Viral infections in hematopoietic stem cell transplantation

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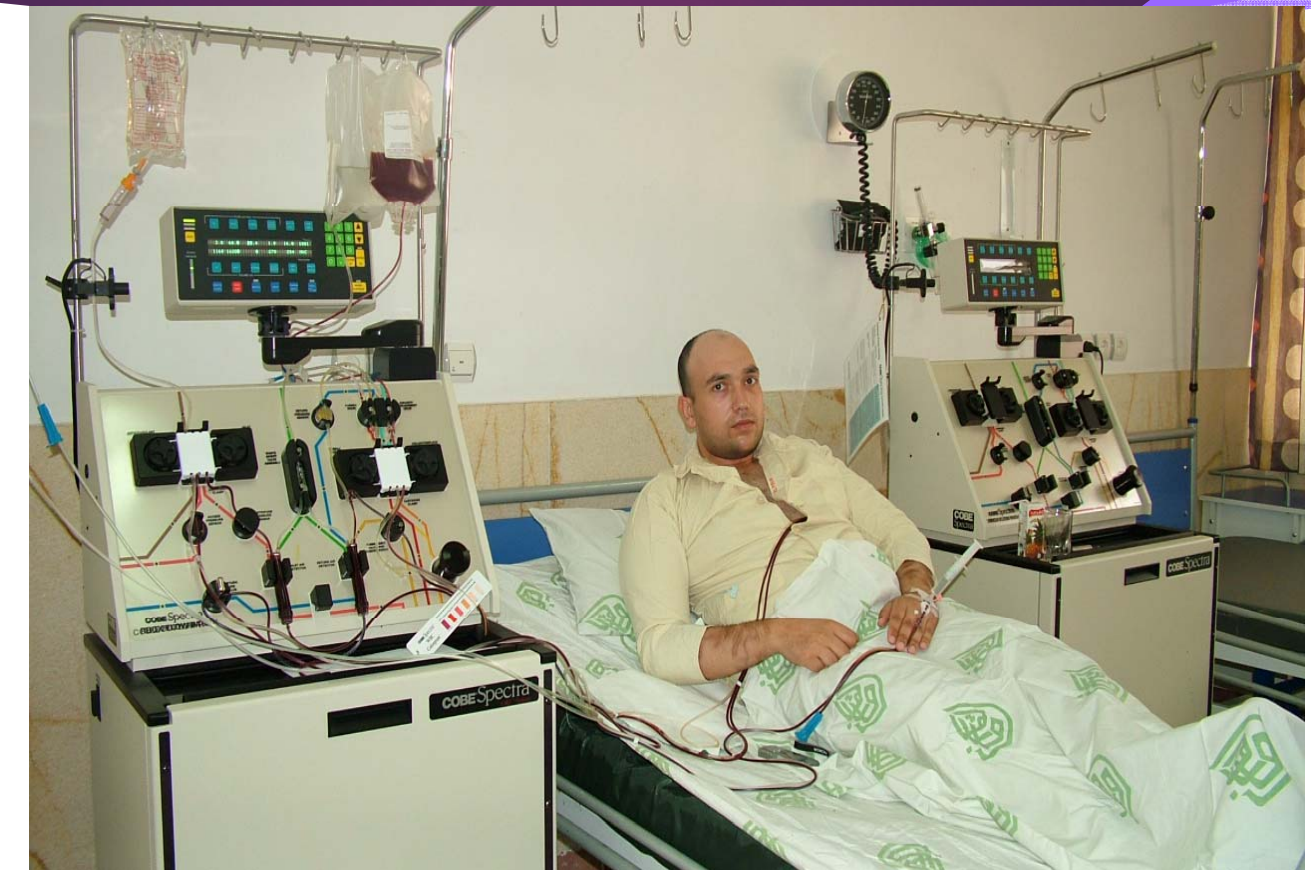
Hematopoietic stem cell transplantation

- Intravenous infusion of autologous or allogeneic stem cells
  - Collected from bone marrow, peripheral blood or umbilical cord blood
- Re-establish hematopoietic function in patients with damaged/defective bone marrow or immune systemsPotentially curative for a wide variety of disorders

Graft Sources

- Allogeneic: from another person
- Syngeneic: from an identical twin
- Autologous: from the patient

- Choice of graft is based on disease type, patient condition, donor compatibility and health


COBE Spectra

Viral infections in HSCT

- HCT recipients, especially those who have received allogeneic transplants, are at increased risk of viral infections depending upon their degree of immunosuppression and exposures.

1. Most important viruses:
2. herpes simplex virus (HSV),
3. varicella-zoster virus (VZV),
4. cytomegalovirus (CMV),
5. Epstein-Barr virus (EBV),
6. respiratory viruses (eg, influenza, parainfluenza, respiratory syncytial virus, adenovirus),
7. human herpes virus 6 (HHV-6)
8. hepatitis B, and hepatitis C.

EVALUATION BEFORE HCT

- excluding unsuitable donors
- specific infection control policies and antimicrobial prophylaxis and therapy

Pretransplant screening to evaluate the risk of infection in hematopoietic cell transplant donors and candidates

Tests and evaluations	Donor	Candidate (allogeneic or autologous)
History, review of systems, physical examination	+	+
Dental evaluation	-	+
Radiology		
Chest radiograph	-	+
Pathogen-specific testing		
CMV IgG	+	+
Hepatitis B (HBsAg, anti-HBsAg, anti-HBc) +/- viral load*	+	+
Hepatitis C (IgM, IgG)	+	+
Hepatitis C viral load¶	+	-
VZV IgG	+	+
HSV IgG	-	+
EBV (VCA IgG)	+	+ (especially allogeneic and T cell-depleted)
HIV-1, -2 antibodies	+	+
HIV-1 viral load	+	-
HTLV-1, -2 antibodies	+	+
RPR or VDRL or a *Treponema pallidum* antibody test	+	+
West Nile virus antibodies$^{\Delta}$	+/-	-
Serum *Aspergillus* galactomannan antigen$^{\diamond}$	-	+/-
Toxoplasma gondii IgG	+	+/- (allogeneic only, particularly T cell-depleted)
Screening for TB§	-	+
Staphylococcus aureus nasal culture	-	+
Vancomycin-resistant *Enterococcus* rectal culture	-	+
Tests for individuals who have resided in or traveled to endemic areas		
Strongyloides stercoralis serology¥	+	+
Coccidioides spp serology‡	-	+/- (especially allogeneic and T cell-depleted)
Histoplasma capsulatum serology‡	-	+/- (especially allogeneic and T cell-depleted)
Trypanosoma cruzi serology$^{\dagger\Delta}$	+	+/-
Malaria blood smears, rapid tests, and/or PCR**	+	+

The recommendations in this table are generally in keeping with the 2009 international guidelines for preventing infectious complications after hematopoietic cell transplantation[1]; some of our recommendations are not included in the guidelines.

CMV: cytomegalovirus; Ig: immunoglobulin; HBsAg: hepatitis B surface antigen; anti-HBsAg: antibodies to hepatitis B surface antigen; anti-HBc: antibodies to hepatitis B core

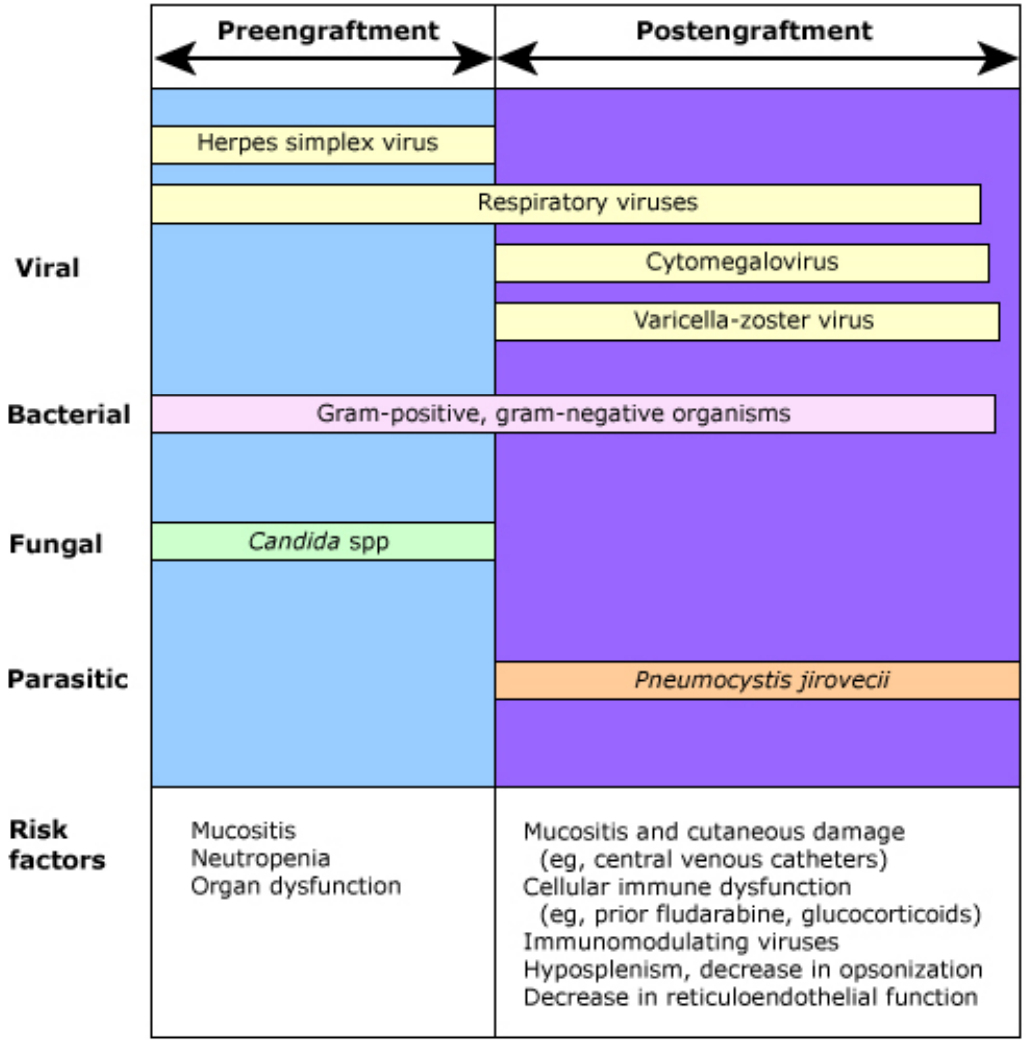
Infections time line

- ●Preengraftment – From transplantation to approximately day 30
- ●Immediate postengraftment – From engraftment to day 100
- ●Late postengraftment – After day 100

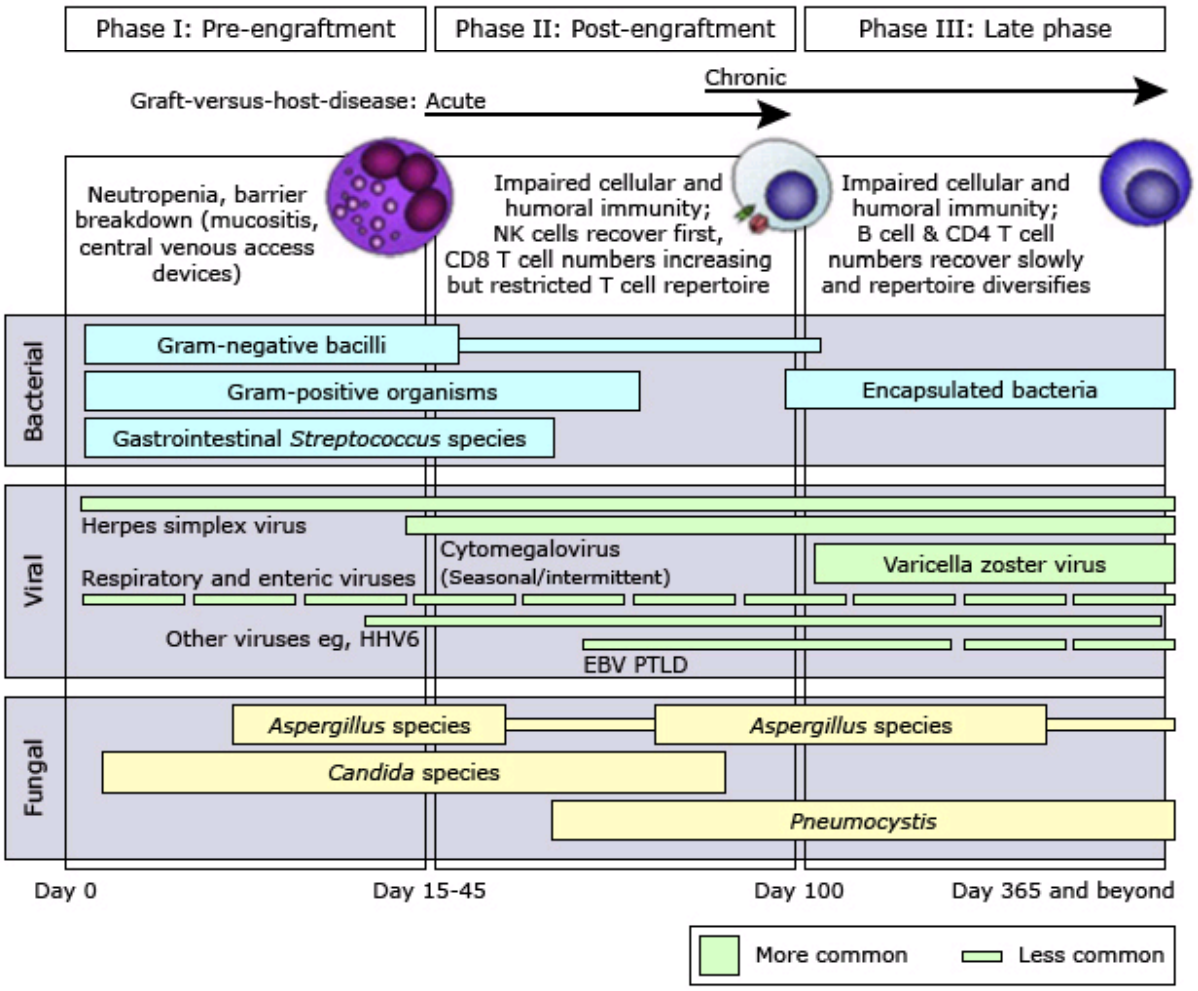
Risk factors of viral infections in HSCT

- the source of stem cells
- degree of HLA matching
- type and intensity of conditioning regimen
- Graft manipulation
- immunosuppressive therapy (especially glucocorticoids)
- graft-versus-host disease

Typical timing of infections among autologous hematopoietic cell recipients receiving antimicrobial prophylaxis



Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients



EBV: Epstein-Barr virus; HHV6: human herpesvirus 6; PTLD: posttransplant lymphoproliferative disease.

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Viral infections management

- **Primary prophylaxis** – Primary prophylaxis involves the administration of an antimicrobial drug to prevent infection in patients at increased risk.
- **Secondary prophylaxis** – Secondary prophylaxis involves the administration of prophylactic doses of an antimicrobial drug to prevent recurrent infection.
- **Preemptive therapy**
- **Treatment**

HERPES VIRUSES

- Herpes simplex virus(HSV)-1 and -2
  - Two trials showed no differences in outcomes between acyclovir and valciclovir
- varicella-zoster virus (VZV)

  at least the first year following autho and allo HCT and for a longer period in those requiring ongoing
- cytomegalovirus (CMV),
- Epstein-Barr virus (EBV)

CMV

- ✓ CMV reactivation could happen any time post HSC.CMV disease is potentially fatal
- ✓ most cases of CMV disease now occur during the late postengraftment period (between days 100 and 270)
- ✓ CMV prophylaxis is mandatory
- ✓ CMV safe blood product

- ✓ the incidence of CMV disease is low in authologus setting
- ✓ But should be monitor in whom who had prior CMV disease or received T cell suppressive drugs

CMV

- Secondary prophylaxis for Patients with a history of CMV disease during the six months preceding HCTis recommended[5 days gan before day 0 and the virabex and weekly monitoring]
- CMV Ig is not recommended as prophylaxis
- primary prophylaxis is not recommended in late phase

Cytomegalovirus [allo transplant]

- Selection of the donor with the most appropriate CMV serologic status
- CMV-seropositive patients should be monitored closely for CMV reactivation
- weekly quantitative CMV PCR at least until day +100 and preemptive therapy for patients with CMV viremia is recommended
- For preemptive therapy, IV gancyclovir or oral valgancyclovir can be given

Cytomegalovirus [allo transplant]

- high risk for CMV disease
  - T cell-depleted allograft,s
  - HLA-mismatched
  - umbilical cord blood allografts receiving alemtuzumab
  - GVHD
- Polymerase chain reaction (PCR) monitoring twice weekly for high risk patients and then weekly and every other until+100 and continue until+365[based on the patient]

Lab Test?

- CMV PCR is superior to PP65 Ag Because of the lower sensitivity of the CMV pp65 antigenemia assay when neutropenia is present
- CMV viral load was >1000 copies/mL or >5 times the baseline value, Or CMV PP65>5/50000 or any in high risk patients
-

When to start preemptive therapy

- Consider patient risk
- The PCR copy number 500-1000/mL
- The level of antigenemia

CMV disease

- Fever
- Pnumonia
- Encephalitis
- Hepatitis
- Colitis
- BM involment
- Retinitis

CMV should be isolated from involved tissue and CMV Agemia is not sufficient

Persistent or rising viremia during preemptive therapy or even in CMV disease

- Not necessarily resistance
- testing for resistance ?
- Change the dose or the medications

Epstein-Barr virus

- High risk patients
  - T cell depletion
  - ATG especially children
  - Cord blood source
- Cause a mononucleosis syndrome or PTLD
- weekly monitoring of EBV DNA by quantitative PCR in high risk patients at least for three months
- consider a level ≥100 /mL significant, but the risk for PTLD is in >1000 /mL
- Rituximab is the treatment

Human herpes virus 6

- most frequent in first month but is associated with disease <1 percent
- Encephalitis
- bone marrow suppression and delayed platelet engraftment, skin rashes, pneumonia, and hepatitis
- Prophylaxis and monitoringis not recommended

RESPIRATORY VIRUSES

- **All should be considered in patients with upper or lower respiratory symptoms**
- **By the case throat sampling or BAL should be performed**
- **Infection control is really important[contacts.hygiene,** Delay of HCT in patients with URTI symptoms **]**

RESPIRATORY VIRUSES

- **Influenza**
  - **Post transplantation vaccination usually 6 months later**
  - **Chemoprophylaxis in exposure**
  - **Treatment [oseltamivir]**
- **Respiratory syncytial virus** [preemptive aerosolized ribavirin or Ig for patients with upper tract respiratory syncytial virus infection
- **Para influenza** [treatment?]
- **Adenovirus** [treatment?]
-

HEPATITIS VIRUSES

- **Hepatitis B virus** :HBV reactivation and transmission can result in severe hepatitis following HCT
- HBsAg, HBsAb, HBcAb for donor and recipient
- Any HBcAb-positive and HBsAg-positive HCT should also undergo HBV DNA (viral load) testing
- High risk patients
  - high-dose glucocorticoids,Fludarabin ,rituximab,alemtuzumab and bortezomib
- HBV vaccination is important in HCT candidates

HBV Infected recipient

- **HBsAg-positive or DNA positive**
- HBV viral load and treatment), liver fibro scan
- Best donors is one with natural immunity (HBsAb-positive and HBcAb-positive)
- should receive an antiviral agen at least six months after autologous HCT and until six months after cessation of immunosuppression in allogeneic HCT recipients [in favor the newer agents rather than lamivudine, entecavir 0.5 mg orally once daily or tenofovir is 300 mg orally once daily

HBV Infected recipient

- **HBcAb-positive, HBsAg-negative, and HBsAb-negative** check HBV DNA,If positive entecavir or tenofovir or lamovodin[someauthors]should be given,Others should be vaccinated
- **•HBcAb-positive and HBsAb**
- monitored after HCT with monthly serum alanine transaminase , if increase testing of DNA levels.
- HBsAb levels e very three months; if redue then HBV DNA testing
- Preemptive therapy with one of the newer anti-HBV if HBV DNA detectable.
- A reasonable alternative is HBV prophylaxis withLamovidine 100 mg daily

Hepatitis C virus

- HCV antibodies and serum alanine aminotransferase,
- HCV antibody-positive
  - PCR for HCV RNA
  - If the HCV RNA is detectable thenHCV genotype liver fibro sis evaluation to decide for the HCT conditioning regimen and HCV treatment regimen
- Positive donors [pre donation treatment?]

Other viruses

- human herpes virus 7
- parvovirus B19
- Enteroviruses
- BK virus
- JC virus
- .....

THANK YOU

Differential diagnosis of specific clinical syndromes after allogeneic hematopoietic cell transplantation

Syndrome	Preengraftment, <3 weeks	Immediate postengraftment, 3 weeks to 3 months	Late postengraftment, >3 months
CNS manifestations			
Localized	Bacteria, molds, *Candida* spp, stroke, drug toxicity	Bacteria, toxoplasmosis, molds, tumor relapse, drug toxicity	Bacteria, molds, PML, tumor relapse, drug toxicity, PRES
Diffuse	Bacteria, HSV, *Candida* spp, drug toxicity	HHV-6, CMV, *Cryptococcus* spp, drug toxicity	VZV, drug toxicity
Ocular manifestations	*Candida* spp, molds	CMV, *Pneumocystis jirovecii* (formerly *P. carinii*), toxoplasmosis	VZV, CMV
Sinusitis	Bacteria, molds, respiratory viruses	Bacteria, molds, respiratory viruses	Bacteria, molds, respiratory viruses
Mucositis, mucosal ulcerations			
Infectious	HSV, *Candida* spp, agents of mucormycosis	HSV, *Candida* spp, agents of mucormycosis, CMV (esophagitis), *Aspergillus* spp (small or large intestine)	HSV, *Candida* spp, agents of mucormycosis, CMV (esophagitis), *Aspergillus* spp (small or large intestine)
Other	GVHD, drug toxicity	GVHD, drug toxicity	GVHD, drug toxicity
Pneumonia			
Localized	Bacteria, *Aspergillus* spp, other molds, pulmonary embolism, hemorrhage	Bacteria, *Aspergillus* spp, other molds, *Nocardia* spp, TB, NTM, tumor relapse	Bacteria, *Aspergillus* spp, other molds, *Nocardia* spp, VZV, EBV-associated PTLD, pulmonary calcinosis
Diffuse	Respiratory viruses, HSV, conditioning regimen, acute GVHD, pulmonary edema, radiation pneumonitis, alveolar hemorrhage, ARDS, hypersensitivity drug reaction, idiopathic interstitial pneumonitis, leukoagglutinin reaction, fluid overload, congestive heart failure	CMV, *P. jirovecii*, respiratory viruses, *Legionella* spp, *Mycoplasma pneumoniae*, *Cryptococcus* spp, adenovirus, TB, NTM, acute GVHD, radiation pneumonitis, idiopathic interstitial pneumonitis, ARDS, hypersensitivity drug reaction, pulmonary VOD, congestive heart failure	Chronic GVHD, EBV-associated lymphoma, ARDS, hypersensitivity drug reaction, alveolar proteinosis, radiation pneumonitis, idiopathic interstitial pneumonitis, COP (formerly BO or BOOP), congestive heart failure
Esophagitis	*Candida* spp, HSV, drug toxicity	CMV, drug toxicity, HSV	Drug toxicity
Diarrhea/colitis	Bacteria (*Clostridium difficile*, *C. septicum*), neutropenic enterocolitis (typhlitis), drug toxicity, bleeding, infarction, enteroviruses	Bacteria (*C. difficile*, *C. septicum*), CMV, enteroviruses, drug toxicity, acute GVHD, bleeding, infarction	CMV, bacteria (*C. difficile*, *C. septicum*), enteroviruses, drug toxicity, acute or chronic GVHD, bleeding, infarction
Hepatitis	Bacteria, HSV, chronic disseminated candidiasis, hepatic SOS (formerly veno-occlusive disease), drug toxicity, acute GVHD, conditioning regimen	HBV, HCV, HEV, EBV, HSV, CMV, HHV-6, *P. jirovecii*, chronic disseminated candidiasis (hepatosplenic candidiasis), SOS, drug toxicity, acute GVHD, conditioning regimen	HBV, HCV, HEV, EBV, VZV, drug toxicity, chronic GVHD
Hemorrhagic cystitis	Adenovirus (rarely), cyclophosphamide toxicity	BK virus, CMV, adenovirus, cyclophosphamide toxicity	BK virus
Nephritis	Bacteria	BK virus, CMV, adenovirus	BK virus, JC virus
Skin lesions	Bacteria, HSV, *Candida* spp, molds, acute GVHD, drug toxicity	Bacteria, *Candida* spp, molds, VZV, HHV-6, NTM, acute GVHD, drug toxicity	VZV, molds, chronic GVHD, drug toxicity
Bone marrow suppression	CMV, HHV-6, graft failure, drug toxicity, acute GVHD	CMV, HHV-6, graft failure, drug toxicity, acute GVHD	Parvovirus, CMV, HHV-6, graft failure, drug toxicity, chronic GVHD
Bloodstream infection	Bacteria, *Candida* spp	Bacteria (especially coagulase-negative staphylococci), *Candida* spp	*Streptococcus pneumoniae*, *Neisseria meningitidis*
Shock (including septic shock)	Bacteria (eg, alpha-hemolytic streptococci, *Pseudomonas aeruginosa*), anaphylaxis, adrenal insufficiency, cardiovascular complications	Same as for the preengraftment period	Same as for the preengraftment period, *Streptococcus pneumoniae*, *Neisseria meningitidis*
Fever without localizing signs	Bacterial sepsis, HSV, respiratory viruses, molds, chronic disseminated candidiasis, tumor fever, drug fever, adrenal insufficiency, acute GVHD, CVL-associated infection	Bacterial sepsis, sinusitis, CMV, EBV, HHV-6, respiratory viruses, molds, chronic disseminated candidiasis, tumor fever, drug fever, acute GVHD, CVL-associated infection	Bacterial sepsis, sinusitis, CMV, EBV, HHV-6, respiratory viruses, molds, chronic disseminated candidiasis, tumor fever, drug fever, chronic GVHD, pulmonary, cardiac, CVL-associated infection

CNS: central nervous system; PML: progressive multifocal leukoencephalopathy; PRES: posterior reversible encephalopathy syndrome; HSV: herpes simplex virus; HHV-6: human herpes virus 6; VZV: varicella-zoster virus; CMV: cytomegalovirus; GVHD: graft-versus-host disease; TB: tuberculosis; NTM: nontuberculous mycobacteria; EBV: Epstein-Barr virus; PTLD: post-transplant lymphoproliferative disease; ARDS: acute respiratory distress syndrome; VOD: veno-occlusive disease; COP: cryptogenic organizing pneumonia; BO: bronchiolitis obliterans; BOOP: bronchiolitis obliterans with organizing pneumonia; SOS: sinusoidal obstruction syndrome; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus; CVL: central venous line.