Infections in the Compromised Host
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Disclosures

- Consultant
  - Shionogi
  - MicroGenDx

- Many slides courtesy of Dr. David van Duin
Overview

- The immunocompromised host
- Testing in the immunocompromised host
- HIV/AIDS
- Autoimmune diseases/biologics
- Solid organ transplant
- Stem cell transplant
- Neutropenia
- Burn

General approach to ID

- Clinical history and physical exam
  - Be thorough
  - Get outside data

- Host
  - Is their immune system normal?
  - What parts of their immune system are abnormal?

- Environment
  - Travel/military service, employment, sick contacts, animal exposures, sexual contacts, hobbies
Who is the host?

- What parts of their immune system are abnormal?
  - Genetic mutations
  - Comorbidities
  - Immunomodulators, chemotherapy
  - Recent treatment for rejection/GVDH/disease flare
  - Prophylactic antimicrobials

Immunocompromising states

- Congenital/acquired immunodeficiency syndromes (CGD, HIV)
- Diabetes
- End-stage liver and kidney disease
- Autoimmune/rheumatologic diseases
- Solid organ transplantation
- Stem cell transplantation
- Malignancy, chemo, neutropenia
- Burns
Net state of immunosuppression

- Type, dose, and timing of immunosuppressive agents administered
- Nutritional, metabolic factors; renal dysfunction; age; comorbidities
- Breach of mucosal barriers (skin, gut); foreign bodies
- Neutropenia
- Lymphopenia
- Hypogammaglobulinemia

Making a diagnosis in immunocompromised hosts

- Clinical presentation
  - May be atypical
  - Fever or pain may be mild or absent
  - Lab changes may be subtle (ie, UA with few WBC in neutropenia)

- Imaging
  - Higher resolution imaging may be needed to detect subtle infection, particularly in the chest and sinuses
Making a diagnosis in immunocompromised hosts

- Serological tests may be unreliable
  - Antibody tests are less reliable after transplant or transfusions
  - Cross-reactivity, false-positives

- Biochemical/immunodiagnostic antigen tests
  - Not always sensitive enough (ie urine Legionella Ag)
  - Not always specific enough, cross-reactivity (ie urine Histoplasma Ag)

Making a diagnosis in immunocompromised hosts

- Molecular testing (NAA, NAT, NAAT, PCR)
  - Detects genetic material (DNA or RNA)
  - Blood, CSF, respiratory fluids, tissue biopsy, stool, urine
  - Can be quantitative (QNAT) for blood
  - Can be overly sensitive: does not always correlate with disease
  - Does not differentiate between live & dead organisms

- Histology & immunohistochemistry
  - More specific (preferred) for diagnosing tissue-invasive disease
  - “the gold standard” but not always realistic
Clinical pearls

- Reactivation of prior infection suggests a high net state of immunosuppression
  - #1 Reduce immunosuppression if possible
- Don’t get the disease: When in doubt isolate
  - Infection Control Isolation Policies
  - Handwashing may be better for non-enveloped viruses (esp. enteric viruses) and spores (*Clostridium*)

Preventing reactivation of latent infections

- Who to screen
  - HIV
  - Cancer chemotherapy
  - Organ transplant
  - Screening protocols may differ among above groups
- Why screen
  - Early identification and treatment
  - Provide therapy to suppress infection
Preventing reactivation of latent infections

Viral
- Cytomegalovirus (CMV)
- Epstein-Barr (EBV)
- Hepatitis (HBV, HCV)
- Herpes simplex (HSV I & II)
- HIV
- Varicella-zoster (VZV)
- BK virus (GU disease)

Bacterial
- Syphilis
- Tuberculosis

Parasitic
- Toxoplasma gondii
- Strongyloides

HIV opportunistic infections

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>Kaposi sarcoma, pulmonary TB, VZV, bacterial pneumonia, lymphoma</td>
</tr>
<tr>
<td>&lt;250</td>
<td>PJP, esophageal candidiasis, PML, HSV</td>
</tr>
<tr>
<td>&lt;100</td>
<td>Cerebral toxoplasmosis, HIV encephalopathy, Cryptococcus, military TB</td>
</tr>
<tr>
<td>&lt;50</td>
<td>CMV retinitis, atypical mycobacteriosis</td>
</tr>
</tbody>
</table>
Biologics

Figure 1
New chemical entities and biologics approved by the FDA in the last two decades

G. de la Torre B, Albericio F. *Molecules* 2019, 24, 809.

NME = new molecular entity

Biologics for inflammatory arthritis

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Brand name</th>
<th>Biosimilar brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour necrosis factor inhibitors (TNF-inhibitors)</td>
<td>Golimumab Cetolizumab Etanercept Adalimumab Infliximab</td>
<td>Simponi Cimzia Enbrel Humira Remicade</td>
<td>Brenzys Flixcell Ernissima Inflectra Jaxinab Remisima Reflexis</td>
</tr>
<tr>
<td>Interleukin-6 inhibitor</td>
<td>Tocilizumab</td>
<td>Actemra</td>
<td></td>
</tr>
<tr>
<td>Interleukin-1 inhibitor</td>
<td>Anakinra</td>
<td>Kineret</td>
<td></td>
</tr>
<tr>
<td>Targeting B-lymphocytes (B-cells)</td>
<td>Rituximab</td>
<td>Mabthera</td>
<td>B-cells (a type of white blood cell)</td>
</tr>
<tr>
<td>Targeting T-lymphocytes (T-cells)</td>
<td>Abatacept</td>
<td>Orecia</td>
<td>T-cells (a type of white blood cell)</td>
</tr>
</tbody>
</table>


http://journalsblog.gastro.org
**TNF-alpha inhibitor-associated infections**

**WARNING: SERIOUS INFECTIONS AND MALIGNANCY**
*See full prescribing information for complete boxed warning.*

**SERIOUS INFECTIONS (5.1, 6.1):**
- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.
- Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.
- Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

**Tocilizumab-associated (anti-IL-6) infections**

**WARNING: RISK OF SERIOUS INFECTIONS**
*See full prescribing information for complete boxed warning.*

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)
- If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)
Rituximab-associated (anti-CD20) infections

WARNING: FATAL INFUSION-RELATED REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

See full prescribing information for complete boxed warning.

- Fatal infusion-related reactions within 24 hours of RITUXAN infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue RITUXAN infusion for severe reactions (5.1).
- Severe mucocutaneous reactions, some with fatal outcomes (5.2).
- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.3).
- Progressive multifocal leukoencephalopathy (PML) resulting in death (5.4).

Biologics for multiple sclerosis

<table>
<thead>
<tr>
<th>Infections</th>
<th>Alemtuzumab (anti-CD52)</th>
<th>Interferon-beta 1a inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>71%</td>
<td>53%</td>
</tr>
<tr>
<td>Serious infections</td>
<td>3% (appendicitis, gastroenteritis, PNA, HZV, tooth infection)</td>
<td>1%</td>
</tr>
<tr>
<td>Herpes viral infection</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Cervical HPV</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Active or latent TB</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>Acute acalculous cholecystitis</td>
<td>0.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Other reported infections</td>
<td>Listeria, PJP, Nocardia, CMV, Aspergillus, dimorphic fungus</td>
<td></td>
</tr>
</tbody>
</table>

http://products.sanofi.us/Lemtrada/Lemtrada.pdf
Eculizumab-associated infections (C5 - terminal complement inhibitor)

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.

- Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See Serious Meningococcal Infections (5.1) for additional guidance on the management of the risk of meningococcal infection.)

- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Solid organ transplant

2018: More transplants than ever

There were more than 10,700 deceased donors in 2018. 8th consecutive record breaking year.


*Based on OPTN data as of Jan. 8, 2019. Data subject to change based on future data submission or correction.
Solid organ transplant

The Balance in Immunosuppression

CNI TOXICITY
INFECTION
REJECTION

<table>
<thead>
<tr>
<th></th>
<th>Belatacept</th>
<th>rATG Alectuzumab</th>
<th>Rituximab Alectuzumab</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits costimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depletes T-cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depletes B-cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depletes plasma cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. A schematic of the mode of action of key immunosuppressants. APC, antigen presenting cell; B, B-cell; C, complement.

O’Leary et al. Transplantation. 2016: 100;39-53
Alemtuzumab

- Anti-CD52
- Profound and sustained T-, B- and NK cell depletion
- Use in induction and/or rejection treatment

Peleg et al. CID 2007;44:204

Increased OI risk when alemtuzumab used for rejection

Table 2. Opportunistic infections (OIs) among the 547 organ transplant recipients who received ≥1 dose of alemtuzumab from September 2002 through March 2004.

<table>
<thead>
<tr>
<th>OI</th>
<th>No. (%) of OIs</th>
<th>Time to infection</th>
<th>OR if receiving alemtuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>62 (100)</td>
<td>94 (2-329)</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV disease</td>
<td>16 (26)</td>
<td>85 (7-264)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4</td>
<td></td>
<td>1 (3)</td>
</tr>
<tr>
<td>GI infection</td>
<td>1</td>
<td></td>
<td>3 (8)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3</td>
<td></td>
<td>1 (3)</td>
</tr>
<tr>
<td>Febrile viral syndrome</td>
<td>1</td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>EBV disease</td>
<td>3 (5)</td>
<td>96 (42-268)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>PTLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV negative PTLD</td>
<td>2 (3)</td>
<td>24, 169</td>
<td>0 (0)</td>
</tr>
<tr>
<td>HHV-6 infection</td>
<td>1 (2)</td>
<td>222</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BK virus infection</td>
<td>12 (19)</td>
<td>134 (18-328)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Parvovirus infection</td>
<td>1 (2)</td>
<td>326</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>1 (2)</td>
<td>51 (2-265)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cryptococcal infection</td>
<td>2 (3)</td>
<td>54, 200</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>1 (2)</td>
<td>34</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>1 (2)</td>
<td>87</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Scedosporum infection</td>
<td>2 (3)</td>
<td>57, 66</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocardia</td>
<td>4 (6)</td>
<td>74 (54-96)</td>
<td>0 (4)</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>3 (5)</td>
<td>77 (63-323)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1 (2)</td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nontuberculous</td>
<td>2</td>
<td></td>
<td>1 (2)</td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>1 (2)</td>
<td>59</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Balamutha mandrillaris</td>
<td>1 (2)</td>
<td>2</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Peleg et al. CID 2007;44:204

Table 3. Characteristics of organ transplant recipients who received alemtuzumab, according to the development of an opportunistic infection (OI).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recipients with an OI after receiving alemtuzumab (n = 56)</th>
<th>Recipients without an OI after receiving alemtuzumab (n = 491)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>51 (18-77)</td>
<td>51 (18-82)</td>
<td>1.5 (0.9-2.6)</td>
<td>.14</td>
</tr>
<tr>
<td>Sex, female</td>
<td>29 (50)</td>
<td>195 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant received</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>16 (29)</td>
<td>235 (48)</td>
<td>0.4 (0.2-0.8)</td>
<td>.007</td>
</tr>
<tr>
<td>Liver</td>
<td>8 (14)</td>
<td>152 (31)</td>
<td>0.4 (0.2-0.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Lung or heart/lung</td>
<td>12 (21)</td>
<td>44 (9)</td>
<td>2.8 (1.4-5.6)</td>
<td>.005</td>
</tr>
<tr>
<td>Pancreas or kidney/pancreas</td>
<td>6 (11)</td>
<td>44 (9)</td>
<td>1.2 (0.5-3.0)</td>
<td>.67</td>
</tr>
<tr>
<td>Intestinal or multivisceral</td>
<td>14 (25)</td>
<td>16 (3)</td>
<td>9.9 (4.5-21.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous transplant received</td>
<td>8 (14)</td>
<td>72 (15)</td>
<td>0.9 (0.4-2.1)</td>
<td>.9</td>
</tr>
<tr>
<td>Alemtuzumab received</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For induction therapy</td>
<td>16 (29)</td>
<td>338 (69)</td>
<td>0.2 (0.1-0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>For reyection therapy</td>
<td>40 (71)</td>
<td>153 (31)</td>
<td>5.5 (3.0-10.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Doses of alemtuzumab received, no. (range)</td>
<td>2 (1-6)</td>
<td>1 (1-5)</td>
<td>2.3 (1.7-3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Received pulse methylprednisolone</td>
<td>15 (27)</td>
<td>152 (31)</td>
<td>0.9 (0.4-1.9)</td>
<td>.5</td>
</tr>
<tr>
<td>Received ≥2 pulses of methylprednisolone</td>
<td>10 (19)</td>
<td>49 (10)</td>
<td>2.0 (0.9-4.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Received another lymphocyte-depleting antibody</td>
<td>29 (50)</td>
<td>117 (24)</td>
<td>3.2 (1.8-5.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Peleg et al. CID 2007;44:204
Timeline of infectious risk (SOT)

Common Infections in Solid-Organ Transplant Recipients

- **<1 Month**
  - Infection with antimicrobial-resistant species:
    - MRSA
    - VRE
    - Candida species (non-albicans)
  - Aspiration
  - Catheter infection
  - Wound infection
  - Anastomotic leaks or ischemia
  - Clostridium difficile colitis
  - Donor-derived infection (uncommon):
    - HSV, LCMV, rhinovirus
    - West Nile virus
    - HIV, Trypanosoma cruzi
  - Recipient-derived infection (colonization):
    - Aspergillus, pseudomonas

- **1–6 Months**
  - With PCP and antiviral (CMV, HBV) prophylaxis:
    - Polyomavirus BK infection, nephropathy
    - C. difficile colitis
    - HCV infection
    - Adenovirus infection, influenza
    - Cryptococcus neoformans infection
    - Mycobacterium tuberculosis infection
    - Anastomotic complications
  - Without prophylaxis:
    - Pneumocystis
    - Infection with herpesviruses (HSV, VZV, CMV, EBV)
    - HVB infection
    - Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, T. cruzi

- **>6 Months**
  - Community-acquired pneumonia, urinary tract infection
  - Infection with aspergillus, atypical molds, mucor species
  - Infection with nocardia, rhodococcus species
  - Late viral infections:
    - CMV infection (colitis and retinitis)
    - Hepatitis (HBV, HCV)
    - HSV encephalitis
    - Community-acquired (SARS, West Nile virus infection)
    - JC polyomavirus infection (PML)
    - Skin cancer, lymphoma (PTLD)

Fishman. NEJM 2007;357:2601

Viral infections after SOT

Fig. 2. Median time of detecting herpesviruses by polymerase chain reaction

Griffiths. Antiviral Res 2006;2-3:192
Risk for infection after SOT

- Exposures
  - Donor-derived
  - Recipient-derived
  - Nosocomial
  - Community

- “net state of immunosuppression”

Donor-derived infections

- Positive RPR/syphilis, *Streptococcus pneumoniae* bacteremia/meningitis

- Always think donor-derived infection for fever 1-3 months after transplant with no clear source
  - Was there anything unusual about the donor?
  - Who gave the history?

- Requires a high degree of suspicion
  - Report suspicions to the OPO - they can ask around to see how the other recipients are doing
Donor-derived infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Donor Reports</th>
<th>Number of Recipients with Confirmed Transmission</th>
<th>Number of DDD-Attributable Recipient Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>86</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Bacteria</td>
<td>38</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Fungus</td>
<td>30</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>26</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Parasite</td>
<td>21</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Total infections</td>
<td>201</td>
<td>106</td>
<td>29</td>
</tr>
</tbody>
</table>

Recipient-derived infections

- Active, uncontrolled infection
  - LVAD associated bacteremia
  - Infection limited to organ to be explanted
- Colonization
- Recurrence of infectious indication for transplant
  - HCV
- Asymptomatic infection
  - Strongyloides
- Latent infection
  - TB
  - Herpes viruses (CMV, EBV, HSV, VZV)
Nosocomial infections

- **Device-related**
  - Line-associated blood stream infection
  - Catheter or stent associated UTI
  - Ventilator-associated pneumonia

- **Surgery-related**
  - Wound infection
  - Intra-abdominal abscess

- **Multi-drug resistant organisms**

- **Outbreaks**

Table 2

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Rate of MDR Pathogens Among Episodes of Infections/Colonization</th>
<th>Main Isolated Pathogens</th>
<th>Comments/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis 68,69,138</td>
<td>25%–47%</td>
<td>MRSA 3%–7% ESBL-E 12%–15% CRE 3%–8% VRE 0%–7%</td>
<td>Major infections are spontaneous bacterial peritonitis, BSI, UTI, and pneumonia</td>
</tr>
<tr>
<td>End-stage renal disease 73,74</td>
<td>12%–25%</td>
<td>MRSA 0%–14% VRE 2%–21% ESBL-E 12%–25%</td>
<td>Most of infections studied are hemodialysis catheter-related BSIs</td>
</tr>
<tr>
<td>Cystic fibrosis 76,139</td>
<td>48%</td>
<td>MRSA 17%–36% MDR Pseudomonas aeruginosa 21%–52% ESBL-E 4%</td>
<td>Studies collected mostly culture (surveillance or diagnostic) samples rather than infectious episodes</td>
</tr>
</tbody>
</table>

Abbreviations: BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacteriaceae; ESBL-E, extended spectrum β-lactamase-producing Enterobacteriaceae; MDR, multidrug-resistant; MRSA, methicillin resistant Staphylococcus aureus; UTI, urinary tract infection; VRE, vancomycin-resistant Enterococci.

Outbreaks

Pneumocystis in pediatric renal transplant recipients

Raghuram et al. Liver Transplant 2012;18:1100
Brunot et al. Transplant Proc 2012;44:2818

C. parapsilosis after liver transplantation

Aspergillus in the cardiac ICU

3 heart transplant recipients developed invasive aspergillosis

2/3 died

Mold in the walls....

Community acquired infections

- Immunosuppression does not prevent common infections...
- Manifestations may be different
- Common pathogens include:
  - Respiratory viruses (influenza)
  - Skin flora (S. aureus, streptococci)
  - Enteric flora (GNR, enterococci)
Hematopoietic stem cell transplant

Indications for HSCT

- Hematologic malignancies
- Selected solid malignancies
- Acquired diseases
  - eg aplastic anemia, Paroxysmal nocturnal hemoglobinuria
- Congenital diseases
  - eg Immunodeficiency syndromes (e.g. SCID)
HSCT principles: maximizing graft vs tumor while minimizing graft vs host effects

Stem cell types

- Allogeneic vs. autologous
- Sources
  - Bone marrow
  - Mobilized peripheral blood stem cells
  - Umbilical cord blood
  - (Fetal liver cells)
Conditioning

Required Contribution of GVT Effect

- BU + CY + TBI (12 Gy)
- BU + TBI (12 Gy)
- CY + TBI (12 Gy)
- FLU + AraC
- BU + CY (± ATG)
- BU + Melphalan
- FLU + Melphalan
- FLU + Treosulfan
- FLU + BU
- TBI (2 Gy) + FLU
- TBI (2 Gy)
- CY

Intensity

Toxicity

Rezvani et al. in Transplant Infections 2009 Ed. Bowden et al.

Immune reconstitution after HSCT

- Neutrophils, monocytes, NK cells
- CD4 T cells, NKT cells
- B cells, CD8 T cells
- Plasma cells, dendritic cells

Timeline of infections

<table>
<thead>
<tr>
<th>Phase I: Pre-engraftment</th>
<th>Phase II: Post-engraftment</th>
<th>Phase III: Late phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft-versus-host-disease: Acute</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Neutropenia, barrier breakdown (mucositis, central venous access devices)</td>
<td>Impaired cellular and humoral immunity; NK cells recover first, CD8+ T cell numbers increasing but restricted T cell repertoire</td>
<td>Impaired cellular and humoral immunity; B cell &amp; CD4+ T cell numbers recover slowly and repertoire diversifies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative bacilli</td>
<td>Herpes Simplex virus</td>
<td>Aspergillus species</td>
</tr>
<tr>
<td>Gram positive organisms</td>
<td>Respiratory and enteric viruses</td>
<td>Aspergillus species</td>
</tr>
<tr>
<td>Gastrointestinal Streptococcal species</td>
<td>Other viruses e.g., HHV</td>
<td>Candida species</td>
</tr>
<tr>
<td>Encapsulated bacteria</td>
<td>Cytomegalovirus (seasonal/intermittent)</td>
<td>Pneumocystis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 15-45</th>
<th>Day 100</th>
<th>Day 365 and beyond</th>
</tr>
</thead>
</table>

Infectious risk

<table>
<thead>
<tr>
<th></th>
<th>Higher risk</th>
<th>Lower risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>allogeneic</td>
<td>autologous</td>
</tr>
<tr>
<td>Type of donor</td>
<td>Unrelated</td>
<td>related</td>
</tr>
<tr>
<td>HLA matching</td>
<td>HLA mismatch</td>
<td>HLA match</td>
</tr>
<tr>
<td>Stem cell source</td>
<td>Cord blood</td>
<td>Peripheral blood</td>
</tr>
<tr>
<td>Graft manipulation</td>
<td>T cell depletion</td>
<td>No manipulation</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>Full intensity</td>
<td>Reduced intensity</td>
</tr>
<tr>
<td>immunosuppression</td>
<td>T cell depleting agents</td>
<td>Minimal IS</td>
</tr>
<tr>
<td>GVHD</td>
<td>Moderate-severe</td>
<td>None or mild</td>
</tr>
</tbody>
</table>


Wingard et al. Inf Dis Clin N Am 2010;24:257
Graft vs Host Disease

- GVHD requiring treatment in 40% of HLA-matched allo-HSCT recipients
- GVHD
  - Skin: pruritic maculopapular rash
  - GI tract: nausea, abd pain, diarrhea
  - Liver: cholestasis
- Graded based on extent of end-organ involvement
  - I mild
  - II moderate
  - III severe (~25% 5-year survival)
  - IV very severe (~5% 5 year survival)
- Steroids remain first line
  - Topical for skin and lung (inhaled)
  - Systemic for more severe disease and other target organs
- Calcineurin inhibitors may be used
- Steroid-refractory GVHD important concern


Bacterial infections after HSCT

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Types of infections encountered at various times after HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Infectious Pathogen</strong></td>
<td><strong>Early Preengraftment (First 2-4 wk)</strong></td>
</tr>
<tr>
<td>Bacteria</td>
<td>Gram-negative bacteria (related to mucosal injury and neutropenia)</td>
</tr>
<tr>
<td></td>
<td>Gram-positive bacteria (related to venous catheters)</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> (related to neutropenia, antibiotics, antiacid medications)</td>
<td></td>
</tr>
</tbody>
</table>

Wingard et al. Inf Dis Clin N Am 2010;24:257
Incidence of fungal infections

Wingard et al. Inf Dis Clin N Am 2010;24:257

Kontoyiannis et al. CID 2010;50:1091
Pulmonary complications after HSCT

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-engraftment (0-30 days)</td>
<td>Post-engraftment (30-100 days)</td>
<td>Late Phase (&gt; 100 days)</td>
</tr>
<tr>
<td>Host immune system defect</td>
<td>Neutropenia, mucositis, catheters and lines, acute GVHD</td>
<td>Impaired cellular immunity and Acute GVHD</td>
</tr>
</tbody>
</table>

Infectious
- gram - bacteria
- Gram + bacteria (Staph, Strept)
- Candida, other fungi
- Aspergillus
- HSV
- P. jiroveci
- Nocardia, mycobacteria
- CMV
- Parainfluenza, RSV, influenza, adenovirus

Non-infectious
- CHF
- VOD
- IPS
- BO
- BOOP
- DAH
- IPS
- PTLD
- ES

GI complications

- Chemotherapy-related nausea and vomiting
- Chemotherapy-related mucositis (SOS)
- Acute liver GVHD
- Transaminitis due to drug toxicity
- Viral hepatitis reactivation
- Diarrhea due to GVHD, infections, drugs
- Chronic GI GVHD
- Conditioning
- Stem cell infusion
- Engraftment

Tuncer et al. W J Gastroenterol 2012;18:1851
CNS complications after HSCT

Nishiguchi et al. AJR 2009;192:1003

Aspergillus outbreak in HSCT

Loo et al. ICHE 1996:360-36

FIGURE. Nosocomial cases of aspergillosis in relation to construction.
Febrile neutropenia

- High risk
  - Prolonged (anticipated >7 days) and profound neutropenia (≤100 cells/mm³)
  - “comorbid medical problems”
    - Hypotension
    - Pneumonia
    - New abdominal pain or new GI symptoms
    - Neurologic changes
    - Line infection
    - Severe mucositis
  - Hepatic or renal insufficiency

MASCC score: less is worse
Multinational Association for Supportive Care in Cancer study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of febrile neutropenia with no or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>No hypotension (systolic blood pressure &gt;90 mmHg)</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or hematologic malignancy with no previous fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration requiring parenteral fluids</td>
<td>3</td>
</tr>
<tr>
<td>Burden of febrile neutropenia with moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt;60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

- 26 maximum score -> lowest risk
- <21 considered high risk

Freifeld et al. CID 2011;52:e56
Mortality risk by MASCC score

Paesmans et al. Support Care Cancer 2011;19:1001

Risk determines initial treatment

Low risk patients...
- May be treated as outpatients
- May be considered for oral antibiotics
- Most commonly solid tumors

High risk patients...
- Require hospitalization
- Require initial IV antibiotics
- Most commonly HSCT preparation or acute leukemia induction chemotherapy
- CT chest +/- sinuses for fever >= 4 days

Freifeld et al. CID 2011;52:e56
Environmental precautions in febrile neutropenia, IDSA 2011

- General
  - Hand hygiene
  - Standard barrier precautions and infection specific precautions
  - HSCT recipients should be housed in private rooms. Allogeneic HSCT recipients should be housed in rooms with >12 air exchanges/h and HEPA filtration
  - Plants and dried or fresh flowers should be prohibited
  - Hospital work exclusion policies should be designed to encourage HCP to report their illnesses or exposures

- Neutropenic diet
  - Consists of well cooked foods
  - Prepared luncheon meats should be avoided
  - Well cleaned, uncooked raw fruits and vegetables are acceptable, as are cooked foods brought from home or restaurants, provided that the freshness of ingredients and means of preparation can be confirmed
Environmental precautions in febrile neutropenia, IDSA 2011

- Patient skin and oral care
  - Patients should take daily showers or baths
  - Skin should be inspected daily
  - Gentle but thorough perineal care after bowel movement
  - Avoid rectal thermometers, enemas, suppositories, and rectal exams
  - Menstruating females should avoid tampons
  - Patients with ongoing mucositis should perform oral rinses 4-6 times per day with sterile water, normal saline, or sodium bicarbonate
  - Patients with brush their teeth >2 times/day with a soft regular toothbrush
  - Avoid fixed orthodontic appliances and space maintainers

- Plants and animals
  - Avoid plants and dried or fresh flowers
  - Do not allow visitation by pets (including pet therapy)

- HCP personnel and visitors
  - Vaccination of HCP or visitors who are symptomatic with infections transmitted by air, droplet, and direct contact (e.g., VZV, infectious gastroenteritis, HSV lip lesions, URI) should not engage in patient care or visit patients unless appropriate barrier (e.g., mask and glove) protection is established

- Infection control surveillance
  - Do not routinely perform bacterial surveillance cultures of the environment, equipment, or devices
Engineering controls

- **Aspergillus** prevention
  - Filtered hospital air
  - Barrier protection during renovation or construction
  - Protective isolation (HEPA filtered) for hematopoietic stem cell transplants
  - Provide respiratory protection when patients must leave a protective environment

- **Legionella** prevention
  - Prohibit showers (use sponge baths)
  - Implement surveillance for Legionella cases
  - Monitor water supply: if Legionella present initiate decontamination (controversial)

Procedures during construction & renovation

- Seal hospital construction areas behind impervious barriers
- Clean construction area daily (i.e., remove dust with HEPA vacuum)
- Assure that ventilation system does not transport dust from inside construction area to other locations
- Move immunocompromised patients from adjacent areas
- Thoroughly clean construction area prior to patient use
- Conduct surveillance for airborne fungal infections
- Assess airborne fungal levels adjacent to construction
- Avoid transporting construction material through patient areas
- Assess compliance with infection control guidelines
Infection in burns

6 of 10 are infectious complications!

Nosocomial infection in burns

Table 3. Risk factors for development of NI

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multiple Analysis Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.02</td>
<td>0.69-1.49</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.99-1.01</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.61</td>
<td>0.96-2.69</td>
</tr>
<tr>
<td>Injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scald</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Flame</td>
<td>3.48</td>
<td>2.32-5.22</td>
</tr>
<tr>
<td>Electrical</td>
<td>1.58</td>
<td>0.87-2.87</td>
</tr>
<tr>
<td>Contact</td>
<td>1.38</td>
<td>0.57-3.37</td>
</tr>
<tr>
<td>STBSA</td>
<td>1.05</td>
<td>1.04-1.06</td>
</tr>
<tr>
<td>ABSt*</td>
<td>1.44</td>
<td>1.33-1.56</td>
</tr>
<tr>
<td>Admission day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 hr</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;24 hr</td>
<td>0.11</td>
<td>0.04-0.38</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.99</td>
<td>0.29-3.32</td>
</tr>
<tr>
<td>First excision day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.01</td>
<td>3.29-7.63</td>
</tr>
</tbody>
</table>

Alp et al. Burn Care Res 2012;379
At UNC from 2008-2012, 32% of hospital-associated respiratory infections in the burn ICU were caused by MDR-GNB vs. 3% in all other ICUs


### MDR-bacterial outbreaks in burn units

<table>
<thead>
<tr>
<th>Study</th>
<th>Microorganism</th>
<th>Duration</th>
<th>Patients Hospitalized, N</th>
<th>Cases, N (%)</th>
<th>Colonization</th>
<th>Infection</th>
<th>Total (Attack Rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babik et al.</td>
<td><em>Acinetobacter baumannii</em></td>
<td>12 mo</td>
<td>73</td>
<td>8 (10.96%)</td>
<td>7 (54)</td>
<td>6 (46)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>Bayati et al.</td>
<td><em>A. baumannii</em></td>
<td>1 yr</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Herruzo et al.</td>
<td><em>A. baumannii</em></td>
<td>12 mo</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Lyytiäinen et al</td>
<td><em>A. baumannii</em></td>
<td>3 mo</td>
<td>247</td>
<td></td>
<td></td>
<td></td>
<td>31 (12.55)</td>
</tr>
<tr>
<td>Roberts et al.</td>
<td><em>A. baumannii</em></td>
<td>10 mo</td>
<td>18 (69)</td>
<td></td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Simon et al.</td>
<td><em>A. baumannii</em></td>
<td>30</td>
<td>4 (13.33)</td>
<td></td>
<td></td>
<td></td>
<td>4 (13.33)</td>
</tr>
<tr>
<td>Fujisawa et al.</td>
<td><em>Acinetobacter calcoaceticus</em></td>
<td>2 mo</td>
<td>30</td>
<td>1 (25)</td>
<td>3 (75)</td>
<td>4 (25)</td>
<td></td>
</tr>
<tr>
<td>Falk et al.</td>
<td><em>Enterococcus faecium</em></td>
<td>1 yr</td>
<td>17 (81)</td>
<td></td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>21</td>
</tr>
<tr>
<td>Sánchez et al.</td>
<td><em>Klebsiella pneumoniae</em></td>
<td>10 mo</td>
<td>18 (69)</td>
<td></td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Huseh et al.</td>
<td><em>P. aeruginosa</em></td>
<td>2 yr</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tredget et al.</td>
<td><em>P. aeruginosa</em></td>
<td>2 yr</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sula et al.</td>
<td><em>Providence stuartii</em></td>
<td>5 mo</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ti et al.</td>
<td><em>Serratia marcescens</em></td>
<td>9 yr</td>
<td>13 (1.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edgar et al.</td>
<td><em>Serratia marcescens</em></td>
<td>1 mo</td>
<td>13 (1.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boers et al.</td>
<td>MRSA</td>
<td>26 mo</td>
<td>12 (71)</td>
<td></td>
<td></td>
<td></td>
<td>21.9/1000 PD</td>
</tr>
<tr>
<td>Dambrosio et al.</td>
<td>MRSA</td>
<td>7 yr</td>
<td>10 (58)</td>
<td></td>
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<td>56</td>
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<tr>
<td>Eibl et al.</td>
<td>MRSA</td>
<td>2 yr</td>
<td>10 (58)</td>
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<td>56</td>
</tr>
<tr>
<td>Espersen et al.</td>
<td>MRSA</td>
<td>1 mo</td>
<td>10 (58)</td>
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<td></td>
<td>10 (58)</td>
</tr>
<tr>
<td>Fuchs et al.</td>
<td>MRSA</td>
<td>8 mo</td>
<td>2 (10)</td>
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<td>10 (58)</td>
</tr>
<tr>
<td>Hunt et al.</td>
<td>MRSA</td>
<td>8 yr</td>
<td>3 (15)</td>
<td></td>
<td></td>
<td></td>
<td>3 (15)</td>
</tr>
<tr>
<td>Lilly et al.</td>
<td>MRSA</td>
<td>2 yr</td>
<td>2 (10)</td>
<td></td>
<td></td>
<td></td>
<td>10 (58)</td>
</tr>
<tr>
<td>Moer et al.</td>
<td>MRSA</td>
<td>4 mo</td>
<td>6 (30)</td>
<td></td>
<td></td>
<td></td>
<td>10 (58)</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>MRSA</td>
<td>1 mo</td>
<td>4 (20)</td>
<td></td>
<td></td>
<td></td>
<td>4 (20)</td>
</tr>
<tr>
<td>Raskid et al.</td>
<td>MRSA</td>
<td>1 mo</td>
<td>176</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Roberts et al.</td>
<td>MRSA</td>
<td>18 mo</td>
<td>15 (83)</td>
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<td></td>
<td></td>
<td>15 (83)</td>
</tr>
<tr>
<td>Rentala et al.</td>
<td>MRSA</td>
<td>5 mo</td>
<td>5 (28)</td>
<td></td>
<td></td>
<td></td>
<td>5 (28)</td>
</tr>
<tr>
<td>Safdar et al.</td>
<td>MRSA</td>
<td>5 mo</td>
<td>5 (28)</td>
<td></td>
<td></td>
<td></td>
<td>5 (28)</td>
</tr>
<tr>
<td>Teare et al.</td>
<td>MRSA</td>
<td>16 mo</td>
<td>5 (28)</td>
<td></td>
<td></td>
<td></td>
<td>5 (28)</td>
</tr>
</tbody>
</table>

Decline in the rate of BSI

van Duin et al. ICHE 2014;35:8;1066-68

Pathogens & infections in burn

Enterobacteriaceae
Pseudomonas aeruginosa
Staphylococcus aureus
Urinary tract infection
Bloodstream infection
Pneumonia
Skin and soft tissue infection
Antibacterial resistance

Prevention of infection in burns

- Topical agents
- Systemic antimicrobial prophylaxis
- Wound care
- Universal isolation precautions
- Frequency of line changes

Interventions to decrease CLABSI rate at UNC

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Intervention(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Enhanced education of medical staff regarding central lines; addition of 2% chlorhexidine plus 70% isopropyl alcohol for skin preparation to central line kits</td>
</tr>
<tr>
<td>2001</td>
<td>Mandatory training for nurses on IV line site care and maintenance</td>
</tr>
<tr>
<td>2003</td>
<td>Central line changes over a guidewire every 3 days with use of a new site every 6 days becomes standard practice; use of full body drape for line insertion and changes</td>
</tr>
<tr>
<td>2003–2005</td>
<td>Introduction of antibiotic-impregnated central venous catheters for all patients</td>
</tr>
<tr>
<td>2004</td>
<td>Enhanced nursing education on central line insertion and maintenance</td>
</tr>
<tr>
<td>2005</td>
<td>Customized catheter-insertion kits</td>
</tr>
<tr>
<td>2006</td>
<td>Universal glove and gown use for all patient encounters</td>
</tr>
<tr>
<td>2007</td>
<td>Implementation of the Institute for Healthcare Improvement bundle to prevent CLABSI</td>
</tr>
<tr>
<td>2009</td>
<td>Use of chlorhexidine patch at insertion site</td>
</tr>
</tbody>
</table>

Specific to burn ICU

van Duin et al. ICHE 2014;35:8;1066-68
Questions?

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