BMT CTN Technical Document

Infectious Diseases

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1.0 Introduction

Infectious complications following cellular therapy, including but not limited to hematopoietic stem cell transplant (HCT), account for significant morbidity and mortality. Because all or most study participants in BMT CTN trials will be receiving therapies resulting in substantial immunosuppression, frequent occurrences of infectious diseases are anticipated in Network trials.

In 2011, the Infectious Disease Technical Committee modified the infection grading system previously published [Cordonnier et al, *Transplantation* 2006; 82 (1): 86 – 92] and defined the BMT CTN Infection Grading System for use in BMT CTN Trials. More or less reporting of information regarding infectious complications may be required for each individual BMT CTN protocol as not all infections and infectious disease practices need to be monitored to the same detail. The information herein is offered as suggested guidelines for protocol development.

The Infectious Disease Technical Committee is an *ad hoc* committee that convenes when necessary for advising Protocol Teams, reviewing infectious disease data, refreshing relevant Manual of Procedures text, etc.

2.0 Purpose

The purpose of the Infectious Disease Technical Committee is to:

- Recommend data collection procedures,
- Define standards for prevention and treatment of infections for both allogeneic and autologous transplantation,
- Provide guidelines for clinical and laboratory monitoring of infections, and
- Define infectious complications and auditing practices.

3.0 Membership

This committee consists of transplant physicians and infectious disease specialists, all with substantial experience in HCT. A BMT CTN Data and Coordinating Center (DCC) co-PI serves on the committee in an ex-officio capacity. There is a core group of interested, experienced investigators who are committed to the work of the Network and who convene upon request of a Protocol Team and/or the DCC.

4.0 Policy

The suggested detail to which infectious complications will be monitored varies from trial to trial and will be made in advance by the Protocol Team during protocol development.

The Protocol Team determines what, if any, variations in medical practice of infection therapy might potentially confound their primary or secondary outcomes. If there are concerns on the part of the Protocol Team, Steering Committee or the Infectious Disease Technical Committee that confounding may occur, the Infectious Disease Technical Committee will assist the Protocol Team in determining what data are necessary to monitor such practices, or the Committee will provide recommendations for standardization of those practices such that they may be collected prospectively.

Procedure: *Recommend data collection procedures*
As a matter of routine, Grade 2 and 3 infections are reported; Grade 1 infections are not reported. A standardized Infection Case Report Form (CRF) is used for all protocols unless Grade 1 reporting is important to the trial endpoint. In this case, a protocol-specific Case Report Form is designed by the

Protocol Team. This approach is also consistent with NIH requirements for collecting Serious Adverse Event (SAE) data. (https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-adverse-event-and-unanticipated-problem-reporting-policy#:~:text=Adverse%20event%20(AE):%20OHRP%20guidance%20external%20link,with%20the%20subject's%20participation%20in%20the%20research%2C)

Data auditing will take place in accordance with BMT CTN guidelines. More information can be found about Site Monitoring in the BMT CTN MOP Chapter 5.

Procedure: Define *standards for prevention and treatment of infections for both allogeneic and autologous transplantation*
Joint guidelines for preventing opportunistic infections were developed and published as a supplement to *Biology of Blood and Marrow Transplantation* (15: 1143-1238, 2009) and are posted on the CDC website at www.cdc.gov. Where updated guidelines for specific infections are available (https://www.astct.org/Education/Practice-Guidelines) (https://www.astct.org/Membership/Community-Forum), the new recommendations will supersede the 2009 joint guidelines. These guidelines are currently used for Network trials, except as specifically modified for particular protocols.

Procedure: Provide *guidelines for clinical and laboratory monitoring of infections*
No specific recommendations for routine infection monitoring are made for primary or secondary endpoint infectious complications. In rare instances, this may be modified for a specific protocol. If there are questions, Protocol Teams are encouraged to consult the Infectious Disease Technical Committee as the Committee can assist in developing a timeline schedule of specific clinical and laboratory evaluations.

Procedure: Define *infectious complications*
Appendix 1-A includes

1. Generalized reporting instructions. Please see additional information in each protocol.
2. Suggested areas to look in the electronic medical record to identify infections.
3. Terminology is often used to describe infections in the medical record.
4. "*BMT CTN Severity Grades by Infection Type*" (Table 1) defines symptomatology associated with bacterial, fungal, viral, parasitic and non-microbiologically defined infections. Grades 1 ("mild", generally not reported), 2 ("moderate") and 3 ("severe/life threatening") infections are specifically noted.
5. Guidelines for infection recurrence intervals.

5.0 APPENDIX 1-A

Generalized Guidelines for Reporting

1. The date of infection is the date the specimen was obtained that identified the infectious organism. If the patient had a non-microbiologically defined infection or severe sepsis without an identified organism, use the date of onset of the symptoms.
2. Patients may have multiple positive cultures or positive tests; however, only report the first date of infection unless the culture results are considered a new infection [see Table 2 Recurrence Intervals].

Sites in the Medical Record to Identify Infections:

1. Microbiology/Infectious section: contains culture results and may contain viral load results.
    a) Cultures: samples taken from the recipient incubated in media supporting organism growth. Presence of infection assessed by colony formation/growth and classification done via microscopy or other methods following incubation. Cultures are positive (growth of clinically relevant organism detected) or negative (no growth, growth of contaminants, or, for non-sterile sites, growth of expected or normal flora).
    b) Cultures can be from a variety of specimens: Blood, bone marrow, cerebrospinal fluid (CSF), stool, urine, lung fluid (from bronchoalveolar lavage, pleural effusion), abscess material, etc.
2. Molecular pathology/immunology:
    a) PCR Assay: samples taken from the recipient are manipulated using polymerase chain reaction techniques. Presence and classification of an organism are assessed by identifying DNA or RNA sequences unique to the specific organism. The lab report will document whether an organism is detected (positive) or not detected (negative) and may provide the number of copies of the organism (ex. CMV Viral load) or the cycle threshold (CT).
    b) Assays for 1,3-Beta-D-glucan and *Aspergillus* galactomannan may be found in this section of the medical record.
    c) Other molecular techniques are in use/development to identify organisms including next generation sequencing (NGS) and microbial cell-free DNA assays. Not all centers are using these methods and, as needed, discussion with a clinician for clinical interpretation of these results and their indication of infection should occur.
3. Pathology: histopathology (biopsy or fine needle aspirate) or other tissue diagnoses for various infections
4. Radiology: imaging studies
5. Progress notes are important for information regarding transfer to intensive care, requirement of mechanical ventilation, need for hemodialysis, etc.

Terminology

1. Bacteremia: the identification of bacteria in the bloodstream (i.e., “positive blood cultures”). Bacteremia can occur without organ (brain, heart, lungs) involvement or sepsis. There may be more than one bacterium identified in the bloodstream as well. Concomitant or polymicrobial infections are graded according to the grade of the infection with the higher grade of severity.
2. Skin and Soft Tissues Infection/Cellulitis: Suspected skin bacterial infection marked by erythema, pain, swelling of the involved area.
3. Viremia: the identification of virus in the bloodstream. This is often reported as a viral load or cycle threshold but may just be “positive”.

4. Invasive Fungal Infections (Table 3): Mold, yeast, PJP and endemic mycoses. Each of these infections then can be categorized based on the strength of evidence as proven, probable, and possible.
5. Fungemia: the identification of fungus (yeast, mold) in the bloodstream. If the organism is Candida spp., it is often called 'candidemia'.
    a. 1,3-Beta-D-glucan (Fungitell®) assay - a sample taken from the recipient is exposed to beta-d-glucan-specific antibodies followed by antibody-specific enzymes (ELISA method). Beta-d-glucan is a molecule found on multiple fungi including Candida and Aspergillus. The enzyme activity is quantified, and the test is considered positive if the activity is above the upper limit of normal (as indicated on the test report). If the report is unclear regarding whether the result is considered positive, negative, or equivocal, contact your center's laboratory to confirm if it supports a "Probable" fungal infection.

6. Aspergillus galactomannan Assay - a sample (i.e., serum, bronchial lavage, bronchial wash or CSF) taken from the recipient is exposed to galactomannan-specific antibodies followed by antibody-specific enzymes (ELISA method). Aspergillus galactomannan is a molecule specific to Aspergillus (though cross-reactivity can occur with other fungi). The enzyme activity is quantified, and the test is considered positive if the activity is above the upper limit of normal (as indicated on the test report). If the report is unclear regarding whether the result is considered positive, negative, or equivocal, contact your center's laboratory to confirm if it supports a "Probable" fungal infection.
7. Pneumonia: an infection of one or both lungs caused by bacteria, viruses, or fungi. An "infiltrate" is generally seen on chest imaging (x-ray, CT scan). Sputum cultures and/or studies of bronchoalveolar lavage fluid may identify the causative organism.
8. End/Deep Organ Involvement: this means that an infection involves solid organs such as the kidneys, lungs, brain, liver, etc.
9. Encephalitis/Meningitis: inflammation of the tissues of the brain (encephalitis) or of the membranes covering the brain/spinal cord (meningitis). This can be caused by bacteria, viral, or fungal organisms and is often identified by tests on the CSF and imaging studies.
10. Treatment (therapy): Not all positive cultures or PCR tests require starting treatment for infection. This is particularly common for certain viral infections. If it is unclear if the infection required treatment, discuss with the provider managing the patient. Therapy includes PO, IV, inhaled, or other delivery of medications.
11. Disseminated Infection: Two or more non-contiguous sites infected with the same organisms.
    a. For infections coded as "Disseminated" per the Infection Form, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.
    b. It can occur at any level of severity, but most will be grade 2 or 3
12. Polymicrobial Infections:
    a. If more than one bacterium is identified in the setting of bloodstream infection, the infection episode will be counted as a single infection episode
    b. If different types of pathogens are identified in the blood at the same time, these will be considered separate infection episodes (e.g., CMV reactivation with candidemia, adenovirus reactivation with a bacterial blood stream infection, etc.). If there is confusion about the designation of multiple vs. single infection episode, please discuss with the treating physician.

13. Oxygen Supplementation definitions:
    a. Low flow: oxygen by nasal cannula at ≤ 6L/minute

b. If patient requires supplemental oxygen at baseline (i.e., on 2L/minute) in the outpatient setting, an increase over the baseline oxygen needs (i.e., increase to 3L/minute) is required to meet "low flow" definition
c. High flow: oxygen by nasal cannula at >6L/minute
d. Positive Pressure: Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), intubation with mechanical ventilation

14. Sepsis (Adult) based on CDC's Sepsis Criteria:
    a. Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection.
    b. Hypotension: A systolic blood pressure of ≤100 mm Hg or a reduction of >40 mm Hg from baseline in the absence of other causes for hypotension
    c. Organ Dysfunction defined by Sequential Organ Failure Assessment (eSOFA) score: Any of the following
        i. Initiation of new vasopressor infusion
        ii. Initiation of mechanical ventilation (invasive or non-invasive)
        iii. Acute renal failure (only for patients without end-stage renal failure) defined as **Either:**
            a. Doubling of serum creatinine compared to baseline **OR**
            b. Decrease in estimated glomerular filtration rate (eGFR) by ≥ 50% compared to baseline
        iv. Hyperbilirubinemia defined as **BOTH**
            a. Total bilirubin ≥ 2mg/dl, **AND**
            b. Total bilirubin increase of ≥ 50% compared to baseline
        v. Thrombocytopenia (only for patients with baseline platelet count >100 cell/µL) defined as **BOTH**
            a. Platelet count <100 cell/µL, **AND**
            b. Decrease in platelet count ≥50% compared to baseline
        vi. Serum lactate ≥2 mg/dL
    d. Adult Sepsis Criteria: Any organ dysfunction PLUS a source and or suspected source of infection
    e. Adult Septic Shock: Sepsis plus vasopressors to maintain adequate blood pressure AND elevated lactate (>2mmol/L or >18 mg/dL).

15. Pediatric Sepsis based on International Pediatric Sepsis Consensus Conference (2005):
    a. Pediatric SIRS definition: Two or more of the following, one of which must be abnormal temperature or leukocyte count
        i. Core temperature >38.5C or < 36C
        ii. Tachycardia, otherwise unexplained and persistent in the absence of external stimulus, chronic drugs, or painful stimuli; or bradycardia, in < 1 year old, otherwise unexplained and persistent.
        iii. Tachypnea or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anesthesia
        iv. Leukocytosis or leukopenia for age (not secondary to chemotherapy) or >10% bands
    b. Pediatric Sepsis: Requires either Pediatric SIRS definition (Table 4) plus suspected or proven infection
    c. Pediatric Severe Sepsis: Sepsis plus either 1) cardiovascular dysfunction or ARDS; or 2) two or more other organ dysfunctions.
    d. Pediatric Septic Shock: Sepsis and cardiovascular organ dysfunction (below)
    e. Pediatric organ dysfunction criteria: (hematological criteria excluded)

I. Cardiovascular:

Despite administration of fluid bolus >40 ml/kg in 1 hour presence of

a. Hypotension <5th percentile for age (or per supplemental Table 1)

OR

b. Blood pressure elevation agents at any dose

OR

c. Two of the following:

I. Capillary refill > 5 secs
II. Core to peripheral temperature gap > 3°C
III. Urine output < 0.5 mL/kg/hr
IV. Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
V. Blood lactate > 2 x ULN

II. Respiratory:

a. ARDS

OR

b. Intubated

OR

c. >50% FiO2 to maintain SaO2 or SpO2 ≥ 92%

III. Neurological:

a. Glasgow Coma Score ≤ 11

OR

b. Acute change in mental status with a decrease in GCS ≥3 pts from abnormal baseline

IV. Renal:

a. Serum creatinine ≥ 2 x ULN for age

OR

b. 2-fold increase in baseline creatinine

V. Hepatic:

a. Total bilirubin ≥4 mg/dL

OR

b. ALT >2 x ULN for age

6.0 TABLE 1: BMT CTN SEVERITY GRADES BY INFECTION TYPE

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacteremia with skin flora [ex. Coag Neg Staph (CoNS, S. epi), Corynebacterium, or Cutibacterium (Proprioniobacterium)] requiring antibiotics for ≤ 14 days of therapy for treatment	Bacteremia due to other organisms (not skin flora)	Bacteremia with deep organ involvement (e.g. with new or worsening pulmonary infiltrates; endocarditis, brain abscess)
			Brain abscess or meningitis without bacteremia
	Bacterial focus NOS requiring antibiotics for ≤ 14 days of therapy for treatment (e.g urinary tract infection) Bacterial focus NOS requiring only topical, ocular, or otic treatments	Bacterial focus (including bacteremia) with persistent signs/symptoms or persistent positive cultures requiring antibiotics for > 14 days of therapy	Severe shock with bacteremia.
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy due to progression or systemic treatment for >14 days	Fasciitis or other skin and soft tissue infection requiring surgical debridement
	Any bacterial pneumonia not requiring supplemental oxygen	Any pneumonia documented or presumed to be bacterial requiring low flow oxygen	Bacterial pneumonia requiring high flow oxygen or positive pressure ventilation
	C difficile toxin or PCR positive stool with diarrhea < 1L/day without abdominal pain (child < 20 mL/kg/day)	C difficile toxin or PCR positive stool with diarrhea > 1L/day (child > 20 mL/kg/day) or with abdominal pain	*C difficile* toxin or PCR positive stool with ileus, colon dilation, or toxic megacolon, or need for surgical bowel resection (colectomy, ileostomy)

Bacterial infections Continued			
		Localized or diffuse infections requiring incision with or without drain placement but no debridement	Endocarditis
			Active Tuberculosis infection
Fungal infections	Mucocutaneous candidiasis (excluding esophagitis) (e.g., oral thrush, vaginal candidiasis) and dermatophyte infections (tinea)	*Candida* esophagitis diagnosed by endoscopy	Fungemia including candidemia
		Fungal sinusitis confirmed radiologically without orbital, brain or bone involvement.	Fungal sinusitis confirmed radiologically with orbital, brain, or bone involvement
		Fungal pneumonia or pulmonary nodules (unless requiring high-flow oxygen or positive pressure ventilation)	Fungal pneumonia or pulmonary nodules presumed to be fungal requiring high-flow oxygen or positive pressure ventilation
		Fungal skin and soft tissue infection without fungemia, involvement of other sites, or need for debridement	Disseminated infections (defined as multifocal pneumonia with 1 or more additional site of involvement, cutaneous spread, CNS involvement) with any fungus (yeast or mold)
		Pneumocystis jirovecii pneumonia (unless requiring high-flow oxygen or positive pressure ventilation)	*Pneumocystis jirovecii* pneumonia requiring high-flow oxygen or positive pressure ventilation

Viral infections	Mucosal (mouth, esophagus, vaginal, penile) HSV infection requiring oral antiviral therapy or observation	Mucosal (mouth, esophagus, vaginal, penile) HSV infection requiring IV nutrition or IV antiviral therapy	HSV infection with end organ involvement (encephalitis, hepatic, lung)
	Dermatomal zoster (shingles) affecting ≤ 2 dermatomes	VZV infection involving 3 or more dermatomes	Severe VZV infection with end organ involvement (coagulopathy, encephalitis, hepatic, lung, eye)
	Asymptomatic CMV viremia not requiring treatment EBV viremia not requiring treatment	CMV viremia requiring therapy or CMV viremia requiring a change in therapy due to resistance or with persistent viremia beyond 4 weeks while on treatment	CMV end-organ involvement (lung, intestines, eye)
	EBV viremia not requiring treatment	EBV viremia requiring institution of therapy	EBV PTLD
	Adenoviral infection not requiring treatment	Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment	Adenovirus with end-organ involvement including pneumonitis but excluding conjunctivitis and upper respiratory tract infections
	HHV-6 viremia not requiring treatment	HHV-6 infection (e.g., symptoms, cytopenias) requiring treatment	HHV-6 with end-organ involvement (such as encephalitis, hepatitis, pneumonitis)
	BK viremia or viruria with cystitis not requiring intervention except anti-spasmodics or pain medication	BK viremia or viruria with clinical consequence requiring therapy (continuous bladder irrigation, antiviral therapy) and/or surgical intervention	BK viremia or viruria with end organ damage (i.e., renal failure requiring dialysis)

Viral infections Continued	Symptomatic upper and lower tract respiratory virus (excludes adenovirus, includes SARS-CoV-2 [COVID]) not requiring oxygen	Enterocolitis with enteric (GI) viruses	
		Lower tract respiratory viruses (excludes adenovirus, includes SARS-CoV-2 [COVID]) requiring low flow oxygen	Lower tract respiratory viruses (excludes adenovirus requiring or high flow oxygen or positive pressure ventilation
		SARS-CoV-2 (COVID) infection requiring low flow oxygen	SARS-CoV-2 [COVID]) requiring or high flow oxygen or positive pressure ventilation
	Viremia (virus not otherwise specified) not requiring therapy		Any viral encephalitis, meningitis, or end organ disease
Parasitic infections	Giardiasis or other parasitic gastrointestinal infection with diarrhea <1L / day (<5 episodes / day) (child < 20 mL/kg/day)	Giardiasis or other parasitic gastrointestinal infection with diarrhea > 1 L / day (5 episodes / day) (child > 20 mL/kg/day) or with abdominal pain	
	Chronic strongyloidiasis treated with oral ivermectin or other oral therapies		Strongyloides hyperinfection or disseminated infection
	Toxoplasma DNAemia without organ involvement resolving spontaneously (without treatment)	Toxoplasma DNAemia without organ involvement requiring treatment	CNS or another organ toxoplasmosis

Non-microbiologically defined infections	Pneumonia or bronchopneumonia not requiring supplemental oxygen	Pneumonia or bronchopneumonia requiring low flow oxygen	Any acute pneumonia requiring high flow oxygen or positive pressure ventilation
	Fever with negative cultures responding to treatment within 14 days	Sepsis without an identified organism (excluding patients receiving immune effector therapy diagnosed with cytokine release syndrome (CRS))	Septic shock without an identified organism (excluding patients receiving immune effector therapy diagnosed with CRS)
	Clinically documented infection not requiring inpatient management	Typhlitis without severe sepsis, ileus, or need for surgical intervention	Typhlitis requiring surgical indication as grade 3

7.0 Table 2: Recurrence Intervals - to Determine Whether an Identified Organism Reflects a Previously Diagnosed Infection or a New Infection

Type of Infection	Recurrence Internal reflects a previously diagnosed Infection
Cytomegalovirus, Herpes simplex virus, Epstein-Barr virus, and Human herpes virus 6 related infections	2 months (< 60 days)
Varicella zoster virus	2 weeks (< 14 days)
Polyomavirus	2 months (< 60 days)
Bacterial, non-*C. difficile*	1 week (< 7 days)
Bacterial, *C. difficile*	1 month (< 30 days)
Yeast infections (non-cryptococcal)	2 weeks (< 14 days)
Invasive mold infections, dimorphic fungal infection, and cryptococcal infection	3 months (< 90 days)
Helicobacter pylori infection	1 year (< 365 days)
Respiratory viruses: Adenovirus, Enterovirus, Influenza A &B, Respiratory syncytial virus, Parainfluenza, Rhinovirus, and SARS-CoV-2 infections	3 months (<90 days)
Parasitic infections (excluding chronic strongyloidiasis)	3 months (< 90 days)
Chronic strongyloidiasis (defined as positive serologies without detection of larvae)	2 years

8.0 TABLE 3: DEFINITIONS FOR INVASIVE FUNGAL DISEASE

Table 3a: Invasive fungal disease (IFD) due to yeasts, yeast-like fungi, and dimorphic fungi

IFD type	Criteria for proven IFD	Criteria for evidence of IFD
Endemic mycoses (for example *Coccidioides*, *Blastomyces*, *Histoplasma*)	*At least one of these criteria:* • Histopathology or direct microscopy of specimens obtained from an affected site showing the distinctive form of the fungus, *or* • Culture of the fungus from blood or specimens from an affected site	Clinical diagnosis (pulmonary, cutaneous, osseous, GI, and/or CNS) and initiation of treatment for endemic mycosis *Plus at least one of these criteria:* • *Histoplasma* or *Blastomyces* antigen in urine, serum, or body fluid • Antibody to *Coccidioides* in cerebrospinal fluid • Two-fold rise of *Coccidioides* antibodies in 2 consecutive serum samples
Pneumocystis jirovecii pneumonia (PJP or PCP) (table continues on the next page)	Detection of the organism microscopically in tissue, BAL fluid, or sputum using conventional or immunofluorescence staining	Clinical diagnosis of PJP with initiation of treatment *Plus at least one of these criteria:* • *ß*-D-glucan (Fungitell®) ≥8 0 ng/L (pg/mL) from one serum sample (if other etiologies for elevated Fungitell have been excluded) • Detection of *Pneumocystis jirovecii* DNA by PCR from a respiratory tract specimen

Cryptococcal infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast consistent with *Cryptococcus* species (based on morphology or PCR) • Recovery of *Cryptococcus* by culture of a sample obtained by a sterile procedure from a normally sterile site showing a clinical or radiological abnormality consistent with an infection • Blood culture with *Cryptococcus* • Positive cryptococcal antigen in cerebrospinal fluid or blood	Clinical diagnosis of cryptococcal infection (pulmonary, CNS, cutaneous, disseminated with initiation of treatment *Plus at least one of these criteria:* • Radiographic evidence of meningeal inflammation • Lesion on imaging consistent with cryptococcal disease
Candida and other yeast infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast • Recovery of yeast by culture of a sample obtained by a sterile procedure from a normally sterile site showing a clinical or radiological abnormality consistent with an infection • Blood culture with yeast	*<u>Applies to Candida only</u>* *Candidemia within the previous 2 weeks with at least one of these criteria:* • Radiographic findings consistent with abscesses in liver, spleen, or brain • Meningeal enhancement • Progressive retinal exudates or vitreal opacities on ophthalmologic examination *Plus initiation of treatment and at least one of these criteria:* • *ß*-D-glucan (Fungitell®) ≥80 ng/L (pg/mL) from one serum sample (if other etiologies for elevated Fungitell® have been excluded) • Positive T2Candida®

Table 3b: Invasive fungal disease (IFD) due to *Aspergillus* and other molds

Proven mold infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a tissue specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage • Recovery of a mold by culture of a specimen obtained by a sterile procedure from a normally sterile site (with clinical or radiological evidence of an infection), excluding BAL fluid, sinus specimens, and urine • Blood culture that yields a mold in the context of a compatible infection • Identification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue		
Probable mold infection	Clinical feature **Pulmonary aspergillosis and other pulmonary mold infections** *At least one of these patterns are seen on CT imaging:* • Dense, well-circumscribed lesions • Air crescent sign • Cavity • Wedge-shaped, segmental, or lobar consolidation • Reverse halo sign (for molds other than *Aspergillus*) ***Aspergillus* or other mold tracheobronchitis** Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopy ***Aspergillus* and other mold sino-nasal disease** *At least one of these criteria:* • Acute localized pain • Nasal ulcer with black eschar • Extension from the paranasal sinus across bony barriers ***Aspergillus* and other mold CNS infection** Focal lesions or meningeal enhancement on imaging	**AND**	Mycologic evidence • *Aspergillus* or other mold recovered by culture from sputum, BAL, bronchial brush, or aspirate • Microscopic detection of mold from sputum, BAL, bronchial brush, or aspirate • *At least one of these criteria applied to Aspergillus galactomannan antigen:* ○ Single serum or plasma: ≥ 1.0 ○ BAL fluid: ≥ 1.0 ○ Single serum or plasma: ≥ 0.7 plus BAL fluid ≥ 0.8 ○ CSF: ≥ 1.0 • *At least one of these criteria applied to organism specific PCR (e.g., Aspergillus or Mucor):* ○ Plasma, serum, or whole blood: 2 or more consecutive PCR tests positive ○ BAL fluid: 2 or more PCR tests positive ○ At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

9.0 Table 4: Pediatric Systemic Inflammatory Response Syndrome Definitions and Laboratory Values Ranges for the four Pediatric Age Groups [Ш]

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia ($10^3/mm^3$WBC)	Hypotension Systolic BP mmHg
1 mo to 1 yr	>180	<90	>34	>17.5 to <5.0	<75
>1 yr to 5 yr	>140	NA	>22	>15.5 to <6.0	<74
>5 yr to 12 yr	>130	NA	>18	>13.5 to <4.5	<83
>12 yr to < 18 yr	>110	NA	>14	>11 to <4.5	<90

Ш Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005 Jan;6(1):2-8. doi: 10.1097/01.PCC.0000149131.72248.E6. PMID: 15636651.