Infectious Complications after Stem Cell Transplant

Data collection

Catherine Cordonnier
Henri Mondor Hospital
Créteil, France

Data manager session
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WHY to collect ID data?

Infection is a major cause of *morbidity* after transplant

Infection is a major cause of *death* after transplant

-> Infection may compromise the benefit of transplant
OBJECTIVES

To know about the epidemiology, agents, symptoms, timing, mortality, of these infections

✓ Better knowledge = early diagnosis = early treatment = better prognosis

✓ Elaborate preventive strategies:
  Drug prophylaxis, vaccines, preventive measures
Classical timing of infection after allogeneic MA HCT (first 3 months)

- **Fungal disease:**
  - CANDIDA
  - ASPERGILLUS

- **HSV**
  - 1 month

- **Bacteria**
  - P carinii

- **CMV**
  - 2 months

- **HCT**
  - 3 months
Infectious complications after SCT

Some are very classical:
*Pneumocystis carinii (now: jiroveci) pneumonia*

Some are « new » infections: *H1N1*

Many are only suspected:
FEVER +++, no microbiological proof…
Are they really infections??

What level of proof for « infection »?
Is there a relationship between both?

The European Group for Blood and Marrow Transplantation
SYMPTOMS of infection

✓ Fever

✓ Symptoms of localized infection
  Pneumonia, Hepatitis, CNS, Gut, Skin, Cystitis, Retinitis

✓ Symptoms of generalized, usually severe, infections:
  Shock, Acute Respiratory Distress Syndrome (ARDS), Multi organ failure (MOF)
PATHOGENS

1 – BACTERIA

2 – FUNGI

3 – VIRUS

4 - PARASITES
**PATHOGENS (1) Bacteria**

<table>
<thead>
<tr>
<th>Gram +:</th>
<th>Streptococcus pneumoniae +++</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Other Streptococci, including enterococci</td>
</tr>
<tr>
<td></td>
<td>Staphylococci</td>
</tr>
<tr>
<td></td>
<td><em>Others: Corynebacteriae, bacillus, lactobacillus</em>…</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram -:</th>
<th>E. coli, Klebsiellae, Proteus, Enterobacter, Serratia, Providencia, Citrobacter, Pseudomonas sp., Salmonella</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haemophilus influenzae …</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others:</th>
<th>Legionella</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mycobacteria: Tuberculosis, or « atypical »</td>
</tr>
</tbody>
</table>
Yeasts: **CANDIDA**, cryptococcus, trichosporon

Molds: **ASPERGILLUS**, mucormycosis (zygomycosis), geotrichum, fusarium

**Pneumocystis carinii** (jiroveci)
### Pathogens (3) Virus

#### Herpes Viruses
- **HSV**: Herpes simplex virus
- **VZV**: Varicella zoster virus
- **EBV**: Epstein Barr virus
- **CMV**: Cytomegalovirus
- **HHV6**: Human herpes virus 6
- **HHV7 and HHV8**

#### Respiratory Viruses
- **RSV**: Respiratory syncytial virus
- Other (Influenza, para influenza)

#### Adenovirus

#### Hepatitis Virus
- **(HAV)**, **HBV**, **HCV**
- Papovavirus, Parvovirus
PATHOGENS (4) Parasites

Toxoplasmosis

Others
Bugs are tricky

- Some pathogens persist in the organism after a primary infection:
  - Herpes viruses
  - Toxoplasmosis

- Some pathogens may be normally found in humans, without any symptom of infection:
  - HHV6 in blood
  - Candida in stools
How to identify the pathogen?

Directly: +++
Direct exam, culture
Identification of parts of the agent, such as antigens (CMV, Fungi) or DNA (PCR)

Indirectly: Detection of specific antibodies
Useful to know BEFORE transplant who can reactivate
Ex: CMV -/- = no risk of CMV infection
Not useful for diagnosis of acute infection after transplant (except for Legionella, and Hepatitis viruses).
Definitions of Infectious Diseases and Complications after Stem Cell Transplant

Available on the EBMT website, IDWP, version # 1, 2001
Definitions of Infectious complications (2)

Written for:
- definitions in the registry
- definitions in the group
All are not useful for data collection

TWO PARTS
1) Clinical entities
2) Specific definitions related to pathogens
To facilitate your work …

Show the IDWP Definitions to the physicians of your center
Ask them if they agree with them

If YES: Ask them to use them and the resident for the medical reports in the charts of the patients +++

If NO: Encourage them to write us and make comments!
Infectious complications in the EBMT registry

WHERE are they collected?

« Complications within the first 100 days » MED B

In: ALLO
AUTO

Follow-up: by disease
### FOLLOW UP

**Unique Identification Code (UIC)**  
_________________________  

**Hospital Unique Patient Number**  
_________________________  

**Initials:**  
_________________________  

**Date of birth**  
__ dd __ mm __ yyyy  

**Date of last transplantation for this patient:**  
__ dd __ mm __ yyyy  

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### PATIENT LAST SEEN

**DATE OF LAST CONTACT OR DEATH:**  
__ dd __ mm __ yyyy  

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### COMPLICATIONS SINCE LAST REPORT

Please use the document “Definitions of Infectious Diseases and Complications After Stem Cell Transplantation” to fill these items. The document is available from [www.ebmt.org](http://www.ebmt.org), Infectious Diseases Working Party.

#### Infection Related Complications V

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathogen</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia/fungemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Blood isolation of virus by viremia  
(for CMV disease and other viral diseases, please enter the data in the section "Endogenous diseases" below) |          |      |
| Blood isolation of virus by antigenemia |          |      |
| Blood isolation of virus by nucleic acid test |          |      |
| Systemic Symptoms of Infection |          |      |
| Septic shock              |          |      |
| ARDS                      |          |      |

Reformatted for Promise 2, December 04  
EBMT - MED-B 2003 ACUTE LEUKAEMIA – p.10
<table>
<thead>
<tr>
<th>Type</th>
<th>Pathogen</th>
<th>Viruses</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>S. pneumoniae</td>
<td>HSV</td>
<td>Other respiratory virus (influenza, parainfluenza, (\text{rhinovirus}))</td>
</tr>
<tr>
<td></td>
<td>Other gram positive (i.e.: other streptococci, staphylococci, (\text{listeria}) ...)</td>
<td>VZV</td>
<td>Adenovirus</td>
</tr>
<tr>
<td></td>
<td>Haemophilus influenzae</td>
<td>EBV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other gram negative (i.e.: (E. \text{coli}) klebsiela, proteus, serratia, (\text{pseudomonas}) ...)</td>
<td>CMV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Legionella sp</td>
<td>HHV-6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycobacteria sp</td>
<td>RSV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: ...........................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td>Candida sp</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspergillus sp</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumocystis carinii</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Other: ...........................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasites</td>
<td>Toxoplasma gondii</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: ...........................................</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NON INFECTION RELATED COMPLICATIONS**

- No complications
- Yes

**Type (Check all that are applicable for this period)**

- Idiopathic pneumonia syndrome
- VOD
- EBV lymphoproliferative disease
- Cataract
- Haemorrhagic cystis, non infectious
- ARDS, non infectious
- Multiorgan failure, non infectious
- TTP / HUS
- Renal failure requiring dialysis
- Result of blood group incompatibility
- Aseptic bone necrosis
- Other: ...........................................

**COMMENTS**

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**Unique Patient Number (UPN): ...........................................**

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**dd mm yyyy**
How to collect the data (1)?

From the **medical report**, consider all the episodes which have been suspect of infection

1 – Enter each episode by symptoms and clinical presentation

2 – Associate the corresponding pathogen(s) if present

*Check in the definitions that for **THIS** focus and **THAT** (these) pathogen(s), there is an established relationship.*
(1) **Bacteremia**
Viable bacteria in the blood  ->  2.1.1.
1 + blood culture, except for coagulase negative
Staph (CNS): 2 blood cultures needed for CNS

(2) **Fungemia**
Candida or any other yeast: 1 + blood culture

(3) **Viremia**
Demonstration of the virus in blood
Different clinical significance according to the virus
Septic shock

Needs to define Sepsis before

**Sepsis:** temperature >38°C or <36°C
HR > 90/mn
RR> 20 /mn or PaCO2<32 mm Hg
WBC> 12 000 or < 4000 or > 10% immature forms

**Septic shock** = Sepsis + hypotension despite adequate fluid resuscitation
Usual cause: bacteria +++, candida
Pneumonia

New or progressive pulmonary infiltrates due to inflammation of the lung
Clinical or imaging diagnostic

Two thirds have an infectious cause in SCT

Causal diagnosis done by endoscopic exams
(fibroscopy with BAL) or lung biopsy
Rarely by indirect methods
How to connect this pneumonia with the pathogen I found in the lung?

- **I found a bacteria:**
  Go to section 2.1.2 « Bacterial pneumonia », check the patient has the quantitative criteria

- **I found Aspergillus:**
  Go to 2.2.1 EORTC criteria for aspergillus pneumonia

- **I found CMV:**
  Go to section 2.3.3. How was CMV found?
  Culture + from BAL : Yes  PCR + from BAL: No

- **I did not find any agent**, and no cause is mentioned in the chart: Pathogen « unknown »
Fungal infections (1)

International definitions published by EORTC/MSG
Ascioglu et al. CID 2002
De Pauw et al. CID 2008

Mainly elaborated for prospective antifungal trials
Three categories:
- PROVEN
- PROBABLE
- POSSIBLE

Composite system: host factors, microbiological criteria, clinical criteria (major/minor)
Fungal infections (2)

Initial objectives of the EBMT data collection:

Identify all the patients/type/cause of FI, without distinction between proven / probable /possible

Ask HELP to your doctor for Fungal Infections!
Patient 1

CML, 35 y, male, Allogeneic geno-id SCT on January 2, 2001
Cy-TBI. CMV D+/R+
Aplastic phase: fever of unknown origin, no documented infection

Day 21: Acute GvHD -> steroids 2mg/kg

Day 40: hospitalized for diarrhea, and fever.
Colonoscopy performed: Colitis, moderate GvHD.
Biopsies of the colon: histology and IF positive for CMV.
Treated with ganciclovir. Improvement. Discharged.

Day 65: fever, pneumonia. Fibroscopy with BAL: no bacteria isolated but the medical chart says « legionellosis » because of Legionella antigens in the urines
1st episode: Fever of unknown origin: 

*not to be collected*
2nd episode:

✓ Colitis: no specific definition given. Belongs to « gut infection »

✓ Is it CMV colitis? Go to section 2.3.3.
    … biopsy specimen … YES
Patient 1

3rd episode:

✓ Is it pneumonia? Go to section 1.6.1: Yes

✓ Is this pneumonia due to legionellosis?
   Section 2.1.4.: Antigens in urines: Yes
Patient 2

Female, 48 y, NH Lymphoma
Autologous SCT in CR2
Conditioning regimen: BEAM
Before transplant: CMV +, HCV +

Aplastic phase: fever of unknown origin (F OU), no documented infection, broad spectrum antibiotics. Resolution. Recover from neutropenia on day 15, discharged on day 18.

Day 35: Regular visit: asthenia. Dyspnea, cough, fever.
Chest X ray: interstitial pneumonitis.
Sputum: streptococci
Fibroscopy with BAL: *P. carinii* (= *P. jiroveci*)
Patient 2

First episode: FUO during the neutropenic phase

--> Not collected in the registry
Second episode:

- Is it a pneumonia? Go to 1.6.1 -> Yes, it is

- Is this pneumonia due to streptococci found in the sputum? Go to 2.1.2 -> NO

- Is this pneumonia due to P. carinii? Go to 2.2.2 -> Yes, it is
Thank you for your attention