Infection in the (non-HIV) Immunocompromised Patient

Outline

- Infectious Risk in Different Types of Immunosuppression
- Approach to Pulmonary Infections in the Immunocompromised Host
- Infections in the Solid Organ Transplant Recipient
- Infections in Patient Taking TNF Antagonists

Case #1

72 year old woman with microscopic polyangiitis on prednisone 20mg daily is admitted with 2 days of productive cough and shortness of breath. She rapidly deteriorates and is intubated for hypoxemic respiratory failure.

Data:
- WBC 5.6
- LDH 409
- Beta-D-glucan >500
<table>
<thead>
<tr>
<th>Your empiric antibiotic regimen should include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ganciclovir</td>
</tr>
<tr>
<td>2. Voriconazole</td>
</tr>
<tr>
<td>3. TMP-SMX</td>
</tr>
<tr>
<td>4. Liposomal amphotericin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common States of Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Neutropenia</td>
</tr>
<tr>
<td>▪ Hypogammaglobulinemia</td>
</tr>
<tr>
<td>▪ Asplenia</td>
</tr>
<tr>
<td>▪ Cell-mediated immunity dysfunction</td>
</tr>
<tr>
<td>▪ HIV</td>
</tr>
<tr>
<td>▪ Solid organ transplantation</td>
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<tr>
<td>▪ Stem cell transplantation</td>
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<tr>
<td>▪ Autoimmune disorders</td>
</tr>
<tr>
<td>▪ TNF-alpha inhibition and other biologic agents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General Principles of Immunocompromised Host ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients can present without overt signs of infection (e.g. afebrile, normal WBC count)</td>
</tr>
<tr>
<td>2. Patients can get very sick, very fast</td>
</tr>
<tr>
<td>3. Threshold for more aggressive diagnostics (imaging, invasive procedures) and for empiric therapy should be lower</td>
</tr>
<tr>
<td>4. The kind of immunocompromise matters – i.e. what kind of infections is the patient at risk for?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Can We Quantify Immunosuppression?</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Infectious risk in HIV-negative patients is hard to determine</td>
</tr>
<tr>
<td>▪ HIV → Quantitative CD4 depletion (can measure)</td>
</tr>
<tr>
<td>▪ Non-HIV immunosuppression → Qualitative CD4 dysfunction (no reliable way to measure this)</td>
</tr>
<tr>
<td>▪ Are there surrogate markers we can use?</td>
</tr>
<tr>
<td>▪ Underlying disorder</td>
</tr>
<tr>
<td>▪ Immunosuppressive drugs: duration and dosage</td>
</tr>
<tr>
<td>▪ Other OIs</td>
</tr>
</tbody>
</table>

Infectious Risk of Different Immune Defects

<table>
<thead>
<tr>
<th>Immune Defect</th>
<th>Bacteria</th>
<th>TB/NTM</th>
<th>Endemic mycoses</th>
<th>Molds</th>
<th>PCP</th>
<th>Herpes viruses</th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>HypoIgG</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asplenia</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell-mediated immunity</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>TNF-inhibition</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Approach to Pulmonary Infections in ICH

- What is the degree/cause of immunosuppression?
- What is the pattern of the pulmonary infiltrates?
- What is the tempo of the pulmonary symptoms?

Pattern of Pulmonary Infiltrates

- Segmental/lobar:
  - Common bacterial pathogens
  - Legionella

- Nodules:
  - Cryptococcus, Histoplasma, Coccioides
  - Aspergillus, Zygomycosis
  - Nocardia
  - Mycobacteria
  - Malignancy

- Diffuse:
  - PCP
  - CMV
  - Respiratory viruses (e.g. influenza, RSV, adenovirus, parainfluenza, metapneumovirus)
  - Drug-induced ALI

Tempo of Pulmonary Symptoms

- Segmental/lobar:
  - Common bacterial pathogens Acute
  - Legionella Acute

- Nodules:
  - Cryptococcus, Histoplasma, Coccioides Subacute
  - Aspergillus, Zygomycosis Subacute
  - Nocardia Subacute
  - Mycobacteria Subacute
  - Malignancy Subacute

- Diffuse:
  - PCP Acute**
  - CMV Subacute
  - Respiratory viruses (e.g. influenza, RSV, adenovirus, parainfluenza, metapneumovirus) Acute to Subacute
  - Drug-induced ALI Subacute
PCP in HIV-negative Patients

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive</th>
<th>HIV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute presentation (weeks)</td>
<td></td>
<td>Acute (&lt;1 week)</td>
</tr>
<tr>
<td>Survival &gt;80%</td>
<td></td>
<td>Survival 50-90%</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
<td>Same</td>
</tr>
<tr>
<td>Diffuse bilateral infiltrates</td>
<td></td>
<td>Same</td>
</tr>
<tr>
<td><strong>Beta-D-Glucan</strong></td>
<td></td>
<td>Same sensitivity</td>
</tr>
<tr>
<td>90-95 % sensitive</td>
<td></td>
<td>85-90% specific</td>
</tr>
<tr>
<td>65-90% specific</td>
<td></td>
<td>Same specificity</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td></td>
<td>Same sensitivity</td>
</tr>
<tr>
<td>92-100% sensitive</td>
<td></td>
<td>64-100% sensitive</td>
</tr>
<tr>
<td>25-85% specific</td>
<td></td>
<td>Same specificity</td>
</tr>
<tr>
<td><strong>BAL Microscopy</strong></td>
<td>&gt;90% sensitive</td>
<td>62-85% sensitive</td>
</tr>
<tr>
<td>(high organism burden)</td>
<td>(low organism burden)</td>
<td></td>
</tr>
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Case #2

68 y/o woman s/p cadaveric renal transplant 5 weeks ago (CMV D+R-) is brought to the ED with progressive shortness of breath over 1 week and rapidly requires intubation.

She had been induced with thymoglobulin and is now taking mycophenolate, tacrolimus, and prednisone.

The Most Likely Diagnosis is:

1. CMV
2. Aspergillus
3. Rhizopus
4. S. aureus

Case #2: Diagnosis

KOH stain

Lactophenol cotton blue stain on culture

Gram stain
The Effects of Thymoglobulin Last For:

1. 1 week
2. 3 months
3. 6 months
4. >12 months

How to Approach Infectious Risk Post-Transplant

- Organ type
- Timing after transplant
- Induction regimen (if within ~1 year of transplant)
- Maintenance regimen and doses
- Augmented immunosuppression because of rejection?
- Other OIs?

Timing of Immunosuppression in SOT

Classic Timeline of Infections Post-transplant
Types of Immunosuppression in SOT

**Induction**
1. Methylprednisolone
2. +/- Anti-lymphocyte Ab
   - Thymoglobulin
   - Alemtuzumab
   - Basiliximab

**Maintenance**
1. Calcineurin inhibitor
   - Tacrolimus > Cyclosporine
2. Antiproliferative
   - MMF > Azathioprine
3. Prednisone
4. Others:
   - Sirolimus

**Rejection**
1. Methylprednisolone
2. +/- Anti-lymphocyte Ab
   - Thymoglobulin
   - Alemtuzumab
3. Others:
   - Sirolimus
   - Rituximab

UCSF Examples of Induction/Maintenance

<table>
<thead>
<tr>
<th>Induction</th>
<th>Maintenance</th>
</tr>
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<tbody>
<tr>
<td>Steroid</td>
<td>Antibody</td>
</tr>
<tr>
<td>Liver</td>
<td>Methylpred</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Renal</td>
<td>Methylpred</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Lung</td>
<td>Methylpred</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Heart</td>
<td>Methylpred</td>
</tr>
<tr>
<td></td>
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Infectious Risk in Solid Organ Transplant

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Lymphocyte Antibodies for Induction

**Antithymocyte globulin**
- Rabbit polyclonal IgG against T and B cells
- Depleting Ab: effect lasts >1 year
- Also used in refractory rejection
- Increases risk for many infections (including viral, PCP, fungal)

**Basiliximab**
- Anti-CD25: inhibits IL-2 binding and T cell proliferation
- Non-depleting Ab: effect lasts 4-6 weeks
- Lower potency, less infectious risk – used for lower risk recipients

Slide courtesy of S.Schwartz

**Duration of Lymphocyte Depletion: Thymoglobulin**

Normal Range of ALC

**Infectious Risk of Maintenance Drugs**

- Most drugs studied together → hard to assign individual risk
  - Calcineurin Inhibitors (tacrolimus, cyclosporine): risk viruses (CMV, PCP)
  - Antiproliferatives (mycophenolate, azathioprine): risk viruses (CMV, VZV)
  - Prednisone: Dose-dependent risk for wide range of infections

- The drugs together put SOT recipients at risk for a wide range of infections (bacterial, fungal, viral, parasitic)

**Meta-Analysis of Glucocorticoids and Infection**

- 63 studies in RA patients, significant heterogeneity

  **Dose dependent risk:**
  - <5mg/day RR 1.37
  - 5-10mg/day RR 1.93
  - 10-20mg/day RR 2.97
  - >20mg/day RR 4.30

**Case #3**

A 55 y/o man with RA on infliximab and low dose MTX x 9 months presents with 4 weeks of severe fatigue, weight loss, and multiple painful skin lesions.

On admission his vitals are: 39°C, HR 125, BP 85/50, RR20, SaO2 92% RA. He is admitted to the ICU.

He had immigrated to the US from Mexico at the age of 45 and now lives in Fresno.
The infliximab puts him at high risk for:

1. Tuberculosis
2. Coccidioidomycosis
3. Histoplasmosis
4. All of the above

Case #3: Diagnosis

Skin biopsy positive for Coccidioides
1 out of 4 blood cultures positive for Coccidioides
Ceci immunodiffusion positive
Ceci comp fix titer 1:256

TNF Antagonists

TNF Antagonists and Granulomatous Infections

- Reduce the risk of granulomatous infections by ~5 fold:
  - TB
  - Histoplasma
  - Coccidioides
- Agents interfere with new granuloma formation and weaken the integrity of existing granulomas
TNF Antagonists and Granulomatous Infections

- **TB infection**
  - Usually occurs within 3-6 months after starting therapy
  - Thought to be reactivation of latent disease given clustering of cases early after starting therapy

- **Coccidioidomycosis**
  - Cases cluster at 3 and 10 months (likely a split of reactivation and acute infection)
  - 25% have disseminated disease

TNF Antagonists: Not All the Same

- Risk with infliximab, adalimumab is ~2-7 fold higher than with etanercept

- Infliximab and adalimumab have:
  - Higher peak and steady state levels
  - More binding sites for TNF
  - Can cause Ab-mediated cytotoxicity of monocytes and T cells

  This may lead to a more prolonged and/or robust TNF inhibition in conjunction with effector cell death

TNF Antagonists and Other Infections

- **Bacterial infections:**
  - Septic arthritis
  - Legionella
  - Listeria
  - Salmonella
  - NTM

- **Viral:**
  - HBV reactivation
  - Herpes zoster?
  - PML

- **Other fungal:** crypto, candida, aspergillus, PCP?

Take Home Points

- Always define the specific type of immunocompromise to better delineate infectious risk

- For pulmonary infections, consider the pattern of infiltrates and tempo of symptoms

- For SOT patients, always check which induction agent the patient received and remember that thymoglobulin lasts for >1 year

- TNF antagonists increase the risk for TB and the endemic mycoses, and the risk is much higher with infliximab and adalimumab
Thank You

- Questions?