

Bacteria and IBD

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Overview

Some thoughts on bacteria as causes of IBD:

- Faulty defense against bacteria causes IBD
- Bacteria such as *Mycobacterium avium paratuberculosis* (MAP) may have a larger role in IBD

Bacteria Basics

- One cell organisms capable of all life cycle functions
- Rigid cell wall
- Has chromosomes (DNA) that help it replicate
- Flagella (thread like structures) help it move

Gastrointestinal Tract

- A tube lined by specialized epithelial cells continuous with the skin
- Exposed to the external environment, organisms and toxic agents
- Cells develop special functions, i.e. - secretion of various fluids, absorbing electrolytes, producing enzymes
- Form a semi-permeable surface that selectively allows passage of nutrients and fluid

Bacteria and the GI tract

Ten times more bacteria in the human gut than cells in the entire body

Majority are vital for health:

- Make vitamins
- Stimulate the immune system
- Break down toxins
- Provide protection from invading organisms
- Fermenting unused food to provide energy
- Preventing growth of harmful species

“Bad” bacteria cause gastroenteritis in the GI tract. Usually self-limiting and not treated unless complications

Salmonella

Shigella

E. coli

Yersinia

Clostridium difficile (toxin)

Staph toxin (food poisoning)

Gut Flora

- Between 300 and 1,000 species in intestine
- About 99% of all bacteria come from 30 to 40 species
- Yeast also present, role unclear

Probiotics

- Dietary supplements that contain potentially beneficial bacteria or yeast, principally lactobacillus and bacidifobacterium
- Can metabolize various food substances such as carbohydrates
- Intended to assist the body's naturally occurring flora
- Rationale is that natural gut flora can be thrown off balance, as in the use of antibiotics, other drugs, alcohol, travel
- Maintenance of a healthy gut flora is dependent on many factors, especially the quality of food intake, including prebiotics ("food" for the bacteria)
- Few proven benefits – perhaps to prevent antibiotic-related symptoms and traveler's diarrhea
- In IBD, no proven benefit seen with Crohn's or UC, only with pouchitis
- Not all probiotics are alike – different species, different viability
- Very commercial – 38 of first 40 "hits" all advertisements
- Pub Med – 3,119 citations, only 333 clinical trials - much is written, little is proven

Pathogenesis of IBD (what may cause or contribute to the development of IBD)

Barrier Dysfunction:

- Intestinal epithelium (lining) acts as a selective barrier to antigens (substance foreign to the body) and organisms
- Junctions exist between the cells lining the intestinal lumen – cells that die may open channels
- Faulty mucosal barrier allows bacteria to get thru causing proteins, known as cytokines to be produced, which cause WBC to be activated and thus an inflammatory response
- Unclear why inflammation starts, but inflammatory proteins increases permeability
- Initial inflammation may be secondary to infection

Genetics: NOD2 / CARD15

- Associated with early onset, ileal and stricturing disease
- Abnormal variation (mutation) present in 30% of Crohn's patients
- Gene is responsible for recognizing protein in the cell wall of bacteria
- Mutation may result in normal bacteria becoming invasive and triggering immune response

Immune Dysregulation

- Mucosal immune function is a balancing act between effector(activated) cells and regulatory cells
- Increase in effector cells (Th1/Th2/Th17) results in excessive inflammation
- Decrease in regulatory cells, will also result in excessive inflammation

Microbial Flora

- Commensal (mutual relationship between two species) bacteria may be the trigger for IBD, not individual organisms
- Some organisms might be protective, others might be aggressive
- Signaling may go back and forth between bacteria and receptor proteins on epithelial cells
- May be genetic predisposition

Mycobacteria Infections

- Over 100 species, most are harmless
- Mycobacterium tuberculosis (causes TB)and mycobacterium leprae (causes leprosy) are not harmless
- Long incubation period, variable host defense, asymptomatic (without symptoms) infection common
- M. avium complex (MAC): M. intracellulare, M. avium hominissuis, M. avium paratuberculosis (MAP)

Why is there interest in MAP?

- Crohn's disease shares some features with intestinal TB and a resemblance to the granulomatous ileitis in animals (Johne's disease) caused by Mycobacterium avium subspecies paratuberculosis (MAP)
- Reports of MAP detected in tissues of patients with Crohn's disease by culture and by molecular methods
- Detection of MAP DNA in milk raises concerns about public health safety

MAP in Crohn's Disease

- MAP found in most patients with Crohn's disease by culture (60%) and by PCR (80%), compared with about 10% of controls undergoing ileocolonoscopy
- Another study detected MAP in the blood of 46% of patients with Crohn's disease, 45% of those with ulcerative colitis, and in 20% without inflammatory bowel disease

Antibody Markers in IBD

- The body normally produces antibodies in response to bacteria in the gut. Persons with IBD make antibodies abnormally. Those with CD are very immunologically reactive. Antibody tests are helpful in distinguishing between CD and UC, although they are not definitive.

ASCA CD 55-65%, UC 5%, non-IBD, 5%

pANCA CD 10-25%, UC 50-65%, non-IBD <5%

Anti-OmpC CD 38-50%, UC 2%, non-IBD <5%

Anti-12 CD 54%, UC 2%, non-IBD <5%

Anti-pancreas CD 30-40%, UC 4%, non-IBD <5%

- Study looked at 303 subjects with CD for ASCA, Anti-OmpC and Anti-12 antibodies. 79.9% were positive to at least one, 24.8% to all three and 20% negative to all three

Circumstantial Evidence for MAP

- Helicobacter pylori in peptic ulcer disease is an example of an infection causing chronic disease

- Data suggest diversity of Crohn's disease and it follows that a subset of the disease might have an infectious basis

- Response to antibiotics - symptoms often improve with antibiotics

- Monozygotic twin studies show rate of about 50% - implicate potential environmental factor

- Increasing incidence in societies that make the transition to developed nation status, consistent with an environmental influence

Circumstantial Evidence against MAP

- Crohn's disease is less common in rural areas and is not an occupational hazard of farming

- Poor sanitation and overcrowding which should favor transmission of an infection, actually appear to protect against Crohn's disease

- Lack of evidence for transmission of CD

- Sustained response to immunosuppressive drugs should cause disseminated or severe Mycobacterium tuberculosis but does not

- No strong cellular or serologic (blood) reactivity to MAP

- No detection of bacterial DNA in the granulomas (removed at biopsy) of intestinal Crohn's disease

Current Thinking (Here at MSH)

- MAP may just be a commensal organism

- Crohn's patients may be more susceptible to it due to defects in their mucosal immunity

- The use of antibiotics in Crohn's disease seems to be of benefit to many patients.

Post Lecture: Question and Answer Session

Q: Are the antibiotics that you use used against MAP?

A: Most of the time, we're not treating with antibiotics with MAP in mind. However, we treat with antibiotics that do have some activity against MAP.

Q: In what areas of the 4 that you discussed (barrier dysfunction, genetics, immune dysregulation and microbial flora) is research going on?

A: Mostly genetics and immunology.

Q: Is there evidence that CD and UC are autoimmune diseases?

A: They are often described that way. Even autoimmune diseases have a trigger. When a faulty immune system is triggered, the response may not be appropriate.

Q: Is there an allergic component to CD?

A: True allergy is mediated by eosinophils which is different from CD. Thus CD does not appear to be allergic- would have eosinophils and an increase in IGE. We do not see that. Additionally, studies have shown if you take away food by methods such as IV nutrition the result is improvement in CD due to lack of protein and thus healing. Taking all food away works but, introducing non-allergic foods does not work.