although fever is a frequent sign of infection, noninfectious causes must also be considered: pyrogenic drugs (cytosine arabinoside), blood products, allergic reactions and underlying malignancy are potential sources of fever.

Definition of fever and neutropenia

The consensus guidelines from the Immunocompromised Host Society[1] state that a single oral temperature of 38.5°C or more, or the occurrence of three temperatures of 38°C or more within a 24-hour period, taken at least 4 h apart, is defined as fever in a neutropenic patient. Neutropenia is defined as an absolute neutrophil count (polymorphonuclear cells plus band forms) of 500/ml or less. From a practical standpoint patients with ANC between 500 and 1000 cells/ml, and rapidly falling because of recent chemotherapy are also considered neutropenic.

The criteria of febrile neutropenia should be defined and rigidly adhered to as a signal for the initiation of empirical antibiotic therapy. This plays an important role in reducing infection related morbidity and mortality in neutropenic patient with fever.

Impaired host defenses in haematological malignancies

Patients with hematological malignancies are immunocompromised as a result of the underlying malignancy or due to the therapeutic interventions employed to manage it. Some malignancies are associated with specific immune defects that predispose to infections with particular pathogens (Table 1). Patients with acute leukemia have increased risk of severe gram-negative bacterial infections as a result of quantitative or functional neutropenia. Patients with chronic lymphocytic leukemia and multiple myeloma are susceptible to invasive bacterial infections from staphylococci and strepto-

Table I - Common host defense impairements and pathogens encountered in patients with hematological malignancies

Disease	Most common host defense impairment	Most common pathogens
Acute myeloid leukemia	Neutropenia/neutrophil dysfunction Altered mucosal and skin integrity Altered cellular and humoral immunity (treatment related) Thrombocytopenia (poor wound healing)	Gram-positive (*Staphylococci*, *Streptococci*) and gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) bacteria Fungi (Candida, Aspergillus) Viruses [Herpes simplex (HSV), varicella-zoster (VZV) viruses; decreased in incidence owing to prophylaxis] Parasites and *Pneumocystis carinii* pneumonia (PCP) (rare)
Acute lymphoblastic leukemia	Neutropenia Altered skin and mucosal integrity Altered cellular and humoral immunity (treatment-related) Thrombocytopenia (poor wound healing)	Gram-positive (staphylococci, streptococci) and gram-negative (*E. coli*, *K. pneumoniae*, *P. aeruginosa*) bacteria Fungi (Candida, Aspergillus)
Hodgkin and non-Hodgkin lymphoma	Altered cellular immunity Neutropenia and altered humoral immunity (less frequent and treatment-related)	Viruses (HSV, VZV - decreased incidence owing to prophylaxis) Parasites and PCP (rare, may be more common than that in AML owing to steroids and radiation) Viruses [VZV, HSV, cytomegalovirus (CMV), Epstein--Barr (EBV)], parasities, and PCP are more frequent than in acute leukemias Bacteria (gram-positive, gram-negative) and fungi (mostly treatment-related)
Chronic lymphocytic leukemia	Altered humoral immunity Altered cellular immunity (end-stage and treatment-related-e.g steroids, fludarabine, cyclophosphamide) Neutropenia (end-stage and treatment-related)	Encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria* spp.) Gram-negative bacteria (end-stage and treatment-related) Viruses, parasites, and PCP infections (end-stage and treatment-related)
Multiple myeloma	Altered humoral immunity Neutropenia (end-stage and treatment-related)	Encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, *Neisseria* spp.) Gram-negative bacteria (end-stage and treatment-related)

Table II - Impact of dose-intensive therapy on infection risk in acute leukemia

Factor	Impact
Neutropenia	Risk of life-threatening bacterial and fungal infections
Thrombocytopenia	Platelet transfusion dependence and attendant risk of bacterial sepsis
Anemia	Risk of transfusion-associated viral infection (CMV. hepatitis, HIV) Transfusion iron overload leading to decreased resistance to fungal infections
Immunosuppression	Impaired resistance to infective agents, especially fungi, viruses
Mucositis	Increased risk of dissemination of gut flora Increased incidence of Clostridium difficile infections. which in turn predispose to dissemination of enterococci
Hospitalization	Risk of nosocomial infections
Prolonged antibiotic use	Risk of development of antibiotic-resistant organisms
Vascular access	Disruption of skin integrity; foreign body provides template for infection colonization
Parenteral nutrition	Increased risk of fungal infection
Graft-versus-host disease	Impaired mucosal defense; increased risk for fungal, bacterial, and viral infection

cocci especially pneumococcus. Conversely patients with lymphoma have abnormalities of the cellular immune system resulting in an increased risk of viral infections (e.g. herpes simplex) and fungal infections (e.g. *Cryptococcus*).

Therapeutic interventions such as corticosteroids, chemotherapy, stem cell transplant, and radiation also produce deficiencies in the host defense [Table 2]. Neutropenia, resulting from cytotoxic chemotherapy is the most common risk factor for severe bacterial infections in hematological malignancies. Impaired T-cell function in patients undergoing allogenic stem cell transplant is associated with an increased susceptibility to invasive viral infections. Other therapy induced alterations in host colonization such as disruption of natural skin and mucosal barriers and interference with nutrition also increase the risk of infection.

Mucositis, which is a common toxicity of cytotoxic chemotherapy, renders the patient vulnerable to infection by bacteria that reside in the gastrointestinal tract.

Similarly common procedures such as venepunctures, bone marrow aspiration and insertion of central venous access devices, disrupt the integument and provide a nidus for colonization. The degree of neutropenia either as a consequence of disease or therapy is directly related to the incidence of serious bacterial and fungal infection. There is a significant increase in the incidence of serious infection once ANC falls below 500 cells/ml. Patients with ANC below 100 cells/ml are at the highest risk of infection.

The duration of neutropenia also contributes significantly to the risk of serious infections. This risk is significantly greater

at lower neutrophil counts, such that 100% patients with ANC <100 cells/ml lasting 3 weeks or more develop documented infections.

Qualitative defects in neutrophil function have been described in hematological malignancies. These include defects in chemotaxis, phagocytosis, bactericidal capacity, and absence of respiratory burst that accompanies phagocytosis. Additionally, chemotherapeutic agents including corticosteroids can decrease phagocytosis and neutrophil migration.

Spectrum of microbial pathogens in haematological malignancies

Over the last three decades, there has been a significant change in the spectrum of infections in neutropenic patients with acute leukemia. In the early 1950s and 1960s staphylococcus aureus was the most frequent isolate in immunosuppressed patients.[2] With the introduction of beta-lactamase-resistant antistaphylococcal pencillins, gram-negative bacilli became the predominant bacterial organisms including *Escherichia coli*, *Klebsiella* species and *Pseudomonas aeroginosa*. Since the 1980s, several studies have collectively demonstrated a shift in the etiology of bacterial infections from a predominance of gram-negative pathogens to gram-positive cocci. Factors responsible for this shift include the widespread use of indwelling central venous access devices,[3] use of intensive chemotherapy toxic to the upper and lower gastrointestinal mucosa, use of quinolone-based antibacterial chemoprophylaxis that suppress aerobic gram-negative bacilli colonizing the gastrointestinal tract but fail to suppress the microaerophilic gram-positive cocci and the use of histamine H_2 receptor blockers, which reduce gastric pH and promote overgrowth with oropharyngeal gram-positive microflora.

Clinically important gram-positive pathogens include the viridans group streptococci such as *S. mitis* and *S. mileri*, *Enterococcus* species such as the glycopeptide resistant strain of *E. faecium* and the coagulase negative staphylococci that comprise the predominant normal skin microflora. Staphylococcus epidermidis is the species most often isolated from patients with coagulase negative staphylococcal bacteremia.[4]

The *Enterococcal* species, *E. faecalis* and *E. faecium* have emerged as virulent pathogens due to the acquisition of antibiotic resistant plasmids. Vancomycin-resistant and aminoglycoside resistant strains are being found increasingly in outbreaks among seriously ill patients.[5]

Anaerobes play a lesser role in primary infections in neutropenic fever, but are responsible for mixed infections in the mouth and perianal area. *Clostridia perfringens*, *C. septicum*, and *C. tertium* have been associated with serious infections. Infection with Bacillus species has been associated in patients with indwelling silastic catheters.

Fungi are major pathogens, especially in patients with prolonged neutropenia and who receive protracted courses of antibiotics.[5] The predominant fungal pathogens are *Candida* species, *Aspergillus* species, *C. neoformans*, and the *Phycomycetes*. Although less common, the mucoraceae (*Mucor*, *Absida*, and *Rhizpus* species) can cause pulmonary disease or rhinocerebral mucomycosis.

Parasite or viral infections are important primary infections or cause secondary complications. Pneumocystic carinii is an important cause of pneumonia, especially in patients receiving corticosteroids. Herpes simplex virus (HSV), varicella-zoster virus (VZV) and cytomegalovirus (CMV) are the most prevalent among viral pathogens. Other viruses that are benign in the normal host, such as adenovirus respiratory syncytial virus (RSV) and human herpes virus type 6 (HHV 6) can cause significant respiratory infections in the immunocompromized host.

Initial evaluation of febrile neutropenic patients

The initial pretreatment evaluation of the patient should be performed as expeditiously and as thorough as possible. There are two important considerations in the initial evaluation. Neutropenia markedly alters the host's inflammatory response, making it difficult to detect infection. Second, an undetected and untreated infection can be rapidly fatal in the neutropenic patient. The classic signs and symptoms of infections are often missing. Therefore a careful history and a detailed physical examination to look for subtle signs of inflammation are necessary. This examination must be frequently repeated in persistently febrile patient.

Even subtle evidence of inflammation must be considered as sign of infection. Minimal perianal erythema and tenderness may rapidly progress to perianal cellulitis. Minimal erythema or serous discharge at the site of a Hickman catheter may herald tunnel or exit site infection. Particular attention should be paid to sites that are frequently infected or serve as foci for dissemination of infection such as oropharynx, lung, paranasal sinuses, perineum, and vascular catheter insertion sites. Prior to initiating empirical antibiotic therapy, at least two sets of blood culture and cultures from other appropriate sites (e.g. throat, urine, stool) should be obtained for bacteria and fungal organisms. In patients with central venous catheters, simultaneous cultures should be obtained from the catheters as well as from a peripheral site. Cultures should be repeated daily while patients remain febrile.

All febrile neutropenic patients should undergo chest radiography to identify pulmonary lesions. Radiographs or CT scans of paranasal sinuses should be performed in patients in whom these sites are potential sources of infection. Imaging techniques such as CT, MRI, ultrasonography and radionuclide imaging and invasive procedures such as bronchoscopic examination, lung, liver or skin biopsy may be extremely useful in a identifying sites of infection. However, the presence of thrombocytopenia often precludes the use of invasive diagnostic techniques.

Risk assessment in febrile neutropenic patients

The risk for developing complication in patients with febrile

Multinational association of supportive care of cancer scoring system for stratification of risk in febrile neutropenia

Characteristic	Weight
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	4
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age <60 years	2

Risk score >21 identified low-risk patients.

neutropenia is variable. Differentiating between high and low risk patients with fever and neutropenia has a significant impact on decisions that affect the patients' quality of life and overall medical costs.

The degree of neutropenia is the most influential risk factor. Patients with ANC <500/ml have a substantially increased risk of infection and an ANC less than 100/ml has the highest risk. The next important factor is the anticipated duration of neutropenia. Patients who are expected to recover their granulocyte counts in less than 1 week are generally considered to have low risk of complications following onset of fever. High-risk patients are considered to be those who have prolonged neutropenia, practically defined as more than 7 days.

In the pivotal study by Talcott *et al*. [6], a risk assessment model for outcome was developed using clinical variables that would be assessed within 24 h of presentation of fever and neutropenia. This model was later validated in 444 consecutive cancer patients and defined three major categories of risk: prior inpatient status, serious independent co morbidity, and uncontrolled cancer. Patients not meeting any of the risk criteria were considered low risk. Serious medical complications occurred in 34% of patients with risk factors compared with 5% incidence in the low risk group.

More recently, an internationally validated scoring system to identify low risk febrile neutropenia cancer patients has been developed by the Multinational Association of Supportive Care in Cancer.[7] (MASCC) This study included 1351 patients from 20 institutions in 15 countries. A numeric risk index score was constructed weighing different features associated with a high probability of favorable outcome.

A higher global score indicated a greater likelihood of fever resolution without any serious complications. A MASCC risk index score of 21 or more points identified low risk patients with a positive predictive value of 91%, a specificity of 68% and a sensitivity of 71%.

Management of febrile neutropenia

The prompt initiation of empirical antibiotics in febrile neutropenia has been the most important advance in the management of the immunocompromised host. Prior to this policy, the mortality from gram-negative infections approached 80%.[8] Since the widespread use of empirical antibiotics, the overall survival rate for febrile neutropenic patients is more than 90%. The first effective treatment for febrile neutropenia was demonstrated in the landmark trial by Schimpff and consisted of a combination of carbenicillin and gentamycin.[9] Treated patients with *P. aeruginosa* infection had dramatically improved survival compared to historic controls.

Some investigators have argued that combination therapy broadens the spectrum of activity, retards the development of resistance and offers the potential of synergistic activity particularly against gram-negative bacilli. Since the 1980s, the development of broad-spectrum antipseudomonal antibiotics with high serum bactericidal level to minimal inhibitory concentration ratio has led to reevaluation of the need for combination antibiotic therapy. There have been concerns about the direct and indirect drug costs and regimen related toxicities. The practice of combination antibiotic therapy was changed by the introduction of newer highly active third generation cephalosporins such as ceftazidime which had a broad spectrum of anti-gram-negative activity including activity against *P. aeruginosa*. Further, the addition of an aminoglycoside did not consistently improve the clinical outcome in neutropenic patients. Other agents such as imipenem/cilastin, meropenem and cefepime have been studied as empirical monotherapy in febrile neutropenia.[10]–[13]

The major concern about monotherapy has been on the beta-lactam resistance among coagulase-negative staphylococci, viridans group streptococci, enteric gram-negative bacilli and methicillin resistant *S. aureus* (MRSA). Fourth generation cephalosporins such as Cefepime are active against most penicillin and ceftazidime resistant viridans group streptococci and against gram-negative bacilli that produce group 1 beta-lactamases including enterobacter and proteus.

The overall response rates for cefepime, ceftazidime, meropenem monotherapy and ceftazidime plus amikacin in

Table III - Effective antimicrobial agents for initial management of neutropenic fever in leukemia patients.

Regimen type	Antimicrobial type	Examples
Monotherapy	Antipseudomonal penicillin + β-Lactamase inhibitor	Piperacillin/tazobactam
	Carbapenem	Imipenem/cilastatin, meropenem
	Fluoroquinolone	Ciprofloxacin,levofloxacin
	Third or fourth generation cephalosporin	Ceftazidime, cefepime
Combination therapy	Antipseudomonal β-lactam +	Piperacillin, carbapenem, or antipseudomonal cephalosporin
	Aminoglycoside or	Gentamicin, tobramycin, amikacin
	Fluoroquinolone	Ciprofloxacin, levofloxacin

febrile neutropenia patients have been comparable ranging from 52 to 56%. The Infectious Disease Society of America (IDSA) guidelines now support the use of agents such as ceftazidime, cefepime, imipenem, and meropenem as alternatives for monotherapy.

However, combination therapy seems to be more effective in patients with documented gram-negative bacillary bacteremia and may be associated with a lower rate of initial empirical treatment modification and shorter duration. It may be reasonable to prescribe initial combination therapy only for patients presenting clinical signs predictive of gram-negative sepsis (e.g. hypotension). Effective antimicrobial agents for the initial management of febrile neutropenia are shown in Table 3. The prevalence of many infections is determined by local antibiotic usage. Hence antibiotic regimens selected, as initial therapy must be based on knowledge of the predominant pathogens at each institution and their antimicrobial susceptibility pattern.[14]

Modification of initial empirical antibiotic regimen

The initial empirical antibiotic regimen started at presentation of the febrile episode frequently requires modifications especially in high-risk febrile neutropenia. If the patient deteriorates, then reassessment of the antibiotic regimen should be promptly undertaken. If cultures identify an etiology and a specific pathogen, then adjustments should be made to optimize the initial antibiotic regimen. Otherwise, an assessment at 3–5 days should be undertaken. If the patient has defervesced, treatment should be continued for a minimum of 7 days, although neutrophil recovery may allow cautious discontinuation of antibiotics earlier. A change to oral antibiotics can be made in patients who are at low risk for infectious complications. If fever persists after 3–5 days, and no source has been identified, a change in antibiotic regimen is indicated or the addition of amphotericin B if prolonged neutropenia is anticipated. The duration for antibiotics in general is guided by neutrophil recovery. Suggestions for this decision making process are given in the Figures 1-3.

Coverage of gram-positive infections

Gram-positive microorganisms, predominantly coagulase-negative staphylococci and viridans group streptococci, may now account for as many as two-thirds of bacteremic episodes in febrile neutropenia.[15] Hence, many studies have evaluated including a glycopeptide in the initial emperic antibiotic regimen. The EORTC randomized 747 febrile neutropenic episodes to receive ceftazidime and amikacin with or without vancomycin.[16] Single gram-positive bacteremia responded more often in the vancomycin arm. However the addition of vancomycin in the initial empiric regimen was not associated with any benefit regarding the duration of fever, morbidity or mortality related to gram-positive infections and was associated with increased nephrotoxicity. Several other smaller studies do not support either the empirical use of vancomycin or teicoplanin in the absence of documented gram-positive infections. The IDSA guidelines recommend using glycopeptides as part of initial empiric therapy only in the following circumstances:[17]

- At institutions where fulminant gram-positive infections are common;
- In clinical situations where there is increased risk of viridans streptococci infections (patients receiving quinolone prophylaxis, mucositis);
- Clear signs of catheter related infections;
- Known colonization with penicillin resistant pneumococci or methicillin resistant staphylococci;
- Patients presenting with hypotension.

Other regimens aiming to improve the antibacterial activity against gram-positive organisms include combinations of broad-spectrum penicillins with b-lactamase inhibitors. (e.g. piperacillin-tazobactam with or without amikacin). Two recently introduced agents, linezolid and quinupristin-dalfopristin, have demonstrated wide spectrum activity against gram positive organisms including MRSA, coagulase negative staphylococci and vancomycin resistant enterococci.

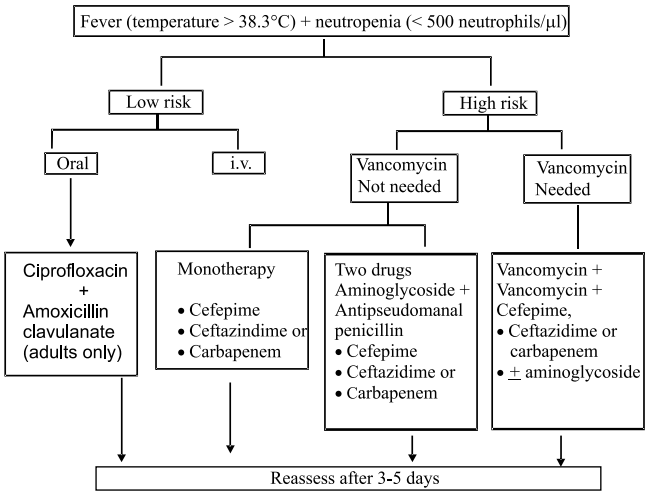

Figure 1: Algorithm for the initial management of febrile neutropenic patients

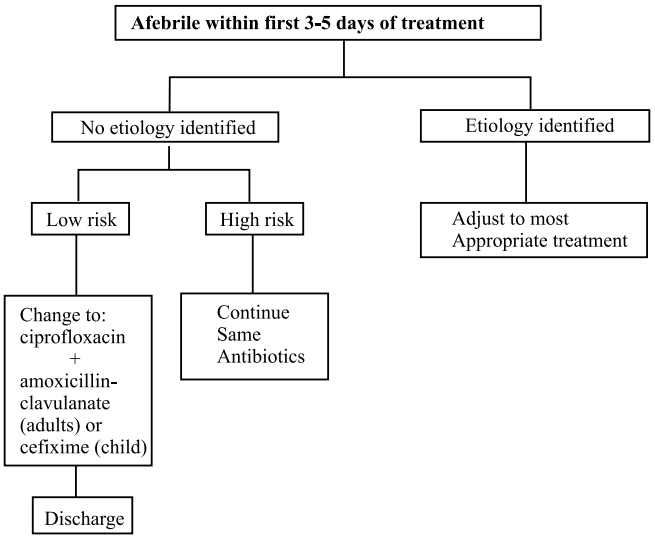

Figure 2: Guide for the management of patients who become afebrile in the 3-5 days of initial antibiotic therapy

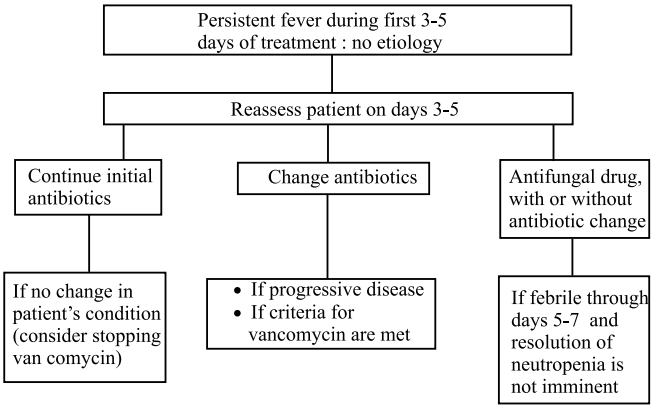

Figure 3: Guide to the treatment of patients who have persistent fever after 3-5 days of empirical treatment

Empirical antifungal therapy

Neutropenic patients who remain febrile despite 4–7 days of broad-spectrum antibacterial therapy are at a high risk of invasive fungal infection. Empirical antifungal therapy is defined as the institution of antifungal treatment in persistently febrile neutropenic patients and other high-risk patients. In two small-randomized studies in the 1980s amphotericin B was shown to reduce the risk of invasive fungal infection by 50–80% and the risk of fungal infection related mortality by 23–45%. The IDSA has recommended that amphotericin B at 0.5–0.7 mg/kg/day be administered till marrow recovery. This approach is limited however by the adverse effects caused by drug infusion (fever, chills, myalgias, nausea, hypotension and bronchospasm). Lipid formulations which improve the therapeutic ratio of the traditional formulation are available: amphotericin B in lipid complex (ABCL), amphotericin B colloid dispersion (ABCD), liposomal amphotericin B (Ambisome) and Indian liposomal amphotericin B (Fungisome). The safety and efficacy of these formulations is well established. These formulations have comparable efficacy and are less nephrotoxic than conventional amphotericin B, however their usage is limited by the high cost.[17],[18]

Comparative studies have shown that all of the lipid formulations are effective to comparable degrees that liposomal amphotericin B is the least toxic and lower doses (1–3 mg/kg/day) are as effective as higher doses (5 mg/kg/day). ABLC was the first lipid formulation to be approved by the FDA for use in children and adults. It was found to be active in the treatment of refractory mycosis and in those with intolerance to conventional amphotericin B. During the course of ABLC therapy among 556 patients, serum creatinine levels significantly decreased from baseline. Similarly greater efficacy and reduced nephrotoxicity has been documented with liposomal amphotericin B. A neutropenic fever showed liposomal amphotericin B to be associated with fewer break through fungal infections, less infusion related toxicity and less nephrotoxicity as compared to amphotericin B deoxycholate.[20] Indigenous brand of liposomal amphotericin is also available (Fungisome$^{\hat{O}}$) for therapeutic use. It is less expensive than Ambisome and is currently undergoing more clinical trials to establish the safety and efficacy in febrile neutropenia. The safety and efficacy of this preparation in systemic fungal infections is documented in the published studies.[21]–[24]

More recently, intravenous itraconazole, a triazole with activity against both molds and yeasts, has been shown to be equivalent to amphotericin B. In view of the limited activity of fluconazole against *Aspergillus* species and some nonalbicans *Candida* species, patients with documented invasive fungal infections should not be treated with this drug. Results of trials assessing the activity of voriconazole, a new azole and capsofungin, a new candin, in the treatment of invasive fungal infections are encouraging. A recently published study compared voriconazole to a lipid preparation of amphotericin B in the empirical treatment of febrile neutropenia.[26] This was an open labeled, randomized study with a noninferiority design. The overall success rate was 26% with voriconazole and 30.6% with liposomal amphotericin B. No statistical significance was observed. However there were fewer documented breakthrough infections with voriconazole as compared to liposomal amphotericin B. (5.3 *Vs* 1.2%). The voriconazole group had fewer cases of severe infusion related reactions ($P < 0.01$) and of nephrotoxicity ($P < 0.001$). The incidence of hepatotoxicity was similar in the two groups. In another trial comparing voriconazole with amphotericin B deoxycholate in documented invasive *Aspergillus* infection, voriconazole was associated with a response rate of 52.8 *Vs* 31.6% for amphotericin B.[27] In the intention to treat analysis, the 12 week overall survival in the voriconazole group was 70.8 *Vs* 57.9% in the amphotericin arm.

Unfornunately the greater cost of therapy of the lipid formulations limits their broader utilization as less toxic alternatives to conventional amphotericin B. The choice of antifungal agent is a critical issue among high-risk neutropenic patients and hematopoetic stem cell transplant patients. Such patients often receive concomitant nephrotoxic drugs and have pre-existing renal impairment or dimished renal reserve. A lipid formulation of amphotericin B is appropriate as initial empirical therapy or as definitive therapy for proven mycosis in high-risk patients receiving concomitant nephrotoxic drugs (cyclosporine), those with pre-existing renal impairment and those with protracted neutropenia during which dose limiting toxicity may occur. Summary of trials of empirical antifungal therapy that have evaluated alternatives to conventional am-

Table 4: Summary of trials of empirical antifungal therapy as an alternative to conventional amphotericin B

Author	No of patients	Arm 1	Arm 2	Rate of success % of patients		Rate of Invasive fungal infection (%)	
				Arm 1	Arm 2	Arm 1	Arm 2
Walsh et al [20]	687	AmB	L-AmB	49	50	8.7	5.0
Boogaerts et al [24]	384	AmB	Itraconazole	38	47	2.7s	2.7
Walsh et al [22]	837	L-AmB	Voriconazole	31	26	5.0	1.9
Walsh et al [25]	1095	L-AmB	Capsofungin	34	34	4.3	5.2

photericin B is shown in table 4.

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