Background

• All IBD drugs except 5-ASA affect immunity

• Immunomodulators and anti-TNF tx are widely used
  – Used earlier in the course of disease
  – Used more often
  – Increased risk of infections

• 80% of IBD pts will require steroids at some point
• 40% will require thiopurines
• 20% will require anti-TNF treatment

Background

• All IBD pts should be counseled regarding opportunistic infx risk

• Opportunistic infx are difficult to recognize and are associated with high morbidity and mortality bcs of difficulty to treat

• Active measures should be taken to prevent these infx

• Despite awareness of this risk many studies show low vaccination rates in IBD pts
Opportunistic Infections

• Defined as a serious, usually progressive infection by a microorganism that has limited pathogenic capacity under ordinary circumstances, but which has been able to cause serious disease as a result of the predisposing effect of another disease or its treatment
What makes an IBD pt immunocompromised?

- IBD causes a defective mucosal innate immunity, but there is NO data to support a defective systemic immunity
  → IBD pts are NOT immunocompromised

- **Immunomodulator therapy** and **severe malnutrition** are the main causes for immunocompromised state

- Unfortunately, to date, there is no method to evaluate the degree of immunosuppression
Opportunistic Infections

• Prevention of opportunistic infx
  – Close monitoring of pts during tx
  – Vaccination when available
  – Recognizing risk factors
    • Older age
    • Co-morbidities
    • Malnutrition
    • Combined immunomodulator use, steroid use
Opportunistic Infections

• Risk factors
  • Combined immunomodulator use, steroid use
  • Malnutrition

1. Treatment with steroids (prednisone ≥20 mg per day for ≥2 weeks, and within 3 months of stopping)

2. Ongoing treatment with effective doses of thiopurines or discontinuation within the previous 3 months

3. Treatment with MTHX or discontinuation within the previous 3 months

4. Treatment with anti-TNF agents or discontinuation within the previous 3 months

5. Significant protein-calorie malnutrition → defective immune response
Immunosuppression

- No strict correlation between an immunomodulator drug and certain infx
- Corticosteroids – fungal (Candida sp)
- Azathioprine – viral infections
- Anti-TNF – mycobacterial infections and fungal infx
- Anti-TNF – Granulomatous infx
- Combination therapy – a lot of overlap
Steroids

- Comparing pts receiving anti-TNF and those not
  - Concomitant steroid use was the only independent risk factor for infx in patients receiving anti-TNF tx
    - 2.69 fold (95% CI 1.18-6.12)

- Corticosteroids tripled the risk of C. diff infx compared with other immunosuppressants
  - RR 3.4 (95% CI 1.9-6.1)
Pre-Biologic Therapy Testing
Pre-Biologic Therapy Testing

1) Viral serology and vaccinations
   – which will be covered in the 2\textsuperscript{nd} section of the talk

2) Tb testing
Tuberculosis

• Best documented infectious complication of anti-TNF tx
  – Reactivation of latent Tb

• Feb 2003: 350/400,000 IFX pts developed active Tb

• Most cases occur within first 2 months of therapy

_Fidder et al. Gut 2009, 58:501-8_
Tuberculosis

• When Tb occurs in IBD pts on anti-TNF, it is commonly atypical
  – >50% extrapulmonary
  – 25% disseminated

• This presentation makes it difficult to diagnose Tb

• Outcomes are usually poor with high mortality rates (~13%)

Fidder et al. Gut 2009, 58:501-8
Pre-anti-TNF therapy

• MANDATORY testing for Tb prior to anti-TNF tx

• Latent Tb should be r/o in ALL pts pre-anti-TNF tx
  1. PPD skin test or IFN-gamma release assay (ELISPOT or QuantiFeron gold)
  2. CXR (calcification, pleural thickening, or linear opacities)

• If positive
  – Tx of latent Tb should be started ≥2 wks prior to anti-TNF tx
  – INH x 6-9 months
• For pts on steroids > 1 month/IMM > 3 months
  – FN results of PPD
  – Consider checking interferon-gamma assays instead of PPD
  – PPD booster (repeat PPD in 1-8 wks)
  – Stop steroids for > 1 month and IMM for > 3 months
Vaccination in IBD
Vaccination in IBD

• No association between vaccination and development or exacerbation of IBD

• In IBD pts on no immunosuppressives, frequency of adverse outcomes following immunization has not been reported

• In immunosuppressed pts, killed vaccines do not lead to infectious complications

• In contrast, live-attenuated vaccines are unsafe
Vaccination in IBD

- **CDC:** Recommends AGAINST live-attenuated vaccine use in pts who are immunosuppressed (even with steroids alone) for at least 3 months after tx

- Live-attenuated vaccines:
  1. measles-mumps-rubella
  2. typhoid Ty21a
  3. yellow fever
  4. live-attenuated influenza vaccine
  5. varicella
  6. herpes zoster
  7. oral polio
  8. BCG vaccine
Vaccination in IBD

• Vaccinate IBD pts early for safety and effectiveness
  – Early, prior to tx to allow for live-attenuated vaccine use
  – Early bcs IMM/biologics attenuate response to vaccination

• So, as soon as a pt is diagnosed with IBD, serologic testing should be done and pts vaccinated as needed
Vaccination in IBD

• In general, all pts should be vaccinated against
  – Tetanus
  – Diphteria
  – Polio *
  – MMR *
  – Varicella *
  – HPV
  – Influenza +/- *
  – Pneumococcus
  – HBV

*Live-attenuated
European Crohn’s & Colitis Organisation (ECCO) Guidelines

- ECCO consensus guidelines on opportunistic infx recommend:
  - Serology testing for specific viruses (*VZV and HBV*) and
  - Administration of a number of vaccinations (*VZV and HBV if negative, influenza, and pneumococcal vaccine*) shortly following the diagnosis of IBD
### Pre-IMM or Biologic Tx
(preferably at time of dx with IBD)

<table>
<thead>
<tr>
<th></th>
<th>Procedure</th>
<th>Action</th>
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<tbody>
<tr>
<td>1</td>
<td>VZV serology&lt;br&gt;History of chickenpox</td>
<td>If negative → Varicella vaccination&lt;br&gt;Wait min 3 wks → Start immunomodulator/anti-TNF</td>
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<tr>
<td>2</td>
<td>HBV serology</td>
<td>If negative → vaccination&lt;br&gt;Start nucleotide/nucleoside analogues&lt;br&gt;Wait min 2 wks → Start immunomodulator/anti-TNF (continue antiviral therapy for 6 mths)</td>
</tr>
<tr>
<td>3</td>
<td>Influenza virus</td>
<td>vaccination yearly</td>
</tr>
<tr>
<td>4</td>
<td>Pneumococcus</td>
<td>vaccination every 3-5 years</td>
</tr>
<tr>
<td>5</td>
<td>Human papilloma virus&lt;br&gt;(young females)</td>
<td>vaccination</td>
</tr>
</tbody>
</table>
Vaccines

- HCV
- HBV
- VZV
- Influenza
- Pneumococcal
- HPV
HBV and HCV

- Vaccinating for HBV and HCV has generated debate

- Prevalence of HBV and HCV infx in IBD pts is similar to that in the general population

- Frequency and severity of liver dysfunction is significantly higher in HBV-infected pts than HCV-infected pts
HCV

- Currently no consensus regarding HCV screening prior to immunosuppression
- Steroids – no detrimental effect on HCV course
- AZA – ok to use in HCV infected pts (may have anti-viral effect)
- MtHX – ok to use
- Anti-TNF – ok to use; may even improve virologic response
- Immunomodulators can be used in IBD/HCV pts
- Controversial if interferon worsens CD
- In HCV positive pts – f/u LFTs/viral load
HBV Vaccine

- All IBD pts should be tested for HBV infx
- HBV vaccination is recommended in all HBV seronegative IBD pts
- Efficacy of HBV vaccination is influenced by number of immunosuppressants
- In non-IBD pts, 3-dose HBV vaccination series is >95% effective in achieving protective Ab concentrations
- In IBD pts on IMM/anti-TNF agents, the response rate is low
  → Vaccination is recommended before starting IBD tx
HBV Vaccine

• Efficacy of HBV vaccination is influenced by the number of immunosuppressants
  – Studies have shown that the efficacy is as low as 33% in pts on IMM

• Double doses or accelerated schedules (0, 1, 2) of immunizing antigen may be necessary to achieve success

• Serological response should be checked 1-3 months after vaccination series
  – If fail, would revaccinate with 3-dose series (and double dose if not done)
HBsAg+ IBD pts

- Treatment with at least 2 immunosuppressants was an independent risk factor for HBV reactivation
  - OR 8.75 (95% CI 1.16-65.66)

- HepBsAg+ carriers should receive prophylactic anti-viral tx regardless of degree of viremia to avoid Hep B flare
  - best to be started 2 wks prior to immunosuppression and for 6 mths after
Vaccines

- HCV
- HBV
- VZV
- Influenza
- Pneumococcal
- HPV
Varicella Vaccine

- Most adults have acquired immunity to varicella

- Varicella infx is aggressive in adults
  - Mortality 20/100,000 pts
  - Disseminated disease in 30% of immunocompromised pts

- IBD pts should undergo serology testing prior to initiation of immunosuppression. If negative, vaccination should occur
  - at least 3 weeks prior to initiation of immunosuppression
  - preferably at dx with IBD
Varicella Vaccine

• Immuno-competent pts
  – Should receive active immunization with a 2-dose series of live varicella vaccine at least 3 wks prior to immunosuppression

• Immuno-compromised pts
  – Live-virus varicella vaccine has been contraindicated until immunosuppression has been d/ced for at least 3 mths
Varicella

- Immunosuppression should not be started in event of acute infection with VZV
- If infection occurs while on immunosuppression, antiviral tx should be started and immunosuppression d/ced
- Restart immunosuppression once vesicles crust and afebrile
Vaccines

- HCV
- HBV
- VZV
- Influenza
- Pneumococcal
- HPV
Influenza Vaccine

• Influenza is usually an acute, self-limiting, respiratory illness that occurs in annual outbreaks

• Immunosuppression increases the rates of infx
• Morbidity/mortality rates are increased with immunosuppression

• Annual vaccination against influenza is effective & recommended starting from time of dx with IBD
  – Trivalent inactivated flu vaccine not the live-attenuated
Influenza Vaccine

• IBD pts are less likely to mount a serologic response to the flu vaccine

• This may be related to IBD itself
  – As is the case with Hep B vaccination

• The response rate seems to be further diminished with the use of immunosuppressive meds

• Two-dose vaccination is sometimes needed, but in most cases it is not needed
Vaccines

- HCV
- HBV
- VZV
- Influenza
- Pneumococcal
- HPV
Pneumococcal Vaccine

- Strep pneumo (GPC) can cause serious and lethal infx: PNA, sepsis, and meningitis

- Bacterial pneumonia is one of the most prevalent infx in IBD pts on immunosuppression

- These pts are at high risk for invasive pneumococcal infx
Pneumococcal Vaccine

• Immunomodulators reduce the Ab response to the vaccine, so it is recommended that pts are vaccinated at time of dx or at least 2 weeks prior to immunosuppression

• Repeat vaccination is recommended in 3-5 years
Vaccines

- HCV
- HBV
- VZV
- Influenza
- Pneumococcal
- HPV
HPV Vaccine

• Although immunomodulators do not aggravate the course of disease, HPV associated tumors may be more common.

• Administration of HPV vaccine is recommended in IBD pts.

• HPV vaccine is limited to pts between ages 9-26 yrs.

• Routine GYN examinations is recommended for screening of cervical cancer particularly if treated with immunosupp.
Other Considerations
HIV Testing

• Testing for HIV should be considered in IBD pts prior to immunosuppression
  – Bcs of increased risk and severity of HIV-related infx in IBD pts on immunosuppression

• Treatment of IBD in HIV pts should be d/w ID specialist
  – Immunosuppressants are not necessarily contraindicated

• Treatment of HIV in IBD pts is ok
Summary...

• IBD pts are not immunocompromised unless
  – Severely malnourished
  – On immunosuppressants

• Vaccinate early – safe and effective

• Pre-IMM, HBV & VZV serology and vaccinate, anti-viral if chronic HBV infx
• Pre-anti-TNF, R/O latent Tb and as above (virus serology and vaccination)

• If already on IMM/anti-TNF tx
  – Just use killed vaccines (NOT live-attenuated)
Thank you