

Inflammatory Bowel Disease: An Update for the Wound Care Clinician

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1

Objectives

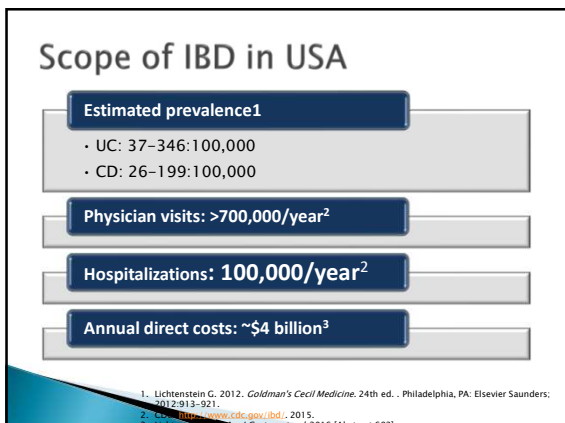
- ▶ 1. Based on both intestinal and extraintestinal symptoms be able to differentiate between Ulcerative Colitis (UC) and Crohn's Disease (CD), including risk factors for both diseases..
- ▶ 2. Discuss new medications, including biologic agents, available for both UC and CD, including Adverse Drug Effects, Patient counselling points, and contraindications.
- ▶ 3. Explain the differences between standard CD and fistulizing disease, and discuss options for treating the latter.
- ▶ 4. Describe monitoring parameters for the drugs used to treat CD and UC, including azathioprine/6-MP, Methotrexate, cyclosporine, the 5-ASA compounds, and infliximab. These would include toxicity parameters.
- ▶ 5. Apply the treatment guidelines for both UC and CD to an individual patient case.

2

Summary Slides Case 10 IBD Background

- ▶ Generic term for a series of chronic inflammatory conditions of the GI tract
- ▶ About 600,000 patients have some form of IBD in the US
- ▶ Wide spectrum of disease
 - Some patients are asymptomatic while others have severe, life threatening disease
- ▶ By convention most patients with IBD have either:
 - Ulcerative Colitis (UC)
 - Crohn's Disease (CD)

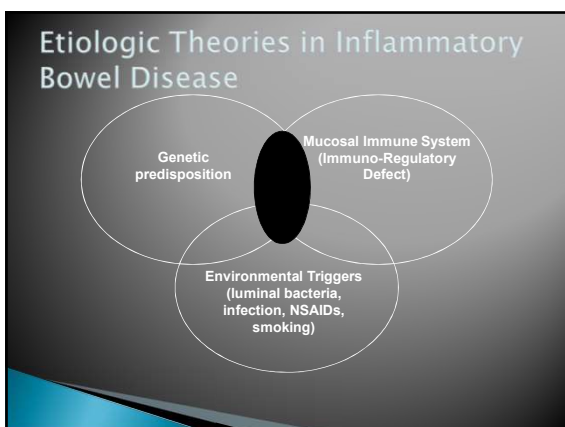
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4

- ### IBD background
- ▶ Peaks between ages of 14 and 30 years
 - ▶ European ancestry
 - ▶ Urban greater than rural dwellers
 - ▶ Whites greater than non-whites
 - ▶ Occurs in familial clusters
 - 44% concordance among twins
 - ▶ NSAIDs can exacerbate IBD and are a risk factor for development
 - ▶ Smoking is a NEGATIVE risk factor for UC while it increases severity of Crohn's disease (CD)

5



6

Components of IBD Diagnosis

- Endoscopy
- Histology
- Radiography
- Clinical course of symptoms

- History
- Physical Examination
- Labs
 - CBC, CMP, ESR, CRP, iron studies, vitamin B12
- Fecal calprotectin or lactoferrin
- Stool
 - C difficile toxin, culture, ova & parasites
- Colonoscopy
 - EGD if CD suspected
 - Wireless capsule endoscopy of small intestine
 - CT and MRI enterography
 - Barium small bowel follow through
 - Device-assisted balloon enteroscopy

CBC = complete blood count; CMP, comprehensive metabolic panel; CRP, C-reactive protein; EGD = esophagogastroduodenoscopy; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; Barium small bowel follow through = barium swallow and follow-through; Device-assisted balloon enteroscopy = balloon-assisted enteroscopy.

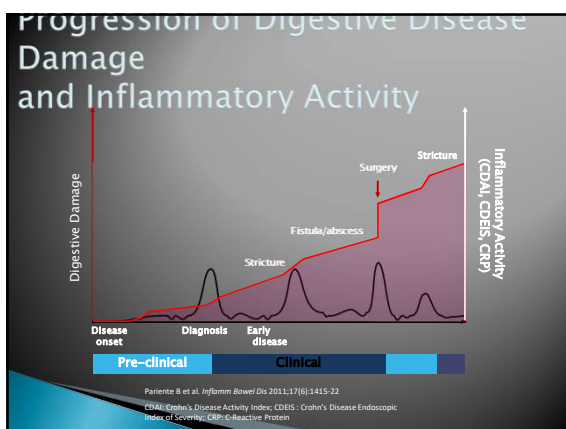
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Treatment Goals

- Induce clinical remission
- Avoid short- and long-term toxicity of treatment
- Enhance quality of life
- Maintain steroid-free remission
 - Avoid repeated courses of steroids!
- Induce "deep" remission
 - Biologic remission (normalization of biomarkers)
 - Mucosal healing
- Prevent complications (hospitalizations, surgery)
- Reduce cancer risk

Reenaers C, et al. *World J Gastroenterol*. 2012;18(29):3823-3827.
 Jones D, et al. *J Crohns Colitis*. 2012;6(Suppl 2):S224-S227.

8



9

Risk Factors for a More Severe Disease Course

<ul style="list-style-type: none"> • Early age at diagnosis (<40) • Perianal involvement • Severe deep ulcerations on endoscopy • Multiple areas of bowel involvement • Current tobacco use • Other <ul style="list-style-type: none"> - Prior resections - Stricturing or penetrating disease - Early steroid treatment 	<ul style="list-style-type: none"> • Early age at diagnosis (<40) • Early steroid treatment • Extensive colitis • Hospitalization @ diagnosis • Elevated inflammatory markers <ul style="list-style-type: none"> - CRP, ESR • Low serum albumin
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Crohn's Disease

Ulcerative Colitis

Peyrin-Biroulet L, et al. Clin Gastroenterol Hepatol. 2016;14(3):348-354.

10

Treatment Paradigm Shift: Decision-Making in IBD

OLD = treat based on symptoms

- But symptoms are insensitive and nonspecific for bowel inflammation

➔

NEW = treat based on objective markers of inflammation

- Serologic (CRP reduction)
- Endoscopic (mucosal healing)
- Radiographic (CTE/MRI improvement)

11

Conventional Approach to Induction Therapy: Step Up

• Therapy is stepped up according to severity at presentation or failure at prior step
 • Clinical approach to use "mildest" form of drug therapy to treat patients first
 • ... next step in non-responders

12

Step Up Management

Advantages

- Patients attain remission with less toxic therapy
- Potentially more toxic therapies reserved for severe or refractory disease
- Minimizes risk of adverse events
- Cost-sparing (short-term?)

Disadvantages

- Patients have to 'earn' most effective treatments
 - ↓ QoL before patients obtain optimal therapy
- High likelihood of surgery
- Disease is not modified

13

New Paradigm: Treating Beyond Symptoms

Anti-TNF Agents	UC	CD
Infliximab	+	+
Adalimumab	+	+
Golimumab	+	
Certolizumab		+
Pegol		+
Anti-Integrin Agents		
Vedolizumab	+	+
Natalizumab		+

IMS, immunosuppressant; UC, ulcerative colitis; CD, Crohn's disease.
Hagens CR. Nat Rev Gastroenterol Hepatol. 2010 Feb;7(2):86-92.
 Hagens CR, et al. Gastroenterology. 2013 Dec;145(6):1459-63.
 Sandborn AB, et al. J Crohn's Colitis. 2014;8(9):927-935; Amezcaga AJ, et al. Curr Gastroenterol

14

Evolving Treatment Approach in UC

Current Approach

- Assessment of prognosis
- Optimization of AZA/6-MP dose or metabolites
- Earlier adoption of biologic therapy when appropriate
- Appreciation for the implications of mucosal healing

Emerging Approach

- Newer therapies w/ favorable safety + side-effect profiles
- Individualized therapy based on genetics + physiology
- Treatment to hard endpoints
 - e.g. mucosal healing or its surrogates
- Disease monitoring to prevent relapse

15

Current Medications for Active Disease

- 5-Aminosalicylic acid derivatives
 - sulfasalazine, mesalamine, balsalazide, olsalazine
- Antibiotics
 - metronidazole, ciprofloxacin, rifaximin
- Corticosteroid agents
 - hydrocortisone, prednisone, methylprednisolone, prednisolone, budesonide, dexamethasone
- Immunomodulator agents
 - azathioprine, 6-mercaptopurine, methotrexate, cyclosporine
- Tumor necrosis factor inhibitors
 - Infliximab, Adalimumab, certolizumab pegol, golimumab
- Anti-integrin agents
 - natalizumab, vedolizumab
- Anti-IL-12/23 agents
 - Ustekinumab

16

Current Medical Therapies for Symptomatic Relief

- Antidiarrheal agents
 - diphenoxylate and atropine, loperamide, cholestyramine
- Anticholinergic antispasmodic agents
 - dicyclomine, hyoscyamine

17

Serious Side Effects of Prolonged GCS Therapy

- Hypertension <20%
- Diabetes 2.33 relative risk for beginning insulin
- Infection 13-20%
- Osteoporosis <50%
- Myopathy 7%
- Cataracts 22% (dose-dependent)
- Psychosis (3-5%)

*Overall GCS therapy (not only therapy for CD). Sandborn W. *Can J Gastroenterol*. 2000;14(suppl C):17C-22C.

18

Predictors of Serious Infection & Death in CD

6273 patients in the TREAT registry; average follow-up: 5.2 years

Predictors of Serious Infection		Predictors of Death	
	HR		HR
Moderate to severe CD	2.2 4	Use of prednisone	2.1 4
Use of narcotic pain relievers	1.9 8	Use of narcotic pain relievers	1.7 9
Use of prednisone	1.5 7		
Use of IFX	1.4 3		

Abbreviations: IFX, infliximab; HR, hazard ratio. P < .05 for all.
Lichtenstein GR, et al. *Am J Gastroenterol*. 2012;107(9):1409-1422.

19

Safety and Toxicity Considerations

Mesalamine ¹	5-ASA	AZA/6-MP ⁴	MTX ⁵⁻⁶
<p>Low incidence of adverse effects</p> <ul style="list-style-type: none"> Diarrhea, headache, nausea most common Abdominal pain Dyspepsia Acute tolerance syndrome Nephrotoxicity Pancreatitis 	<p>Incidence of kidney impairment occurs in less than 1 in 200 (<0.5%) patients treated with 5-ASA²</p> <p>Clinically important interstitial nephritis occurs in 1 in 500 patients—50% of cases occur in the first year, and others may occur many years later³</p>	<p>Pancreatitis (4%) Allergy (2%) Bone marrow suppression (4%) Liver toxicity (9%) Serious infection (2%)</p> <p>Increased risk of lymphoma Nonmelanoma skin cancer Abnormal Pap smears</p>	<p>Nausea/vomiting Bone marrow suppression Liver scarring</p> <p>Contraindicated if attempting pregnancy</p>

1. Feagan BG, et al. *Cochrane Database Syst Rev*. 2012;10:CD000544. 2. Gisbert JP, et al. *Inflamm Bowel Dis*. 2007;13(5):629-638. 3. World MJ, et al. *Nephrol Dial Transplant*. 1996;11(4):618-621. 4. Kotlyar O, et al. *Clinical Gastroenterology and Hepatology*. 2015;13:847-858. 5. Lichtenstein GR, et al. *Am J Gastroenterol*. 2009;114(12):1811-1818. 6. Methotrexate injection USP [package insert]. Lake Forest, IL: Hospira, Inc.; 2011.

20

Anti-TNF Drug Safety

- Infection and malignancy**
 - Black-box warning for serious infection and malignancy for all anti-TNF therapies¹⁻³
- Black-box warning for HSTCL (ADA and IFX)^{1,2}**
- Reactivation of hepatitis B⁴**
- Skin cancer⁴**
- Psoriasis⁴**
- Autoimmunity (lupus-like syndrome <1%)⁴**
- Immunogenicity—antibodies to anti-TNF⁴**
- Demyelinating disorders, CHF, liver toxicity⁴**

CD, Crohn's disease; HSTCL, hepatosplenic T-cell lymphoma; CHF, congestive heart failure.

1. Remicade [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2013.
2. Humira [package insert]. North Chicago, IL: AbbVie, Inc.; 2013.
3. Simponi [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2013.
4. Lichtenstein GR, et al. *JAMA*. 2006;295(19):2275-2285.

21

Anti-Integrin Drug Safety

- Should not be used in patients:**
 - With impaired immunity
 - Taking immunosuppressants (i.e Natalizumab)
 - Taking TNF inhibitors
- Increased risk for progressive multifocal leukoencephalopathy (PML)**
- Headache, fatigue, depression, rash, nausea, abdominal discomfort, UTI, arthralgia, respiratory infection**

22

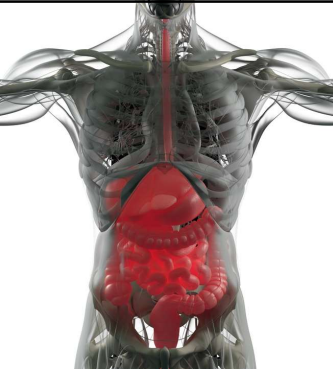
Ongoing Therapeutic Monitoring

- Mesalamines**
 - Periodic kidney function w/urine + blood tests
- Corticosteroids**
 - Bone health issues
- Thiopurines**
 - TPMT, CBC, LFT during therapy
- Methotrexate**
 - CBC, LFT, renal function during therapy, alcohol avoidance, pregnancy prevention
- Anti-TNF**
 - Consider annual TB test
 - Coccidiomycosis + histoplasmosis testing for patients living or who have lived in high prevalence regions
- Anti-Integrin**
 - Monitor for PML, LFTs, TB screening according to local practice, infection, neurological symptoms

TPMT, thiopurine methyltransferase; CBC, complete blood count; LFT, liver function tests; TB, tuberculosis; TNF, tumor necrosis factor.

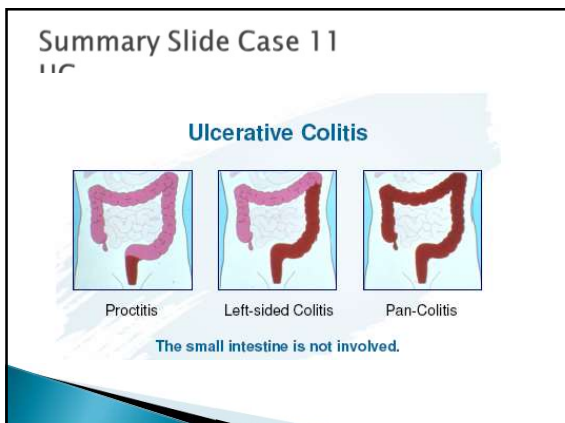
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Clinical Features Ulcerative Colitis

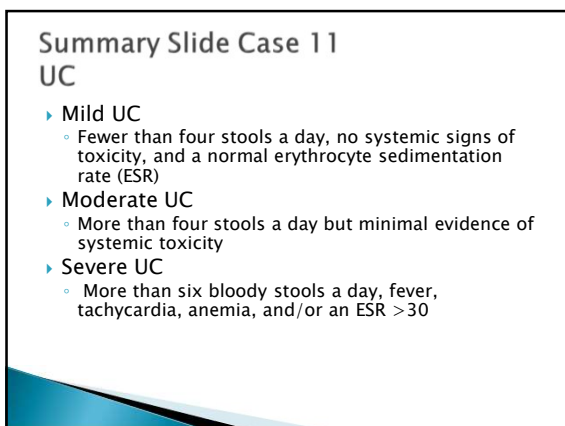


- Colon only
- Rectal involvement
- Mucosal disease
- Diffuse ulceration, granularity, friability, bleeding, exudate
- No fistulas or granulomas
- Non-smokers
- No prior appendectomy

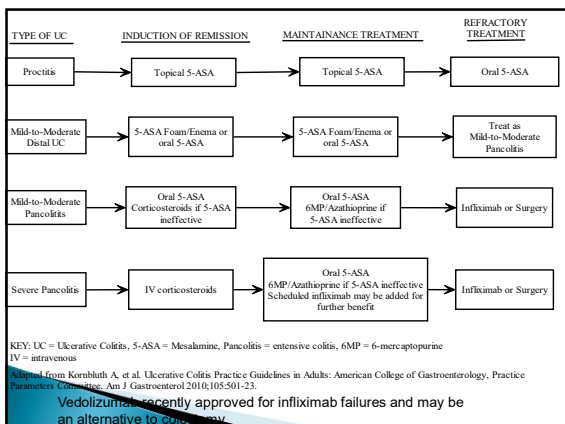
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25



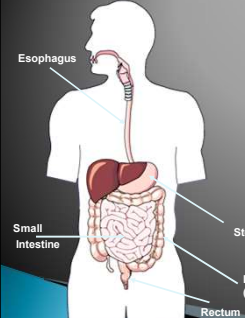
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27

Summary Slide Case 12

CD

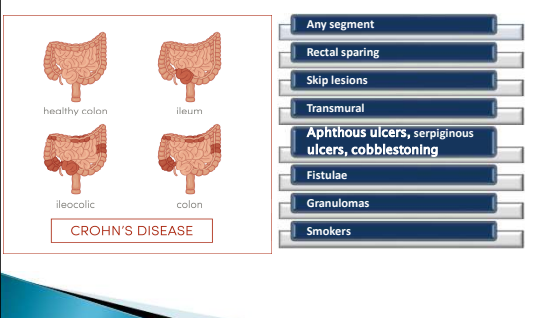


- ▶ Crohn's disease encompasses a spectrum disease manifested by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation affecting the gastrointestinal tract
- ▶ Unlike UC, CD can affect ANY part of the GI tract—from mouth to anus

Hanauer SB, et al. Am J Gastro. 2001;96:635-643.

28

Clinical Features of Crohn's Disease



<input type="checkbox"/>	Any segment
<input type="checkbox"/>	Rectal sparing
<input type="checkbox"/>	Skip lesions
<input type="checkbox"/>	Transmural
<input checked="" type="checkbox"/>	Aphthous ulcers, serpiginous ulcers, cobblestoning
<input type="checkbox"/>	Fistulae
<input type="checkbox"/>	Granulomas
<input type="checkbox"/>	Smokers

29

Summary Slide Case 12

CD Symptoms

- ▶ Diarrhea, usually severe with nocturnal episodes
- ▶ Abdominal pain and tenderness
- ▶ Weight loss
- ▶ Fever
- ▶ Nausea
- ▶ Anorexia

Knutson D et al. Am Fam Physicians. 2003; 68: 707-716.

30

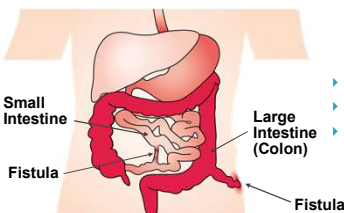
Complications of Crohn's Disease

- ▶ Ulcers
- ▶ **Fistulas** ← Of Particular Importance to Wound Care Clinicians
- ▶ Abscesses
- ▶ Intestinal blockage
- ▶ Extra-intestinal disorders
 - More common in CD than UC
- ▶ Malnutrition
- ▶ Growth failure in children

Hanauer SB, et al. Am J Gastro. 2001;96:635-643.

31

Summary Slide Case 12 CD




- ▶ A tunnel between two sections of the intestines or between the intestines and other organs, including the skin
- ▶ VERY painful
- ▶ Source of Infection
- ▶ Psychosocial problems


32

Complications of CD: Fistulas

Abdominal Fistula



Perianal Fistula




33

Extraintestinal Complications of IBD

- ▶ Acute arthropathy
- ▶ Erythema nodosum
- ▶ Pyoderma gangrenosum
- ▶ Iritis/uveitis
- ▶ Ankylosing spondylitis
- ▶ Primary sclerosing cholangitis
- ▶ "Metastatic" CD
- ▶ Treatment of luminal disease will usually treat these problems as well

34

Aphthous Stomatitis in IBD



Courtesy of J-F Colombel, MD.

35

Extra-Intestinal Complications of Crohn's Disease: Arthritis



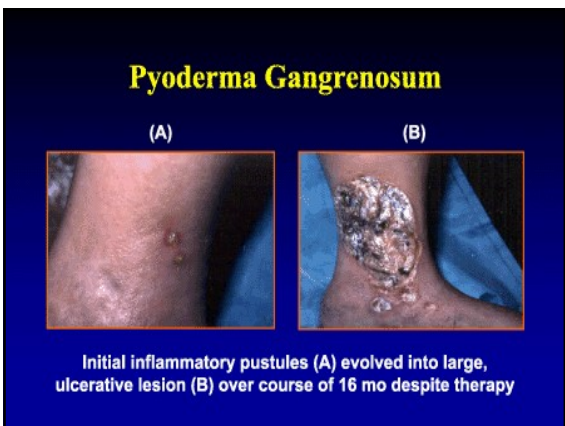
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37



38



39



40

Summary Slides Case 13 Stratifying severity in CD

- ▶ Mild-moderate CD
 - Ambulatory patients who are able to tolerate oral feeding without signs of systemic toxicity
- ▶ Moderate-severe disease
 - Fever, weight loss, abdominal pain, nausea and vomiting, and/or significant anemia
- ▶ Severe-fulminant disease
 - Patients with persistent symptoms despite standard induction regimens or those with signs of severe systemic toxicity.

41

Summary Slides Case 13 Treatment of CD

- ▶ Mild to Moderate Disease (Induction)
 - Budesonide or Corticosteroids
- ▶ Moderate to Severe Disease (Induction)
 - Corticosteroids or TNF Blocking drugs
- ▶ Maintenance Therapy for all types of CD
 - Start 6-MP/Azathioprine if moderate or severe symptoms or relapse occurs. MTX is an alternative therapy. If these agents (or TNF blockers) induced remission continue on those agents

Lichtenstein GR. The Management of Crohn's Disease in Adults. Am J Gastroenterol 2009;104:465-83

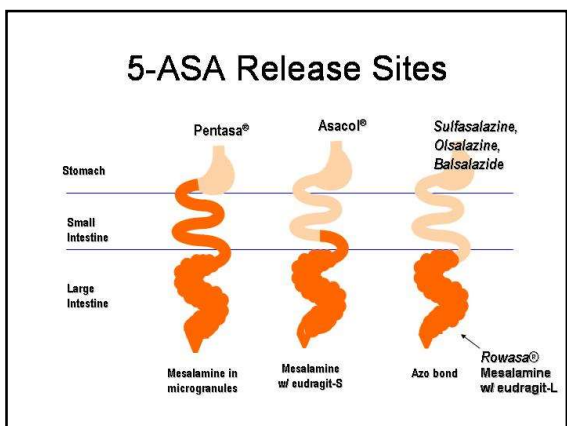
42

Summary Slides Case 13
Treatment of CD 2

- ▶ **Fistulizing disease**
 - TNF Agents (infliximab, adalimumab (Humira) and golimumab (Simponi)) or Surgery
- ▶ **Fulminant Disease**
 - IV Corticosteroids or TNF agents or Surgery
- ▶ **Refractory Disease**
 - Natalizumab/ Vedolizumab or Surgery

Lichtenstein GR, et al. Management of Crohn's Disease in Adults. Am J Gastroenterol. 2019;114(1):1-11.

43



44

5-ASA

- ▶ 5-ASA suppositories are indicated for proctitis, while enema formulations can be useful in IBD confined to the distal colon
- ▶ **ADRs**
 - Sulfasalazine has largely fallen out of favor due to sulfa side effects (fever, rash, nausea, BMS, etc)
 - Mesalamine has fewer ADRs but headache, arthralgias, abdominal pain, and nausea can occur
 - Olsalazine causes diarrhea more than other 5-ASA preparations
- ▶ Balsalazide can increase 6-MP/AZA levels

45

Budesonide

- ▶ Corticosteroid with a high first-pass effect and low bioavailability that is delivered directly to colon
- ▶ Now considered a standard treatment for induction of mild/moderate ileocolonic disease
- ▶ Fewer **short-term** ADRs than traditional steroids, but no data past 1 year of use
- ▶ Still some experts are using the drug long-term in mild CD

46

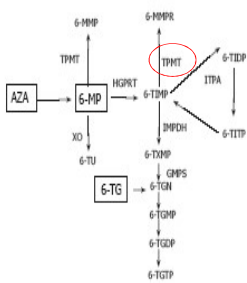
6-Mercaptopurine/Azathioprine (6-MP/AZA)

- ▶ Immunomodulators are the standard agents for maintenance therapy in moderate-to-severe IBD
- ▶ Onset of action is usually weeks to 3 months which often requires steroids in the interim
- ▶ ADRs
 - Rash, nausea, pancreatitis (look for epigastric pain and an increased serum lipase), and diarrhea.
 - Myelosuppression/neutropenia, (monitor the complete blood count monthly for the first 3 months of treatment, then every 3 months thereafter)

47

Summary Slide Case 14 Pharmacogenetic Testing Of ASA/6-MP

- ▶ AZA/6-MP have multiple metabolic pathways
- ▶ TPMT activity is genetically determined
 - LOW TPMT levels = increase risk for neutropenia
 - HIGH TPMT levels = decreased efficacy
- ▶ IBD specialists will check these levels to guide dosing of these agents



Pierik et al. World J Gastroenterol 2006;12: 3657-3667

48


Summary Slides Case 15 TNF- α Blockers

- ▶ Infliximab, Adalimumab, Certolizumab, golimumab
- ▶ Work by blocking Tumor Necrosis Factor- α , which is responsible for much of the pro-inflammatory response in IBD
- ▶ Often effective in refractory disease, but is quite expensive (about \$25,000/yr) and has numerous adverse effects
- ▶ One of the few treatments effective for fistula

49

Summary Slides Case 15 Infliximab in Patients With Fistula

Perianal Fistula Case Study



Pretreatment 2 Weeks
10 Weeks 18 Weeks

Present DH et al. *N Engl J Med.* 1999;340:1398.

50

TNF- α Blockers

- ▶ Infliximab usually started first
 - Most experience with drug
- ▶ Adalimumab
 - usually second-line—if infliximab is not effective or well tolerated

51

α₄β₇ integrin Blockers

- ▶ Natalizumab/ Vedolizumab
 - Inflammatory pathway in gut and brain
 - Former drug implicated in reactivating of JC virus in brain which could lead to progressive multifocal leukoencephalopathy (PML) which is usually fatal
 - Latter drug does not penetrate BBB

In progressive multifocal leukoencephalopathy, lesions appear, gradually demyelinating the nerve cells (white matter) of the brain, causing loss of coordination and weakness

Normal brain Brain with lesions

52

Effective Medications for Smoking Cessation

- Nicotine replacement products
- Over-the-counter (nicotine patch [which is also available by prescription], gum, lozenge)
- Prescription (nicotine patch, inhaler, nasal spray)
- Prescription non-nicotine medications: bupropion SR,² varenicline tartrate
- Counseling and medication are both effective for treating tobacco dependence, and using them together is more effective than using either one alone

SR, sustained release.
http://www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting/index.htm#met

53

Depression Screening

- ▶ Affects 15%–35% of IBD patients
 - Relapsing nature of disease
 - Chronic pain
 - Steroids
- ▶ American College of Preventive Medicine/USPSTF recommend screening

SCREENING QUESTIONS

1. Over the past month, have you felt down, depressed, or hopeless?
2. Over the past month, have you felt little interest or pleasure in doing things?

Siu AL, et al. JAMA. 2016;315(4):380-7

54

Self-Management in IBD

Self-management is critical to patient improvement

- Entails clear goals, understanding of the disease, plan of action to reduce symptoms or prevent disease activity

Psychological issues, shared decision making, and individual patient characteristics should be discussed

- Depends on a good patient/clinician relationship

Kennedy A, et al. Health Educ Res. 2005;20(5):567-578.
Bennett AL, et al. World J Gastroenterol. 2015;21(15):4457-

55

Health Maintenance Summary

- Vaccinations: influenza, pneumococcal pneumonia, zoster, Hep A, Hep B
- DEXA Scan
 - All CD and UC patients with conventional risk factor for abnormal BMD
- Refer to GI to attempt corticosteroid withdrawal
 - 6-MP / AZA, MTX, anti-TNF, Anti-integrin therapy Anti-IL-12/23
- A multivitamin daily; folate, calcium
- Colon cancer surveillance
 - After 8-10 years colonoscopy with biopsies [1-3 years] to assess for dysplasia
- Annual Pap smears if immunocompromised

DEXA, dual-energy X-ray absorptiometry; GI, gastrointestinal; AZA, MTX, TNF

56

Health Maintenance Summary

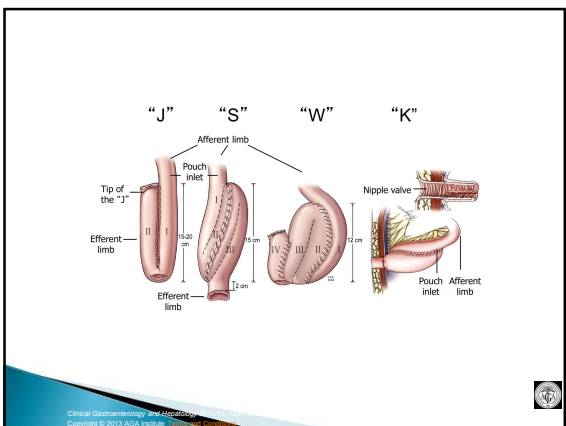
- Frequent dermatological evaluation: melanoma/NMSC
- Beware of NSAIDs in IBD
 - Disease may flare, bleeding may occur
- Beware of other steroid side effects
 - Cataracts, hypogonadism, osteonecrosis, etc.
- Pregnancy
 - Ensure that medications are safe + disease is in remission
- Diagnosis
 - In those with symptoms/signs, remember genetics
 - When EIM present, think of disease

NMSC, non-melanoma skin cancer
NSAIDs, non-steroidal anti-inflammatory drugs; EIM, extraintestinal manifestations.

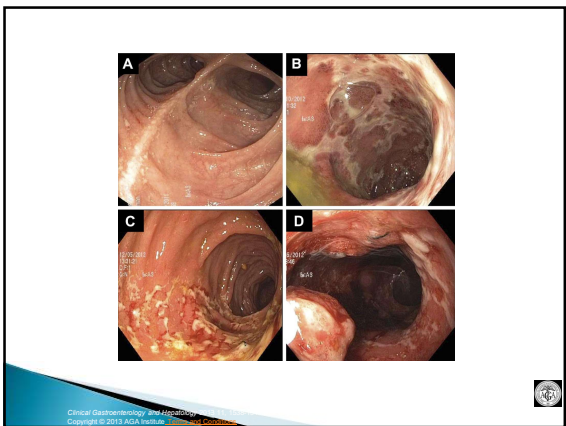
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Pouchitis

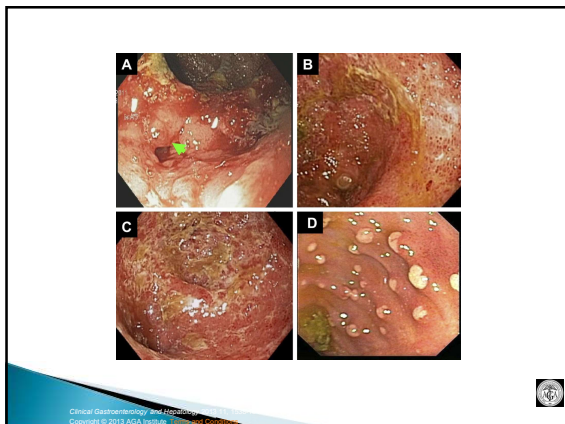
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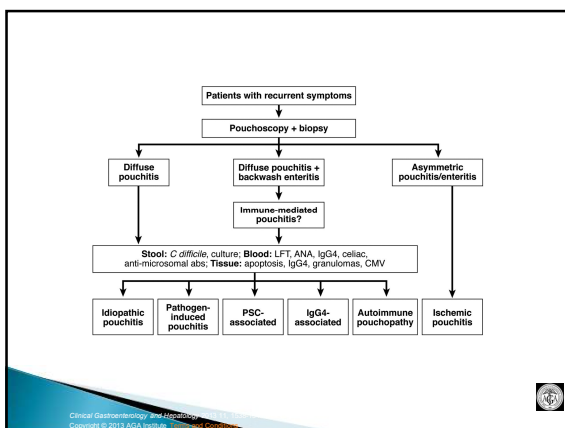
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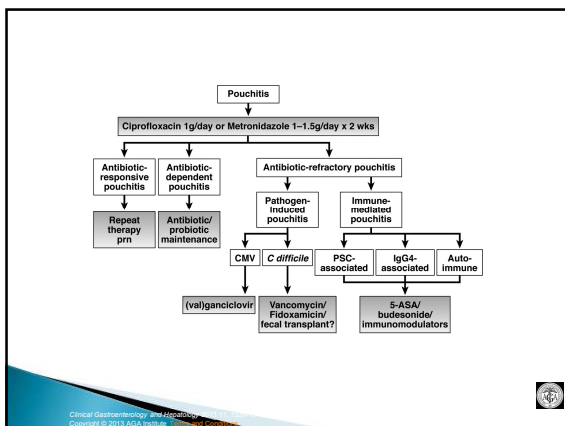
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61



62



63

Conclusions

- ▶ IBD is an uncommon but serious set of diseases affecting primarily the GI tract
- ▶ More therapies available than ever
 - In many patients NO surgery is a goal
- ▶ AS Wound Care Clinicians
 - Look for infections of ostomy or fistula
 - Treatment of Pouchitis
 - Health Maintenance
 - Drug ADRs

64

Questions?

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65
