



# BMT Settings, Infection and Infection Control

# 7

John Murray, Iris Agreiter, Laura Orlando,  
and Daphna Hutt

## Abstract

Despite improvements over the past several decades, infection remains a significant risk to all haematological patients receiving therapy. Those requiring allogeneic transplant and especially those that have HLA disparity or T-cell-depleted grafts have an even higher risk of infective complications due to delayed recovery of T- and B-cell function. Early identification with prompt effective treatment is paramount to improve all patients' survival. Patient safety through robust adherence to hand hygiene and maintenance of the environment with cleaning and disinfection are the backbone of an effective preventative program. Basic nursing care and a sound knowledge base of the risks, presentation, diagnosis and treatment will improve patient care.

## Keywords

Viral infection • Bacterial infection • Fungal infection • Handwashing  
Isolation

J. Murray (✉)

Haematology and Transplant Unit, The Christie NHS  
Foundation Trust, Manchester, UK  
e-mail: [John.Murray@christie.nhs.uk](mailto:John.Murray@christie.nhs.uk)

I. Agreiter

Department of Haematology and BMT Unit, Hospital  
San Maurizio, Bolzano, Italy  
e-mail: [IRIS.AGREITER@sabes.it](mailto:IRIS.AGREITER@sabes.it)

L. Orlando

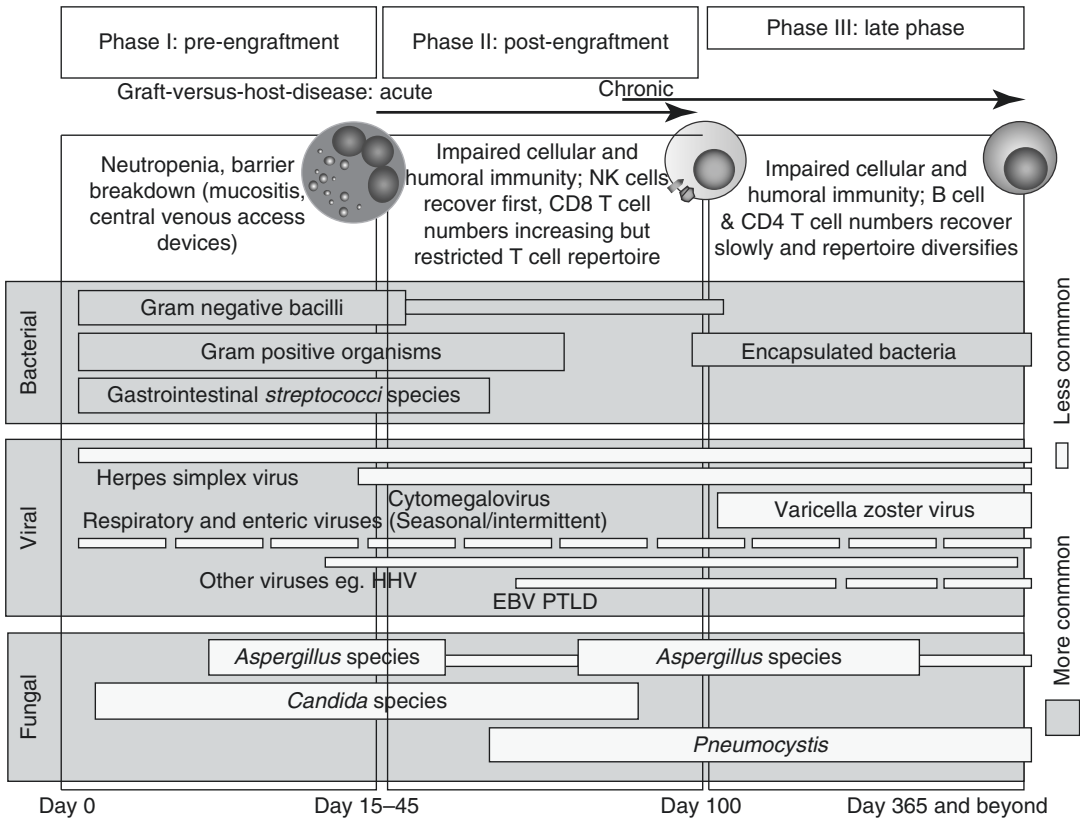
Division of Haemato-oncology, European Institute  
of Oncology, Milan, Italy  
e-mail: [lauraorlando25@libero.it](mailto:lauraorlando25@libero.it)

D. Hutt

Department of Pediatric Hematology-Oncology and  
BMT, Edmond and Lily Safra Children Hospital,  
Sheba Medical Center, Tel-Hashomer, Israel  
e-mail: [dhutt@sheba.health.gov.il](mailto:dhutt@sheba.health.gov.il)

## 7.1 Introduction

Infection is a major cause of mortality and morbidity in the haematopoietic stem cell transplant (HSCT) population due to regimen-related toxicity. Improvements over the past couple of decades especially in supportive care have helped to reduce this risk. The development of neutropenic fever is a frequent occurrence, and centres have algorithms for identifying and treating infection promptly. In this chapter we will discuss the common viral, bacterial and fungal infections that our transplant patients develop.



**Fig. 7.1** Phases of opportunistic infections among allogeneic HCT recipients. HHV6 human herpesvirus 6, NK natural killer, PTLD post-transplant lymphoproliferative disease (Mackall et al. 2009)

Mackall et al. (2009) displays the variety of infections in Fig. 7.1 that may occur and the approximate timeframe for their development which aids the clinical team to refine and direct investigations and potential treatments appropriately.

## 7.2 Viral Infections

Viral infection is spread by close contact with infectious secretions, either by large particle aerosols, fomites or subsequent self-inoculation. Coughing and sneezing will produce aerosol particles, and a virus can also be picked up after contact with contaminated surfaces.

### 7.2.1 Cytomegalovirus

#### 7.2.1.1 Introduction

Cytomegalovirus (CMV) disease is a serious potential complication of allogeneic stem cell transplantation leading to life-threatening complications. CMV is usually acquired in childhood. It is a virus that is present worldwide, and whilst in developed countries approximately 50% of the population is seropositive, this rises to almost 100% in developing countries. CMV is shed intermittently from the oropharynx and from the genitourinary tract of both immunocompetent and immunosuppressed people. Prior to allograft the serostatus (IgG) of the patient and potential donors are assessed to gauge risk (Zaia et al. 2009).

CMV belongs to the human herpesvirus family HHV5 and comes from the subfamily Betaherpesvirinae. Betaherpesvirinae infects the mononuclear cells, establishes latency in the leukocytes and once reactivated replicates slowly. CMV is able to lie dormant for protracted lengths of time, and immunity to the CMV complex involves both the humoral and cell-mediated pathways. Patients treated with stem cell transplantation in the context of haematological malignancies can reactivate the latent virus, either from native host leucocytes, from those derived from the donor, or from both. The risk of reactivation varies dependent upon the patient and/or donor's previous exposure to CMV. CMV status can be shown as follows:

Risk factors for reactivation

	Recipient	Donor
High risk	Positive	Negative
Medium risk	Negative	Positive
Medium risk	Positive	Positive
No risk	Negative	Negative

The patient's CMV status is indicated on the left and donor CMV status on the right.

Careful measures are taken to minimize the risk of primary infection with CMV when prescribing blood products in allograft patients. All blood products should be obtained from CMV-seronegative donors and leukocyte depletion.

Risk Factors for *CMV Reactivation*

- CMV serostatus of recipient/donor (+/- or +/- >> -/+)
- Previous CMV reactivation
- Time post-transplant – increased in early post-transplant period (to day 100)
- T-cell-depleted transplant conditioning protocols (e.g. Campath 1-H)
- Systemic immunosuppression (particularly corticosteroids, antibodies directed against T-cells, e.g. ATG/Campath 1-H)
- Recipient age – increased in older patients
- Graft versus host disease (GvHD)

Risk Factors for *Primary CMV Infection*

- Person-to-person transmission
- Low risk in use of blood not screened negative for CMV (Meijer et al. 2003)

### 7.2.1.2 Presentation

CMV can occur as a primary infection or as a reactivation of the previously latent virus. When a CMV IgG-negative patient develops CMV, this is termed a primary infection. When a patient, or donor, is known to be CMV antibody positive and then develops CMV, this is termed reactivation. The diagnosis of CMV disease requires the presence of symptoms and signs compatible with end-organ damage, together with the detection of CMV. If left untreated, asymptomatic CMV infection can progress to CMV disease.

### 7.2.1.3 Diagnosis

It is important to diagnose reactivation early and institute timely treatment; therefore regular monitoring of CMV levels is of paramount importance. Polymerase chain reaction (PCR) is the most sensitive and quantitative method of monitoring at-risk patients especially in the early post-transplant period (until at least day 100 post-transplant) and longer in those on systemic immunosuppression.

CMV infection most commonly affects the lung, gastrointestinal tract, eye, liver or central nervous system, with CMV pneumonia being the most serious complication with >50% mortality (Tomblyn et al. 2009).

All bone marrow transplant patients and donors will have their CMV status tested in clinic pre-transplant along with the CMV status of the donor.

### 7.2.1.4 Monitoring and Surveillance

For disease monitoring post-transplant, all patients who are seropositive themselves or whose graft is seropositive must receive twice weekly (if an in-patient) monitoring of CMV levels by whole blood (EDTA sample) for PCR (or once weekly in the outpatient setting). This mon-

itoring must continue whilst the patient is considered high risk of reactivation; the first 100 days post-transplant or until systemic immunosuppression has been discontinued, and there is no evidence of graft versus host disease.

### 7.2.1.5 Treatment

Treatment of CMV reactivation will be undertaken following two consecutive positive CMV PCR levels at, or greater than, the limit of sensitivity, 500 copies/ml or one result of greater than 1000 copies/ml (or depending on local policy). Treatment will also be initiated regardless of PCR if signs of organ-specific disease are identified. Some centres may adopt a policy of pre-emptive treatment; please refer to your own institution guidelines for advice.

The treatment regimen is often undertaken as an in-patient. In which case, first-line therapy is with intravenous ganciclovir 5 mg/kg twice daily for a minimum of a week. Second-line treatment may be given if there is significant ganciclovir-related bone marrow suppression (neutrophil count less than 1) or treatment failure with rising viral levels or evidence of viral resistance after at least 1 week of treatment.

Second- and third-line treatment is with foscarnet 90 mg/kg twice daily and cidofovir 5 mg/kg weekly for 2 weeks followed by fortnightly until negative. Foscarnet may be adopted as a first-line treatment if the patient reactivates within the first month of transplant when blood counts have not fully recovered as it is less myelotoxic than ganciclovir. It does, however, have more renal complications, and regular electrolyte replacement is often required.

Similarly, cidofovir leads to renal impairment, and a urine sample should be tested prior to infusion for the presence of protein. If proteinuria is greater than 2 on dipstick, or renal function has deteriorated (please refer to hospital/unit guidelines), then cidofovir should not be given.

In asymptomatic patients, or in those with viral levels responsive to the above treatments that are fit for discharge, oral therapy with valganciclovir may be used. Outpatient use of valganciclovir in asymptomatic reactivation is

usually confined to those with low-level reactivation around log 3.

### Treatment with Ganciclovir and Valganciclovir, Dosing and Administration for Nursing Staff

For detailed instructions consult the summary of product information at website address

<http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=3497>

<http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=9315>

(accessed 28/7/17)

The normal dose for ganciclovir is 5 mg/kg given every 12 h by intravenous infusion in 100 ml normal saline over an hour, rounded dose to the nearest 25 mg. The drug is an irritant; it is alkaline and may cause chemical phlebitis, so care should be taken to observe the cannula and ensure that it is functioning well prior to each use.

The normal dose for valganciclovir is 900 mg taken every 12 h orally. Valganciclovir is the oral prodrug of ganciclovir, so the same considerations should be made as when using ganciclovir.

Both ganciclovir and valganciclovir should be used with caution in patients with impaired renal function; there is additive toxicity in patients taking other nephrotoxic drugs (e.g. ciclosporin, amphotericin B). In such patients, the dose should be adjusted and must not be given or used together with imipenem-cilastatin due to the increased risk of convulsions.

Ganciclovir and valganciclovir treatment commonly results in cytopenias, and extreme caution should be applied when using it in patients with impaired bone marrow function (neutrophils  $<1 \times 10^9/l$  or platelets  $<50 \times 10^9/l$ ), and the drug is contraindicated with severely impaired bone marrow function (neutrophils  $<0.5 \times 10^9/l$  or platelets  $<25 \times 10^9/l$ ). Dose adjustment must be made if there is any degree of renal impairment. Creatinine clearance must be calculated, using the Cockcroft-Gault equation for dosing decisions or another formula at your own institution.

### Toxicity

Teratogenicity has been shown in animal models and therefore care should be used in handling the drug. It should not be administered by pregnant staff. Bone marrow suppression is very common, and blood counts should be monitored daily during therapy and visualized prior to infusion. Patients with significant cytopenias should be treated with haemopoietic growth factors and/or discontinuation of therapy if growth factor support is not available or clinically safe. A patient developing a cytopenia must be discussed with the treating consultant for a clinical decision to be made with regard to continuation of therapy.

Gastrointestinal toxicity is common with nausea, vomiting and diarrhoea and should be recorded. Other drugs, e.g. ciclosporin, amphotericin B or MMF, may also potentiate the toxicity of ganciclovir; for further details consult the SmPC email link or discuss with your pharmacist or lead clinician.

### Treatment with Foscarnet Dosing and Administration

For detailed instructions consult the summary of product characteristics

<http://www.medicines.org.uk/emc/medicine/174> (accessed 28/7/17)

The normal dose is 90 mg/kg given every 12 h by intravenous infusion. The drug is an irritant; it is alkaline and causes chemical phlebitis; therefore it must be diluted if administered via a peripheral vein; the undiluted solution (24 mg/ml) may be used if administered via a central venous catheter.

Foscarnet should be used with caution in patients with impaired renal function; there is additive toxicity in patients taking other nephrotoxic drugs, e.g. ciclosporin and amphotericin B. To minimize the risk of renal impairment, an additional 500 ml of fluid (saline or dextrose) should be co-administered with each dose of foscarnet.

### Toxicity

Nephrotoxicity is a major side effect, with 12–30% of patients showing a significant decline

in renal function. Electrolyte disturbance occurs frequently with low magnesium, calcium, phosphate and potassium most commonly requiring regular monitoring at least once daily whilst on treatment and following therapy. Hypocalcaemia complicating the use of foscarnet has been implicated in patients developing seizures on therapy. Local irritation to veins may occur, and it is advised that central venous access should be used if possible together with maintenance of good hydration and diuresis during treatment. Local ulceration in the genital area may also occur in both men and women, and patients should be informed of this at the start of treatment and asked to be vigilant and inform staff if and when this occurs. Strict hygiene should be advised to reduce risk of skin ulceration.

Gastrointestinal toxicity is common with nausea, vomiting and diarrhoea. CNS toxicity is not infrequent, and patients may suffer with headache, dizziness, anorexia and altered mental state. Haematological toxicity is also common and mainly results in anaemia; leucopenia is less common, whilst thrombocytopenia occurs infrequently.

### Treatment with Cidofovir Dosing and Administration

For detailed instructions consult the summary of product characteristics

<http://www.mhra.gov.uk/spc-pil/?prodName=CIDOFOVIRILLOMED75MG/MLCONCENTRATEFOR SOLUTION FOR INFUSION&subsName=CIDOFOVIRDIHYDRATE&pageID=SecondLevel> (accessed 28/7/17)

The normal dose is 5 mg/kg given once weekly by intravenous infusion for two doses, as an induction, and then given twice weekly as a maintenance. Maintenance treatment starts 2 weeks after completion of induction therapy and will continue until clearance of virus. Often the first dose is given as an in-patient, and further doses are given in outpatients if well staffed with appropriate training.

Cidofovir is markedly nephrotoxic and if damage occurs this is often irreversible. As such cidofovir is contraindicated in patients with pre-

existing renal dysfunction. Renal toxicity occurs frequently during treatment, and renal function must be monitored closely; deterioration is likely to necessitate discontinuation of therapy. There is additive toxicity in patients taking other nephrotoxic drugs, e.g. ciclosporin and amphotericin B.

To minimize renal toxicity, hydration and probenecid must be administered with each dose of cidofovir. In patients with hypersensitivity to probenecid or sulpha-containing drugs, cidofovir is likely to be contraindicated; such cases must be discussed with the treating consultant before initiating therapy.

Cidofovir also frequently causes non-dose-dependent neutropenia, although this may resolve spontaneously whilst continuing on treatment. Dose interruption is not mandatory in patients developing neutropenia although the risk benefit of continued treatment in such patients must be discussed with the treating consultant or transplant physician.

### **Toxicity**

Renal dysfunction is the major dose-limiting toxicity and may be irreversible. Eighty percent of patients develop proteinuria due to tubular dysfunction whilst on therapy. Gastrointestinal toxicity is common with nausea and vomiting. Haematological toxicity is common and is mainly neutropenia. Alopecia, uveitis and fever are also frequently observed during treatment with cidofovir but resolve on discontinuation.

There are currently several new emerging drugs for the treatment of CMV although these have so far not shown superiority to the above four drugs following phase 1 and 2 clinical trials. These newer therapies include maribavir, brincidofovir and letermovir. Another option for those patients who are difficult to treat could be the use of CMV-specific CTLs. Unfortunately, they are expensive and difficult to obtain.

## **7.2.2 EBV**

### **7.2.2.1 Introduction**

Epstein-Barr virus (EBV) is a latent herpesvirus that is thought to infect as much as 95% of the

adult population by the age of 40 years. It is an enveloped and double-stranded DNA virus and human herpesvirus 4 (HHV4). Primary infection with EBV usually results in mild, self-limiting illness of the oropharynx in childhood and the clinical syndrome of infectious mononucleosis in adults and is often asymptomatic.

During the primary infection, an immunocompetent individual will mount a vigorous response. Once the initial infection has cleared, the linear EBV genome becomes circular forming an episome in infected B cells and becomes established as a latent infection awaiting reactivation. This has relevant implications for clinical approaches as antiviral agents such as ganciclovir inhibit the replication of the linear EBV-DNA but are ineffective against episomal DNA. These drugs therefore fail to prevent B-cell proliferation and are of no clinical use in treatment plans (Rasch et al. 2014).

Epstein-Barr virus post-transplant lymphoproliferative disease (EBV-PTLD) results from outgrowth of EBV-infected B cells that are normally controlled by an effective EBV-specific cytotoxic T-cell response that occurs in the immunocompromised host (Deeg and Socie 1998; Heslop 2009). PTLDs are classified as either early-onset lesions which develop within 1 year or late onset occurring greater than a year post-transplant (Ibrahim and Naresh 2012).

### **7.2.2.2 Presentation and Manifestations**

The clinical manifestations of PTLD vary widely and may include nonspecific symptoms such as fever, malaise, sweats, weight loss and in some cases obvious enlargement of lymphoid tissue (Ibrahim and Naresh 2012).

Post-transplant lymphoproliferative disease (PTLD) is a rare but potentially life-threatening disease with an incidence of 1–11% and a mortality of >80% in the pre-rituximab era (Landgren et al. 2009). It is defined as a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in a recipient of a solid organ or bone marrow transplant. The immunosuppression required to preserve graft function post-transplant leads to an impairment of T-cell

immunity. This allows an uncontrolled proliferation of EBV-infected B cells. This results in monoclonal or polyclonal plasmacytic hyperplasia, B-cell hyperplasia, B-cell lymphoma or immunoblastic lymphoma. Immune surveillance is impaired; the balance between latently infected B-cell proliferation and the EBV-specific T-cell response is disrupted and leads to the infected B cells developing into PTLD (Heslop 2009).

The early detection of EBV viral load by polymerase chain reaction (PCR) in whole blood is widely accepted as the preferred method of monitoring patients and should commence on the day of cell infusion. Viral levels should be monitored weekly for 3–6 months and longer in those with GvHD or on immunosuppression. Those at greater risk are recipients of T-cell-depleted HSCT, HLA mismatches or patients conditioned with antithymocyte globulins (Landgren et al. 2009). Other risk factors that have been identified as predictive for the development of PTLD include recipient pre-transplant EBV seronegativity and donor EBV seropositivity (Styczynski et al. 2009).

It is presumed that EBV is transmitted from donor to recipient via the graft at a time of considerable immunosuppression for the recipient, or the patient develops primary EBV infection unrelated to donor EBV status. It is therefore advisable if possible to choose a seronegative donor if one is available. Reactivation is common but does not always lead to end-organ disease requiring treatment (Styczynski et al. 2009).

Cohen (1991) reviewed cases of PTLD in the literature involving renal, cardiac, heart-lung, liver and bone marrow transplantation. Allogeneic bone marrow transplantation-related PTLD had an incidence of 1.6%. This was much higher if the patient had received mismatched T-cell-depleted bone marrow (24%) or if the patient had received anti-T-cell monoclonal antibodies for graft versus host disease (17%). The mean time interval from transplantation to a diagnosis of PTLD was 5 months, with the majority by 3 months.

The pathological diagnosis of PTLD is based on the WHO classification and includes four main categories and is the basis for the UK BCSH guidelines:

1. Early lesions  
Are those that show features when biopsied of infectious mononucleosis and plasmacytic hyperplasia. These are the first signs in the spectrum of PTLD diagnosis.
2. Polymorphic PTLD  
Comprises small- and medium-sized lymphocytes and Reed-Sternberg-like cells. Underlying cell structure is destroyed and may show malignant features.
3. Monomorphic PTLD  
Comprises large lymphocytes and plasma cells that are uniform in appearance with most being B cells with a clonal abnormality.
4. Classic Hodgkin lymphoma  
This is a rare form of PTLD usually found in renal transplant patients (Swerdlow et al. 2008).

In practice, a clear separation between the different subtypes is not always possible; early lesions, polymorphic PTLD and monomorphic PTLD probably represent a spectrum of diseases (Parker et al. 2010). More recently Styczynski et al. (2009) published definitions of EBV that are in common use across Europe.

EBV-DNA-emia:	Detection of EBV-DNA in the blood
Primary EBV infection:	EBV detected in a previously EBV-seronegative patient
Probable EBV disease:	Significant lymphadenopathy (or other end-organ disease) with high EBV blood load, in the absence of other aetiologic factors or established diseases
Proven EBV disease:	(PTLD or other end-organ disease): EBV detected from an organ by biopsy or other invasive procedures with a test with appropriate sensitivity and specificity together with symptoms and/or signs from the affected organ

### 7.2.2.3 Diagnosis

Early diagnosis is important so that treatment can be initiated promptly. The exact copy or log number to commence therapy has not yet been fully established. Action from a blood test alone is not indicated and should be in parallel with clinical symptoms such as fever and lymphadenopathy and imaging studies (Heslop 2009).

Whether PTLD presents as localized or disseminated disease, the tumours are aggressive and rapidly progressive and often are fatal. Clinical presentation is very variable and includes fever (57%), lymphadenopathy (38%), gastrointestinal symptoms (27%), infectious mononucleosis-like syndrome that can be fulminant (19%), pulmonary symptoms (15%), CNS symptoms (13%) and weight loss (9%). Patients may report fever, weight loss, anorexia, lethargy, sore throat, swollen glands, diarrhoea and abdominal pain, shortness of breath, neurological symptoms or symptoms that initially would not suggest a diagnosis of PTLD. CNS involvement is of particular concern as it offers a dismal prognosis (Deeg and Socie 1998).

The most common sites for involvement are the lymph nodes (59%), liver (31%), lung (29%), kidney (25%), bone marrow (25%), small intestine (22%), spleen (21%), CNS (19%), large bowel (14%), tonsils (10%) and salivary glands (4%). T-cell lymphoproliferative disorders not associated with EBV infection tend to occur at extranodal sites.

#### 7.2.2.4 Monitoring

Reactivation usually occurs in the first 6 months and up to 1 year post-transplant and is predominantly derived from donor B cells before reconstitution of the EBV-specific cytotoxic T-lymphocyte response but can occur later if patients are still heavily immunosuppressed, e.g. when taking ciclosporin (Kuriyama et al. 2014).

#### 7.2.2.5 Treatment

Withdrawal of immunosuppression in the first instance and if patients are still positive then treatment with rituximab monoclonal antibody (anti-CD20) once a CT scan and if possible biopsy has been taken is the standard therapy for transplant PTLD.

The removal of immunosuppression to restore immune response is usually not effective for treating those who develop PTLD very close to their transplant date due to their profound immunosuppressed state. The regenerating immune system is not able to recover fast enough to eradicate the malignant cells. It also carries a risk of

graft rejection. Those who are significantly further away from transplant may reduce the EBV load by removal of immunosuppression alone.

Rituximab has been shown to improve outcome when initiated early as it targets B-cell-specific surface antigens present on the EBV-transformed malignant cells. Rituximab is a chimeric murine/human monoclonal anti-CD20 antibody. As CD20 cells are not only expressed on malignant cells, normal B cells are destroyed in a patient who will already be immunocompromised and may lead to other viral infections. The effect of rituximab on the B-cell compartment can be up to 6 months following treatment and should therefore be used with caution and under strict surveillance in specialist centres. Failure to respond to single-agent rituximab leads to the option of chemotherapy in the form of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone).

Additional options such as adoptive T-cell therapies are still unavailable in many centres, but some series of studies suggest that this may offer response to those in whom standard rituximab has failed. EBV-specific cytotoxic T cells (CTL) aim to selectively restore the impaired immune function by the adoptive transfer of EBV-specific cytotoxic T cells. CTLs can be generated by using EBV-infected lymphoblastic cell lines to sufficiently stimulate donor-derived T cells, expand them over a 3–4-week period and then give to the patient. This is a time-consuming process and one that the patient can often not wait for. A quicker process for rapidly generating CTLs by overnight stimulation of donor mononuclear blood cells with EBV-specific peptides, selection of Ag-specific T cells by IFN-gamma surface capture assays and subsequent immunomagnetic selection has been developed although not widely available. There is an associated high risk of developing acute or chronic GvHD post infusion, and so risk benefit should be discussed with the patient (Rasch et al. 2014).

Rituximab is given by IV infusion and is not a vesicant. It is initially given slowly to reduce the risk of a reaction with each subsequent cycle given quicker as tolerated. A reaction to rituximab is thought to be mediated by a cytokine release from both normal and malignant B cells.



The most common adverse events (AEs) with rituximab include infusion reactions, the majority of which are mild to moderate (grades 1 and 2) in nature. Seventy-seven percent of any grade infusion reactions occur during the first infusion, and the incidence decreases with each subsequent infusion. These infusion reactions generally resolve with the slowing or interruption of the infusion and with supportive care. The incidence of grade 3 or 4 infusion-related events in patients is reported to be 9% for the first infusion of rituximab. The majority of severe reactions occur approximately 30–120 min after starting the first infusion.

## 7.2.3 HHV6

### 7.2.3.1 Introduction

Human herpesvirus 6 (HHV6) is a ubiquitous virus, and more than 90% of the population over the age of 2 years are seropositive as it is easily passed person to person via saliva. It is usually latent and is commonly reactivated in approx. 30–70% of post-allogeneic stem cell transplant patients.

### 7.2.3.2 Risk

Those at increased risk are HLA mismatches, and those on corticosteroid therapy for GvHD and highest of all are umbilical cord (UCBT) allografts with an incidence of 9% compared to 1% in BM or PBSC recipients. It is postulated that the higher incidence is due to the lack of memory T cells in the UCBT against HHV6 that are present in adult donors.

### 7.2.3.3 Presentation

HHV6 may be associated with the development of encephalitis in 1–11% of patients and also in some reports of pneumonia (Zerr et al. 2005). HHV6 can be divided into two groups HHV6 variants A and B. Primary infection with HHV6B causes exanthema subitum (roseola infantum) in infants, whilst the role of HHV6A in disease is not yet fully explored (Ljungman et al. 2000). HHV6 typically reactivates earlier than cytomegalovirus post allograft.

The evidence for the relationship between HHV6 positivity and encephalitis is not conclusive especially as HHV6 is often asymptomatic. Clinically patients present 2–6 weeks post allograft with delirium, amnesia, confusion, ataxia and seizure. During the transplant process, HHV6 has been cited by Zerr et al. (2005) to cause a delay in engraftment with up to 60% more platelet requirements in those who become positive.

### 7.2.3.4 Diagnosis

Memory loss is cited as the most common feature; this can develop to confusion and then finally to unconsciousness. HHV6 may accompany the syndrome of inappropriate antidiuretic hormone (SIADH). On magnetic resonance imaging (MRI) of the head, there are hyperintense lesions noted, and these are referred to as post-transplant acute limbic encephalitis (PALE). Upon examination of the cerebrospinal fluid (CSF), HHV6 DNA is observed. For a confirmed diagnosis to be made, the gold standard would be tissue biopsy. This is impossible in the acutely unwell post-transplant patient, and therefore the accepted approach is PCR testing of CSF and the exclusion of other causes for the patient's symptoms.

### 7.2.3.5 Treatment

Foscarnet and ganciclovir are the recommended treatments and should be started as soon as possible following symptoms suggestive of HHV6 (Ogata et al. 2015).

## 7.2.4 *Pneumocystis jirovecii*

### 7.2.4.1 Introduction

*Pneumocystis jirovecii* (PCP) is an atypical fungus that causes severe pneumonia in immunocompromised patients. Recognized as a protozoan initially and reclassified in 1988 as a fungus, pneumocystis cannot be propagated in culture, and few treatment options exist for those with PCP pneumonia. It is ubiquitous with almost universal seropositivity by 2 years of age (Thomas and Limper 2004). The accepted belief for

contracting PCP was as a reactivation of a latent virus. However, evidence suggests that PCP may occur following recent infection and may also be transmitted person to person. Many hospital policies do not mandate isolation, but a pragmatic approach is often taken, and HSCT recipients should avoid exposure to those with proven PCP (Gea-Banacloch et al. 2009).

#### 7.2.4.2 Risk Factors

It is recommended that all allograft patients are adequately covered with prophylaxis for PCP for at least 6 months and up to 1 year or more if on immunosuppression with combination trimethoprim-sulfamethoxazole (TMP-SMX) as this has reduced incidence of infection to approximately 5% (Castro et al. 2005). Prophylaxis usually starts at the point of engraftment or upon discharge as TMP-SMX can cause engraftment delay.

The most effective first-line prophylaxis is a combination of trimethoprim-sulfamethoxazole given in a variety of doses dependent upon your local policy. If the patient develops any sensitivity to these drugs, then alternatives are pentamidine nebulizer, atovaquone and oral dapsone. If dapsone is to be used, then glucose 6-phosphate dehydrogenase (G6PD) deficiency should be ruled out. G6PD is highly prevalent in African, Asian, Oceanian and Southern European populations, and those with G6PD deficiency may develop acute haemolytic anaemia. Nebulized pentamidine can cause bronchospasm, and patients need to be informed of this prior to inhalation. Atovaquone is generally well tolerated but poorly absorbed unless taken with a high fat diet. Patients in the immediate post-transplant setting may struggle with this especially those with GI GvHD issues (Gea-Banacloch et al. 2009).

#### 7.2.4.3 Presentation

Those with PCP present with symptoms of subtle onset dyspnoea, a low-grade temperature and a non-productive cough, and when examined, the chest is clear on auscultation. However, this may rapidly change with the onset of hypoxia requiring admission to a critical care unit. Imaging of the chest with X-ray reveals bilateral perihilar interstitial infiltrates that become increasingly

homogenous and diffuse as the disease progresses. Computed tomography (CT) scans show extensive ground-glass attenuation or cystic lesions (Thomas and Limper 2004).

#### 7.2.4.4 Diagnosis

Patients have a 50% mortality associated with the development of PCP; prompt diagnosis and treatment are warranted with adherence to prophylactic cover. Due to the difficulties of culturing samples, the diagnosis of PCP is made through microscopic examination of sputum or bronchoalveolar fluid or by polymerase chain reaction (PCR).

#### 7.2.4.5 Treatment

If PCP pneumonia is suspected, treatment is with trimethoprim-sulfamethoxazole and the addition of systemic steroids to reduce the inflammatory lung processes. For those that are intolerant to trimethoprim-sulfamethoxazole, then atovaquone or a combination of clindamycin with primaquine is licenced for use (Chen et al. 2003).

### 7.2.5 Varicella Zoster Virus

#### 7.2.5.1 Introduction

Varicella zoster virus (VZV) infection or chickenpox is usually a childhood disease, and transmission is either by inhalation of respiratory secretions or direct physical contact. Following exposure the virus remains latent in the dorsal root ganglion, and when it reactivates, it is referred to as “shingles” or herpes zoster. Herpes zoster is grouped painful vesicular lesions that can affect several dermatomes in immunocompetent people. In the setting of allogeneic stem cell transplantation, VZV carried a major risk of morbidity and mortality with 18–52% patients having clinically apparent infection related to reactivation of latent virus; however, with the use of aciclovir, this number has decreased (Thomson et al. 2005). Complications such as post-herpetic neuralgia, skin scarring and bacterial superadded infection are factors in morbidity (Steer et al. 2000; Boeckh et al. 2006).

### 7.2.5.2 Risk Factors

All stem cell transplant patients should receive prophylaxis for (VZV) with oral aciclovir or valaciclovir for 6 months to 1 year (according to local policy) or until immunosuppression is discontinued (Kanda et al. 2001). Transmission of VZV is difficult to prevent as the period prior to symptoms where an individual is contagious can be up to 48 h before the appearance of a rash. The incubation period varies from 10 to 21 days, and an individual remains contagious until all of the vesicles have crusted over. If the immunocompromised patient is in contact with an individual with VZV infection (varicella or HZ), they are at significant risk of developing varicella themselves and will require prompt action from the transplant team (Styczynski et al. 2009).

HSCT will probably destroy any previous immunity to VZV. Immunization of family contacts especially children is advised to reduce risk.

### 7.2.5.3 Presentation

VZV infection occurs in 40–50% if prophylaxis stopped at 6–12 months, with a peak incidence around 5 months and a spread of 2–10 months, usually occurring within 5 weeks of cessation of oral prophylaxis (Steer et al. 2000). Risk factors include unrelated donors, myeloablative conditioning, graft versus host disease (GvHD) and the use of systemic corticosteroids. Pain in the back or abdomen with distension and a rise in ALT are seen in approx. Ten % of patients prior to the development of a rash. The rash may spread to more than 1–3 dermatomes in patients with visceral dissemination and is more difficult to treat.

### 7.2.5.4 Diagnosis

The best method for diagnosing VZV is by polymerase chain reaction (PCR) testing of blood or a glass slide touched to a vesicle as the DNA is highly specific and sensitive.

### 7.2.5.5 Treatment

Treatment for those who have been exposed to a healthy individual with VZV infection is advised depending upon the serostatus of the recipient and availability of drug. Patients who are seronegative and are less than 2 years post allograft or

who have active chronic GvHD or are taking immunosuppressive medications should have intravenous varicella zoster immunoglobulins (VZIG). If this passive immunization medication is unavailable, then high-dose aciclovir, valaciclovir or famciclovir (nucleoside analogues that interfere with viral thymidine kinase activity) can be employed.

Post treatment for VZV, it is advisable to restart prophylactic aciclovir if this was previously discontinued. The length of time prophylaxis should be continued will be guided by local policy and may range from 1 year to lifelong.

## 7.2.6 Adenovirus

### 7.2.6.1 Introduction

Adenovirus (ADV) is a ubiquitous non-enveloped double-stranded DNA virus. It currently has more than 50 serotypes and is divided into six subgroups A–F (La Rosa et al. 2001). Adenovirus is more prevalent in children but is becoming more prevalent in adults in the transplant population.

### 7.2.6.2 Risk Factors

Adenovirus is spread by aerosolization or the faecal-oral route with approx. 80% of children aged 1–5 years old seropositive. Risk factors include mismatched or unrelated donor, acute graft versus host disease (aGvHD) and isolation of ADV from multiple sites (Ljungman et al. 2003).

### 7.2.6.3 Presentation

In healthy individuals, infection is self-limiting causing conjunctivitis and upper respiratory tract, urinary tract or gastrointestinal infections and remains latent in lymphocytes post exposure. Chakrabarti et al. (2002) report a 5–29% incidence of ADV after allogeneic stem cell transplantation.

### 7.2.6.4 Diagnosis

Those with viral-like symptoms usually have a full screen of virology requested that will include ADV. Samples taken from nasopharyngeal, rectal and corneal secretions, urine and

unfixed biopsy tissue can be examined with PCR to assess viral load. Similar to those with viral reactivation of CMV and EBV, low level of ADV infection does not carry a high mortality. However, those patients that develop invasive disease, such as ADV colitis, have a significant mortality of 20–80% (Robin et al. 2007).

### 7.2.6.5 Treatment

Cidofovir is first-line treatment and is a monophosphate nucleotide analogue of cytosine. Cidofovir inhibits viral DNA polymerase and has a low bioavailability with 90% of the drug excreted in the urine. Patients require hyperhydration and oral probenecid pre, during and post cidofovir to protect nephrons.

## 7.2.7 Hepatitis B

### 7.2.7.1 Background

The hepatitis B virus (HBV) is a DNA virus classified in the hepadna virus family. Patients infected by HBV prior to transplantation have a higher risk (70–86%) of HBV reactivation 5 years after HSCT transplantation. An active immunization of donors and early post-transplant vaccination of recipients have been suggested to avoid HBV reactivation. Donors should optimally receive more than one immunization, a rather high Ag dose and a highly immunogenic vaccine (Lindemann et al. 2016).

The use of chemotherapy and immunosuppression can reactivate latent hepatitis B. Further, HBV infection or reactivation contributes to liver-related morbidity and mortality; it occurs in 21–53% of patients, especially after conditioning regimens containing alemtuzumab. Transplantation of HBV-negative patients with stem cells from an infected donor (HBsAg positive) is associated with a high risk of transmission; some patients develop chronic hepatitis B. Donors with active HBV (DNA detection) should receive, if possible, antiviral treatment (Ullmann et al. 2016).

### 7.2.7.2 Clinical Features

Post-transplant HBV infection can arise in different ways. Patients may have active HBV (HBsAg positive) prior to transplant or reactive latent HBV infection (HBsAg negative). Infection may also occur during the transplantation process, from an infected HSC donor or rarely from infected blood products. HBV DNA titer may rise to very high levels, particularly in patients receiving corticosteroids. At the time of immune reconstitution or during reduction of immunosuppressive drugs, a flare is given by a rise in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Another clinical symptom is jaundice and fulminant liver failure as a result of HBV (liver-related mortality) (Lau et al. 2003).

### 7.2.7.3 Treatment

Lamivudine (100 mg/day) is the first choice for antiviral therapy for treatment, which should be continued for at least 6 months following discontinuation of immunosuppressive drugs in allogeneic haematopoietic cell transplantation patients (Tomblyn et al. 2009).

### 7.2.7.4 Prevention

Several studies in the literature describe prevention of HBV reactivation in the setting of immunosuppression. HBV reactivation has been variably reported as ALT elevation above upper limit of normal or by increases from baseline. Patients who undergo HSCT for haematological malignancy are an “at-risk” population because of the prolonged immunosuppression following the conditioning chemotherapy.

The nucleoside analogue antiviral drugs lamivudine, adefovir, telbivudine, entecavir and tenofovir may all be of potential use in the prevention of HBV reactivation in such patients. The majority of reports describe the use of lamivudine or entecavir, and both drugs appear to reduce the incidence of HBV reactivation. However, entecavir (and potentially tenofovir) may be superior to lamivudine because of more potent viral suppression and lower risk of antiviral resistance.

Prophylaxis for HBV reactivation with antiviral nucleoside analogues should be commenced in susceptible individuals before the initiation of chemotherapy, in order to lessen the risk of HBV reactivation and the associated adverse clinical outcomes (Pattullo 2016).

## 7.2.8 Hepatitis C

### 7.2.8.1 Background

The hepatitis C virus (HCV) is a double-stranded RNA virus classified within the Flaviviridae. Six major genotypes have been identified, from HCV1 to HCV6. It can be responsible for several systemic complications. The extrahepatic manifestations include vasculitis, fatigue, cryoglobulinemia and autoimmune disorders. HCV replication is significantly increased by immunosuppression and may cause a direct cytopathic effect in infected cells. The identification of pre-transplant HCV infection appears clinically relevant. Being infected with HCV has been indicated as an independent risk factor for post-transplant veno-occlusive disease (VOD) of the liver. Reactivation of chronic HCV infection after tapering immunosuppressive therapy can sometimes lead to fulminant hepatic failure (Locasciulli et al. 2009).

### 7.2.8.2 Clinical Features

HCV infection is responsible for hepatic and extrahepatic manifestations. After 1 year post HSCT, HCV infection course has an increased risk of fatal sinusoidal obstruction syndrome and later hepatic inflammation occurring 3–6 months after HCT, coincident with immune reconstitution and interruption of immunosuppressive medications. The symptom of liver decompensation among patients who had cirrhosis at the time of transplant has been described in the literature, and rarely, fatal fibrosing cholestatic HCV can occur before day 100 in recipients receiving mycophenolate mofetil (Torres et al. 2015).

HCV infection is associated with high risk for several complications, which include accelerated liver disease progression, acute HCV exacerbation

and viral reactivation. The last two are common, but not associated with increased liver-related mortality rates or changes in HSCT care (Kyvernitakis et al. 2016).

A reported case of severe HCV reactivation occurred early (<30 days after HCT) with elevated ALT and bilirubin levels. Liver biopsy revealed chronic portal inflammation, bile duct injury and moderate cholestasis (Oliver et al. 2017).

HCV adversely impacts on platelet recovery, non-relapse mortality and overall survival. Sinusoidal obstruction syndrome (SOS), liver graft versus host disease (GvHD) and hepatic problems are more likely to be severe and fatal in recipients with HCV. Pre-transplant HCV infection is associated with a lower rate of platelet recovery. An excess of bacterial infections in HCT recipients with HCV infection has been reported, and these findings suggest that the defence mechanisms against bacterial infections are impaired in recipients with HCV (Nakasone et al. 2013).

### 7.2.8.3 Treatment

All HSCT recipients with HCV infection should be evaluated for HCV therapy before the start of conditioning therapy. Whenever possible, HCV-infected HSCT candidates should commence and complete HCV therapy before transplant. If there is an oncologic imperative for moving quickly to transplant, a therapy with direct-acting antiviral agents (DAAs) should be able to clear extrahepatic HCV from donors more quickly than interferon and ribavirin.

Treatment of post-transplant HCV infection must be an urgent consideration for patients with fibrosing cholestatic HCV, patients with cirrhosis whose condition is deteriorating and patients who underwent HSCT for HCV-related lymphoproliferative disorders. Once HCV therapy is initiated, treatment interruption is not recommended because it is associated with increased risk of treatment failure. The alternative to pre-HSCT therapy for HCV is to treat after HCT using DAAs following immune reconstitution.

All long-term HCV-infected HSCT survivors should be offered DAAs therapy.

HCV therapy should be undertaken by providers experienced in management of HCV in HSCT. There are many combinations of DAAs, depending on HCV genotype. Commonly used DAAs include daclatasvir, sofosbuvir, ledipasvir, ombitasvir, paritaprevir, ritonavir, dasabuvir, simeprevir and ribavirin. The choice of regimen should be individualized on the basis of patient-specific data, and take into consideration potential drug interactions with tacrolimus, sirolimus and ciclosporin (Torres et al. 2015).

#### 7.2.8.4 Prevention

A vaccination against HCV does not exist. However, to prevent the complication of coinfection, people with hepatitis C should be vaccinated against hepatitis A and B. Standard precautions are recommended for the care and treatment of all patients, regardless of their perceived or confirmed infectious status and in handling of blood, all other body fluids, secretions and excretions, non-intact skin and mucous membranes (ASHM 2012).

HCV-infected donors should be evaluated for HCV therapy and treated before cell harvest, in order to prevent transmission of HCV to uninfected recipients (Torres et al. 2015).

### 7.2.9 Emerging Infections (Hepatitis E)

#### 7.2.9.1 Background

Hepatitis E virus (HEV) is a single-stranded, non-enveloped RNA virus. It was discovered in 1983 by investigators of an outbreak of unexplained hepatitis in Russian soldiers in Afghanistan. In areas with poor sanitation, HEV 1 and 2 are spread orofaecally between humans,

usually via contaminated water. In developed countries, HEV 3 and HEV 4 are transmitted from animal reservoirs. HEV antibodies were found in pig farmers, slaughterhouse workers, veterinarians, and farm labourers. In Western Europe the food chain is the main source of infection, where HEV is transmitted through the consumption of contaminated animal meat (undercooked pig liver). Person-to-person transmission is uncommon, although nosocomial and parenteral transmission in haemophiliac and in haemodialysis patients has been reported (Marano et al. 2015).

#### 7.2.9.2 Clinical Features

The most common symptom of HEV is jaundice, followed by:

- Malaise/lethargy
- Nausea and vomiting
- Abdominal pain
- Loss of appetite
- Myalgia
- Fever
- Loss of weight
- Neurological features

Extrahepatic manifestations of acute and chronic hepatitis E involve the following systems and organs (Dalton et al. 2015) (Table 7.1).

#### 7.2.9.3 HEV in Developing Countries

After an incubation period of 2–6 weeks, genotypes 1 and 2 develop to HEV infection. The source of infection is human, mostly by faecal-oral route via infected water. Outbreaks can occur at times of flooding/monsoon and can involve thousands of cases. Symptoms of HEV progress with fever, nausea, abdominal pain, vomiting,

**Table 7.1** Extrahepatic manifestations of acute and chronic hepatitis E

Neurological system	Haematological system	Other organs
Guillain-Barré syndrome	Thrombocytopenia	Acute pancreatitis
Brachial neuritis	Lymphopenia	Arthritis
Transverse myelitis	Monoclonal immunoglobulin	Autoimmune thyroiditis
Bell's palsy		
Vestibular neuritis		

anorexia, malaise and hepatomegaly. Jaundice is present in about 40% of patients. Pregnant females and individuals with underlying chronic liver disease present a high mortality.

#### 7.2.9.4 HEV in Developed Countries

Numerous studies report that autochthonous HEV is a problem across Europe and that infection has a predilection for middle-aged elderly males (mean age  $\approx$  60 years). Large outbreaks do not occur, most cases are sporadic and the source of infection remains uncertain in most cases. In the developed countries, we can distinguish between acute and chronic hepatitis E.

##### Acute

Acute HEV is mostly caused by genotypes 3 and 4. Jaundice occurs in about 75% of patients, and the clinical manifestations are the same as those of hepatitis E in developing countries. HEV infection may be misdiagnosed as drug-induced liver injury (DILI) and is responsible for extrahepatic disorders: neurological disorders, kidney injury, acute pancreatitis associated with HEV 1 and haematological disorders as thrombocytopenia and aplastic anaemia.

##### Chronic

No studies have assessed the prevalence or incidence of HEV infection among haematological patients receiving chemotherapy. A small number have been found to have a chronic HEV infection and include a patient with untreated hairy cell leukaemia, a patient with idiopathic CD4 T lymphopenia and patients treated for lymphoma, chronic myelomonocytic leukaemia and B-cell chronic lymphocytic leukaemia. HEV RNA was found in 8 of 328 stem cell transplant patients and 5 developed chronic hepatitis (Kamar et al. 2014).

One case of chronic HEV infection following allogeneic haematopoietic stem cell transplantation was reported in 2015 as differential diagnosis for graft versus host disease (Bettinger et al. 2015).

#### 7.2.9.5 Treatment

In haematological patients, pegylated interferon alone and ribavirin alone for 3 months have been used (Kamar et al. 2014).

#### 7.2.9.6 Prevention

Immunocompromised patients should be screened for HEV antibodies and RNA not only prior transplantation but also post-transplantation and during episodes of liver enzyme abnormalities.

In immunocompetent patients adequate cooking procedures for porcine and boar/deer meat are useful to prevent HEV disease (De Keukeleire and Reynders 2015).

This is a list of the more common virus that patients develop during transplantation.

Rhinovirus	Role of treatment is limited by lack of agents and RCT
Influenza	Oseltamivir +/- zanamivir (research and some limited European areas use IV peramivir, favipiravir)
Respiratory syncytial virus	Ribavirin (research and Europe again use palivizumab)
Parainfluenza	Ribavirin +/- IVIg in some centres
Metapneumovirus	Ribavirin +/- IVIg in some centres
Coronavirus	Role of treatment is limited by lack of agents and RCT
Bocavirus	Role of treatment is limited by lack of agents and RCT

#### 7.2.10 Multiply-Resistant Bacteria: Reducing the Spread

##### 7.2.10.1 Background

Multidrug-resistant organisms (MDRO) have emerged as significant pathogens in haematology and haematopoietic stem cell transplant recipients. Neutropenia and malignancy are independent risk factors for MDRO-invasive infections. Resistant *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia and carbapenemase-producing *K. pneumoniae* (KPC) are emerging in haematology populations with associated mortality, as well as increasing rates of vancomycin-resistant *Enterococci* that are responsible for up to 41% of all gram-positive bacteraemias.

Infection prevention, antimicrobial stewardship and antimicrobial prophylaxis are essential for control and management of MDRO. Hand hygiene, environmental cleaning/disinfection, isolation and surveillance are indeed the backbone of effective prevention programs (Trubiano et al. 2013).

In 2014 the World Health Organization declared antimicrobial resistance a worldwide threat that requires urgent action.

### 7.2.10.2 Contact Precautions

The application of contact precautions (CP) requires that gowns and gloves should be worn when entering the patient's room and removed before leaving it. Dedicated equipment such as stethoscopes or blood pressure cuffs should remain in the patient's room and not be used for other patients. CP may include single-room isolation, an entire isolation ward or cohorting of a group of patients (with or without designated staff). The aim of CP is preventing transmission of epidemiologically important pathogens from a colonized or infected patient through direct (patient or healthcare personnel) or indirect (surfaces or roommates in the patient's environment) contact. In addition to hand hygiene, appropriate CP measures should decrease the risk of MDRO transmission.

Current controversies remain whether patients only colonized, rather than infected, with MDROs should be subjected to isolation. Another issue is the impact of CP on patient's well-being. Healthcare workers who care for patients in contact isolation enter their rooms less frequently and have significantly less direct contact with them. Patients express greater dissatisfaction with their treatment and have less documented care (Landelle et al. 2013).

A review by Cohen et al. (2015) reports that CP do not represent a statistically significant improvement in MDRO infection control. Five of the six reviewed studies did not find significant association between CP and reduction in MDRO transmission (Cohen et al. 2015).

## 7.2.11 Gram-Positive Bacteria

Gram-positive (gram+) pathogens cause significant morbidity and mortality in bone marrow transplant recipients.

- *Enterococci*
- Vancomycin-resistant *Enterococci* (VRE)
- *Coagulase-negative Staphylococcus* (CNS)
- *Staphylococcus aureus*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- *Streptococcus viridans*
- *Streptococcus pneumoniae*

### 7.2.11.1 Enterococci

*Enterococci* are gram-positive aerobes and facultative anaerobes which are seen microscopically as single, pairs and short chains and are part of the normal flora of the gastrointestinal tract. In transplant recipients, enterococcal infections are usually nosocomial and occur generally as invasive infections in the immediate post-transplant period, mostly as a consequence of endogenous gram-positive translocation.

### 7.2.11.2 Vancomycin-Resistant *Enterococci* (VRE)

VRE, also known as glycopeptide-resistant *Enterococci*, are increasingly causing outbreaks in haematology units.

At many transplant centres, VRE are the predominant organism causing pre-engraftment bacteraemia among HSCT recipients.

The evidence for an association between acting contact precautions and surveillance testing or not and the incidence of VRE bacteraemia starts to stagger.

VRE are strongly associated with colonization pressure, and strategies to reduce VRE burden in colonized patients may reduce VRE transmission. Infection control efforts should include contact precautions, and the need for active surveillance testing should be guided by local epidemiology (Kamboj and Sepkowitz 2014).



However, Almyroudis et al. (2016) reported on the discontinuation of systemic surveillance and contact precautions for VRE and its impact on the incidence of VRE faecium bacteraemia in patients with haematological malignancies. In this study, the incidence of VRE bacteraemia remained stable after discontinuation of surveillance and contact precautions. Furthermore, contact isolation can be associated with medication errors, reduced visits of physicians and nurses, safety concerns such as increased falls and bedsores, anxiety and depression among patients and a significant increase in the cost of care (Almyroudis et al. 2016).

### 7.2.11.3 *Coagulase-Negative Staphylococcus (CNS)*

CNS are members of the Micrococcaceae family, produce catalase and divide in irregular clusters to produce packets of cells. Transplant recipients with a central venous catheter (CVC) are particularly vulnerable to CNS infections. CNS cause surgical wound infections and infections associated with lines, including CVC bacteraemia, CVC local infections and drain-associated peritonitis.

### 7.2.11.4 *Staphylococcus aureus*

*Staphylococcus aureus* occurs microscopically as single, pairs and short chains and has a strong tendency to form clusters. *Staphylococcus aureus* is mainly found in the nasopharynx and on the skin.

Methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) are major causes of infections after transplantations. The prevalence of vancomycin-intermediate *S. aureus* (VISA) and heterogeneous or heteroresistant VISA (hVISA) is reported to be increasing worldwide. *S. aureus* truly resistant to vancomycin (VRSA) is very rare, and no data are available for the transplant population (Garzoni 2009).

### 7.2.11.5 *MRSA*

According to the Center for Disease Control and Prevention guidelines (ref website? access date?), HSCT centres should follow stringent infection control practices handwashing, contact precautions, including wearing gloves whenever entering the MRSA-infected or colonized patient's room. MRSA is indeed transmitted via an infected or colonized patient or by a colonized healthcare worker.

Patients with MRSA should be placed under CP until all antibiotics are discontinued and until three consecutive cultures, taken >1 week apart, are negative. Screening cultures for MRSA include the anterior nares, any body site previously positive for MRSA and any wounds or surgical site (Dykewicz and Kaplan 2000).

### 7.2.11.6 *Streptococcus viridans*

*Streptococcus viridans* are facultative anaerobic, gram-positive cocci and are part of the normal microflora, found mainly in the oral cavity but also in the upper respiratory, gastrointestinal and female genital tract. Septicaemia is the most common manifestation in bone marrow transplant (BMT) recipients (Ihendyane et al. 2004).

To lessen the risk of oral sources of infection following HSCT, dental treatment and oral hygiene instructions given 3–4 weeks before the HSCT are required (Tomblyn et al. 2009).

### 7.2.11.7 *Streptococcus pneumoniae*

*Streptococcus pneumoniae* is a gram-positive diplococcus causing significant morbidity and mortality in all age groups, wherein children, the elderly and immunocompromised patients are especially vulnerable. Pneumococcal infection may occur during hospitalization for the transplant procedure but more commonly occurs as a community-acquired infection, months or years following the transplantation as meningitis or fulminant sepsis.

## 7.2.12 Gram-Negative Bacteria

Over the last decade, multidrug-resistant (MDR) gram-negative (gram-) pathogens have been implicated in severe healthcare-associated infections, and their occurrence has increased steadily. The emerging problem of carbapenemase-producing *Enterobacteriaceae* has become a major healthcare threat with associated mortality also in haematology populations.

The recommended strategies to prevent healthcare-associated transmission of gram-negative bacteria are prompt laboratory-based identification, adherence to contact precautions and strict hand hygiene. Further, more expensive approaches include dedicated equipment and staff, especially for patients with MDR in the respiratory tract. Cohorting patients in a specific hospital area can be effective but also very disruptive. Finally, integration of antimicrobial stewardship efforts based on dominant MDR organisms may help prevent future problems (Kamboj and Sepkowitz 2014).

The ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant gram-negative bacteria in hospitalized patients by Tacconelli et al. (2014) summarize the importance of adherence to hand hygiene, wearing contact precautions and using disposable single-use or patient-dedicated care equipment and performing active screening cultures, as well as the role of environmental cleaning and antimicrobial stewardship and the role of infrastructure and education to reduce the spread.

### 7.2.12.1 *Enterobacteriaceae*

*Enterobacteriaceae* are facultative anaerobes and are intestinal colonizers. *Enterobacteriaceae* encompass a large heterogeneous family of gram-negative bacteria, which are divided into lactose fermenters as *Escherichia coli*, *Citrobacter*, *Klebsiella spp.* and *Enterobacter spp.* and non-lactose fermenters *Salmonella*, *Shigella*, *Proteus* and *Yersinia*.

### 7.2.12.2 *Klebsiella pneumoniae*

*K. pneumoniae* is encountered as a saprophyte in humans and other mammals, colonizing the gas-

trointestinal tract, skin and nasopharynx. In the past it has been seen as an important causative agent of community-acquired infections, including a severe form of pneumonia. In the early 1970s, infections caused by *K. pneumoniae* became a leading cause of nosocomial infections. High carriage rates have been recorded in patient's nasopharynx and hands, as well as the gastrointestinal tract. *K. pneumoniae* has a considerable efficiency of colonization, enhanced by acquired resistance to antibiotics, which enables it to persist and spread rapidly in healthcare settings.

*K. pneumoniae* is a notorious "collector" of multidrug resistance mechanisms, such as the "carbapenemases" encoded by transmissible plasmids. The clinically most important carbapenemases in *Enterobacteriaceae* are the class A enzymes of the KPC type, then the zinc-dependent class B metallo- $\beta$ -lactamases (MBLs), represented mainly by the VIM, IMP and NDM types and the plasmid-expressed class D carbapenemase of the OXA-48 type. Carbapenemase-producing *Enterobacteriaceae* (CPE) cause serious infections in immunocompromised patients, in association with prolonged hospital stay and increased mortality rates, because of panresistance to antimicrobials (Tzouveleki et al. 2012).

### 7.2.12.3 Carbapenemase-Producing *Klebsiella pneumoniae*

Carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) are emerging in immunosuppressed patients, and their expansion represents a challenging problem in terms of outcome and management. A retrospective study by Girmenia et al. reports that CP-Kp were documented in 87 allogeneic HSCT in 52 Italian centres, and a colonization documented before or after transplant was followed by an infection in 39% of allogeneic HSCT (Girmenia et al. 2015). An analysis of 50 cases of KPC bloodstream infections (BSI) in neutropenic patients with haematological malignancies or aplastic anaemia, conducted by Tofas et al. reports that all episodes of KPC BSI were hospital-acquired, the median duration of hospitalization before the onset of bacteraemia was

22 days and 48 of 50 CP-Kp produced KPC enzyme and 2 produced VIM enzyme (Tofas et al. 2016).

#### 7.2.12.4 *Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* is a glucose non-fermenting gram-negative rod. It is a strict aerobic pathogen, cosmopolitan in distribution, with a particular predilection for moist environments. *Pseudomonas aeruginosa* has shown the ability to acquire resistance to all traditionally effective agents, such as anti-pseudomonal penicillins, third- and fourth-generation cephalosporins, aminoglycosides, fluoroquinolones and carbapenems.

Patient gastrointestinal colonization serves as an important reservoir for endogenous infection, as well as the source of horizontal transmission to other patients.

In patients with haematological malignancies, enteric colonization by *Pseudomonas aeruginosa* occurs typically after chemotherapy.

#### 7.2.12.5 *Acinetobacter baumannii*

*Acinetobacter baumannii* is a nonfermentative gram-negative pathogen. Its ability to survive on dry, inanimate surfaces for long periods of time suggests that the hospital environment serves as a reservoir for MDR strains. *Acinetobacter baumannii* can be resistant to many or all available antibiotics. Multidrug resistance is common in the US hospital-acquired infections, estimated up to 60%.

Colonized patients' skin may serve as effective reservoirs, and healthcare workers' hands can serve as vehicles for transmission. Commonly employed strategies to avoid the spread of *Acinetobacter baumannii* include identifying and eliminating common sources of contamination, optimizing contact isolation and hand hygiene to minimize cross-transmission, enhancing environmental cleaning to reduce contamination and reducing broad-spectrum antibiotic use (Lin et al. 2014).

### 7.2.13 *Clostridium difficile*

#### 7.2.13.1 Background

*Clostridium difficile* is an anaerobic, gram-positive spore-forming bacterium and increas-

ingly identified as the cause of nosocomial diarrhoea in growing numbers of patients. Patients who are admitted for treatment of haematological malignancies or undergoing HSCT are at high risk for *Clostridium difficile* infection (CDI). Risk factors for CDI include exposure to broad-spectrum antibiotics, which can cause changes to the microbiota of the gut, total body irradiation, long hospitalization, immunocompromised state, older age and irritation of the intestinal mucosa by chemotherapy drugs (Gu et al. 2015).

#### 7.2.13.2 Infection Control Management

(Adapted from Debby Weston, Fundamentals of Infection Prevention and Control, 2013).

##### Isolation

- In the event of confirmation of a *Clostridium difficile* (CD) toxin-positive result in a patient with diarrhoea, who is not already isolated, the patient must be moved to a single room with en suite bathroom or dedicated night commode.
- An isolation notice must be displayed on the door.
- The nurse looking after the patient should inform the infection prevention control team.
- Isolation can be discontinued once the patient has been asymptomatic for 48 h and is passing "normal" stools.

##### Equipment and Cleaning

- Dedicated patient equipment must be used, including disposable blood pressure cuffs and tourniquet.
- Floors, night commodes, toilets and bed-frames are subject to the heaviest faecal contamination; it is important that the ward environment should not be cluttered in order to facilitate thorough and effective ward cleaning.
- On discharge or transfer of the patient, it is important that an accurate clean of the room is undertaken using 1000 ppm available chlorine and/or a sporicidal agent.

### Hand Hygiene

- The patient should be assisted with hand hygiene after using the toilet or night commode and before eating if unable to wash his or her hands independently.
- Healthcare workers must wash their hands with soap and water after contact with the patient or his/her environment. Alcohol hand rubs or gels are not effective against *Clostridium difficile* spores.

### Personal Protective Equipment (PPE)

- Wear gloves and apron before entering the patient's room.
- Remove apron and gloves before leaving the patient's room.
- Hands must be decontaminated before putting on and after removing gloves.
- Ensure that all healthcare workers and visitors wear and dispose of PPE appropriately.

### Waste and Linen

- Any clinical waste and linen, including bedding and, if present, curtains, should be considered contaminated and managed properly.

### Movement of Patients

- Patients with CD should not be transferred to other wards in the hospital, except for isolation purposes or if they require specialist care on another ward.
- When patients need to attend departments for essential investigations, the nurse looking after the patient is responsible for informing the receiving area in advance of the patient's CD-positive status; if possible, symptomatic patients should be seen at the end of the working session and should be sent for only when the department is ready to see them; it should be avoided to leave them in a waiting area with other patients.

CD spores are known to contaminate the environment, are resistant to standard disinfectants and are capable of surviving for long periods on dry surfaces. 10% bleach solutions are sporicidal and should be used for environmental decontamination during outbreaks.

The combination of strict hand hygiene and contact precautions (gloves and apron) significantly reduces the incidence of CD (Dubberke and Riddle 2009).

### 7.2.13.3 Treatment

First-line treatment is given by oral metronidazole (500 mg three times daily for 10–14 days) and/or vancomycin (125 mg every 6 h for 10–14 days) (Kamboj et al. 2014).

Gu et al. (2015) report a treatment with berberine when CDI first symptoms appeared and they did not have severe cases of CDI in the study. Berberine is a traditional Chinese medicine that has been used to treat bacterial or secretory diarrhoea for 12,000 years in China. Additional studies are needed to demonstrate whether berberine could be a new useful therapeutic agent to alleviate clinical symptoms of CDI (Gu et al. 2015).

Further treatments of recurrent CDI are fidaxomicin, probiotics, intravenous immunoglobulin and faecal transplants.

### 7.2.13.4 Faecal Microbiota Transplant

The treatment with faecal microbiota therapy consists in a technique that involves transfer of fresh stool from a healthy donor to the gastrointestinal tract of the patient suffering from severe or recalcitrant *Clostridium difficile* infection (CDI). In the case report by Neemann et al. (2012), the donated stool sample was screened for transmissible pathogens, ova and parasites, *Clostridium difficile*, *Salmonella*, *Shigella*, *Campylobacter* and *Escherichia coli*. After a brief liquefaction procedure, 30 ml of fresh stool suspended in non-bacteriostatic saline was slowly injected via nasojejunal tube into upper jejunum, followed by non-bacteriostatic saline flush. Within 2 days of faecal transplant, the patient had no further diarrhoea or haematochezia. For fulminant CDI unresponsive to metronidazole and/or vancomycin, the definitive treatment has been colectomy, but faecal microbiota therapy should be considered a potentially bowel- and life-saving intervention, if other medical modalities fail (Neemann et al. 2012).

Another case reported by Castro et al. (2015) describes a persisting CDI infection and diarrhoea 10 months after bone marrow transplantation. The patient had an allergic response to oral vancomycin and was subsequently treated with oral metronidazole and i.v. meropenem. After performing faecal microbiota transplantation with material from two different donors, the patient's bowel showed significant improvements, and any antibiotic were not needed anymore (Castro et al. 2015).

## 7.3 BMT Setting, Infection and Infection Control

### 7.3.1 Introduction

Haematopoietic stem cell transplantation (HSCT) can be defined as the transfer of haematopoietic stem cells (HSCs) from one individual to another (allogeneic HSCT) or the return of previously harvested cells to the same individual (autologous HSCT) after manipulation of the cells and/or the recipient (Tomblyn et al. 2010).

Haematopoietic stem cell transplantation (HSCT) is a major procedure, which needs the use of chemotherapy. Some patients who are undergoing allogeneic transplantation for haemato-oncological malignancies will require radiotherapy. The use of these treatments, coupled with the patient's disease, compromises the immune system. The administration of immunosuppressant to prevent graft rejection contributes also to the high risk of infections in this patient group (Brown 2010).

In recent years, improvement in HSCT supportive care measures, better understanding of the mechanism of immunosuppression, the introduction of reduced intensity conditioning (RIC) regimens and new anti-infectious agents and prophylactic strategies have decreased infectious morbidity and mortality. However, there is still scope for improvement since infection remains a leading cause of morbidity and mortality in patients undergoing HSCT (Gratwohl et al. 2005).

### Principal risk factors for infections after HSCT are:

- Status of the haematological disease after HSCT
- Comorbidities of the patient
- Degree and duration of neutropenia
- Disruption of anatomical barriers (mucositis and indwelling catheters)
- Depressed T- and B-cell function and immunosuppressive therapy

### Reconstitution of immune status after HSCT depends on:

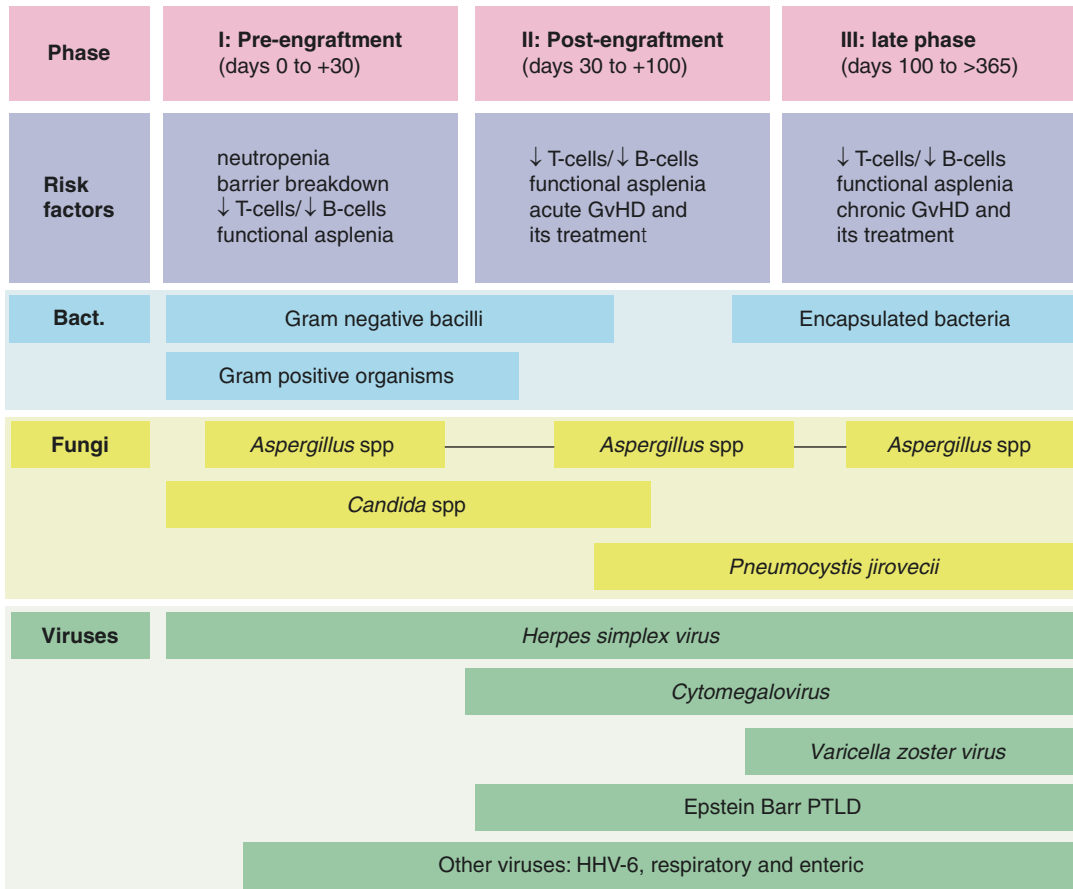
- Type of transplantation (autologous or allogeneic)
- Source of progenitor cells (bone marrow, peripheral blood or cord blood)
- Conditioning regimen (myeloablative, RIC or non-myeloablative)
- Degree of histocompatibility between the donor and the recipient (sibling, unrelated or mismatch)
- Type of GvHD prophylaxis (calcineurin or mTOR inhibitors, mono or polyclonal antibodies or T-cell depletion)
- Presence and grade of GvHD and its treatment

Depending on these factors, the patient can be rendered immunodeficient for months or even years after HSCT (Rovira et al. 2012).

There is a clear relationship between the type of immunodeficiency after HSCT and the incidence of certain infections. According to this, three different periods can be distinguished, with a predominance of specific pathogens in each phase (Fig. 7.2) (Tomblyn et al. 2010; Rovira et al. 2012).

The chronology of the previously mentioned infections was described in patients receiving a myeloablative HSCT, and some differences can be observed in recipients of autologous HSCT or RIC-HSCT. Thus, in the autologous setting, bacterial infections are less frequent and severe, and the other infections are exceptional (Rovira et al. 2012).

However, autologous candidates who receive immunosuppressive agents (steroids, purine ana-



**Fig. 7.2** Chronology of predominant infections after HSCT (Adapted from [1] and granted permission from (EBMT Handbook 2012))

logues or monoclonal antibodies such as rituximab or alemtuzumab) or with severe hypogammaglobulinaemia prior to the auto-HSCT run the same risk of developing infections as those patients undergoing allogeneic SCT.

In the past two decades, RIC-HSCT has been used increasingly worldwide (Rovira et al. 2012). Infections related to neutropenia and mucositis are less common with this modality of HSCT than after conventional HSCT. However, viral and fungal infections occurring in the intermediate and late period are comparable because the incidence and severity of GvHD are similar to that observed in myeloablative HSCT. Additionally, RIC-HSCT is usually used in older patients, who are usually

in poorer general condition with or without the presence of comorbidities; for all these reasons, the infection-related mortality has not decreased in this setting (Rovira et al. 2012; Masszi and Mank 2012).

### 7.3.2 Reverse Barrier Nursing and Protective Isolation

Infections are a major cause of morbidity and mortality in allogeneic transplantation (Parody et al. 2006). Therefore, it is crucial to have a skilled nursing team to assess, prevent, detect and treat infections.

Delays in diagnosing an infection that results from a depressed inflammatory response may lead to increased susceptibility to a broad range of potentially life-threatening organisms. For this reason, in addition to antimicrobial prophylaxis, there are other important strategies to prevent infections, for example, building a multi-professional network team specialized in infection control measures (Masszi and Mank 2012).

### 7.3.2.1 Protective Isolation and Cleaning

The large number of patients considered at risk requires an evaluation of all proposals of protective systems, in relation to the effectiveness, applicability and cost benefit (Pizzo 1981).

The Centres for Disease Control and Prevention (CDC) has published in 2007 very specific recommendations regarding precautions to be taken in haematopoietic stem cell transplant.

(HSCT) reported and updated in 2009.

The CDC recommends a protective isolation for patients who are undergoing allogeneic HSCT. The indications are the use of single room and the use of filtered air entering through a central or portable high-efficiency filter (HEPA), capable of removing 99.97% of  $\geq 0,3 \mu\text{m}$  in diameter particles.

For autologous HSCT, there is no specific indication other than the reference to “standard” precautions (as shown in Table 7.2) for each interaction with the patient. Protection with lab

**Table 7.2** Standard precautions of infection control (<https://www.dhs.wisconsin.gov/ic/precautions.htm>)

Standard precautions	Standard precautions are a set of infection control practices used to prevent transmission of diseases that can be acquired by contact with blood, body fluids, non-intact skin (including rashes) and mucous membranes. These measures are to be used when providing care to all individuals, whether or not they appear infectious or symptomatic
Hand hygiene	Hand hygiene refers to both washing with plain or antibacterial soap and water and to the use of alcohol gel to decontaminate hands. When hands are not visibly soiled, alcohol gel is the preferred method of hand hygiene when providing healthcare to clients
Personal protective equipment (PPE)	PPE includes items such as gloves, gowns, masks, respirators and eyewear protectors used to create barriers that protect the skin, clothing, mucous membranes and the respiratory tract from infectious agents PPE is used as a last resort when work practices and engineering controls alone cannot eliminate worker exposure The items selected for use depend on the type of interaction a public health worker will have with a client and the likely modes of disease transmission Wear gloves when touching blood, body fluids, non-intact skin, mucous membranes and contaminated items. Gloves must always be worn during activities involving vascular access, such as performing phlebotomies Wear a surgical mask and goggles or face shield if there is a reasonable chance that a splash or spray of blood or body fluids may occur to the eyes, mouth or nose Wear a gown if skin or clothing is likely to be exposed to blood or body fluids remove PPE immediately after use and wash hands. It is important to remove PPE in the proper order to prevent contamination of skin or clothing
Needle stick and sharp injury prevention	Safe handling of needles and other sharp devices is a component of standard precautions that are implemented to prevent healthcare worker exposure to blood-borne pathogens. The Needlestick Safety and Prevention Act (link is external) mandates the use of sharps with engineered safety devices when suitable devices exit
Cleaning and disinfection	Client care areas, common waiting areas and other areas where clients may have potentially contaminated surfaces or objects that are frequently touched by staff and clients (doorknobs, sinks, toilets other surfaces and items in close proximity to clients) should be cleaned routinely with EPA-registered disinfectants, following the manufacturer’s instructions for amount, dilution and contact time

(continued)

**Table 7.2** (continued)

Respiratory hygiene (cough etiquette)	<p>Clients in waiting rooms or other common areas can spread infections to others in the same area or to local public health agency staff. Measures to avoid spread of respiratory secretions should be promoted to help prevent respiratory disease transmission. Elements of respiratory hygiene and cough etiquette include:</p> <ul style="list-style-type: none"> <li>Covering the nose/mouth with a tissue when coughing or sneezing or using the crook of the elbow to contain respiratory droplets</li> <li>Using tissues to contain respiratory secretions and discarding in the nearest waste receptacle after use</li> <li>Performing hand hygiene (handwashing with non-antimicrobial soap and water, alcohol-based hand rub or antiseptic handwash) immediately after contact with respiratory secretions and contaminated objects/materials</li> <li>Asking clients with signs and symptoms of respiratory illness to wear a surgical mask whilst waiting in common areas or placing them immediately in examination rooms or areas away from others. Provide tissues and no-touch receptacles for used tissue disposal</li> <li>Spacing seating in waiting areas at least three feet apart to minimize close contact among persons in those areas</li> <li>Supplies such as tissues, wastebaskets, alcohol gel and surgical masks should be provided in waiting and other common areas in local public health agencies. Place cough etiquette signs (link is external) where the general public can see them</li> </ul>
Waste disposal	
Safe injection practices	<p>Outbreaks of hepatitis B and hepatitis C infections in US ambulatory care facilities have prompted the need to re-emphasize safe injection practices. All healthcare personnel who give injections should strictly adhere to the CDC recommendations</p>

coat, gloves and mask is not indicated in the absence of suspected or confirmed infection of patients (Tomblyn et al. 2010). The effectiveness of specific precautions in preventing infections in patients undergoing autologous HSCT has not been evaluated but must follow the standard precautions for every patient contact.

Some centres use additional protection in an effort to reduce the risk of infection, but there are insufficient data to recommend such behaviours (Tomblyn et al. 2010). Consistent with the organization of the department, it would be advisable to hospitalize the patient in a single room with attached bathroom, in order to give them greater comfort. The ventilation system should ensure at least 12 air changes per hour; a direct flow area of the room must have the way out on the opposite side with respect to that of entry. The optimum ambient air quality can be obtained without using the expensive laminar flow. The rooms, housing highly immunocompromised patients, need to be placed under positive pressure to prevent the entry into the room of airborne pathogens in the hallway or in adjacent spaces. In the rooms it is forbidden to keep fresh flowers and/or dried and potted plants (Tomblyn et al. 2010). Although it

is unlikely that exposure to plants causes invasive fungal infections in patients undergoing HSCT, it is recommended that plants and dried or fresh flowers do not enter the room during hospitalization (conditioning phase included) because of the *Aspergillus sp.*, isolated from soil of ornamental plants and flowers. In addition it was found a high proportion of gram-negative bacteria in the water of the cut flower vase (*Pseudomonas*) (Tomblyn et al. 2010).

For the patient hospitalized in a protective environment, exits from the room should be restricted just for the execution of diagnostic tests and for a short period. If a construction site is present nearby the hospital, it is indicated to use a filter mask (N95) to prevent inhalation of spores. There are no recommendations regarding use of the mask with filter in the absence of the construction work (Tomblyn et al. 2010).

### 7.3.2.2 Handwashing

The most important point in the prevention of infections in hospitalized patients, being in protective isolation, remains handwashing. Hand hygiene is a key element of the standard precautions for all types of patients (Tomblyn et al. 2010).



All staff and visitors must wash their hands before entering the patient's room in order to reduce the risk of cross infection.

Hand hygiene should be performed before touching the patient, before a clean/aseptic procedure, after body fluid exposure risk (blood, body fluids or excretions, mucous membranes, non-intact skin or dressing), after touching a patient and after touching patient's surrounding (WHO "My five moments for hand hygiene" 2009). It is also advisable not to wear false nails or extensions during direct contact with the patient and maintain the natural nails short. Even if there is still an unsolved problem, many studies have shown that the skin below the rings is more colonized than that without; rings and dirty jewellery can host microorganisms.

Furthermore hand hygiene cannot be done in a perfect way if you wear bulky rings. The experts' recommendation is strongly discouraging the use of rings during assistance (WHO guidelines 2009).

Nurses have an important role in educating the family, patient and visitors to an effective hand-washing (as shown in Fig. 7.2) and to provide all relevant information to reduce the risk of contracting infections.

Some transplant centres display cartoons near the sinks at the entrance of the hospital room, where they describe the handwashing procedure step by step and how it needs to be performed (WHO guidelines 2009).

### 7.3.2.3 Environmental Cleaning

The environmental cleaning plays an important role in the prevention of nosocomial infections, particularly in patients with haematological cancers and diseases undergoing transplantation of haematopoietic stem cells. The cleaning staff must be well prepared and needs to be informed and trained, with particular attention to the problems of immunosuppressed patients. It is preferable to assign stable staff to the division, in order to ensure a continuity of service. The hospital room must be cleaned more than once a day, with special dust control, which must be removed by damp.

The light fixtures and outdoor grills of ventilation vents and all horizontal surfaces should be cleaned with pre-moistened disposable cloths with a disinfectant FDA and Environmental Protection Agency approved. The design and selection of the furniture of a transplant program should be focused in creating and maintaining an environment: free of dust and the floors and finishes should be brushable, waterproof, easy to disinfect and antistatic (Tomblyn et al. 2010).

To verify that hospital rooms are at effective reduced environmental load, periodic monitoring of the environments must be guaranteed.

### 7.3.2.4 Management of Linen

All linen should be changed daily and pillows and mattresses should have protective coatings. During the hospital stay for the patient undergoing HSCT, it is enough to wash clothes and linens at high temperatures in a washing machine (Tomblyn et al. 2010).

### 7.3.2.5 Access to Low Environmental Loading Department

Each centre has its own policy on the number of visitors allowed and the frequency of visits. However, all centres are in agreement in pointing out that they cannot come into contact with the patient when cooled or suffering from other infections, rashes, eyes' infections, nausea and/or vomiting or recent exposure to exanthematous diseases such as chickenpox or measles (Tomblyn et al. 2010).

### 7.3.2.6 Personal Hygiene

Personal hygiene is a key aspect for the patient undergoing HSCT. It represents the most effective way to reduce infections caused by endogenous organisms. The interview with the patient and his family is a very important moment and must be programmed before HSCT. The nurse must be able to define when, how and which are the major needs for the patient. It is important to explain the importance of personal hygiene and its role in preventing infections. Several centres are supported by audio-visual media and information booklets to reinforce the provided infor-

**Table 7.3** Recommendations for personal hygiene, Carreras 2006, CDC 2007

When	How	What
Take a shower every day using mild liquid soap in dispensers Thorough intimate hygiene must be performed after each evacuation, especially in case of diarrhoea	Patients are advised to gently rub the skin and dry it accurately especially at the level of the armpits and groin, where the body microorganisms can proliferate if they find a moist environment	Do not use sponges or knobs (only if disposable) For teeth cleaning, it is recommended to use synthetic brushes with soft bristles
Towels need to be replaced every day	The material for the toilet must be new and in closed packs For dry and peeling skin, it may be useful to apply moisturizer on the body	During the hospitalization period, the following products should not be used: Soaps, perfumes, deodorants and aftershave containing alcohol, cotton sticks for ear cleaning (patient should clean the external pinna with soap and water only), lipsticks
Patients should be advised to cut the nails of the hands and feet before admission, as, during aplasia, they are more susceptible to infections and bleeding. Also keeping short nails facilitates good hand hygiene. Enamel or false nails should be removed	Thorough personal hygiene will allow the patient to evaluate daily the state of his/her skin and promptly notify the physician and nursing staff of any changes such as erythema, desquamation, haematomas	For men an electric razor is recommended; razor blades and scissors are forbidden due to their increased bleeding risk

mation. The nurse, giving precise indications, must be able to explain with thoughtfulness and sensitivity how incident personal hygiene is on the individual's intimate and personal sphere.

Table 7.3 shows recommendations of panel expert and of CDC (Carreras 2006; CDC 2007).

### 7.3.2.7 Oral and Gastrointestinal Mucositis

Oral and gastrointestinal mucositis caused by high-dose chemotherapy and/or radiation continues to be an important clinical problem.

Incidence of WHO grade 3 or 4 oral mucositis can be as high as 75% in patients undergoing HSCT, depending on the intensity of the conditioning regimen used and the prophylactic use of methotrexate to prevent graft versus host disease. Management of oral and gastrointestinal mucositis is one of the main challenges during the period of aplasia, with risk of sepsis related to degree of mucosal barrier breakdown and depth of marrow suppression (Peterson et al. 2015).

Oral care is an important aspect in the control of infections in transplant patients (Quinn et al. 2008). In order to improve oral care in patients undergoing chemotherapy/HSCT, it is useful to

build a multi-professional team including medical, dental and nursing, nutrition, physical therapy and counselling providers. Training and continuing education programs will ensure that the knowledge will spread to an extensive community of healthcare providers, which can make a positive impact on patients' healthcare (Sharon Elad et al. 2014). All treatment strategies aimed to improve mouth care are dependent on four key principles: accurate assessment of the oral cavity, individualized plan of care, timely preventive measures and correct treatment initiation (Quinn et al. 2008).

### 7.3.2.8 Central Venous Devices

The use of central venous catheters (CVC) is linked to the need to infuse complex therapies for a long time, having available a valid and secure access. Generally the choice of the most appropriate catheter is shared by a multidisciplinary team taking into account the patient's compliance and the therapeutic process which he/she will face. The goals of care, for the CVC management, must aim to ensure prevention of infections and maintenance of the patency. This is feasible if the device is managed by competent healthcare

workers and if the process is based on continuous improvement of performance (RCN 2010; INS 2011; CDC 2011).

The most important recommendations concerning the prevention of CVC-related bloodstream infections are:

- Hand hygiene and maximum barrier precaution.
- Appropriate choice of insertion site and catheter material.
- Plan an echo-guided insertion when possible, for both centrally and peripherally inserted central lines.
- Use of 2% chlorhexidine for skin antiseptics for continuous and discontinuous antiseptics of the exit site.
- Use of sutureless devices (StatLock) for fixing the catheter, wherever possible.
- Use of appropriate dressing.
- Removing the venous catheter when no longer necessary.
- Assessment → inspection (visual and palpation) of the exit site should be performed daily.
- Proper handling of parenteral solutions.
- Proper management of infusive lines.
- Education of the patients on the need to inform the nurse if changes at the level of the CVC are noticed.

### 7.3.2.9 Low Bacterial Diet

The low bacterial diet (LBD), also known as neutropenic diet or low microbial diet, is a diet aimed at reducing the ingestion of bacterial and fungal contaminants excluding it from foods such as fresh fruits and vegetables, raw eggs, raw meat and fish, unpasteurized dairy products, ice and yogurt that will be excluded from any type of diet or raw food containing probiotics. The consumption of fruits with thick skin, if peeled and washed, in accordance with good hygienic practices has low probability to be contaminated (Todd et al. 1999).

For decades, the concept of a neutropenic diet or diet containing food with low levels of bacteria (LBD) has implied a strict limitation of foods allowed for consumption, as a presumptive means of reducing the risk of infection in cancer patients.

The rationale was to limit the introduction of potentially harmful bacteria into the gastrointestinal tract by the restriction of certain foods that might harbour those organisms (Fox and Freifeld 2012).

However, there is no clear evidence that the use of a low bacterial diet (LBD) actually decreases the number of infections. It is clear from numerous surveys of current practice that the majority of hospitals place neutropenic patients on a restricted diet (Mank et al. 2008).

Many studies have limitations and conclude that there are no differences in terms of infectious episodes and survival when comparing a normal to a neutropenic diet (Van Tiel et al. 2007; Gardner et al. 2008; Trifilio et al. 2012).

In a randomized study of 153 patients with acute myeloid leukaemia undergoing induction therapy, no difference in terms of infectious episodes and survival was reported between patients prescribed with a LBD and those put on a normal diet. The conclusion was that the LBD has not prevented major infections or death (Gardner et al. 2008).

Notably, a study on the use of a non-neutropenic diet showed an increase in satisfaction for the meal from a 42.9% to a maximum of 75%. The feedback of the team was positive (Tarr and Allen 2013).

Patients who are prescribed a neutropenic diet may have a poor nutritional status and often need counselling and nutritional support (Murray and Pindoria 2009).

A study conducted in Brazil shows how dietary restrictions can lead to a deficiency of vitamin C (Galati et al. 2013).

A retrospective study in 2012 of 726 patients undergoing HCT showed that the rate of acute grade II–IV GI GvHD was higher in the neutropenic diet (ND) group, although the difference between the groups did not reach statistical significance. An association between GvHD and ND has not been reported previously. Almost one-half of the patients in the ND group who subsequently developed GvHD had a previous *C. difficile* infection, and non-relapse mortality was very high in this group. Nutritional support guidelines for patients with GI GvHD, which are

also on common sense, include a low microbial diet (Trifilio et al. 2012).

The study results are in line with preclinical experiments conducted on mice where the presence of a mixed intestinal flora (e.g. *Lactobacillus rhamnosus* GG) would be able to decrease the proliferation of the most virulent bacterial species and of the system that immunomodulate what is in their intestine (Docampo et al. 2015).

A more liberal diet could bring benefits in terms of palatability, cholesterol reducing, use of parenteral nutrition and an improvement in quality of life.

The LBD, usually poorer from a nutritional point of view and less attractive compared to a normal diet, may be an unnecessary burden on patients who already have difficulties with eating. The studies reviewed do not support significant results on the effectiveness or ineffectiveness of the LBD, and many useful results still do not encourage the use of LBD.

### 7.3.2.10 Psychological Support

Protective isolation can have significant psychological effects on the patient. Patients are encouraged to personalize their rooms with family pictures. Some may have computer access and are able to maintain communication with family members and friends in this way. However, the length of time spent in isolation does lead to many patients having feelings of anxiety, fear for the future, concerns about the family and worry about whether engraftment will occur (Brown 2010). The need for regular monitoring of blood is a constant reminder of the patient's situation. Loss of body image as a result of weight loss or scars, sexuality issues and concerns about employment may preoccupy a patient (Gruber et al. 2003). Nurses should be aware of the potential effect that both, the transplant and the isolation, can have on patients. Spending time with the patient and offering him or her an opportunity to talk about concerns can be helpful. Providing information, education and advice may reduce the negative psychological effects of isolation (Brown 2010). However it should be considered for selected categories of patients the possibility

of an early discharge after transplantation to provide a more comfortable environment for patients and their family.

Increasing implementation of ambulatory treatment has the potential to decrease patient exposure to multidrug-resistant organisms in the hospital and to provide patients with the possibility to spend the neutropenic phase at home and to facilitate more admissions to the haematology ward (Mank et al. 2015).

### 7.3.2.11 Health Education at Discharge

Discharging is much desired by the patient, but it is the "most difficult time" in the course of treatment. Patient and family will have to face everyday life far from a safe hospital environment. In fact, in the hospital, the continued support of the multidisciplinary team makes them feel protected; in hospital, doctors, nurses and other professionals are always present to clarify doubts, give advice and also try to reduce anxiety and fears. Being aware of the risks of infection means that going home can be stressful (Brown 2010).

Nurses should spend time with the patient, identify and explore any concerns before discharge. In some cases, the patient may become overdependent on nursing staff, and this may need to be addressed. Allogeneic transplant patients have a high risk of readmission as a result of infection, and it is critical that discharge planning provides patients with the understanding and information on how best to minimize the risk of infection (Grant et al. 2005).

A checklist of information, which patients should receive on discharge, is provided in Table 7.4.

Patients should be advised to continue their oral care routine. It is very important.

reiterating to patients when handwashing should be carried out, particularly:

- Before eating
- Before and after meal preparation
- Before and after handling pets
- After sneezing or coughing
- Before taking oral tablets

**Table 7.4** Discharge checklist for patients following allogeneic stem cell transplantation (Brown 2010 modified)

Discharge checklist for patients following allogeneic stem cell transplantation
Patients should avoid contact with people who have respiratory illnesses
Care should be taken when around schoolchildren, as there is a risk of exposure to sick children
Patients should be advised to stop smoking and avoid smoky areas for the first few months following transplantation
Patients should avoid communal swimming pools in the early weeks of discharge
It is advisable to avoid house cleaning, which will disturb dust
When considering travel, patients should seek advice regarding travel vaccinations, particularly if they would need live vaccines
It is essential that patients continue to take their medication and attend all follow-up outpatient appointments

- After touching soiled linen
- After going outdoors

(Brown 2010).

The patient will require a great deal of information before and at discharge, and this would include information on follow-up treatment.

## 7.4 Respiratory Infections

As recent research suggests, pulmonary complications are a leading cause of post-transplant complications and death in HSCT recipients (Alsharif 2009; Roychowdhury et al. 2005). Post-transplant pulmonary complications are classified as either infectious or noninfectious. The rate of complications is significantly lower for autologous transplant recipients than for allogeneic transplant recipients. This is because of the absent risk of GvHD in autologous transplants, the infrequent use of immunosuppressive medications such as ciclosporin or tacrolimus and the absence of radiation therapy in the preconditioning regimen (Ho et al. 2001; Kotloff et al. 2004). Methods that healthcare professionals can use to

improve patient outcomes in autologous and allogeneic recipients include raising clinical awareness, improving diagnostics, shortening time to medical intervention and continuing multidisciplinary research (Stephens et al. 2013). The spectrum of pulmonary complications for transplant recipients will continue to change, due in part to rapid advances in supportive care, the increasing age of transplant recipients, new antiviral and antifungal agents and an increasing use of prophylactic broad-spectrum antibiotics post-transplant (Sharma et al. 2005). The real key, however, to decreasing morbidity and mortality in adult and paediatric HSCT patient populations remains in effective diagnostic techniques (Stephens et al. 2013).

Pulmonary infections are the largest cause of post-HSCT infective morbidity and have been reported in most recipients, carrying a mortality rate of 20% (Cooke et al. 2008; Zuccotti et al. 2005). The principal cause of infection is the severe immunocompromised status of the patients from the disease process (malignant or non-malignant), conditioning regimens (non-myeloablative and myeloablative) and immunosuppressive prophylaxis to prevent and treat GvHD. A CT study by Escuissato et al. (2005) found that viral infections (51%) were the most common in post-transplant recipients, followed by bacterial infections (23%), fungal infection (19%) and protozoal infections (less than 1%). In 5% of the cases examined, patients had two or more infectious agents concurrently.

### 7.4.1 Typical Onset of Pulmonary Complications Following Stem Cell Transplantation

Table 7.5.

### 7.4.2 Diagnostics

Diagnostic techniques for pulmonary disease in HSCT patients are similar to that for non-

**Table 7.5** Typical onset of pulmonary complications following stem cell transplantation divided into three stages based on information from Antin and Raley (2009) Camus and Costabel (2005), Coomes et al. (2010), Polovich et al. (2009), and Soubani and Pandya (2010)

<i>Day 0 to day 30</i>	
Infections related to conditioning regimen and neutropenia	<ul style="list-style-type: none"> <li>Pulmonary oedema</li> <li>Pleural effusion</li> <li>Transfusion-related acute lung injury</li> <li>Idiopathic pneumonia syndrome</li> <li>Engraftment syndrome</li> <li>Diffuse alveolar haemorrhage</li> <li>Aspergillosis</li> <li>Candidaemia (<i>Candida</i> sepsis) and candidiasis (general <i>Candida</i> infections)</li> <li>Respiratory viruses – Respiratory syncytial virus, parainfluenza, influenza</li> <li>Bacteraemias of gastrointestinal origin</li> <li>Infections of central venous catheter origin</li> <li>Acute respiratory distress syndrome (ARDS)</li> <li>Chemotherapy-associated pulmonary toxicity</li> </ul>
<i>Day 31 to day 100</i>	
Classic opportunistic infections	<ul style="list-style-type: none"> <li>Pulmonary veno-occlusive disease (due to hepatic sinusoidal obstructive Syndrome)</li> <li>Diffuse alveolar haemorrhage</li> <li>Cytomegalovirus</li> <li>Aspergillosis</li> <li><i>Pneumocystis carinii</i> pneumonia</li> <li>Respiratory viruses – Respiratory syncytial virus, parainfluenza, influenza</li> <li>Toxoplasmosis</li> <li>ARDS</li> <li>Idiopathic pneumonia syndrome</li> <li>Chemotherapy-associated pulmonary toxicity</li> </ul>
<i>Greater than day 100</i>	
Infections from encapsulated organisms	<ul style="list-style-type: none"> <li>Aspergillosis</li> <li>Respiratory viruses – Respiratory syncytial virus, parainfluenza, influenza</li> <li>Varicella zoster virus</li> <li>Cytomegalovirus</li> <li><i>Pneumocystis carinii</i> pneumonia</li> <li>Post-transplant lymphoproliferative disorder</li> <li>Pneumonia</li> <li>ARDS</li> <li>Bronchiolitis obliterans</li> <li>Bronchiolitis obliterans organizing pneumonia</li> <li>Chemotherapy-associated pulmonary toxicity</li> </ul>

transplant patients. Chest radiograph (X-ray) and thoracic computed tomography (CT) scan remain the most popular and less invasive options. CT scans are particularly useful when compared with two-dimensional X-rays because they can expose acute and chronic changes in the lung parenchyma. Respiratory CT scans involve taking pictures of cross-sections of lung tissue using high

special-frequency reconstruction during inhalation and exhalation (Stephens et al. 2013).

Changes such as nodules, “white out” and a “glassy” appearance signal the physician and radiology staff to consider additional diagnostics (Truong et al. 2010). This could include collecting sputum samples, bronchoscopy with or without bronchoalveolar lavage (BAL), open lung

biopsy and needle biopsy (Kaplan et al. 2011; Truong et al. 2010).

Sputum samples can be collected by nurses, physicians or respiratory therapists according to transplant program protocols. Respiratory virus detection is highly dependent on the type of sample collected, the time of collection after the onset of clinical symptoms, the age of the patient and the transport and storage of the sample prior to testing. Several different upper respiratory tract specimens are applicable for testing, including nasopharyngeal (NP) washes, NP aspirates and NP swabs placed in virus transport media (Specter 2009; Storch 2000). Expectations in the early morning or after a respiratory procedure can be the easiest for the patient to produce because of the natural accumulation of secretions at these times. About 15 ml of sputum is usually required for adequate laboratory analysis, and a recent study suggested that the sputum must reach the laboratory within a few hours from expectoration (Murray et al. 2010). Sputum can also be collected during a bronchoscopy. In some cases, bronchoalveolar lavage (BAL) will be performed during the bronchoscopy. BAL involves the flushing of fluid (usually a sterile normal saline solution) into a localized area of the lower respiratory tract and then immediately suctioning the fluid up the bronchoscope and into a sterile specimen container. BAL allows for the detection and characterization of several respiratory pathogens, including viral, fungal and bacterial agents, and is considered a major diagnostic mechanism for *Pneumocystis carinii* (now called *Pneumocystis jirovecii*) pneumonia (PCP) (Forslöw et al. 2010). In patients with focal pulmonary lesions, aspergillosis or pulmonary GvHD, fine-needle aspiration biopsy is considered the first-line diagnostic method (Gupta et al. 2010).

### 7.4.3 Bacterial Infections

These most commonly occur in the first month but can occur at any time. Both gram-negative and gram-positive organisms can cause pneumonia, the most common being *Escherichia coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Acinetobacter*,

*Staphylococcus aureus*, coagulase-negative *Staphylococcus*, *Streptococcus pneumoniae*, *Streptococcus viridans* and *Enterococcus*. One also needs to recognize the risk of *Mycoplasma* and Chlamydia infections, although the common use of fluoroquinolones will empirically treat these organisms. Other causes of late pneumonia that should not be missed include *Nocardia*, *Listeria* and *Actinomyces*.

### 7.4.4 Viral Causes of Pneumonia

These include CMV, herpes simplex virus (HSV), varicella zoster virus (VZV), adenovirus, respiratory syncytial virus (RSV), influenza, parainfluenza type III, herpesvirus-6 (HHV6), metapneumovirus and a variety of other respiratory pathogens. Non-CMV viral infections may occur earlier than 30 days or later in the transplant course. CMV typically occurs after 30 days. Early detection of CMV and advances in treatment have reduced disease and mortality associated with CMV disease. VZV can lead to pneumonia with or without classic vesicular rash. HSV/VZV prophylaxis should be initiated with the conditioning regimen and continue for 1 year or until the patient is off all immunosuppressant agents and CD4 numbers have been restored. Community-acquired viral infections can be lethal, especially parainfluenza type III. Since, with the exception of influenza, there is no effective therapy, the best approach is prevention through isolation.

#### Diagnosis of Viral Pathogens

Diagnosis is based on fever, cough, signs and symptoms of URI, nasal washing, viral swabs or PCR.

### 7.4.5 Fungal Pulmonary Infections

Invasive fungal diseases are a major obstacle to patients after transplant and are a major cause of pulmonary-related mortality (Ji et al. 2011). *Aspergillus* is the most common and most virulent fungal cause of pneumonia following HSCT

(Blaes et al. 2009; Wilson et al. 2009). Other fungal respiratory infections in post-HSCT patients, particularly those receiving myeloablative conditioning, include *Malassezia*, *Zygomycetes* and *Candida* species (Wilson et al. 2009). Over the past decade, several new antifungal medications have demonstrated increased success, showing improved remission rates and thereby decreasing morbidity.

### Diagnosis

- Fever, pleuritic chest discomfort, dyspnoea.
- Imaging shows nodules or cavitating infiltrates.
- The classic “halo sign” may be seen on chest CT, but imaging may not be helpful.
- A BAL may be useful.
- Galactomannan and beta-glucan testing may be helpful but are not always informative.

#### *Pneumocystis jirovecii* Pneumonia

Risk of *Pneumocystis jirovecii* pneumonia (PCP) starts at around day +30.

Effectively administered prophylaxis eliminates PCP.

### Diagnosis

- Fever, cough,  $\pm$  hypoxemia.
- Positive BAL. CXR – bilateral ground-glass infiltrates.
- Beta-glucan is typically detectable.
- A history of noncompliance with prophylaxis medication should be elicited.

Typically involves the brain, heart and lung.

Biopsy sample has Giemsa stain to confirm diagnosis.

## 7.4.6 Mycobacteria

Testing with purified protein derivative (PPD) is often not helpful after allogeneic stem cell transplantation because of depressed delayed-type hypersensitivity reactions. Therefore a skin reaction with PPD will likely not occur.

### Diagnosis

Cultured sputum sample/BAL various indirect assays such as Quantiferon gold are helpful.

## 7.4.7 Nursing Implications

All patients undergoing HSCT are at risk for pulmonary complications. Bedside nurses are the most likely to observe subtle changes in the patient’s condition, and for this reason it is critical that nursing staff working with the HSCT population be highly trained in oncology and critical care interventions. Prompt reporting of symptoms can ensure proper and timely medical intervention and facilitate improved patient outcomes. This has been found particularly true in identifying GvHD, with clinical nurses at the forefront of identifying and reporting suspicious symptoms to the healthcare team (Mattson 2007). Nurses take a central role in patient and family education regarding the course of treatment, complications and other key pieces of the HSCT process, including caring for a central line (Stephens et al. 2013). By educating patients on what to expect after transplant with regard to troubling symptoms, nurses ensure patient participation in identifying developing complications early and improving HSCT outcomes. A thorough assessment can assist the nursing staff in detecting changes indicative of developing complications. Vital signs, including the rate and quality of respirations, and oximetry should be performed per program protocols, usually every 4 h and more frequently for patients at risk for pulmonary insufficiency. Taking the patient’s temperature every 4 h or as necessary is another critical respiratory intervention, as most post-HSCT complications are infectious in nature (Stephens et al. 2013). Nurses are crucial in assessing patients for symptoms of bacterial infection and should perform routine laboratory tests as necessary. Regarding pulmonary infections, nurses should closely monitor patients for symptoms of progressing respiratory disease, such as decreased auscultation of air sounds in the lungs, increasing fevers and appearance of a productive cough with coloured sputum. Antibiotics should start as soon as possible in these patients. A nursing study of neutropenic patients in the early HSCT phase showed that commencement of antibiotics within 1 h of the onset of infectious symptoms can significantly reduce infectious complications, including sepsis



(Hyman 2005). The recent addition of monoclonal antibodies (MoAbs) to GvHD prophylaxis protocols has been met with mixed results. For example, a study using infliximab did not lead to lower rates of GvHD but did suggest higher rates of bacterial or fungal pulmonary infection in patients who participated in the study (Hamadani et al. 2008). It is important that patients in the post-transplant period are encouraged to pace their activity with their level of ability. Coughing and deep breathing exercises accompanying the regular use of an incentive spirometer constitute critical ways to open deep alveolar tissue and encourage pulmonary toileting on patients prone to fatigue and malaise and whose blood counts are very low (Stephens et al. 2013).

## 7.5 BMT Settings, Infections and Infection Control for Paediatric Patients

### Be Aware

In Primary Immunodeficiency Patients.

Immunization with live viral or bacterial vaccines is a known hazard to patients with serious immunodeficiencies (Shearer et al. 2014).

They have no protective immune response and therefore are at risk of developing the disease itself (Marciano et al. 2014).

Avoid immunization with live *Bacillus Calmette-Guerin* (BCG), rotavirus vaccine or live poliovirus since they can cause persistent and disseminated infection (Shearer et al. 2014; Rivers and Gaspar 2015).

Patients with SCID that received BCG vaccine prior to diagnosis will need to start antituberculosis treatment (Rivers and Gaspar 2015).

Patients who received BCG vaccine prior to diagnosis will need to start antituberculosis treatment.

### BCGitis

If BCG vaccine is given to infants with severe primary immune deficiencies, they will develop BCGitis. It is characterized by local erythema and purulent regional lymph node enlargement.

BCG-osis.

The more severe form is disseminated infection that could be fatal. It involves distant lymph nodes, bone, liver and spleen.

Shrot et al. (2016).

## References

- Almyroudis NG, Osawa R, Samonis G, Wetzler M, Wang ES, McCarthy PL, Segal BH. Discontinuation of systematic surveillance and contact precautions for *Vancomycin-Resistant Enterococcus* (VRE) and its impact on the incidence of VRE *faecium* bacteremia in patients with hematologic malignancies. *Infect Control Hosp Epidemiol.* 2016;37(4):398–403.
- Alsharif M. Time trends in fungal infections as a cause of death in hematopoietic stem cell transplant recipients: An autopsy study. *Am J Clin Pathol.* 2009;132:746–55.
- Antin JH, Raley DY. *Manual of stem cell and bone marrow transplantation.* New York, NY: Cambridge University Press; 2009.
- ASHM. Nurses and hepatitis C. Darlinghurst: ASHM; 2012. <http://www.aph.gov.au/DocumentStore.ashx?id=4799afa2-cddb-46cd-a393-f23719622ef8&subId=303939>
- Bettinger D, Schorb E, Huzly D, Panning M, Schmitt-Graeff A, Kurz P, Bertz H, Finke J, Brass V, Thimme R, Hasselblatt P. Chronic hepatitis E virus infection following allogeneic hematopoietic stem cell transplantation: an important differential diagnosis for graft versus host disease. *Ann Hematol.* 2015;94:359–60.
- Blaes A, Cavert W, Morrison V. *Malassezia*: Is it a pulmonary pathogen in the stem cell transplant population? *Transpl Infect Dis.* 2009;11:313–7.
- Boeckh M, Kim HW, Flowers MF, Meyers JD, Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation—a randomized double-blind placebo-controlled study. *Blood.* 2006;107(5):1800–5.
- Boeckh M. The challenge of respiratory virus infections in hematopoietic cell transplant recipients. *Br J Haematol.* 2008;143:455–67.
- Brown M. Nursing care of patients undergoing allogeneic stem cell transplantation. *Nurs Stand.* 2010;25(11):47–56.
- Camus P, Costabel U. Drug-induced respiratory disease in patients with hematological diseases. *Semin Respir Crit Care Med.* 2005;26:458–81.

- Carreras E. Preventing exposure to moulds. *Clin Microbiol Infect.* 2006;12(Suppl 7):77–83.
- Castro ND, Neuville S, Sarfati C, Ribaud P, Derouin F, Gluckman E, Sociè G, Molina JM. Occurrence of *Pneumocystis jirovecii* pneumonia after allogeneic stem cell transplantation: a 6-year retrospective study. *Bone Marrow Transplant.* 2005;36:879–83.
- Castro CG, Ganc AJ, Ganc RL, Petrolis MS, Hamerschlack N. Fecal microbiota transplant after hematopoietic SCT: report of a successful case. *Bone Marrow Transplant.* 2015;50:145.
- Chakrabarti S, Mautner V, Osman H, Collingham KE, Fegan CD, Klapper PE, Moss PAH, Milligan D. Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. *Blood.* 2002;100(5):1619–27.
- Chen CS, Boeckh M, Seidel K, Clark JG, Kansu E, Madtes DK, Wagner JL, Witherspoon RP, Anasetti C, Appelbaum FR, Bensinger WI, Deeg HJ, Martin PJ, Sanders JE, Storb R, Storek J, Wade J, Siadak M, Flowers MED, Sullivan KM. Incidence, risk factors, and mortality from pneumonia developing late after hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2003;32:515–22.
- Cidofovir SmPC. <http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1585>. Accessed 2017.
- Cohen J. Epstein Barr virus lymphoproliferative disease associated with acquired immunodeficiency (review). *Medicine.* 1991;70:137.
- Cohen CC, Cohen B, Shang J. Effectiveness of contact precautions against multidrug-resistant organism transmission in acute care: a systematic review of the literature. *J Hosp Inf.* 2015;90:275–84.
- Cooke KR, Jannin A, Ho V. The contribution of endothelial activation and injury to end-organ toxicity following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2008;14(Suppl. 1):23–32.
- Coomes S.M, Hubbard L.L, Moore B.B. Impaired pulmonary immunity post-bone marrow transplant. *Immunologic Research.* Advance online publication. 2010.
- Dalton HR, Saunders M, Woolson KL. Hepatitis E virus in developed countries: one of the most successful zoonotic viral diseases in human history? *J Virus Erad.* 2015;1(1):23–9.
- De Keukeleire S, Reynders M. Hepatitis E: an underdiagnosed, emerging infection in nonendemic regions. *J Clin Transl Hepatol.* 2015;3:288–91.
- Deeg J, Socie G. Malignancies after haematopoietic stem cell transplantation: many questions, some answers. *Blood.* 1998;91(6):1833–44.
- Docampo MD, Auletta JJ, Jenq RR. Emerging influence of the intestinal microbiota during allogeneic hematopoietic cell transplantation: control the gut and the body will follow. *Review ASBMT.* 2015;21(8):1360–6.
- Dougherty L, Bravery K, Gabriel J, et al. Standard for infusion therapy. 2010; Royal College of Nursing. INFUSION NURSING STANDARDS OF PRACTICE Developed by Infusion Nurses Society REVISED 2011.
- Dubberke ER, Riddle DJ. *Clostridium difficile* in solid organ transplantation recipients. *Am J Transplant.* 2009;9(4):S35–40.
- Dykewicz CA, Kaplan JE. Guidelines for preventing opportunistic infections among haematopoietic stem cell transplant recipients. *MMWR Recomm Rep.* 2000;49(RR-10):1–125.
- Elad S, Raber-Durlacher J, Michael T, Brennan, Deborah P, Saunders, Arno P, Mank, Yehuda Zadik, Barry Quinn, Joel B. Epstein, Nicole M.A. Blijlevens, Tuomas Waltimo, Jakob R. Passweg, M. Elvira P. Correa, Göran Dahllöf, Karin U. E. Garming-Legert, Richard M. Logan, Carin M. J. Potting, Michael Y. Shapira, Yoshihiko Soga, Jacqui Stringer, Monique A. Stokman, Samuel Vokurka, Elisabeth Wallhult, Noam Yarom, Siri Beier Jensen. Basic oral care for hematology–oncology patients and hematopoietic stem cell transplantation recipients: a position paper from the joint task force of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT). 2014.
- Escuissato D, Emerson G, Marchiori E, de Melo Rocha G, Inoue C, Pasquini R, Muller N. Pulmonary infections after bone marrow transplantation: High-resolution CT findings in 111 patients. *Am J Roentgenol.* 2005;185:608–15.
- Forslöw UU, Remberger M, Nordlander AA, Mattsson JJ. The clinical importance of bronchoalveolar lavage in allogeneic SCT patients with pneumonia. *Bone Marrow Transplant.* 2010;45:945–50.
- Foscarnet SmPC. <http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=174>. Accessed 2017.
- Fox N, Freifeld AG. The neutropenic diet reviewed: moving toward a safe food handling approach. *Oncology (Williston Park).* 2012;26(572–575):580, 582 passim
- Galati PC, Lataro RC, Souza VM, de Martins ECP, Chiarello PG. Microbiological profile and nutritional quality of raw foods for neutropenia patients under hospital care. *Rev Bras Hematol Hemoter.* 2013;35(2):94–8.
- Ganciclovir SmPC. <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=3497>. Accessed 2017.
- Gardner A, Mattiuzzi G, Faderl S, Borthakur G, Garcia-Manero G, Pierce S, Brandt M, Estey E. Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. *J Clin Oncol.* 2008;26:5684–8.
- Garzoni C. Multiply resistant gram-positive bacteria *Methicillin-Resistant, Vancomycin-Intermediate and Vancomycin-Resistant Staphylococcus aureus* (MRSA,

- VISA, VRSA) in solid organ transplant recipients. *Am J Transplant.* 2009;9(4):S41–9.
- Gea-Banacloch J, Masur H, Arns da Cunha C, Chiller T, Kirchoff L, Shaw P, Tomblyn M, Cordonnier C. Regionally limited or rare infections: prevention after hematopoietic cell transplantation. *Bone Marrow Transplant.* 2009;44:489–94.
- Girmentria C, Rossolini GM, Piciocchi A, Beryainia A, Pisapia G, Pastore D, Sica S, Severino A, Cudillo L, Ciceri F, Scime R, Lombardi L, Viscoli C, Rambaldi A. Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy. *Bone Marrow Transplant.* 2015;50:282–8.
- Grant M, Cooke L, Bhatia S, Forman S. Discharge and unscheduled readmissions of adult patients undergoing hematopoietic stem cell transplantation: implications for developing nursing interventions. *Oncol Nurs Forum.* 2005;32(1):E1–8.
- Gratwohl A, Brand R, Frassoni F, Rocha V, Niederwieser D, Reusser P, Einsele H, Cordonnier C. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. *Bone Marrow Transplant.* 2005;36:757–69.
- Gruber U, Fegg M, Buchmann M, Kolb HJ, Hiddemann W. The long-term psychological effects of haematopoietic stem cell transplantation. *Eur J Cancer Care.* 2003;12(3):249–56.
- Gu SL, Chen YB, Lv T, Zhang XW, Wei ZQ, Shen P, Li LJ. Risk factors, outcomes and epidemiology associated with *Clostridium difficile* infection in patients with haematological malignancies in a tertiary care hospital in China. *J Med Microbiol.* 2015;64:209–2016.
- Gupta S, Mahipal A. Fatal pulmonary toxicity after a single dose of cyclophosphamide. *Pharmacotherapy.* 2007;27:616–8.
- Hamadani M, Hofmeister CC, Jansak B, Phillips G, Elder P, Blum W, et al. Addition of infliximab to standard acute graft-versus-host disease prophylaxis following allogeneic peripheral blood cell transplantation. *Biol Blood Marrow Transplant.* 2008;14:783–9.
- Heslop H. How I treat EBV lymphoproliferation. *Blood.* 2009;114:4002–8.
- Ho V, Weller E, Lee S. Prognostic factors for early severe pulmonary complications after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2001;7:223–9.
- <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm>. Retrieved on 10 Sep 2016.
- Hyman J. Neutropenic patients—Are they receiving their antibiotics on time? *Nursing Monograph.* 2005. 15–18.
- Ihendyane N, Sparrelid E, Wretling B, Remberger M, Andersson J, Ljungman P, Ringden O, Henriques Normark B, Allen U, Low DE, Norrby-Teglund A. Viridans streptococcal septicaemia in neutropenic patients: role of proinflammatory cytokines. *Bone Marrow Transplant.* 2004;33(1):79–95.
- Ji Y, Xu LP, Liu DH, Chen YH, Han W, Zhang XH, Huang XJ. Positive results of serum galactomannan assays and pulmonary computed tomography predict the higher response rate of empirical antifungal therapy in patients undergoing allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2011;17:759–64.
- Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E virus infection. *Clin Microbiol Rev.* 2014;1(27):116–38.
- Kamboj M, Sepkowitz K. Healthcare-associated infections in transplant recipients. In: Jarvis WR, editor. *Bennett & Brachman's hospital infections.* 6th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2014. p. 707–8.
- Kamboj M, Xiao K, Kaltsas A, Huang YT, Sun J, Chung D, Wu S, Sheahan A, Sepkowitz K, Jakubowski AA, Papanicolaou G. *Clostridium difficile* infection after allogeneic hematopoietic stem cell transplant: strain diversity and outcomes associated with NAP-1/027. *Biol Blood Marrow Transplant.* 2014;20(10):1626–33.
- Kanda Y, Mineishi S, Saito T, Saito A, Yamada S, Ohnishi M, Chizuka A, Niiya H, Suenaga K, Nakai K, Takeuchi T, Makimoto A, Tanosaki R, Kami M, Tanaka Y, Fujita S, Watanabe T, Kobayashi Y, Tobinai K, Takaue Y. Long-term low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2001;28:689–92.
- Kaplan R, Bashoura L, Shannon VR, Dickey BF, Stover DE. Noninfectious lung infiltrates that may be confused with pneumonia in the cancer patient. In: Safdar A, editor. *Principles and practice of cancer infectious diseases;* 2011. p. 153–65.
- Kotloff R, Ahya V, Crawford S. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. *Am J Respir Crit Care.* 2004;170:22–48.
- Kuriyama T, Kawano N, Yamashita K, Ueda A. Successful treatment of rituximab-resistant Epstein-Barr virus-associated post-transplant lymphoproliferative disorder using R-CHOP. *J Clin Exp Haem.* 2014;54(2):149–53.
- Kyvernitakis A, Mahale P, Popat UR, Jiang Y, Horsy J, Champlin RE, Torres HA. Hepatitis C virus infection in patients undergoing hematopoietic cell transplantation in the era of direct-acting antiviral agents. *Biol Blood Marrow Transplant.* 2016;22:717–22.
- La Rosa AM, Champlin RE, Gajewski N, Giralt S, Rolston KV, Raad I, Jacobson K, Kontoyannis D, Elting L, Whimby E. Adenovirus infections in adult recipients of blood and marrow transplants. *Clin Infect Dis.* 2001;32:871–6.
- Landelle C, Pagani L, Harbarth S. Is patient isolation the single most important measure to prevent the spread of multidrug-resistant pathogens? *Virulence.* 2013;4(2):163–71.
- Landgren O, Gilbert ES, Rizzo JD, Sociè G, Banks PM, Sobocinski KA, Horowitz MM, Jaffe ES, Kingma DW, Travis LP, Flowers ME, Martin PJ, Deeg H, Curtis

- RE. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. *Blood*. 2009;113:4992–5001.
- Lau GKK, Strasser SI, McDonald GB. Hepatitis virus infections in patients with cancer. In: Wingard JR, Bowden RA, editors. *Management of Infection in oncology patients*. London: Martin Dunitz; 2003. p. 322–3.
- Lin M, Weinstein R, Hayden MK. Multidrug-resistant organisms: epidemiology and control. In: Jarvis WR, editor. *Bennett & Brachman's hospital infections*. 6th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2014. p. 198–9.
- Lindemann M, Koldehoff M, Fiedler M, Schumann A, Ottinger HD, Heinemann FM, Roggendorf M, Horn PA, Belen DW. Control of hepatitis B virus infection in hematopoietic stem cell (HSC) recipients after receiving grafts from vaccinated donors. *Bone Marrow Transplant*. 2016;51:428–31.
- Ljungman P, Wang FZ, Clark DA, Emery VC, Remberger M, Ringden O, Linde A. High levels of human herpesvirus 6 DNA in peripheral blood leucocytes are correlated to platelet engraftment and disease in allogeneic stem cell transplant patients. *Br J Haematol*. 2000;111:774–81.
- Ljungman P, Ribaud P, Eyrich M, Matthes-Martin S, Einsele H, Bleakley M, Machaczka M, Bierings M, Bosi A, Gratecos N, Cordonnier C. Cidofovir for adenovirus infections after allogeneic hematopoietic stem cell transplantation: a survey by the infectious diseases working Party of the European Group for blood and marrow transplantation. *Bone Marrow Transplant*. 2003;31:481–6.
- Locasciulli A, Montante B, Morelli E, Gulino V, Proia A, Pinazzi MB. Hepatitis B and C in hematopoietic stem cell transplant. *Med J Hemat Infect Dis*. 2009;1:3.
- Mackall C, Fry T, Gress R, Peggs K, Storek J, Toubert A. Background to hematopoietic cell transplantation, including post transplant immune recovery. *Bone Marrow Transplant*. 2009;44:457–62.
- Mank AP, Davies M, for the EBMT-NG. Examining low bacterial dietary practice: a European survey on low bacterial food. *Eur J Oncol Nurs*. 2008;12:342–8.
- Mank APM, Charlot Schoonenberg, Kim Bleeker, Susanne Heijmenberg, Koen de Heer, Marinus H. J. van Oers & Marie José Kersten. Early discharge after high dose chemotherapy is safe and feasible: a prospective evaluation of 6 years of home care. *Leukemia & Lymphoma* ISSN: 1042-8194 (Print) 1029–2403 (Online). 2015 Journal homepage: <http://www.tandfonline.com/loi/lilal20>
- Marano G, Vaglio S, Pupella S, Facco G, Bianchi M, Calizzani G, Candura F, Catalano L, Farina B, Lanzoni M, Piccinini V, Liumbro GM, Grazzini G. Hepatitis E: an old infection with new implications. *Blood Transfus*. 2015;13:6–20.
- Marciano BE, Huang CY, Joshi G, Rezaei N, Carvalho BC, Allwood Z, Ikinciogullari A, Reda SM, Gennery A, Thon V, Espinosa-Rosales F, Al-Herz W, Porras O, Shcherbina A, Szaflarska A, Kiliç Ş, Franco JL, Gómez Raccio AC, Roxo P Jr, Esteves I, Galal N, Grumach AS, Al-Tamemi S, Yildiran A, Orellana JC, Yamada M, Morio T, Liberatore D, Ohtsuka Y, Lau YL, Nishikomori R, Torres-Lozano C, Mazzucchelli JT, Vilela MM, Tavares FS, Cunha L, Pinto JA, Espinosa-Padilla SE, Hernandez-Nieto L, Elfeky RA, Ariga T, Toshio H, Dogu F, Cipe F, Formankova R, Nuñez-Nuñez ME, Bezrodnik L, Marques JG, Pereira MI, Listello V, Slatter MA, Nademi Z, Kowalczyk D, Fleisher TA, Davies G, Neven B, Rosenzweig SD. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. *J Allergy Clin Immunol*. 2014;133(4):1134–41.
- Masszi T., Mank AP. Chapter 10. Haematopoietic stem cell transplantation – Handbook EBMT supportive care page. 2012. 157–159.
- Mattson M. Graft-versus-host disease: Review and nursing implications. *Clin J Oncol Nurs*. 2007;11:325–8.
- Meijer E, Bolland GJ, Verdonck LF. Prevention of cytomegalovirus disease in recipients of allogeneic stem cell transplants. *Clin Microbiol Rev*. 2003;16:647–57.
- Murray SM, Pindoria S. Nutrition support for bone marrow transplant patients. *Cochrane Database Syst Rev*. 2009;
- Murray MP, Doherty CJ, Govan JR, Hill AT. Do processing time and storage of sputum influence quantitative bacteriology in bronchiectasis? *J Med Microbiol*. 2010;59:829–33.
- Nakasone H, Kurosawa S, Yakushijin K, Taniguchi S, Murata M, Ikegame K, Kobayashi T, Eto T, Miyamura K, Sakamaki H, Morishima Y, Nagamura T, Suzuki R, Fukuda T. Impact of hepatitis C virus infection on clinical outcome in recipients after allogeneic hematopoietic cell transplantation. *Am J Hematol*. 2013;88:477–84.
- Neemann K, Eichele DD, Smith PW, Bociek R, Akhtari M, Freifield A. Fecal microbiota transplantation for fulminant *Clostridium difficile* infection in an allogeneic stem cell transplant patient. *Transpl Infect Dis*. 2012;14(6):E161–5.
- Ogata M, Fukuda T, Teshima T. Human herpesvirus-6 encephalitis after allogeneic hematopoietic cell transplantation: what we do and do not know. *Bone Marrow Transplant*. 2015;50:1030–6.
- O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention 2011. <http://www.cdc.gov/hicpac/pdf/guidelines/bsguidelines-2011.pdf>. Retrieved 11/09/2016.
- Oliver NT. Severe hepatitis C reactivation as an early complication of hematopoietic cell transplantation. *Bone Marrow Transplant*. 2016; 1-3 published online 18 July 2016; exact reference: *Bone Marrow Transplantation* 2017;52:138–140.
- Parker A, Bowles K, Bradley AJ, Emery V, Featherstone C, Gupte G, Marcus R, Parameshwar J, Ramsay A, Newstead C On behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society. Management of post-transplant lymphoprolifera-

- itive disorder in adult solid organ transplant recipients – BCSH and BTS guidelines. *Br J Haematol.* 2010;149:693–705.
- Parody R, Martino R, Rovira M, Vazquez L, Vázquez MJ, De la Cámara R, Blazquez C, Fernández-Avilés F, Carreras E, Salavert M, Jarque I, Martín C, Martínez F, López J, Torres A, Sierra J, Sanz GF, Infectious/Non-infectious Complications Subcommittee of the Grupo Español de Trasplante Hematopoyético (GETH). Severe infections after unrelated donor allogeneic hematopoietic stem cell transplantation in adults: comparison of cord blood transplantation with peripheral blood and bone marrow transplantation. *Biol Blood Marrow Transplant.* 2006;12:734–48.
- Pattullo V. Prevention of hepatitis B reactivation in the setting of immunosuppression. *Clin Mol Hepatol.* 2016;22:219–37.
- Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J on behalf of the ESMO Guidelines Committee. Management of oral and gastrointestinal mucosal injury: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. *Ann Oncol.* 2015;26(Supplement 5):v139–51.
- Pizzo PA. The value of protective isolation in preventing nosocomial infections in high risk patients. *Am J Med.* 1981;70(3):631–7.
- Polovich M, Whitford JM, Olsen M. Chemotherapy and biotherapy guidelines and recommendations for practice. 3rd ed. Pittsburgh, PA: Oncology Nursing Society; 2009.
- Quinn B, Potting C, Stone R, Blijlevens NM, Fliedner M, Marquiles A, Sharp L. Guidance for the assessment of oral mucositis in adult chemotherapy, radiotherapy and haematopoietic stem cell transplant patients. *Eur J Cancer.* 2008;44(1):61–72.
- Rasch L, Kapp M, Einsele H, Mielke S. EBV-induced post-transplant lymphoproliferative disorders: a persisting challenge in allogeneic haematopoietic SCT. *Bone Marrow Transplant.* 2014;49:163–7.
- Rivers L, Gaspar HB. Severe combined immunodeficiency: recent developments and guidance on clinical management. *Arch Dis Child.* 2015;100:667–72.
- Robin M, Marque-Juillet S, Scieux C, Peffault de Latour R, Ferry C, Rocha V, Molina J, Bergeron A, Devergie A, Gluckman E, Ribaud P, Socié G. Disseminated adenovirus infections after allogeneic hematopoietic stem cell transplantation: incidence, risk factors and outcome. *Haematologica.* 2007;92:1254–7.
- Rovira M., Mensa J., Carreras E.. Chapter 10. Haematopoietic stem cell transplantation – Handbook EBMT, infections after HSCT. 2012, 197–200.
- Royal College of Nursing. Standards for infusion therapy. 3rd ed. 2010. <https://www.rcn.org/professional-development/publications/pub-005704>. Retrieved 15/09/2016.
- Roychowdhury M, Pambuccian S, Aslan D, Jessurun J, Rose A, Manivel J. Pulmonary complications after bone marrow transplantation: An autopsy study from a large transplantation center. *Archives of Pathology and Lab Med.* 2005;129:366–71.
- Sharma S, Nadrous H, Peters S, Tefferi A, Litzow M, Aubry M, Afessa B. Complications in adult blood and marrow transplant recipients. *Chest.* 2005;128:1385–92.
- Shearer WT, Fleischer TA, Buckley RH, Ballas Z, Ballow M, Blease M, Bonilla F, Comley M, Cunningham C, Filipovich A, Fuleihan R, Gelfand E, Hernandez-Trujillo V, Holland S, Hong R, Lederman H, Malech h MS, Notarangelo L, Ochs H, Orange J, Puck J, Routes J, Stiehm E, Sullivan K, Torgerson T, Winkelstein J. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts medical advisory Committee of the Immune Deficiency Foundation. *J Allergy Clin Immunol.* 2014;133:961–6.
- Shrot S, Barkai G, Ben-Shlush A, Soudack M. BCGitis and BCGosis in children with primary immunodeficiency — imaging characteristics. *Pediatr Radiol.* 2016;46:237. <https://doi.org/10.1007/s00247-015-3464-z>.
- Siegel JD, Rhinehart E, Jackson M, Chiarello L. Health Care Infection Control Practices Advisory Committee. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007;35(10 Suppl 2):S65-164.
- Soubani AO, Pandya CM. The spectrum of noninfectious pulmonary complications following hematopoietic stem cell transplantation. *Hematol Oncol Stem Cell Ther.* 2010;3:143–57.
- Specter S. Clinical virology manual. 4th ed; 2009.
- Steer CB, Szer J, Sasadeusz J, Matthews JP, Beresford JA, Grig A. Varicella-zoster infection after allogeneic bone marrow transplantation: incidence, risk factors and prevention with low-dose aciclovir and ganciclovir. *Bone Marrow Transplant.* 2000;25:657–64.
- Stephens Jennifer M.L. Hematopoietic stem cell transplantation. A manual for nursing practice. ONCOLOGY NURSING SOCIETY Edited by Susan A. Ezzone, MS, RN, CNP, AOCNP® Oncology Nursing Society Pittsburgh, PA; 2nd ed. 2013.
- Storch GA. Essentials of diagnostic virology. 1st ed; 2000.
- Styczynski J, Einsele H, Gil L, Ljungman P. Outcome of treatment of Epstein-Barr virus-related post-transplant lymphoproliferative disorder in haematopoietic stem cell recipients: a comprehensive review of reported cases. *Transpl Infect Dis.* 2009;11:383–92.
- Swerdlow AJ, Webber SA, Chadburn A, Ferry JA. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: World Health Organisation Press; 2008.
- Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, Kahlmeter G, Pan A, Petrosillo N, Rodriguez-Bano J, Singh N, Venditti M, Yokoe DS, Cookson B. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect.* 2014;20:1–55.
- Tarr S, Allen DH. Evidence does not support the use of a neutropenic diet. *Clinical journal oncology. Nursing.* 2013;13(6):617–8.

- Thomas CFJ, Limper AH. Pneumocystis Pneumonia. *N Engl J Med*. 2004;350:2487–98.
- Thomson KJ, Har DP, Banerjee L, Ward KN, Peggs KS, Mackinnon S. The effect of low-dose aciclovir on reactivation of varicella zoster virus after allogeneic haemopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35:1065–9.
- Todd J, Schmidt M, Christian J, Williams R. The low-bacteria diet for immunocompromised patients: reasonable prudence or clinical superstition? *Cancer Pract*. 1999;7(4):205–7.
- Tofas P, Skiada A, Angelopoulou M, Sipsas N, Pavlopoulou I, Tsaousi S, Pagoni M, Kotsopoulou M, Perlorentzou S, Antoniadou A, Pirounaki M, Skoutelis A, Daikos GL. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infection in neutropenic patients with haematological malignancies or aplastic anaemia: analysis of 50 cases. *Int J Antimicrob Agents*. 2016;47:335–9.
- Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young JH, Boeckh M. Guidelines for preventing infectious complications among Haematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15:1143–238.
- Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: A global perspective. *Biol Blood Marrow Transplant*. 2010;15:1143–238.
- Torres HA, Chong PP, Lima M, Friedman MS, Giralt S, Hammond SP, Kiel PJ, Masur H, McDonald GB, Wingard JR, Gambarin-Gelwen M. Hepatitis C virus infection among hematopoietic cell transplant donors and recipients: American Society for Blood and Marrow Transplantation Task Force Recommendations. *Biol Blood Marrow Transplant*. 2015;21:1870–82.
- Trifilio S, Helenowski I, Giel M, Gobel B, Greenberg D, Mehta J. Questioning the role of a neutropenic diet following Hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(9):1385–90.
- Trubiano JA, Worth LJ, Thursky KA, Slavin MA. The prevention and management of infections due to multidrug resistant organisms in haematology patients. *Br J Clin Pharmacol*. 2013;79(2):195–207.
- Truong MT, Sabloff BS, Ko JP. Multidetector CT of solitary pulmonary nodules. *Radiol Clin North Am*. 2010;48:141–55.
- Tzouveleakis LS, Markogiannakis A, Psychogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Re*. 2012;25(4):682–707.
- Ullmann AJ, Schmidt-Hieber M, Bertz H, Heinz WJ, Kiehl M, Kruger W, Mousset S, Neuburger S, Neumann S, Penack O, Silling G, Vehreschild JJ, Einsele H, Maschmeyer G. Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. *Ann Hematol*. 2016;95:1435–55.
- Valganciclovir SmPC. <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=9315>. Accessed 2017.
- Van Tiel F, Harbers MM, Terporten PH, van Boxtel RT, Kessels AG, Voss GB, Schouten HC. Normal hospital and low-bacterial diet in patients with cytopenia after intensive chemotherapy for hematological malignancy: a study of safety. *Ann Oncol*. 2007;18(6):1080–4.
- Weston D. *Clostridium difficile*. In: Fundamentals of infection prevention and control. Theory and practice. 2nd ed. Chichester: Wiley; 2013. p. 332–9.
- WHO guidelines on hand hygiene in health care: a summary. 2009.
- Wilson D, Drew R, Perfect J. Antifungal therapy for invasive fungal diseases in allogeneic stem cell transplant recipients: An update. *Mycopathologia*. 2009;168:313–27.
- Zaia J, Baden L, Boeckh MJ, Chakrabarti S, Einsele H, Ljungman P, McDonald GB, Hirsch H. Viral disease prevention after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2009;44:471–82.
- Zerr DM, Corey L, Kim HW, Huang M, Nguy L, Boeckh M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis*. 2005;40(7):932–40. Zuccotti G, Strasfeld L, Weinstock DM. New agents for the prevention of opportunistic infections in haematopoietic stem cell transplant recipients. *Expert Opin Pharmacother*. 2005;6:1669–79.

**Open Access** This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.

