The Role of the APN in Diagnosis, Treatment and Management of Inflammatory Bowel Disease

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Objectives
By the end of this presentation, the Advanced Nurse Practitioner should be able to:
• Identify the differences between Crohn’s Disease and Ulcerative Colitis
• Determine how each is diagnosed and diagnostic tools used to monitor disease state.
• Understand medications prescribed for Inflammatory Bowel Disease (IBD)
• Know which labs to monitor and vitamin deficiencies to be aware of.
• Understand extra-intestinal signs of IBD
• Know what to tell patients with IBD during pregnancy
• Understand how to manage the psychological effects of IBD
• Identify the need for hospitalization in a patient with IBD
• Understand surgical options for patients

What is inflammatory Bowel Disease?
• Chronic, inflammatory disorder of the GI tract
• Can remit and relapse throughout the course of one’s life
• Includes Crohn’s disease (CD), ulcerative colitis (UC) and indeterminate colitis (10-15% of cases)
Environmental factors that contribute to the development of IBD include all of the following except:
A) Low Vitamin D level
B) Low Vitamin B12 level
C) Smoking
D) Presence of appendix

What causes Inflammatory Bowel Disease?

- Genetic Susceptibility and Heredity
  - Ulcerative Colitis: Inflammatory bowel disease II, chromosome 12q
  - Crohn’s disease: Inflammatory bowel disease I, chromosome 16
    - Gene NOD2/CARD15
    - Patient’s with IBD, earlier age of onset, stricture disease
    - 5% to 20% of affected individuals have a first degree relative with IBD.
    - Risk is greater with Crohn’s disease than ulcerative colitis.
    - Risk is higher when both parents have IBD.
    - Most common among eastern European backgrounds, strong disposition among those of Israeli Jewish descent.
    - Increasing number of cases among African American populations.

What Causes Inflammatory Bowel Disease?

- Environmental Factors
  - Smoking
    - Increased risk for Celiac disease
    - Positively correlated with development and progression
  - Childhood obesity
    - Raising can be protective

- Infections
  - Protective against Crohn’s disease
  - Low phagocytic activity
  - Increased risk of Celiac disease

- Genetic Factors
  - Risk is increased in families with a history of IBD
  - Specific genetic markers associated with IBD

Crohn’s Disease vs. Ulcerative Colitis:
What is the difference?

??QUESTION??

Environmental factors that contribute to the development of IBD include all of the following except:
A) Low Vitamin D level
B) Low Vitamin B12 level
C) Smoking
D) Presence of appendix
True or False: Perianal Disease is a sign/symptom of Ulcerative colitis

Crohn’s Disease

- Patchy, transmural inflammation that can occur from mouth down to anus
- Characteristic “skip” lesions
- Fistulizing or stricturing disease, abscess formation
- 40% involve small and large intestines
- 30% small bowel only
- 25% large bowel involvement
- Signs and Symptoms:
  - Abdominal pain, weight loss
  - Change in bowel habits (diarrhea)
  - Fever, chills, night sweats
  - Anemia
  - Irregular or loss of menstrual cycle
  - Fatigue
  - Perirectal drainage, pain, bleeding (perianal disease)
- Extra Intestinal Manifestations

Floch, Martin H. (2010)
Crohn’s Disease: Perianal Disease

- Major perianal complications:
  - Fissures
  - Fistulas
  - Abscesses
  - Stenosis
- Affects 35-45% of patients
- Detrimental to quality of life
- Often requires surgical management
- Can be extremely painful, uncomfortable


Perianal Crohn’s Disease

- Limited to the colon
- Travels from distal (anus) to proximal (small bowel)
- Inflammation is diffuse, ulcerative, erythematous
- Signs and Symptoms:
  - Recent infectious gastroenteritis
  - Diarrhea with mucus or blood
  - Abdominal pain, cramping
  - FEVERS, chills
  - Racial discomfort/pain
  - Extra intestinal manifestations
- Cured with surgery (proctocolectomy)
Diagnostic Characteristics of Crohn's Disease vs. Ulcerative Colitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Segmental predominance, often proximal</td>
<td>Widespread, distal predominance</td>
</tr>
<tr>
<td>Rectum</td>
<td>Often spared</td>
<td>Often involved</td>
</tr>
<tr>
<td>Microscopic distribution</td>
<td>Often focal</td>
<td>Widespread</td>
</tr>
<tr>
<td>Extent of inflammation</td>
<td>Transmural</td>
<td>Mucous</td>
</tr>
<tr>
<td>Perianal involvement</td>
<td>Often present</td>
<td>Absent</td>
</tr>
<tr>
<td>Stricture</td>
<td>Often present</td>
<td>Absent</td>
</tr>
<tr>
<td>Granuloma</td>
<td>Often present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

??QUESTION???

True or False: Perianal Disease is a sign/symptom of Ulcerative colitis

Medications Used for Achieving and Maintaining Remission

In Inflammatory Bowel Disease
5-Aminosalicylic Acid (5-ASA) Therapies

- First line therapies
- Oral or rectal administration
- Most target/are most effective in ulcerative colitis
- Examples:
  - Mesalamine
  - Sulfasalazine
  - Olsalazine
  - Balsalazide
- Monitoring: Kidney function (q 6 months)
- Potential side effects: pancreatitis, nausea, vomiting, diarrhea, hair loss, decreased sperm count (sulfasalazine).
- Contraindications: Allergy to sulfa, other 5-asa therapies

Steroids

- Corticosteroids (Systemic)
  - Used for inducing remission (short-term use only)
  - Effective, BUT not to be used long-term due to undesirable side effects and risk for adrenal insufficiency.
  - Examples: methylprednisolone, prednisone, hydrocortisone
- Budesonide (Non-systemic)
  - Used for mild-moderate disease
  - Entocort (Crohn’s disease)
  - Uceris (ulcerative colitis)
- Topical Rectal Steroids (Non-systemic)
  - Foams, Enemas and suppositories

Monitor for side effects:
- Moon face: Weight gain
- Acne: Emotional lability
- Insomnia: Cataracts
- Psychosis: Facial Hair
- Hypertension: Weakened bones
- Hyperglycemia: Infections

Slow taper to avoid adrenal insufficiency
Immunomodulators

- **Thiopurines** (Azathioprine, 6 mercaptopurine)
  - Maintenance of remission of IBD, not responsive to 5-asa therapy
  - Very effective in treatment of perianal Crohn's disease
  - Can use with 5-asa therapy, biologics or alone
  - Check thiopurine methyltransferase (TPMT) to determine ability to metabolize
    - Low (high risk for toxicity, side effects)
    - Normal (standard dose of medication)
    - High (may require higher than standard dosing of medication)
  - Dosing: 1.5-2.5 mg/kg/day (25 mg-250 mg/day)
  - Allopurinol
  - Side effects: Pancreatitis (stop medication), nausea, vomiting, headache, malaise, fever, rash, leukopenia, thrombocytopenia, hepatotoxicity, infection, myelosuppression.
  - Two to four fold increased risk of lymphomas, nonmelanoma skin cancers
  - Monitoring: CBC, LFTs, thiopurine metabolites, annual skin exams

- **Methotrexate**
  - Maintenance therapy for Crohn's disease
  - Can be used with 5-asa therapy, biologics or alone
  - Dosing: 10-25 mg PO/SQ weekly + Folic Acid 1 mg daily
  - Side effects: Flu-like symptoms including headache, nausea, malaise
    - Pre-medicate with ondandersteron, acetaminophen
  - Monitoring: CBC, LFTs
  - Contraindications: Pregnancy for women or reproducing males (fetal anomalies), alcohol use (risk for hepatotoxicity).

- **Cyclosporine**
  - Use limited to induction of remission of severe Ulcerative Colitis
  - Initiated inpatient as a bridge to another medication (short-term use only)
  - Side effects: hypertension, nephrotoxicity, neoplasm and infection risk.
  - Contraindication: uncontrolled hypertension, renal impairment
  - Frequent labs: CBC, CMP, cyclosporine trough

Biologic Therapies

- **Anti-TNF Therapies**
  - Work by blocking inflammatory proteins (cytokines)
  - Injections: Adalimumab (Humira), Certolizumab (Cimzia), Golimumab (Simponi)
  - IV infusion: infliximab (Remicade)
  - Screening: Hepatitis B panel, Quantiferon Gold
  - Side effects: Injection site reactions, allergic reaction (anaphylaxis), rash, headache, fever, chills, infections, Tuberculosis, lupus-like reaction
  - Contraindications: Allergic reaction, Tuberculosis, active Hepatitis B
  - Monitoring: CBC, CMP
  - Adalimumab and Infliximab: concentration/anti-drug drug antibody
Biologic Therapies

- **Anti-Adhesion**
  - Block migration of inflammation-producing leukocytes to the gut
  - Anti-α4-integrin: Natalizumab (Tysabri)
    - Treatment of Multiple Sclerosis and Crohn's Disease
    - JC virus testing to determine risk of progressive multifocal leukoencephalopathy (PML)
    - Side effects: allergic reaction, headache, dizziness
    - Contraindications: Allergic reaction
    - Monitoring: Routine CBC, CMP, JC virus every 6 months
  - Anti-α4-B7 integrin: vedolizumab (Entyvio)
    - Approved (May 2014) for Crohn’s disease and Ulcerative Colitis
    - Gut specific, theoretically no increased risk for PML
    - Side effects: Rash, headache
    - Contraindication: Allergic reaction
    - Monitoring: Routine CBC, CMP (every 6 months)

Concomitant Therapies

- Methotrexate, azathioprine, 6-MP can be used in combination with Anti-TNF therapies to help increase drug levels, prevent antibody formation.
- Concomitant therapy not indicated with natalizumab
- Optimize both immunomodulator therapy and biologic therapy for best response.

Nutritional Deficiencies in Inflammatory Bowel Disease
Nutritional Deficiencies in IBD

- Decreased nutritional intake and increased losses (poor digestion and malabsorption) occur as a result of:
  - Small bowel resection and/or diseased small bowel
  - Increased energy expenditure during flares
  - Medications (steroids, methotrexate, sulfasalazine)
  - Restricted diets
  - Bacterial overgrowth

- Deficiencies differ among patients depending on location of disease.

- Most common deficiencies:
  - Water-soluble vitamins: Folic Acid, Vitamin B12
  - Fat-soluble vitamins: Vitamins A, D, E, K
  - Minerals: Iron, Zinc, Calcium, Phosphate, Copper, Magnesium

- Collaborate with your Dietician for Supplementation Recommendations

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Daily Requirements</th>
<th>Signs or Symptoms of Deficiency</th>
<th>Recommended Dose for Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>15 mg</td>
<td>Dry, flaky skin, peeling palms, diarrhea</td>
<td>50 mg PO elemental/day Zinc gluconate/sulfate</td>
</tr>
<tr>
<td>Iron</td>
<td>10-15 mg</td>
<td>Anemia, Fatigue, angular cheilitis, SBE</td>
<td>300 mg PO 3-IV/day Ferrous Sulfate</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>1 mcg</td>
<td>Megaloblastic Anemia, paresthesias, anemia, diarrhea</td>
<td>1000 mcg/day PO/M</td>
</tr>
<tr>
<td>Folate</td>
<td>400 mcg</td>
<td>Sore mouth, glossitis, diarrhea, Megaloblastic Anemia</td>
<td>1 mg/day</td>
</tr>
<tr>
<td>Calcium</td>
<td>800-1500 mg</td>
<td>Osteopenia, Osteoporosis, bone pain</td>
<td>1500-2000 mg/day</td>
</tr>
<tr>
<td>Magnesium</td>
<td>400 mg</td>
<td>Nausea, Atyrhythmias, muscle weakness</td>
<td>350mg elemental Mg 4x/day (Mg gluconate/sulfate)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>400 IU</td>
<td>Bone pain, muscle weakness, bone pain</td>
<td>1,000 IU daily</td>
</tr>
</tbody>
</table>

Nutritional Deficiencies in Inflammatory Bowel Disease

- Iron Deficiency Anemia: Microcytic, Hypochromic
  - CBC
    - MCV (decreased)
    - MCHC (decreased)
  - RDW (increased)
  - Iron Panel
    - TIBC (increased)
    - % Saturation (decreased)
    - Serum Iron (decreased)
  - Ferritin
    - Intracellular protein, store iron
    - Serves as an earlier indicator of anemia
  - Try oral iron first (Ferrous sulfate, gluconate)
  - IV Iron Infusions (Injectafer, Venofer)
Pertinent Diagnostics Tests in IBD

“T’ll do some tests rather than give you a guess.”

Diagnosing IBD

• Clinical manifestations/symptomatology
  – Growth failure in children
• Serologic markers in IBD
• Stool markers
• Endoscopy
• Imaging
  – UGI/SBFT, MRI, CT
• Other modalities
  – Capsule endoscopy

IBD SEROLOGY
ANCA & ASCA

ANCA
- Anti-Neutrophilic Cytoplasmic Antibody
  - "p" = perinuclear
- ASCA
  - Anti-Saccharomyces Cerevisiae Antibody
    - Antibodies directed against common brewer’s yeast.

Useful IBD Serology

- CBC
  - Anemia
- CMP
  - Elevated alkaline phosphatase
  - Low albumin
- Elevated ESR (more common in children)
- Vitamin deficiencies

Stool Studies

- Fecal calprotectin
  - Measures the amount of inflammation in the intestine
  - Elevated in IBD patients
  - In a meta-analysis including six studies with 670 adult patients, the presence of fecal calprotectin was 93% sensitive and 96% specific for identifying patients with IBD
- C. difficile
- Stool cultures, O&P
  - Campylobacter
Non-Serologic Diagnostic Studies

- Evaluation of small bowel disease
  - CT enterography
  - MR enterography
  - SBFT
  - Capsule endoscopy
- Evaluation of colonic disease
  - CT abd/pelvis
  - MRI abd/pelvis
  - Colonoscopy
  - Flexible sigmoidoscopy
- Evaluation of perianal disease
  - MRI abdomen/pelvis
  - EUA

Endoscopic Severity Index for Ulcerative Colitis

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
</table>
| • Granular mucosa  
  • Edematous  
  • Loss of normal vascular pattern | • Coarsely granular  
  • Small ulcerations  
  • Friable | • Frank ulcerations  
  • Spontaneous hemorrhage |

Endoscopic Appearance of Crohn’s Colitis

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
</table>
| • Loss of normal vascular pattern  
  • Edema | • Deep, linear “bear claw” ulcers | |
Small Intestinal Crohn’s Disease as Seen by Wireless Capsule Endoscopy

Images compliments Russell Cohen, MD

MR ENTEROGRAPHY
Ileal and Jejunal Inflammation and Stenoses

Enteroclysis MRI, no IV gadolinium MRI with gadolinium

Important reminders when ordering tests

- All ways get biopsies with EGDs and colonoscopies
- DO NOT order a capsule endoscopy on a pt with a known stricture!!
- CT scan is best imaging tool to assess for abscess
- MRI is best imaging tool to assess for fistula
- Limit the amount of radiation you expose your patient to!!

?? Question ???

A patient with known IBD presents to your office with fevers and abdominal pain. You are concerned for infection. What is the best possible test to order to assess for an abscess?

A: MRI abdomen/pelvis
B: Colonoscopy
C: Small Bowel Follow Through
D: CT abdomen/pelvis

Extra-Intestinal Disease
Manifestations of IBD
Inflammatory Bowel Disease can effect other areas and organs of the body outside of the GI tract.

A: True
B: False

Extra-Intestinal Disease Manifestations of IBD

Types:
• Joint disorders
• Ocular disorders
• Skin disorders
• Hepatobiliary
• Renal
• Other manifestations

Extra-Intestinal Disease Manifestations

• Most parallel course of IBD and respond to IBD treatment

• No correlation with IBD disease course or treatment for:
  ✓ Ankylosing spondylitis (AS)
  ✓ Uveitis
  ✓ Primary sclerosing cholangitis
Peripheral Arthritis in IBD

- Most common extraintestinal manifestation
  - More common if also other EIM
- Occurs in 5% to 20% of patients with IBD
  - CD: 9% to 20%
  - UC: 10%
  - Males and females equally
- Usually asymmetric, migratory; large lower extremity joints affected more than upper
- Cartilage or bone destruction is rare

Peripheral Arthritis in IBD: Treatment

- Usually responds to IBD treatment
- Rest
- Physical therapy
- Intra-articular steroid injection

Ankylosing Spondylitis (AS):

Epidemiology

- Can occur without associated bowel disease
- Commonly starts in 2nd or 3rd decade of life
- Associated with HLA-B27 phenotype
- Male-to-female ratio 2 to 3:1
- Etiology uncertain – includes genetic, immunologic, and environmental factors
Ankylosing Spondylitis (AS): Disease Course

- Course is variable for each patient but most often is progressive
- Not related to IBD activity
- Leads to permanent skeletal damage
  - Squaring of vertebral bodies
  - Marginal syndesmophytes
  - Bony proliferation
  - Ankylosis (bamboo spine)

Aphthous Stomatitis in IBD

- May be seen in either Crohn’s or UC
- Common in children with Crohn’s disease
  - Occurs in about 10% of children with IBD, about 3x more common in CD
- Treatment includes:
  - Treating underlying disease
  - Topical oral solutions to provide pain relief (vexcous lidocaine, “magic mouthwash”)
  - May resolve on their own

Episcleritis

- Occurs in 2-5% of patient with IBD
- S&S:
  - burning, itching, injected slera
- Treatment:
  - directed at underlying IBD and topical glucocorticoids
Uveitis

- Less common
- Requires prompt diagnosis and treatment
- S&S: bilateral eye pain, blurred vision, photophobia, headaches
- Treatment:
  - Topical
    - Dilating drops
    - Intraocular corticosteroids
    - Intraocular implants
  - Systemic
    - Corticosteroids: oral, IV
    - Immunomodulators
    - Infliximab for patients with refractory disease!

Ankylosing Spondylitis (AS):

Epidemiology

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- Etiology uncertain – includes genetic, immunologic, and environmental factors

Erythema nodosum in IBD

- Occurs in 10% to 20% of patients
- Hot, red tender nodules usually on extensor surfaces of lower extremities
- Activity correlates with IBD activity
- Often occurs in conjunction with peripheral arthritis
Erythema nodosum in IBD: Treatment

- May resolve as underlying IBD is treated
- May require systemic corticosteroids or immunomodulatory therapy
- Case reports of successful treatment with infliximab

Pyoderma gangrenosum in IBD

- Occurs in 1% to 10% of patients
- More common in UC than CD
- Typically on extensor surface of lower extremities
- Begins as erythematous pustule or nodule
- Becomes burrowing sterile ulcer with irregular edges

Pyoderma gangrenosum in IBD: Treatment

- Oral sulfasalazine / S-ASA's
- Dapsone
- Corticosteroids
- Immunomodulators
  - AZA
  - Tacrolimus
  - Cyclosporine
  - Mycophenolate mofetil
  - MTX
  - Cyclophosphamide
  - Infliximab

References:
- Foster EN et al. Gastroenterology. 2002;122:A618
Primary Sclerosing Cholangitis

- Most patients asymptomatic, may have fatigue or pruritus
- How is it diagnosed?
  - Abnormal LFTS (high alk phos)
  - Referral to hepatologist
  - Confirmed with MRCP/ERCP or liver biopsy
  - Annual surveillance colonoscopies !!!!
- High rate of colon cancer
  - If any dysplasia, they need surgery!
- High rate of cholangiocarcinoma – refer pts with PSC to transplant center!

Hypercoaguable State

- Coagulation and inflammation
  - Activation of coagulation is part of inflammatory process in IBD
  - Primary coagulopathy: active thrombin can stimulate inflammation
- Incidence of thromboembolism ranges from 1.3% to 39%
  - Deep vein thromboses
  - Pulmonary emboli
  - Cerebrovascular accidents
  - Arterial emboli

Hypercoaguable State in the Hospitalized IBD Patient

- Must give heparin SUBQ TID or low molecular weight heparin.
- If DVT / PE: you should anticoagulate, just as you would patient without IBD
  - Heparin has been shown to be anti-inflammatory as well.
Inflammatory Bowel Disease can effect other areas and organs of the body outside of the GI tract.

A: True
B: False

A patient with IBD comes to see you for a routine visit and tells you that she is 6 weeks pregnant and has stopped her balsalazide because she is pregnant.

A correct response would be:
A: “Good job! Do not take the balsalazide unless you start to flare.”
B: “You should restart the balsalazide but only take ½ the dose because it’s safer.”
C: “You should stop the balsalazide and take methotrexate instead.”
D: “Restart the balsalazide at the dose you were previously on. It is important to maintain remission while pregnant and balsalazide is Pregnancy Category B. Please contact your IBD doctor with further questions.”
Safety of IBD medications during pregnancy

Category B:
- Oral, topical mesalamine
- Balsalazide
- Sulfasalazine
- Corticosteroids
- Budesonide
- Loperamide
- Anti-TNF agents
- Metronidazole*

Category C:
- Ciprofloxacin
- Diphenoxylate
- Tacrolimus
- Olsalazine
- Cyclosporine
- Asacol HD
- Natalizumab

Category D:
- Azathioprine
- 6-Mercaptopurine

* Safe for use after first trimester. † Increasing use in pregnancy.


IBD Medications to AVOID During Pregnancy

- FDA Category “X” – positive evidence of serious fetal abnormalities
  - Methotrexate
  - Thalidomide

IBD Pregnancy “Potpourri”

- Imaging:
  - Ultrasound
  - MRI (no gadolinium 1st trimester)
  - CT (after 25 weeks if required)
- Sigmoidoscopy rather than colonoscopy
- Sedation:
  - None
  - Meperidine: Class B
  - Fentanyl: Class C
  - Versed: Class D
- C-section if perianal disease !!
IBD Flare in Pregnancy

- PREVENT the flare by continuing effective therapy at conception.
- TREAT flares quickly with fast acting agents (corticosteroids, anti-TNF agents)
- MAINTAIN on therapy to keep well; limit corticosteroid exposure if possible.
- Anti-TNF agents seem to be safe and effective.
- Surgery may be required if refractory; timing to 2nd trimester if possible.

IBD Surgery During Pregnancy

Timing
- 2nd trimester preferred
  - Important pieces already developed
  - Baby not too big to interfere with surgeon
  - Vice versa

Procedure
- Loop ileostomy:
  - Shorter procedure
  - Less “mucking around” in the belly
  - Immediate need for surgery often resolved

?? Question ??

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How to manage the Psychological Effects of IBD

• Transitioning from Pediatric to Adult provider (ease into change)
  - Transition Clinic
    - Dr. Stacy Kahn (Peds GI)
    - Dr. David Rubin (Adult GI)
  - Communication
    - Moving from speaking through parents to speaking only to patient
    - Dealing with difficult family members
      - Importance of updating with plan of care (especially important)
      - Addressing that pt must take responsibility for his/her own healthcare
      - Importance of addressing how adult side may function differently from pediatric side to avoid anxiety with change

• Psychiatric Consultation
  - Multiple issues with chronic illness
  - Surgical implications (body image disturbance/scar/fear of additional surgery down the road)
  - Loss of control

Psychological Issues

• Historically in the 1930s, Gastroenterologists and Psychiatrists suggested emotional life events/experiences are likely r/t exacerbations of intestinal symptoms.

• At that time, IBD was considered a psychosomatic disease, and its relation to stress and other psychological factors was thought so strong, researchers felt no use for any controls
  - Environmental factors
  - Genetic
  - Antibiotic use as a child
  - NSAID use

• For awhile it was considered an organic disease, psychological influences were then discounted.
  - Further anecdotal and clinical observations indicate stressful experiences could adversely affect the course of IBD.

• Now major trends in recent studies were to differentiate CD from UC patients, to utilize the notion of perceived stress, which emphasizes on one’s subjective perception of stress and his/her response to it

Possible Mechanisms of Effects of Psychological Stress on Patients with IBD

• Nonspecific
  - Brain-gut axis: nerve plexus between the enteric nervous system and its spinal and autonomic connections to the CNS
    - Can be affected by psychological and emotional stress directly/indirectly through this axis
    - Symptoms as abdominal pain/change in bowel function occur in IBD when stress alters the sensory and motor function

• Intestinal Permeability
  - Stress can increase intestinal permeability alterations in cholinergic nervous system and mucosal mast cell production
  - Soderholm and Perdue (2001) pointed out various types of physical/psychological stress that increase secretion of ions, water, mucus, and IgA
  - Increased permeability reduces mucosal barrier function and alters bacteria-host interaction
Psychological Issues

• Immunological Mechanisms
  - Stress is likely to mediate its affect on IBD via the immune system
  - On one hand, it is believed that an inadequately controlled response within the intestinal mucosa leads to inflammation in pts who are genetically predisposed to IBD.
  - Dysfunction of the intestinal immune system and cross-reactivity of its cells against host epithelial cells have been implicated as major mechanisms by which inflammatory response occurs.
  - On the other hand, the hypothalamus-pituitary-adrenal (HPA) axis, autonomic nervous system, and enteric nervous system can interact directly with the immune system.
  - Cytokines are essential molecules in the pathogenesis of IBD
  - Many researchers reported that chronic/acute stress can alter profiles of Cytokines

• Indirect Effects
  - Actions that promote recurrence
    - Noncompliance
    - Smoking (if CD, can help at times with UC)

Caring for the Difficult Patient/Family

• Empathizing with those Coping with IBD
  - When one is given the diagnosis of IBD, uncertainty, unpredictability, and chronic course of the disease can cause a wide range of psychosocial and interpersonal concerns of patients.
  - Loss of control of bowel function
  - Impairment of body image (what if I need an ileostomy?)
  - Fear of sexual inadequacy (prolonged steroid use, hair growth with Cyclosporine)
  - Social isolation of dependency
  - Fear of not reaching full potential (failure to thrive, fear of death, life long TPN)
  - Fecal incontinence (feeling dirty)
  - Feelings of self-unworthiness
  - Stigma (difficult personality assumption)

Management of Disorders in Patients with IBD

• Effect on psychological interventions on IBD Activity
  - Psychological intervention aimed at stress reduction may potentially reduce disease activity
  - Neiss et al and Thornton and Anderson proposed psychological interventions such as relaxation training influence stress-mediated alterations of the immune system.
  - More work needed to assess proposal that psychological approaches could affect the course of IBD itself

• Potential Psychosocial Therapies
  - Stress management, relaxation training, and IBD focused counseling have useful both for psychosocial problems and the clinical symptoms of IBD
  - Improving Patient's Control
    - Whereas medical adherence focuses on compliance to doctor's orders and medications, psychological engage the pt in treatment process

• Antidepressants
  - Tricyclic antidepressants have been reported to alleviate psychological distress, but also have side effects of helping to reduce pain, irritability, and urgency of defecation.
Psychological Issues

- Personality traits
  - Some pts with IBD feel their own personality is a major contributor to the development of their IBD.
  - Thornton and Anderson (2006) suggest personality can modulate the relationship between stress and the immunological reaction to it.
    - Neuroticism
      - Most reported personality trait in IBD population
      - High neuroticism scores reduce psychological well-being, psychological adjustment, and quality of life with IBD
    - Perfectionism
      - Negative impact on IBD can be explained by its relationship with negative cognitive biases, heightened reactivity to stressors, feeling pressure to look “perfect”
      - Trait associated with emotional preoccupation coping and maladaptive way of coping w/the disease
  - Alexithymia
    - Studies shown to be another common personality characteristic in IBD patients.
    - Difficulty recognizing and verbalizing emotions, and their ability to regulate emotions and express them to others is reduced.
    - Drossman and Ringel (2004) reemphasized that although not specific to IBD, may lead pts to communicate their psychological distress through somatic and behavioral symptoms rather than verbal communication
      - May happen particularly when pts have limited perceived social support or personality trait as introversion
  - Although discrete personality traits have been studied among the IBD population, no certain type matches this disease to date.
  - It is recommended that further research considers discrete personality traits observed, so they can be integrated into types as D and C, which are unregulated immune and hormonal systems that are characteristic of IBD.

- Anxiety and Depression
  - Awareness of incurability, uncertain course of prognosis, fear of surgery and fear of developing cancer likely contribute to anxiety
  - Seligman’s theory (2004): unpredictable and incurable course of disease impairs and individual’s belief about self control and self-efficacy, and thereby causing helplessness and predisposing the pt to depression
  - While some researchers found no evidence of any psychiatric disorders and either CD or UC, others confirmed depression and anxiety are common in IBD pts.
    - Prevalence of anxiety and/or depression has been estimated to be as high as 29-35% during remission
    - 80% for anxiety during relapse
    - 60% for depression during relapse
    - Anxiety more prevalent than depression in IBD
Psychological Issues

• Anxiety and Depression
  - Controversy if psychological disorder precede and/or follow onset of IBD
  - Kurina et al. used a database of linked hospital abstract records, in a retrospective nested case control study of 12,499 pts (7268 UC and 5231 CD) and 800,000 controls with minor medical conditions, not r/t conditions of interest
    - Found both depression and anxiety preceded UC (but not CD) significantly more often than would be predicted by chance.
    - Relationships were strongest when medical conditions were diagnosed shortly before UC.
    - However, these disorders were significantly more common after the diagnosis of CD, and UC was followed by anxiety, not depression.

• In contrast Tarter et al reported anxiety prior to diagnosis was common in CD, but found no significant antecedent psychological disorder in UC.
  - These researchers studies 53 consecutive IBD pts including 26 CD and 27 UC patients, 28 healthy controls.
  - In this study compared to normal controls, CD pts manifest an increased prevalence of depression, anxiety, and panic disorder occurring at any time in their life.
  - Only panic disorder had excess prevalence in CD.
  - Individuals with UC did not demonstrate increased prevalence of psychiatric disorder before or after disease onset.
  - It is difficult to reconcile these two divergent findings, as neither study was appropriately controlled. Kurina et al’s group was substantially larger and had substantial methodological strength.
  - Psychological data suggests these mood disorders can stimulate production of proinflammatory cytokines and therefore adversely affect the course of IBD.
  - Priority to pay careful attention to possibility of mood disorders in pts with IBD.

Psychological Issues

• Quality of life
  - Life expectancy same as healthy individual, but quality of life greatly impacted.
  - Chronicity of IBD
  - Complications (abcess, stricture/recurrent obstruction, fistulas)
  - Physician visits/hospitalizations (time away from school/work, scheduling medication infusions)
  - Side effects of medical treatment (moon faces/weight gain with prolonged steroid use, hair growth with Cyclosporine)
Identifying the Need For Hospitalization

- APN/RN Triage
  - Phone call/direct page with symptoms, failing of current plan (home)
  - May be directed to ED if significant symptoms (anemic, SOB, intolerable pain, persistent obstruction)
  - Direct admit from clinic after direct evaluation
  - Clinic APN notifies inpatient APN of admission and plan of care/orders
  - OSH transfer request
    - OSH MD must initiate transfer request
    - OSH MD can directly contact our transfer center to request transfer
    - APN can call transfer center to state transfer was accepted by one of our IBD attending's

Need for Hospitalization

- What needs to be done prior to admission?
  - Negative stool studies (c.diff, Ova and Parasites, Stool Culture)
  - Did the patient try and fail a 7-day course of po Prednisone
  - Willingness for admission (refusing of IV steroids)
Admission – Cyclosporine Initiation

- 32 y.o. female with a history of Ulcerative Colitis initially maintained on Mesalamine and 6MP, who developed mastitis during breastfeeding. She was prescribed a course of Clindamycin by her GYN. Began with watery bloody BMs up to 15 times/day with urgency and abdominal cramping. She was found to be c.diff positive and started on po Vancomycin therapy. She had some improvement, but still with 8-10 watery BMs/day, despite addition of po Prednisone 40mg/day for 7 days. She was admitted for IV steroids and Remicade was initiated. She improved and was discharged on a steroid taper, but then again lost response, despite dose escalations of Remicade. She is admitted from home for planned initiation of Cyclosporine.

Work-up

- Stool Studies (repeat c.diff, O&P, stool culture)
- Cholesterol (>100?)
- Blood cultures if febrile
- Basic labs: CBC w/diff, BMP, Mag (can decrease with Cyclo), Phos, Creatinine (can increase with Cyclo)
- TPMT (thiopurine methyltransferase)
- Blood pressure
- Past seizure activity?

GETTING THINGS STARTED

- Is infection negative and labs WNL?
- Cyclosporine is initiated at 2-4mg/kg in addition to Solumedrol 20mg IV BID
- Trough level drawn 48 hours after initiation
- Goal target 300-400 with continuous infusion
  - Side Effects
    - Tremor
    - Elevated BP
    - Elevated creatinine
    - Seizure
  - NO NARCOTICS OR NSAIDS
    - Ultram or Tylenol fine
WHAT ARE WE LOOKING FOR?
- Along with a therapeutic range, we need to see the following before changing the patient over from IV to po regimen
  - Patient needs to be "perfect"
    - Decreased stool frequency (1-3 BMs/day)
    - No urgency
    - Formed BMs
    - Able to pass flatus without passing stool (can pt differentiate?)
    - No pain
    - Decreased blood (may not completely dissipate as mucosal healing can take time)

PATIENT IS PERFECT, NOW WHAT?
- Patient is perfect, now what?
  - One thing at a time
    - Solumedrol is changed to 40mg po daily (or split dosing, 20mg BID).
    - 24 hours later, if pt well, change Cyclosporine from IV to oral. Oral dose is IV dose twice daily (example: 175mg/kg continuous IV equals 175mg po BID).
    - Pills come in 25mg increments.
    - Check Cyclosporine trough prior to fourth oral dose (target 200-300)
    - Imuran initiated at low dose 50mg daily. Will be titrated gradually to 2.5mg/kg.
      - Very close clinic follow-up for level/symptom management
      - Once therapeutic on Imuran (6-8 weeks), Cyclo will start to be tapered
      - Most recently, have been bridging to Vedolizumab (Entyvio). Majority of patients have been found to respond by week 10 on Vedolizumab (Entyvio).

WHAT HAPPENS IF CYCLOSPORINE FAILS?
- Surgery
  - 2-pouch option if pathology consistent with UC (colectomy, IPAA, takedown)
- Permanent ileostomy
- Medical Therapy
  - If Cyclosporine had been tried first, Remicade could have been an option as can induce remission.
Admission: Remicade Initiation

- 28 y/o male with a one year history of Ulcerative Colitis. He had initially done well with Mesalamine, but was recently admitted to an outside hospital with a flare. He had been admitted the week before, did well on IV steroids, and was discharged home, but again, did poorly on po Prednisone. He transfers to us for further management. Colonoscopy shows moderate to severe Ulcerative Colitis.

WORK-UP

- Is infection negative and labs WNL?
- Quantifuran Gold (gold standard especially when on IV steroids)
  - Travel history?
  - Previous TB exposure?
  - History of positive TB test?
  - Cough?
- Hepatitis B, C antigen/antibody
- CXR (in event of indeterminate Quantifuran Gold)
- Stool Studies (O&P, c.diff, stool culture)
- Basic labs: CBC/diff, CMP, Mag, Phos

HISTORY IS EXTREMELY IMPORTANT

- Active infection (recurrent cuts/sores/fevers)?
- Heart failure or other heart conditions?
- Blood problems (leucopenia, neutropenia, thrombocytopenia, pancytopenia)?
- Easy bruising/bleeding/paleness?
- h/o lymphoma or other cancers?
- Condition of the nervous system (MS)?
- Pregnancy or nursing?
- Received or scheduled to take live vaccine?
- Taking any other TNF (Humira, Cimzia, Enbrel)?
- Lupus-like symptoms (chest discomfort, recurrent rash)?
WORK-UP NEGATIVE, NOW WHAT?

- **Administer Remicade at 5mg/kg**
  - We may do an escalated dose of 10mg/kg for patients that have severe disease to hopefully attain remission quicker
- **Infusion 2 hours in duration with vitals**
  - Initiate at 10mL/hr x 15 minutes
  - Increase to 20mL/hr x 15 minutes
  - Increase to 40mL/hr x 15 minutes
  - Increase to 80mL/hr x 15 minutes
  - Increase to 160mL/hr x 10 minutes
  - Increase to 250mL/hr x 30 minutes
- **Continue IV steroids**

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**Side Effects**

- **Mild**
  - Pruritus/rash
  - Lightheadedness with <20-point drop in systolic BP
  - Drowsiness without slurred speech
  - Tachycardia
  - Tachypnea
  - Non-syncope with temperature elevation
  - Headache
  - SOB
  - Warmth without temperature elevation
  - Flushing without wheezing

- **Treatment**
  - Pause Remicade infusion
  - Give Benadryl 25mg po x 1
  - Give Tylenol 650mg po x 1
  - Monitor vitals every 10 minutes
  - Increase infusion rate as tolerated when patient is stabilized

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**Moderate**

- Pruritus and/or rash
- Hives without respiratory difficulty
- Wheezing without dyspnea
- Hypertension or hypotension with greater than 20-point, but less than 40-point drop in systolic BP
- Severe hypotension
- Fever

- **Treatment**
  - Pause infusion
  - Give Benadryl 50mg IVP x 1
  - Give Tylenol 650mg po x 1
  - If wheezing present, give Hydrocortisone 100mg IVP x 1
  - Monitor vitals q 10 minutes
  - Restart infusion after symptoms resolve and vitals stabilize
Side Effects
- Severe
- Dyspnea with wheezing
- Dyspnea requiring ventilator support
- Cardiopulmonary symptoms or urticaria
- Hypotension with greater than 40 point drop in systolic BP
- Stridor (call for emergency support)

Treatment
- Stop Remicade
- Maintain NS at 100mL/hr
- Give Benadryl 50mg IVP x 1
- Give Tylenol 650mg po x1
- Give Hydrocortisone 100mg IVP x 1
- Monitor vitals every 10 minutes
- If indicated: give Epinephrine (1:1000) 0.1 mL – 0.5 mL subcutaneous; may repeat every 5 minutes x 3
- Call for emergency support
- Start oxygen to keep saturation > 90%
- Transfer to ICU if needed

What are we looking for?
- Response
  - Some patients have a quick response 1-2 days post-infusion (decrease frequency/urgency/pain/CRP)
  - If they improve, but are not perfect, we can transition to po prednisone and discharge them and reassess after their second infusion (0, 2, 6, then 8 weeks)
  - If they improve some, we can also opt to give the second infusion a week early.
  - If no improvement, we can consider Cyclosporine or surgery, however, need to consider impact of dual immunosuppression.

Outpatient planning
- Insurance approval
  - Insurance card given to prior auth RN to set up outpatient infusions as soon as we know we are giving Remicade, to avoid delays
- Follow-up
  - Typically after 2nd infusion, so that we can assess response rate and begin to taper Prednisone
  - Patient will continue infusions as scheduled: can increase dose, or decrease frequency over time if patient has loss of response
  - Able to check drug levels helpful if responded initially, then loses response.
Surgical Options

- Ulcerative Colitis
  - Total proctocolectomy with permanent end ileostomy
    - Removal of colon, rectum, and anal opening sutured closed.
  - Staged J-Pouch surgery (typically 3 stages, 3 months apart)
    - Colectomy with end ileostomy and Hartmann’s Pouch
    - Ileal pouch anal anastomosis (IPAA) – diverting ileostomy
    - Ileostomy takedown

- Crohn’s
  - Ileocectomy
    - Removal of distal ileum and cecum
  - Ileocolonectomy
    - Removal of distal ileum and larger portion of colon
  - Small bowel resection
  - Subtotal colonic resection

Surgical Treatment

- Strictureplasty
Surgical Procedures
- Diverting Ileostomy
  - Used in perianal disease or to help heal anastomosis
  - Exam under anesthesia with abscess drainage/seton

Role of the APN in Post-op Care
- Post-op patients that are followed by a Gastroenterologist at UCMC are seen by myself daily as a consult
  - Medical plan formulated so that
    - Pt can resume necessary meds timely to prevent recurrence
    - Pt's are not left on steroids for longer than necessary
    - Post-op scope can be scheduled as well as subsequent appointments with NP or attending
    - Pt seen on same day and at same appointment in clinic to avoid having the patient return again for medical follow-up on a different day
    - Gastroenterologist at UCMC is updated everyday, from day of surgery until day of discharge
    - Local Gastroenterologists are kept in loop by sending of op/path/clinic notes with recommendations

Importance of Medical/Surgical Team Relationship
- Patients feel reassured that both of their "teams" are involved in their care
- Shows a multidisciplinary approach that improved pt satisfaction
- There is no uncertainty about what the medical plan will be or how the surgeons feel about the medical plan, as all is discussed when pt is recovering inpatient
- Pt has a well formulated plan before discharge and follow-up with both the same day, so less room for confusion
- Both teams have APNs, which greatly improves continuity, as residents/fellows change monthly, so reassuring to pt's to see a familiar face, especially with recurrent admissions/complications.
- APN is often the pt's "life-line" to his/her attending.