

CMEARTICLE

Infectious disease trends among immunocompromised hosts

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ABSTRACT With our rapidly ageing population and advancing treatments for patients with haematological, oncologic and rheumatological diseases, there are increasing numbers of immunocompromised patients presenting to primary care and general hospitals with opportunistic infections. This review considers the trends of these infections across four representative subgroups: fungal infections following haematopoietic stem cell transplant; viral infections post solid organ transplant; mycobacterial infections during treatment with targeted biological agents; and bacterial infections as a cause of fever in neutropenia. We also consider the impact of host, pathogens, environments and treatments on the epidemiology and outcomes of these infections.

Keywords: haematology, immunodeficiency, oncology, opportunistic infections, transplant
Singapore Med J 2012; 53(4): 223–230

INTRODUCTION

The range of conditions treated with immunosuppression has expanded to include solid organ cancers, leukaemia, transplants, autoimmune conditions and some congenital diseases. An increased number of immunocompromised hosts in Singapore and worldwide has raised the importance of opportunistic infections. This review focuses on four representative examples: (1) fungal infections following haematopoietic stem cell transplant (HSCT); (2) viral infections post solid organ transplant (SOT); (3) mycobacterial infections during treatment with targeted biological agents; and (4) bacterial infections as a cause of fever in neutropenic patients.

CASE 1

A 48-year-old Chinese woman with acute lymphoblastic leukaemia was admitted for an allogeneic peripheral blood stem cell (PBSC) transplant. She received myeloablative chemotherapy, a transplant from a matched unrelated donor and anti-fungal prophylaxis with posaconazole. On Day 5 post transplant, she developed febrile neutropenia with severe mucositis, and thus, posaconazole was converted to intravenous (IV) caspofungin. Two weeks later, a new fever developed, with respiratory symptoms. Computed tomography (CT) of the thorax identified a lung lesion suspicious for an invasive fungal infection (IFI) (Fig. 1). Serum galactomannan antigen index was negative at 0.3, and bronchoscopy with lavage was performed. After two weeks, fungal cultures of the lavaged fluid grew *Hormoglyphiella aspergillata*, and anti-fungal treatment was changed to IV amphotericin B deoxycholate. Repeat bone marrow examination determined that the leukaemia was not in remission, and despite aggressive anti-fungal treatment, the patient died shortly after.

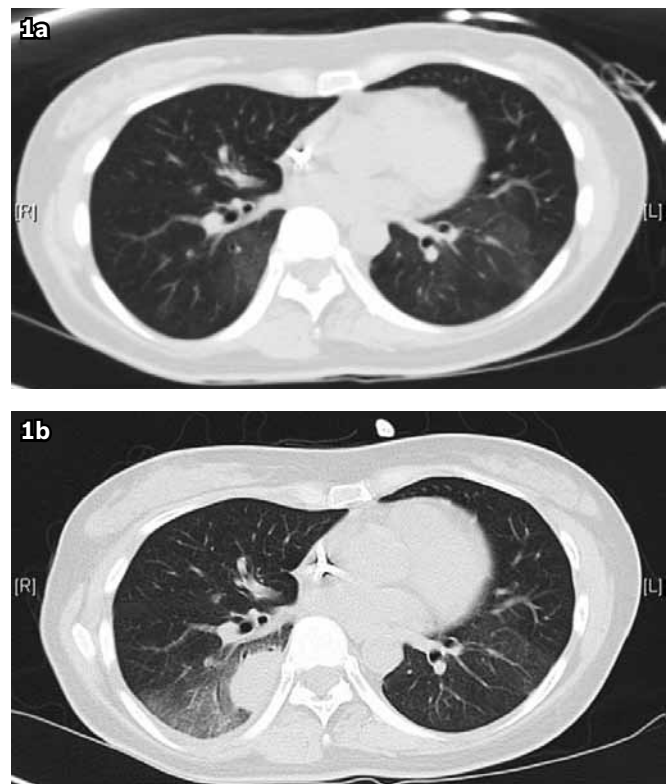


Fig. 1 Case 1. CT shows rapid development of an invasive fungal infection in the right lower lobe of the lung. A smaller nodule in the left upper lobe can be seen. Image (a) was acquired one week before image (b).

Fungal infection following haematopoietic stem cell transplant

The common fungal pathogens are ubiquitous in the environment and frequent colonisers of the skin, gastrointestinal tract and oropharyngeal mucosa (e.g. *Candida*), or routinely inhaled (e.g. *Aspergillus*). Protection against these organisms invading host

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tissues and causing disease relies on an intact innate immune system that is able to detect characteristic fungal signatures, amplify a defensive response and recruit the adaptive immune pathways.⁽¹⁾

The duration and depth of neutropenia is traditionally a major risk factor for IFI.⁽²⁾ After HSCT, this places the greatest risk in the early pre-engraftment period following chemotherapy-induced myeloablation. Shortening the duration of neutropenia — thus reducing the risk of early IFI — has been accomplished by harvesting stem cells from peripheral blood rather than bone marrow and with chemotherapy regimens that are not completely myeloablative, known as reduced intensity conditioning (RIC).^(3,4) The development of these regimens has enabled treatment of a population at higher risk of complications, i.e. those who are older and have greater comorbidity and more advanced disease.^(5,6) Following engraftment, the risk of IFI remains high if the underlying disease does not enter remission, or if graft-versus-host disease (GVHD) develops.⁽⁷⁾ GVHD delays complete immune reconstitution from direct graft effects on the immune system, including marrow suppression. GVHD also often requires treatment with immunosuppressive agents, including high-dose corticosteroids, for long periods. PBSCs may increase the risk of GVHD, while RIC appears to delay its onset.^(8,9)

The risk of IFIs following HSCT has also been reduced by the introduction of effective anti-fungal prophylaxis. Fluconazole was developed in the 1980s from modifications to the azole ring of ketoconazole. Randomised placebo-controlled trials of fluconazole post stem cell transplant have reported dramatic reductions in *Candida* IFIs from 15.8% to 2.8%.⁽¹⁰⁾ A reduction in mortality was demonstrated in a separate trial.⁽¹¹⁾ The limited anti-fungal range of fluconazole, however, exposed two consequences: first, an increased risk of colonisation and infection with azole-resistant *Candida* (*C.*) species, including *C. glabrata* and *C. krusei*;⁽¹²⁾ and second, it contributed to a rise in IFI from moulds such as *Aspergillus*.⁽¹³⁾ Invasive pulmonary aspergillosis (IPA) is now the most common IFI following HSCT.

Voriconazole has aided in solving both problems. On average, the minimum inhibitory concentrations of *Candida* for voriconazole are at least log₁₀ lower compared to fluconazole, allowing for treatment and prevention of some resistant yeast.⁽¹⁴⁾ It has also expanded the anti-fungal spectrum to include *Aspergillus*, *Fusarium* and *Scedosporium*. Indeed, voriconazole has become the drug of choice for IPA following a randomised, unblinded comparative trial with amphotericin B deoxycholate, where the 12-week overall survival improved from 58% to 71%.⁽¹⁵⁾ Despite these therapeutic successes, voriconazole prophylaxis did not improve survival when compared to fluconazole in a randomised, double-blind trial.⁽¹⁶⁾ This may reflect the relatively low rates of invasive pulmonary aspergillosis following HSCT (6% in the first year) and the improving outcomes of IPA due to effective treatment and early diagnosis with galactomannan testing and CT.⁽¹⁷⁾ The introduction of voriconazole (and itraconazole) resulted in *Aspergillus* azole resistance, which was first identified in 1999 and uncommon until 2004.⁽¹⁸⁾ It is also likely

that voriconazole contributed to the rise of mucormycosis as the second most common IFI, against which it has little activity.⁽¹⁹⁾

Posaconazole is the latest azole to be widely introduced into clinical practice, and is effective against a wide range of fungi, including mucormycosis. This is the only other anti-fungal prophylactic agent demonstrated to improve survival in a randomised controlled trial (RCT) following HSCT and to have reduced the rates of proven/probable IPA from 7% to 1%.⁽²⁰⁾ The effects that routine posaconazole prophylaxis may have on fungal epidemiology remain to be determined, but no increase in the rate of mucormycosis was identified during the RCT. The incidence of adverse effects and drug-drug interactions with all the azoles places limitations on their effectiveness in preventing IFI in patients receiving sirolimus and many other agents.

Although patients who have received HSCT most often present to their haematologists when ill, primary care physicians need to be aware of the risk of IFI in these patients. These can progress rapidly, especially in those with GVHD or disease that has not gone into remission, as described in Case 1.

CASE 2

A 35-year-old Chinese man received a cadaveric liver transplant for Hepatitis B cirrhosis with hepatocellular carcinoma. He was cytomegalovirus (CMV)-positive pre-transplant, and was maintained on oral prednisolone, tacrolimus and prophylactic cotrimoxazole postoperatively. An episode of early acute rejection occurred one month following the transplant, and he was successfully treated with IV methylprednisolone and mycophenolate mofetil. The patient presented seven months post transplant with fever and pain when swallowing. Esophagogastroduodenoscopy (EGD) demonstrated severe gastritis with multiple erosions (Fig. 2). Biopsy revealed enlarged stromal cells with intra-nuclear and intra-cytoplasmic inclusions. Immunostains were positive for CMV, and plasma CMV polymerase chain reaction (PCR) was 2.1×10^3 copies/ml. IV ganciclovir was administered for three weeks, with rapid resolution of symptoms and lesions on follow-up EGD.

Viral infections post solid organ transplant

Infections following SOT can be grouped into several time points: the first month after transplant when donor derived and surgical infections predominate; the following five months when immunosuppression and risk for opportunistic infection are highest; and the period post six months when infection is usually described from community-acquired organisms.

CMV is the most common viral infection post SOT, occurring in 8%–39% of recipients.⁽²¹⁾ Diagnosing CMV disease requires distinguishing asymptomatic reactivation from end-organ disease and 'CMV syndrome' with fever and bone marrow suppression.⁽²²⁾ Donor/recipient CMV status, the organ transplanted as well as the choice of immunosuppressive agent significantly affect the incidence rate. CMV disease is also an independent risk factor

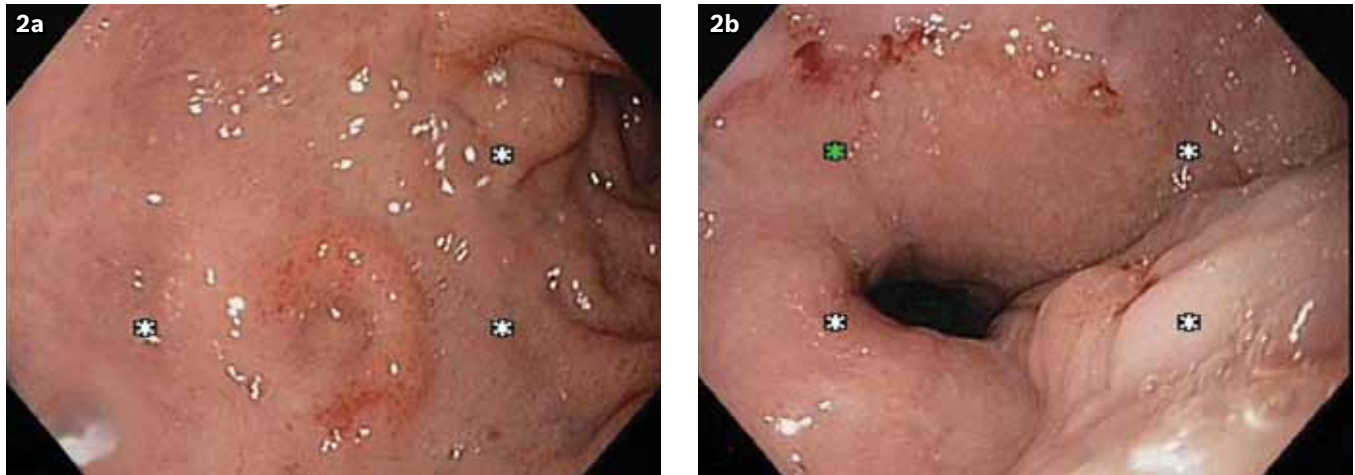


Fig. 2 Case 2. Esophagogastroduodenoscopy images show (a) severe pangastritis with duodenitis and (b) multiple antral erosions.

for other infections and acute/chronic allograft injury due to the immunomodulating effects of CMV disease.

Anti-viral prophylaxis reduces CMV disease and mortality in all CMV-positive (R+) and CMV-negative (R-) recipients from CMV-positive donors (D+).⁽²³⁾ A consequence of prophylaxis is an increase in the rate of late-onset disease, after six months post transplant. This may be due to CMV suppression preventing the development of immunity to CMV.⁽²⁴⁾ Prolonging prophylaxis with valganciclovir from 100 days to 200 days following high-risk (D+/R-) renal transplants reduces the rates of CMV disease during the treatment period but results in substantially more late-onset disease.⁽²⁵⁾ A lower dose of maintenance valganciclovir therapy may overcome this problem while reducing cost and adverse effects such as leucopenia.⁽²⁶⁾

CMV resistance to ganciclovir is also an emerging problem following SOT.⁽²⁷⁾ In prospective studies, resistance has been observed in less than 5% of kidney and liver transplant recipients who received valganciclovir prophylaxis or treatment.^(28,29) Treatment options for patients infected with ganciclovir-resistant CMV are available, but they are costly and toxic. Vaccination against CMV has shown promise in phase II randomised placebo-controlled studies of adults awaiting kidney or liver transplants, and for preventing maternal/congenital CMV.^(30,31) Vaccination reduced CMV viral titres, with a decreased need for anti-viral treatment. However, well-conducted phase III studies are still required.

Newer immunosuppressives have reduced the risk of acute transplant rejection, with mixed effects on the incidence of opportunistic infections. Transition of calcineurin inhibitors from cyclosporine to tacrolimus increases the potency of immunosuppression while appearing to reduce the risk of infection – possibly due to a reduced need for corticosteroids. MMF has largely replaced azathioprine, with a better side effect profile. Suggestions of an increased risk for CMV or other infections have not been confirmed by meta-analysis.⁽³²⁾ Anti-lymphocyte transplant induction therapies with anti-thymocyte globulins (ATG) reduce acute rejection and allow for lower doses of other immunosuppressive agents. However, their potent

immunosuppression results in an increased risk of infections, mainly viral such as CMV, Epstein-Barr virus and BK polyomavirus.⁽³³⁾ Newer alternatives, such as IL-2 receptor antagonists, offer more targeted anti-lymphocyte activity and may reduce the risk of CMV infection compared with ATG.⁽³⁴⁾

Despite these treatment improvements, the rates of chronic graft failure have not fallen as expected, along with the attendant long-term infectious risks.⁽³⁵⁾ For kidney transplants, at least, donor shortage may impact outcomes by prolonging the need for dialysis pre-transplant. The median waiting time in Singapore for a kidney transplant was 9–10 years in 2008.⁽³⁶⁾ Primary care physicians need to be aware of the risk of CMV disease in SOT recipients, which can present with gastrointestinal bleeds, ulcers or nonspecific symptoms.

CASE 3

A 54-year-old Chinese woman with rheumatoid arthritis presented to our institution after two months of right lower leg erythema and pain. Ten days prior to her admission, the cellulitis had spread to the left arm, with multiple tender, non-ulcerating nodules (Fig. 3). At that time, she was receiving 11 mg of prednisolone daily, azathioprine and monthly infliximab to maintain disease remission. She was treated for pulmonary tuberculosis (TB) one year ago. When the cellulitis did not respond to broad-spectrum IV antibiotics, a skin biopsy was performed. Histology identified septal panniculitis without granulomas. Numerous acid-fast bacilli were seen, and culture was positive after four weeks for *Mycobacterium haemophilum*. The cellulitis responded well to combination treatment with clarithromycin, ciprofloxacin and rifampicin, and a reduction in immunosuppression.

Mycobacterial infections during therapy with biologics

The term 'biologics' encompasses monoclonal antibodies and similar targeted therapies. More than 120 biologics are currently approved by the European Union and the United States (US).⁽³⁷⁾ The largest group of immune modulators are the tumour necrosis factor (TNF)-inhibitors – monoclonal antibodies such as



Fig. 3 Case 3. Photograph shows mycobacterial nodular cellulitis of the left arm.

infliximab and soluble receptors such as etanercept, which have been licensed in the US since 1998, for inflammatory bowel disease, rheumatoid arthritis, psoriasis and a number of other autoimmune conditions.⁽³⁸⁾ A decade after their introduction, biologics now account for 75% of worldwide drug sales for rheumatoid arthritis.⁽³⁹⁾ This trend is expected to continue with the earlier use of biologic agents in Crohn's disease and rheumatoid arthritis shown to reduce disease activity.^(40,41)

TNF- α , along with interleukin-1 (IL-1), has a central role in the initiation and amplification of the inflammatory response via the triggering of cytokine cascades. TNF is particularly important for granuloma formation and protection against intracellular pathogens.⁽⁴²⁾ Inhibition is associated with an increased risk of mycobacterial infections, *Listeria monocytogenes*, fungal pathogens such as *Histoplasma capsulatum*, and Hepatitis B reactivation among others. A significant number of extra-pulmonary non-tuberculosis mycobacterial infections have been observed in the US, mainly involving skin and soft tissue.⁽⁴³⁾

Screening and treating latent TB infection prior to starting TNF inhibitors is recommended. The incidence of TB with TNF-inhibitors in the United Kingdom has been estimated at 103/100,000 person-years, against a background rate of 14.5/100,000 person-years in 2005.⁽⁴⁴⁾ Singapore is an intermediate incidence TB country, with almost 40/100,000 person-years in 2010.⁽⁴⁵⁾ However, having transitioned from being a high-incidence country in the past 30 years, latent TB infection rates must remain high. The effects of TNF-inhibitors in this epidemiological context are not known.

Overall, TNF-inhibitors may not significantly increase the risk of infection if the alternative is active disease requiring high-dose corticosteroids and other immunosuppressive agents.⁽⁴⁶⁾

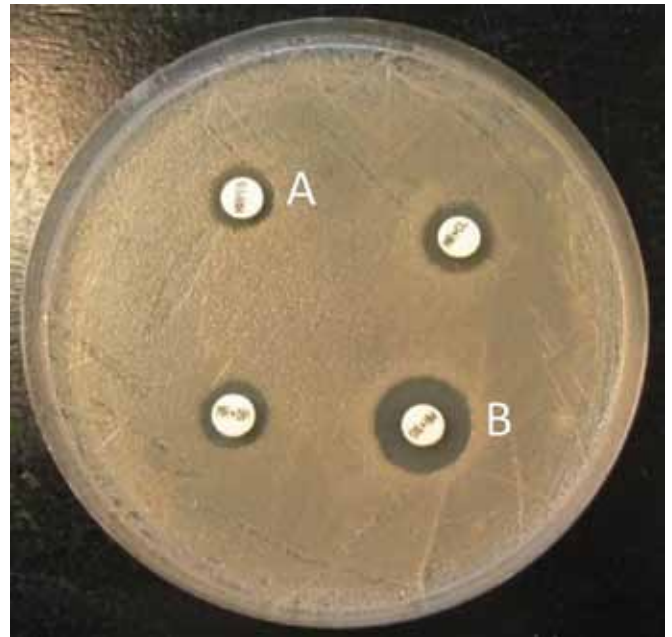


Fig. 4 Case 4. An agar plate shows growth of carbapenem-resistant bacteria. Disc A contains meropenem and disc B contains meropenem with a class A/serine carbapenemases inhibitor (boronic acid) such as *Klebsiella pneumoniae* carbapenemase.

The infection risk associated with long-term steroids is well known but under-appreciated. Even low-dose prednisolone of less than 5 mg/day is associated with an increased risk of hospitalisation for pneumonia.⁽⁴⁷⁾ A patient receiving biologics may present with a common illness due to an uncommon organism. A heightened awareness of pulmonary TB and other mycobacterial infections in this population would enable early diagnosis and treatment.

CASE 4

A 60-year-old Chinese man presented to the emergency department with a three-day history of fever, abdominal pain and black stools. Full blood count revealed acute leukaemia with a white cell count of $272 \times 10^9/L$, 89% blast cells. Broad-spectrum antibiotics were started and quickly escalated to meropenem when the fever persisted. Progressive renal dysfunction developed from tumour lysis syndrome, and a catheter was inserted for haemodialysis. When the patient's condition had stabilised, standard induction chemotherapy with cytarabine/danarubicin was administered. Profound neutropenia rapidly developed, accompanied by a new febrile illness with diarrhoea. Stool examination was positive for *Clostridium difficile* toxin by PCR. Multiple sets of blood cultures from the central line and peripheral blood grew carbapenem-resistant *Klebsiella pneumoniae* (Fig. 4). An IMP-1-like metallo-beta-lactamase was identified by PCR. With multiple additional resistance mechanisms, polymyxin B was the only antibiotic that tested susceptible. The patient defervesced rapidly following line removal and polymyxin B. Renal function remained stable and haemodialysis was discontinued.

Bacterial infections during febrile neutropenia

Cancers release soluble factors such as vascular endothelial

Host: Increased age with more comorbidities and treatment of more advanced disease.

Pathogen: Increasing rates of antibiotics resistance, emergence of new pathogens, improved detection/diagnostics.

Environment: Ambulatory care during acute phase, longer survival with immune deficiency increases exposure to leisure and travel acquired organisms.

Treatment: Broad-based and targeted immunosuppressive agents, prevention of infection with antimicrobial prophylaxis, G-CSF etc.

Fig. 5 Chart shows the epidemiological triangle of opportunistic infection in immunocompromised hosts.

growth factor, IL-10 and TNF, which modulate the immune response. These diminish anti-tumour immune processes to promote tumour progression, but also impair the host defence against infections.⁽⁴⁸⁾ Infection risk is highest in the neutropenic period following cytotoxic chemotherapy. A shift in the epidemiology of sepsis during neutropenia has been observed in the West, from predominately Gram-negative bloodstream infections 30 years ago to Gram-positive.⁽⁴⁹⁾ This was attributed to an increased use of indwelling intravascular catheters, thus promoting invasion by skin colonising organisms such as coagulase-negative *Staphylococcus*, *Bacillus cereus* and the coryneform bacteria. The rise also correlates with the emergence of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* in hospitals.

Over the past ten years, a small shift back to Gram-negative organisms has occurred.⁽⁵⁰⁾ This may reflect the spread of genetic elements that convey resistance to first-line antibiotics—primarily the β -lactams via extended-spectrum β -lactamases, cephalosporinase AmpC, and more recently, carbapenemases such as IMP-1 and the New Delhi metallo- β -lactamase 1.^(51,52) Coupled with this is an increased problem with the Gram-negative glucose non-fermenters, which are often intrinsically resistant to multiple antimicrobials such as *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*.^(53,54) The problem of infections with Gram-negative bacteria is particularly acute in Asian febrile neutropenic patients.⁽⁵⁵⁾ Many approaches, including the use of polymyxins, as in this patient, or combination therapies, have to be used for these increasingly resistant pathogens.⁽⁵⁶⁾

Despite these problems with resistance, a recent Cochrane review highlighted the benefits of antibiotic prophylaxis for high-risk malignancies. Prophylaxis has been found to reduce the incidence of fever, infection, infection-related mortality and all-cause mortality.⁽⁵⁷⁾ Surprisingly, less resistance was observed in breakthrough infections. It is possible that short courses of prophylaxis that do not require hospital admission may be sufficient to maintain benefit. Applying this data locally is hampered by the high rates of fluoroquinolone resistance in

South East Asia; a retrospective audit in Singapore of 78 patients receiving 301 chemotherapy cycles did not identify any benefit.⁽⁵⁸⁾ The rate of febrile neutropenia for high-risk patients has also been reduced by prophylactic granulocyte-colony stimulating factor (G-CSF). However, there has been no documented mortality benefit.⁽⁵⁹⁾

The Human Microbiome Project aims to “characterize the microbial communities found at several different sites in the human body... and to analyze the role of these microbes in human health and disease”.⁽⁶⁰⁾ Chemotherapy alters the gut microbiome, reducing the amount of obligate anaerobic bacteria and allowing overgrowth with potential pathogens such as *Enterococcus*, *Enterobacteriaceae* and, as described in Case 4, *C. difficile*.^(61,62) Inflammation of the gastrointestinal mucosa by chemotherapy disrupts the intestinal epithelial barrier, promoting bacterial invasion. Reducing mucositis with keratinocyte growth factors reduces febrile neutropenia from 92% to 75%, but due to high cost and the lack of significant mortality benefit, it is not routinely used in Singapore.⁽⁶³⁾

Patients receiving combination chemotherapy with febrile neutropenia often present to their primary care physicians. A thorough history and physical examination is essential to accurately triage care. If the duration of neutropenia is anticipated to be short and the patient is clinically well without comorbidities, outpatient management is feasible.⁽⁶⁴⁾ However, if there is a significant risk of complications, a prompt referral to a tertiary care centre is critical.

CONCLUSION

The epidemiological triangle of host, pathogen, environment and vector (treatment) can be usefully adapted to consider the reasons underlying trends in infectious diseases among immunocompromised hosts (Fig. 5). With more of these vulnerable patients presenting at various levels of our healthcare system, it is important to be aware of some recent trends in these diseases in order to optimise outcomes. Continued expansion of therapeutic immunosuppression and the development of agents increasingly directed at molecular targets will continue to create challenges for the management of consequent infectious diseases.

ENDNOTE

Case histories are for illustration purposes only.

ACKNOWLEDGEMENTS

With thanks to Dr Florante Isais, Dr Michelle Balm and Dr Jeanette Teo for providing the images, and to Ms Nicole Lim for assistance in proofreading.

CONFLICTS OF INTEREST

BY has no relevant financial interests to declare. PAT has received research support from Sanofi-Pasteur, honoraria from Novartis and consultancy fees from Astra-Zeneca.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201204A)

Question 1. Regarding fungal infections following haematopoietic stem cell transplant:

- (a) Fluconazole is the preferred agent for anti-fungal prophylaxis post stem cell transplant.
- (b) Prophylactic voriconazole reduces the rate of invasive pulmonary aspergillosis.
- (c) The increased risk of invasive fungal infections after a stem cell transplant is largely the result of neutropenia and graft-versus-host disease.
- (d) Posaconazole prevents fungal infections from mucormycosis.

Question 2. Regarding viral infections post solid organ transplant:

- (a) Surgical infections are the most common infections in the first month following solid organ transplant.
- (b) The risk of cytomegalovirus end-organ disease after transplant is most closely related to donor and recipient sero-status.
- (c) Cytomegalovirus infections can be prevented after transplant with anti-virals.
- (d) Cytomegalovirus infections in the late post transplant and post anti-viral prophylaxis periods are rare.

Question 3. Regarding mycobacterial infections during therapy with biologics:

- (a) Screening for tuberculosis is recommended before starting TNF inhibitors.
- (b) Latent tuberculosis infection during therapy with TNF inhibitors is prevented by antibiotic prophylaxis.
- (c) Non-tuberculosis mycobacterial skin and soft tissue infections have been particularly associated with TNF inhibitors.
- (d) Biologics increase the overall risk of infections compared with disease modifying anti-rheumatic drugs and prednisolone.

Question 4. Regarding bacterial infections during febrile neutropenia:

- (a) The major source of bacteria that cause infections during neutropenia is the gastrointestinal tract.
- (b) Local studies have not proven the benefit of anti-microbial prophylaxis for preventing neutropenic sepsis in Singapore.
- (c) All patients with febrile neutropenia require urgent hospital admission.
- (d) Spread of anti-microbial resistance from hospitals into the community is rare, as the increased genetic load impairs virulence.

Question 5. Regarding the epidemiological principles of immunosuppression and infection:

- (a) Increasing age of patients exposed to immunosuppressive agents increases the risk of opportunistic infection.
- (b) The 'strongest antibiotic' with the best outcomes for treating an infection is one with the broadest anti-microbial spectrum.
- (c) Newer non-biologic immunosuppressive agents are able to suppress the immune system more effectively without increasing the risk of infections.
- (d) Immunosuppressed patients should be advised not to travel due to the increased risk of exotic infections.

True False

Doctor's particulars:

Name in full : _____

MCR number : _____ Specialty: _____

Email address : _____

SUBMISSION INSTRUCTIONS:

(1) Log on at the SMJ website: <http://www.sma.org.sg/cme/smj> and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:

(1) Answers will be published in the SMJ June 2012 issue. (2) The MCR numbers of successful candidates will be posted online at www.sma.org.sg/cme/smj by 21 May 2012. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council. (6) One CME point is awarded for successful candidates.

Deadline for submission: (April 2012 SMJ 3B CME programme): 12 noon, 14 May 2012.