



IDWP

Definitions of Infectious Diseases and Complications after Stem Cell Transplant

A proposal from the Infectious Diseases Working Party of the EBMT

November 1st, 2001. Version n° 1.

Catherine Cordonnier, Dan Engelhard, Per Ljungman, Adrian Dekker, J. P. Donnelly, Hermann Einsele, Ernst Holler, Hartmut Link, Anna Locasciulli, Rodrigo Martino, Fritz Offner, Pierre Reusser, Montserrat Rovira, Andrew Ullman, Kate Ward

on behalf of the Infectious Diseases Working Party of the EBMT

In the past, some confusion and variability in reporting has been noted with significant differences in incidences of infection among centres which may not be accurate. The growing knowledge of infectious complications after stem cell transplant makes it important that investigators agree on common definitions in the reporting of data, to insure that series are comparable.

This proposal aims to provide standard definitions for infectious complications occurring after stem cell transplantation within the EBMT. This should be useful for two purposes:

- **to make the data given to the EBMT Registry, more precise and common to all the centres.** This should improve data management, insure the quality of the data in the EBMT centres and facilitate prospective and retrospective studies through the registry. Although these definitions are not fully exhaustive and will probably evolve in the future, the Infectious Diseases Working Party and the Registry Committee recommend the EBMT members use the present version of these definitions when filling the infection-related complication section in the MED B forms.
- **to provide official definitions for the Group,** so that authors may refer to these definitions for studies or surveys, including those done outside the registry. It is not the purpose of this text to force the EBMT members to use these definitions, but only to facilitate their work, so that they may choose, when publishing on a topic, between referring to the EBMT definitions, or to others.

These definitions are drawn either from published guidelines whenever possible, or from the consensus emerging from the members of the Infectious Diseases Working Party when no satisfactory definition has previously been proposed in the literature.

These definitions are presented in two parts:

- the first part summarizes the different **clinical entities** which are usually observed. Most of these entities - but not all - are intended for entering infectious complications in the EBMT data base.
 - the second part covers definitions regarding **specific pathogens:** bacteria, fungi, viruses, others.
- Most of the items concern clinical entities defined in the first part, and aim to help the investigator to establish the relationship between the clinical presentation, and the role of a pathogen. We have restricted the definitions to the most difficult items and do not mention obvious definitions of widely accepted infections or diseases.

Because of the introduction of more and more sensitive tests to detect pathogens, the definitions should be as clear as possible concerning the diagnostic value of each new test in a given clinical setting. It is clear that definitions for infectious diseases or syndromes may evolve with the progress of investigative procedures, or understanding of the disease. Therefore, once a consensus is obtained, these definitions should be reviewed every two years, or more often where necessary. The EBMT members are encouraged to make suggestions on this version to the chairperson of the IDWP.

1 - CLINICAL ENTITIES

1. 1. FEBRILE NEUTROPENIA

1. 1. 1. Fever of unknown origin or unexplained fever

1. 1. 2. Clinically defined infection

1. 1. 3. Microbiologically defined infection

1.2. BACTEREMIA, FUNGEMIA, VIREMIA

1.2.1. Bacteraemia

1.2.2. Fungaemia

1.2.3. Viraemia

1. 3. SEPSIS and SEPTIC SHOCK

1. 4. SEVERE SEPSIS and MULTIORGAN FAILURE

1. 5. ACUTE RESPIRATORY DISTRESS SYNDROM (ARDS)

1.6. PNEUMONIA

1.6.1. Pneumonia

1.6.2. Idiopathic pneumonia syndrome

1. 7. HEPATITIS

1. 8. CENTRAL NERVOUS SYSTEM INFECTION

1.9. GUT INFECTION

1.9.1. Typhlitis/Neutropenic Enterocolitis

1.9.2. Clostridium difficile associated diarrhoea or pseudomembranous colitis

1. 10. SKIN INFECTION

1. 11. CYSTITIS

1. 12. RETINITIS

1. 13. CATHETER RELATED INFECTION

1. 13. 1. Catheter related bloodstream infection

1. 13. 2. Infusate-related bloodstream infection

1. 13. 3. Catheter colonization

1. 13. 4. Exit-site infection

1. 13. 5. Tunnel infection

1. 13. 6. Septic thrombophlebitis

1. 13. 7. Insertion site infection

1. 13. 8. Pocket (Port-A-Cath) infection

2. SPECIFIC DEFINITIONS RELATED TO PATHOGENS

2. 1. BACTERIAL INFECTIONS

2. 1. 1. Bacteraemia

2. 1. 2. Bacterial pneumonia

2. 1. 3. Mycobacterial infections

2. 1. 4. Legionellosis

2. 2. FUNGAL INFECTIONS

2. 2. 1. Common fungal infections

2. 2. 2. Pneumocystis carinii pneumonia

2. 3. VIRAL INFECTIONS

2. 3. 1. HSV

- 2.3.2. VZV**
- 2.3.3. CMV**
- 2.3.4. EBV**
- 2.3.5. HHV-6**
- 2.3.6. HHV-7**
- 2.3.7. HHV-8**
- 2.3.8. Respiratory viruses**
- 2.3.9. Adenovirus**
- 2.3.10. HBV**
- 2.3.11. HCV**
- 2.3.12. HIV**
- 2.3.13. Papovavirus**
- 2.3.14. Parvovirus B19**

2.4. OTHERS

- 2.4.1. *P. carinii* (section 2.2.2)**
- 2.4.2. Toxoplasmosis**
 - 2.4.2.1 Toxoplasma disease**
 - 2.4.2.2 Toxoplasma infection**

1 - CLINICAL ENTITIES

5

1. 1. FEBRILE NEUTROPENIA

Febrile neutropenia is defined by the onset of fever (a single oral temperature 38.3 °C or 38.0°C twice within 12 hours, in the absence of known causes), local inflammation, or any infectious symptom in a patient with polymorphonuclear count <500/mm³, or expected at this level in the next 48 hours, due to a recent chemotherapy.

According to the presence of local inflammation evocative for infection, and to the microbial documentation, the episodes of febrile neutropenia are separated in three categories:

1. 1. 1. Fever of unknown origin or unexplained fever

Isolated fever, no local inflammation evocative for clinical infection, and no microbial documentation of the episode.

1. 1. 2. Clinically defined infection (Clinically documented infection)

Fever associated with a local inflammation such as pneumonia, skin-infection, or cellulitis, whose microbiological pathogenesis cannot be proven or which cannot be examined.

1. 1. 3. Microbiologically defined infection (Microbiologically documented infection), with or without bacteremia

Infectious organisms detected in blood cultures, even without localized inflammation (no clinical focus), OR localized, microbiologically documented, infection, with, or without positive blood cultures.

Infectious Disease Society of America: <http://www.idsociety.org>.

Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Hughes WT, et al. *Clin Infect Dis* 1997;25:551–73

1. 2. BACTERAEMIA, FUNGAEMIA, VIRAEMIA

1.2. 1. Bacteraemia is defined by the presence of viable bacteria in the blood.

For more details, *please see section 2.1.1: Bacterial infections.*

1.2. 2. Fungaemia

Yeasts: Fungemia is defined by at least one positive blood culture of *Candida* and other yeasts in patients with temporally related clinical signs and symptoms compatible with the relevant organism.

Moulds: Fungemia is defined by positive blood culture of fungi excluding *Aspergillus* spp. And *Penicillium* spp. Other than *P. marneffei*, accompanied by temporally related clinical signs and symptoms compatible with the relevant organism.

See also section 2.2.: Fungal infections.

1. 2. 3. Viraemia is defined by the presence of virus demonstrated by culture, antigenemia, or nucleic acid detection in a blood sample. However, due to the high sensitivity of the techniques, and to the possible presence of viruses in the blood without clinical consequences, the significance of viraemia should be carefully considered according to the type of virus.

1. 3. SEPSIS AND SEPTIC SHOCK

Although not specifically mentioned in the original text, the following definitions have been designed for non-neutropenic patients.

Most neutropenic patients with clinically documented or microbiologically documented infections have criteria for Sepsis according to the definition below. Consequently, we recommend that

- for uncomplicated episodes of Febrile neutropenia, the patients be classified according to the definitions of Febrile neutropenia (Section 1.1)
- for episodes of septic shock or multivisceral failure in neutropenic patients, the patients be classified both according to the definitions of Febrile neutropenia AND to the definitions of septic shock and multivisceral failure (Sections 1.3 and 1.4.)

Sepsis is the association of a clinically or microbiologically documented infection AND of 2 or more of the SIRS (Systemic inflammatory response syndrome) conditions which are:

- temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
- heart rate $> 90/\text{minute}$
- respiratory rate $> 20 /\text{minute}$ or $\text{Pa CO}_2 < 32\text{mmHg}$
- white blood cell count $> 12,000$ or $< 4,000/\text{mm}^3$ or $> 10\%$ immature (bands) forms.

Septic shock is defined by the presence of sepsis and hypotension (systolic blood pressure < 90 or reduction of > 40 mmHg from baseline) despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Muckart DJJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definition of the systemic inflammatory response syndrome (SIRS) and allied disorders in relation to critically injured patients. Crit Care Med 1997; 25: 1789-1795.

1. 4. SEVERE SEPSIS AND MULTI-ORGAN FAILURE OF INFECTIOUS ORIGIN

Sepsis is defined **severe** when associated with at least one of the following signs of acute organ dysfunction, not explained by any cause except severe infection:

- (1) metabolic acidosis (arterial blood pH < 7.36 or increased blood lactate level);
- (2) arterial hypoxaemia ($\text{PaO}_2 < 75$ mmHg or $\text{PaO}_2 / \text{FiO}_2 < 250$);
- (3) acute oliguria ($< 0.030\text{L}/\text{h}$ for 3h, or $0.7 \text{L}/24\text{h}$);
- (4) coagulopathy (50% decrease in Quick time or platelet count or a decrease in platelet count to $< 100 \times 10^9/\text{L}$);
- (5) acute alteration in mental status (Glasgow score < 14);
- (6) hypotension (a systolic blood pressure $< 90\text{mmHg}$ or a decrease in systolic blood pressure of at least 40 mmHg from baseline).

Multi-organ failure of infectious origin is defined by the presence of two or more of these parameters, associated with sepsis (section 1.3)b.

Bone RC, Balk RA, Cerra FB, et al. Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101: 1644-55.

Muckart DJJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definition of the systemic inflammatory response syndrome (SIRS) and allied disorders in relation to critically injured patients. *Crit Care Med* 1997; 25: 1789-1795.

1. 5. ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is defined by the acute onset of respiratory failure, associated with:

- (1) bilateral infiltrates seen on frontal chest radiograph;
- (2) PaO₂ / FiO₂ < 200 mmHg (regardless of PEEP level);
- (3) Pulmonary artery wedge pressure > 18 mmHg when measured, or no clinical evidence of left atrial hypertension.

Bernard GR, Artigas A, Brigham KL et al. The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care* 1994; 149: 818-824.

1. 6. PNEUMONIA

1.6.1.Pneumonia indicates the development of new or progressive pulmonary infiltrates due to inflammation of the lung parenchyma. Pneumonia may be documented clinically and/or radiologically. The term is modified to indicate a specific clinical setting such as:

- community-acquired, nosocomial pneumonia, aspiration pneumonia, others
- tempo of the disease: acute, subacute, chronic
- imaging pattern: lobar, bronchopneumonia, interstitial pneumonia, lung abscess.

Pneumonia occurring in the setting of stem cell transplant is mostly caused by a microbial agent. However, non-infectious causes are also observed. A minimal set of investigations is necessary to rule out non-infectious causes of respiratory symptoms, especially pulmonary oedema, and pulmonary embolism. According to the pathogen involved, different criteria and different investigations are needed to establish a causal relationship for each pneumonia. These criteria are listed in Section 2 for each pathogen.

1.6.2. Idiopathic pneumonia syndrome (IPS)

Diffuse pulmonary infiltrates detected by diagnostic procedures, and in which no infectious aetiologies are found after cytological, histological, microbiological, and virological studies of respiratory samples.

The minimal list of the investigative procedures required to exclude an infectious cause has not been established and will probably change over time with the validation of indirect procedures such as aspergillus antigenemia. However, the IDWP recommends to take at least a set of blood cultures, and that a fiberoptic bronchoscopy with aspiration and broncho-alveolar lavage (BAL) be carried out, before making the diagnosis of IPS.

1. 7. HEPATITIS

Hepatitis is defined by an elevation of ALT level 2.5 times above the upper limit of the normal range on two consecutive determinations at least 5 days apart.

Acute hepatitis: ALT elevation lasting less than 6 consecutive months

8

Chronic hepatitis: ALT elevation lasting for more than 6 consecutive months

Fulminant hepatitis: Fulminant hepatitis is defined as subacute hepatic failure according to standard criteria .

Hepatitis may be of infectious, or non infectious origin (i.e. Graft versus Host Disease). Investigations are needed in order to establish a causal relationship between a pathogen and the presence of hepatitis. Please see HBV, HCV, and CMV-related hepatitis in section 2.3.

Bernuau J, Reuff B, Benhamou JP. Fulminant and subfulminant liver failure: definition and causes. Semin Liver Dis 1986; 6: 97-106.

1. 8. CENTRAL NERVOUS SYSTEM INFECTION

CNS infection is defined by any central neurological symptoms associated with:

- evidence of a pathogen in cerebrospinal fluid (CSF) or brain biopsy (proven infection),
- or CSF abnormalities and/or CNS imaging highly suggestive of CNS infection (probable).

A definite diagnosis of **meningitis** is made on the presence of fever, headache, cervical stiffness, sometimes associated with other infectious or neurological symptoms, and the isolation of a bacterial, fungal, or viral agent from the CSF. In case of neutropenia, CSF pleiocytosis may be absent.

1. 9. GUT INFECTION

1.9.1. Typhlitis / Neutropenic Enterocolitis (NEC)

Typhlitis is an inflammatory and/or necrotic process involving the caecum and/or the terminal ileum and appendix associated with bacterial infiltration.

When a larger portion of the small and/or large intestine is involved clinically or radiologically the term **Neutropenic Enterocolitis** is more appropriate.

Typhlitis and NEC are associated with two host factors which are (1) Neutropenia (PMN $<0.5 \times 10^9/L$) and (2) fever (body temperature $>38^\circ C$ or $<36^\circ C$).

The best imaging may be obtained by CT scan, which shows diffuse wall thickening, occasionally associated with low attenuation of intramural areas consistent with edema or necrosis. CT scan findings may also include pneumatosis, pericolonic fluid, and thickening of fascial planes. In the absence of a CT scan, an abdominal ultrasound showing signs of mural and mucosal oedema/necrosis is also consistent with the diagnosis.

1.9.2. Clostridium difficile associated diarrhoea (CDAD) or pseudomembranous Colitis

Definition: Colitis associated with *C. difficile* enterotoxin-induced inflammation of the colonic mucosa.

Colonoscopy usually shows pseudomembrane formation. However, typical pseudomembranes involving the colonic mucosa may be absent when patients are neutropenic.

The diagnosis is proven when the diarrhoea is associated with histological or visual (colonoscopic) evidence of colonic lesions, and with detection of the enterotoxin in the stool.

Gomez L, Martino R, Rolston KV Neutropenic Enterocolitis: spectrum of the disease and comparison of definite and possible cases. *CID* 1998;27:695-7

9

Gorbach SL: Editorial response: neutropenic enterocolitis
JID 1998;27:700-1

Urbach DR, Rolstein OD. Typhlitis *Cand. J. Surg.* 1999;42:415-9

Wall SD, Jones B Gastrointestinal tract in the immunocompromised host: opportunistic infections and other complications. *Radiology* 1992;185:327-35

1. 10. SKIN INFECTION

Primary or secondary cutaneous involvement due to any infectious bacterial, fungal, viral, or parasitic agent.

1. 11. CYSTITIS

Presence of signs and symptoms typical of bladder inflammation, i.e., dysuria, haematuria, cystic pain, with or without fever.

Cystitis is considered to be due to bacteria when there are 10^5 bacteria /mL urines.

1. 12. RETINITIS

Characteristic ophthalmoscopic picture of retinitis, with or without haemorrhage, as determined by an ophthalmologist.

1. 13. CATHETER RELATED INFECTION

1. 13. 1 Catheter related bloodstream infection

Definite catheter-related bloodstream infection

Bacteremia or fungemia in a patient who has an intravascular device and 1 positive result of culture of blood samples obtained from the peripheral vein, clinical manifestations of infection (e.g., fever, chills, and/or hypotension), and no apparent source for bloodstream infection (with the exception of the catheter). One of the following should be present:

- a positive result of semiquantitative (15 cfu per catheter segment) or quantitative (100 cfu per catheter segment) catheter culture, where by the same organism (species and antibiogram) is isolated from a catheter segment and a peripheral blood sample
- simultaneous quantitative cultures of blood samples with a ratio of 5 : 1 (CVC vs. peripheral); differential time to positivity (i.e., a positive result of culture from a CVC is obtained at least 2 h earlier than is a positive result of culture from peripheral blood)

Probable catheter-related bloodstream infection

(a) when catheter tip is available

In a patient with accompanying clinical symptoms of bloodstream infection and no other apparent source of infection: isolation of the same organism (bacteria or fungi) (i.e., identical species, antibiogram) from peripheral percutaneous blood cultures*, and from on of the following:

- catheter tip, when the catheter-tip culture yielded a bacterial count of less than 15 colony-forming units (cfu) by semiquantitative or <1000 cfu/ml by quantitative culture techniques) while patients were receiving antibiotics active against the micro-organisms recovered from the catheter, or:
- catheter tip, when bacterial count was not performed.

*For the following bacteria, 2 consecutive positive blood cultures are needed, at least one from peripheral blood, for documentation of true bacteremia: coagulase-negative staphylococcus, *Micrococcus*, *Corynebacterium* (other than JK), *Bacillus* spp.

(b) when catheter tip is not available

In a patient with accompanying clinical symptoms of bloodstream infection and no other apparent source of infection: isolation of the same organism (i.e., identical species, antibiogram) from peripheral percutaneous blood cultures, and from one of the following:

- infected exit site
- insertion site
- pocket site

1. 13. 2. Infusate-related bloodstream infection

Concordant growth of the same organism from infusate and cultures of percutaneously obtained blood samples, with no other identifiable source of infection.

1. 13. 3. Catheter colonization

In the absence of accompanying clinical symptoms, significant growth of an organism from the catheter tip, subcutaneous catheter segment, or catheter hub, in a quantitative or semiquantitative culture

- >15 colony-forming units by semiquantitative
- or:
- >1000 by quantitative culture techniques

Or:

2 consecutive positive hub-blood cultures with same organism (i.e., identical species, antibiogram), while a peripheral blood culture is negative (to be noted that it is not recommended to send blood cultures from patients who have no clinical symptoms).

1. 13. 4. Exit-site infection

Signs of inflammation (i.e., erythema, induration, and/or tenderness) of the skin within 2 cm of the catheter exit site. This may be associated with other signs and symptoms of infection, such as fever or pus emerging from the exit site, with or without concomitant bloodstream infection. The exit-site infection may be clinically only, or microbiologically documented when an exudate at catheter exit site yields a microorganism with or without concomitant bloodstream infection.

1. 13. 5. Tunnel infection

Erythema, tenderness, and/or induration > 2 cm from the catheter exit site, along the subcutaneous tract of a tunneled catheter (e.g. Hickman or Broviac catheter), with or without concomitant bloodstream infection.

1. 13. 6. Septic thrombophlebitis

Venous occlusion proximal to the catheter, associated with bacteremia* and with accompanying clinical symptoms of blood stream infection.

* For the following bacteria, 2 consecutive positive blood cultures are needed, at least one from peripheral blood, for documentation of true bacteremia: coagulase-negative staphylococcus, *Micrococcus*, *Corynebacterium* (other than JK), *Bacillus* spp.

1. 13. 7. Insertion site infection

Erythema and necrosis of the skin over the insertion site of the Hickman/Broviac catheter or purulent exudate in the subcutaneous pocket containing the reservoir.

1. 13. 8. Pocket (Port-A-Cath) infection

Infected fluid in the subcutaneous pocket of a totally implanted intravascular device ; often associated with tenderness, erythema, and/or induration over the pocket ; spontaneous rupture and drainage, or necrosis of the overlying skin, with or without concomitant bloodstream infection, may also occur.

Elishoov, Or, Strauss, Engelhard. Medicine, 1998 77:83

Blot, Lancet 1999; 354: 1071

Mermel et al. Clin Infect Dis 2001 ; 32 : 1249.

2. SPECIFIC DEFINITIONS RELATED TO PATHOGENS

2. 1. BACTERIA

2. 1. 1. Bacteraemia: presence of viable bacteria in the blood. One positive blood culture is enough to make the diagnosis of bacteraemia, except for coagulase negative staphylococci (CNS). Although no clear data in the literature prove that two positive blood cultures are clinically more significant than one, it is usual to consider that two positive blood cultures are needed for a diagnostic of CNS bacteraemia. The Group recommends this practice to be followed until additional data are available.

The term septicaemia is not recommended and should be replaced by the use of bacteraemia plus sepsis, severe sepsis, or septic shock.

Muckart DJJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus conference: Definition of the systemic inflammatory response syndrome (SIRS) and allied disorders in relation to critically injured patients. Crit Care Med 1997; 25: 1789-1795.

2. 1. 2. Bacterial pneumonia

In intubated patients, it is considered in most European countries that the diagnosis of proven bacterial pneumonia requires quantitative evaluation of the number of bacteria in the lower respiratory airways. In this setting, a bacterial cause of pneumonia is accepted if:

- in the presence of pneumonia (see above), an endobronchial sampling has demonstrated bacteria in culture in the following amounts:

- 10^3 CFU/mL for protected brush (Wimberley or comparable) or distal protected catheter
- 10^4 CFU/mL for BAL fluid
- 10^5 CFU/mL for non-protected transtracheal aspirates.

These thresholds have been established in ventilated patients, mostly not immunocompromised, but there are no data on the value of these predetermined thresholds after stem cell transplant, so that it is unknown whether they are appropriate in this setting.

Since there are no comparable data on bacterial pneumonia for the stem cell transplant population, the Group recommends the use of above.

A positive blood culture in presence of pneumonia is presumptive evidence for a bacterial pneumonia when there is no other cause identified in the lungs, but is not a proof of bacterial pneumonia.

Although it is a common practice in some countries to use routine bacterial cultures of sputum to manage patients with pneumonia, the sensitivity and specificity of sputum examination is poor and their value is not established for pneumonia in immunocompromised patients, except for pathogens which are never part of the normal respiratory flora (i.e. *Mycobacterium* sp., *Legionella* sp.). Therefore, the presence of a common bacterium in the sputum cannot be considered as proof for bacterial pneumonia.

American Thoracic Society: Hospital-acquired pneumonia in adults: Diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement. Am J Respir Crit Care Med 1996; 153: 1711-1725.

2. 1. 3. Mycobacterial infections

The diagnosis of microbiologically proven mycobacterial (tuberculosis or atypical mycobacteria) infection is defined by the isolation, in any body sample, of mycobacteria. Tuberculosis is due to *M. tuberculosis*, *M. bovis*, or *M. africanum*.

The presence of acid-fast bacilli demonstrated by Zielh-Nielsen or comparable stains in any sample, associated with the presence of granuloma or any tissue lesion compatible with the diagnosis of mycobacterial infection on histological sections is defined as a histologically proven mycobacterial infection.

2. 1. 4. Legionellosis

Legionellosis is defined by the presence of consistent clinical symptoms (mostly febrile pneumonia), associated with one of the following laboratory criteria:

- isolation of *Legionella* sp. by culture, or detection by direct fluorescent antibody testing from respiratory secretions (bronchial aspiration, BAL), blood, or any normal sterile fluid or tissue, or
- demonstration of a fourfold or greater rise in the specific antibody titer to greater than, or equal to 128 against *L. pneumophila*, or
- demonstration of *L. pneumophila* antigens in urines by radioimmunoassay or enzyme-linked immunosorbent assay.

2. 2. FUNGAL INFECTIONS

2. 2. 1. Common fungal Infections

The Group proposes to use the definitions presented by the EORTC-Invasive Fungal Infection Cooperative Group in their preliminary version. These definitions have not been so far validated for stem cell transplant patients but should certainly help to report on fungal diseases until they be validated or modified.

S. Ascoglu, B De Pauw, et al. Analysis of definitions used in clinical research on invasive fungal infections. Consensus proposal for new, standardized, definitions. Abstract 1639; ICAAC Meeting 1999.

Table 1. DEFINITIONS OF INVASIVE FUNGAL INFECTIONS

PROVEN INVASIVE FUNGAL INFECTION

Deep Tissue Infections	
Moulds¹	Yeasts¹
Histo/cytopathology showing hyphae from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging).	Histo/cytopathology showing yeast cells (<i>Candida</i> may also show pseudohyphae or true hyphae) from a needle aspiration or biopsy excluding mucous membranes.
OR	OR
Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection.	Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses and mucous membranes.
	OR
	Microscopy (India ink, mucicarmine stain) or antigen positivity ² for cryptococcus in CSF.
Fungemia	
Moulds¹	Yeasts¹
Positive blood culture of fungi excluding <i>Aspergillus</i> spp. and <i>Penicillium</i> spp. other than <i>P. marneffeii</i> , accompanied by temporally related clinical signs and symptoms compatible with the relevant organism.	Positive blood culture of <i>Candida</i> and other yeasts in patients with temporally related clinical signs and symptoms compatible with the relevant organism.
Endemic Fungal Infections (Histoplasmosis, blastomycosis, coccidioidomycosis and paracoccidioidomycosis):	

¹ Append identification at genus or species level from culture if available

² False-positive cryptococcal antigen reactions due to infection with *Trichosporon beigellii* [13], infection with *Stomatococcus mucillagenosus* [14], circulating rheumatoid factor [15], and concomitant malignancy [16] may occur and should be eliminated if a positive antigen test is the only positive result in this category.

Either systemic or only confined to lungs, must be proven by culture from the site affected, in a host with symptoms attributed to the fungal infection. If cultures are negative or unattainable, histopathological or direct microscopic demonstration of the appropriate morphological forms is considered adequate for those dimorphic fungi (*Blastomyces*, *Coccidioides* and *Paracoccidioides*) having a truly distinctive appearance.

Table 1 (part 2)

PROBABLE INVASIVE FUNGAL INFECTIONS

Defined as at least one criterion from host section

AND

one microbiological criterion

AND

one major (**or** two minor) clinical criteria from an abnormal site consistent with infection.

POSSIBLE³ INVASIVE FUNGAL INFECTIONS

Defined as at least one criterion from host section

AND

One microbiological **OR** one major (**or** two minor) clinical criteria from an abnormal site consistent with infection.

³ This category is NOT recommended for use in clinical trials on antifungal agents, but might be considered in studies on empirical treatment, epidemiological studies and studies on health economics.

Table 2. CRITERIA for PROBABLE and POSSIBLE INVASIVE FUNGAL INFECTIONS IN PATIENTS WITH CANCER AND HEMATOPOIETIC STEM CELL TRANSPLANTATION
Possible and Probable IFI

Host Factors

1. Neutropenia: PMN < 500/mm³ for more than 10 days.
2. Persistent fever for >96 hrs refractory to appropriate broad spectrum antibacterial treatment.
3. Body temperature either >38°C or <36°C **AND** any of the following predisposing conditions:
 - a. Prolonged neutropenia (>10 days) in the previous 60 days,
 - b. Recent or current use of significant immunosuppressive agents in the previous 30 days,
 - c. Proven or probable invasive fungal infection during a previous episode of neutropenia,
 - d. Co-existence of symptomatic AIDS
4. Signs and symptoms indicating GVHD, particularly grade 3-4
5. Prolonged (>3 weeks) use of corticosteroids in the previous 60 days.

Microbiological Criteria

1. Positive culture of a mould (including *Aspergillus* spp., *Fusarium* spp., Zygomycetes, *Scedosporium* spp.), or *C. neoformans* from sputum, BAL.
2. Positive culture or cytology/direct microscopy for moulds from sinus aspirate.

3. Positive cytology/direct microscopy for a mould or *Cryptococcus* from sputum, BAL.
4. Positive *Aspergillus* antigen in BAL, CSF, or ≥ 2 blood samples.
5. Positive cryptococcal antigen in blood (see footnote to Table 1 for causes of false-positive reactions that must be considered and eliminated from consideration).
6. Positive cytology/direct microscopy for fungal elements in sterile body fluids (see Table 1, for *Cryptococcus* in CSF).
7. Two positive urine culture of yeasts in the absence of urinary catheter.
8. *Candida* casts in urine in the absence of urinary catheter.
9. Positive blood culture of *Candida* spp.

Table 2 (part 2)**Clinical Criteria**

Must be related to the site of microbiological criteria and temporally related to current episode.

Major**Minor****Lower Respiratory Tract Infection**

Any of the following new infiltrates on CT imaging: halo sign, air-crescent sign or cavity within an area of consolidation

1. Symptoms of LRTI (cough, chest pain, hemoptysis, dyspnea)
2. Physical finding of pleural rub
3. Any new infiltrate not fulfilling major criterion
4. Pleural effusion

Sinonasal Infection

Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction).

1. Upper respiratory symptoms (nasal discharge, stuffiness etc)
2. Nose ulceration or eschar of nasal mucosa or epistaxis
3. Periorbital swelling
4. Maxillary tenderness

	5. Black necrotic lesions or perforation of the hard-palate
Radiological evidence suggesting CNS infection (e.g., mastoiditis or other parameningeal foci, extradural empyema)	<p>Central Nervous System Infection (CSF negative for other pathogens by culture, microscopy and malignant cells)</p> <ol style="list-style-type: none"> 1. Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies) 2. Mental changes 3. Meningeal irritation findings 4. Abnormalities in CSF biochemistry and cell count
<ol style="list-style-type: none"> 1. Papular or nodular skin lesions without any other explanation. 2. Intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis. 	<p>Disseminated Fungal Infection</p>
Small, peripheral, target-like abscesses (Bull's eye) in liver and/or spleen demonstrated by CT, MRI or USG . Supporting microbiological criteria are not required for probable category.	<p>Chronic Disseminated Candidiasis</p>
Clinical criteria are not required for probable candidemia. There is no definition for possible candidemia.	<p>Candidemia</p>

Footnotes to table 1:

1 Append identification at genus or species level from culture if available

2 False-positive cryptococcal antigen reactions due to infection with *Trichosporon beigeli* [1], infection with *Stomatococcus mucilaginosus* [2], circulating rheumatoid factor [3], and concomitant malignancy [4] may occur and should be eliminated if a positive antigen test is the only positive result in this category.

3 This category is not recommended for use in clinical trials on antifungal agents, but might be considered in studies on empirical treatment, epidemiological studies and studies on health economics.

2. 2. 2. *P. carinii* pneumonia (PcP)

PcP is diagnosed by the presence of *Pneumocystis carinii* identified through cytological examination (Gomori-Grocott or Gram-Weigert staining) or immunofluorescence in a lung sample (broncho-alveolar lavage, bronchial aspiration, transbronchial biopsy, transthoracic needle aspiration, lung biopsy, or sputum) in a patient with fever or abnormal chest X-ray, or hypoxemia.

Patients with pneumonia of undetermined origin and responding to empiric treatment with Bactrim alone, and patients documented by nucleic acid detection alone, cannot be considered as having PcP.

Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. Hughes WT, Rivera, GK, Schell MJ, et al. N Engl J Med 1987; 316 (26): 1627-1632.

2. 3. VIRAL INFECTIONS

It is particularly important for viruses to distinguish between infection alone and infection causing disease as many viruses can be latent throughout life and virus replication and shedding may be asymptomatic.

2. 3. 1. Herpes simplex virus (HSV) infections

Mucocutaneous disease:

Focal lesions together with detection of HSV antigen by immunohistochemistry, immunofluorescence, or by culture. HSV nucleic acid detection is not enough to diagnose HSV-associated mucocutaneous disease.

Encephalitis

Signs and/or symptoms of encephalitis with or without focal neurologic signs combined with HSV in the CSF as found by culture or nucleic acid detection.

Meningitis

Signs and/or symptoms of meningitis combined with detection of HSV from the CSF by culture or detection of HSV nucleic acid.

Other visceral disease

Signs and symptoms from the appropriate visceral organ (lung, liver) together with detection of HSV by culture or immunofluorescence or immunochemistry in biopsy or autopsy material.

Gastrointestinal disease

Combination of clinical symptoms from the upper or lower gastrointestinal tract, macroscopic mucosal lesions seen at endoscopy and demonstration of HSV by culture, immunofluorescence or immunochemistry in a biopsy specimen from the gastrointestinal tract. As for oropharyngeal lesions, detection of HSV nucleic acid is not enough to diagnose gastro-intestinal infections due to HSV.

2. 3. 2. Varicella-zoster virus (VZV) infections

Localized herpes zoster

Where there is a classical clinical picture of herpes zoster with typical cutaneous lesions, detection of VZV is not necessary.

In other cases, a sample to detect VZV by immunohistochemistry, immunofluorescence, nucleic acid detection or culture is recommended.

Disseminated herpes zoster.

Disseminated vesicular lesions in a patient who was VZV antibody positive prior to stem cell transplant, together with detection of VZV by immunohistochemistry, immunofluorescence, nucleic acid detection or culture. 20

Varicella

If there are disseminated vesicular lesions in a patient who was VZV antibody negative prior to transplant, detection of VZV is not necessary when cutaneous lesions are typical, and there is no other apparent cause (probable varicella). In other cases, a sample to detect VZV by immunohistochemistry, immunofluorescence, nucleic acid detection, or culture, is recommended (confirmed varicella).

Visceral varicella-zoster disease

Signs and symptoms from the appropriate organ (lung, liver) together with detection of VZV from biopsy or autopsy material by immunohistochemistry, nucleic acid detection, or culture.

VZV encephalitis

Signs and/or symptoms of encephalitis with or without focal neurologic signs combined with VZV in the CSF as found by culture or nucleic acid detection.

2. 3. 3. Cytomegalovirus (CMV)

CMV infection is defined as detection of viral proteins or nucleic acid from any site. It is recommended that the source of the specimens tested are clearly given for example plasma, serum, whole blood, peripheral blood leukocytes, CSF, or urine.

Primary CMV infection:

Detection of CMV or specific antibodies to CMV in a previously CMV seronegative individual.

Recurrent infection:

Detection of CMV protein, DNA, or RNA in a previously seropositive individual.

Reinfection:

Detection of a new CMV strain documented either by gB typing or molecular techniques such as sequencing of the viral genome

CMV detection from blood

The following specific definitions for CMV detection from blood are recommended:

Viremia: Detection of CMV by culture either standard or by the shell vial technique.

Antigenemia: Detection of CMV pp65 in leukocytes

DNAemia: Detection of DNA from plasma, whole blood, isolated peripheral blood leukocytes or buffy coat specimens. There are several techniques available such as PCR, hybrid capture, or branched DNA. The tests can be either qualitative or quantitative. In the latter situation, the technique used for quantitation should be given.

RNAemia: Detection of RNA from Detection of DNA from plasma, whole blood, isolated peripheral blood leukocytes or buffy coat specimens

CMV organ disease

Pneumonia: Combination of signs and/or symptoms of pulmonary disease together with detection of CMV in bronchoalveolar lavage fluid or from lung tissue. Detection of CMV should be done by virus

isolation, histopathology, immunohistochemistry, or in situ hybridisation. Detection of CMV by PCR alone is not sufficient for the diagnosis of CMV pneumonia. 21

Gastrointestinal disease: Combination of clinical symptoms from the upper or lower gastrointestinal tract, macroscopic mucosal lesions seen at endoscopy, and demonstration of CMV in a biopsy specimen from the gastrointestinal tract by culture, histopathology, immune histochemistry, or in situ hybridisation. Detection of CMV by PCR alone is not sufficient for the diagnosis of CMV gastrointestinal disease.

Hepatitis: Elevated liver function tests, no other documented cause of hepatitis, and CMV detected from liver biopsy.

CNS disease: CNS symptoms together with CMV detected by culture or PCR.

Retinitis: Typical lesions of retinitis confirmed by an ophthalmologist.

CMV syndrome: The term CMV syndrome should be avoided. Although it is recognized that CMV can cause the symptom combination of fever and bone marrow suppression usually used as definition of the entity, several other different causes in stem cell transplant patients can give the same symptoms including other viral infections such as human herpesvirus 6 (HHV-6), possibly human herpesvirus 7 (HHV-7), and adenovirus. Antivirals might have different effect against these viruses making interpretation of causality difficult. Thus, if the term is to be used, it must be combined with investigation also of at least analysis of HHV-6 as well.

Ljungman, Paya, and Griffiths, submitted.

2. 3. 4. Epstein Barr Virus (EBV)

EBV infection in the blood

There is no currently accepted definition for EBV infection in the blood of SCT patients. However, quantitative PCR for EBV DNA is being evaluated for the prediction of EBV-induced post-transplant lymphoproliferative disease (EBV-post-transplant lymphoproliferative disease / PTLD) and monitoring the response of such disease to treatment.

EBV disease

(a) EBV-post transplant lymphoproliferative disorder (PTLD)

Despite the identification of risk factors for EBV-PTLD, the optimal management of this heterogeneous group of lymphoproliferative diseases is hampered by limited understanding of their pathogenesis, the lack of randomised studies addressing their prevention and treatment, and variable criteria for establishing the diagnosis which requires tissue biopsy. Until there is further clarification of the natural history of EBV-PTLD, the term "PTLD" should be used to encompass a large spectrum of EBV lymphoproliferative processes including both hyperplastic, polyclonal proliferations resembling mononucleosis, and neoplastic disease. Post-transplant infectious mononucleosis and plasma cell hyperplasia should, however, be clearly segregated as reactive hyperplasia type EBV-PTLD and the term "EBV-PTLD" without further qualification should be reserved for neoplasias. Diagnosis of neoplastic forms of EBV-PTLD should have at least two and ideally three of the following features:

- 1) Disruption of underlying cellular architecture by a lymphoproliferative process
- 2) Presence of monoclonal or oligoclonal cell populations as revealed by cellular and/or viral markers
- 3) Evidence of EBV infection in many of the cells i.e. DNA, RNA or protein.

(b) Other EBV disease

As regards other possible disease, as tentative definitions, it is logical to use similar definitions as for CMV disease i.e. a combination of signs/symptoms of organ disease together with detection of EBV from the organ. However it should be noted that even for immunocompetent individuals, EBV is commonly shed in saliva and may be cultured from blood. Nucleic acid detection of EBV is not enough for the diagnosis of EBV disease.

2. 3. 5. Human herpesvirus-6 (HHV-6)

HHV6 infection in the blood

There is no currently accepted definitions for HHV6 infection in the blood of SCT patients. Recently developed nucleic acid detection techniques such as quantitative PCR should be evaluated.

HHV6 encephalitis

CNS symptoms and EEG changes compatible with encephalitis, HHV-6 DNA documented in CSF, no other infectious agent documented by culture (bacteria, fungi), microscopy, or nucleic acid detection (CMV, EBV, VZV, HSV), or signs of malignant disease (CT or MRI scans, microscopy and immune staining of CSF).

HHV6 pneumonia: Combination of signs and/or symptoms of pulmonary disease together with detection of HHV-6 in bronchoalveolar lavage fluid or from lung tissue. Detection of HHV-6 should be done by virus isolation or immunohistochemistry. Detection of HHV-6 DNA by PCR alone is not sufficient for the diagnosis of HHV-6 pneumonia. Interpretation of simultaneous detection of another infectious agent must be done on a patient-by-patient basis

2. 3. 6. Human herpesvirus 7 (HHV7)

Apart from a childhood rash, there is currently no recognized disease caused by HHV-7 even in immune competent patients. No definition of HHV-7 disease in SCT patients can therefore be proposed at this time.

2. 3. 7. Human herpesvirus 8 (HHV-8)

HHV-8 infection

There is currently no generally available diagnostic technique for HHV-8. However, serologic techniques are available in reference laboratories and could be used for defining patients previously infected by HHV-8.

HHV-8 disease

HHV-8 infection is causally related to classical Kaposi's sarcoma and to this disease in transplant and HIV-infected patients.

2. 3. 8. Respiratory viruses

(Respiratory syncytial virus (RSV), Influenza, Para-Influenza, Rhinovirus)

Upper respiratory tract infection: Detection of a respiratory virus (influenza, respiratory syncytial virus (RSV), parainfluenza, rhinovirus) by immunofluorescence or other method of antigen detection, or culture from nasal, nasopharyngeal, sputum or throat specimens without signs or symptoms of lower airway disease. Recently developed techniques for detection of nucleic acid are being evaluated.

Lower airway disease: Detection of a respiratory virus (influenza, RSV, parainfluenza) as described above from bronchoalveolar fluid or from lung tissue together with signs and/or symptoms of bronchitis or pulmonary disease. There may be simultaneous detection of another infectious agent, and decision must be made on a patient-by-patient basis. Currently there is no existing information allowing interpretation of a finding of rhinovirus from lower respiratory tract specimens.

2. 3. 9. Adenovirus

Asymptomatic adenovirus infection

Any detection of adenovirus in an asymptomatic patient from stool, blood, urine, or upper airway specimens by viral culture, antigen tests, or nucleic acid detection.

Definite adenovirus disease

Non-gastrointestinal locations: Symptoms and signs from the appropriate organ combined with histopathological documentation of adenovirus and/or adenovirus detection by culture, antigen test, or nucleic acid detection from biopsy specimens (liver or lung), broncho-alveolar lavage fluid, or cerebrospinal fluid and without another identifiable cause.

Gastrointestinal location: Symptoms together with detection of adenovirus from biopsy material by culture, antigen test, or nucleic acid detection.

Probable adenovirus disease

Gastrointestinal tract: Detection of adenovirus in stool by culture, antigen test, or nucleic acid test, together with symptoms.

Urinary tract: Symptoms of dysuria or hematuria combined with detection of adenovirus by culture, antigen test, or nucleic acid detection without other identifiable cause.

Flomemberg P, Babbitt J, Drobyski WR, et al. Increasing incidence of Adenovirus disease in bone marrow transplant recipients. Clin Infect Dis 1994; 169: 775-81.

Howard DS, Gordon L, Phillips H, et al Adenovirus infections if hematopoietic stem cell transplant recipients. Clin Infect Dis 1999; 29: 1494-501

La Rosa AM, Champlin RE, Mirza R et al. Adenovirus infections in adult recipients of blood and marrow transplants. Clin Infect Dis 2001 ; 32 :871-876

Cidofovir for adenovirus infections after allogeneic stem cell transplantation: A survey by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation.

P. Ljungman et al, submitted.

2. 3. 10. Hepatitis B virus (HBV)

HBV-related hepatitis: ALT elevation preceding or concomitant with

a. Acute: seroconversion from

HBsAg negative to HBsAg positive, and/or

HBV-DNA negative to HBV-DNA positive,
AND/OR

24

b. Reactivation: elevation of serum HBV-DNA to more than 10 times the baseline value.

2. 3. 11. Hepatitis C virus (HCV)

HCV-related Hepatitis: ALT elevation preceding or concomitant with seroconversion from HCV-RNA negative to HCV-RNA positive.

2. 3. 12. Human Immunodeficiency virus (HIV-1 and HIV-2) infection

For adults, adolescents, or children aged greater than, or equal to 18 months, HIV infection is defined by at least one of the following criteria, irrespectively of AIDS criteria:

Positive result on a screening test for HIV antibody (e.g., repeatedly reactive enzyme immunoassay), followed by a positive result on a confirmatory (sensitive and more specific) test for HIV antibody (e.g., Western blot or immunofluorescence antibody test), or by positive results on two confirmatory enzyme immunoassays for HIV antibody each of a different format to the original screening assay

OR

Positive result or report of a detectable quantity on any of the following HIV virologic (nonantibody) tests:

- HIV nucleic acid (DNA or RNA) detection (e.g., DNA PCR or plasma HIV-1 RNA)
- HIV p24 antigen test, including neutralization assay
- HIV isolation (viral culture)

A negative plasma HIV-1 RNA test does not rule out the diagnosis of HIV Infection.

For children aged less than 18 months, the IDWP recommends to use the proposed definitions of the Center for Diseases Control cited above.

Center for Diseases Control Prevention Guidelines. Case definitions for Infectious Conditions under public health surveillance (cdc.gov). MMWR 48 (RR13); 29-31.

2. 3. 13. Papovavirus

BK-virus urinary tract infection

BK-virus has been associated with the development of haemorrhagic cystitis after SCT. However, shedding excretion of BK-virus in urine is very common. It is currently not possible to define the role of BK-virus in the pathogenesis of haemorrhagic cystitis.

Progressive multifocal leucoencephalopathy (PML)

Neurological signs/symptoms combined with classical MRI appearance. Detection of JC-virus DNA in CSF is specific for the diagnosis but a negative PCR does not exclude PML.

2. 3. 14. Parvovirus B19

Parvovirus B19 infection:

Nucleic acid detection from blood, marrow or tissue positive without clear symptoms

1) aplastic crisis or pure red cell aplasia with

- reticulocytopenia
- characteristic morphological changes in red blood cell progenitors in marrow aspiration
- positive Parvovirus B19 DNA from blood or marrow

2) erythema infectiosum-like skin rash with rapidly changing exanthema, sometimes similar to graft-versus-host disease, and recovery of Parvovirus B19 from skin or blood by PCR

Possible parvovirus B19 disease (occasional observations so far): myocarditis, hepatitis or liver failure, nephritis, with documentation of Parvovirus B19 from tissue

M Schleuning, G Jäger, E Holler et al: Human Parvovirus B19-Associated Disease in Bone Marrow Transplantation. Infection 27: 114-117, 1999.

2.4. OTHERS

2.4.1 For *P. carinii* pneumonia, please see section 2.2.2

2.4.2. Toxoplasmosis

2.4.2.1 Toxoplasma Disease

Definite Toxoplasmosis

Histologic or cytologic demonstration of tachyzoites of *Toxoplasma gondii* in tissue samples obtained by biopsy, bronchoalveolar lavage (BAL) or at autopsy.

Probable Toxoplasmosis

(PCR-documented)

Clinical and radiologic evidence suggestive of organ involvement plus at least one positive PCR test from blood, CSF and/or BAL but no histologic confirmation and absence of another pathogen which may explain the findings.

Possible Toxoplasmosis (Imaging-documented)

CT or MRI highly suggestive of CNS toxoplasmosis (as considered by each hospital's neuroradiologists) and response to anti-toxoplasma therapy, but no laboratory evidence of toxoplasmosis and absence of another pathogen which may explain the findings.

2.4.2.2. Toxoplasma Infection

Positive PCR in blood in a patient without any evidence of organ involvement or seroconversion for *Toxoplasma gondii* after transplant in a previously seronegative patient (with or without fever).

Toxoplasmosis after hematopoietic stem cell transplantation. A study by the European Group for Blood and Marrow Transplantation Infectious Diseases Working Party.

R. Martino, J. Maertens, S. Bretagne, et al. Clin Infect Dis 2000; 31 (5): 1188-94.