Topics in IBD

Vaccination
Bone Health
Initial Treatment Considerations

Dr. Jesse Siffledeen, MD FRCPC
Department of Gastroenterology, Grey Nuns hospital
Division of Gastroenterology, University of Alberta

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Dr. Jesse Siffledeen
- **Relationships with commercial interests:**
  - **Speakers Bureau/Honoraria:** Abbvie Corp., Shire Pharmaceuticals
  - **Consulting Fees:** Abbvie Corp., Janssen Inc, Shire Pharmaceuticals

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has not received financial support from outside agencies**
- **Potential for conflict(s) of interest:**
  - Dr. Jesse Siffledeen has received funding from Shire Pharmaceuticals, whose product(s) are being discussed in this program.
  - The potential for bias has been mitigated through discussion of all in-class products, regardless of commercial source.

Today…

- OBJECTIVES:
- 1. List appropriate vaccinations for the IBD patient
- 2. Incorporate bone health into the annual health exam for IBD patients
- 3. Determine the appropriate initial therapy for the known IBD patient during a flare

Vaccinations

- **Physician reluctance re: vaccinations**
  - **Amongst primary care physicians, only 30% felt comfortable coordinating vaccinations for immunocompromised IBD patients**
  - **GI docs are not any better…**
    - **Approx. 1/3 would give a live vaccine in an immunocompromised patient**
    - **1/3 will withhold live vaccines in immunocompetent patients**

Only 52% of GIs took an immunization history most or all of the time

How Often	N (%)
Always	20 (18.5)
Most of the time	36 (33.3)
Half of the time	5 (4.7)
Sometimes	40 (37)
Never	7 (6.5)

1. Wasan et al. *Inflamm Bowel Dis* 2011;17:2536-40 http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1536-4844 ; 2. Selby et al. *Dig Dis Sci* 2011;56:819-24 http://www.springerlink.com/content/0163-2116/

Vaccinations

Recommendations Regarding Vaccination

General vaccination considerations for patients with IBD

Titres to check at first office visit		
MMR - if vaccination history unknown		
Varicella - if vaccination history or history of chicken pox/zoster unknown		
Hepatitis A and B - except those with evidence of protective titre within 5 years		
Vaccinations to administer in specific patient groups regardless of immunosuppressive drug use		
Tdap HPV Influenza	Pneumococcal Hepatitis A	Hepatitis B Meningococcal
Vaccinations to consider if no plans to start immunosuppressive therapy in 4-12 weeks		
MMR	Varicella	Zoster

Immunosuppression defined as:

1. Glucocorticoids treatment for ≥2 wks or recent d/c (≤3 mos)
   - Prednisone >20 mg/d equivalent, or 2 mg/kg/d if <10 kg
2. Ongoing treatment with effective doses of 6-MP/ azathioprine or recent d/c (≤3 mos)
3. Methotrexate treatment or recent d/c (≤3 mos)
4. Infliximab treatment or recent d/c (≤3 mos)
5. Significant protein-calorie malnutrition

d/c=discontinuation; HPV=human papillomavirus; MMR=measles, mumps, rubella; Td/Tdap=tetanus, diphtheria, pertussis
Wasan et al. *Am J Gastroenterol* 2010;105:1231-8 http://www.nature.com/ajg/index.html

Vaccinations

Recommendations Regarding Vaccination

Recommendations for inactivated vaccine for patients with IBD

Vaccine	Check titre first?	Before initiation of immunomodulator or biologic?	What to do if already on immunomodulator or biologic?
Td/Tdap	No	Administer vaccine if not given over the past 10 y or give Tdap if Td ≥2 y	Administer vaccine if not given over the past 10 y or give Tdap if Td ≥2 y
HPV (females 9-26 yo)	No	3 doses (0, 2, 6 months)	3 Doses (0, 2, 6 months)
Influenza	No	Annual vaccine. Administer trivalent inactivated influenza vaccine. Avoid live attenuated influenza vaccine (FluMist)	Annual vaccine. Administer trivalent inactivated influenza vaccine. Avoid live attenuated influenza vaccine (FluMist)
Pneumococcal	No	Vaccinate if none previously, and 1-time revaccination after 5 y if immunosuppressed	Vaccinate if none previously, 1-time revaccination after 5 y if immunosuppressed
Hepatitis A	Yes	2 doses at 0, 6–12 months; or 0, 6–18 months; booster > 10 y	2 doses at 0, 6–12 months; or 0, 6–18 months; booster > 10 y
Hepatitis B	Yes	3 doses at 1, 1–2, 4–6 months; check postvaccine titers at 1 month after finishing last dose. If no response, then revaccinate with double dose	3 doses at 1, 1–2, 4–6 months; check post-vaccine titers at 1 month after last dose. If no response, then revaccinate with double dose
Combination hepatitis A/B (Twinrix)	Yes	May be given instead of HAV and HBV individually or to individuals without a response to HBV vaccination	May be given instead of HAV and HBV individually or to individuals without a response to HBV vaccination
Meningococcal	No	Vaccinate in at-risk patients if none previously	Vaccinate in at-risk patients if none previously

HPV=human papillomavirus; MMR=measles, mumps, rubella; Td/Tdap=tetanus, diphtheria, pertussis

Wasan et al. *Am J Gastroenterol* 2010;105:1231-8 http://www.nature.com/ajg/index.html

Vaccinations

Recommendations Regarding Vaccination

Recommendations for live vaccine for patients with IBD

Vaccine	Check titre first?	Before initiation of immunomodulator or biologic?	What to do if already on immunomodulator or biologic?
MMR	Yes if vaccination history unknown	Contraindicated if plans to start therapy in 6 weeks	Contraindicated
Zoster (for age >60)	No	Contraindicated if plans to start therapy in 1–3 months	Contraindicated — could consider if on short-term corticosteroids (<14 days), or low doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6-mercaptopurine (<1.5 mg/kg/day)
Varicella	Yes if vaccination history unknown or no prior varicella infection	Contraindicated if plans to start therapy in 1–3 months	Contraindicated — no adequate data to suggest otherwise

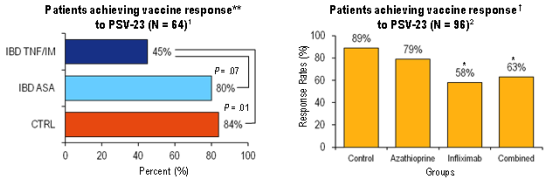
HPV=human papillomavirus; MMR=measles, mumps, rubella; Td/Tdap=tetanus, diphtheria, pertussis

Wasan et al. *Am J Gastroenterol* 2010;105:1231-8 http://www.nature.com/ajg/index.html

Vaccinations

Will Vaccines Work in Patients With IBD?

Immune response to pneumococcal vaccine



- Patients being treated with biologics or combined immunosuppression showed impaired response[1,2]
- No significant differences in vaccine response rates with 5-ASA or azathioprine alone[1,2]

*P < .05; **Both geometric mean titre >1 mg/100 mL and ≥2-fold increase in baseline titers to at least 3 or more serotypes
†≥2-fold increase in antipneumococcal antibodies in the serum compared with baseline

IBD TNF/IM=IBD on combination TNF-blockers & immunomodulators; IBD ASA=IBD on 5-ASA only; CTRL=age-matched healthy controls

1. Melmed et al. *Am J Gastroenterol* 2010;105:148-54 http://www.nature.com/ajg/index.html; 2. Fiorino et al. *Inflamm Bowel Dis* 2011;Online:DOI 10.1002/ibd.21800 http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1536-4844

Vaccinations

- What I do in my practice:
  - Patients asked to provide **vaccination history**
    - Available from public health clinic
  - **Influenza**: annually for all patients
    - advised to avoid the live flu vaccines
  - Other **inactivated** vaccines – based on immunization history.
    - TdDap, Hep A/B, HPV
  - All smokers > 50 on IS receive the **Pneumovax** vaccine
  - Live vaccines: not while on immunosuppressive therapy
    - MMR, VZV, HZV
  - In General: try to give vaccines before initiation of immune suppressing therapy

Bone Health in IBD

- Low bone mass and osteoporosis are common in IBD
  - 20-50%
- Have an increased risk of osteoporotic fractures
  - Vertebral fractures: 15-20% of IBD population, most<40 yrs old
  - Hip: predominantly in older patients (rare in pts<50yrs of age)
- Risks:
  - Age
  - Persistent disease activity
  - Repeated corticosteroid use
  - Malnutrition
  - Smoking

Vestergaard et al, Gut 2000;46:176–181, Vestergaard & Mosekilde, Am J Epidemiol 2002;156:1–10
Bernstein et al, Ann Intern Med 2000; 133: 795-99, Siffledeen et al, Clin Gastro Hep 2007;5:721-28

Bone Health in IBD

- FRAX: WHO Fracture Risk Assessment tool:
  - Accounts for 9 risk factors for osteoporosis, plus BMD, to give a composite 10 year absolute risk score (in percentage)
    - **Age – strongest risk factor**
    - BMI
    - Smoking status
    - Glucocorticoid use - >7.5 mg/day for >3 months
    - **Prior fragility fracture – vertebral fractures!**
    - Maternal history of hip fracture
    - Rheumatoid arthritis
    - Secondary osteoporosis risk factors: **includes IBD**, DM1, thyroid dz, organ transplant, hypogonadism, prolonged immobility
    - Daily EtOH > 2 units a day

J clin densitom 2011;14:212-29, AGA position statement. Gastro 2003;124:791-954
ECCO UC consensus guidelines 2013;7:1-33, ECCO CD consensus guidelines 2010;4:63-101

Bone Health in IBD

Table 1 Ten-year probability (%) of a major osteoporotic fracture or hip fracture in men and women aged 65 years according to the presence of a single clinical risk factor

	Without BMD				T-score −2.5 SD			
	Men		Women		Men		Women	
	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip
No clinical risk factors	4.9	0.8	8.6	1.3	9.8	3.6	12.4	3.0
Parental history of hip fracture	9.3	1.0	16.0	1.7	16.5	3.7	22.1	3.2
Current cigarette smoking	5.1	1.1	9.2	1.9	11.0	5.6	13.7	5.1
Alcohol intake >2 units daily	6.0	1.2	10.4	2.0	12.5	5.4	15.4	4.6
Rheumatoid arthritis	6.8	1.4	11.7	2.3	12.8	5.0	16.1	4.3
Oral glucocorticoids	7.5	1.5	13.7	2.7	15.0	6.1	19.7	5.5
Previous fragility fracture	9.6	1.9	16.4	3.2	16.0	5.9	20.2	5.0

BMI is set at 25 kg/m^2. The right-hand panels show probabilities at a T-score of −2.5 SD at the femoral neck
[a] Hip, clinical spine, humeral or forearm fracture

Kanis et al. Osteoporos Int 2008;19:385-97

Bone Health in IBD

- **Assessment**
  - DXA/FRAX every 3 years if patients have risk factors
  - Vertebral X-rays at least once after the age of 50 (thoracolumbar AP/Lateral)
- **Management**
  - Minimize corticosteroid dosing!!
  - Calcium and vitamin D supplementation in all IBD patients
    - (500-1000 mg/800-1000 IU) – esp. if on corticosteroids
  - Bisphosphonates in those with established osteoporosis (or osteoporotic/vertebral fractures) – based on FRAX index
  - May consider SERM in postmenopausal females, testosterone in deficient males
  - Exercise, better nutrition, smoking cessation
  - Minimize inflammatory activity – IS, anti-TNF

AGA position statement. Gastro 2003;124:791-954
ECCO UC consensus guidelines 2013;7:1-33, ECCO CD consensus guidelines 2010;4:63-101

Treatment strategies for IBD

- Gather information – be objective about disease activity
  - Known degree of intestinal involvement (extent and severity)
  - **Determine adherence to meds!**
  - # of liquid and bloody BM daily
  - Presence of abdominal pain
  - Peri-anal disease (abscesses/fistulae)
  - Skin involvement, eye involvement
- ~ 1/3 of IBD patients who are symptomatically well will have endoscopically active disease
- ~ 1/5 with active symptoms will not have endoscopically active disease
- Therefore…

Treatment strategies for IBD

- When clinical suspicion of IBD (or flare of known IBD) arises, the following should be obtained:
  - CRP, ESR
  - CBC, ferritin,
  - Potentially helpful in Dx: ATTG (quant Ig), ASCA, ANCA
- Fecal calprotectin is a potentially powerful tool to distinguish IBS from IBD
  - And also to predict IBD activity
  - Assays are cheap in Europe and so it should become regularly available soon (I hope)
- CT-E, MR-E, colonoscopy

Extent & Severity of UC

How is the extent and severity of UC determined?

ACG Guidelines – Categories of UC

Category	Criteria
Mild	• <4 stools/day with or without blood • Normal erythrocyte sedimentation rate (ESR); no signs of systemic toxicity
Moderate	• ≥4 stools/day • Minimal signs of toxicity
Severe	• >6 bloody stools/day • Signs of toxicity (fever, tachycardia, anemia or elevated ESR)
Fulminant	• >10 stools/day • Continuous bleeding; toxicity • Abdominal tenderness/distension • Transfusion requirement • Colonic dilation on x-ray

Kornbluth A, Sachar D. Am J Gastroenterol. 2004;99:1371-85.
Baumgart DC, Sandborn WJ. Lancet. 2007;369:1641

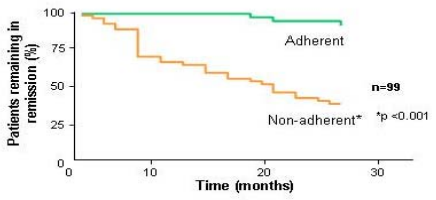
Predictors of Disabling Disease: *Requirement for Steroids Is Turning Point*

	5-year clinical course after diagnosis		
Variable	**Nondisabling, % (n = 166)**	**Disabling, % (n = 957)**	***P value***
Age at onset			
< 40 years	**77.1**	**87.7**	**.0004**
≥ 40 years	**22.9**	**12.3**	
Location of disease			
Small bowel only	**44.6**	**32.8**	**.002**
Small bowel + colon	**25.9**	**39.4**	
Colon only	**29.5**	**27.8**	
Smoking status			
Smoker	**50.3**	**57.4**	**.09**
Ex or nonsmoker	**49.7**	**42.6**	
Perianal lesions at diagnosis			
Yes	**17.5**	**26.4**	**.01**
No	**82.5**	**3.6**	
Required steroids for first flare			
Yes	**37.3**	**65.2**	**.0001**
No	**62.7**	**34.8**	

Evolving Treatment Strategies for IBD – mucosal healing

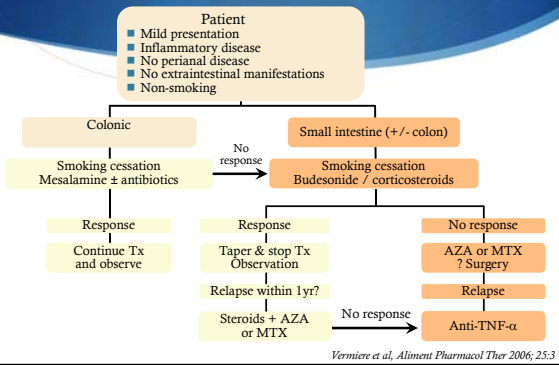
- Large amount of debate regarding the precise definition of mucosal healing and its role in IBD management
- Much evidence emerging that mucosal healing predicts better IBD prognosis
  - Applicable for all types of disease presentations (ie. Mild, moderate or severe)
- Therefore…have patient follow-up with GI doc

Effect of adherence on remission



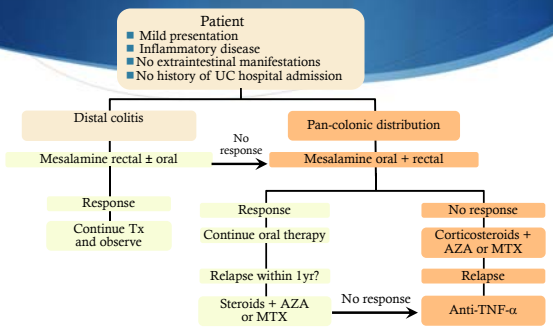
Kane et al, Am j Med 2003114:39;

Suggested approach for CD pts at low risk of progression



Vermiere et al, Aliment Pharmacol Ther 2006; 25:3

How about UC?



5-ASA

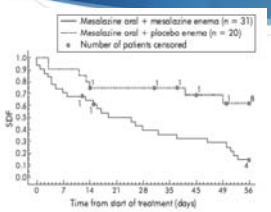
- **Limited mostly to mild-moderate UC, and occasionally in CD**
- **A big list of different agents**

Agent (Trade Name)	Abbreviation	Form & Dose	Delivery Mechanism
Sulfasalazine	SSZ	**Form:** 500 mg tablet **Dose:** 1000 mg, 3-4 times daily (evenly spaced, no more than 8 hours apart)	Prodrug cleaved by colonic bacteria to 5-ASA and sulfapyridine (200 mg of 5-ASA)
Olsalazine (Dipentum)	OSZ	**Form:** 250 mg capsule **Dose:** 500 mg 2-4 times daily	Prodrug cleaved by colonic bacteria to 5-ASA (225 mg of 5-ASA)
Mesalamine (Salofalk)	M-DRL	**Form:** 500 mg delayed-release tablet **Dose:** 1000 mg , 3-4 times daily	Eudragit-L coated tablets (release at pH >6)
Mesalamine (Asacol)	M-DRS	**Form:** 400 mg & 800 mg delayed-release tablet **Dose:** 400-1600 mg TID	Eudragit-S coating dissolves at pH ≥7
Mesalamine (Mezavant)	M-MMX	**Form:** 1.2 g delayed- & extended-release tablet **Dose:** 2.4-4.8 g QD	Polymer film coating dissolves at pH ≥7; Multi Matrix System (MMX) technology prolongs dissolution in colon
Mesalamine (Pentasa)	M-CR	**Form:** 500 mg extended-release tablet **Dose:** 500-1000 mg QID	Ethylcellulose-coated microgranules provide time-dependent release

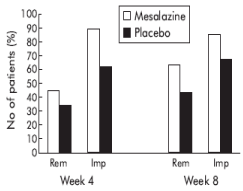
A little about best use of 5-ASA

- Probably best limited to UC patients, or Crohn's disease patients with mild colitis
- Sometimes combinations are better (ie. Oral + rectal in extensive disease)
- Many preparations: no dose-appropriate head-head studies that one is superior to the other
- No difference in once-daily vs multiple daily administration during maintenance
  - Once daily administration might even be better for adherence

Oral + Rectal 5-ASA in mild-moderate extensive UC



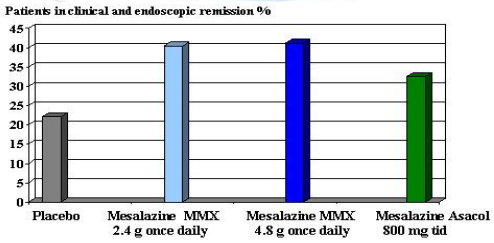
Time to cessation of bleeding



Remission and improvement rates

Marteau et al, Gut 2005;54:960

Optimal dose:



Kamm et al,. Gastroenterology 2007;132:66

Thank you