Health Maintenance in IBD:  
*Role of Prevention*

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**Case**

- 23-year-old female with history of small bowel Crohn’s disease (CD)  
  - Right sided abdominal pain  
  - Diarrhea (8-10 BMs/day)
- CD history  
  - Diagnosed 1 year prior  
  - On Azathioprine (2.5 mg/kg)  
  - Unable to taper off of prednisone
Case

Colonoscopy and CT enterogram demonstrate long segment (20 cm) active inflammation in the terminal ileum without stenosis

Case

- Infliximab initiated
  - After 4 weeks diarrhea and pain resolved
  - Able to taper off of corticosteroids
  - Current medications include azathioprine/infliximab
- She is worried about the complications that can arise from CD and its therapies
  - She asks: How can I prevent complications?
Forms of prevention

- Primary prevention
  - Preventing disease from developing, such as immunizations
- Secondary prevention
  - To detect disease early, to prevent disability, such as through screening programs
- Tertiary prevention
  - Measures that reduce the impact of long-term disease and disability, and maximize potential years.

Outline: Health Maintenance and Prevention

- Osteoporosis
- Cervical cancer / dysplasia
- Colon cancer
- Infections
  - Tuberculosis
  - Herpes Zoster
  - Pneumonia
- Skin cancer
  - Non-melanoma
  - Melanoma
Osteoporosis

- Associated with bone fragility and fractures
- Fractures of the hip and spine are associated with significant morbidity including hospitalizations, major surgery and even death
- Risk Factors in general population
  - Female, thin frame, postmenopausal
  - Family history
  - Smoking and alcohol use
  - Corticosteroid use

National Osteoporosis Foundation
Osteoporosis

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Osteoporosis in IBD

- Prevalence of osteoporosis in IBD is approximately 15%
  - Strongly affected by age
- Males and females are at similar risk
- Corticosteroid use is the strongest risk factor
- The overall relative risk of fractures is 40% greater than that of the general population
  - Increases with age

Gastro 2003;124:795-841
### Guidelines: Management of Osteoporosis

- All patients should receive education on the importance of lifestyle changes
  - Weight bearing exercise
  - Quitting smoking
- Preventive measures should be used for anyone on >5 mg prednisone/day for 3 months
  - DEXA scan
  - Calcium (1500 mg) /Vitamin D (1000 IU)
  - Consideration of bisphosphonates
    - Possible implications in women of childbearing age

American College of Rheumatology 2001.

### Vitamin D

- Vitamin D deficiency is common in IBD
  - Higher Vitamin D and reduced risk of incident CD
  - Low Vitamin D associated with complications of IBD (c. diff infection, cancer)
  - Emerging data on Vitamin D for the treatment of IBD
- Small study of 1200 IU Vitamin D3 or placebo in CD over 12 months, outcome of clinical relapse
  - Relapse rate for vitamin D3 (6/46 or 13%), placebo (14/48 or 29%)

Ananthakrishnan AN, et al. Gastroenterology 2012 Mar;142
## Summary: Osteoporosis prevention

- **Know the risk factors**
  - Corticosteroids
- **Primary prevention**
  - Calcium/vitamin D supplementation
  - Weight bearing exercise
- **Secondary prevention**
  - Screening DEXA if risk factors

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## Cervical Cancer
Cervical Cancer

- In 2013, 12,340 women diagnosed with cervical cancer, with 4,030 deaths in U.S. alone
- Largely preventable disease via screening: Pap smear
- It is estimated that 50% of women who receive diagnoses of cervical cancer have never been screened

ACOG practice bulletin: clinical management guidelines—no. 44, July 2003

Cervical Dysplasia in IBD

- Higher incidence of abnormal Pap smears in women with IBD compared to healthy controls
  - 42.5% vs 7%, (OR 3.4, 95% CI 1.7–12, p< 0.001)
  - Within IBD, immunosuppression associated with increased risk (OR 1.5, 1.2–7.1, p= 0.02)
- A population-based study from Canada showed no overall association between IBD and abnormal Pap smears
  - Increased risk with combination corticosteroids and immunosuppressants OR 1.41 (95% CI, 1.09-1.81)

### Cervical Testing in IBD

#### Pap Smear over 36 months (%)

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>No IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap Smear (%)</td>
<td>70.4</td>
<td>65.2</td>
</tr>
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</table>


### USPSTF guidelines: Pap Smears

- Women should have their first screening Pap smear at age 21, with repeat every 3 years up until age 65
  - Screen with cytology every 3 or co-testing (cytology and HPV testing every 5 years)
- USPSTF reports that these guidelines DO NOT APPLY to women with cervical dysplasia, in utero exposure to DES or immunocompromised women

U.S. Preventive Services Task Force.
ACOG: Immunosuppression

- Women with HIV, organ transplant, long-term immunosuppression should have Pap smear at onset of sexual activity, with screening twice in the first year, and then annually
  - Data from SLE and organ transplant populations

ACOG Committee Opinion No. 463 Obstet Gynecol 2010;116(2 Pt 1):469.

HPV vaccine

- Approved in women age 9-26 (and now men 9-26 for genital warts)
- Active against HPV types 6,11,16,18
- Has been evaluated in IBD population, no change in efficacy as compared to general population and no association with flare of disease or serious adverse events

<table>
<thead>
<tr>
<th>Summary: Cervical Cancer</th>
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<tbody>
<tr>
<td><strong>Primary prevention:</strong></td>
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<td>– HPV vaccine for women aged 9-26</td>
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<td><strong>Secondary prevention:</strong></td>
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<td>– Screening Pap smears as recommended by USPSTF/ACOG</td>
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Colon Cancer
Colon Cancer in IBD

- Crohn’s disease
  - SIR, 1.9; (95% CI 1.4–2.5) for CRC
- Ulcerative colitis
  - CRC incidence rate increases with disease duration
  - 2/1000 py in first decade
  - 7/1000 py in second decade
  - 12/1000 py in third decade


Relative risk by decade: Crohn’s disease

Relative risk by decade: UC


Mechanism of risk: Inflammation?

- In a large US case-control study, histologic inflammatory activity independently increased CRN risk (OR 2.6 per unit increase)
  - Immunomodulators reduced the risk (OR 0.4)

- Separate case-control (Finland) with similar findings, severe inflammation increased risk (OR 31.8, 95% CI 15.6-64.9 for dysplasia or carcinoma)
  - Disease duration increased the annual risk for dysplasia or CRC by 4.5%
  - Thiopurines (OR 0.09, 95% CI: 0.02-0.33) and 5-aminosalicylic acid (OR 0.17, 95% CI: 0.017-1.01) protected against CRC

### Colorectal Cancer Prevention

- **Primary prevention**
  - Chemoprevention
    - 5ASA
    - Thiopurines
    - Folate
- **Secondary prevention**
  - Surveillance colonoscopy to evaluate for dysplasia
  - Colectomy for dysplasia
  - Polypectomy for sporadic (non-UC) adenomas

### Infections
Tuberculosis

- Globally
  - 9 million with active *M. tuberculosis* (TB) each year
  - 2 billion are thought to be latently infected (LTBI) with TB
- People with LTBI have increased risk for TB
  - Approximately 11 million U.S. residents (4.2% of the U.S. population aged >1 year) have LTBI
  - Rates of LTBI and active TB vary based on the presence of risk factors
  - U.S. residents with no risk factors are at low risk (≤1%).


Risk Factors for TB

- Close contacts of persons with active TB
- Foreign-born persons or visitors of endemic areas
- Residents of congregate settings
  - Correctional facilities, long-term care facilities, and homeless shelters
- Health-care workers
- Populations with increased incidence
  - Low income, ETOH/drug abuse, children exposed to adults with increased risk, etc.

Reactivation with anti-TNF therapy

- The risk of serious infection is doubled with anti-TNF therapy, with a risk of 95/100,000 person-years for active TB.
  - Much higher than risk of other opportunistic infections
- Effective screening tools are available
  - Skin test (PPD) or blood (IGRA)
- Treatment of latent TB prior to initiation of anti-TNF therapy decreases the incidence of active TB by >80%


Herpes Zoster

- Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus (VZV)
- 1 million cases annually
- In the U.S., lifetime risk approaching 1 in 3
- About 10%-18% of persons with HZ develop post-herpetic neuralgia (PHN)

Herpes Zoster in IBD

- Incidence of zoster is higher in IBD
  - 20 - 50% increase in UC
  - 60 - 90% increase in CD
- Incidence increases with age
- Medications associated with zoster
  - Corticosteroids (adjusted OR 1.5 – 1.7)
  - Azathioprine/6-mp (adjusted OR 1.9 - 3.1)
  - Biologic anti-TNF (adjusted OR 1.8)
  - Combo therapy (adjusted OR 3.3)


Pneumonia

- Community acquired pneumonia (CAP) is the most common infectious cause of death in U.S.
- Hospitalization rates for CAP have increased
- Overall mortality among those hospitalized for pneumonia in 2005 was 4.7%

Pneumonia in IBD

Risk Factors for Pneumonia

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<th>Adjusted OR (95% CI)</th>
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<td>Thiopurine</td>
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***Conditional logistic regression models adjusted for health care utilization, comorbidities, 5-ASA, biologic, thiopurine, corticosteroid, PPI medication use as appropriate

Source: IMS Health, LifeLink™ Health Plan Claims Database, From 1997 to 2009

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Immunization Guidelines in IBD*

- Standard recommended immunization scheduled for adults should be adhered to
- At diagnosis, all adults should have review of immunization history, with catch up vaccination given as needed
- Live vaccines should be avoided in patients on immunosuppression

*Prior to several newly licensed vaccines
Immunization Guidelines in IBD

- Patients with chronic immunologic illnesses seem to respond well to vaccines
- Patients do not experience worsened disease activity as a result of immunization
- Killed or inactivated vaccines do **NOT** present a risk of infection to patients on immunomodulators or biologics


Live Vaccines: Contraindicated (?) in Immunosuppression

- Anthrax vaccine
- Intranasal influenza
- Measles-Mumps-Rubella (MMR)
- Polio live oral vaccine (OPV)
- Smallpox vaccine
- Tuberculosis BCG vaccine
- Typhoid live oral vaccine
- Varicella
- Zoster
- Yellow fever

Melmed GY. Inflamm Bowel Dis 2009;15(9):2009
What defines immunosuppression?

- ACIP (Advisory Committee on Immunization Practices)
- Warning against live vaccines on anti-TNF
  - JAMA paper with no increased safety issues after vaccination on anti-TNF and reduced risk of zoster
- For low levels of immunosuppression, live vaccines (such as zoster) can be given
  - < 0.4 mg/kg methotrexate weekly
  - <3 mg/kg Aza or <1.5 mg/kg 6mp
  - Prednisone <20 mg for < 2 weeks

Summary: Prevention by Immunization

<table>
<thead>
<tr>
<th>Recommend</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunization review to determine “catch-up” vaccinations needed</td>
<td>HPV vaccine</td>
</tr>
<tr>
<td>Seasonal influenza vaccine</td>
<td>For women and men up to age 26</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Varicella vaccine</td>
</tr>
<tr>
<td>Standard age appropriate adult immunizations</td>
<td>Prior to or on low dose immunosuppression*</td>
</tr>
</tbody>
</table>
  - Hepatitis A and B | Zoster vaccine |
  | >60 years old | Prior to or on low dose immunosuppression* |

*<3.0 mg/kg Aza, <0.4 mg/kg week mtx, <20 mg prednisone for < 2 weeks
Skin Cancer (non-melanoma)

- 1 in 5 Americans develops skin cancer, which accounts for 1/3 of all cancers in the US
  - Categorized into squamous and basal cell carcinoma

- Environmental risk factors for NMSC
  - Ultraviolet light
  - Chemical exposures

- Host risk factors
  - Human papilloma virus
  - Genetic susceptibilities
  - Immunosuppression

Incidence of Skin Cancer in IBD


NMSC: Risks of Immunosuppression

<table>
<thead>
<tr>
<th>Medication Class*</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
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<tbody>
<tr>
<td>Thiopurines</td>
<td>OR 4.25 (2.81-6.42)</td>
<td>OR 4.34 (2.53-7.43)</td>
</tr>
<tr>
<td>Biologic Anti-TNF</td>
<td>OR 2.18 (1.07-4.46)</td>
<td>N/A</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>OR 2.69 (0.63-11.56)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Persistent medication use, > 1 year

### NMSC: Risks of Immunosuppression

**Crohn’s disease**

<table>
<thead>
<tr>
<th>Medication Class*</th>
<th>Cases (n=228)</th>
<th>Controls (n=913)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>154 (68%)</td>
<td>817 (89%)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>56 (25%)</td>
<td>73 (8%)</td>
<td>4.45 (2.94-6.75)</td>
</tr>
<tr>
<td>Biologic Anti-TNF</td>
<td>7 (3%)</td>
<td>13 (1%)</td>
<td>3.23 (1.24-8.45)</td>
</tr>
<tr>
<td>Combined thiopurine and biologic</td>
<td>11 (5%)</td>
<td>10 (1%)</td>
<td>6.75 (2.74-16.65)</td>
</tr>
</tbody>
</table>

*Persistent medication use, > 1 year

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**Melanoma in general population**

- 20.8/100,000 p-y incidence
- Rate tripled in Caucasians over the past 20 yrs
- Risk factors
  - Environmental
  - Intermittent high intensity exposure
  - Genetic
  - Immunosuppression
    - Transplant patients with 3.4 fold increased risk

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Incidence of Melanoma

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>UC</th>
<th>IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRR</td>
<td>1.45</td>
<td>1.13</td>
<td>1.29</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.13-1.85</td>
<td>0.89-1.42</td>
<td>1.09-1.53</td>
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NMSC: Risks of Immunosuppression

**Crohn's disease**

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<th>Medication Class*</th>
<th>IBD overall</th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
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<tbody>
<tr>
<td>5ASA</td>
<td>1.06 (0.77-1.45)</td>
<td>0.98 (0.63-1.53)</td>
<td>1.22 (0.76-1.96)</td>
</tr>
<tr>
<td>Biologic</td>
<td>1.88 (1.08-3.29)</td>
<td>1.94 (1.03-3.68)</td>
<td>1.73 (0.53-5.63)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>1.10 (0.72-1.67)</td>
<td>0.92 (0.53-1.59)</td>
<td>1.31 (0.66-2.60)</td>
</tr>
</tbody>
</table>

*Any use, adjusted OR controlled for other medication use, comorbidities, health care utilization

Summary: Skin cancer in IBD

- NMSC risk driven by thiopurine use
- Melanoma risk driven by anti-TNF
- Innate differences in underlying IBD immune dysfunction may contribute to these risks
- Mechanisms likely differ, as do absolute risks

Summary: Skin Cancer Prevention

- Primary prevention
  - Sun protective clothing with a UPF of 30
  - Broad-spectrum sunscreens (UVA and UVB) with a SPF of 30 or greater
  - Reapplication of sunscreen every 2 hours

Skin Cancer Prevention in IBD

- Secondary prevention
  - No current recommendation for annual skin examination in IBD (or in the general population), but this should be considered
    - Annual skin examinations are recommended in post-transplant patients on immunosuppression
    - Consideration of routine skin examinations in IBD patients on immunosuppression
  - Any skin lesion suspicious for malignancy in a patient with IBD on immunosuppression should be evaluated by a trained dermatologist


Summary Recommendations for our case
<table>
<thead>
<tr>
<th>Summary: Prevention in IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevention of osteoporosis</strong></td>
</tr>
<tr>
<td>– Calcium (1500 mg) and Vitamin D (1000 IU) replacement</td>
</tr>
<tr>
<td>– DEXA due to &gt;3 month history of corticosteroids</td>
</tr>
<tr>
<td><strong>Prevention of cervical dysplasia</strong></td>
</tr>
<tr>
<td>– HPV vaccine</td>
</tr>
<tr>
<td>– Pap smears at recommended intervals by USPSTF / ACOG</td>
</tr>
<tr>
<td><strong>Prevention of infections</strong></td>
</tr>
<tr>
<td>– Review of immunization records</td>
</tr>
<tr>
<td>– Immunizations as appropriate (pneumococcal, influenza)</td>
</tr>
<tr>
<td>– TB test prior to anti-TNF</td>
</tr>
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<td>– Hepatitis B s Ag prior to anti-TNF</td>
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<td><strong>Prevention of skin cancer</strong></td>
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<td>– Sun protective clothing, broad spectrum sunscreen</td>
</tr>
<tr>
<td>– Consideration of regular skin screening</td>
</tr>
<tr>
<td>– Referral to dermatologist for suspicious skin lesions</td>
</tr>
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</table>
Prevention in IBD

Primary prevention
- Med, sunscreen, vaccines

Secondary prevention
- Colonoscopy, Skin exam, Pap

Tertiary prevention

IBD Diagnosis
- Colon dysplasia
- Cervical cancer
- Skin Cancer
- IBD Surgery