Prevention of Infectious Diseases in the Immunocompromised Host

David van Duin, MD, PhD, FACP
Overview

• Solid organ transplantation
• Stem cell transplantation
• Neutropenia
• Burns
Timeline of Infectious Risk

Donor-Derived Infection
- Nosocomial, technical (donor or recipient)
- Activation of latent infection (relapsed, residual, opportunistic)
- Community-acquired

Recipient-Derived Infection
- Transplantation

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 and ischemia
- Clostridium difficile colitis
- Donor-derived infection (uncommon):
  - HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, Trypanosoma cruzi
- Recipient-derived infection (colonization):
  - Aspergillus, pseudomonas

1–6 Months
- With PCP and antiviral (CMV, HBV) prophylaxis:
  - Polymavirus 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)
  - HBV 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 post Transplant

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”

Fishman. NEJM 2007;357:2601
Donor-derived infections

| TABLE 2. Definitions of imputability for donor origin infectious diseases transmissions |
|-----------------------------------|-----------------------------------------------------------------------------------|
| Term                              | Definition                                                                                                                                 |
| Proven                            | Clear evidence of the same infection disease in the donor and at least one of the recipients |
| Probable                          | Strong evidence suggesting but not proving a disease transmission                   |
| Possible                          | Used for all situations where data suggest a possible transmission but are insufficient to fulfill criteria for confirmed transmission (proven and/or probable), and transmission cannot be formally excluded |
| Unlikely                          | Used for situations where it is possible that the disease in question could have been transmitted from the donor to at least one of the recipients, but the available data suggest that donor origin is unlikely |
| Excluded                          | Clear evidence of an alternative, non-donor origin of disease                        |
| IWDT                              | All or some of the recipients received an intervention (i.e., antimicrobial therapy, specific immunoglobulins, or organ removal), and no disease was recognized in any of the recipients |
| Positive assay without apparent disease transmission | Used for instances in which a donor assay is positive for infection (i.e., coagulase-negative Staphylococcus in perfusate culture), which is felt by the clinicians not to be clinically significant, is not treated, and not associated with disease transmission |
| Not assessable                    | When there are insufficient data available to assess imputability of the disease transmission (either from insufficient data being provided in a published document or sufficient donor and/or recipient testing) |

Garzoneti al. Transplantation 2011;92:1297
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>

Unusual donor-derived infections

• Rabies
  – 1 donor, 4 recipients: 100% mortality
• West Nile Virus
  – 2 donors, 8 recipients: 1 death, 2 coma
• Lymphocytic choriomeningitis virus
  – 2 donors, 8 recipients: 88% mortality
  – LCMV could not be detected in either donor
  – 1 donor had pet hamster with LCMV
• Balamuthia mandrillaris
  – 2 donors, 8 recipients: 2 deaths, 1 neuro sequellae

Srinivasan et al. NEJM 2005;352:1103
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
- Outbreaks
- Multi-drug resistant organisms
Outbreaks

*Pneumocystis* in pediatric renal transplant recipients

*C. parapsilosis* after liver transplantation

Raghuram et al. Liver Transplant 2012;18:1100
Brunot et al. Transplant Proc 2012;44:2818
Aspergillus in heart surgery ICU

3 heart transplant recipients developed invasive aspergillosis

2/3 died

Mold in the walls....
MDR-O: carbapenem resistance in *K. pneumoniae* after SOT

- Retrospective single center cohort study
- All post- SOT *K. Pneumoniae* BSI 2006 – 2012
- 84 episodes of *Kp* BSI in 65 recipients
- 23/84 (27%) episodes of BSI were CR*Kp* occurring in 19 SOT recipients

Cober et al. AJT 2013;S5:186, abstract #504
## All episodes *Kp* BSI

<table>
<thead>
<tr>
<th></th>
<th>CS<em>Kp</em>, n = 61</th>
<th>CR<em>Kp</em>, n = 23</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after transplant (median)</td>
<td>316 d</td>
<td>73 d</td>
<td>0.009</td>
</tr>
<tr>
<td>Onset &gt; 48 hrs after admission</td>
<td>21 (34%)</td>
<td>15 (65%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (8%)</td>
<td>4 (17%)</td>
<td>0.25</td>
</tr>
<tr>
<td>CVC</td>
<td>9 (15%)</td>
<td>5 (22%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Receipt of in vitro S antibiotics &lt; 48 hrs</td>
<td>54 (88%)</td>
<td>17 (74%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Per episode of *KP* BSI

Cober et al. AJT 2013;S5:186, abstract #504
Time to Death in *Kp* BSI

Cober et al. AJT 2013;S5:186, abstract #504
Community acquired infections

• Immunosuppression does not prevent common infections…
• Manifestations may be different
• Common pathogens include:
  – Respiratory viruses
  – Skin flora (S. aureus, streptococci)
  – Enteric flora (GNR, enterococci)
## H1N1 Influenza post-SOT

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38°C</td>
<td>115/144 (80%)</td>
<td>78/82 (95%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cough</td>
<td>132/145 (91%)</td>
<td>67/73 (92%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sore throat</td>
<td>50/134 (37%)</td>
<td>30/51 (59%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>40/134 (30%)</td>
<td>42/59 (71%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>33/136 (24%)</td>
<td>26/50 (52%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myalgias</td>
<td>70/135 (52%)</td>
<td>21/43 (49%)</td>
<td>0.866</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>66/154 (43%)</td>
<td>39/83 (47%)</td>
<td>0.636</td>
</tr>
<tr>
<td>Pneumonia on chest radiograph or CT scan</td>
<td>60/149 (40%)</td>
<td>13/81 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission to hospital</td>
<td>112/154 (73%)</td>
<td>55/83 (66%)</td>
<td>0.373</td>
</tr>
<tr>
<td>Admission to the intensive care unit</td>
<td>27/154 (17.5%)</td>
<td>10/83 (12.0%)</td>
<td>0.357</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>18/153 (12%)</td>
<td>3/83 (4%)</td>
<td>0.063</td>
</tr>
<tr>
<td>Antiviral treatment within 48 h</td>
<td>43/138 (31%)</td>
<td>47/77 (61%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiviral treatment after 48 h</td>
<td>95/138 (69%)</td>
<td>30/77 (39%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>10/154 (7%)</td>
<td>0/83 (0%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*Statistical differences are by χ² test.

Table 2: Clinical presentation and complications of influenza A in adult and paediatric recipients of solid-organ transplants

Kumar et al. Lancet ID 2010;10:521
S. aureus bacteremia post-SOT

![Graph showing survival rates over time]

**TABLE 3.** Cox proportional hazards analysis 30-day mortality in entire SAB cohort (n = 2959)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Methicillin resistance</td>
<td>1.21 (1.03–1.41)</td>
<td>0.02</td>
</tr>
<tr>
<td>SOT recipient</td>
<td>0.37 (0.11–0.88)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

SAB: S. aureus bacteremia. SOT: solid organ transplant recipient.

Malinis et al. Transplantation 2012;93:1045
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
- Hypogammaglobulinemia
- Neutropenia
Immunosuppressive Medications

• Steroids
  – Prednisone
  – methylprednisolone

• Calcineurin inhibitors
  – Cyclosporine (“neoral”)
  – Tacrolimus (FK506, “prograf”)

• Purine antagonists
  – Azathioprine (“imuran”)
  – mycophenolate mofetil, “MMF”)

• Antilymphocyte therapies
  – Thymoglobulin (ATG)
  – Muromonab (anti-CD3, “OKT3”)
Immunosuppressive Medications

• IL-2 receptor inhibitors
  – Basiliximab (“simulect”)
  – Daclizumab (“zenapax”)

• mTOR inhibitors
  – sirolimus (rapamycin, “rapamune”)
  – everolimus (“afinitor”)

• Leflunomide (“arava”)

• Alemtuzumab (“campath”, anti-CD52 antibody)

• Rituximab (anti-CD20)

• Bortezomib (“velcade”, proteasome inhibitor)
Alemtuzumab

- Popular at UNC
- 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 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 (16–82)</td>
<td>...</td>
<td>.81</td>
</tr>
<tr>
<td>Sex, female</td>
<td>28 (50)</td>
<td>195 (40)</td>
<td>1.5 (0.9–2.6)</td>
<td>.14</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 (49)</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>.07</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>.09</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 rejection therapy</td>
<td>40 (71)</td>
<td>153 (31)</td>
<td>5.5 (3.0–10.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Doses of alemtuzumab received, no. (range)</td>
<td>2 (1–5)</td>
<td>1 (1–5)</td>
<td>2.3 (1.7–3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Received pulse methylprednisolone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 (27)</td>
<td>152 (31)</td>
<td>0.8 (0.4–1.5)</td>
<td>.5</td>
</tr>
<tr>
<td>Received &gt;2 pulses of methylprednisolone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 (18)</td>
<td>49 (10)</td>
<td>2.0 (0.9–4.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Received another lymphocyte-depleting antibody&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28 (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
Overview

• Solid organ transplantation
• Stem cell transplantation
• Neutropenia
• Burns
Indications: malignancy

• Hematologic malignancies
  – Leukemias
  – Lymphoma
  – Multiple myeloma
  – Myelodysplastic/myeloproliferative syndromes

• Selected solid malignancies
  – Renal cell carcinoma
  – Ewing sarcoma
  – neuroblastoma

Tallman et al. Blood 2009;114:5126
HSCT: other indications

- Acquired
  - Aplastic anemia
  - Paroxysmal nocturnal hemoglobinuria
  - Auto-immune disorders
- Congenital
  - Immunodeficiency syndromes (e.g. SCID)
  - Hemoglobinopathies
  - Congenital anemias
  - Storage diseases
  - Bone marrow failure syndromes
  - osteopetrosis
- HIV
Rationale for HSCT differs by indication

- Graft vs tumor effect
  - malignancies
- Dose escalation of therapy
  - malignancies
- Replacement therapy
  - Hematologic deficiencies
- Gene therapy
  - Enzyme deficiencies
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)
Transplant Conditioning

• Goals:
  – Eradicate disease, or decrease number of malignant cells
  – Suppress host immunity and prevent rejection of donor cells

• Modalities:
  – Irradiation
  – Chemotherapy
  – Biologics
Reduced Intensity Conditioning

• AKA “mini”-transplant, “non-myeloablative”
• Aimed at decreasing early mortality and enhancing donor anti-host (anti-disease) reactivity

Rezvani et al. in Transplant Infections 2009 Ed. Bowden et al.
Immune reconstitution after HSCT

Timeline of infections

## 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 seen in 40% of HLA-matched allo-HSCT recipients

• Acute 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)

Treatment of GVHD

• Steroids remain first line
  – Topical for skin and lung (inhaled)
  – Systemic for more severe disease and other target organs
• Calcineurin inhibitors may be added
• Steroid-refractory GVHD important concern
  – Alternative approaches under investigation
    • Imatinib (platelet-derived growth factor signaling inhibition)
    • Sirolimus (mTOR inhibition)
    • Ex vivo cellular manipulation (e.g. tolerogenic DC induction)
    • Bortezomib (proteasome inhibition)
### Table 2
**Types of infections encountered at various times after HSCT**

<table>
<thead>
<tr>
<th>Type of Infectious Pathogen</th>
<th>Early Preengraftment (First 2-4 wk)</th>
<th>Early Postengraftment (Second and Third Month)</th>
<th>Late Postengraftment (After Second or Third Month)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>Gram-negative bacteria (related to mucosal injury and neutropenia)</td>
<td>Gram-positive bacteria (related to venous catheters)</td>
<td>Encapsulated bacteria (related to poor opsonization with chronic GVHD)</td>
</tr>
<tr>
<td></td>
<td>Gram-positive bacteria (related to venous catheters)</td>
<td>Gram-negative bacteria (related to enteric involvement of GVHD, venous catheters)</td>
<td><em>Nocardia</em> (related to chronic GVHD)</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>(related to neutropenia, antibiotics, antiacid medications)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bacteremia

<table>
<thead>
<tr>
<th>Type of Infectious Pathogen</th>
<th>Early Preengraftment (First 2–4 wk)</th>
<th>Early Postengraftment (Second and Third Month)</th>
<th>Late Postengraftment (After Second or Third Month)</th>
<th>Time Independent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungi</td>
<td><strong>Candida</strong> (related to mucosal injury and neutropenia)</td>
<td><strong>Aspergillus</strong>, other molds and <strong>Pneumocystis jirovecii</strong> (related to GVHD)</td>
<td><strong>Aspergillus</strong>, other molds and <strong>P jirovecii</strong> (related to GVHD)</td>
<td></td>
</tr>
<tr>
<td>Herpesviruses</td>
<td><strong>HSV</strong></td>
<td>CMV (related to GVHD and impaired cellular immunity)</td>
<td>CMV and VZV (related to GVHD and impaired cellular immunity and viral latency before transplant)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EBV (in patients who have T-cell depleted grafts, receive ATG, or whose donor is mismatched)</td>
<td>EBV (in patients who have T-cell depleted grafts, receive ATG, or whose donor is mismatched)</td>
<td></td>
</tr>
<tr>
<td>Other viruses</td>
<td>BK virus (related to GVHD and cyclophosphamide in conditioning regimen)</td>
<td>Respiratory viruses (temporally tracks with community outbreaks)</td>
<td>Adenoviruses</td>
<td></td>
</tr>
</tbody>
</table>
Incidence of fungal infections

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 Acute GVHD</td>
</tr>
</tbody>
</table>

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

**Non-infectious**
- CHF
- VOD
- ES
- DAH
- IPS
- BO
- BOOP
- PTLPD

GI complications

Tuncer et al. W J Gastroenterol 2012;18:1851
GI Infections

- **Mucositis, dysphagia**
  - CMV, HSV, VZV
  - Candida
  - bacteria

- **Diarrhea**
  - C. difficile
  - CMV, HSV
  - Adeno-, rota-, noro-, astrovirus
  - Cryptosporidium, microsporidium, giardia
  - MTB, NTM
  - fungal

Tuncer et al. W J Gastroenterol 2012;18:1851
Non-ID GI complications

Neutropenic colitis
• AKA typhlitis
• Up to 30% of neutropenic patients

Graft vs host disease
• Acute vs chronic

CNS complications after HSCT

Nishiguchi et al. AJR 2009;192:1003
CNS infections after HSCT

Brain abscess on day 31 after HSCT for AML

EBV-related PTLD on day 180 after HSCT

Nishiguchi et al. AJR 2009;192:1003
Aspergillus outbreak in HSCT

FIGURE. Nosocomial cases of aspergillosis in relation to construction. Loo et al. ICHE 1996:360-36
Overview

- Solid organ transplantation
- Stem cell transplantation
- Neutropenia
- Burns
Febrile Neutropenia

Multinational Association for Supportive Care in Cancer study

- Prospective observational study
- N=1,139
- Bacteremia documented in 26%
- Outcomes:
  - Resolution: 84%
  - Alive with at least one serious complication: 11%
  - Death: 5%

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,1 Eric J. Bow,9 Kent A. Sepkowitz,2 Michael J. Boeckh,4 James I. Ito,5 Craig A. Mullen,3 Issam I. Raad,6 Kenneth V. Rolston,6 Jo-Anne H. Young,7 and John R. Wingard8

Table 2. Strength of Recommendation and Quality of Evidence

<table>
<thead>
<tr>
<th>Category/Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of Recommendation</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for or against use.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for or against use.</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation.</td>
</tr>
<tr>
<td><strong>Quality of Evidence</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from ≥1 properly randomized, controlled trial.</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from &gt;1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</td>
</tr>
</tbody>
</table>
Guideline recommendations

• 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

Freifeld et al. CID 2011;52:e56
### MASCC score: less is worse

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of febrile neutropenia with no or mild symptoms&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or hematologic malignancy with no previous fungal infection&lt;sup&gt;c&lt;/sup&gt;</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&lt;sup&gt;a&lt;/sup&gt;</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

High risk patients…
- Require hospitalization
- Require initial IV antibiotics
- Most commonly HSCT preparation or acute leukemia induction chemotherapy

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

Freifeld et al. CID 2011;52:e56
ENVIRONMENTAL PRECAUTIONS IN MANAGING FEBRILE NEUTROPENIC PATIENTS, 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 probited
  – Hospital work exclusion policies should be designed to encourage HCP to report their illnesses or exposures
ENVIRONMENTAL PRECAUTIONS IN MANAGING FEBRILE NEUTROPENIC PATIENTS, IDSA 2011

• 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 MANAGING FEBRILE NEUTROPENIC PATIENTS, 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
ENVIRONMENTAL PRECAUTIONS IN MANAGING FEBRILE NEUTROPENIC PATIENTS, IDSA 2011

• 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 PE

• *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
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
LATENT PATHOGENS

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*
Overview

- Solid organ transplantation
- Stem cell transplantation
- Neutropenia
- Burns
Prevention of Infection in Burns

• Topical agents
• Systemic antimicrobial prophylaxis
• Wound care
• Universal isolation precautions
• Frequency of line changes
# 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>%TBSA</td>
<td>1.05</td>
<td>1.04–1.06</td>
</tr>
<tr>
<td>ABSI*</td>
<td>1.44</td>
<td>1.33–1.56</td>
</tr>
<tr>
<td>Admission day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 hr</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;24 hr</td>
<td>0.11</td>
<td>0.04–0.30</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>1.14</td>
<td>1.10–1.18</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>
### TABLE 2. Management of Burn Wounds Based on Depth\(^{16,17,20,52–55,58,59}\)

<table>
<thead>
<tr>
<th>Wound</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>Symptomatic care</td>
</tr>
<tr>
<td>Superficial partial</td>
<td>Topical antibiotics with twice-daily dressing change,</td>
</tr>
<tr>
<td>thickness</td>
<td>silver-impregnated dressing changed every 3–5 d, or</td>
</tr>
<tr>
<td></td>
<td>Biobrane*</td>
</tr>
<tr>
<td>Deep partial</td>
<td>Topical antibiotics with twice-daily dressing change,</td>
</tr>
<tr>
<td>thickness</td>
<td>or silver-impregnated dressing changed every 3–5 d and excision and grafting</td>
</tr>
<tr>
<td>Full thickness</td>
<td>Topical antibiotics with twice-daily dressing change and excision and grafting</td>
</tr>
</tbody>
</table>

* Recommend restriction to individuals experienced with its use.

### TABLE 3. Topical Antimicrobial Agents\(^{1,58–63,65–67,71–73}\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Application</th>
<th>Penetration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mafenide acetate cream</td>
<td>Apply 1/16 inch layer twice daily*</td>
<td>Penetrates eschar</td>
<td>Painful on application, metabolic acidosis</td>
</tr>
<tr>
<td>Silver sulfadiazine</td>
<td>Apply 1/16 inch layer twice daily*</td>
<td>Poor eschar penetration</td>
<td>Transient leucopenia</td>
</tr>
<tr>
<td>Silver nitrate solution</td>
<td>Dress wounds with multiple layers of coarse gauze and apply solution to keep gauze continually moist</td>
<td>Poor eschar penetration</td>
<td>Electrolyte disorders</td>
</tr>
<tr>
<td>Acticoat, Silverlon, or</td>
<td>Moisten dressing with sterile water, cut to size, secure to wound with secondary dressing, change in 3–5 d</td>
<td>Poor eschar penetration</td>
<td></td>
</tr>
<tr>
<td>Silverseal(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Consider alternating mafenide in the morning with silver sulfadiazine in the evening.

\(^1\) Application information obtained from package insert.
Decline in the Rate of Bloodstream Infections

van Duin et al. ICHE 2014;35:8;1066-68
## 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 encounter</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?