8.2.4 Infection in the immunocompromised host 673

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8.2.4 Infection in the immunocompromised host 673 which produces large amounts of toxin due to the deletion of a regu- lator gene tcdC. C. difficile-associated diarrhoea delays discharge from hospital by about one week. Since attack rates in older patients are around 5% and relapse can occur in up to 25%, the disease can have a major impact on hospital resources (see Chapter 8.6.24). Diagnosis is by two-stage testing; a stool sample is first tested for the presence of the organism by polymerase chain reaction or enzyme-linked immunosorbent assay, and, if positive, is then tested for the presence of cytotoxin. This strategy has sensitivity of 95% but limited specificity for C. difficile disease: toxin may be found in the stool of asymptomatic patients, and for many weeks after full recovery in those with symptoms. Patient management includes ad- equate rehydration, avoiding drugs which inhibit gut motility and stopping the provoking antibiotics. Treatment is with oral vancomycin, fidaxomicin, or metronida- zole. Surgical review is required for severe cases. Relapse may occur in up to 25% of cases but is less common (15%) if fidaxomicin is used as the initial therapy. The use of intravenous immunoglobulin and faecal transplant are controversial but there is growing evidence in favour of their use in severe or recurrent disease. Prevention is by restricting the use of antibiotics according to agreed and audited protocols. The importance of antibiotic restric- tion has been emphasized by recent studies using bacterial whole genome sequencing, which show that the C. difficile strains cul- tured from symptomatic patients in hospital are extremely diverse; nearly half of all patients were infected with their own unique strain rather than one acquired from other patients in the hospital. Hand washing after patient contact, isolation of patients with diarrhoea, and cleaning the ward environment are employed on microbiological grounds, despite a lack of prospective studies

showing their efficacy. Nosocomial bacteraemia Bacteraemia may occur secondarily to the infections mentioned earlier. The incidence is approximately 3 per 1000 hospital admis- sions. The case fatality is about 40%, but varies with the severity of the underlying disease and comorbidities, being as low as about 2% in obstetric patients. Most cases are related to a urinary catheter, intra-vascular catheter, or postsurgical infection. Management should include the identification and, if possible, removal of the infective focus, as well as appropriate antimicrobial therapy after obtaining blood and other relevant samples for microbiological culture. Future developments The increasing cost of healthcare will drive governments to impose mandatory surveillance and targets for reduction of selected nosoco- mial infections as these measures are highly cost-effective. In United Kingdom this has been manifest by legislation ('The Health Act 2006: A code of practice for the prevention and control of healthcare-associated infection') which mandates hospitals to have in place processes for the continuous improvement of infection rates. The UK government has published 'care bundles' of 'high impact interventions' outlining evidence-based practice for how this can be achieved. Coincident with the implementation of these measures since 2006, MRSA bacter- aemia and C. difficile infection rates have declined significantly in the United Kingdom. Rapidly developing techniques of molecular biology are likely to reveal more clearly the relationship between hospital patients and the organisms which infect them, pointing the way to new risk-reducing strategies. Whole genome sequencing will improve our understanding of transmission pathways, virulence, and patho- genicity of the organisms involved, and will enable targeted interven- tions. Recent sequencing studies have shown that the global increase in Candida auris infections is due to the co-evolution of multiple separate clades, each with different polymorphisms for antifungal resistance. Human genetic studies may also identify polymorphisms which pre- dispose certain individuals or groups of individuals to infection. FURTHER READING Chand M, et al. (2017). Insidious risk of severe Mycobacterium chimaera infection in cardiac surgery patients. Clin Infect Dis, 64, 335–42. Edgeworth JD, et al. (2007). An outbreak in an intensive care unit of a strain of methicillin-resistant Staphylococcus aureus sequence type 239 associated with an increased rate of vascular access device- related bacteraemia. Clin Infect Dis, 44, 493–501. Eyre DW, et al. (2013). Diverse sources of C. difficile infection iden- tified on whole-genome sequencing. N Engl J Med, 369, 1195–205. Flores C, et al. (2006). A CXCL2 tandem repeat promoter poly- morphism is associated with susceptibility to severe sepsis in the Spanish population. Genes Immun, 7, 141–9. Harris SR, et al. (2010). Evolution of MRSA during hospital transmis- sion and intercontinental spread. Science, 327, 469–74. Lockhart SR, et al. (2017). Simultaneous Emergence of Multidrug- Resistant Candida auris on 3 Continents Confirmed by Whole- Genome Sequencing and Epidemiological Analyses. Clin Infect Dis, 64(2), 134–40. Magill SS, et al. (2014). Multistate point-prevalence survey of health care-associated infections. N Engl J Med, 370, 1198–208. World Health Organization (2005). Global patient safety challenge: 2005– 6/world alliance for patient safety. World Health Organization, Geneva. Jarvis WR (2007). Bennett and Brachman's hospital infections, 5th edition. Lippincott Williams & Wilkins, Philadelphia, PA. Websites Department of Health England. High Impact Interventions. http://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAnd Guidance/DH_078134 Department of Health (2006). UK Health Act 2006. http://www.legislation. gov.uk/ukpga/2006/28/contents Information on New Delhi metallo-beta-lactamase 1. http://en.wikipedia.org/wiki/New_Delhi_metallo-beta-lactamase_1. 8.2.4 Infection in the immunocompromised host Jon Cohen and Elham Khatamzas ESSENTIALS The term 'immunocompromised host' embraces a group of overlapping conditions in which the ability to respond normally to

 an infective challenge is in some way impaired. This includes patients with underlying conditions such as protein–calorie malnutrition and diabetes, as well as organ transplant recipients, those with haem- atological malignancies and others receiving therapeutic immuno- suppression, and patients with HIV infection. Many patients have multiple risk factors that increase the risk of opportunistic infection. General clinical approach A high level of awareness is essential for the management of patients who are immunocompromised; infections can progress very quickly, the early physical signs are often muted, and the microbiology can be confusing. Aside from a full history and detailed physical exam- ination, assessment should take account of risk factors such as the depth and duration of neutropenia, and the dose and duration of immunosuppressive therapies as well as history or exposure to antimicrobial agents or colonisation with antimicrobial resistant or- ganisms. It is particularly helpful to try to form a judgement of how quickly the condition is progressing. Patients must be reviewed fre- quently and will often require empirical antimicrobial therapy, but when possible it is better to try to establish the cause of the infection before starting treatment. This is partly because the differential diag- nosis is wide and choosing the right treatment depends on knowing the causative organism, and partly because it is not uncommon for multiple organisms of different types to be involved. Particular clinical syndromes Fever of unknown origin—this is common in patients with neutro- penia, with the risk of bacteraemia being most acute when the neutrophil count falls to less than 0.1 × 109/litre; in 50% of cases an organism is never identified. Empirical antibiotic therapy is vital and needs to be directed against both Gram-negative and Gram- positive organisms. The risk of invasive fungal infection rises if fever persists, in which case empirical antifungal therapy is justified. Fever and new pulmonary infiltrates—this is a challenging problem with a wide range of potential causes depending on the clinical setting, including conventional respiratory pathogens, nosocomial pathogens, ‘atypical’ organisms, mycobacteria and re- lated organisms, viruses, fungi, parasites, and also noninfectious causes such as pulmonary oedema, pulmonary haemorrhage, pulmonary emboli/infarction and drug toxicity. The clinical and radiological features are very rarely pathognomonic, hence there should be a low threshold for performing a diagnostic procedure such as bronchoalveolar lavage. Acute neurological syndromes—these include both (1) meningoencephalitis—associated with conventional bac- terial infections, listeriosis, and tuberculosis, as well as fungi such as cryptococcus and candida; and (2) space-occupying lesions—caused by, for example, toxoplasma, aspergillus, and nocardia. Gastrointestinal syndromes—these are frequent and include (1) stomatitis—the three most common causes (candida, herpes simplex virus and chemotherapy-induced mucositis) are clinically indistinguishable and can coexist; (2) diarrhoea—graft-versus-host disease is very difficult to distinguish from infective causes in haem- atopoietic stem cell transplant (HSCT) recipients; (3) abnormalities of liver function tests—mild derangements are a common accom- paniment to many systemic infections, but hepatitis is a particular feature of both toxoplasmosis and cytomegalovirus infection. Prevention This is an integral part of the management of patients who are im- munosuppressed and, depending on context, comprises interven- tions such as nursing them in single rooms and chemoprophylaxis (e.g. co-trimoxazole to prevent pneumocystis and valganciclovir to prevent cytomegalovirus), but perhaps the single most important factor is being aware of the different and often subtle presentations of infection in this vulnerable group of patients. Classification The term ‘immunocompromised host’ has no formal definition but it embraces a group of overlapping conditions in which the ability to respond normally to an infective challenge is in some way impaired. By convention, this does not include otherwise healthy individuals whose only risk factor is a genetic polymorphism which may confer a slightly enhanced risk, for instance, to malaria or

tuberculosis. It is helpful to think of immunocompromised patients as falling into one of several distinct groups (Fig. 8.2.4.1). Primary immunodeficiency syndromes These are patients with congenital defects in immunity that render them more susceptible to infection. At the most extreme, children with severe combined immunodeficiency have virtually no func- tioning cellular or humoral immunity and, if unprotected, they will die from infection within a few months of birth. In contrast, some patients with chronic granulomatous disease, an inherited defect in neutrophil function, remain undiagnosed until early adult life. A complete description of the diagnosis and management of this group of disorders is given in Chapter 5.2. AIDS HIV causes AIDS which is a model for an acquired defect of cellular immunity leading to an increased risk of infection. Although there are inevitably parallels with other groups of immunocomprom- ised patients, there are particular issues both in the diagnosis and management of infection in AIDS that warrant separate discussion (Chapter 8.5.23). Infection related to the underlying condition The notion of opportunistic infection in the immunocomprom- ised host is most familiar with haematological malignancy or organ Immunocompromised host AIDS Primary immunodeficiency syndromes Related to the underlying disease Related to therapeutic immunosuppression Secondary immunodeficiency syndromes Fig. 8.2.4.1 A classification of the immunocompromised host.

 transplantation, discussed in detail next. Less obvious, but prob- ably more numerous, are the many physiological conditions and other diseases associated with an increased incidence of infection (Box 8.2.4.1). These immune defects are usually mixed and fre- quently poorly characterized. The susceptibility to infection varies considerably both in the pattern and severity of infection that oc- curs, but the clinical problem is real enough. For example, in mal- nutrition infection due to mycobacteria and salmonella is more common, and pneumocystis pneumonia was first described in children with protein–calorie malnutrition. There is an extensive literature documenting multiple defects of host defence in asso- ciation with alcohol abuse; clinically, this is reflected in an excess of lower respiratory tract infections with Streptococcus pneumo- niae, Mycobacterium tuberculosis, and Klebsiella pneumoniae. In Cushing’s disease, the excess endogenous steroid production can result in a pattern of opportunistic infections that mirrors that seen in patients receiving corticosteroid therapy (see next). Diabetes mellitus is a good example of a disease that is frequently compli- cated by infection, typically with staphylococcal skin abscesses. In myeloma and chronic lymphocytic leukaemia, the primary defect is hypogammaglobulinaemia. This is manifested clinically by an excess of bacterial infections, typically those caused by en- capsulated organisms such as S. pneumoniae and H. influenzae. In contrast, patients with rheumatoid arthritis, systemic lupus erythematosus, or polyarteritis nodosa predominantly have im- paired cellular immunity, although because they also commonly receive treatment with immunosuppressive drugs it can be very difficult to attribute cause and effect. Finally, patients who have had their spleen removed or who have functional (or more rarely congenital) asplenia are at increased risk of certain infections caused by particular organisms, notably S. pneumoniae and H. in- fluenza. The degree of risk is related to the underlying cause; overall, approximately 5% of patients will have a serious infec- tion, but this varies from 1.5% following traumatic splenectomy to as high as 25% in patients with thalassaemia. Serious infections are most common during the first 5 years following splenectomy and particularly during the first year, but overwhelming post- splenectomy infection can occur decades after the surgery. Infection complicating therapeutic immunosuppression In addition to the well-recognized risk groups, such as those with haematological malignancy or allograft recipients, infective com- plications of immunosuppression are now being recognized in a much broader range

of patients. Conditions as diverse as severe skin disease, asthma, inflammatory bowel disease, and rheumatoid arthritis are routinely treated with immunosuppressive drugs such as prednisolone, azathioprine, ciclosporin, cyclophosphamide, and biological agents such as antitumour necrosis factor (anti-TNF) drugs. These patients are not so profoundly immunosuppressed as HSCT recipients, but they are certainly at risk of opportunistic infections. Immunosuppressed patients have multiple risk factors; a bone marrow transplant recipient may have been neutropenic, receiving corticosteroids and ciclosporin for management of graft-versus- host disease, and have an indwelling right atrial catheter for feeding purposes. Clearly each of these factors represents a substantial and very different type of risk factor for infection and it is important to remember that, in such patients, multiple pathogens can cause disease simultaneously. Further complexity comes from the recog- nition that some opportunistic infections can themselves be im- munosuppressive; for instance, cytomegalovirus reactivated in the context of critical illness can itself reduce cell mediated immunity. Factors such as the precise nature and intensity of the immunosup- pressive regimen, anatomical and/or surgical considerations, and the premorbid status of the patient will all have some influence on the pattern of opportunistic infections that occur. For instance, BK virus is a human polyoma virus that can cause renal allograft re- jection but virtually never causes clinical problems in other organ recipients; liver transplantation is notable for the high incidence of invasive candida infections, and toxoplasmosis is recognized to be a particular problem following cardiac transplantation. The increasingly widespread use of biological agents led to the rec- ognition that these too have particular risk profiles for causing opportunistic infection (Table 8.2.4.1) although in many cases ex- perience is still very limited. Finally, there is an extensive, although still somewhat confused literature indicating that a variety of single nucleotide polymorphisms can either increase, or reduce suscepti- bility to opportunistic infection, for example, invasive aspergillosis in stem cell transplant recipients. The following sections describe the management of some of the common clinical syndromes that present as infection in immunosuppressed patients. Common clinical syndromes A general approach to management Infections in immunosuppressed patients can progress with frightening rapidity; the early physical signs are often muted and the microbiology can be confusing. Patients need to be reviewed fre- quently and will often need empirical therapy, but this need not be totally ‘blind’; a structured and informed assessment will generally allow a logical response to what are the most likely pathogens. Most hospitals will have antimicrobial policies to guide empirical therapy in immunocompromised patients. Box 8.2.4.1 Examples of conditions associated with impaired immune responses and an increased risk/severity of infection • Alcohol abuse and severe liver disease • Severe burns • Cushing’s disease • Cystic fibrosis • Primary infections with respiratory viruses such as influenza • Diabetes mellitus • Down’s syndrome • Extremes of age • Haemodialysis • Intravenous drug abuse • Malnutrition • Obesity • Pregnancy • Psychological stress • Sarcoidosis • Spinal cord injury • Splenectomy • Trauma/surgery/critical care • Uraemia

 History This might reveal exposure to community-acquired infections such as varicella zoster or tuberculosis, which can be particularly severe in the immunocompromised patient. Note should be made of any past history of infection; bronchiectasis, for instance, can be very troublesome in transplant recipients. A detailed travel history is im- portant; patients who have visited certain parts of the United States of America might have been exposed to the systemic mycoses such as histoplasmosis or coccidioidomycosis, which are unfamiliar to many clinicians. Visitors to Central America or the Far East, even many years ago, might have acquired an asymptomatic infection with the helminth Strongyloides stercoralis;

immunosuppression can lead to overt disease (the hyperinfection syndrome) with a high mortality (see next). Physical examination This might be unhelpful as immunosuppressed patients often do not mount a good inflammatory response. Thus, there might be only a low-grade fever, a thin serous exudate may suffice for pus, and mild abdominal tenderness can be the only sign of peritonitis. Nevertheless, careful, and if necessary repeated clinical examination is worthwhile, as signs of inflammation might be- come apparent only when immune function returns. The pres- ence of mucositis is strongly associated with risk of bacteraemia. Particular attention should be paid to new skin lesions. In neu- tropenic patients, bacteraemias can be accompanied by striking embolic lesions (Fig. 8.2.4.2); pseudomonas infections (and less commonly klebsiella and aeromonas) can cause a focal necrotic cellulitis called ecthyma gangrenosum. Fungal infections pre- sent as indolent locally invasive lesions; aspergillus infections often have a black eschar. The perianal area and the insertion sites of indwelling catheters repay careful examination. Aspiration and/or biopsy of any new skin lesion in immunosuppressed pa- tients are well worthwhile, since they might quickly point to an otherwise inapparent diagnosis. Lymphadenopathy is always im- portant and will usually require aspiration or biopsy. It can be a manifestation of a lymphoproliferative condition, post-transplant lymphoproliferative disease (PTLD), arising as a consequence of the intense immunosuppressive regimens now in widespread use. Epstein–Barr virus infection or reactivation play a major role in the pathogenesis of PTLD. Underlying disease This can provide valuable clues. Neutropenia is a major risk factor for infection and renders the patient susceptible to bacteraemia, particularly with Gram-negative organisms such as Escherichia coli and Pseudomonas aeruginosa, often due to mucosal transloca- tion. A patient with an obstructing bronchial neoplasm might de- velop a lung abscess due to inadequate drainage. Corticosteroids are used widely; when given in doses exceeding 15–20 mg daily for Fig. 8.2.4.2 Disseminated Gram-negative sepsis in a neutropenic patient. Table 8.2.4.1 Biological agents and the association with opportunistic infection. Some risks are well recognized: anti-TNF agents and tuberculosis for instance. In many other cases the evidence suggests that there is a very small but nevertheless clearly increased risk Name of agent Target molecule Clinical indication Risk of infection Infliximab; etanercept; adalimumab; certolizumab; golimumab TNF RA, IBD, AID Mycobacteria; Listeria; Nocardia, Salmonella, fungi; PCP; hepatitis B/C; herpesviruses Anakinra IL-1 receptor RA; AID Mycobacteria; fungi; herpesviruses Abatacept T-cells RA; AID Mycobacteria; fungi; herpesviruses Tocilizumab IL-6 RA Mycobacteria; fungi; herpesviruses Rituximab CD20 RA; AID; B-cell lymphoproliferative disorders Hepatitis B reactivation; PML; occasionally other OIs Alemtuzumab CD52 CLL; NHL; multiple sclerosis HSV; VZV; PCP; CMV; PML Bortezomib NF-kB Myeloma; NHL VZV Natalizumab α 4 integrin Multiple sclerosis PML Vedolizumab α 4 integrin IBD Nasopharyngeal infections; occasionally other OIs Etrolizumab α 4 integrin IBD Nasopharyngeal infections; occasionally other OIs Secukinumab; ixekizumab; brodalumab IL-17 Psoriasis Nasopharyngeal infections Canakinumab IL-1 Juvenile RA Minor infections? (insufficient data) TNF, tumour necrosis factor; NF-kB, nuclear factor kappa B; IL, interleukin; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; AID, autoimmune diseases; CLL, chronic lymphatic leukaemia; NHL, non-Hodgkins's lymphoma; PCP, Pneumocystis jirovecii pneumonia; PML, progressive multifocal leukoencephalopathy (JC virus); OI, opportunistic infection; HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus.

 long periods they increase susceptibility to infections with viruses, fungi, parasites, and bacteria such as Mycobacterium tuberculosis and Pneumocystis jirovecii, all organisms normally associated with impaired cellular immune defences.

Duration of immunosuppression This often has a profound effect on the type of infection that occurs, and is well illustrated by comparing the ‘timetables’ of infec- tions in renal transplant recipients with patients receiving an HSCT (Fig. 8.2.4.3). In the first 6 weeks after renal transplantation bac- terial infections predominate, typically surgical complications of the procedure or urinary infections. Between 6 weeks and 6 months post-transplantation the patient is most at risk from the ‘classic’ op- portunistic infections; as time continues and the intensity of immunosuppression declines, typical community-acquired infections become more common. In HSCT, the initial period of neutropenia is characterized by bacterial infections; later, when many patients re- ceive high-dose steroids for graft-versus-host disease, cytomegalo- virus, and fungal infections (candida and aspergillus) develop. Speed of progression An assessment of this is helpful in both differential diagnosis and in deciding on empirical therapy. In neutropenic patients, the onset of fever is usually an indication for immediate empirical antibiotic therapy (see next). In contrast, the response to a fever and new pul- monary infiltrates in a patient who is 8 months postrenal transplant- ation will depend on the pace of the illness. Rapid deterioration over the space of a few hours will suggest a bacterial infection or a noninfectious cause, and will need urgent therapy; a more indolent presentation would point to a fungal or mycobacterial aetiology, and treatment can be delayed for a short period to try and establish the diagnosis. Investigations It is important that the diagnostic laboratories be made aware of the clinical problem since handling of specimens from immunosup- pressed patients—and interpretation of the results—will often differ substantially from routine procedures. Fever of unknown origin In neutropenic patients, fever is often the first and only sign of bac- teraemia, and prompt action is necessary. In this setting, a fever of unknown origin is defined as a single measurement of 38.3°C or greater, or a temperature of 38°C or greater sustained for 1 h and not obviously due to an identifiable cause such as concomitant blood transfusion. The risk of bacteraemia is directly related to the depth of the neutropenia; the incidence of infection rises when the neutrophil count falls to below 0.5 × 109/litre, and is particularly severe when the count falls to less than 0.1 × 109/litre (Fig. 8.2.4.4). Some years ago, the most common bloodstream isolates were Gram-negative bacteria such as E. coli and klebsiella, generally derived from the patient’s gut flora, and P. aeruginosa, a common environmental pathogen. Gram-negative bacteraemia in neutropenic patients carried a very high mortality and led to the introduction of several preventative strategies such as the use of prophylactic antibiotics and colony-stimulating factors. Although these approaches have not been entirely successful and might have contributed to the increasing incidence of multiresistant enterobacteriaceae, the incidence of Gram-negative bacteraemias has declined substantially, and in most units Gram-positive organisms, notably coagulase- negative staphylococci (Staphylococcus epidermidis) are now the most common isolates. Importantly though, tissue-based infec- tions such as pneumonia continue to be caused predominantly by Gram-negative bacteria. Renal transplantation Bone marrow transplantation BACTERIA OPPORTUNISTIC INFECTIONS VIRUSES FUNGI FUNGI 0 1 2 3 4 5 6 Months HSV CMV VZV Deep candidiasis Aspergillosis, trichosporon etc. Wound, UTI, pneumonia Pneumonia*, UTI, M. tuberculosis GNR bacteraemia GPC Oral candida S. pneumoniae N. meningitidis Cytomegalovirus Mycobacteria Pneumocystis Listeria Nocardia Candida, Aspergillus Toxoplasma (Interstitial pneumonitis) UTI = urinary tract infection

- Includes community acquired viral infections GNR = Gram-negative rod GPC = Gram positive cocci HSV = Herpes simplex virus VZV = Varicella zoster virus CMV = Cytomegalovirus BACTERIA Months 4 1 3 2 0 Pneumocystis Fig. 8.2.4.3 Timetable for the development of infective complications in renal transplant and HSCT recipients.

 Clinical features are frequently unhelpful. Sometimes a focus will be suggested by erythema around the point of entry of an indwelling catheter, a finding often associated with staphylococcal infec- tion. Septic shock is infrequent, although it can be associated with viridans streptococci; interestingly, endocarditis is rare. Blood cultures should be drawn before treatment is begun. Ideally two sets should be obtained, at least one of which should be from a peripheral vein (rather than an indwelling catheter), although this is not always possible. Culturing larger volumes of blood (e.g. 30 ml compared to the more conventional 10 ml) will increase the yield. Appropriate samples must also be taken from other potential foci of infection. Nevertheless, it has been one of the enduring frustra- tions of this subject that even the most rigorous of microbiological investigations in the febrile neutropenic patient will yield only 40–50% of positive cultures. The explanation for this is unknown; some studies have suggested that it is due to endotoxaemia in the absence of bacteraemia, but the data are inconclusive. What is clear, however, is that treatment must begin before the results of the cul- tures are available. The choice of the initial empirical antibiotic regimen for the febrile neutropenic patient has been the subject of intense in- vestigation. The ideal regimen will be safe and have good bac- tericidal activity against all the common pathogens. No single regimen is perfect; much will depend on the availability (and cost) of antibiotics in a given institution, and on local patterns of antibiotic susceptibility. Well-validated hospital-based regimens include the combination of an antipseudomonal penicillin plus an aminoglycoside or the use of single agents such as a third- or fourth-generation cephalosporin (e.g. ceftazidime or cefepime), a carbapenem such as meropenem, or a β-lactam/β-lactamase in- hibitor combination (e.g. piperacillin–tazobactam). The Infectious Diseases Society of America has published helpful guidelines on the management of these patients (see Further reading). All these regimens are very active against the common Gram- negative organisms, but are relatively ineffective at treating antimicro- bial resistant Gram-positive bacteria, such as coagulase-negative staphylococci, meticillin (methicillin)-resistant Staphylococcus au- reus (MRSA) and vancomycin-resistant enterococci, that are now- adays common problems in many units. Unfortunately, there are only a very limited number of drugs that are reliably active against these organisms. Some clinicians have advocated adding an anti-Gram- positive agent such as vancomycin to the initial empirical regimen; disadvantages of this approach include the toxicity of vanco- mycin, which may not be justified, particularly because coagulase- negative staphylococci rarely cause death, and the increasing rate of glycopeptide-resistant organisms. Based on available evidence, guidelines recommend that unless there are strong grounds for con- sidering MRSA infection, vancomycin can usually be withheld until the results of blood cultures are known. An important development in practice has been the risk assess- ment of febrile neutropenic patients. The goal is to distinguish those high-risk patients that need hospital admission and parenteral anti- biotics, from a low-risk group (<5% risk of complications) who can be managed as outpatients with oral therapy. Patients who are as- sessed as being in a low-risk group can be managed either with a brief period of inpatient parenteral therapy followed by rapid conversion to oral agents, or by oral therapy from the outset. A suitable regimen is the combination of a fluoroquinolone plus amoxicillin-clavulanate. In patients who respond to the initial regimen, the treatment should be continued for at least 7 days, and ideally until the neutrophil count has returned to over 0.5×10^9/litre. Sometimes this is not possible; the patient may have a persistent or unresponsive neutropenia (e.g. aplastic anaemia, or following HSCT). In these patients, treatment is usually cautiously stopped after an arbitrary period such as 14 days. However, there is undoubtedly a tension between the need to main- tain adequate antimicrobial cover during high risk periods and the wish to minimise exposure in line with the principles of good anti- biotic stewardship. In some parts of the world, multi-

resistant Gram negative bacteria are re-emerging as threats to neutropenic patients. A common problem is the patient who continues to have high swinging fevers after 48–72 h of broad-spectrum antibacterial anti- biotics. The patient must be carefully re-evaluated: Has some new clin- ical sign appeared? Could there be a resistant organism or an occult source of the sepsis? Simply changing the antibiotic regimen or adding vancomycin in the absence of any evidence to support these moves is not supported by clinical trial data. In this situation, invasive fungal infection becomes more likely and empirical addition of an antifungal agent with activity against moulds should be considered. Most centres will have their own antifungal policies and the choice of agent should take into account local epidemiology, antifungal prophylaxis, and screening strategies for pre-emptive treatment. Recommended drugs include triazoles such as voriconazole, isavuconazole, amphotericin B formulation, or echinocandins but the emergence of newly recog- nized multi-resistant species such as Candida auris means that pre- cise diagnosis is mandatory in order to choose the most appropriate treatment. The Infectious Diseases Society of America and European Conference on Infections in Leukaemia have published comprehen- sive guidelines (see Further reading). Fever of unknown origin in the nonneutropenic immunosup- pressed patient presents as a completely different problem. Fever in this setting is rarely immediately life-threatening, and the wide Percentage of patient days with infection Granulocyte level Relapse Total Remission <100 100– 500 500– 1000 1000– 1500

> 1500 60 50 40 30 20 10 Fig. 8.2.4.4 Relationship between neutrophil count and the risk of invasive Gram-negative infection. From Bodey GP, et al. (1966). Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med, 64, 328–40, with permission.

 differential diagnosis means that it is generally better to pursue the cause rather than embark on empirical therapy. Fever and new pulmonary infiltrates The development of fever and new pulmonary infiltrates is one of the most challenging clinical problems in this group of patients. Pneumonia is a very common infective cause of death in immuno- compromised patients. In the presence of diffuse airspace disease, the mortality approaches 50% irrespective of the underlying defect in host defence, although the epidemiology varies both between dif- ferent patient groups and at different times reflecting the intensity of the immunosuppression (Table 8.2.4.2). The condition can progress extremely quickly, and conventional diagnostic procedures can be unhelpful. The list of possible causes is so daunting (Box 8.2.4.2) that clinicians might be tempted to use multiple empirical anti- microbial agents, sometimes to the patient's detriment. It is often not possible to 'guess' with any certainty the precise cause of the problem (indeed, it can be dangerous to do so, since it is not uncommon for multiple causes to be present simultaneously), but by considering the available information one can construct a 'short list', which will guide further investigation and treatment. The initial evaluation should follow the approach outlined earlier, in particular making an assessment of the intensity of the immuno- suppression and the speed of progression of the pulmonary disease as well as the use of prophylactic agents, such as those advocated for prevention of invasive fungal infections. The main purpose of this is to determine the need for empirical therapy, either because the clinical picture is suggestive of a 'simple' bacterial pneumonia or because of a potentially more

serious progressive cause of uncertain aetiology. Factors that would favour a bacterial aetiology include the presence of neutropenia, a rapidly developing clinical evolution (e.g. deterioration over a period of 12 h), progressive hypoxia, or a chest radiographic appearance that has worsened significantly over a short period. High fever is not necessarily a part of this syndrome; indeed, it is important to emphasize that this rapidly evolving clinical picture is not inevitably due to infection. Noninfective causes such as acute lung haemorrhage or pulmonary oedema can present in an identical fashion, and the most appropriate therapy might be diuretics rather than antimicrobials. However, antimicrobials will often need to be given as well because of what has been termed 'infection-provoked relapse'. In immunologic- ally mediated diseases such as systemic lupus erythematosus or antiglomerular basement membrane (GBM) disease (Goodpasture's syndrome) infection can precipitate a relapse of the underlying dis- ease. Thus, the development of fever and new pulmonary shadows in a patient with anti-GBM disease might be primarily due to lung haemorrhage associated with a rise in anti-GBM antibodies, but this in turn can be precipitated by an infection that need not ne- cessarily be in the lung. Treatment must be directed both towards improving oxygenation and the underlying infection. Blood cultures should always be obtained, and sputum obtained if it is available. A chest radiograph and arterial blood gas analysis are essential. The initial treatment will be dictated by the clinical circumstances, but the temptation to use a complex regimen to provide very broad-spectrum cover is best avoided. Rapid clinical Table 8.2.4.2 Aetiology of the 'febrile pneumonitis' syndrome in different patient groups Renal transplantation Bone marrow transplantation Less than 1 month Aspiration Nosocomial LRTI Aspiration Nosocomial LRTI Aspergillus 1–3 monthsa Cytomegalovirus Pneumocystis Aspergillus Nocardia Mycobacteria Mucor Cytomegalovirus Pneumocystis Aspergillus Respiratory syncytial virus Mycobacteria Mucor Noninfective causesb More than 3 monthsa Influenza Legionella Common respiratory bacteria Varicella zoster GVHD Common respiratory bacteria and viruses GVHD, graft-versus-host disease; LRTI, lower respiratory tract infection. a Six months in renal transplant recipients. b Includes idiopathic interstitial pneumonitis in bone marrow transplant recipients. Modified from Wilson WR, Cockerill FR 3rd, Rosenow EC 3rd (1985). Pulmonary disease in the immunocompromised host (2). Mayo Clin Proc, 60, 610–31. Box 8.2.4.2 Causes of fever and new pulmonary infiltrates in the immunocompromised host Infections Bacterial • Conventional respiratory pathogens - S. pneumoniae, H. influenzae, klebsiella • Nosocomial pathogens - E. coli, pseudomonas, legionella • 'Atypical' organisms - Chlamydia psittaci, C. pneumoniae, mycoplasma • Mycobacteria and related organisms - M. tuberculosis, nontuberculous mycobacteria, nocardia Viral • Herpes viruses - Cytomegalovirus, herpes simplex virus, varicella zoster virus • Respiratory viruses - Respiratory syncytial virus, influenza and parainfluenza viruses, adenovirus, measles Fungi • Systemic mycoses - Blastomycosis, histoplasmosis, coccidioidomycosis • Opportunistic mycoses - Pneumocystis jirovecii, candida, aspergillus, mucor, cryptococcus • Other rare fungi - Trichosporon, Pseudallescheria boydii/Scedosporiosis Parasites • Strongyloides stercoralis, Toxoplasma gondii Noninfective causes Pulmonary pathology • Pulmonary oedema, pulmonary infarction/emboli, pulmonary haemorrhage • Primary or secondary malignancy Other causes • Drugs (e.g. sulphonamides, methotrexate, bleomycin, procarbazine, cyclophosphamide, sirolimus) • Activity of the underlying disease (e.g. systemic lupus erythematosus) • Radiation pneumonitis

 deterioration is usually caused by bacterial infections; a combin- ation of piperacillin–tazobactam plus a macrolide will usually be appropriate. The addition of vancomycin might be necessary if there are clinical or epidemiological grounds to be concerned about MRSA infection. Unusual ('opportunistic') organisms such as mycobacteria, nocardia, or

cytomegalovirus rarely cause such a rapid clinical deterioration and it is extremely difficult to distin- guish them on clinical grounds alone. For these reasons, the add- ition of further empirical agents is usually not warranted. In patients in whom immediate empirical therapy is not neces- sary, additional diagnostic procedures can be done. These should in- clude serological tests for atypical organisms (including histoplasma and coccidioides in patients who have been in endemic areas), swabs of the upper respiratory tract for viruses and examination of blood for cytomegalovirus DNA. The radiographic appearances are rarely sufficiently specific as to suggest a precise diagnosis, although they can provide helpful pointers. Thus, a bilateral interstitial midzone infiltrate associated with marked hypoxia is typical of pneumonia due to Pneumocystis jirovecii (previously called P. carinii), and a pleura-based infarct is suggestive of aspergillus. However, there are pitfalls in relying on the radiographic appearance alone in guiding the choice of therapy. First, no radiographic appearance is path- ognomonic of any single pathological process; for example, cyto- megalovirus or pulmonary oedema can mimic pneumocystis, and legionella pneumonia cannot be distinguished from aspergillus. Second, multiple agents can be present simultaneously, and each may require separate treatment. Other imaging techniques such as high-resolution CT can often provide useful additional informa- tion on the extent of the process, and might sometimes point to the cause (e.g. the ‘halo sign’ associated with invasive aspergillosis, or the ‘ground glass’ appearances of pneumocystis; see Fig. 8.2.4.5). Radiological abnormalities and the presence of a fever not re- sponding to appropriate antibiotics should prompt further inves- tigations to try to make a specific diagnosis by obtaining material directly from the bronchial tree. In most cases the method of choice is bronchoscopy with bronchoalveolar lavage. This should be insti- gated early, before clinical deterioration of the patient with progres- sive hypoxia precludes invasive procedures. It will provide adequate material without incurring a serious risk of bleeding (many such patients are thrombocytopenic). In most series, bronchial brush or transbronchial biopsy specimens produce only a marginal increase in the diagnostic yield, and are usually not done unless the clinical picture is suggestive of a noninfective process such as an infiltrating tumour. Close liaison with the microbiology laboratory is very im- portant because additional diagnostic procedures will need to be performed. These should include conventional cultures including fungal cultures, cytology, as well as antigen-based assays detecting fungal cell wall products (galactomannan, β-glucan) and molecular polymerase chain reaction-based techniques detecting viruses and fungi. Acute neurological syndromes Many conventional and opportunistic pathogens can lead to neuro- logical infection in immunocompromised patients. Although there is some degree of overlap, the underlying defect in host defence is often a good indicator of the likely cause (Table 8.2.4.3). The clinical features might help suggest the diagnosis. Meningitic syndromes are more likely to be associated with conventional bacterial infections, listeriosis, and tuberculosis, as well as fungi such as cryptococcus and candida. In contrast, infections with toxoplasma, aspergillus, or nocardia more com- monly present as space-occupying lesions. Pure encephalitic syn- dromes are less common, but can occur with herpes simplex virus or rarely human herpesvirus 6. Rhinocerebral mucormycosis is a progressive, destructive infection caused by mucor and re- lated moulds that usually begins in the paranasal sinuses and spreads caudally to involve the orbits or the frontal lobes of the brain (Fig. 8.2.4.6). It is seen particularly in patients with un- controlled diabetes mellitus or as a complication of neutropenia. Progressive multifocal leukoencephalopathy is a subacute neuro- logical disease caused by the JC polyomavirus. It presents with the insidious onset of impairment of speech, vision, and higher functions without evidence of raised intracranial pressure. The condition progresses inexorably, usually leading to death in about 6 months. Bacterial infections generally proceed rapidly, while fungi and parasites

pursue a more indolent course. However, exceptions to this are common and there is no substitute for obtaining a precise diag- nosis. Examination of the skin (see next) and fundoscopy may be valuable. Retinitis is not usually a feature of systemic infection with toxoplasma; in contrast, candida endophthalmitis can be the only manifestation of deep-seated infection (Fig. 8.2.4.7). Examination of the cerebrospinal fluid is mandatory. A high index of suspicion is necessary, since the clinical features of menin- gitis are often muted in these patients. An unexplained low-grade fever and mild headache might be the only clues; frank meningism, photophobia, or focal neurological signs occur late. Examination of the cerebrospinal fluid should include direct microscopy and cul- ture for bacteria, mycobacteria, and fungi, a cryptococcal antigen Fig. 8.2.4.5 Pneumocyctis jirovecii pneumonia. Chest radiograph showing bilateral reticular infiltration in characteristic central distribution in a patient with autoimmune disease on corticosteroid therapy.

 test, antigen tests for S. pneumoniae, and the demonstration of spe- cific antibody production or DNA sequences by the polymerase chain reaction (e.g. for herpes simplex, polyomaviruses, and toxoplasma). Certain organisms are notable for their absence on direct micros- copy: mycobacteria are seen in less than 10% of cases, and nocardia and aspergillus only very rarely. A predominance of lymphocytes suggests partially treated bacterial infection, tuberculosis, or a viral aetiology. A low cerebrospinal fluid glucose points to bacterial men- ingitis or tuberculosis but is not specific. Sometimes the only ab- normality is a modest elevation of the cerebrospinal fluid protein; this should never be ignored, even in the seeming absence of other features of neurological infection. Where appropriate, cytological examination of the cerebrospinal fluid should be done to exclude carcinomatous or leukaemic meningitis, which can mimic an acute infective presentation. Certain neurological infections are often associated with pul- monary disease; these include legionella, tuberculosis, aspergillus, mucor, and nocardia. A contrast-enhanced CT brain scan should be performed. Focal, usually contrast-enhancing lesions are par- ticularly associated with pyogenic abscesses and toxoplasmosis. Tuberculomas can appear as single lesions. MRI is superior to CT scanning, particularly for abnormalities of the brain stem (e.g. the basal meningitis associated with cryptococcal infection), and fre- quently reveals lesions in toxoplasmosis that are not seen on CT scans. MRI can be particularly helpful in avoiding a brain biopsy when a diagnosis of progressive multifocal leukoencephalopathy is considered. Any new skin lesions should be biopsied, and a nasal biopsy might reveal mucor. An electroencephalogram is rarely helpful. Brain bi- opsy is done very rarely; it should not be considered unless empirical therapy has failed and there is a real prospect of therapeutic benefit to the patient. If the cerebrospinal fluid is nondiagnostic but bacterial infec- tion cannot be excluded, empirical antibiotics should be given im- mediately. Ceftriaxone (together with amoxicillin to provide cover for listeria) is used first-line but a carbapenem such as meropenem should be considered in patients who have recently received broad- spectrum antibacterials or in whom nocardia is a possibility. Serological tests for toxoplasmosis are not specific in this setting, and if the infection is suspected it is better to start empirical therapy with pyrimethamine and sulfadiazine. Cerebral aspergillosis and Table 8.2.4.3 Organisms causing neurological infections in different patient groups Bacteria Fungi Parasites Viruses Neutropenia Gram-negative Enterobacteriaceae Candida Aspergillus Mucor T cell/monocyte defect Listeria Cryptococcus Toxoplasma Varicella zoster Legionella Aspergillus Strongyloides Herpes simplex Nocardia Mucor Polyomavirus Mycobacteria Coccidioides Human herpesvirus-6 Splenectomy S. pneumoniae H. influenzae Neisseria (b) (a) Fig. 8.2.4.6 Invasive mucormycosis. (a) Clinical appearances. (b) CT scan showing extensive sinus involvement.

 mucormycosis have a very poor prognosis; treatment should be begun with high-dose amphotericin B, and surgical debridement considered if possible. Herpes simplex virus should be treated with aciclovir; the effectiveness of foscarnet for HHV-6 is not established. There is no effective treatment for progressive multifocal leukoencephalopathy. Acute gastrointestinal syndromes The organisms associated with specific gastrointestinal syndromes in immunocompromised patients are shown in Table 8.2.4.4. Severe stomatitis is a common complaint in immunosuppressed patients. The three most common causes, candida, herpes simplex virus, and chemotherapy-induced mucositis, are clinically indistinguishable and can indeed coexist. For these reasons, the diagnosis should always be confirmed by microscopy and culture. Herpetic stomatitis in particular can be atypical in these patients; the classic appearance of groups of small vesicles is unusual, and a more common presentation is ulceration, which can be extensive (Fig. 8.2.4.8). In profoundly immunosuppressed patients such as HSCT recipients, oral candidiasis is very common, and in patients who are seropositive before transplantation, reactivation of herpes simplex virus is almost universal. For these reasons, anti- viral prophylaxis is usually given. Both herpes simplex virus and candida can cause oesophagitis, generally (but not exclusively) as an extension of oral disease. If necessary, oesophagoscopy with brush cytology and/or biopsy is the investigation of choice. Proven oesophageal candidiasis should be regarded as ‘invasive’ disease and treated with systemic antifungals (fluconazole or an echinocandin). Many organisms can cause acute diarrhoeal syndromes; in add- ition, noninfective conditions such as radiation enteritis, drugs, and graft-versus-host disease must be included in the differential diagnosis. There are no distinguishing clinical features of note, and diagnosis depends on microbiological examination of the faeces. The diarrhoea due to Clostridium difficile is usually caused by a cytotoxin resulting in pseudomembranous colitis. However, patients with leukaemia or aplastic anaemia might develop neutropenic en- terocolitis (previously called typhlitis), a fulminating invasive col- itis characterized by diffuse dilatation and oedema of the bowel walls, haemorrhage, ulceration, and a high mortality. Classically this has been associated with clostridial bacteraemia, in particular Clostridium septicum, but other clostridia, including C. difficile, and even Gram-negative bacteria can also be found. Strongyloides stercoralis is a nematode that can be carried asymptomatically for many years after exposure. Strongyloidiasis has been recognized as a complication of human T-lymphotropic virus 1 (HTLV-1) infection, and also occurs secondary to immuno- suppression (typically with high-dose corticosteroids and in solid organ transplant recipients). A rise in the worm burden results in the hyperinfection syndrome, which can present as pneumonitis or intermittent intestinal obstruction. The movement of the worms through the gut wall can carry with them enteric bacteria, resulting in polymicrobial bacteraemia and Gram-negative meningitis when the worms penetrate the blood–brain barrier. Giardiasis is particularly associated with hypogammaglobulinaemia, and curiously is rarely seen in other groups. Cryptosporidia, micro sporidia, and isospora are now well-recognized causes of severe and Fig. 8.2.4.7 Candida endophthalmitis (arrows indicate fungal microcolonies). Table 8.2.4.4 Gastrointestinal syndromes in the immunocompromised host Bacteria Fungi Parasites Viruses Oral infection Candida Herpes simplex virus Diarrhoeal syndromes Neutropenic enterocolitis Candida Giardia lamblia Enterovirus C. difficile Isospora belli Adenovirus Salmonella Shigella Campylobacter Shiga toxin producing E. coli Cryptosporidium Cytomegalovirus Nontuberculous mycobacteria Microsporidium Rotavirus Hepatic syndromes Candida Toxoplasma gondii Cytomegalovirus Hepatitis B, C, and E viruses Herpes simplex virus Varicella zoster virus Epstein–Barr virus

 sometimes chronic diarrhoea in AIDS patients, but can also occur in other less severely immunocompromised patients. Among the viruses the

most problematic is cytomegalovirus. Cytomegalovirus can cause a severe colitis, and in these cases ganciclovir is beneficial. Ideally the diagnosis should be confirmed by biopsy, but ultimately might depend on the result of a therapeutic trial since demonstra- tion of the organism does not necessarily indicate that it is causing disease. Mild abnormalities of liver function tests are a common accom- paniment to many systemic infections, but hepatitis is a particular feature of both toxoplasmosis and cytomegalovirus infection. An increased prevalence of hepatitis B has been found in patients on chronic haemodialysis (10%) and those with Hodgkin's disease (8%) and lepromatous leprosy (20%). The acute hepatitic episode is mild, often anicteric, and might pass unnoticed. However, persistent viral replication and the development of complications associated with chronic infection are more likely. Cirrhosis secondary to hepatitis C is currently the third most common indication for liver transplant- ation, however the prognosis is improving with the advent of new combinations of different classes of directly acting antiviral agents. Unfortunately, recurrence of infection post-transplantation is al- most inevitable and requires specific approaches to prevention and treatment. Chronic hepatitis E virus infection has also been reported in solid organ transplant recipients. Epstein–Barr virus replication can be detected in 20–30% of solid organ transplant recipients and up to 80% of those who receive antithymocyte globulin and high doses of immunosuppressants. Clinical manifestations range from a benign mononucleosis syndrome to hepatitis to post-transplant lymphoproliferative disorder. Acute urinary tract syndromes In renal transplant recipients the most common site of infection is the urinary tract, giving rise to complications such as bacteraemia, graft pyelonephritis, and cystitis. Recurrent infections should prompt investigations for anatomical abnormalities. Haemorrhagic cystitis can occur following HSCT. In the early post-transplantation period it is almost exclusively related to drug toxicity. However, its occurrence in the late post-transplantation period can be a mani- festation of graft-versus-host disease or viral infections. Polyoma BK and adenovirus are implicated most commonly. Prevention of infection Approaches designed to prevent infection in immunosuppressed pa- tients have assumed increasing importance. In general, meticulous adherence to infection prevention and control practices are essential to prevent hospital-acquired infections. For profoundly neutropenic Fig. 8.2.4.8 Severe herpetic stomatitis in a patient with lymphoma. Table 8.2.4.5 Infection prevention strategies in organ transplant recipients and patients with neutropenia Strategy Comment Bacterial infections Bacterial sepsis in neutropenia Oral quinolones Re-emerging following earlier concerns with efficacy and risk of resistance High-efficiency particulate air (HEPA)-filtered rooms Very expensive and no clear advantage in survival Adherence to intravenous catheter care bundles Overwhelming postsplenectomy sepsis Immunization (pneumococcal, Hib, and meningococcal) and oral penicillin Tuberculosis Isoniazid In exposed or high-risk patients, especially if receiving prolonged high-dose corticosteroids Viral infections Herpes simplex, cytomegalovirus Aciclovir, ganciclovir, valganciclovir Dose and drug varies depending on specific indication Hepatitis B reactivation Lamivudine, entecavir, tenofovir In risk groups (B-cell depleting agents, anthracycline derivates, monoclonal antibodies) Influenza Immunization Not routine except in high-risk groups Fungal infections Candida, aspergillus Fluconazole, itraconazole, voriconazole, posaconazole, and liposomal amphotericin B Choice and duration of drug depends on type of transplant or haematological risk group Pneumocystis jirovecii Co-trimoxazole Used for both bone marrow transplantations and in some solid organ transplantations

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