Preventing Complications in IBD

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Epidemiology

- Inflammatory bowel disease affects approximately 1.4 million Americans

  - peak onset is in persons 15 to 30 years of age.
  - second peak 60 to 80
Accumulating evidence suggests that inflammatory bowel disease results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host.

The Physical Barrier DEFENSE

1. Mucosal barrier (defensin, IgA)
2. Epithelium

THE CELL DEFENSE
- Innate
- Adaptive

Abraham, C N Engl J. 2009
Figure 2  The therapeutic pipeline in Crohn’s disease. Drugs are categorised based on the mechanism of action. Purple symbols indicate oral drugs. JAK, janus kinase; IL, interleukin; CAM, cell adhesion molecule; TNF, tumor necrosis factor.
Management

Randomized Evaluation of an Algorithm for CD (REACT-2)

- Currently investigating whether an accelerated step-up treatment aiming to achieve and maintain deep remission leads to less CD-related complications as compared with the classical step-care approach.

- This trial will provide us unique information on the potential of thiopurines and biologics for disease modification in IBD.
Mesalamine
Pentasa, Lialda,
(Inducing remission agent and maintenance)

Immunomodulators
(NOT AN INDUCING remission agent used for maintenance)
6MP, Azathioprine, Methotrexate

Biologic Agents
Inducing remission & Maintenance agent

STEROID:
Prednisone
Budenoside

SURGICAL INTERVENTION

-INDUCING AGENTS

-NOT MAINTENANCE
Figure 4  High definition endoscopic images of patients with active Crohn’s disease (CD) and ulcerative colitis (UC) are shown. In addition, examples of endoscopic mucosal healing (MH) are given for both diseases. Drugs that have been described to promote mucosal healing in CD and UC are highlighted. The levels of evidence (USPSTF) for the induction of MH are highlighted by different colours.
Prevention

- Altering disease progression
- Vaccination
- Medication Specific
- Lifestyle
  - Smoking cessation
  - Osteoporosis
- Clostridium difficile
Prevention

Altering disease progression

• population-based study
  – more than 80% of patients had uncomplicated inflammatory disease at diagnosis

Cumulative risk of developing either stricturing or penetrating disease

- After 90 days 19%
- 1 year 22%
- 5 years 34%
- 20 years 51%

FIGURE 1. Typical progression of digestive damage and inflammation over the course of CD. CDEIS, Crohn’s Disease Endoscopic Index of
• “low risk”
  • (fibrotic phenotype, nonsmoker, first resection)

• “high risk”
  • (perforating phenotype, smoking, second or more resection)
Vaccination
Vaccination

- 169 patients with IBD
  - 86% of whom had past or current immunosuppressive medication use

  - 45% had tetanus immunization within the last 10 years
  - 28% received regular flu shots
  - 9% received pneumococcal vaccination
  - 28% had been vaccinated against hepatitis B.
Basis of an expert consensus report on patients with IBD immunosuppression is defined as:

1. Treatment with glucocorticoids (> prednisone 20 mg / day equivalent, or 2 mg / kg / day if < 10 kg, for 2 weeks or more, and within 3 months of stopping)

2. Ongoing treatment with effective doses of 6-MP / azathioprine or recent discontinuation within the previous 3 months

3. Treatment with methotrexate or recent discontinuation within the previous 3 months

4. Treatment with infliximab or recent discontinuation within the previous 3 months

5. Significant protein-calorie malnutrition.
IBD immunosuppression is defined as:

- Adalimumab, certolizumab, and natalizumab, same window after discontinuation.

  - Adalimumab  using a half life of 10 – 20 days
  - Certolizumab  14 days
  - Natalizumab  7– 15 days

Applying pharmacokinetic principles, one can extrapolate that the drugs are 98.44% cleared at the end of six half lives or ~ 3 months.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)</td>
<td>Substitute one-time dose of Tdap for Td booster; then boost with Td every 10 years. For patients &gt;65 years, Td booster every 10 years</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>3 Doses in females between 19 and 26 years</td>
</tr>
<tr>
<td>Varicella</td>
<td>2 Doses</td>
</tr>
<tr>
<td>Zoster</td>
<td>1 Dose for patients &gt;60 years</td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)</td>
<td>1 Or 2 doses for patients between 19 and 49 years. 1 Dose after the age of 50, if some other risk factor (medical, occupational, lifestyle) is present</td>
</tr>
<tr>
<td>Influenza</td>
<td>1 Dose annually</td>
</tr>
<tr>
<td>Pneumococcal (polysaccharide)</td>
<td>1 Or 2 doses between 19 and 49 years if some other risk factor (medical, occupational, lifestyle) is present. 1 Dose for all patients &gt;65 years</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2 Doses in patients with risk factor (medical, occupational, lifestyle)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3 Doses in patients with risk factor (medical, occupational, lifestyle)</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>1 Or more doses in patients with risk factor (medical, occupational, lifestyle)</td>
</tr>
</tbody>
</table>

Modified from the Centers of Disease Control and Prevention (5).
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Check titer before vaccination?</th>
<th>Before initiation of immunomodulator or biologic?</th>
<th>What to do if already on immunomodulator or biologic?</th>
<th>Can family members be vaccinated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>Yes if vaccination history unknown</td>
<td>Contraindicated if plans to start therapy in 6 weeks</td>
<td>Contraindicated</td>
<td>Yes</td>
</tr>
<tr>
<td>Zoster (for age &gt;60)</td>
<td>No</td>
<td>Contraindicated if plans to start therapy in 1–3 months (32,33)</td>
<td>Contraindicated—could consider if on short-term corticosteroids (&lt;14 days), or low doses of methotrexate (&lt;0.4 mg/kg/week), azathioprine (&lt;3.0 mg/kg/day), or 6-mercaptopurine (&lt;1.5 mg/kg/day) (34)</td>
<td>Yes. Vaccine recipients who have a vaccine-related rash should avoid contact with the immunosuppressed patient.</td>
</tr>
<tr>
<td>Varicella</td>
<td>Yes if vaccination history unknown or no prior varicella infection</td>
<td>Contraindicated if plans to start therapy in 1–3 months (32,33)</td>
<td>Contraindicated—no adequate data to suggest otherwise</td>
<td>Yes. Vaccine recipients who have a vaccine-related rash should avoid contact with the immunosuppressed patient.</td>
</tr>
</tbody>
</table>

MMR, measles, mumps, rubella.
### Table 5. Live and inactivated vaccines for the traveler

<table>
<thead>
<tr>
<th>Live vaccines</th>
<th>Inactivated vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever virus</td>
<td>Japanese encephalitis virus</td>
</tr>
<tr>
<td>Measles mumps rubella (MMR)</td>
<td>Rabies virus</td>
</tr>
<tr>
<td>Oral typhoid</td>
<td>Injectable typhoid</td>
</tr>
<tr>
<td>Oral polio (OPV)</td>
<td>Injectable polio (IPV)</td>
</tr>
<tr>
<td>Intranasal influenza</td>
<td>Injectable influenza</td>
</tr>
<tr>
<td>Tuberculosis BCG</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A</td>
</tr>
<tr>
<td></td>
<td>Human papillomavirus (HPV)</td>
</tr>
<tr>
<td></td>
<td>Meningococcal</td>
</tr>
<tr>
<td></td>
<td>Tetanus diphtheria (Td)</td>
</tr>
<tr>
<td></td>
<td>Tetanus diphtheria acellular pertussis (Tdap)</td>
</tr>
</tbody>
</table>

BCG, Bacillus Calmette-Guérin.
Medication specific

-Labs to follow

-Malignancy
Medication specific

Lab Test

- Aminosalicylates: annual creatinine

- Corticosteroids: 25-OH Vitamin D, metabolic panel, and glucose.

- Azathioprine/6MP
  - A thiopurine methyl transferase (TPMT) should be checked prior to initiation of therapy.
  - Weekly CBC with differential for the first 4 weeks, at least every 3 months thereafter (our practice is monthly for 6 months and then every 2–3 months).
  - Periodic liver function tests at least every 3 months.
Medication specific

Lab Test

- Methotrexate
  - Periodic CBC and liver function tests.
  - CBC every 2 weeks for 1 month, every month for 6 months, and then at least every 3 months
Medication specific

Lab Test

- Biologic therapy (infliximab, adalimumab, certolizumab pegol, natalizumab)

- Prior to initiating therapy: hepatitis A, B, and C. If no evidence of prior exposure to A or B, vaccinate.

- Active hepatitis B infection is a relative contraindication to anti-TNF therapy. Patients should be on appropriate antiretrovirals prior to initiating anti-TNF therapy.
Lymphoma

- Even people on no medication risk of lymphoma is approximately a risk of 2 people out of 10,000.
- Thiopurine 4 people out of 10,000
- Anti-TNF medications 6 people out of 10,000.
### Risk of lymphoma with immune suppression

**Ten Thousand People** pictures to help you see your odds

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**Siegel CA, Inflamm Bowel Dis 2010;16:2168.**

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The Pelletier® of 10,000 People • Risk Communication Format © John Pelling 2007 • See www.riskcomm.com

We can only show you estimates. It is impossible to be certain whether your results will be positive or negative.
Hepatosplenic T-cell lymphoma (HSTCL)

- The absolute risk of HSTCL for all patients receiving concomitant thiopurine and anti-TNF for men younger than 35 years is approximately 1:3534
Skin cancer non melanoma

- thiopurine exposure and an increased risk of NMSC in patients with IBD.

- Skin exam and sun block
Colonoscopy
Risk factors for colorectal cancer (CRC) in ulcerative colitis (UC)
- longer duration of disease
- greater extent of disease
- primary sclerosing cholangitis
  • family history of CRC
  • precancerous dysplasia in other parts of the bowel
Colonoscopy surveillance

- It was estimated that 33 biopsy specimens were required to have a 90% chance of finding the highest degree of dysplasia present

Rutter, M. D. and RIDDELL R. H. CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013; 1–8
Colonoscopy surveillance

- Historical retrospective series and reviews have indicated that when endoscopically invisible high-grade dysplasia (HGD) is detected → colectomy
  - Owing to high rates either of synchronous or metachronous cancer in 32% to 42% of patients.
Endoscopically invisible low-grade dysplasia (LGD) is detected

-Dilema reported rates of progression to HGD or cancer vary from as low as 0% to more than 50%.

However, before any decision is made, the colonoscopy should be repeated by a colonoscopist experienced in the use of CE and interpretation of colonoscopic findings. This is to ensure that an endoscopically visible and resectable lesion is not present, particularly because many apparently random biopsy specimens actually may have been taken from an area of mucosal irregularity, which can be detected endoscopically.
Osteoporosis
Osteoporosis

• Dual-energy x-ray absorptiometry scanning (DXA)
  – **osteooporosis =** Low bone mineral density 2.5 standard deviations below the average bone density in gender-matched young adults (T-score less than 2.5) or when patients sustain a fragility fracture (a fall from standing height or less).
Who do we screen?

- postmenopausal women or men over the age of 50
- prolonged corticosteroid use (greater than 3 consecutive months or recurrent courses)
- patients with a personal history of a low trauma fracture
- patients with hypogonadism
Osteoporosis

PREVENTION

- lifestyle modifications
  - smoking cessation
  - regular weight-bearing exercise
  - minimizing alcohol and caffeine
  - Minimizing consumption or discontinuing medications that affect perception and balance
    - Benzodiazepines
    - Tricyclics
    - Antipsychotics
    - Antihistamines
PREVENTION

calcium (1200 mg per day in postmenopausal women) and vitamin D (400–800 IU per day) intake have been shown to be effective in fracture prevention
Clostridium difficile
Clostridium difficile

- Gram-positive, anaerobic spore-forming bacillus
- 5% of healthy adults are colonized by C. difficile
- IBD increased susceptibility to C. difficile
  - Dysregulated immune system
  - Presence of colonic inflammation
  - Exposure to antibiotic
  - Gastrointestinal surgery
  - Proton pump inhibitors
Clostridium difficile

Prevention

– hand hygiene with soap and water, instead of alcohol-based cleansers, to eliminate spores
Prevention

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Key points

• Mucosal healing and deep remission are goals of IBD therapy with the intention to alter disease progression

• Side effect of immunosuppressive medication increase risk of infections
  – Plan a head vaccinate
  – Avoid Live Vaccines if on immunosuppressants
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Key points

- Surveillance colonoscopy for colon cancer after 8 years or 15 years of disease dependent on extent of disease

- Bone densitometry

- Hand hygiene with soap and water for clostridium difficile