Caring for the Immunosuppressed Patient in the Primary Care Setting

Kevin Gregg, MD
Associate Professor of Medicine
Division of Infectious Diseases
June 21, 2018
Disclosure

I have no conflicts of interest related to the information in this presentation
Goals of this talk

1. Illustrate how the mechanisms of immunosuppressant therapies can affect the differential diagnosis (‘what should I be worried about in this patient’)

2. Highlight some important infections in immunocompromised hosts that may present to an outpatient clinic

3. Provide a framework for how to start an infectious work-up in a primary care clinic

4. Raise awareness of detecting immunodeficiency in the primary care clinic
The Immune System

Cellular immunity
- Adaptive
  - B-cells
  - T-cells
- Innate
  - Monocytes
  - Macrophages
  - Neutrophils
  - NK cells
  - Mast Cells

Humoral immunity
- Adaptive
  - Immunoglobulins
- Innate
  - Complement cascade
  - Cytokines
  - Skin
  - Mucous membranes
What does it mean to be immunocompromised?

- Primary immune deficiencies
- HIV infection
- Stem cell transplantation recipients
- Malignancy
- Immune suppression for autoimmune diseases
- Asplenia
- Diabetes?
There is a growing population of immunocompromised hosts (ICH)
## U.S. SOT recipient survival – 2007

<table>
<thead>
<tr>
<th></th>
<th>5-years (%)</th>
<th>10-years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney – deceased donor</td>
<td>81.9</td>
<td>61.2</td>
</tr>
<tr>
<td>Kidney – living donor</td>
<td>91.0</td>
<td>77.1</td>
</tr>
<tr>
<td>Liver – deceased donor</td>
<td>73.8</td>
<td>60.0</td>
</tr>
<tr>
<td>Liver – living donor</td>
<td>79.0</td>
<td>69.9</td>
</tr>
<tr>
<td>Heart</td>
<td>74.9</td>
<td>56.0</td>
</tr>
<tr>
<td>Lung</td>
<td>54.4</td>
<td>28.6</td>
</tr>
</tbody>
</table>
Hematopoietic stem-cell transplantation in the U.S.

Nearly 20,000 bone marrow or umbilical cord blood transplants were performed in the United States in 2014.¹

<table>
<thead>
<tr>
<th>Number of Transplants Performed</th>
<th>Type of Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>11,392b</td>
<td>Autologous (the cells for transplant were provided by the patient)</td>
</tr>
<tr>
<td>3,544</td>
<td>Related allogeneic (the cells for transplant were provided by the patient's sibling or another family member)</td>
</tr>
<tr>
<td>4,926</td>
<td>Unrelated allogeneic (the cells for transplant were provided by a volunteer donor)</td>
</tr>
</tbody>
</table>
Autoimmune and acquired immunodeficiencies

- ~25 million people suffer from an autoimmune disorder (NIH estimate)
- More than 1.1 million people with HIV in the U.S.
- Primary immune deficiencies in adults remain rare
Not all immune deficiencies are created equal

• Primary immune deficiency
  • Variable. Common variable immune deficiency – primarily a B-cell defect
• HIV
  • Primarily T-cell defect (CD4+ cell loss, mostly reversible)
• Solid-organ transplantation
  • Primarily adaptive cellular immune defect secondary to immune suppression
• Stem cell transplantation
  • Adaptive and innate cell lines affected (slowly reversible)
• Autoimmune disorders
  • Variable depending upon the treatment indicated
ICH with infectious symptoms in a primary clinic ... first steps

1. **Common things are common!**
2. What are the symptoms?
   - What systems might be involved?
3. How long have the symptoms been present?
   - Longer durations may indicate a greater likelihood of indolent / opportunistic infection
4. Have there been sick contacts or other exposures?
   - Outdoor hobbies, travel, unusual or risky food intake, animal exposures
   - These clues can often help to guide evaluation and expedite a diagnosis
Case 1: Cough, fatigue and fever in a rheumatoid arthritis patient

67 year-old woman with long-standing history of RA presents to her PCP in June with 4 weeks of dry cough, intermittent fevers up to 101.5F and progressive fatigue

• She has been treated with numerous RA therapies, currently on adalimumab (Humira®) for the past 6 months

• Two visits to a local urgent care twice in the past 2 weeks
  • Was told her CXR was normal
  • Prescribed azithromycin x 5 days with no improvement
History

- Lives with her husband and their dog; no other animal exposures
- Retired schoolteacher and avid gardener
- No recent travel or sick contacts
- Negative TB testing prior to adalimumab treatment

Exam

- T 37.7, P 110, R 18, 93% room air; appears mildly fatigued
- Weight is down #12 since visit 3 months ago
- Exam unremarkable
  - Lungs clear to auscultation
  - No rashes or skin lesions
Studies

• Basic labs:
  • WBC count 2.1
  • HGB 11.5
  • Platelets 160
  • Normal creatinine
  • Normal LFTs
Where to go from here?

• Likely to the local hospital for admission...

• How does her adalimumab affect her immune function?

• What tests can be ordered immediately to expedite work-up?
<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Trade name</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-alpha</td>
<td>Infliximab</td>
<td>Remicade®</td>
<td>RA, IBD, Psoriasis, Ankylosing spondylitis, Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>Enbrel®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>Humira®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
<td>Simponi®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerolizumab</td>
<td>Cimzia®</td>
<td></td>
</tr>
<tr>
<td>IL-1 receptor</td>
<td>Anakinra</td>
<td>Kineret®</td>
<td>RA</td>
</tr>
<tr>
<td>IL-2 receptor</td>
<td>Basiliximab</td>
<td>Simulect®</td>
<td>Induction in SOT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled – GVHD, SOT rejection</td>
<td></td>
</tr>
<tr>
<td>IL-6 receptor</td>
<td>Tocilizumab</td>
<td>Actemra®</td>
<td>RA, SJIA</td>
</tr>
<tr>
<td>T-cell co-stimulation</td>
<td>Abetalcept</td>
<td>Ocrenia®</td>
<td>RA, JIA</td>
</tr>
<tr>
<td>CD52</td>
<td>Alemtuzumab</td>
<td>Campath®</td>
<td>CLL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled - Conditioning chemo, GVHD, AIHA due to CLL, SOT immune suppression, MS</td>
<td></td>
</tr>
<tr>
<td>CD20</td>
<td>Rituximab</td>
<td>Rituxan®</td>
<td>NHL, CD20+ CLL, RA, GPA, MPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled – Multiple lymphomas, PTLD, AIHA, ITP, GVHD, SLE, TTP-HUS</td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td>OKT3</td>
<td>Muromonab®</td>
<td>SOT rejection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled – Induction IS in SOT</td>
<td></td>
</tr>
<tr>
<td>Multiple T-cell molecules</td>
<td>Thymoglobulin</td>
<td></td>
<td>SOT rejection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled – Induction renal transplant IS</td>
<td></td>
</tr>
<tr>
<td>Integrin alpha-4 subunit</td>
<td>Natalizumab</td>
<td>Tysabri®</td>
<td>MS, Crohn’s disease</td>
</tr>
</tbody>
</table>
Importance of TNF-alpha in immune function

• Specific involvement in:
  • Macrophage activation
  • Phagosome activation
  • Recruitment of neutrophils and macrophages
  • **Granuloma formation**
  • **Maintenance of granuloma integrity**

• Immunologic defense against:
  • Mycobacteria
  • Fungi (Aspergillus, Cryptococcus, endemic mycoses, Candida)
RA patients with pulmonary TB

Keane J, et al. NEJM, 2001; 345:1098-1104
Differential dx

- Bacterial pneumonia (unlikely)
  - Atypical duration & failed azithromycin tx
- Viral pneumonia (unlikely)
  - Duration of symptoms, leukopenia
- TB (unlikely)
  - TB testing previously negative
- Fungal pneumonia (very possible)
  - Gardener, indolent symptoms, lives in MI
- Pneumocystis (PJP, possible)
  - Leukopenia unusual
- Bacterial endocarditis (possible)

Initial ID investigation

- Bacterial blood cultures
- Fungal blood culture
- Fungal serology panel
- Histoplasma urine and serum antigen
- Blastomyces urine and serum antigen
- Serum cryptococcal antigen
- Fungitell (B-D glucan testing)
- Sputum culture, PJP pcr
Hospital course

- Admitted to the hospital from clinic
- Patient continued to have fevers despite broad-spectrum abx
- On day 3, Histoplasma serum and urine antigens return positive
- Patient is started on liposomal amphotericin B and defervesced the following day
- Transitioned to oral itraconazole for 12 months

- Diagnosis: disseminated histoplasmosis
Histoplasmosis

- Endemic, dimorphic fungus
- ‘Ohio River Valley fever’
- Lives in soil, particularly in areas with bird/bat droppings
- Infection typically through inhalation & often asymptomatic
- Infectious symptoms are variable and may be indolent
  - Progressive febrile illness is common (~80%)
  - Pulmonary symptoms in >75%
  - HSM, lymphadenopathy, skin lesions, GI/adrenal masses, cytopenias, hepatitis
Histoplasmosis
Histoplasmosis diagnosis

• Most disease in ICH is reactivation
• Have a low threshold to evaluate for infection with appropriate symptoms
• If histoplasmosis is considered:
  1. ≥2 fungal blood cultures
  2. Histoplasma urine and serum antigen
  3. Biopsy of mass lesions
  4. Serology (immunodiffusion, complement fixation) only valuable if other tests are negative
     • May be falsely negative in immunosuppressed patients
• Early consultation with infectious diseases
Histoplasmosis treatment

• IDSA guidelines

• Duration of therapy guided by response and presence of continued immune suppression
  • For severe/disseminated disease, typically 12 months of itraconazole

• If TNF-alpha inhibitors need to be restarted:
  • Consider serial urine antigens to detect recurrent infection
  • Consider suppressive itraconazole for duration of therapy
Patients... are at increased risk for serious infections which may result in hospitalization and/or fatality... Active tuberculosis (or reactivation of latent tuberculosis), invasive fungal (including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and pneumocystosis) and bacterial, viral or other opportunistic infections (including legionellosis and listeriosis) have been reported in patients receiving TNF-blocking agents...

<table>
<thead>
<tr>
<th>Pathogen, type of infection</th>
<th>Infliximab group (n = 233,000)</th>
<th>Etanercept group (n = 113,000)</th>
<th>Rate ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>335 (14.8%)</td>
<td>39 (10.4%)</td>
<td>4.17</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>39 (16.7%)</td>
<td>3 (0.7%)</td>
<td>6.30</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Candida species</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>38 (16.3%)</td>
<td>8 (7.1%)</td>
<td>2.39</td>
<td>.006*</td>
</tr>
<tr>
<td>NS</td>
<td>26 (11.2%)</td>
<td>7 (6.2%)</td>
<td>1.88</td>
<td>.085*</td>
</tr>
<tr>
<td>Systemic</td>
<td>10 (4.3%)</td>
<td>1 (0.9%)</td>
<td>4.85</td>
<td>.046*</td>
</tr>
<tr>
<td>Listeria species</td>
<td>36 (15.9%)</td>
<td>2 (1.8%)</td>
<td>8.73</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Mycobacterium species (NS)</td>
<td>30 (12.9%)</td>
<td>7 (6.2%)</td>
<td>2.06</td>
<td>.023*</td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>29 (12.4%)</td>
<td>10 (8.6%)</td>
<td>1.41</td>
<td>.17*</td>
</tr>
<tr>
<td>Cryptococcus species</td>
<td>11 (4.7%)</td>
<td>8 (7.1%)</td>
<td>0.67</td>
<td>.91*</td>
</tr>
<tr>
<td>Nocardia species</td>
<td>10 (4.3%)</td>
<td>1 (0.9%)</td>
<td>4.85</td>
<td>.046*</td>
</tr>
<tr>
<td>Salmonella species</td>
<td>7 (3.0%)</td>
<td>4 (3.6%)</td>
<td>1.88</td>
<td>.75*</td>
</tr>
<tr>
<td>Toxoplasma species</td>
<td>5 (2.1%)</td>
<td>0 (0%)</td>
<td>...</td>
<td>.088*</td>
</tr>
<tr>
<td>Brucella species</td>
<td>2 (0.9%)</td>
<td>0 (0%)</td>
<td>...</td>
<td>.38*</td>
</tr>
<tr>
<td>Bartonella species</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>...</td>
<td>.02*</td>
</tr>
<tr>
<td>Leishmania species</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>...</td>
<td>.02*</td>
</tr>
<tr>
<td>Mycobacterium leprae*</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>...</td>
<td>.02*</td>
</tr>
<tr>
<td>Overall</td>
<td>666 (23.2%)</td>
<td>83 (7.3%)</td>
<td>3.26</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

NOTE: Data are no. of patients (no. per 100,000 patients who received the drug). NS, species was not specified.

* By χ² analysis.

* By Poisson analysis.

* Resulted in log-rank.
Take home points

• When evaluating patients on TNF-inhibitors with atypical fever/infectious symptoms consider opportunistic infections
  • Prolonged duration, lack of response to standard empiric therapy, etc
• Prior to TNF-inhibitor use, patients should have TB testing performed (PPD or Quantiferon assay)
• When including fungal infection in the infectious differential of patients on TNF-inhibitors, think:
  • Michigan/upper Midwest resident – histoplasmosis, blastomycosis
  • Travel/residence in the southwest – coccidiodiomycosis
  • Bird exposure -- cryptococcosis
Case 2: Solid-organ transplant recipient with fevers, fatigue and leukopenia

- 37 year-old man with FSGS who underwent a deceased donor renal transplant 1 year ago
- Immunosuppression regimen: prednisone 5mg, tacrolimus, mycophenolate
- Prior to transplant his cytomegalovirus (CMV) IgG was negative; donor was CMV IgG positive
- Presents in February with 1 week of fatigue, malaise, fevers and non-bloody diarrhea
- Occasional nausea, no vomiting
- Reports no respiratory symptoms
Health history

• Lives with his wife and two children, ages 3 and 6, and 2 cats
• Kids with diarrheal illnesses 1 month ago
• Recent dental implant, given 7 days abx post-procedure
• Swims with his kids at local pool

Exam

• T 38.0, P 95, R 15, 99% room air, BP 105/60
• Dry mucous membranes
• Lungs clear
• Abd with hyperactive BS but no tenderness or distention
• No rashes or skin lesions
Exam visit

- Basic labs:
  - WBC count 1.5
  - HGB 10.9 (chronic)
  - Platelets 132
  - Creatinine 1.8 (baseline 1.5)
  - Normal LFTs

- Abdominal X-ray unremarkable

Differential diagnosis

- Viral gastroenteritis (possible)
  - Sick contacts; cytopenias unusual

- Bacterial gastroenteritis (possible)

- C difficile enteritis (possible)
  - Recent antibiotic use; cytopenias unusual

- Mycophenolate toxicity (possible)
  - Can cause colitis, leukopenia; fevers unusual

- CMV infection (very possible)
  - High-risk recipient, cytopenias, syndrome fits

- Cryptosporidiosis (less likely)
  - Pool exposure

- Influenza (unlikely)
  - Right season but no respiratory symptoms
Where to go from here?

• What are the most urgent diagnoses to confirm/exclude?

• What does it mean to be high-risk for CMV infection?

• What tests can be ordered immediately to expedite work-up?
Solid-organ transplant infection risk

Fishman, NEJM, 2007
CMV infection after SOT without prophylaxis

**Recipient CMV serology**

- **-**
  - **D-/R-**
    - <10%
  - **D+/R-**
    - 50-90%
- **+**
  - **D-/R+**
    - <10-60%
  - **D+/R+**
    - 20-60%
Initial evaluation

• Stool culture for bacterial pathogens ➔ Negative
• Stool GI pcr to assess for viruses, parasites ➔ Negative
• C difficile assay ➔ Negative
• Blood cultures ➔ Negative
• Serum CMV pcr ➔ Positive (70,000 IU/mL)

Diagnosis: CMV infection
Natural history of CMV infection

- CMV disseminates during primary infection
  - In children, mild illness or asymptomatic infection
  - In adolescents and adults → mononucleosis-like syndrome
- Establishes latency in various myeloid cell lines
  - Macrophages, dendritic cells, progenitor cells
- Latent virus expresses immune evasion genes
  - Prevents host eradication of the virus
  - Host immune response persists indefinitely and maintains viral suppression

...until the immune system is deficient
Post-transplant CMV disease

- Fever, fatigue, malaise
- Hepatitis
- Colitis, enteritis, esophagitis, pancreatitis
- Nephritis
- Leukopenia, anemia

**Indirect viral effects**

- *Increased risk of acute and chronic rejection*
- *Increased risk of other opportunistic infections (Pneumocystis, Aspergillus)*
- *Oncogenesis*

- Meningoencephalitis
- Pneumonitis
- Myocarditis (rare)
Impact of early cytomegalovirus infection and disease on long-term recipient and kidney graft survival

- CMV in first 100 days of transplant (n=471)
  - Infection in 62.8%
  - Disease in 23.4%

Case revisited

• Patient was urgently referred to ID clinic
• Started on valganciclovir (Valcyte) 900mg bid x 21 days
• Symptoms resolved within 5 days; leukopenia resolved in 2 weeks
• Viral load negative after 21 days
• No recurrences since treatment

• Patient will always be at risk for recurrence; prognosticating risk is difficult
Take home points

• CMV infection is remains the most important infection after solid-organ transplantation

• In CMV+ SOT recipients presenting with fevers/infectious symptoms that do not have a definite etiology, serum CMV pcr is an appropriate test to order

• Treatment is generally straightforward but should involve an ID specialist or transplant physician experienced in treatment
Case 3: 31 year-old woman with pneumonia

• 31 year-old woman presenting with 3 days of low-grade fever, cough productive of green sputum and malaise

• She reports being treated for lower-respiratory tract infection ‘at least yearly’ for the past 5 years
  • Has been admitted twice for pneumonia

• Feels that she has a sinus infection ‘constantly’
  • Treated for seasonal allergies

• Feels like antibiotics never seem to work well for her

• Loose stools; attributed to IBS.
Clinic visit

• T 37.7, P 90, BP 125/70, R 18, SPO2 97% on RA
• Boggy nasal mucosa
• Lungs, few scattered ronchi
• Cardiac exam unremarkable
• Abdominal exam unremarkable
• Skin; no rashes or lesions noted
Studies

• Basic labs:
  • WBC count 12.7
  • HGB 12.5
  • Platelets 277
  • Creatinine 0.8
  • Normal LFTs

• Sputum cx:
  • *Haemophilus influenzae*

Treatment course

• Started on Augmentin 875/125mg bid x 5 days

Is there anything else to consider?
Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
10. A family history of PI.

Presented as a public service by:

Jeffrey Modell Foundation

Funding was made possible in part by a grant from the U.S. Centers for Disease Control and Prevention (CDC).

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. © 2013 Jeffrey Modell Foundation

For more information, contact the Jeffrey Modell Foundation: info@pi.org | 866-INFO-4-PI
Primary immune deficiencies are rare in adults

- Most common is common variable immune deficiency (CVID)
- Incidence ~ 1:75,000 live births
- Prevalence ~ 1:25,000
  - In one European database of PIDD, 30% of patients had CVID
- Sexes affected equally
- Bimodal distribution of age at diagnosis
  - Peak in childhood (1-5 years)
  - Larger peak in 3rd decade of life

<table>
<thead>
<tr>
<th>CVID</th>
<th>Age of symptom onset</th>
<th>Age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>23 years</td>
<td>29 years</td>
</tr>
<tr>
<td>Women</td>
<td>28 years</td>
<td>33 years</td>
</tr>
</tbody>
</table>
Review of 248 patients with CVID

- Bronchitis, sinusitis, otitis – 98%
- Pneumonia – 77%

**TABLE 4**

<table>
<thead>
<tr>
<th>Infections</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent bronchitis, sinusitis, otitis</td>
<td>243</td>
<td>98</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>190</td>
<td>76.6</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>16</td>
<td>6.5</td>
</tr>
<tr>
<td>History of severe <em>Herpes zoster</em></td>
<td>9</td>
<td>3.6</td>
</tr>
<tr>
<td>Giardia enteritis</td>
<td>8</td>
<td>3.2</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> infections</td>
<td>7</td>
<td>2.8</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Salmonella diarrhea</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Campylobacter enteritis</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Meningitis <em>(H. influenzae, pneumococcus, and pseudomonas)</em></td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Recurrent parotitis</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nocardia brain abscess</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anaerobic leg infection leading to amputation</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cryptococcal lung abscess</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Viral myocarditis</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cytomegalovirus, intestinal infection</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td><em>Mycobacterium avium</em>, lung</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatal mesiales encephalitis</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mycoplasma joint infection</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Psoas abscess <em>(Escherichia coli</em> and <em>Bacteroides)</em></td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pelvic abscess after appendectomy, unknown organism</td>
<td>1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Clin Imm, 1999; 92(1):34-48
Diagnosis of CVID

• Suspected patients should undergo a stepwise diagnostic process
• Thorough H&P, HIV test, ± ENT evaluation
• Initial tests
  • CBC with differential
  • Quantitative immunoglobulins (IgA, IgG, IgM)
  • Urine protein assay
    • Urinalysis (urine dipstick not adequate)
    • UPEP if UA abnormal (to rule out nephrotic syndrome)
Immunoglobulin levels at time of diagnosis (n=248)
Case revisited

• HIV test negative
• Serum immunoglobulins
  • IgG 275 mg/dL
  • IgA 21 mg/dL
  • IgM 6 mg/dL
• Referred to immunologist for further evaluation and started on monthly IVIG infusions for diagnosis of CVID
• After 2 months, IgG level 735 (normal >550mg/dL)
• Single episode of sinusitis, occasional viral URI since treatment initiation
CVID & pneumonia: effect of treatment

Patients with at least 1 episode of pneumonia (n=50)

- 84% Before IVIG
- 22% After IVIG

- 29 episodes of pneumonia over 7 year follow-up
- 19/29 episodes in 3 patients with structural lung disease

J All Clin Imm, 2002; 109(6):1001-1004
Take home points

• Primary immune deficiencies in adults are very rare

• Low incidence often leads to significant delays in diagnosis

• In patients with unusual frequency of infection, unusual duration of infection, lack of response to therapy or atypical infections, primary immune deficiency may be considered
Vaccination of the immunocompromised host

• One of the most important aspects of care that can be accomplished in a primary care clinic

• Well-established guidelines on who can receive vaccines and when they should receive them
# 2018 Recommended Immunizations for Adults: By Health Condition

If you have this health condition, **talk to your healthcare professional about these vaccines**.

<table>
<thead>
<tr>
<th>Health Condition</th>
<th>Flu Vaccine</th>
<th>Tetanus, diphtheria, pertussis</th>
<th>Shingles Vaccine</th>
<th>Pneumococcal Vaccine</th>
<th>Meningococcal Vaccine</th>
<th>MMR Vaccine</th>
<th>HPV Vaccine</th>
<th>Chickenpox Vaccine</th>
<th>Hepatitis A Vaccine</th>
<th>Hepatitis B Vaccine</th>
<th>Hib Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Weakened immune system</td>
<td></td>
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<td></td>
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<tr>
<td>HIV: CD4 count less than 200</td>
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<tr>
<td>HIV: CD4 count 200 or greater</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Kidney disease or poor kidney function</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Spleen removed or does not work well</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Heart disease</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Chronic lung disease</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chronic liver disease (Type 1 or Type 2)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Diabetes</td>
<td></td>
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</tbody>
</table>

**More Information:**

- You should get the tetanus vaccine every 10 years. Women should get 1 dose of Tdap vaccine during every pregnancy.
- There are 2 types of meningococcal vaccine. You should get 1 dose of PCV13 at age 2-5 years or older (preferably) or 1 dose of PCV13 at age 10 years or older, even if you had meningitis before.
- There are 2 types of meningococcal vaccine. You should get 1 dose of PCV13 at age 6-11 years or older, even if you had meningitis before. There are 2 types of meningococcal vaccine. You may need one or both types depending on your health condition.
- You should get the Hepatitis A vaccine if you were born before 1957 or if you are a medical occupant or if you are involved in a bone marrow transplant.

For more information, call 1-800-232-4636 or visit www.cdc.gov/vaccines

**Factors to Consider:**

- Your age
- Your health status
- The presence of any underlying health conditions

**YOU SHOULD NOT GET THIS VACCINE**

Factors due to your health condition. Talk to your healthcare professional to see if you need this vaccine.
Disease specific states: SOT

- Toronto Invasive Bacterial Disease Network surveillance study: 1995-2004

- Prospective study of invasive pneumococcal disease (IPD)

- 2796 solid-organ transplant recipients tracked during the study
  - 14344 person-years evaluated
Cohort | Cases of IPD / 100,000 person-years
--- | ---
General population | 11.5
All transplants | 146
Kidney transplant | 344
Liver transplant | 354
Lung transplant | 3262

*24% of patients with IPD had received any pneumococcal immunization

Kumar D, et al. AJT, 2007; 7:1209-1214
How well are SOT recipients vaccinated?

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Liver recipients (n=267)</th>
<th>Kidney recipients (n= 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-transplant</td>
<td>Post-transplant</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>2.3%</td>
<td>13.1%</td>
</tr>
<tr>
<td></td>
<td>15.4%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>5.2%</td>
<td>43.5%</td>
</tr>
<tr>
<td></td>
<td>48.7%</td>
<td>60.4%</td>
</tr>
</tbody>
</table>

Barriers to immunization after SOT

1. Questionable efficacy in immunosuppressed patients

2. Concerns about side effects... inducing rejection

3. Knowledge and implementation of vaccine recommendations by providers
Vaccination response after renal transplant

Table 1.—Antibody Responses to Pneumococcal Vaccine in Renal Transplant Recipients and Hemodialysis Patients, Including Effect of Steroid Dose and Splenectomy

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Before Vaccination</th>
<th>After Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>104</td>
<td>113</td>
<td>440</td>
</tr>
<tr>
<td>After transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6 mo</td>
<td>18</td>
<td>64†</td>
<td>303‡</td>
</tr>
<tr>
<td>&gt; 6 mo</td>
<td>96</td>
<td>128</td>
<td>476</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>33</td>
<td>136†</td>
<td>592‡</td>
</tr>
<tr>
<td>Steroid dose (mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in transplant recipients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>63</td>
<td>150§</td>
<td>476</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>41</td>
<td>74§</td>
<td>390</td>
</tr>
<tr>
<td>Splenectomies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>85</td>
<td>116</td>
<td>393</td>
</tr>
<tr>
<td>Dialysis</td>
<td>79</td>
<td>117</td>
<td>394</td>
</tr>
<tr>
<td>Without splenectomies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>52</td>
<td>123</td>
<td>639</td>
</tr>
<tr>
<td>Transplant</td>
<td>25</td>
<td>101</td>
<td>626</td>
</tr>
<tr>
<td>Dialysis</td>
<td>27</td>
<td>148</td>
<td>850</td>
</tr>
</tbody>
</table>

RCT – PPV23 vs. PCV7 after kidney transplant

% patients responding by IgG quantitation

% patients responding by opsonophagocytic activity

Kumar D, et al. JID, 2003; 187:1639-1645
2012 ACIP recommendations

• Adults (≥19 years) with immune compromising conditions (including SOT) should receive PCV13 (Prevnar®) in addition to PPV23 (Pneumovax®)
  • Category A recommendation
  • For unvaccinated patients, PCV13 vaccine should be followed >8 weeks later with PPV23
  • If PPV23 previously received, PCV13 should given >12 months after PPV23 vaccination

MMWR, 2012; 61(40):816
Barriers to immunization

1. Questionable efficacy in immunosuppressed patients

2. Concerns about side effects... including inducing rejection

3. Knowledge and implementation of vaccine recommendations by providers
Vaccination safety after SOT

• Live vaccines are generally not administered
• Inactivated vaccines are considered safe
• There is no data linking clinical rejection to vaccination (II-2)
  • Previous concerns arose from case series
  • Larger datasets without risk of rejection
  • Temporary rises in alloantibodies seen in transplant recipients and non-transplant patients
• When in doubt, reach out to primary transplant provider or ID physician

Avery R. Curr Opin Inf Dis, 2012; 25(4):464-468
A caveat about non-live vaccines...

- The newly licensed Zoster vaccine (Shingrix®) is a highly immunogenic, non-live vaccine
- There are concerns regarding the potential for immunologic reactions that could precipitate allograft rejection
- At present, the vaccine is not indicated post-transplant
- This could change with further data
- If possible, vaccinate pre-transplant patients with the live varicella vaccine (Zostavax®) if they are >50 years old
Barriers to immunization

1. Questionable efficacy in immunosuppressed patients

2. Concerns about side effects... inducing rejection

3. Knowledge and implementation of vaccine recommendations by providers
2002 US renal transplant center survey (147 centers)

22% of centers did not recommend vaccinations to patients!

Table 9. Vaccination practices prior to transplantation

<table>
<thead>
<tr>
<th>Vaccinations against</th>
<th>Programs vaccinating (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>15</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>89</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>60</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>4</td>
</tr>
<tr>
<td>H. influenza</td>
<td>21</td>
</tr>
<tr>
<td>Tetanus</td>
<td>44</td>
</tr>
<tr>
<td>Influenza</td>
<td>43</td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 10. Vaccinations given or prescribed following renal transplantation in centers advising vaccinations in all patients (74 centers)*

<table>
<thead>
<tr>
<th>Vaccinations</th>
<th>Always give (%)</th>
<th>Never give (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>62</td>
<td>5</td>
</tr>
<tr>
<td>H. influenza</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Diphtheria/pertussis/typhoid</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Tetanus</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Travelers' illnesses</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>
Provider practice – influenza vaccine after renal transplant (>200 centers)

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney transplant recipients</td>
<td>84.4%</td>
<td>94.5%</td>
</tr>
<tr>
<td>Kidney/pancreas transplant recipients</td>
<td>48.5</td>
<td>76.8</td>
</tr>
<tr>
<td>Family members</td>
<td>21.0</td>
<td>52.5</td>
</tr>
<tr>
<td>Health care workers</td>
<td>40.7</td>
<td>79.6</td>
</tr>
<tr>
<td>Do not recommend</td>
<td>11.4</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Other infection prevention measures in ICH

• Water Exposure
  • Avoid well water
  • No lakes/rivers
  • Bottled “spring” water may be contaminated

• Food safety
  • No unpasteurized juice/cider milk
    • Salmonella, E coli 0157:H7
  • Adequate cooking of meat, eggs
  • Cook hot dogs
  • Reheat leftovers to steaming hot (Listeria)
  • Wash hands
Pets/Animals

- Do not need to give up pets, but...
  - Avoid scratches (*Bartonella*)
  - Litter box (*Toxoplasma*)
  - Avoid new pet < 1 year old
  - Keep pet healthy
  - Avoid pet with diarrhea
  - Wash hands
  - Gloves to clean aquarium (*Mycobacterium marinum*)

- Animals exposures
  - No reptiles or chicks (*Salmonella*)
  - Avoid mosquito bites (West Nile Virus)
  - Avoid stray animals, dead birds
  - Avoid monkeys
Travel

- Avoid developing countries early after transplantation
- Traveler’s clinic mandatory before international travel
- Live vaccines must be avoided (Yellow Fever, oral Typhoid vaccines)
Summary

• Immunocompromised hosts are a growing population with unique risks for infectious complications

• Providers must be alert for unusual or atypical signs and symptoms when evaluating ICH hosts to determine when to escalate evaluation and/or hospitalize patients

• Thinking about potential opportunistic / atypical infections early may expedite diagnosis

• Have a low threshold to involve an infectious disease specialist if concern for a potentially severe infection arises in an ICH