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CHAPTER

40 Infections associated with neutropenia and transplantation

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Neutropenic patients and transplant recipients are at risk of a number of life-threatening opportunistic infections. Neither patient group suffers from a single specific immunological deficit, there being a subtle blend of physical and immunological defects which evolve with time. Judgments about management need to be based upon knowledge of the balance of these defects and the timing of the infection.

The majority of hemato-oncology centers and transplant units base patient management (including that of infection) upon agreed protocols and the evidence base for these has become more robust in recent years. In addition there are now more national and international guidelines on which to base these. It is important that protocols are regularly updated and take account of local variations in risk, organisms and antimicrobial sensitivities.

INFECTIONS IN NEUTROPENIC PATIENTS

The inverse relationship between the numbers of circulating neutrophils and the risk of infection was established more than four decades ago.[1] This effect becomes apparent when the absolute neutrophil count is less than 1.0×10^9/L. The risk increases considerably as the count falls below 0.5×10^9/L and all patients with a count of less than 0.1×10^9/L for more than 3 weeks have been found to develop an infective episode.[1] Criteria for enrollment in a febrile neutropenia trial usually include a neutrophil count less than 0.5×10^9/L.

CAUSES OF NEUTROPENIA

Most of these patients are neutropenic following chemotherapy for leukemia while some leukemic patients will present with neutropenia before chemotherapy. In addition, the neutrophils of patients with myelodysplastic syndrome (MDS) or leukemia, particularly those with acute myeloid leukemia (AML), may have impaired microbicidal activity.[2,3]

Patients receiving chemotherapy for high-risk or relapsed leukemia may be neutropenic for 2–3 weeks, and longer if receiving regimens containing fludarabine. Those undergoing standard chemotherapy for lymphoma or for solid tumors may also suffer a reduction in circulating neutrophils, but this is rarely less than 0.1×10^9/L and is often not below 0.5×10^9/L with the duration of neutropenia often less than 7 days. In patients with aplastic anemia, or bone marrow transplant (BMT) recipients who fail to engraft, neutropenia is often profound and prolonged. Normal engraftment in allogeneic BMT recipients takes place between 2 and 3 weeks after transplantation.

There has been a steady increase in the numbers of peripheral blood stem cell transplants (PBSCT) performed in Europe and autologous PBSCT has virtually replaced autologous bone marrow transplantation. Autologous PBSCT recipients have a shorter duration of neutropenia.

Patients undergoing allogeneic bone marrow transplantation behave essentially like neutropenic patients during the early post-transplant phase, but remain immunosuppressed for up to 2 years, even without complications such as graft-versus-host disease (GVHD).

Other causes of neutropenia are shown in Box 40.1.

Box 40.1 Non-malignant causes of neutropenia

Congenital

- Cyclical neutropenia
- Chronic benign neutropenia
- Severe congenital neutropenia

Acquired

- Drug-induced
  - Cytotoxic chemotherapy (the most common cause of neutropenia)
  - Antimicrobial associated: chloramphenicol; β-lactams; sulfonamides; trimethoprim; nitrofurantoin; flucytosine; ganciclovir; zidovudine
  - Other drugs (e.g. phenothiazines, tolbutamide)
- Alcohol
- Radiation
- Megaloblastic anemia
- Autoimmune neutropenia

FACTORS PREDISPOSING TO INFECTION

The pathogenesis of infection in these patients is multifactorial and is often the consequence of a breach in the skin or oral mucosa plus defects in cellular or humoral immunity.

Some defects are associated with specific infections (Table 40.1). Lymphopenia, as a consequence of lymphoid malignancy or treatment, is associated with reactivation of intracellular organisms such as mycobacteria, the herpes viruses, *Toxoplasma gondii* and *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*). Patients with chronic lymphoid malignancies and those receiving immunosuppressive chemotherapy, such as BMT recipients, have impaired antibody production which predisposes to infection with encapsulated organisms such as *Streptococcus pneumoniae*. The use of indwelling central venous catheters and mucosal damage caused by chemotherapy and herpes simplex virus (HSV) infection[4] allows penetration by commensal flora. In recent years changes in cytotoxic chemotherapy have rendered the oropharynx a major portal of entry for α-hemolytic streptococci. Likewise, splenectomy undertaken as treatment or for diagnosis renders the patient susceptible to infection with encapsulated organisms such as *Str. pneumoniae*. Others have pre-existing sites of chronic infection such as middle-ear disease or bronchiectasis, which may act as reservoirs of infection with organisms such as *Pseudomonas aeruginosa*. Ethnic origin and foreign travel may increase exposure to infections such as tuberculosis, malaria or strongyloidiasis.

Table 40.1 Factors predisposing to infection in the neutropenic patient

Immune defect/risk factor	Example of opportunistic organisms
Neutropenia	*Streptococcus oralis* *Pseudomonas aeruginosa* *Candida* spp. *Aspergillus* spp.
Lymphoid cell defect	*Mycobacterium* spp. *Toxoplasma gondii* Herpes viruses *Pneumocystis jirovecii*
Humoral	*Str. pneumoniae*
Mucosal barrier (e.g. HSV/chemotherapy-induced mucositis)	*Str. oralis* Enterobacteriaceae Fungi
Vascular access	Coagulase-negative staphylococci Fungi Non-tuberculous and environmental mycobacteria
Foreign travel/ethnic origin	*Mycobacterium* spp. *Strongyloides stercoralis* *Blastomyces dermatitidis* *Coccidioides immitis* *Histoplasma capsulatum*
Anatomical defect/reservoir (e.g. chronic sinusitis)	*Pseudomonas* spp.
Splenectomy	*Str. pneumoniae* Other encapsulated bacteria

CAUSATIVE ORGANISMS

Between 30% and 50% of febrile episodes in neutropenic patients can be confirmed microbiologically, and of these, most are due to bacteremia. Infections with Gram-positive bacteria, especially the coagulase-negative staphylococci and α-hemolytic streptococci, have increased in frequency over the past two decades. In the EORTC (European Organisation for Research and Treatment of Cancer) participatory centers the incidence of bacteremia due to Gram-positive organisms increased from 29%[5] to 67% during the 1970s and 1980s.[6] This increase correlates with the escalating use of central venous catheters, the development of alternative high-dose chemotherapy with attendant mucositis, and better prevention of Gram-negative infections. However, subsequent trials have shown a fall again, possibly associated with the decline in quinolone prophylaxis usage associated with emerging resistance. Of recent interest is the finding that cell-wall deficient (mostly Gram-positive) bacteria may be responsible for up to 25% of episodes of neutropenic fever in BMT recipients.[7]

Gram-negative bacteria continue to cause some of the most serious episodes of sepsis. Infections caused by the Enterobacteriaceae and *Ps. aeruginosa* carry a mortality of 40–60%.[8,9] Oropharyngeal candidosis is extremely common in patients not receiving prophylaxis, while invasive candidosis and aspergillosis account for 20–30% of fatal infections when treating acute leukemia.[10,11] Invasive aspergillosis is the most important infective cause of death in childhood acute myeloid leukemia[12] and in adult allogeneic bone marrow transplant/hematopoietic stem cell transplant patients. Other important infectious agents are listed in Box 40.2.

CHEMOPROPHYLAXIS

Allogeneic hematopoietic stem cell transplant (HSCT) recipients are at risk of a wide range of infections based upon extent of exposure and degree of immunosuppression. Autologous HSCT recipients are also at risk of infection although to a lesser degree due to shorter periods of neutropenia and time to engraftment. However, patients receiving CD34-enriched autografts appear to be at a similar level of risk as allogeneic HSCT recipients for cytomegalovirus (CMV) and other opportunistic infections.[13] These risks are summarized in Box 40.3.

Prevention of these serious infections has been the goal of clinicians for many years. Strategies for preventing acquisition of organisms, such as the provision of a low microbial diet, or the use of high-efficiency particulate air (HEPA) filtration, appear important in some profoundly neutropenic patients at risk from aspergillosis and have been increasingly emphasized in recent years.[14]

Box 40.2 Important infectious agents in neutropenic and hematopoietic stem cell transplant patients

Bacteria
Staphylococci
Streptococci
Enterobacteriaceae
Pseudomonads
Mycobacterium spp.
Legionella spp.
Clostridium septicum
Clostridium difficile
Rothia spp.

Fungi
Candida spp.
Aspergillus spp.
Zygomycetes
Cryptococcus neoformans
Pneumocystis jirovecii

Viruses
Herpes simplex virus
Varicella zoster virus
Cytomegalovirus
Epstein–Barr virus
Hepatitis A, B, C viruses
Parvovirus
Adenovirus
Polyomavirus
Measles virus
Human herpesvirus-6

Protozoa/helminths
Toxoplasma gondii
Strongyloides stercoralis

Box 40.3 Summary of overall infection risk

Overall infection risk	Disease/chemotherapy regimen/ duration of neutropenia
Low	Standard solid tumor chemotherapy regimens
	Duration of neutropenia <7 days
Intermediate	Autologous HSCT
	Lymphoma
	Multiple myeloma
	Chronic lymphocytic leukemia
	Purine analog therapy (fludarabine, 2-CdA)
	Duration of neutropenia 7–10 days
High	Allogenic HSCT
	Acute leukemia, induction and consolidation phases
	Campath (alemtuzumab) therapy
	Graft-versus-host disease treated with high-dose steroids
	Duration of neutropenia >10 days

HSCT, hematopoietic stem cell transplant.

The infections to which these HSCT recipients are most vulnerable can be temporally categorized into three periods following transplantation:

- Pre-engraftment – less than 3 weeks
- Immediate postengraftment – 3 weeks to 3 months
- Late postengraftment – more than 3 months.

These periods, pathogens, immune defects and associated host factors in HSCT recipients are illustrated in Figure 40.1.

BACTERIAL CHEMOPROPHYLAXIS

Various trials have examined the efficacy of oral non-absorbable antibiotics. Although a number of these were flawed, several controlled trials showed a benefit only when they were combined with a protective environment.[15–23]

Although trimethoprim–sulfamethoxazole was first used in patients with acute leukemia to prevent *Pn. jirovecii* pneumonitis, it also reduced the incidence of bacterial infection.[24] Further studies demonstrated the greatest benefit in patients with prolonged neutropenia, where a reduction in Gram-negative bacterial infections was seen.[25–28] However, the incidence of side effects (including bone marrow suppression) and the selection of multiresistant organisms led to a decline in its use for this indication.

Oral quinolones are currently the most commonly used prophylactic antibacterial agents in adult patients with chemotherapy-induced neutropenia. Initially oral quinolones (ciprofloxacin, ofloxacin and norfloxacin) were compared in a number of studies with placebo, trimethoprim–sulfamethoxazole and non-absorbable antibiotics. In the majority of these the 4-quinolone treated patients had significantly fewer Gram-negative bacterial infections, a delayed onset of fever and a reduction in the number of days of fever. Importantly, a reduction in mortality was not demonstrated.[29] There has been concern that quinolone resistance is increasing in some units[30] and this has led to the discontinuation of quinolone prophylaxis. However, initial meta-analysis did not show this to be a significant problem, and recent EORTC and Health Protection Agency (HPA) data further support these findings. A sequential study has shown that combining ciprofloxacin with colistin was associated with no significant change in quinolone resistance over a 12-year period.[31]

However, a more recent meta-analysis[32] that evaluated 95 randomized trials in afebrile neutropenic patients (the majority of whom had hematological malignancies) comparing antibiotic prophylaxis with placebo, no intervention or with another antibiotic class has shown a significant reduction in the risk for death when compared with placebo or no treatment (relative risk [RR], 0.67). The survival benefit was more substantial when the analysis was limited to fluoroquinolones. Fluoroquinolone prophylaxis reduced the risk for all-cause mortality (RR 0.52, 95% CI, 0.35–0.77), as well as infection-related mortality, fever, clinically documented infections and microbiologically documented infections. Although there was no significant increase in resistant bacteria with fluoroquinolone prophylaxis, the length of observation may have been insufficient to detect the emergence of resistant bacteria. All prophylactic antibiotics were associated with an increased risk for adverse events.

Following on from this meta-analysis, two randomized, double-blind, placebo-controlled trials of levofloxacin prophylaxis in neutropenic patients undergoing chemotherapy were performed.[33,34] Levofloxacin has similar activity against Gram-negative bacteria in comparison with ciprofloxacin, with the exception of pseudomonads; however, it has improved activity against certain Gram-positive pathogens, including streptococci. The first trial evaluated levofloxacin prophylaxis from the initiation of chemotherapy until neutrophil recovery, in higher-risk, mainly inpatient adult leukaemic or stem cell transplant patients in whom chemotherapy-induced neutropenia was expected to last for more than 7 days. The second

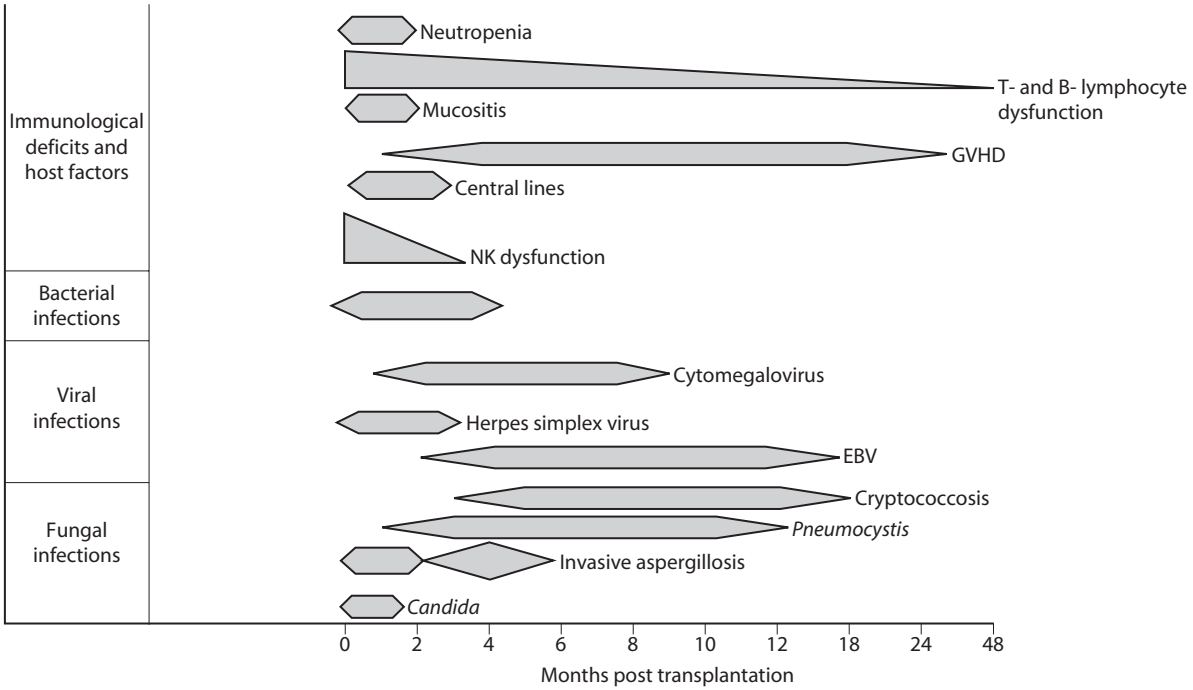


Fig. 40.1 The time course of infections after HSCT. EBV, Epstein–Barr virus; GVHD, graft-versus-host disease; LRTI, lower respiratory tract infection; NK, natural killer [cell]; UTI, urinary tract infection.

trial was in the outpatient setting and evaluated levofloxacin prophylaxis after chemotherapy for solid tumors and lymphomas for patients anticipated to have periods of neutropenia of 7 days or less. The effects of prophylaxis were similar between both patient groups in the two trials, as were mortality and tolerability. Both trials failed to demonstrate a significant survival benefit with prophylaxis. The results reflected previous meta-analyses and a review of both trials demonstrated that the numbers needed to treat to prevent one death by any cause was 24 in all patients and 43 in patients with an expected duration of neutropenia of >7 days.

The decision whether to use antibiotic prophylaxis and the selection of agent is a fine balance between calculated risk and expected benefit. Risks to consider include associations between fluoroquinolone use and severe *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA), adverse drug reactions, antibiotic resistance, and whether prophylaxis will preclude the use of quinolones in empirical therapy of neutropenic fever in those patients stratified as low risk. The benefit of prophylactic antibiotics in other patient subsets with chemotherapy-induced neutropenia remains controversial.

With regard to timing and length of prophylaxis, guidelines from the European Conference on Infections in Leukemia (ECIL) suggest it should start with chemotherapy and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia.

The problem of Gram-positive infections, particularly those due to α-hemolytic streptococci, has been addressed by a number of studies using different agents, including oral penicillins,[35] macrolides[36,37] and rifampicin (rifampin).[38] However, these have given mixed results and have been associated with the emergence of resistance. It is difficult, therefore, to make recommendations for prophylaxis of Gram-positive pathogens other than to use levofloxacin which has been shown to be of benefit. Some centers advocate prophylaxis against pneumococcal infection in allogeneic HSCT recipients, functionally asplenic patients and in patients receiving immunosuppressive therapy for GVHD. Where pneumococcal isolates have intermediate to high-level resistance rates to penicillin approaching 35%, alternative agents should be considered based on local susceptibility patterns. Trimethoprim–sulfamethoxazole prophylaxis for *Pn. jirovecii* is likely to be protective against pneumococcal disease.

FUNGAL CHEMOPROPHYLAXIS

Attempts at antifungal prophylaxis have met with variable success. Initial studies examined oral polyenes. Nystatin, in doses up to 12×10^6 units per day, had little effect on the incidence of invasive candidosis in neutropenic patients,[11] whereas amphotericin B was superior to placebo in preventing the disease.[39]

While most invasive candidal infections are thought to gain entry via the gut,[39] non-absorbable antifungal agents do not protect against fungal infections at other sites, namely the skin, intravenous catheter sites and the respiratory tract. The oral, systemically active azoles have the potential to control colonization as well as prevent dissemination.

Ketoconazole reduces yeast carriage and the incidence of both local and systemic candidosis compared with placebo or non-absorbable agents.[39] Absorption is impaired in neutropenic patients, particularly in BMT recipients,[40] and breakthrough infections have occurred.[41] Ketoconazole also causes elevated ciclosporin A levels as a result of activity on hepatic P_{450} enzymes and serious idiosyncratic hepatotoxicity.

Fluconazole reduces colonization, mucosal thrush and the number of disseminated yeast infections.[42,43] Two placebo-controlled studies in HSCT recipients showed a significant reduction in invasive fungal infections (IFI).[44,45] Fluconazole was associated with a reduced mortality,[45] and fluconazole prophylaxis reduced the incidence of IFI, overall mortality and empirical antifungal therapy in allogeneic HSCT recipients but not autologous HSCT recipients. Unfortunately, its use in some centers has been associated with an increase in colonization and infection with *Candida krusei*, which is intrinsically resistant to fluconazole.[46] Fluconazole is also inactive against the important invasive molds that affect this population, especially *Aspergillus* spp. and the zygomycetes.

In contrast, itraconazole has activity against the molds, particularly *Aspergillus* spp. (*see* Ch. 32). However, in its original capsule formulation it was poorly absorbed in HSCT patients. This has been overcome by the introduction of an itraconazole–cyclodextrin complex in solution. Meta-analysis has shown this formulation to be associated with a lower overall incidence of fungal infection, lower mortality from fungal infection and a reduction in the use of intravenous amphotericin for suspected invasive fungal infection than fluconazole, oral amphotericin and placebo.[47–49] There was also a reduction in the incidence of invasive aspergillosis.

In a randomized trial involving neutropenic patients with AML or MDS, prophylaxis with posaconazole led to a decrease in IFI due to aspergillosis and reduced overall mortality compared with the comparator group receiving fluconazole or itraconazole prophylaxis.[50] A similar effect was shown in allogeneic HSCT patients with GVHD.[51] However, posaconazole prophylaxis has not been evaluated to date in allogeneic HSCT recipients in the neutropenic period post conditioning. Voriconazole has been used in prophylaxis, although large trial data of its use in this setting are still awaited. Extended-spectrum triazole prophylaxis should be avoided in patients receiving vinca alkaloid-based chemotherapy regimens such as vincristine in acute lymphoblastic leukemia. In these cases amphotericin regimens or an echinocandin could be considered.

Micafungin, an echinocandin, is approved for prophylaxis of candidal infections in patients undergoing HSCT. In a randomized, double-blind trial of neutropenic autologous and allogeneic HSCT recipients, comparing 50 mg per day of micafungin with 400 mg per day of fluconazole for antifungal prophylaxis, micafungin was superior to fluconazole based on the absence of breakthrough fungal infection.[52]

In the absence of trial data it would be appropriate to recommend that prophylaxis continue until absolute neutrophil counts are above 0.5×10^9/L in chemotherapy patients. In allogeneic HSCT there is an argument for continuing prophylaxis until at least day +75 or until the end of immunosuppression (in the case of supervening GVHD).

Amphotericin administered as a nasal spray has produced conflicting results in preventing invasive aspergillosis,[53,54] although some studies have shown greater benefit when it is aerosolized.[55,56] One study showed no significant difference in proven, probable or possible invasive aspergillosis between aerosolized amphotericin and no inhalation (4% vs 7%).[57]

Prophylaxis against *Pn. jirovecii* infection has proved remarkably effective in those undergoing treatment for acute lymphoblastic leukaemia[24] and for the first 6 months post-BMT. Trimethoprim–sulfamethoxazole three times weekly has been most studied, although some units are now using a 2-day regimen. Nebulized pentamidine is often used during marrow engraftment to avoid the myelosuppressive effects of trimethoprim–sulfamethoxazole, although data suggest that it may be inferior when used prophylactically in allogeneic transplant recipients. Other alternatives include dapsone and atovaquone.

VIRAL CHEMOPROPHYLAXIS

Most virus infections in the neutropenic patient are due to reactivation of the human herpes viruses. Up to 80% of adult patients with leukemia are herpes simplex virus (HSV) seropositive and the incidence of HSV infection among HSV-seropositive HSCT recipients is about 80%. HSV infection in patients with leukemia is subsequent to reactivation of latent virus in most cases.

Aciclovir (acyclovir), 200 mg every 8 h to 800 mg every 12 h, is effective as prophylaxis against HSV infection in HSV-seropositive patients with leukemia undergoing chemotherapy or in BMT recipients.[58,59] An alternative regimen is valaciclovir 500 mg every 12 h.

Chemoprophylaxis against CMV infection, defined as the use of antiviral agents to prevent a primary CMV infection or a CMV reactivation, has been investigated in detail only in HSCT recipients, although CMV disease also occurs in patients with acute leukemia receiving chemotherapy. Allogeneic HSCT recipients comprise the group at highest risk of CMV reactivation and disease.

High-dose aciclovir has been shown to be partially effective in preventing CMV infection and disease post-BMT. A multicenter randomized trial compared 500 mg/m^2 intravenously every 8 h for 1 month followed by 800 mg every 6 h by mouth for 6 months with 200 or 400 mg every 6 h orally for 1 month followed by placebo.[60] The incidence of CMV infection reduced and survival increased by day 210 post-BMT, although the rates of CMV pneumonia were similar in the two groups. Valaciclovir is also being used in this setting.

The use of ganciclovir as prophylaxis against CMV infection has shown some benefit in reducing the incidence of CMV disease but has no effect on survival during the first 4 months post-BMT.[42,61]

Pre-emptive therapy, defined as the use of antiviral agents in an asymptomatic patient with CMV detected by a screening assay, includes ganciclovir, valganciclovir and foscarnet. The choice depends on the risk of toxicity and which antiviral drugs have been used previously. Weekly monitoring in allogeneic HSCT recipients using a CMV antigenemia assay or a technique for detection of either CMV DNA or RNA is of use for the pre-emptive management of CMV infection.[62,63] Centers vary with regard to the cut-off value used after which therapy is commenced and studies are in progress to better define this. When ganciclovir has been used as pre-emptive therapy following detection of CMV infection, survival was improved at 100 and 180 days post-transplant.[64] Foscarnet may be considered for second-line pre-emptive therapy, or in combination. Cidofovir can be considered for second-line pre-emptive therapy (3–5 mg/kg) but careful monitoring of renal function is required. Other therapeutic options in patients with multiresistant CMV disease are leflunomide and artesunate; however, experience with these agents is very limited.

To date there is no evidence to support the use of prophylaxis for other human herpesvirus (HHV) infections such as HHV-6 following HSCT.

A summary of prophylactic regimens is shown in Table 40.2.

EMPIRICAL THERAPY

The use of empirical antibiotic therapy in febrile neutropenic patients is almost universally practiced, because to await microbiological diagnosis is associated with a high mortality, particularly in patients with Gram-negative bacteremia. The trigger for this is usually a single oral temperature of 38.3°C or two separate temperatures of 38.0°C at least 1 h apart.

The regimen chosen should be active against the common organisms likely to result in overwhelming sepsis or death, and influenced by local antibiotic sensitivity patterns, the incidence of particular infections, the specific needs of the patient and the prophylactic regimen used. Traditionally the significant organisms have been the Enterobacteriaceae and *Ps. aeruginosa*, which carry a mortality of 40–60%.[8,9] Earlier regimens included an aminoglycoside in combination with a β-lactam antibiotic in an attempt to achieve broad-spectrum and synergistic activity against organisms such as *Ps. aeruginosa.* Aminoglycoside use carries the inherent risk of renal and ototoxicity, and data for its combination with β-lactams in empirical therapy have been conflicting. National Comprehensive Cancer Network (NCCN) guidelines recommend aminoglycosides in patients at high risk of pseudomonal infections (history of previous pseudomonal infections or the presence of ecthyma gangrenosum) whereas Infectious Diseases Society of America (IDSA) guidelines suggest they may be added in cases of progressive infection or documented resistant Gram-negative infection. A Cochrane review of 68 randomized controlled trials[65] concluded that for the primary outcome measure of all-cause mortality, there was no significant difference between monotherapy and combination (RR = 0.85). For the second outcome measure of treatment failure there was an advantage to monotherapy in 37 trials comparing different β-lactams (this was for patients with documented infection or hematological malignancy) (RR = 0.86). There was no difference between the two comparator arms in the number of superinfections but significantly more adverse events in the combination group for nephrotoxicity. Another meta-analysis also concluded that monotherapy is as

Table 40.2 Current antimicrobial prophylactic regimens for patients with prolonged neutropenia

Prophylaxis	Agent	Dosage	Duration
Antibacterial	Ciprofloxacin Levofloxacin	500 mg 12-hourly 500 mg daily	During period of neutropenia During period of neutropenia
Antifungal (high-risk patients)	Itraconazole suspension Posaconazole Voriconazole	See Chapter 60 for recommended regimens	During period of neutropenia 6 months post-BMT
Anti-*Pn. jirovecii*	Trimethoprim–sulfamethoxazole (Nebulized pentamidine in adults)	960 mg 12-hourly (150 mg fortnightly)	1 week pre- and 6 months post-BMT 3 times/week throughout treatment in acute lymphoblastic leukemia During period of neutropenia
Antituberculosis[a]	Isoniazid	5 mg/kg daily	During period of neutropenia 6 months post-BMT
Herpes simplex virus[b]	Aciclovir	400–800 mg 4–5 times per day	During period of neutropenia
Cytomegalovirus[c]	Seronegative blood products Aciclovir Ganciclovir	High dose	Not yet established Not yet established

[a]At-risk patients only.
[b]Seropositive patients only.
[c]HSCT recipients only.

effective as aminoglycoside–β-lactam combinations.[66] Data from patients in non-neutropenic studies have shown that once-daily dosing aminoglycoside regimens are as efficacious as multiple-dose regimens.

The first studies of double β-lactam therapy gave results inferior to aminoglycoside-containing regimens,[5,67,68] but later studies using ceftazidime, latamoxef and cefoperazone in combination with a ureidopenicillin[69–71] concluded that such combinations were of equal efficacy and less nephrotoxic than aminoglycoside-containing regimens. However, it was unclear whether they were any better than β-lactam monotherapy. A number of antibiotic regimens have subsequently been evaluated for empirical therapy in febrile neutropenic patients[70–77] and are listed in Box 40.4.

There have been reports that *Stenotrophomonas maltophilia* is selected out by the carbapenems, to which it is intrinsically resistant.[78] In addition, there have been concerns over central nervous system (CNS) toxicity with high-dose imipenem[71] or in patients receiving ciprofloxacin prophylaxis.[79]

One advantage of the carbapenems is their activity against the α-hemolytic streptococci,[80] allowing them to be used alone without the need for early glycopeptide therapy. Similar streptococcal activity can be provided by piperacillin–tazobactam.[81]

A recent meta-analysis of randomized trials examining the choice of β-lactam agent as empirical therapy for the treatment of febrile neutropenia reported that cefepime was associated with an increase in all-cause mortality but not with an increase in infection-related mortality.[82] The authors have concluded that ceftazidime, imipenem, meropenem and piperacillin–tazobactam are suitable monotherapy agents.

The high incidence of Gram-positive infections suggests that empirical therapy should contain a broad-spectrum anti-Gram-positive agent. Clinical trials of glycopeptides have provided conflicting evidence as to whether and when to add such an agent.

Early studies in centers in which there were significant numbers of Gram-positive infections showed that initial vancomycin or teicoplanin increased response rates and reduced morbidity,[83,84] although no study showed a reduction in mortality. In addition, vancomycin is associated with increased toxicity.[84,85] A large joint study conducted by the EORTC and the National Cancer Institute of Canada showed that including vancomycin in the initial therapy conferred no additional benefit,[86] and this has been reinforced by a meta-analysis showing no benefit of empirical Gram-positive therapy either initially or for persistent fever.[87]

The increasing isolation of vancomycin-resistant enterococci (VRE)[88,89] prompted the Centers for Disease Control and Prevention (CDC) to issue guidelines on the use of vancomycin that specifically excluded its use as empirical therapy in the neutropenic patient. This seemed prudent, although the IDSA suggests that vancomycin may be used in initial regimens in institutions where fulminant Gram-positive infections are common, particularly where MRSA may be a problem, and discontinued 3–4 days later if such an infection is not identified.[90]

Box 40.4 Representative antibiotic regimens that have been evaluated for empirical therapy in febrile neutropenic patients[73]

Penicillin and aminoglycoside combinations

Carbenicillin and gentamicin/amikacin/sisomicin
Ticarcillin and gentamicin/tobramycin/amikacin/netilmicin
Mezlocillin and tobramycin
Piperacillin and gentamicin/amikacin/netilmicin/tobramycin
Azlocillin and amikacin/netilmicin
Piperacillin–tazobactam and amikacin

Penicillin/β-lactam allergy

Vancomycin–teicoplanin + ciprofloxacin + gentamicin/amikacin

Cephalosporin and aminoglycoside combinations

Cefalotin and gentamicin
Latamoxef and gentamicin/amikacin
Cefotaxime and amikacin
Ceftazidime and tobramycin/amikacin
Cefoperazone and amikacin
Ceftriaxone and amikacin/netilmicin

Double β-lactam combinations

Carbenicillin and cefalotin
Carbenicillin and cefamandole
Ceftazidime and flucloxacillin
Ticarcillin and latamoxef
Piperacillin and latamoxef
Ceftazidime and azlocillin
Ceftazidime and piperacillin

Triple agent combinations

Carbenicillin, cefalotin and gentamicin
Carbenicillin, cefazolin and amikacin
Cefotaxime, piperacillin and netilmicin

Monotherapy regimens

Latamoxef
Ceftazidime
Cefoperazone
Ceftriaxone
Imipenem
Meropenem
Ciprofloxacin
Cefpirome
Cefepime
Piperacillin–tazobactam

Outpatient empirical regimens

Co-amoxiclav and ciprofloxacin p.o. (clindamycin and ciprofloxacin in penicillin allergy)
Ceftriaxone ± aminoglycoside

Other agents and combinations

Aztreonam and vancomycin
Imipenem and vancomycin
Trimethoprim–sulfamethoxazole and amikacin
Ticarcillin–clavulanate

From Liang R, Yung R, Chiu E, et al. Ceftazidime versus imipenem–cilastatin as initial monotherapy for febrile neutropenic patients. **Antimicrob Agents Chemother.** 1990;34:1336–1341.

Table 40.3 Options for initial empirical therapy

Regimen	Advantages	Disadvantages
Aminoglycoside + β-lactam	Broad spectrum Proven efficacy Synergy vs Gram-negative bacteria and streptococci	Poor activity vs coagulase-negative staphylococci Nephrotoxic and ototoxic Serum assays required
Double β-lactam therapy	Broad spectrum Avoids aminoglycoside toxicity No monitoring required	No more effective than single-agent therapy Possible prolongation of neutropenia Electrolyte imbalance Possible antagonism
Monotherapy	Broad spectrum Avoids aminoglycoside toxicity Avoids antagonism No monitoring required Cheaper	Lack of synergy (? less effective vs *Ps. aeruginosa*) Less active versus Gram-positive bacteria (with ceftazidime) Risk of resistance Potential central nervous system toxicity (with imipenem)
Single agent + glycopeptide	Broad spectrum including coagulase-negative staphylococci and α-hemolytic streptococci No monitoring required (with teicoplanin)	Expensive Unnecessary in some units Nephro- and ototoxicity (with vancomycin) Monitoring required (with vancomycin) Risk of glycopeptide resistance

There is also evidence that the choice of broad-spectrum agent for empirical therapy can influence the emergence of glycopeptide-resistant enterococci (GRE).[91] At present glycopeptide-intermediate *Staph. aureus* (GISA) infections are not a significant problem in the UK, but provide another reason for selective use of glycopeptides in institutions where they do occur.

The oxazolidinone linezolid, the streptogramin quinupristin–dalfopristin and daptomycin are alternatives in patients intolerant of vancomycin and teicoplanin and for treatment of GRE and GISA infections. A multicenter, randomized study of febrile neutropenic patients comparing the safety of linezolid and vancomycin showed that clinical success rates 7 days after completion of therapy were equivalent, as was mortality at 16 days after completion of therapy. Drug adverse events were more frequent in the vancomycin arm and time to defervescence was shorter in the linezolid arm in patients with documented Gram-positive infections. Slower times to neutrophil recovery seen in the linezolid arm may have been secondary to the myelosuppressive effects of linezolid but were not statistically significant.

The duration of treatment has not been studied independently, but since the first EORTC trial the evidence has suggested that prolonged treatment is associated with more superinfections, often fungal, but no improvement in outcome. Current EORTC trials are conducted on the basis of discontinuing antibiotics after 7 days minimum treatment and four consecutive afebrile days, and this is similar to the IDSA and NCCN guidelines where 5–7 days without fever is recommended.[90] Options are summarized in Table 40.3.

With health services moving towards earlier discharge of all groups of patients, attempts have been made to achieve this in the neutropenic population. Talcott and colleagues derived a risk assessment model in which patients were divided into four groups.[92] The fourth group was found to be at low risk and was studied in subsequent trials, which showed that amoxicillin–clavulanate plus ciprofloxacin was as effective as intravenous ceftazidime or ceftriaxone plus amikacin in treating these patients.[93,94]

Examples of outpatient oral/intravenous regimens are included in Box 40.4.

MANAGEMENT OF THE PATIENT WITH PERSISTENT PYREXIA

Approximately 20–30% of febrile patients who remain persistently neutropenic fail to respond to apparently appropriate antibiotic therapy. Some remain febrile until recovery of their neutrophil counts, irrespective of the antimicrobial therapy administered. Many patients with persistent fever will have an occult fungal infection. Patients with acute leukemia and allogeneic HSCT recipients are at highest risk due to prolonged neutropenia and immunosuppression for GVHD. Autopsy studies have shown that up to 25% of those neutropenic patients who die have an undiagnosed fungal infection.[10]

In view of the difficulties in diagnosis, the use of empirical antifungal therapy has been advocated. Recent ECIL 2009 guidelines are consistent with this viewpoint and current British Committee for Standards in Haematology (BCSH) guidelines advocate empirical antifungal therapy where IFI is suspected in conjunction with high-resolution computed tomography (HRCT) scanning and mycological tests (*see* Ch. 60). The main randomized study on which empirical antifungal therapy is based compared the effect of amphotericin (0.6 mg/kg per day or equivalent) with no treatment in patients remaining febrile 4 days after empirical therapy.[95] Although more responded in the amphotericin-treated group, the effect was only significant in patients not given antifungal prophylaxis (78% vs 45%; $p = 0.04$). Following this a number of other agents have been shown to be at least as effective as conventional amphotericin. Liposomal amphotericin B (AmBisome) is less nephrotoxic than conventional amphotericin, at least

as effective in rendering patients afebrile and is associated with significantly fewer breakthrough fungal infections.[96,97] Subsequently, caspofungin has been shown to be at least as effective as AmBisome in this setting.[97]

Patients who deteriorate during the first 48 h of empirical therapy pose a particularly difficult therapeutic challenge. It is important that there are no gaps in the spectrum of the selected regimen. Deterioration may be due to Gram-negative or Gram-positive organisms, such as α-hemolytic streptococci, which may cause features similar to those of sepsis syndrome (including acute respiratory distress syndrome and septic shock), or enterococci. Gram-negative activity (including antipseudomonal activity) is essential. Consequently, the addition of an aminoglycoside to initial β-lactam monotherapy is recommended, and this is also supported by the ECIL guidelines for patients with septic shock. A glycopeptide should also be considered. The above approach is summarized in Figure 40.2.

ASPECTS OF THERAPY FOR SPECIFIC ORGANISMS AND INFECTIONS

INTRAVENOUS CATHETER-ASSOCIATED INFECTIONS

Most neutropenic patients undergoing chemotherapy have an indwelling central line, which commonly becomes infected. The predominant pathogens are coagulase-negative staphylococci and *Staph. aureus*.[98] Others include *Candida* spp., coryneforms, *Acinetobacter*, *Stenotrophomonas* and *Pseudomonas* spp.[99] Ideally, infected catheters should be removed, but coagulase-negative staphylococcal infections may be effectively suppressed or eliminated by administering antibiotics via the catheter until neutropenia has resolved.[98] A high percentage of coagulase-negative staphylococci isolated on hematology units are resistant to methicillin and other β-lactams.

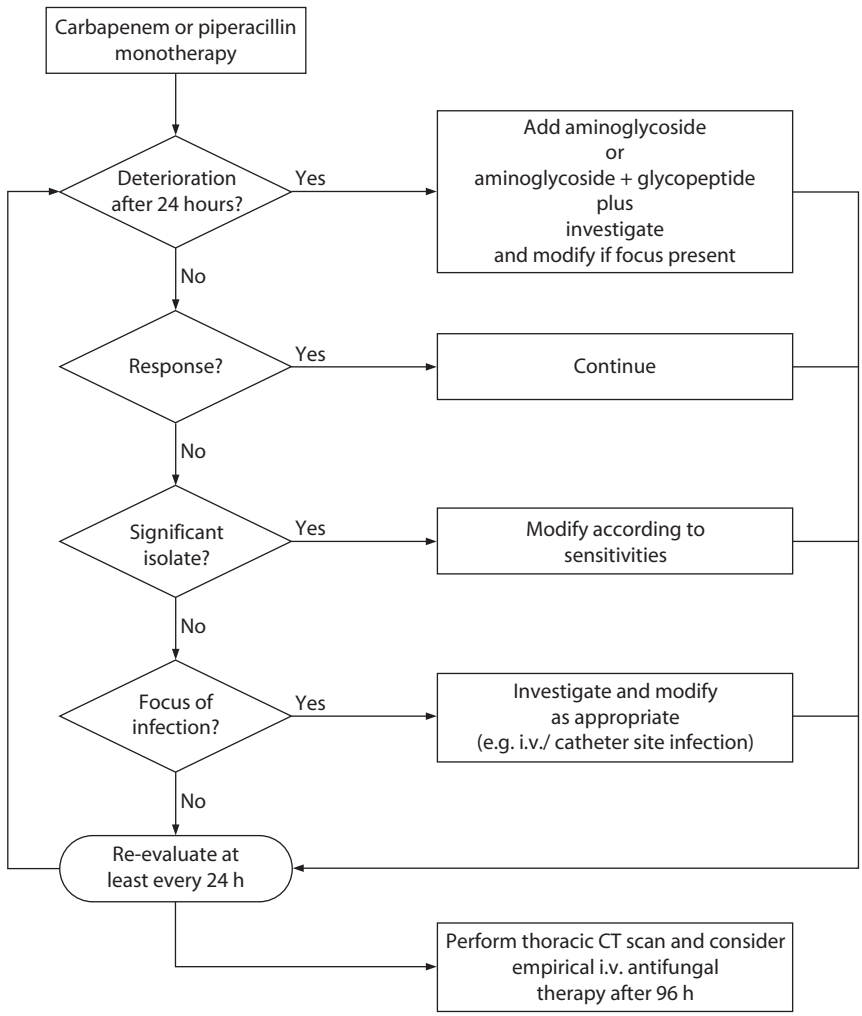


Fig. 40.2 An algorithm for the initial management of febrile neutropenic patients receiving prophylaxis.

A glycopeptide (most frequently vancomycin) is given for these, with the chance of successful resolution of bacteremia and fever being more than 50%. Similar response rates can be obtained with coryneform infections but those due to *Candida* spp., Enterobacteriaceae, *Staph. aureus*, *Ps. aeruginosa*, *Acinetobacter*, *Sten. maltophilia*, non-tuberculous mycobacteria, and any form of tunnel infection, require the catheter to be removed and appropriate antimicrobial therapy administered.[100] The presence of port infection or septic phlebitis in association with long-term indwelling catheters are also indications for catheter removal and antimicrobial therapy.

PULMONARY INFECTIONS OF UNKNOWN CAUSE

Pulmonary infiltrates commonly occur in the febrile neutropenic patient and have a number of causes, especially in the BMT recipient. These include non-infective conditions such as pulmonary edema, alveolar hemorrhage, adverse drug reactions, radiation injury and the idiopathic pneumonitis syndrome. Focal lesions are more indicative of fungal infection, and HRCT or MRI scanning may reveal characteristic features of these.[101] If clinical status permits, the causative organism(s) may be obtained by bronchoalveolar lavage. However, in many cases treatment has to be given empirically.

Initial therapy should certainly include agents effective against common respiratory pathogens such as *Str. pneumoniae* and *Haemophilus influenzae*, as well as Gram-negative organisms including *Ps. aeruginosa*, and hence a carbapenem, piperacillin–tazobactam or ceftazidime, with or without an aminoglycoside, is recommended.

Atypical pneumonias are extremely uncommon in this population and, unless there are particular clinical or epidemiological reasons to suggest Legionnaires' disease, erythromycin can be omitted from the initial therapy unless the infection appears to be community related. Mycobacterial infections may occasionally complicate hematological malignancies. Patients with lymphoid malignancy and BMT recipients who have not been receiving trimethoprim–sulfamethoxazole prophylaxis are at risk of *Pn. jirovecii* pneumonitis; empirical high-dose trimethoprim–sulfamethoxazole therapy (120 mg/kg per day in divided doses) is warranted in such patients. BMT recipients are particularly at risk of CMV pneumonitis post-transplant. However, CMV or *Pn. jirovecii* pneumonitis usually presents a month or so post-transplant, when the patient is no longer neutropenic, and the timing of the presentation should be taken into account when decisions are being made regarding empirical therapy. CMV pneumonitis is treated with intravenous ganciclovir (5 mg/kg every 12 h) plus intravenous immunoglobulin (200–400 mg/kg on alternate days for 14–21 days).[102–104] Despite this, mortality from CMV pneumonitis is still in excess of 50% in BMT recipients. Furthermore, the myelosuppressive effect of ganciclovir can present a particular problem in these patients.

Patients discharged into the community are at risk of respiratory viral infections with agents such as respiratory syncytial virus, influenza and paramyxoviruses, which occasionally cause outbreaks on hematology units.[105]

INVASIVE FUNGAL INFECTIONS

Despite recent advances in the diagnosis and treatment of invasive fungal infections (IFI), failure rates approach 50% in invasive aspergillosis. Case fatality rates of 87% for HSCT and 50% for leukemia patients are quoted,[106] with 30-day mortality rates of 45% for candidemia in hematological malignancy.[107] Current BCSH guidelines advocate the use of caspofungin and liposomal amphotericin for empirical therapy of suspected IFI as they have the lowest rates of toxicity and are of equal efficacy. This is also in keeping with the current ECIL guidelines. Other options include voriconazole and posaconazole. The therapy of fungal infection is considered in detail in Chapter 60.

INVASIVE CANDIDAL INFECTIONS

A trend towards non-*albicans* species such as *C. glabrata* and *C. krusei* displaying a decreased susceptibility or resistance to azoles has been documented in both Europe and North America. These species are responsible for more than 60% of invasive candidal infections in patients with hematological malignancy.[108]

Recent trials of the three licensed echinocandins – caspofungin, micafungin and anidulafungin – have demonstrated response rates in excess of 70% and these are now considered to be among the first-line agents for invasive candidal infections, especially where the species is not known, where the patient has received azole prophylaxis or in severe sepsis. This is supported by the ECIL-2 guideline update and IDSA candida guidelines, together with the use of AmBisome and other lipid formulations of amphotericin. Voriconazole is an alternative agent but should be used with care in patients where previous azole prophylaxis has been used. Recommendations for duration of therapy consist of 14 days following the last positive blood culture, together with extensive investigation for dissemination of infection. Further trials regarding the use of efungumab (Mycograb), a human recombinant antibody consisting of an Fv fragment that binds to the domain structure HSP90 of *Candida* spp., are needed before recommendations regarding its use in combination with antifungals can be made, and it is currently not licensed.

INVASIVE ASPERGILLOSIS

Mortality due to invasive aspergillosis remains high in neutropenic patients; the infection is now the most important cause of death in childhood AML and adult BMT recipients. In BMT recipients case fatality rates are as high as 87%.[106] Successful outcome is dependent upon early treatment and, to a considerable extent, on bone marrow recovery. Agents active against *Aspergillus* spp. include amphotericin deoxycholate and its

lipid-associated preparations, the extended-spectrum triazoles and echinocandins. High-dose conventional amphotericin is also associated with a high incidence of nephrotoxicity. Lipid-associated formulations of the drug have been licensed for use in patients failing treatment or experiencing unacceptable toxicity with conventional amphotericin. Liposomal amphotericin (AmBisome) has been studied in a randomized prospective trial comparing two doses (1 mg/kg per day and 4 mg/kg per day) for the treatment of invasive aspergillosis in neutropenic patients:[109] 6-month mortality was approximately 60% with attributable mortality of around 20% in the two arms. A double-blind comparison of AmBisome 3 mg/kg and AmBisome 10 mg/kg in primary therapy by Cornely and colleagues demonstrated no additional benefit of 10 mg/kg dosing over 3 mg/kg dosing of liposomal amphotericin B.[110]

Voriconazole has been assessed by Denning and colleagues in two open-labeled studies in which response rates of 44% and 48% were reported, respectively.[111,112] Superiority of voriconazole over amphotericin deoxycholate in terms of efficacy, safety and survival has been demonstrated by Herbrecht and colleagues in a randomized trial.[112] Superiority was irrespective of the host group, site of lesion or neutropenic status. Voriconazole has been given the highest graded recommendation in the recent ECIL-2 guideline update, followed by AmBisome. In North America the NCCN currently recommends voriconazole as the agent of choice for first-line therapy of invasive pulmonary aspergillosis. There are insufficient data to recommend the use of caspofungin, itraconazole and posaconazole as agents in first-line therapy of invasive aspergillosis, but these have all been used in salvage therapy with similar efficacy. There are also currently insufficient data to recommend combination therapy in first-line therapy. One retrospective study[113] comparing the combination of voriconazole and caspofungin given as salvage therapy after failure of amphotericin formulations in allogeneic HSCT recipients with voriconazole monotherapy in a historical control group demonstrated substantially improved 3-month survival.

The development of mycotic lung sequestra (which have been mistakenly termed mycetomas) may require additional therapy. These lesions appear once the bone marrow is regenerating. Patients are at risk of life-threatening hemoptysis.[114] In addition, patients who require further chemotherapy or bone marrow transplantation are at considerable risk of relapse of the original infection. Resection of these lesions has been shown to be effective, preventing relapse following bone marrow transplantation, and is associated with a lower mortality than antifungal therapy alone in some studies,[115] although there are no large randomized studies in this setting.

ADDITIONAL THERAPIES

GROWTH FACTORS

Hematopoietic growth factors have been extensively used to treat neutropenic patients. Studies have consistently shown that granulocyte–colony-stimulating factor (G-CSF) reduces the duration of neutropenia. However, the reduction in infectious complications has been modest and most trials have been unable to demonstrate a reduction in infectious morbidity and mortality.[116–118] This is probably because the major effect of G-CSF is to accelerate the recovery of neutrophils, whereas it has no impact on the critical lag period of profound neutropenia.[119] The American Society of Oncology and the NCCN have published guidelines for the use of these agents in the setting of anti-cancer chemotherapy.

Granulocyte–macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) may be beneficial in the treatment of invasive fungal infections,[120] although large-scale trials demonstrating this are regrettably still lacking.

GRANULOCYTE TRANSFUSIONS

Renewed interest is now being shown in this modality, coupled with improved methods of harvesting and increased yield following the use of growth factors.[121,122]

IMMUNOGLOBULIN THERAPY

Routine prophylactic use of intravenous immunoglobulin does not reduce viral infections; however, the addition of intravenous immunoglobulin to ganciclovir may improve survival in CMV pneumonitis and post-exposure immunoglobulin is indicated for the prevention of hepatitis A, measles and varicella-zoster infection.

INFECTIONS IN TRANSPLANT RECIPIENTS

IMMUNOSUPPRESSIVE THERAPY

Since the first successful human cadaveric kidney transplant in 1954, solid organ transplantation has proceeded to become a viable option in the management of end-organ failure worldwide. Current 1- and 5-year graft survival for cadaveric (non-extended criteria donor) renal transplants in the USA is 95% and 82%, respectively.[123] The results are similar for Europe. Developments in surgery and better control of rejection and infective complications have allowed a steady improvement in the survival of other organ grafts.

Most transplant units use a triple regimen of azathioprine or mycophenolate, a calcineurin inhibitor such as ciclosporin A, and corticosteroids for immunosuppression. Azathioprine is a purine analog which inhibits both B- and T-cell proliferation; as a consequence, both cell-mediated immunity (CMI) and humoral immunity are inhibited. The drug may take weeks or months to exert its full effect. Ciclosporin, a calcineurin inhibitor, arrests the lymphocyte cell cycle in the resting

phase, having most effect on CD4-positive T cells and a minimal effect on B cells. This results in effective suppression of CMI, has little effect on humoral immunity and no effect on phagocytosis. The inflammatory response is preserved.

Corticosteroids in high dose have a very broad immunosuppressive action, producing a reduction in antigen-stimulated lymphocyte proliferation and a blunting of the primary antibody response. They also inhibit neutrophil chemotaxis and monocyte phagocytosis, dramatically reducing inflammatory responses at high dosage and disguising the presence of infection.

The aim of these regimens is to achieve a balance between graft rejection and risk of infection. Episodes of subsequent acute rejection require considerable immunosuppression and are accompanied by an increased risk of opportunistic infections. The phase of acute rejection varies in length for different transplants. Most episodes occur in the first 3 months of liver transplantation, whereas the phase of acute rejection lasts for 6 months for renal transplants.[124] Rejection episodes are usually treated with high-dose methylprednisolone or various antibody preparations such as polyclonal antithymocyte globulin (ATG), antilymphocyte globulin (ALG) or the pan-T-cell monoclonal antibody OKT3. Patients requiring a second or third graft are usually even more immunosuppressed and at increased risk of opportunistic infection.

Tacrolimus (FK506), another calcineurin antagonist, has been substituted for ciclosporin for certain indications; several studies have demonstrated it to have fewer infective complications,[125–128] which may be a consequence of the need for less episodic antirejection therapy. Mycophenolate mofetil, an inhibitor of inosine monophosphate dehydrogenase which inhibits purine synthesis, has been used as a substitute for calcineurin inhibitors. Although it has no associated renal toxicity (and allows improvement in renal function), some studies have shown it to result in increased risk of rejection.[124] A recent review comparing the use of azathioprine with mycophenolate in liver transplantation concluded that, to date, little if any clinical benefit could be observed of mycophenolate mofetil over azathioprine.[129] There is still considerable scope for refining immunosuppression with these and other new agents, hopefully enabling a further reduction in infective complications.

THE SEQUENCE OF INFECTIONS FOLLOWING TRANSPLANTATION

The risk of infection in the organ transplant patient is influenced by previous epidemiological exposures and the degree of immunosuppression. Epidemiological exposures can be divided into donor-derived infections, recipient-derived infections, nosocomial infections and community infections. The extent of immunosuppression is determined by the type of immunosuppressive therapy, its dose and duration (*see* Box 40.5), underlying diseases and co-morbid conditions, the presence of devitalized tissues or fluid collections in the transplanted organ, and the presence of invasive devices. Other important factors include concomitant infection with immunomodulating viruses such as CMV and other human herpes viruses, HIV-1, and hepatitis B and C viruses. Infectious complications follow a relatively predictable chronological order after any transplantation procedure. Knowledge of this is helpful in guiding the use and duration of prophylaxis, establishing a diagnosis through appropriate investigations and administering empirical treatment if necessary. This is summarized in Figure 40.3.

In the first month after transplant, infections are largely associated with the transplant surgical procedure, particularly those complicating the anastomoses associated with the specific procedure. Some infections are transmitted with the allograft or are present in the recipient before transplantation. An important component of the pretransplant evaluation is to recognize and treat such infections. Nosocomial infections such as those due to VRE or MRSA, and *Clostridium difficile* colitis are also important at this time.

Between the first and the sixth month following transplantation the most important infections are caused by the herpes group viruses (especially CMV), *Nocardia* species, *Listeria monocytogenes*, *Toxoplasma gondii*, *Pn. jirovecii* and other fungi. In addition, latent infections such as tuberculosis or histoplasmosis may reactivate at this time. The risk of infection correlates with the severity of immunosuppression required to treat rejection episodes.

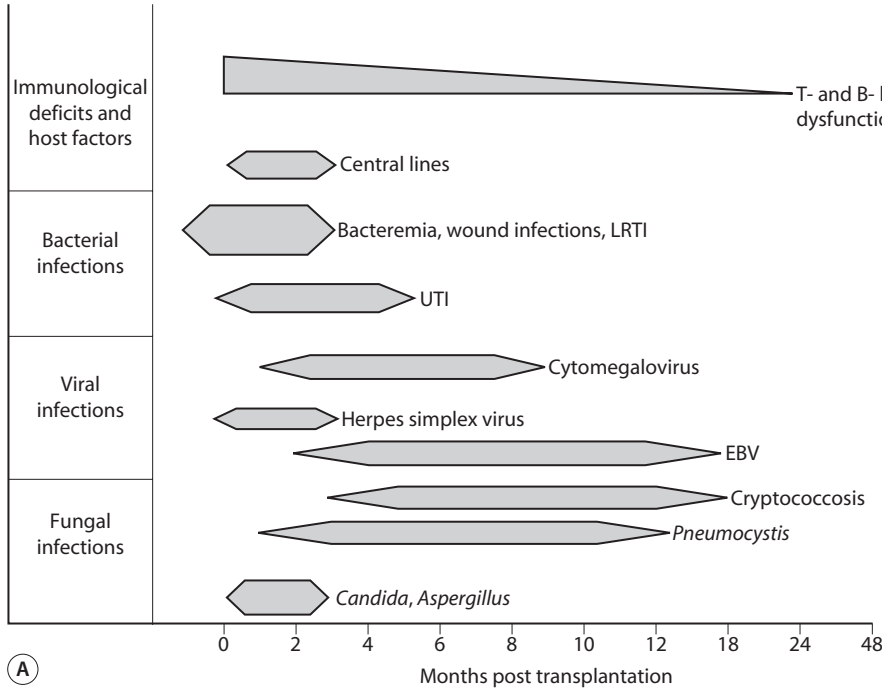
Subsequent infections are usually the result of community-acquired organisms. A few patients will suffer chronic viral infections affecting the graft, while others who have been intensively immunosuppressed remain at risk of opportunistic infections. Other rare infections in the late post-transplant period have been described, including chronic infection with hepatitis E virus causing cirrhosis as a late complication.[130]

BACTERIAL INFECTIONS

Bacterial infections occur in approximately 50% of renal transplant recipients and in up to 70% of liver transplant patients. In some series patients have suffered at least one bacterial infection in the post-transplant period.[131] The common infections are intra-abdominal abscess, cholangitis, bacteremia, wound infection, lower respiratory tract infection and urinary tract infection, with intra-abdominal infection responsible for approximately 30% in liver transplantation.[131–134] The overall mortality is less than 5%, but varies according to site and organ.

Subsequently resistant organisms have become established as endemic pathogens in many transplant units. MRSA was found to be the leading cause of bacteremia in liver transplant recipients in one center, responsible for 37% of all episodes.[135] VRE and extended-spectrum β-lactamase-producing Gram-negative organisms are also increasingly causing infections in these patients.

Representative organisms isolated from infected patients in the postoperative period are shown in Box 40.6. Bacteria isolated from the graft perfusion fluid differ in their propensity to cause post-transplantation infection. Positive



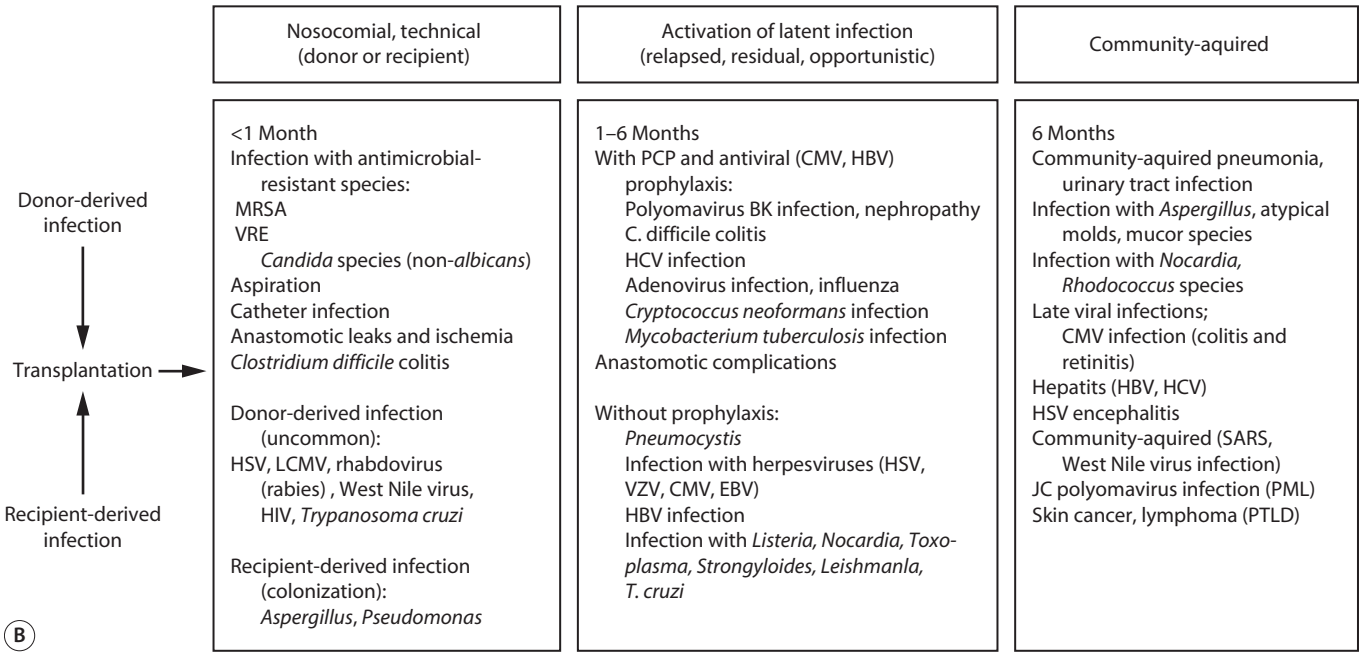


Fig. 40.3 (A) The time course of infections after solid organ transplantation. (B) Changing timeline of infection after transplantation. Infections occur in a generally predictable pattern. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug toxic effects that may cause leukopenia, or immunomodulatory viral infections such as infection with cytomegalovirus (CMV), hepatitis C virus (HCV) or Epstein–Barr virus (EBV). At the time of transplantation, a patient's short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent graft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust both prophylaxis and immunosuppressive therapy. HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; PTLD, post-transplantation lymphoproliferative disorder; SARS, severe acute respiratory syndrome; VRE, vancomycin-resistant *Enterococcus* spp.; VZV, varicella-zoster virus. (Adapted from Fishman, JA. Infection in solid organ transplant recipients. *New England Journal of Medicine* 2007; 357:2601. Copyright ©2007 Massachusetts Medical Society.)

Box 40.5 Infections associated with specific immunosuppressive regimens

- *Antilymphocyte globulins*: T-cell depleting antibodies mimic the alloimmune response with activation of latent (herpes) virus, fever, cytokine release
- *Corticosteroids*: Bacteria, *Pneumocystis* pneumonia, activation of hepatitis C and hepatitis B
- *Azathioprine*: Neutropenia, uncertain role in human papillomavirus infection
- *Mycophenolate mofetil*: Early bacterial infection, B-cell depression, late cytomegalovirus infection
- *Ciclosporin/tacrolimus*: Increased viral replication, B-cell depression, gingival infection, intracellular pathogens
- *Rapamycin*: Excess infections in combination with current agents (requires monitoring), idiosyncratic pulmonary syndrome, often with other respiratory pathogens
- *Plasmapheresis*: Encapsulated bacteria
- *Co-stimulatory blockade*: Unknown so far
- *Rituximab*: B-cell depletion, bacterial and viral infections
- *Alemtuzumab*: Cytomegalovirus infection, viral infection, fungal infections

Box 40.6 Organisms causing post-transplant infections

Gram-positive bacteria

Coagulase-negative staphylococci
Staphylococcus aureus
Enterococci
Streptococci
Listeria monocytogenes
Nocardia spp.

Gram-negative bacteria

Enterobacteriaceae
Pseudomonas spp.
Stenotrophomonas maltophilia
Legionella spp.

Anaerobic bacteria

Bacteroides spp.
Clostridium spp.

Fungi

Candida spp.
Aspergillus spp.
Pneumocystis jirovecii
Cryptococcus neoformans
Blastomyces dermatitidis
Coccidioides immitis
Histoplasma capsulatum

Viruses

Herpes simplex virus
Cytomegalovirus
Hepatitis B virus
Hepatitis C virus
Varicella zoster virus
Polyoma viruses
Adenovirus
Human herpesvirus-6
Human herpesvirus-8

Others

Mycobacterium spp.
Toxoplasma gondii

cultures have been found in up to 40% of cases in renal transplantation, but most of these have been due to Gram-positive skin bacteria and do not seem to have serious consequences. However, the isolation of the Enterobacteriaceae and *Ps. aeruginosa* correlate with vascular infection and postoperative sepsis,[136–138] and warrant systemic antibiotic therapy following transplantation.

Infections due to *Nocardia* spp. are important late complications following transplantation, usually occurring after the first month, and which correlate with the degree of immunosuppression. Outbreaks in renal transplant units have been described[139] and the incidence is up to 4% in this group.

Tuberculosis tends to occur several months after transplantation. The onset is significantly later in renal transplants than in other groups of organ transplant recipients.[140] Approximately one-third have disseminated infection and the overall mortality is 29%. The overall incidence of mycobacterial infection in the transplant population is 1%, more than 50-fold greater than the incidence in the general population.[141]

Transplant recipients are at increased risk of Legionnaires' disease by virtue of their immunosuppression. In addition, a UK study demonstrated that *Legionella* spp. could be isolated from the water in approximately 50% of transplant units[142] and *Legionella* control is now an important component of water and air conditioning management in hospitals.

FUNGAL INFECTIONS

Colonization with yeasts is common in this population, although the incidence varies according to the number and frequency of sites sampled and the use of antifungal prophylaxis. Infection rates vary, with the lowest in renal transplant recipients (approximately 5%).[143] The incidence of fungal infections is falling, possibly as a consequence of reduced immunosuppression and improvement in surgical technique.[144] Most infections are caused by *Candida* spp. (approximately 80%), with *Aspergillus* spp. accounting for the majority of invasive mold infections.[143,145] *Pn. jirovecii* pneumonitis occurred in 4–10% of kidney, 10–11% of liver, 5–41% of heart, and 16–43% of heart–lung and lung transplant recipients before routine prophylaxis was implemented.[146] It is closely linked with CMV disease.

Candidal infections are associated with death in more than 50% and invasive aspergillosis is almost universally fatal in this group.[143] The site of infection is transplant dependent. Thus urinary tract candidosis is mostly confined to the renal transplant group and lung transplant recipients have a much increased risk of pulmonary infections. Although occurring very infrequently, focal brain infection in solid organ transplant patients is almost exclusively due to fungi, usually *Aspergillus* spp.;[147–149] *Cryptococcus neoformans* is the most frequent cause of meningitis.

Most fungal infections occur in the first 2 months after transplant,[143] although *Pn. jirovecii* infection tends to be delayed and cryptococcosis usually affects patients in the late transplant period. Infections due to the endemic fungi, including *Coccidioides immitis* (most often following exposure in the southwestern United States), *Histoplasma capsulatum* (most often following exposure in the Ohio River Valley, but also elsewhere in the world) and *Blastomyces dermatitidis*, may also be seen in the late post-transplant period. In one series, the median time to symptoms from histoplasmosis was 11 months after transplantation.[150] The management of these infections is discussed further in Chapter 60.

VIRAL INFECTIONS

Since the earliest days of transplantation, virus infections have caused problems in transplant recipients. Members of the Herpesviridae are the most commonly implicated.

Cytomegalovirus is responsible for the greatest number of all types of infection in these patients. The incidence varies from 45% to 100%,[151] reflecting the incidence of seropositivity among the recipient population and the numbers of seropositive to seronegative transplantations. However, the incidence of disease is transplant dependent, being lowest in renal transplant recipients, in whom it is symptomatic in less than 10%.[152]

Overall, 25–30% of infected patients develop disease,[151–153] although of those at highest risk (seropositive to seronegative transplants) 50–60% will develop clinical disease.[141] The site of disease is transplant dependent, being focused on the graft. About 3% of all transplant recipients affected will develop CMV pneumonitis.[153]

Post-transplant hepatitis occurs in more than 10% of solid organ transplant recipients overall. The most common cause is hepatitis C virus (HCV). In liver transplant patients most of these infections occur as a result of reinfection in patients who have been transplanted for HCV-related cirrhosis. Polymerase chain reaction (PCR) techniques have shown that virtually all infected patients suffer reinfection post-transplant. Before universal screening of blood donors and awareness of donor status, primary HCV infections occurred in more than 35%;[154] the incidence is now much lower. In one study, 95% of patients with pretransplant infection developed post-transplant hepatitis, mostly due to HCV.

Reinfection with hepatitis B virus (HBV) following liver transplantation is almost inevitable unless long-term prophylaxis is used. The highest recurrence is seen in those who are HBV-DNA positive before transplant.[155]

Epstein–Barr virus (EBV) infection following transplant is probably underdiagnosed. Most clinical disease is due to reactivation, although primary infection does occur, usually after the patient is discharged, and is responsible for more severe disease. The most important complication of EBV infection is post-transplant lymphoproliferative disorder (PTLD). The overall incidence of this condition is approximately 1%.[156] In a large series of various solid organ graft recipients, viremia was found in 3.9%, and 75% of those with primary viremia developed PTLD compared with 11% of secondary viremia cases.[156] The risk of this disease is also increased by the use of antirejection therapy such as OKT3 anti-T-cell antibodies.

Before the advent of aciclovir, HSV infections (almost exclusively the consequence of reactivation) were responsible for clinical disease in approximately 50% of seropositive patients.[141] HSV infections are now much less clinically significant than other herpes group infections.

Human herpesvirus-6 (HHV-6) may be responsible for central nervous system disease post transplantation. CNS symptoms occurred in 25% of liver transplant recipients with HHV-6 viremia compared with 12% of those without.[157] Infection with HHV-6 may also have an immunomodulatory role, being associated with an increased risk of CMV infection and fungal infection.[158]

Human herpesvirus-8 (HHV-8) is transmitted from donor to recipient, resulting in Kaposi's sarcoma in up to 8% of cases who seroconvert.[159]

Polyomavirus causes latent infection in the kidney in the immunocompetent subject, and in renal transplant recipients may be responsible for tubulointerstitial nephritis and graft dysfunction.[160]

INFECTIONS DUE TO OTHER ORGANISMS

The incidence of toxoplasmosis varies according to the type of transplant and is most common in heart transplant recipients, of whom more than 50% of seronegative patients receiving a heart from a seropositive donor will seroconvert.[161] In addition, toxoplasmosis is governed by the seroprevalence of the infection (20% in the UK and higher in other countries such as France) and the serological status of donor and recipient: the highest rate and most severe infections occur when transplanting a seropositive donor to a seronegative recipient. In renal transplant recipients less than 1% develop primary toxoplasmosis. Most such cases occur within 2 months of transplant and are characterized by encephalitis, brain abscess, retinitis, pneumonitis, cardiac involvement and hepatitis.[162–164]

CHEMOPROPHYLAXIS

Antimicrobial prophylaxis, along with vaccination and preemptive therapy, form the mainstay of preventive strategies against infection. Until recently, most prophylactic regimens used in transplant recipients have been based on the risk of infection and likely organisms. Regimens shown to be effective in the neutropenic patient or in surgical prophylaxis have been adopted, yet few have been subject to randomized comparative trials. A short course of prophylactic antibiotics is probably appropriate to prevent wound infection related to the procedure itself. Selective decontamination of the digestive tract may be of benefit in some transplant groups, although there is conflicting evidence. Gram-negative infections are reduced in liver transplant recipients[165] but an increase in Gram-positive infections, including MRSA and VRE, has been seen in several heart transplant centers.[166]

A number of studies have demonstrated the benefit of long-term prophylaxis for urinary tract infections in renal transplant recipients. Both trimethoprim–sulfamethoxazole (960 mg nightly) and ciprofloxacin have been effective, although the former has the additional benefit of preventing *Pn. jirovecii* infection.[167,168]

The issue of mycobacterial prophylaxis remains controversial and policies vary internationally. As there is a significant risk of isoniazid hepatic toxicity, this drug should be used selectively. However, this risk varies according to the transplant, from 2.5% in renal transplant recipients to 41% in liver transplant recipients.[140] Patients in whom such prophylaxis is justified are those of Asian or other high-risk ethnic origin, those with a history of tuberculosis and those with radiographic changes suggesting past chest infection.

The high risk of fungal infection in liver transplant recipients has led to the administration of antifungal agents in the post-transplant period. Non-absorbable agents such as amphotericin or nystatin, sometimes in combination with oral antibiotics such as gentamicin and polymyxin B, have been widely used. Fluconazole and itraconazole have been studied in randomized comparative trials in liver transplantation and both are better than placebo in preventing superficial and invasive candidosis.[169,170]

Prophylaxis against *Pn. jirovecii* pneumonia with trimethoprim–sulfamethoxazole is probably only necessary during the first year post-transplant, except in lung transplant recipients when there is a significant persisting risk of the disease.[171]

The current American Society of Transplantation guidelines recommend antiviral prophylaxis in all CMV donor-positive, recipient-negative solid organ transplant recipients.[172] Several randomized comparative studies have demonstrated that early (first 14 days or until discharge) post-transplant ganciclovir, with[173] or without[174] gammaglobulin, is more effective than aciclovir (various doses) in preventing CMV symptomatic infection in liver transplants. Symptomatic infection was reduced to 5–9%.

Pre-emptive prophylaxis targets patients at highest risk of disease and limits duration of drug administration, reducing toxicity and cost. Hence, kidney–pancreas transplant patients receiving OKT3 pan-T-cell monoclonal antibody therapy and CMV-shedding liver transplant recipients both appear to benefit from pre-emptive prophylaxis with ganciclovir or foscarnet.[175,176] CMV antigenemia or PCR-guided pre-emptive therapy based on attainment of a pre-defined viral load is as effective as, but less expensive than, universal oral ganciclovir prophylaxis for 90 days or intravenous ganciclovir for 14 days.[177] The duration of this pre-emptive therapy is not fixed and is determined by viral load and varies in length between centers.

Trials of prophylaxis with lamivudine to prevent recurrence of HBV following liver transplantation have shown that, although HBV-DNA levels become undetectable in virtually all patients, this effect is not sustained because of the emergence of resistant mutants.[178] As a consequence, alternative strategies involving a combination of adefovir, lamivudine and hepatitis B immune globulin are being employed.

TREATMENT

Although transplant recipients are severely immunocompromised, they do not have the same paucity of signs as neutropenic patients in the face of serious sepsis and, in the immediate postoperative period, behave more like non-transplant patients with surgical sepsis.[179] Consequently, the concept of early empirical therapy in response to fever alone has not been applied to these patients.

All attempts should be made to identify a focus of sepsis or the non-infective cause for fever in a transplant patient. Antimicrobial therapy may reasonably be withheld if the patient is otherwise well and there is no identifiable infective cause, but this should be kept under review. If empirical treatment is considered necessary, the choice of antimicrobials should be governed by the timing of the infection (and hence the probable organisms), the type of transplant, the site of sepsis, knowledge of colonization with resistant organisms (such as MRSA and VRE), and local antimicrobial resistance patterns, as discussed previously.

ASPECTS OF THERAPY FOR SPECIFIC INFECTIONS

FUNGAL INFECTIONS

Fungal infections should be managed using the same agents as used in the neutropenic patient. No antifungal is contraindicated but care is required in their use because of toxicity (especially in renal and liver transplant recipients) and drug interaction (especially flucytosine with antimetabolites and triazoles with ciclosporin and tacrolimus – *see below*).

It is probably appropriate to reduce immunosuppression in the face of a progressive life-threatening fungal infection such as invasive aspergillosis, especially in the setting of a non-essential organ graft such as a kidney transplant, although the evidence for benefit is anecdotal. Other attempts at immunomodulation have included the use of colony-stimulating factors. G–CSF antagonizes the effect of triazoles in an immunocompromised mouse model of invasive aspergillosis.[180] GM-CSF has been used with some success in the neutropenic patient and might prove of more use than G-CSF in the transplant setting.

PULMONARY INFECTIONS OF UNKNOWN CAUSE

Patients presenting with pulmonary infiltrates and fever 1 month or more post-transplant are most likely to have CMV or *Pn. jirovecii* infection (unless they are receiving trimethoprim–sulfamethoxazole prophylaxis). These infections should be managed as in the HSCT recipient. The possibility of other community-acquired respiratory tract infections, including those due to influenza and respiratory syncytial viruses, should always be borne in mind.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

The incidence of this occurring in renal transplant recipients is 1–2%,[181,182] is related to the degree of immunosuppression (it is seen particularly in patients receiving OKT3) and is more likely in primary EBV infection.[183] At present, the mainstay of therapy is the reduction of immunosuppression together with intravenous aciclovir (10 mg/kg every 8 h). However, many patients will require local resection or radiotherapy of affected

tissue and/or antilymphoma chemotherapy. Developments in this field include the possibility of immunotherapy by means of donor leukocyte infusions.[184] Most recently the efficacy of rituximab, an anti-CD20 monoclonal antibody in the treatment of EBV-driven PTLD, has been described.[185]

DRUG INTERACTIONS DURING TREATMENT OF INFECTION

Ciclosporin and tacrolimus are metabolized by the cytochrome P_{450} enzyme system and therefore interact with a number of important antimicrobial agents likely to be prescribed in transplant recipients (Table 40.4). Levels of these drugs may be altered by the induction or inhibition of this system and it is essential that these are measured to prevent toxicity, as well as to avoid inadequate or excessive immunosuppression with the consequences of rejection or infection. Rifampicin is a potent inducer of these cytochrome isoenzymes and causes increased metabolism of ciclosporin and tacrolimus, as well as reducing the bioavailability of corticosteroids. Erythromycin, some of the newer macrolides (particularly clarithromycin), and the azole antifungal agents, especially ketoconazole, itraconazole and voriconazole (and fluconazole at high doses), competitively inhibit this pathway, thus increasing levels of ciclosporin and tacrolimus.

Renal function is often impaired in the transplantation setting and there may be a complex interaction between ciclosporin (itself potentially nephrotoxic, particularly during initial therapy) and nephrotoxic antimicrobial agents such as the aminoglycosides, high-dose trimethoprim–sulfamethoxazole, vancomycin and amphotericin. Therapeutic drug monitoring is mandatory (with the exception of amphotericin) to prevent additional toxicity and alternative agents should be chosen whenever possible (Table 40.4).

CONCLUSION

Prevention should always be the goal in the management of infective complications in neutropenia and organ transplantation. This has become increasingly important over the past decade with the advent of MRSA, VRE and other resistant organisms. Despite the development of antimicrobials with good activity against the infecting agents, the mortality from many of these infections remains high. The spectrum of immunocompromised patients is changing with the evolution of chemotherapy, stem-cell transplantation, immunosuppression regimens, and tissue and organ transplantation techniques – thus we can expect to see the pattern of opportunistic infections shift as well.

Table 40.4 Potential drug interactions during management of infections in organ transplant recipients

Antimicrobial agent	Immunosuppressive agent	Effect
Aminoglycosides	Ciclosporin	Exacerbation of nephrotoxicity
Amphotericin	Ciclosporin	Exacerbation of nephrotoxicity
Trimethoprim–sulfamethoxazole	Ciclosporin	Possible exacerbation of nephrotoxicity Reduced levels of ciclosporin
Doxycycline	Ciclosporin	Increased ciclosporin levels
Erythromycin[a]	Ciclosporin	Increased ciclosporin levels
Fluconazole	Ciclosporin	Increased ciclosporin levels
Flucytosine	Azathioprine	Possible exacerbation of myelosuppression
Ganciclovir	Azathioprine	Possible exacerbation of myelosuppression
Itraconazole	Ciclosporin Vincristine	Increased ciclosporin levels Increased neurotoxicity
Ketoconazole	Ciclosporin	Increased ciclosporin levels
Pentamidine (i.v.)	Ciclosporin	Possible exacerbation of nephrotoxicity
Rifampicin (rifampin)	Ciclosporin Prednisone	Reduced levels of ciclosporin Reduced levels of prednisone
Sulfonamides	Azathioprine	Possible exacerbation of myelosuppression
Trimethoprim	Azathioprine	Possible exacerbation of myelosuppression
Vancomycin	Ciclosporin	Exacerbation of nephrotoxicity

[a]And other macrolides.

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Further information

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