Infection in the Immunocompromised Host

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- Disclosures
- Research funding from Merck
- I will discuss the use of medications for non-FDA approved indications

Overview
- Introduction and Basic Principles
- Drug-induced Immunodeficiency
  - Corticosteroids
  - TNF-α inhibitors
  - Rituximab
  - Anatomic Immunodeficiency
    - Asplenia
    - Transplant
- Introduction and Basic Principles
  - In 1998 Fishman and Rubin described key principles of managing infection in transplant recipients
  - Also applicable to ICH population
- Basic Principles
  - In 1998 Fishman and Rubin described key principles of managing infection in transplant recipients
  - Also applicable to ICH population
  - Net state of immunosuppression
    - Dose and duration of suppressive medications
    - Mechanical factors (eg. lymphatic compromise)
    - Infections contributing to compromise (eg. HIV)
  - Important epidemiologic exposures
    - New exposures
    - Remote exposures with possibility of reactivation

Infection in Compromised Host
- The immunocompromised host (ICH) is susceptible to opportunistic infections and community-acquired infections
  - Infection can result from exposure to a lower number of organisms
  - Canary in a coal mine
- The inflammatory response to infection is suppressed in ICH
  - Attenuated signs and symptoms of infection
  - ICH with infection typically has high burden of organisms once infection established
Drug-Induced Immunosuppression

- In last 20 years the number of immunosuppressive drugs approved to treat malignant and non-malignant conditions has greatly expanded
  - Monoclonal antibodies in particular
  - Understanding drug mechanism and impact on host defenses is key to predicting host susceptibility

Immunosuppressive Drugs

- Corticosteroids
- Antimetabolites
  - Methotrexate
  - Azathioprine
  - 6-mercaptopurine
  - Mycophenolate
  - Lefunomide
- T lymphocyte agents
  - Tacrolimus
  - Cyclosporine
  - Sirolimus
- Allylating agents
  - Cyclophosphamide
- Monoclonal antibodies
  - Tumor necrosis factor-α (TNF-α) inhibitors
  - Infliximab
  - Etanercept
  - Adalimumab
  - Certolizumab pegol
  - Golimumab
  - Anakinra
  - Rituximab
  - Alemtuzumab
  - Natalizumab
  - And many others...

Corticosteroids

- Acute effect of corticosteroids on host defenses includes
  - Neutrophil demargination and reduced chemotaxis
  - Lymphopenia and depletion of T lymphocytes
- Long term effect of corticosteroids on host defenses includes
  - Skin weakening and poor wound healing

Corticosteroids and infection

- In general, steroids increase risk of infection
  - In study of rheumatoid arthritis (RA), patients on steroids vs. non-immunosuppressive therapy
    - Rate ratio of mild infection: 1.15 (95% CI 1.11, 1.19)
    - Rate ratio of severe infection: 1.9 (95% CI 1.75, 2.05)
  - In metanalysis of 71 controlled trials of steroid vs. non-steroid therapy, steroid recipients had significantly higher rate of infection (12.7% vs. 8.0%) and lethal infection (1.2% vs. 0.5%)
    - Included studies of GI, pulmonary, renal, neurologic and rheumatic conditions

Corticosteroids: dose and duration

- Dose and duration of steroids impacts infection risk
  - In metanalysis, there was no increased infection risk in patients treated with <10 mg prednisone (or equivalent) per day

Corticosteroids and specific infections

- Specific types of infection associated with steroids
  - Community-acquired
  - Opportunistic
    - Bacterial (e.g., *Listeria*)
    - Fungal (e.g., *Aspergillus*)
    - Reactivation of latent tuberculosis
    - *Pneumocystis jiroveci* pneumonia (PCP)
    - Strongyloides hyperinfection syndrome

Corticosteroids and PCP

- Steroids are a major risk factor for PCP
- In a study of 116 non-HIV patients, 105 (91%) were on steroids
- Similarly, in a study of 134 non-HIV cancer patients with PCP, 116 (87%) were on steroids
- PCP in non-HIV patients is associated with significant mortality
  - Mortality rate among 114 non-HIV cancer patients was 49% in one study
  - Among 223 patients with connective tissue disease with PCP, the in-hospital mortality was 45.7%

Corticosteroids and Strongyloides

- Strongyloides initial infection
  - Larvae penetrate skin → travel to GI tract via venous and pulmonary systems
  - Often clinically silent (chronic) but can cause eosinophilia
- Hyperinfection syndrome
  - First described in 1966 in 5 patients on high-dose steroids mostly for nephrotic syndrome
  - Accelerated infection in which larvae become infectious prior to excretion → invade bloodstream directly from GI tract
  - Clinical illness associated with significant increase in worm burden and transit
    - Diarrhea, vomiting, pulmonary infiltrates, sepsis
    - Enteric gram-negative bacteremia and meningitis

Mortality associated with hyperinfection is significant
- 14% mortality among 37 patients with hyperinfection in a study from SE Asia
- Patients from endemic area or with unexplained eosinophilia being started on significant steroids should be assessed for strongyloides
  - Strongyloides antibody testing (EIA)
  - Can sometimes be detected on stool O+P but is notoriously insensitive due to intermittent excretion
  - If a patient tests positive, treat with ivermectin or albendazole before steroids initiated

Case Presentation #1

- A 57 year old woman with a history of rheumatoid arthritis presents with one week of malaise, weakness, low grade fevers, and nausea
- Past medical history: Rheumatoid arthritis, s/p right shoulder and left knee replacements, HBV carrier
- Medications
  - Infliximab (started 2 months ago)
  - Methotrexate weekly
  - Tylenol
  - Taking several doses per day for her symptoms in the 2-3 days
- Social history: Born in China, immigrated to the US 35 years ago. Lives in Connecticut with her husband and 3 dogs
Exam is remarkable for a chronically ill-appearing women; cardiac exam normal; the abdomen is non-tender non-distended; the right shoulder and left knee are non-tender with FROM

Labs are notable for normal renal function, ALT 210, AST 179, TBili 2.5, normal coags

The least likely cause of her illness is:
A. Tylenol toxicity
B. Hepatitis A infection
C. Hepatitis B reactivation
D. Tuberculosis
E. Methotrexate toxicity

TNF-α is an inflammatory cytokine produced by macrophages
- Important for control of infection with intracellular organisms and for granuloma formation
- Currently 5 FDA-approved drugs that inhibit TNF-α
  - Infliximab, adalimumab, and etanercept are monoclonal antibodies that bind TNF-α
  - Certolizumab pegol is a pegylated portion of a monoclonal antibody that binds TNF-α
  - Etanercept is soluble TNF-α receptor that binds soluble TNF-α
- All are approved for treatment of RA
- Most are also approved for treatment of psoriatic arthritis and ankylosing spondylitis

Several studies and registries have assessed if TNF-α inhibitors increase general infection risk
- Many studies have assessed risk for bacterial infection; results have been mixed
- Metanalysis including 9 trials assessed infection risk in RA patients treated with infliximab or adalimumab vs. non-TNF-α therapy
  - Pooled odds ratio for serious infection: 2.0 (95% confidence interval 1.3, 3.1)
  - Most infections in this study were bacterial (114 of 126)

TNF-α inhibitors have been associated with several specific infections
- Tuberculosis (TB)
- Hepatitis B reactivation (see rituximab)
- Listeria monocytogenes
- Non-tuberculous mycobacteria
- Endemic mycosis (histoplasma, coccidioides)

Keane, et al. analyzed all cases of TB associated with infliximab reported to FDA 1998-2001
- 40/70 (57%) had extrapulmonary TB
- Median time to TB: 12 weeks
- Overall TB rate: 24.4 cases per 100,000 RA patients on infliximab (vs. 6.2 cases per 100,000 in RA patients)
- Since this publication differences in TB after infliximab vs. etanercept have emerged
  - Risk after infliximab is higher than after etanercept
  - TB develops earlier after infliximab (~3months) than etanercept (~12 months)
  - Less known about TB risk in newer TNF-α agents
  - Screening for TB with PPD or interferon gamma release assay necessary prior to TNF-α therapy
Case Presentation #2

- A 23 year old woman with idiopathic thrombocytopenic purpura presents with 10 days of fevers, malaise, arthralgias, and progressive shortness of breath
- Past medical history: ITP, seasonal allergies
- Medications
  - Prednisone 20 mg po daily
  - Rituximab given 3 weeks ago
- Social history: Lives in rural Wisconsin on a dairy farm with her parents and siblings. Works as the bookkeeper for the farm. Spends free time hiking and rafting.

Exam is remarkable for a tired-appearing pale young woman; cardiac exam notable for tachycardia; abdominal exam notable for palpable spleen tip; no rash is present

Labs are notable for AST 67, ALT 78, HCT 24.3, PLT 90

Chest x-ray is clear

Rituximab

- Rituximab is a monoclonal antibody directed at CD-20, a B lymphocyte marker
- Immunologic effect is depletion of B lymphocytes
- Functionally this leads to inability to mount antibody response to new antigens
- Poor response to vaccines after treatment with rituximab
- FDA approved for treatment of some lymphomas, chronic lymphoid leukemia (with other chemo), and RA (with methotrexate)
- Used off-label to treat immune-mediated anemia and thrombocytopenia, lupus, and pemphigus


HBV reactivation

- Pre-marketing trials showed no increase in infection in lymphoma and RA patients on rituximab vs. non-rituximab regimens
- With clinical use, there have been several case reports of various opportunistic infections
  - PCP and Progressive multifocal leukoencephalopathy due to JC virus are most commonly cited in case reports/studies
  - Others include CMV reactivation, pure red cell aplasia due to parvovirus, and enterovirus encephalitis
  - Interpretation of case reports is difficult since patients often on multiple immunosuppressants
- Rituximab is definitively associated with
  - Hepatitis B virus (HBV) reactivation
  - Increased severity of babesiosis (in exposed patients)

Exposure
  - Perinatal
  - Percutaneous
  - Sexual

Inactive Carrier
  - HBsAg+
  - HBeAg+
  → HBeAb+
  - HBV DNA low (or -)

Chronic active infection
  - HBsAg+
  - HBeAg+
  → HBV DNA high
  - Abnormal LFTs

Reactivated HBV infection
  - HBsAg+
  - HBeAb+
  → HBeAg
  - HBV DNA high

Chronic HBV infection
  - HBsAg+
  - HBeAb+
  → HBV DNA low

Resolved HBV infection
  - HBsAg−
  - HBV DNA−

Reactivated HBV infection
  - HBsAg+
  - HBeAb+
  → HBeAg
  - HBV DNA high

HBV reactivation

RITUXIMAB

RITUXIMAB

RITUXIMAB
Rituximab and HBV Reactivation

- Defined as redevelopment of active liver damage
- Concomitant with rise in HBV virus load (or newly detectable virus load) and transaminases
- Fulminant hepatic failure and death have been reported with reactivation
- Risk of reactivation is higher in chronic carriers (HBsAg+) than in patients with resolved HBV

Prevention
- All patients in whom rituximab or TNF-α inhibitor therapy is being considered should be screened for HBV
- Antiviral prophylaxis should be considered for chronic carriers
- Close monitoring for reactivation should be implemented for patients with evidence of previous resolved HBV

Fulminant hepatic failure and death have been reported with reactivation. Risk of reactivation is higher in chronic carriers (HBsAg+) than in patients with resolved HBV. Prevention: All patients in whom rituximab or TNF-α inhibitor therapy is being considered should be screened for HBV. Antiviral prophylaxis should be considered for chronic carriers. Close monitoring for reactivation should be implemented for patients with evidence of previous resolved HBV.


Rituximab and Babesiosis

- A tick-borne malaria-like parasitic infection
- Northeastern US, Wisconsin and Minnesota
- Causes fevers, malaise, anemia (due to hemolysis) and thrombocytopenia

Patients treated with rituximab who acquire babesiosis shortly before or after treatment have worse illness. In case-control study of persistent babesiosis vs. uncomplicated infection, over half cases had received rituximab. Rituximab-treated patients with babesiosis: Often have a higher parasite burden. More likely to develop severe complications including ARDS. More likely to have relapse requiring repeat or prolonged treatment courses.


Anatomic Immunodeficiency

Case Presentation #3

- A healthy 47 year old man presents to his PCP for evaluation after he was bitten by a pit bull puppy
- The bite broke skin on his shin, but bled minimally
- Past medical history: s/p splenectomy 3 years ago after he sustained blunt abdominal trauma in MVA. Vaccinated for S. pneumoniae, H. influenzae, and N. meningitidis 1 week after splenectomy
- Medications
  - None
- Social history: Lives with his wife and 3 children in Maine. Works construction during spring/summer; shovels snow in winter.Breeds pit bulls at home.

Case Presentation #3 (con’t)

- Vital signs are normal
- Exam is remarkable for well-appearing man with multiple tattoos
- On the right shin there is a small puncture mark without significant surrounding erythema or purulence

Case Presentation #3 (con’t)

- Which of the following is the most appropriate treatment?
  A. Oral cephalaxin
  B. Human rabies immunoglobulin followed by vaccination series for rabies
  C. Oral amoxicillin-clavulanate
  D. Admit for IV piperacillin-tazobactam
  E. No further treatment needed
Asplenia

- Immunologically the spleen plays an important role in filtering blood
  - Important for clearance of extracellular bacteria and intracellular parasites (e.g., malaria)
- Many important medical reasons for surgical splenectomy including trauma, malignancy, and refractory hematologic disorders
  - Infection risk may vary depending upon reason for splenectomy
  - Patients with sickle cell anemia are typically functionally asplenic

Asplenia and bacterial infection

- Asplenic patients are at risk for overwhelming bacterial infection, often due to encapsulated organisms
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Neisseria meningitidis*
- Progression of infection can be rapid
  - Associated with high mortality—38-69%
  - Risk is likely highest in first 2 years after splenectomy
  - Lifetime risk of overwhelming infection is approximately 5%

Asplenia and other infections

- *Capnocytophaga canimorsus*
  - Gram-negative bacterial colonizer of canine mouth
  - Cause of severe infection/sepsis in asplenic patients
  - Occasionally associated with digital or nasal necrosis
  - Usually susceptible to beta-lactam/beta-lactamases
  - Asplenic patients should be educated about careful cleaning after animal bite (especially dog) and medical evaluation
- Babesiosis and Malaria
  - Severity of babesiosis and malaria are increased and parasite burden higher in asplenic patients
  - May require prolonged or repeated courses of treatment

Prevention

- Vaccination for *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* is important
- Vaccinate at least 2 weeks pre-splenectomy in planned cases and 1-2 weeks after (or before hospital discharge) in unplanned splenectomy cases
- Management of fever
  - Asplenic patients should be educated about the risk of severe bacterial infection
  - "Pill in pocket" approach

Transplantation

- A 52 year old woman who underwent a renal transplant 7 years ago presents with 2 days of fever, cough, and body aches
  - Past medical history: HTN, hypercholesterolemia, history of IgA nephropathy s/p renal transplant 7 years ago (baseline Cr 1.1)
    - Donor CMV-recipient CMV+: never had CMV post-transplant
    - Never had rejection since transplant
- Medications
  - Tacrolimus
  - Mycophenolate mofetil
  - Lisinopril
  - Atorvastatin
Case Presentation #4 (con’t)

- Social history: Lives with her husband in Massachusetts; 2 adult children; takes care of her 3 year old granddaughter 4 days a week
- Vital signs: T 100.1 P 85
- Exam is notable for crackles at the left base

The least likely cause of her illness is:
A. Influenza
B. Viral upper respiratory tract infection
C. CMV
D. Community-acquired pneumonia

Timing of Infection after Transplant

<table>
<thead>
<tr>
<th>Time after transplant</th>
<th>Nosocomial</th>
<th>Opportunistic</th>
<th>Community-acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 Month</td>
<td>Hostly Bacteria</td>
<td>Viral</td>
<td>Viral</td>
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<tr>
<td></td>
<td>Catheter-related UTI</td>
<td>CMV</td>
<td>Influenza</td>
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<tr>
<td></td>
<td>Line infection</td>
<td>VZV</td>
<td>IVY</td>
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<tr>
<td></td>
<td>Pneumonia</td>
<td>Listeria</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Procedure-related</td>
<td>Wound infection</td>
<td>Aspergillosa</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Fever + neutropenia</td>
<td>Fungal</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Donor-derived Bacteria</td>
<td>vasive</td>
<td>Fungal</td>
<td>PCP</td>
</tr>
</tbody>
</table>

>6 Months

|                       | Bacterial | Parasitic | Fungal |
|                      | Nocardia | Strongyloides | Cryptococcus |
|                      | Listeria | Toxoplasma | Endemic fungi |

* Patients treated for rejection or graft-versus-host disease after 6 months are also at risk for these infections

Summary

- ICH with infection often presents with attenuated signs and symptoms of infection
- Approach to ICH with infection should include consideration of mechanism, dose and duration of immunosuppression and epidemiologic exposures
- Steroids increase infection risk in dose/duration dependent manner
- Preventable infections include PCP and strongyloides hyperinfection
- TNF-α inhibitors also increase infection risk and specific risk for TB in exposed patients
- Pre-treatment screening and treatment for latent TB is indicated
- Rituximab impairs generation of humoral immunity to new pathogens
  - Associated with poor vaccine response and HBV reactivation

Summary (Con’t)

- Asplenia increases risk for overwhelming bacterial infection
  - Vaccinate against encapsulated organisms
  - Educate about appropriate management of fever
- Stem cell and solid organ transplant recipients are susceptible to a wide range of infections
  - Infection risk at any point in time depends upon:
    - When the transplant occurred
    - Whether significant rejection or graft-versus-host disease have developed recently