Disclosures

- I do not have any disclosures to report that affect the content of this presentation.
- I have served as a speaker for Abbott Nutrition and Centocor.
- I am the primary investigator for the pediatric trial for Certolizumab (UCB Inc).
- I am the primary investigator for a pediatric registry for Centocor.

Outline

- Introduction
  - Cases
  - Definition
  - Epidemiology
  - Pathoetiology
- Diagnosis
- Therapeutic Options
- Research
- Conclusion

A little bit of history.....

- In 1932, Dr Burrill Bernard Crohn, a Jewish-American gastroenterologist affiliated with Mt. Sinai Hospital in New York City published a description of 14 cases of terminal ileitis that came to be known as “Crohn’s disease.”

Distinguishing IBD

- 12 y/o Caucasian male presents to your office with a 6 week history of increased diarrheal consistency stools, no overt evidence of bleeding, but heme-occult positive in your office.
- Complains of a 7-8 pound weight loss during that time.
- Complains of right lower quadrant tenderness and low grade fever.
- Family history: mom has Crohn’s disease
- Ethnicity: Jewish

- 15 y/o African American male presents to your office with a 4 week history of bright red blood per rectum, going 8-10 times per day.
- Patient appears pale and a CBC reveals a hemoglobin of 5, platelets of 750,000 and WBC 18.
- Patient has tenderness in the left lower and upper quadrants.
- No significant weight loss of growth failure.
- No family history.
6 y/o Asian American female presents with a 4-5 month history of joint pain.
On further questioning, associated vague abdominal cramping and foul smelling flatulence.
Joint pain is typically localized to a single joint, complains of knee swelling and ankle swelling with pain on movement.
Rectal exam reveals heme positive stools and multiple perianal tags.

14 year old Caucasian female presents with growth failure.
Growth and weight are below the 3%.
Sexual development is Tanner 1 with no evidence of menarche.
Patient has recently developed raised exquisitely tender lesions on the extensor surfaces of her legs, dermatologist diagnosed erythema nodosum.

Inflammatory bowel disease is a chronic relapsing and remitting condition involving the gastrointestinal tract as well as extra intestinal manifestations.
It is a systemic disease with the primary site of involvement being the gastrointestinal tract.
Includes the disease spectrum of
- Crohn's Disease
- Ulcerative Colitis
- IBD Unclassified (formerly indeterminate colitis)

Can involve the gastrointestinal tract from mouth to anus, propensity for the TI
- Granulomas
- “Skip” lesions
- Rectal sparing
- Strictures
- Fistulas
- Growth failure
- No cure

Localized to the large intestine, starting distally and extending proximally
- Granulomas uncommon
- Continuous inflammation
- Rectal involvement
- No strictures (carcinoma)
- No fistulas
- Growth issues uncommon
- Surgery is curative

Abdominal pain
Diarrhea
Hematochezia
Growth/Weight problems

Type of disease: Crohn's, UC, IBDU
Location: upper tract, small bowel, large bowel, perianal
Behavior: inflammatory, penetrating, stricturing
Clinical Variability

- The clinical variability is highly dependant on the involved location of diseases.
- For example, small bowel disease is more likely to lead to occult bleeding associated with growth failure or weight loss.
- On the other hand, large bowel disease often presents with bright red bleeding, anemia, and less likely associated with growth failure or weight loss.
- IBD does not discriminate by age, sex or ethnicity.

Epidemiology

- Several unique features of the disease
  - A North-South gradient –
    - Higher incidence in countries within the Northern hemisphere.
    - Rarely diagnosed in South America and Africa.
    - Within both Europe and North America, higher incidence of disease in the northern latitudes.
  - Male to female ratio 1:1
  - Two peaks in diagnosis
    - 15-30 years of age (2nd to 3rd decade of life)
    - 60 years of age (5th to 6th decade of life)

Worldwide Incidence Rates of Crohn’s Disease

- Olmstead County, MN
- Cardiff, Wales
- Rochester, NY
- Iceland
- Aberdeen, Scotland
- Helsinki, Finland
- Florence, Italy

Worldwide Incidence Rates of Ulcerative Colitis

- Olmstead County, MN
- Rochester, NY
- Iceland
- Florence, Italy
- Malmo, Sweden
- Heraklion, Crete
- Seoul, South Korea

Genetics/Ethnicity

- Known risk factor, especially in the pediatric population is a first degree relative with IBD.
- Relative risk is 15 times the general population
- Higher prevalence in the Jewish population, regardless of geographic location.
- Ashkenazi Jews (eastern Europe) have a two to fourfold higher risk of developing IBD than non-Jews.
- 67% concordance for Crohn’s in monozygotic twins.

Question of genetic anticipation?
Genes
Currently close to 100 different genes identified as potential contributing factors to the development of IBD

- IBD1 locus (NOD2/CARD15 – chromosome 16)
- Mediates innate immune response to microbial pathogens = Activation of NF-kappa B
- Variants in NOD2 have a 40 fold increase in relative risk
- IBD2-6 locus (chromosomes 12, 6, 14, 5, 19 respectively)

Other Ethnic Groups
- African Americans – initially thought do not develop IBD
  - Our center has over 150 African American children with IBD
  - In press – a phenotypic description of IBD in our African American population
  - NIH grant (R01) – identify genotypic differences in African American patients with IBD

Environment vs Genetics
- In multiple different animal models, regardless of genetic profile/risk factors, animals raised in a STERILE environment never developed disease consistent with inflammatory bowel disease.
- Expression of inflammatory bowel disease in these animal models is dependant on exposure to bacteria.

Hygiene Hypothesis
- First described by Dr. David Starchan in 1989
  - “declining family size, improved household amenities and higher standards of personal cleanliness”

Hygiene Hypothesis
- Microorganisms that were common in our environment are essentially gone
  - Lactobacillus
  - Saprophytic mycobacteria
  - Parasitic worms or helminths

Joel Weinstock, a gastroenterologist at the University of Iowa, has shown that feeding helminths to patients with inflammatory bowel disease can down regulate intestinal inflammation and even temporarily push the disease into remission

Pathoetiology of Crohn’s Disease
- Genetic susceptibility
- Environmental triggers & modifiers
- Immune response
Routine Evaluation

- CBC – anemia, leukocytosis, thrombocytosis
- ESR/CRP – non specific inflammatory markers
- CMP
- TTG & Total IgA
- Stool studies
  - Culture
  - O&P
  - C. Difficile
  - Giardia
  - Heme occult

Where can we help?

Routine testing now turns to specialized evaluation

- Referral to a pediatric gastroenterologist
- Esophagogastroduodenoscopy with biopsy
- Colonoscopy with biopsy
- Upper GI / MR Enterography / Capsule Endoscopy
- Stool studies / Serologies

Novel diagnostic tools

- Stool studies
  - Calprotectin
  - Lactoferrin
  - Stool studies that assess the presence of inflammation.
- These can be measured in the stool in a non invasive manner and can assist in differentiating true inflammation from irritable bowel symptoms.

Capsule Endoscopy

- Swallowed capsule contains camera, battery and transmitter.
- Multiple images taken as camera transits thru the small intestine.
- Software creates video from images taken.

Capsule endoscopy has lead to the reclassification of disease from UC to Crohn's disease in both the pediatric and adult population.
MR Enterography

- Utilizing MR to evaluate the gastrointestinal tract
  - Benefits:
    - High image resolution
    - Differentiate between inflammation and fibrosis
    - No radiation
  - Cons:
    - Not standardized in children
    - Costs

Serologies

- Perinuclear anti-cytoplasmic Ab
  - pANCA

- Anti-Saccharomyces cerevisiae Ab
  - ASCA

- Antibody to the outer membrane porin type C of E coli
  - OmpC

- Antibody against flagellin expressed by a certain Clostridial phylum
  - CBir

Serology Sum and Disease Behavior

- Odds Ratio
- N=199
- N=262
- N=194
- N=57

Response to Infliximab

- P<0.006

Taylor K et al., Gastroenterology 2001
Therapeutic Options

- Therapy for pediatric IBD requires more than just medications
- The need for a multidisciplinary team approach
  - Pediatric Gastroenterologist
  - Pediatric Surgeons
  - Child Psychology/Psychiatry
  - Clinical Nutritionist
  - Research Coordinator
  - Adult Gastroenterologist / Surgeons

Southwestern Pediatric IBD Center

- Our center, here at Children’s Medical Center of Dallas, was created with those specific clinical resources to provide the most comprehensive clinical care for children with IBD.
  - What makes our center unique?
    - Coupling excellent clinical care with cutting edge research in the areas of quality improvement, genetics, minority populations, and risk stratification.
    - A transitions program that is defining how to seamlessly transfer patients from the pediatric setting to an adult one.

Therapeutic Options

- The algorithm for the treatment of Crohn’s disease and ulcerative colitis have been integrated into one pathway.
  - The caveat being that:
    - we try to avoid surgery in Crohn’s disease
    - surgery, specifically total colectomy in ulcerative colitis can be curative.

Corticosteroids

- Most consistent and rapid clinical benefit
  - Oral, rectal or ileal release
- Many difficult and damaging side effects
  - Weight gain
  - Acne/Stretch marks/Striae
  - Growth suppression
  - Bone disease
  - Psychological effects

Immunomodulators

- Azathioprine or 6-MP
- Methotrexate
- Cyclosporine
- Tacrolimus

- These drugs have the most history in the treatment of IBD, however they are best utilized as maintenance drugs due to the longer onset of action.
The first biologic agent for the treatment of IBD was used in the late 80’s. The drug, infliximab, was thought to revolutionize the therapy of IBD by directing an antibody against a circulating pro-inflammatory cytokine, TNF alpha.

Since the introduction of infliximab, the majority of research in the treatment of IBD has centered around biological agents that block different points in the inflammatory cascade.

**Biologics**
- Infliximab
- Remicade
- Adalimumab
  - Humira
  - Natalizumab
  - Tysabri
  - Certolizumab
  - Cimzia

**Infliximab (Remicade)**
- Chimeric Anti-TNF alpha infusion
- Works by binding TNF alpha which is a potent pro-inflammatory agent
- Requires regular infusions
- Risk of antibody formation

**Adalimumab (Humira)**
- Human Anti-TNF alpha injection
- Given as a subcutaneous injection every other week
- Very low risk of antibody formation

**Natalizumab (Tysabri)**
- First used in multiple sclerosis
- Targets adhesion molecules (alpha 4 integrins)
- Showed good results in Crohn’s patients
- Pulled from the market b/c of progressive multifocal leukoencephalopathy (PML)
- Recently re-applied for FDA approval and back on the market as solo therapy
Certolizumab (Cimzia)
- Pegolated human anti-TNF alpha injection
- Pegolation allows for longer half life
- Needs to be given monthly
- Does not cross the placental barrier

Risks associated with biologics
- All anti TNF alpha drugs come with a black box warning for:
  - Overwhelming infection
    - All patients should have a PPD prior to initiation
    - Hepatitis titers – confirm immunity
  - Increased risk of lymphoma
    - Hepatosplenic T-cell lymphoma
- Can also be associated with infusion reactions, psoriasis, and psychological changes.

Our experience with biologics
- We have approximately 20-25% of our pediatric IBD population on a biologic agent
- We take a conservative approach to advancing therapy, though there are situations where a biologic agent may be used as first line therapy:
  - Severe growth failure
  - Perianal/Fistulizing disease
- We have reported the diagnosis of several different tumors, serum sickness-like reactions, and invasive infections like Histoplasmosis in patients receiving biologic agents

Vaccines
- In your patients on immunomodulators, in particular biologic agents, please avoid live/attenuated vaccines:
  - Live attenuated vaccines include:
    - Varicella
    - Live Cholera
    - Yellow fever
    - Intranasal influenza
    - Anthrax
    - Shingles
    - BCG
    - Oral typhoid
    - MMR
    - Adenovirus
    - Smallpox
    - Herpes Zoster
    - Oral Polio

Research
- One of the missions of our IBD center is to be at the forefront of clinical and epidemiological research
- Center Focus:
  - Epidemiology & Natural History
  - Ethnic groups
  - Risk Stratification
  - Quality Improvement

CCFA - Risk Stratification
- In general, step up therapy is ineffective in many patients.
- 80% of complications, health care and hospital cost are generated from a subset of 25% of Crohn's patients with moderate to severe disease.
- Significant rate of growth disturbances in children with Crohn's disease.
- 20% risk of surgery within 3 years of diagnosis in pediatric onset Crohn's disease.
A prospective cohort study in individuals at risk of developing rapid complications:

- Genetic makeup
- Bacteria in bowel
- Serology (reactive to bacteria, food, infections etc)
- Environmental Exposures

1100 children with Crohn's at diagnosis

CCFA Risk Stratification Study (Pediatric Network)

- Study:
- 3 years
- 160 - 200 patients with complication / surgery

Improve Care Now

- The largest multicenter registry in pediatric IBD.
- Over 3000 patients enrolled
- Goal is to improve the quality of pediatric IBD care, in particular thru a reduction in systems variability.
- Develop consistency in evaluation and diagnostic techniques, improved medication utilization, and improved overall nutrition and growth.
- UT Southwestern Medical Center and Children's Medical Center were one of the original 12 centers.

What is the reliability of medical care?

- Patients receive only 60% of recommended care
- Patients take only 60% of recommended treatment
- There is a gap between recommended care and the care actually carried out
- If medical care and patient self-management were more reliable, would outcomes be better?

Goals of Pediatric Care

- Preservation of the gastrointestinal tract
- Steroid free remission
- Longitudinal growth
- Avoidance of drug side effects
  - Lymphoma
  - Reproductive health
- Effective transition to adult health care
- Mucosal healing
  - Reduce the risk for colon cancer

Percent of patients in remission
Conclusion

- Pediatric IBD is a complex gastrointestinal disorder that requires a multidisciplinary approach to evaluation, diagnosis, therapy and long term surgery and steroid free survival.

- It is a MARATHON …not a sprint

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Questions??

Improve Care Now Video