Infections in the immunocompromised host: secondary immunodeficiency disorders

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Abstract

Individuals with secondary immunosuppression are increasingly encountered in medical practice. Many common and varied states are associated with secondary immunosuppression including malignancy, diabetes, HIV, chronic kidney disease, receipt of chemotherapy, solid organ and haemopoietic stem cell transplantation and immunomodulatory agents. Patients have a risk of an increased frequency and severity of the pathogens seen in immunocompetent individuals, as well as opportunistic pathogens. A useful framework for thinking about immunosuppression is to consider the spectrum, degree and duration of immunosuppression. Geographical exposures, including to healthcare settings, devices such as indwelling urinary and vascular catheters, and surgical interventions must also be considered. By understanding these factors, predictions can be made about the most likely infective organisms, and screening, prophylaxis, monitoring and empirical treatments can be initiated. Blood tests to ascertain the neutrophil count, lymphocyte subsets for CD4 T-cell count and serum immunoglobulin concentrations can help to stratify risk based on the degree of immunosuppression.

Keywords Cytotoxic chemotherapy; haemopoietic stem cell transplantation; human immunodeficiency virus; immunocompromised host; monoclonal antibodies; opportunistic infection; secondary immunodeficiency; solid organ transplantation

Key points

- Secondary immunodeficiencies are caused by a wide range of conditions including viral infections, malignancy, corticosteroids, diabetes, immunosuppressive chemotherapy and biological agents
- Understanding the nature of the host's immune compromise can help to predict the opportunistic infections to which they are vulnerable
- Screening followed by primary and secondary prophylaxis as well as pre-emptive treatment is important to prevent predictable infections in secondary immunosuppression

Introduction

Not all secondary immunodeficiencies affect the same part of the immune system; some act broadly over multiple areas and others are more targeted. Understanding the broad types of immunodeficiency can help predict the organisms that require screening, prophylaxis and monitoring, and treatment can be initiated empirically.

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Neutrophil dysfunction

Neutrophils are critical in the initial defence against bacteria and fungi. Neutropenia is classified according to severity (mild, 1 -1.5×10^9/litre; moderate, $0.5-1 \times 10^9$/litre; severe, $<0.5 \times 10^9$/litre). In severe neutropenia, the patient is at risk of endogenous microbial flora (mouth, gastrointestinal tract) translocating and causing infections.[1] Cytotoxic chemotherapy-induced myelosuppression is the predominant cause of secondary neutropenia observed in clinical practice.

The most common infections include cellulitis, skin abscesses (including perianal abscesses), pneumonia, enterocolitis and iatrogenic catheter site infections. Skin infections can be caused by *Staphylococcus aureus* and other Gram-positive agents (viridans group streptococci, *Enterococcus* species) as well as Gram-negative organisms such as *Pseudomonas aeruginosa* (ecthyma gangrenosum) (Table 1).

Pneumonia can be caused by classical community-acquired organisms (*Streptococcus pneumoniae*) or those causing hospital-acquired infections, including Gram-negative organisms. Enterocolitis can result in the translocation of bowel flora leading to *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia as well as candidaemia (Table 1). Because of the ever-increasing antimicrobial resistance, debate continues over the role of fluoroquinolone prophylaxis for bacterial infections during neutropenia.

Prolonged neutropenia (>7 days) leads to a higher risk of invasive fungal mould infections with *Aspergillus*, *Fusarium* and *Mucor* species. Prophylaxis for prolonged neutropenia may include a mould-active antifungal agent such as posaconazole, or early treatment based on positive fungal markers (galactomannan, β-D-glucan).

Individuals with neutropenic fever should be investigated with a thorough full-body examination, encompassing the skin, peri-rectal areas and catheter sites. Imaging of the chest is routine and should be extended to include the abdomen if no other source of infection is found or there are suggestive clinical signs. The risks and benefits of skin biopsy for culture and histology should be considered.

Summary of clinical significance of pathogens encountered in secondary immunosuppression

	Host factors	Presentation	Diagnosis	Treatment[a]	Screening and prevention
Bacteria					
Gram-positive (*Staphylococcus* spp., *Streptococcus* spp.)	Neutropenia, mucositis, indwelling catheters	Pneumonia, sepsis, cellulitis, SSI, CRBSI	Sepsis screen, culture indwelling catheters	Antibiotics as per local guidance, past cultures and taking into account antibiotic prophylaxis	Screen for antibiotic resistance (MRSA/VRE), pneumococcal vaccine
Gram-negative (*Escherichia coli*, *Klebsiella* spp., *Pseudomonas* spp.)	Hospital-acquired infection, biofilm on prosthetic material (e.g. indwelling lines)	Urinary tract, intra-abdominal, ventilatory-associated pneumonia, CRBSI	As above	As above	Antibiotic resistance (e.g. CPE) an increasing concern
Legionella spp.	Contaminated water outbreaks (hospitals, hotels), T cell dysfunction	Pneumonia, diarrhoea, confusion, hyponatraemia	Urine antigen testing, BAL PCR	Levofloxacin, macrolides, doxycycline	
Nocardia spp.	T cell dysfunction/anti-TNF	Lung, brain and skin abscesses	Biopsy for histology/ microbiological tests	Prolonged and multidrug involving co-trimoxazole, carbapenem ± aminoglycoside	
Listeria spp.	T cell dysfunction/anti-TNF	Meningoencephalitis, bacteraemia	Blood cultures, lymphocytic CSF	High dose i.v. amoxicillin	
Mycobacterium tuberculosis	Risk factors for exposure; anti-TNF, HIV (any CD4+ cells/ml)	Pulmonary, extrapulmonary, disseminated	Sputum for acid-fast staining/culture; biopsy of extrapulmonary sites	6 months HRZE, 12 months in *M. tuberculosis*	Screening pre-anti-TNF for latent *M. tuberculosis*; treatment is 3 months with HR or 6 months with H alone
Mycobacterium avium complex	For disseminated disease; particular association with anti-TNF/advanced HIV (CD4+ <50 cells/ml)	Pyrexia of unknown origin, cytopenia, lymphadenopathy	Blood/lymph tissue mycobacterial culture	Multidrug regimen depending on species; agents include macrolides, rifabutin, aminoglycosides, quinolones	
Fungi					
Moulds (*Aspergillus* spp., *Mucor* spp.)	Prolonged neutropenia, SOT/ HSCT/GVHD, B/T cell dysfunction, corticosteroids	Antibiotic-refractory fever with pulmonary signs on imaging (cavity/halo sign/ nodules)	HRCT chest, BAL fungal culture, serum/BAL galactomannan	Voriconazole, amphotericin B	Mould-active prophylaxis agents include itraconazole/ posaconazole (not fluconazole)
Yeasts (*Candida* spp.)	Corticosteroids, mucositis, GVHD, indwelling catheters, antibiotic exposure	Oral/genital thrush, SSI or invasive (e.g. candidaemia)	Swab, culture of drain fluid/ blood culture, BDG	For invasive infection, initially an echinocandin (e.g. caspofungin), then azole stepdown	Patients taking antifungal prophylaxis (e.g. fluconazole, posaconazole) can develop resistance
Yeasts (*Cryptococcal* spp.)	T cell dysfunction, HIV (CD4+ <200 cells/ml)	Subacute meningitis (fever and headache), symptoms of raised ICP	Lymphocytic CSF, high OP; Blood/CSF CrAg, brain imaging	Amphotericin B and flucytosine, LPs to reduce ICP	Serum CrAg screening when HIV diagnosed

Yeast-like (PCP)	T cell dysfunction/SOT/HSCT, HIV (CD4+ <200 cells/ml)	Subacute breathlessness, dry cough, hypoxia	Perihilar haze/interstitial infiltrates on CXR; induced sputum ± BAL PCP PCR	Co-trimoxazole ± corticosteroids if hypoxic	Co-trimoxazole prophylaxis common, e.g. HIV with CD4+ <200 cells/ml, SOT/HSCT
Viruses					
HSV	Reactivation in IgG+; disseminated only with severe immune suppression (SOT/HSCT)	Oro/genital ulcers, encephalitis, disseminated disease (e.g. hepatitis)	Swab/blood/CSF HSV PCR	Oral aciclovir/valaciclovir in oro/genital; i.v. aciclovir in severe disease	Aciclovir prophylaxis has made disseminated disease uncommon
Cytomegalovirus (CMV)	A seronegative CMV recipient of a solid organ from a CMV positive donor (CMV in graft), and any seropositive (CMV IgG) HSCT (recipient reactivation)	CMV syndrome (fever, cytopenia, transaminitis) or end-organ disease (e.g. colitis, pneumonitis)	Blood CMV PCR, biopsy of relevant site (e.g. bowel in colitis)	Valganciclovir	Valganciclovir prophylaxis in SOT, letermovir in HSCT
Epstein—Barr virus (EBV)	Reactivation in IgG+; T cell dysfunction/SOT/HSCT	Encephalitis rare, main concern is LPD/PTLD	EBV blood/CSF PCR, biopsy of lymph tissue	Chemotherapy incorporating rituximab	
Varicella-zoster virus	T cell dysfunction/SOT/HSCT; non-exposed (IgG) — severe primary infection (chickenpox); exposed (IgG) — reactivation (shingles)	Severe primary infection, recurrent/severe/disseminated zoster (shingles)	Clinical/swab of de-roofed vesicle for VZV PCR	Oral aciclovir/valaciclovir/IV aciclovir depending on severity; VZIG/aciclovir after exposure	VZV vaccination, aciclovir prophylaxis
BK virus	After renal transplant and HSCT	BK nephropathy after renal transplant and haemorrhagic cystitis after HSCT	Urine/blood BK PCR, renal graft biopsy	Cidofovir can have a role	
Human polyomavirus 2/John Cunningham virus (PML)	T cell dysfunction/SOT/HSCT; HIV (CD4+ <200 cells/ml) and some biologics (e.g. natalizumab)	PML — subacute progressive confusion and focal neurology	Bilateral, asymmetrical, non-enhancing white-matter lesions on MRI without oedema; CSF JC virus PCR	No specific antiviral treatment	
Hepatitis B virus	HBV surface antigen/core antibody positive. B cell dysfunction (e.g. rituximab); SOT/HSCT	HBV flares/reactivation, hepatocellular carcinoma	Monitoring of HBV DNA PCR and surface antigen	Tenofovir/entecavir	Tenofovir/entecavir prophylaxis in high-risk patients, hepatitis B vaccination
Adenovirus	HSCT and SOT	Wide spectrum from asymptomatic viraemia to multiorgan disease	Monitoring adenovirus DNA in blood, stool (quantitative PCR)	Cidofovir; brincidofovir can have a role but availability limited	Weekly viral load in vulnerable patients, pre-emptive treatment where indicated
HHV8	SOT, advanced HIV	Kaposi sarcoma, primary effusion lymphoma, Kaposi sarcoma inflammatory cytokine syndrome, multicentric Castleman disease	HHV8 DNA PCR	Reduction or switching class of immunosuppression, rituximab in certain clinical contexts	Pre-transplant screening (serology)

(*continued on next page*)

Table 1 (*continued*)

	Host factors	Presentation	Diagnosis	Treatment[a]	Screening and prevention
SARS-CoV-2	Systemic glucocorticoids, haematological malignancy, SOT, severe lymphopenia	COVID-19 pneumonitis	Nose and throat swab — SARS-CoV-2 PCR	Dexamethasone, IL-6 inhibitor (tocilizumab) in COVID-19 pneumonitis Other therapies in high-risk individuals include Paxlovid (nirmatrelvir plus ritonavir), sotrovimab, remdesivir	National vaccination programmes, infection prevention and control in healthcare settings
Mpox	SOT, advanced HIV (CD4+ <200 cells/ml)	Necrotizing skin lesions, bacterial superinfection, pneumonia, encephalitis, multiorgan involvement	Swab for mpox DNA PCR from a lesion	Paucity of data, tecovirimat where available	Vaccination in high-risk individuals where applicable
Parasites					
Toxoplasma spp.	IgG+, T cell dysfunction/SOT/HSCT; HIV (CD4 <200 cells/ml)	Focal neurology, seizures; symptoms/signs of raised ICP	Ring-enhancing lesions with oedema on MRI; CSF PCR, brain biopsy	Pyrimethamine, sulfadiazine and folinic acid	Co-trimoxazole prophylaxis reduces risk substantially
Strongyloides spp.	Risk factors for exposure (can be years previously); HTLV and corticosteroids	Eosinophilia, gastrointestinal, breathlessness/cough (larval migration), multiorgan failure (hyperinfection)	Serology; stool culture often negative; in hyperinfection, microscopy of respiratory specimens often positive	Ivermectin	Patients with risk factors should be screened before immunosuppression; probably currently underperformed

BAL, bronchoalveolar lavage; BDG, β-D-glucan; CPE, carbapenemase-producing *Enterobacterales* (Enterobacteriaceae); CrAg, cryptococcal antigen; CRBSI, catheter-related bloodstream infection; CSF, cerebrospinal fluid; CXR, chest X-ray; D+/R-, donor CMV; HBV, hepatitis B virus; HRCT, high-resolution computed tomography; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus; HZRE, isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E); ICP, intracranial pressure; i.v., intravenous; LP, lumbar puncture; LPD, lymphoproliferative disorder; MRSA, methicillin-resistant *Staphylococcus aureus*; MTB, *Mycobacterium tuberculosis*; OP, opening pressure; PCP, Pneumocystis jirovecii pneumonia; PCR, polymerase chain reaction; PTLD, post-transplant lymphoproliferative disorder; R+, recipient CMV IgG positive; SOT, solid organ transplant; SSI, surgical site infection; TNF, tumour necrosis factor; VRE, vancomycin-resistant Enterococcus; VZIG, varicella-zoster immunoglobulin; GVHD, graft-versus-host disease. For other abbreviations, see text.

[a] Treatment involves reduction of immunosuppression wherever possible.

Table 1

In all patients, blood cultures should be requested from a peripheral site sample or intravenous catheters before prompt initiation of broad-spectrum antibacterial agents. Other tests should include: sputum for bacterial culture; a throat swab for polymerase chain reaction (PCR) to detect common viral pathogens; urine for culture; and stool for culture and *Clostridioides* (*Clostridium*) *difficile* testing if there are symptoms. A travel history to assess the risk of exposure to non-endemic pathogens and carbapenem-resistant organisms should also be considered.

Fungal markers may be requested. β-D-glucan is a non-specific test for *Candida* as well as other invasive fungal infections including *Pneumocystis* pneumonia (PCP). The *Aspergillus* galactomannan antigen test is more specific for aspergillosis, but can be more useful on bronchial aspiration fluid than on serum.

Cell-mediated (T cell) dysfunction

Cell-mediated immunity is critical for defence against intracellular organisms such as viruses, fungi and certain parasites. Infections that occur with cell-mediated defects are often referred to as opportunistic infections.

Cell-mediated dysfunction occurs with certain malignancies, after certain chemotherapy agents including the purine analogue fludarabine, high-dose methotrexate and cyclophosphamide.[2] Other causes include infectious agents including HIV infection, malnutrition, corticosteroids, the antibody preparation antithymocyte immunoglobulin plus monoclonal antibodies targeting T cells (e.g. alemtuzumab, a CD52 antibody) (Table 2).[3]

Preventing infection in situations with T cell dysfunction involves screening for both active and latent infections.[3] These tests include but are not limited to tuberculosis (TB) interferon-γ release assay (IGRA), serology for herpes viruses – cytomegalovirus (CMV) immunoglobulin (Ig) G, Epstein–Barr virus (EBV) IgM/IgG/Epstein–Barr nuclear antigen, varicella-zoster virus (VZV) IgG, herpes simplex virus (HSV) 1 and 2 IgG – *Toxoplasma* IgG, hepatitis B (sAg, core Ab and sAb), hepatitis C antibody and HIV antigen/antibody (Table 2).[3]

Vaccination should be considered if risk factors are present and circumstances allow in the case of planned immunosuppression (hepatitis A and B vaccination). Vaccination is followed by primary prophylaxis (co-trimoxazole for the fungus *Pneumocystis jirovecii*, the cause of PCP pneumonia) and secondary prophylaxis (aciclovir for HSV and VZV, isoniazid for TB, tenofovir or lamivudine for hepatitis B and co-trimoxazole for toxoplasmosis central nervous system disease) (Table 1).

Pre-emptive therapy is indicated where antimicrobial therapies have significant adverse effects (CMV treatment with ganciclovir based on repeated screening for detectable CMV viral loads in solid organ transplantation (SOT) and haemopoietic

Immunosuppressive agents and particular pathogen associations

Agent/effect on immunity	Bacteria	Fungi	Viruses	Parasites	Pre-screening tests to consider
Corticosteroids	Gram-positive and Gram-negative bacteria. *Mycobacterium tuberculosis*	*Candida* spp.; localized (thrush) and invasive. Moulds. PCP	HSV (e.g. oral/genital herpes), HBV	*Strongyloides* spp. hyperinfection	TB IGRA, hepatitis B sAg/core total Ab/sAb, *Strongyloides* serology
Cytotoxic chemotherapy neutropenia – antimetabolites, alkylating agents, anthracyclines	Gram-positive and Gram-negative; CRBSI, gut translocation, *Clostridioides* (*Clostridium*) *difficile*	*Candida* spp., moulds			
Chemotherapy T cell dysfunction/T cell biologics – high-dose methotrexate, antimetabolites, calcineurin inhibitors antithymocyte globulin, monoclonals (basiliximab)	Gram-positive, Gram-negative and intracellular bacteria (*Nocardia* spp., *Legionella* spp., *Listeria* spp., *M. tuberculosis*, NTM)	*Candida* spp., moulds, PCP, *Cryptococcus* spp.	HSV, CMV, VZV, EBV (LPD), BK virus, JC virus (PML), HBV	*Toxoplasma* spp.	TB IGRA, HSV/CMV/VZV serology, hepatitis B sAg/core total Ab/sAb, *Toxoplasma* serology
B cell monoclonal agents – rituximab, ocrelizumab			HSV, CMV, VZV, EBV (LPD), BK virus, JC virus (PML), HBV		HSV/CMV/VZV serology, hepatitis B sAg/core total Ab/sAb
Cytokine monoclonal antibodies – anakinra (IL-1), tocilizumab (IL-6), infliximab (TNF)	Intracellular bacteria: *Nocardia* spp., *Listeria* spp., *M. tuberculosis*, NTM	Candida spp., moulds, PCP, histoplasmosis	HSV, VZV, HBV	*Toxoplasma* spp.	TB IGRA, HSV/VZV serology, hepatitis B sAg/core total Ab/sAb, *Toxoplasma* serology

CRBSI, Catheter related blood stream infection; HBV, hepatitis B virus; LPD, lymphoproliferative disease; MTB, Mycobacterium Tuberculosis; NTM, non-tuberculous mycobacteria.

Table 2

stem cell transplantation (HSCT)). Further screening based on travel history can also be appropriate (e.g. *Strongyloides* serology in individuals who have lived in Africa, *Trypanosoma cruzi* for those from South America).

All patients newly diagnosed with HIV should be screened for opportunistic infections; the initiation of prophylaxis is determined by the CD4 count. At a CD4 count of <200 cells/ml, co-trimoxazole should be initiated, and at <50 cells/ml further screening for disseminated *Mycobacterium avium complex* should be undertaken via mycobacterial blood cultures.

Other pathogens that can be significant with low CD4 counts include John Cunningham (JC) virus, the cause of progressive multifocal leucoencephalopathy (PML), and *Cryptococcus* spp., an important cause of meningitis.

EBV reactivation is associated with malignancy and human herpesvirus (HHV) 8 reactivation with Castleman disease and Kaposi sarcoma. TB can occur at any CD4 count.

Clear protocols exist for screening and prophylaxis in SOT and HSCT. After SOT and HSCT, the risk of acquiring different pathogens changes with time, as the spectrum of immunosuppression changes (Tables 3–5).

In the first month after SOT, infections are directly related to surgery/postoperative recovery and catheter devices. Donor screening minimizes the risk of graft-derived infection, and the list of suggested screening tests continues to expand. Months 1–6 carry the highest risk of opportunistic infection, necessitating prophylactic antimicrobials (Table 3). Beyond month 6, the risk of reactivation of latent viral infection remains.

Stratification of infection risk after HSCT relates to whether engraftment has occurred (Tables 4 and 5). At <30 days before engraftment, the risk of HSV is mitigated by aciclovir prophylaxis, and common bacterial and *Candida* spp. infections relating to mucositis and neutropenia predominate. The early post-engraftment period (<100 days) is the period of greatest risk, especially for individuals with allografts, donor-recipient mismatch or graft-versus-host disease (GVHD).

After 100 days, unlike autograft recipients, allograft recipients retain defects in humoral immunity that predispose to serious infections with encapsulated bacteria. Continuing GVHD in this period is associated with VZV and EBV-associated post-transplant lymphoproliferative disease (PTLD).

In the case of measles (−ssRNA *Morbillivirus* from the *Paramyxoviridae* family), primary infection itself results in suppression of cellular immunity, as it preferentially infects and depletes memory and naive T cells (specifically CD4+ and CD8+). This is known as immune amnesia and, acutely, lymphopenia is evident. Measles also induces a T helper cell (Th) 1 to Th2 cytokine profile shift and has deleterious effects on antigen presentation and T cell activation.

This immunosuppressed state after primary infection with measles lasts for weeks to months, with a increased risk of infection for several years.[1]

Humoral immunity and B cell deficiency

Secondary hypogammaglobuinaemia and B cell dysfunction occur in up to 80% of cases of chronic lymphocytic leukaemia (CLL), as well as in multiple myeloma (MM) and renal and gastrointestinal causes of protein loss, and with chemotherapy, SOT and HSCT, GVHD and biological agents targeting B cells. Alkylating agents such as cyclophosphamide and melphalan cause cytotoxicity of B cell precursors. Purine analogues such as fludarabine result in T cell as well as B cell dysfunction.

Sinopulmonary infections (pyogenic bacteria) and gastrointestinal (enterovirus, *Giardia*) are common in these situations and can be the presenting feature in CLL and MM. Treatment includes treating infections, antibiotic prophylaxis, pre-emptive vaccination and immunoglobulin replacement therapy.

Splenic dysfunction

Splenic dysfunction occurs after splenectomy (e.g. in haematological conditions), after trauma and in sickle cell disease as a result of autoinfarction. It leads to an increased risk of encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*. Patients should be vaccinated against

Infection timeline after SOT

	<1 month	1–6 months	>6 months
Bacteria	Operatively related (SSI, HAP, catheter-related UTI); Gram-positive and Gram-negative; resistant organisms (MRSA/VRE); *Clostridioides* (*Clostridium*) *difficile*	Antimicrobial resistance more common with increased hospital/antibiotic exposure (MRSA, VRE, CPE); *Clostridioides difficile*, *Mycobacterium tuberculosis*, *Listeria* spp., *Nocardia* spp., *Legionella* spp.	CAP organisms and common presentations more likely (e.g. CAP/UTI)
Fungi	*Candida* spp.	PCP. Moulds. *Cryptococcus* spp.	
Viruses	Donor-derived HIV/HBV/HCV rare with screening; HSV rare with prophylaxis; HHV8	CMV, VZV, EBV, HBV, BK virus, HHV8; respiratory viruses (e.g. influenza, adenovirus)	Late CMV, HBV, JC virus (PML), EBV (PTLD), HHV8
Parasites		*Toxoplasma* spp. *Strongyloides* spp.	*Toxoplasma* spp., *Strongyloides* spp.

CAP, community-acquired pneumonia; CPE, carbapenemase-producing *Enterobacterales* (*Enterobacteriaceae*); HAP, hospital-acquired pneumonia; HBV, hepatitis B virus; HCV, hepatitis C virus; MRSA, methicillin-resistant *Staphylococcus aureus*; ulosis; SSI, skin and soft tissue infection; UTI, urinary tract infection; VRE, vancomycin-resistant *Enterococcus*. For other abbreviations, see text.

Table 3

Infection timeline after allogenic HSCT

	< 30 days/pre-engraftment	30–100 days/early post-engraftment	> 100 days/late post-engraftment
Bacteria	Gram-positive and Gram-negative; CRBSI; gut translocation with neutropenia/ mucositis; *Clostridioides* (*Clostridium*) *difficile*	Antimicrobial resistance more common with increased hospital/antibiotic exposure (MRSA, VRE, CPE); *Mycobacterium tuberculosis*, NTM, *Legionella* spp., *Listeria* spp., *Nocardia* spp.	Community-acquired more likely, especially encapsulated (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*); *M. tuberculosis*, *Legionella* spp., *Listeria* spp., *Nocardia* spp.
Fungi	*Candida* spp.	*Candida* spp., moulds, PCP, *Cryptococcus* spp.	*Candida* spp., moulds (if GVHD), PCP, *Cryptococcus* spp.
Viruses	HSV, respiratory viruses (influenza, adenovirus)	HSV, CMV, EBV (PTLD); respiratory viruses; BK virus, HBV	HSV, CMV, VZV, EBV (PTLD); respiratory viruses; HBV, JC virus (PML)
Parasites		*Toxoplasma* spp., *Strongyloides* spp.	*Toxoplasma* spp., *Strongyloides* spp.
Prophylaxis	HSV: aciclovir/valaciclovir VZV: aciclovir/valaciclovir Gram-negative bacteria: initiation of antibiotic prophylaxis until recovery from severe neutropaenia (but subject to change according to local guidelines) *Candida* spp. and moulds: initiation of prophylaxis until recovery from severe neutropenia with a mould-active agent, e. g. posaconazole in high-risk patients	VZV: aciclovir/valaciclovir Gram-negative bacteria: initiation of antibiotic prophylaxis until recovery from severe neutropenia (but subject to change according to local guidelines) *Candida* spp. and moulds: initiation of prophylaxis until recovery from severe neutropenia PCP: co-trimoxazole is first-line prophylaxis	VZV: aciclovir/valaciclovir PCP: co-trimoxazole is first-line prophylaxis

CPE, carbapenemase-producing Enterobacterales (*Enterobacteriaceae*); CRBSI, Catheter related blood stream infection; MRSA, methicillin-resistant *Staphylococcus aureus*;ulosis; NTM,non-tuberculous mycobacteria; VRE, vancomycin-resistant *Enterococcus*. For other abbreviations, see text.

Table 4

pneumococcal and meningococcal infection, be given an annual influenza vaccination and take penicillin prophylaxis afterwards.[4]

Immunotherapy

Biologic and small molecule targeted immunomodulatory therapies are used to treat inflammatory and autoimmune conditions, as well as malignancy. These agents target cytokine pathways (e.g. tumour necrosis factor (TNF)-α) and cell signalling receptors (e.g. CD20) leading to cell death, and inhibit downstream messenger signalling (Janus kinase (JAK) inhibitors).[2] They should have a narrower spectrum of activity, but the immunological effects can be wider than predicted.

The type of infection associated depends on the immune cell or cytokine inhibited, and the duration of action (Table 2). Reactivation of latent infections may be observed and responses to pathogen exposure may not be adequate.

Monoclonal antibodies

Monoclonal antibodies are similar to human immunoglobulin, with a binding site (Fab) and effector region (Fc). They are

Infection timeline after autologous HSCT

	< 30 days/pre-engraftment	30–100 days/early post-engraftment	> 100 days
Bacteria	Gram-positive and Gram-negative; CRBSI; gut translocation with neutropenia/mucositis; *Clostridioides* (*Clostridium*) *difficile*	Antimicrobial resistance more common with increased hospital/antibiotic exposure (MRSA, VRE, CPE)	No longer increased risk
Fungi	*Candida* spp.	PCP	
Viruses	HSV; respiratory viruses (influenza, adenovirus)	CMV (end-organ disease rare), VZV; respiratory viruses	
Parasites		*Toxoplasma* spp., *Strongyloides* spp.	

CPE, carbapenemase-producing Enterobacterales (*Enterobacteriaceae*); CRBSI, Catheter related blood stream infection; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*. For other abbreviations, see text.

Table 5

artificially made from human, murine or hybrid sequences and have the ending 'mab' in their names (e.g. infliximab, a TNF-α blocker). Fusion proteins work similarly to monoclonal antibodies and are genetically engineered (e.g. etanercept, also a TNF blocker).[2]

Latent TB and past hepatitis B may be reactivated with the use of monoclonal antibodies that target TNF-α (e.g. infliximab), and the new infection can be severe and disseminated. Screening is therefore advised before treatment. Hepatitis B and JC virus can reactivate with monoclonals that target B cells (e.g. rituximab) and new enteroviral infections can be severe.[2] Agammaglobulinaemia caused by B-cell depletion can last for years after rituximab cessation (Table 2).

Anakinra (a recombinant interleukin (IL)-1 receptor antagonist used in rheumatoid arthritis and proinflammatory conditions such as haemophagocytic lymphohistiocytosis) and tocilizumab (an IL-6 receptor antagonist used in severe coronavirus disease (COVID-19) pneumonitis) affect the cytokines important in the acute-phase inflammatory response; therefore, acute bacterial infection must be excluded before use.[2]

Small molecule targeted therapies

Tyrosine kinase enzymes are involved in intracellular signalling in response to cytokines or immune cell activation. JAK inhibitors (e.g. baricitinib) are examples of these small molecule treatments.[2] They work on T, B and natural killer cells. There are increased risks of TB and herpes zoster.

Chimeric antigen receptor T-cell therapy (CAR-T)

CAR-T immunotherapy involves genetically engineering a patient's own T cells to bind to specific receptors expressed by cancer cells and other immune cells. These patients are often significantly immunosuppressed through extensive previous chemotherapy, pre-conditioning for CAR-T therapy leading to lymphodepletion and management of toxicities with immune-modulating agents (e.g. anakinra for haemophagocytic lymphohistiocytosis, tocilizumab for cytokine release syndrome).[5]

Bacterial infections are more common in the first 30 days and viral infections after this because of the long-lasting depletion of lymphocytes.[5] ◆

KEY REFERENCES

1 Pourshahnazari P, Betschel SD, Kim VyHD, et al. Secondary immunodeficiency. *Allergy Asthma Clin Immunol* 2025; **20**(suppl 3)**:** 80.

2 Davis JS, Ferreira D, Paige E, et al. Infectious complications of biological and small molecule targeted immunomodulatory therapies. *Clin Microbiol Rev* 2020; **33**: e00035-19.

3 Malinis M, Boucher HW. Screening of donor and candidate prior to solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: c13548.

4 Ladhani SN, Fernandes S, Garg M, et al. Prevention and treatment of infection in patients with an absent or hypofunctional spleen: a British Society for Haematology guideline. *Br J Haematol* 2024; **204:** 1672–86.

5 Cuvelier GDE, Paulson K, Bow EJ. Updates in hematopoietic cell transplant and cellular therapies that enhance the risk for opportunistic infections. *Transpl Infect Dis* 2023; **25**(suppl 1): e14101.

FURTHER READING

Advisory Committee on the Safety of Blood Tissues and Organs. SaBTO microbiological safety guidelines. www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation (accessed 23 July 2025).

British Transplantation Society. Guidelines and standards. Available via www.bts.org.uk/guidelines-standards (accessed 23 July 2025).

Kampouri E, Little JS, Rejeski K, et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. *Transpl Infect Dis* 2023; **25**(suppl 1): e14157.

Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new (accessed 23 July 2025).

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 55-year-old man presented with fever, pleuritic chest pain and haemoptysis.

He was undergoing induction chemotherapy for acute myeloid leukaemia. He had been neutropenic for 12 days.

Investigation

- Chest CT showed nodular infiltrates with surrounding ground-glass opacities ('halo sign')

What pathogen is the most likely cause?

A. *Pneumocystis jirovecii*
B. *Candida albicans*
C. *Aspergillus fumigatus*
D. *Cryptococcus neoformans*
E. *Histoplasma capsulatum*

Question 2

A 45-year-old woman presented with fever, malaise and neutropenia.

She had undergone renal transplantation 6 weeks previously and was on tacrolimus, mycophenolate mofetil and low-dose prednisolone.

Investigations

- Bilirubin 73 micromol/litre (5–21)
  - alanine transaminase (ALT) 634 U/litre (10–50)
  - aspartate transaminase (AST) 575 U/litre (10–40)
  - alkaline phosphatase (ALP) 452 U/litre (30–130)
- Cytomegalovirus polymerase chain reaction positive

What best describes the mechanism underlying this infection?

A. Primary viral acquisition from community exposure
B. Superinfection resulting from nosocomial spread
C. Reactivation of latent virus in the donor organ or recipient
D. Drug-induced immunodeficiency with bacterial superinfection
E. Co-infection with Epstein–Barr virus

Question 3

A 62-year-old man presented with respiratory distress, sepsis and gastrointestinal symptoms. He had recently been started on high-dose dexamethasone for presumed immune thrombocytopenia. He was originally from rural Thailand.
On clinical examination, he had diffuse wheezing and abdominal tenderness.

Investigation

- Blood cultures grew Gram-negative bacilli

What is the most likely underlying cause of his deterioration?

A. coronavirus disease (COVID-19) pneumonitis
B. *Mycobacterium tuberculosis* reactivation
C. *Strongyloides stercoralis* hyperinfection
D. *Pneumocystis jirovecii* pneumonia
E. Cytomegalovirus colitis