Prevention and treatment of opportunistic infections in IBD patients

Kim Isaacs, Gil Y. Melmed, Corey Siegel
Advances in IBD
Orlando, FL Dec 2015
HZV in 32 ym with Crohn’s on adalimumab
Live vaccines are generally contraindicated if immune-suppressed

- Live attenuated influenza virus
- Yellow fever
- BCG vaccine
- Measles/mumps/rubella
- Varicella
- *Zoster (shingles)*
  - Per CDC, zoster vaccine can be given if on prednisone <20mg, or 6MP <1.5mg/kg or AZA <3 mg/kg (NOT biologics)

www.cdc.gov/mmwr
http://www.phac-aspc.gc.ca/
Zoster vaccination while immunosuppressed?

Risk of vaccination
- Can cause infection??

Risk of no vaccination
- Risk of zoster??

How dogmatic should we be??
Risk of Herpes Zoster ("shingles") is increased in IBD

- Case control study, GPRD 1988-1997
  - 7823 (Crohn’s), 11,930 (UC), and 79,563 (HC)
- Incidence of HZV is about 1.5x higher in IBD
- Risk increases with immunosuppression
  - Corticosteroids OR 1.5 (1.1 – 2.2)
  - AZA/6MP OR 3.1 (1.7 – 5.6)

Gupta, Lautenbach, and Lewis. *Gastroenterology* 20
Zoster in IBD increases with Age

Long et al. Alim Pharm Ther 2013
Shingles vaccine

• Concentrated varicella (live virus)
• Generally recommended for >60 yrs old
• Vaccine is generally contraindicated if immunosuppressed
  - CDC: “Low dose immunosuppression is ok”
    • Prednisone <20mg/day
    • 6MP <1.5mg/kg/day or AZA <3 mg/kg/d or MTX <25/wk
    • Biologics???

Harpaz et al. MMWR 2008
**Zoster vaccine in TNF-exposed**

- 463,541 Medicare beneficiaries with various CID
  - >60y, 2006-2009
  - 4% received zoster vaccine
  - 633 were on biologics at time of vaccination
  - Assessed for Shingles within 6 weeks of vaccine

- No cases of HZV infection in biologic-treated pts

- Vaccine was protective HR 0.61 (95% CI, 0.52-0.71)

Zhang et al. JAMA 2012
Should IBD patients receive HZV vaccination at younger age?

Long et al. Alim Pharm Ther 2013
Latest IDSA Guidelines

• How long do you have to wait to start immune suppression after a live virus vaccine?
  - At least 4 weeks

• DO NOT give live influenza*, MMR or yellow fever if immune suppressed

• Household contacts
  - CAN receive: MMR, rotavirus for infants, Varicella/Zoster (but watch for lesions), yellow fever, oral typhoid
  - CANNOT receive: live influenza, live polio

Rubin, LG, et al. Clinical Infectious Diseases, December 2013
TB or not TB and anti-TNF therapy

Kim Isaacs MD PhD
University of North Carolina @ Chapel Hill
December 11, 2015
Case Presentation

- 49 year old male with small bowel and perineal Crohn’s disease x 7 years
- S/P IC resection
- Intermittent 6-MP for 4 years after surgery
- 2 years ago restarted 6-MP
- 1 year ago colonoscopy with active ileitis – started 9 week course of budesonide

- 6 months ago thought he was taking 6-MP but really only taking metronidazole 500 mg q day
Case Presentation

- Presented with severe peri-rectal pain.
- On exam, area with ? Fluctuance in the peri-rectal area – no fistula seen
- CT of abdomen and pelvis performed: 2.4 x 2.4 cm fluid collection in the left perineal region, linear soft tissue lesion along the right perineum extending from the right obturator internus to the perianal skin surface concerning for a fistulous tract
Case Presentation

- Area was incised and drained in clinic
- 2 weeks later with new swelling in same area - retreated
- Probable fistula – needs something more definitive to manage it.
- Had an MI

- Surgical therapy recommended – EUA of this area – but now with recent MI – holding off
- Discussed infliximab – but in discussion found out that the patient had a positive PPD
- Grew up in India – wife thinks that everyone got BCG as a child – but he is not sure whether he had BCG or not
Case
Raises the Following Questions?

• What are the guidelines for screening for TB prior to anti-TNF therapy and during anti-TNF therapy?
• What is the best test for screening?
• What should be done in the patient who has had BCG?
• What to do with an equivocal QuantiFERON Gold?
• What should be done with positive screening test for TB?
• Should this patient get anti-TNF therapy?
## Risk factor for reactivation of TB

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relative Risk for Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDs</td>
<td>110 - 170</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>50 - 110</td>
</tr>
<tr>
<td>Solid Organ Transplant</td>
<td>20 - 74</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>10 - 25</td>
</tr>
<tr>
<td>TNF alpha therapy</td>
<td>1.7 - 9</td>
</tr>
<tr>
<td>Glucocorticoid Therapy</td>
<td>4.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 – 3.6</td>
</tr>
<tr>
<td>Under weight (BMI &lt; 20)</td>
<td>2-3</td>
</tr>
<tr>
<td>Smoker (1 ppd)</td>
<td>2-3</td>
</tr>
<tr>
<td>Healthy Individual</td>
<td>1</td>
</tr>
</tbody>
</table>
Why is there an increased incidence of TB with anti-TNF therapy?

- TNF acts in multiple steps in protective granuloma formation in response to *M tuberculosis* infection.
  - *Induces recruitment of mixed cellular and alveolar infiltrate*
  - *Induces mononuclear cells to accumulate to form highly structured granuloma*
- TNF needed to continuously promote the recruitment of mononuclear cells into granulomas to contain M Tb

Keane et al (2001) NEJM 345:1098-1104

What are the guidelines for screening for TB prior to anti-TNF therapy?

<table>
<thead>
<tr>
<th>History/Physical</th>
<th>Testing</th>
</tr>
</thead>
</table>
| • Careful review of past medical history  
  ▫ Potential contact with TB patients  
  ▫ Birth in or prolonged stay in TB endemic area | • Chest X ray  
• Tuberculin skin test and/or an interferon-\(\gamma\) release assay (IGRA)  
  ▫ QuantiFERON – TB gold (QFT-G) (Cellestis Limited)  
  ▫ QuantiFERON – TB gold  
  ▫ In Tube (QFT-GIT)  
  • This adds one additional TB antigen TB 7.7)  
  ▫ ELISpot (T-SPOT® TB, Oxford Immunotech) |

TB Skin Test

Method

5 TU of PPD

Read in 48 – 72 hours

T cells sensitized by prior TB infection recruited to the skin site where they release lymphokines. → induration
What is a positive test?

<table>
<thead>
<tr>
<th>5 mm</th>
<th>10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV</td>
<td>• Recent immigrants from high incidence countries</td>
</tr>
<tr>
<td>• Other immunosuppression – equivalent to receiving $\geq 15$ mg of prednisone for a month</td>
<td>• IV drug users</td>
</tr>
<tr>
<td>• Close contacts of an active TB patient</td>
<td>• Residents and employees of high risk facilities – Nursing homes, prisons</td>
</tr>
<tr>
<td>• Patients with CXR C/w prior TB</td>
<td>• Mycobacterial lab personnel</td>
</tr>
<tr>
<td></td>
<td>• Patients with underlying medical conditions and low body weight ($&lt; 10%$)</td>
</tr>
</tbody>
</table>

## TB Skin test

<table>
<thead>
<tr>
<th>False Negatives</th>
<th>False Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disease related</td>
<td>• Infection with non-tuberculous mycobacteria</td>
</tr>
<tr>
<td>▫ Poor nutrition</td>
<td>• BCG vaccination</td>
</tr>
<tr>
<td>▫ Infections</td>
<td></td>
</tr>
<tr>
<td>▫ Immunosuppressive drugs</td>
<td></td>
</tr>
<tr>
<td>▫ Malignancy</td>
<td></td>
</tr>
<tr>
<td>▫ Age</td>
<td></td>
</tr>
<tr>
<td>▫ Stress</td>
<td></td>
</tr>
<tr>
<td>• Technical factors</td>
<td></td>
</tr>
<tr>
<td>▫ Application techniques</td>
<td></td>
</tr>
<tr>
<td>▫ Reading</td>
<td></td>
</tr>
<tr>
<td>▫ Improper storage of PPD</td>
<td></td>
</tr>
</tbody>
</table>
QuantiFERON ® TB Gold

The Test

• If prior infection with MTB – patients have lymphocytes in blood that recognize mycobacterial antigens
• When stimulated the cells produce interferon $\gamma$
• Detection of interferon $\gamma$ is the basis of this test.
• 2 synthetic peptides ESAT-6 and CFP-10 simulate mycobacterial proteins
• QuantiFeron TB Gold in-tube test has one additional antigen TB 7.7

QuantiFERON® TB Gold

Indeterminate and False Negative

- Elderly patients
- History of ICU Stay
- Lymphocytopenia
  - Low CD4 count
- High CRP
- Decreased protein levels
- Steroid therapy

Age and Indeterminate Results

Belard et al (2011) Inflamm Bowel Dis 11:2340-9
QuantiFERON® TB Gold vs. TST in IBD patients IM vs. no IM

Study

- Observational, prospective single center study
- LTB screening prior to anti-TNF therapy
- TST vs. QFT-G-IT
- Patients on thiopurine or MTX vs. 5 ASA or no therapy
- No steroids
- % of patients with positive tests

Results

1. Concordance between tests moderate $\kappa = 0.584$
2. No difference between the two groups regarding TST and QFT-G-IT positivity.

BCG

What is it?

• Bacille Calmette-Guerin
• Vaccine made from an attenuated strain of Mycobacterium bovis
• Protection against TB meningitis in children as well as some protection against leprosy
• Ability to protect against pulmonary TB is questionable.

Where it is BCG given?

BCG and TB skin test

- Skin test positivity to BCG wanes over time
- Greater than 5 years from vaccination positive TB skin test *more likely due to latent TB* than BCG
- Reactive skin tests more than 15 years since vaccination or with more than 15 mm of induration were unlikely to be due to prior BCG vaccination
IGRAs may be used in place of (but not in addition to) a TST in all situations in which the CDC recommends TST as an aid to diagnosis of MTB infections.

IGRAs are the preferred method for TB infection testing in:

- Patients who have received BCG
- Patients who are unlikely to return to have skin test read.

http://www.cdc.gov/tb/topic/testing/default.htm
## Guidelines for treatment of latent TB in patients on anti-TNF therapy

<table>
<thead>
<tr>
<th>Country/Year</th>
<th>CXR</th>
<th>TST</th>
<th>Positive TST cutoff</th>
<th>IGRAs</th>
<th>Active TB Prophylaxis</th>
<th>Anti-TNF starting delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain 2003</td>
<td>Yes</td>
<td>All</td>
<td>5 mm or 2 step TST</td>
<td>No</td>
<td>INH 9 months</td>
<td>1 month</td>
</tr>
<tr>
<td>Italy 2011</td>
<td>Yes</td>
<td>All</td>
<td>&gt; 5 mm</td>
<td>Yes</td>
<td>INH 9 months</td>
<td>1 month</td>
</tr>
<tr>
<td>TBNET Consensus 2010</td>
<td>Yes</td>
<td>No/BCG</td>
<td>&gt; 10 mm</td>
<td>Yes</td>
<td>INH 9-12 months or Rif/INH 3 months</td>
<td>1 month</td>
</tr>
<tr>
<td>USA 2012</td>
<td>No</td>
<td>All No/BCG</td>
<td>5 mm</td>
<td>Yes</td>
<td>INH 9 months</td>
<td>1 month</td>
</tr>
</tbody>
</table>

Have IBD, Will Travel

Corey A. Siegel, MD, MS
Director, Dartmouth-Hitchcock IBD Center
Geisel School of Medicine at Dartmouth
Travel vignette part 1

• Background
  ▫ 21-yo male with mild-to-moderate pan-UC for 4 years. Experiences minor relapses once per year, due to transient periods of non-adherence, which respond to resumption of oral 5-ASA. However, an exacerbation 8 months ago required prednisone. Currently well on mesalamine 4.8 g/day.
  
  ▫ Getting married and planning honeymoon, wants to know if safe for him to travel.
Traveling with IBD

Distribution of medications used during trips by IBD patients (n=222)

- Thiopurines/MTX: 29%
- Steroids: 4%
- Double Immunosuppression: 6%
- Biologics: 5%
- No Immunosuppression: 56%

Traveling with IBD

Rates of illness during trips by IBD patients and controls (n=446)

- 92% of illness while traveling was related to GI symptoms (in both IBD and non-IBD groups)

Safety of Traveling with Immunosuppressive Medications

Rates of illness during trips by IBD patients according to immunosuppression status and controls (n=446)

P-values vs. controls
Traveling with IBD

• IBD patients have an increased rate of illness when they travel to industrialized, but not developing countries

• **Increased risk**
  - History of more disease flares over their disease course
  - History of ever being hospitalized for IBD

• **Decreased risk**
  - *Being in remission for >3 months prior to embarking on trip*

• Being immunosuppressed did not seem to confer a greater risk of illness while traveling to tropical or developing countries

Travel vignette part 2

• Background
  ▫ 21-yo male with mild-to-moderate pan-UC for 4 years. Experiences minor relapses once per year, due to transient periods of non-adherence, which respond to resumption of oral 5-ASA. However, an exacerbation 8 months ago required prednisone. Currently well on mesalamine 4.8 g/day PLUS 6MP 1.5 mg/kg
  ▫ Now, planning their honeymoon to Sub-Saharan Africa
## Vaccination Recommendations for Travel for Patients With IBD

<table>
<thead>
<tr>
<th>Illness</th>
<th>Regions with high and intermediate endemicity</th>
<th>Vaccine/schedule</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>hepatitis A</td>
<td>High: Africa; S. America; Middle East; SE Asia; China Intermediate: Southern &amp; Eastern Europe</td>
<td>Inactivated virus (every 10 y)</td>
<td>Authorized</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Africa: Sub-Saharan Africa</td>
<td>Live attenuated (every 10 yr) 17D strain (17D-204 /17DD)</td>
<td>Contraindicated during immunosuppression</td>
</tr>
<tr>
<td></td>
<td>America: Central and S. America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal disease</td>
<td>Europe: serogroups B, C</td>
<td>Conjugate polysaccharide C</td>
<td>Authorized</td>
</tr>
<tr>
<td></td>
<td>Americas: serogroups B, C, Y</td>
<td>Polysaccharide combined A+C</td>
<td>Authorized</td>
</tr>
<tr>
<td></td>
<td>Africa and Asia: serogroups A, C, W135</td>
<td>Polysaccharide combined A+C+W+Y (single dose among persons aged 11-55)</td>
<td>Authorized</td>
</tr>
<tr>
<td>Typhoid</td>
<td>High: Southern Africa; Western, Eastern South central, and SE Asia Intermediate: Eastern, Middle, and Northern Africa; Western Asia; Latin America/Caribbean; Oceania</td>
<td>Vi Capsular polysaccharide (single dose IM. Booster dose every 2-3 yr for those at risk)</td>
<td>Authorized</td>
</tr>
</tbody>
</table>

Esteve et al. *World J Gastroenterol* 2011;17:2708-14
<table>
<thead>
<tr>
<th>Illness</th>
<th>Regions with high and intermediate endemicity</th>
<th>Vaccine/schedule</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera</td>
<td><strong>Africa</strong>: Congo, Kenya, Mozambique, Uganda, Tanzania, and West Africa</td>
<td>Oral Killed (2 doses at 1-6 wk interval with a buffer to protect the B-subunit against stomach acidity)</td>
<td>Authorized</td>
</tr>
<tr>
<td></td>
<td><strong>South and Central America</strong>: Peru, Ecuador, Guatemala, Nicaragua <strong>Asia</strong>: Afghanistan, India, Cambodia, Malaysia, Nepal, Sri Lanka</td>
<td>Oral live</td>
<td>Contraindicated during immunosuppression</td>
</tr>
<tr>
<td>Rabies</td>
<td><strong>High</strong>: Africa, Asia, parts of Central and S. America <strong>Intermediate</strong>: Eastern Europe, parts of Central and S. America (Chile, Argentina)</td>
<td>Cell culture-derived vaccine (travelers, not handling animals: 2 doses, at days 0-28. If risk continues booster dose at 6-12 mo)</td>
<td>Authorized</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Southeast Asia Far East</td>
<td>Cell culture-derived vaccine (2 doses, at days 0-28 booster dose?)</td>
<td>Authorized</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td><strong>Europe</strong>: Central &amp; Eastern Europe, Russia <strong>Asia</strong>: China, Siberia, Russian Far-east</td>
<td>Inactivated virus (3 doses at 0,1, and 12 mo)</td>
<td>Use with caution</td>
</tr>
</tbody>
</table>

Esteve et al. *World J Gastroenterol* 2011;17:2708-14
Travel vignette part 3

• Background
  ▫ 21-yo male with mild-to-moderate pan-UC for 4 years. Experiences minor relapses once per year, due to transient periods of non-adherence, which respond to resumption of oral 5-ASA. However, an exacerbation 8 months ago required prednisone. Currently well on mesalamine 4.8 g/day. Negotiated to stop 6MP, receive Yellow Fever vaccine and travel to Sub-Saharan Africa
  
  ▫ GREAT trip, BUT
  ▫ Now returns with fevers...
# Tips for Returning Travelers

<table>
<thead>
<tr>
<th>Condition</th>
<th>S. America</th>
<th>Maghreb &amp; W. Orient</th>
<th>Sub-Saharan Africa</th>
<th>SE Asia &amp; India</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick drop</td>
<td>Consider</td>
<td>No</td>
<td><strong>Always</strong></td>
<td>Consider</td>
<td>No</td>
</tr>
<tr>
<td>Stool parasite</td>
<td><strong>Always</strong></td>
<td>Consider</td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td>No</td>
</tr>
<tr>
<td>Urine parasite</td>
<td>No</td>
<td>No</td>
<td><strong>Always</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Strongyloides (culture, serology)</td>
<td><strong>Always</strong></td>
<td>Consider</td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td>No*</td>
</tr>
<tr>
<td>Trypanosoma (serology)</td>
<td><strong>Always</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Histoplasma (serology)</td>
<td><strong>Always</strong></td>
<td>No</td>
<td><strong>Always</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HBV and HCV (serology)</td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
</tr>
<tr>
<td>Tuberculin skin test or IGRA</td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
<td><strong>Always</strong></td>
</tr>
</tbody>
</table>

*Consider in case of Chinese individuals with eosinophilia; HBV=hepatitis B virus; HCV=hepatitis C virus; IGRA=interferon gamma release assay

Esteve et al. *World J Gastroenterol* 2011;17:2708-14
Travel Vignette part 4

• Background

  ▫ 21-yo male with mild-to-moderate pan-UC for 4 years. Experiences minor relapses once per year, due to transient periods of non-adherence, which respond to resumption of oral 5-ASA. However, an exacerbation 8 months ago required prednisone. Currently well on mesalamine 4.8 g/day

  ▫ 1 year anniversary – planning another trip. Wants to go skiing in the alps. He asked if any safety issues here?
High altitude journeys and flights are associated with an increased risk of flares in IBD patients
Vavricka SR, et al. JCC 2013

- Flares counted if within 4 weeks of travel
Should we recommend DVT prophylaxis for IBD patients on long flights?

- We know that IBD patients are at an increased risk for DVTs.
- In the **general population**, the risk for DVT is 3-12% in a long-haul flight.
- Risk factors include sitting in crowded condition (“economy class syndrome”), hypoxia in the airplane cabin, and dehydration.
- Individual risk factors for air travel-related VTE include:
  - age over 40 years, gender (female), use of oral contraceptives, varicose veins in lower limbs, obesity and genetic thrombophilia.

Should we recommend DVT prophylaxis for IBD patients on long flights?

- Preventive measures include avoiding dehydration and prolonged sitting (get up and go get a drink!).
- For individuals at increased risk, venous blood stasis can be reduced by wearing elastic stockings and prophylactic use of low-molecular-weight heparin.

Knowing what we know about DVTs and IBD, should we be thinking about this with our patients?