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PEARLS OF LABORATORY MEDICINE

Inflammatory Bowel Disease (IBD)

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Introduction to IBD

Inflammatory bowel disease (IBD)

- Chronic inflammatory disease of the gastrointestinal system
  - Exact etiology unclear
    - Combination of environmental and genetic components

Includes 2 distinct diseases

- Ulcerative colitis
  - Primarily affects colon and/or rectum
  - Diffuse inflammation with shallow erosions
- Crohn's disease
  - Affects any portion of GI tract
  - Discontinuous transmural inflammation with deep fissures

Clinical Symptoms of IBD

Ulcerative colitis (UC)

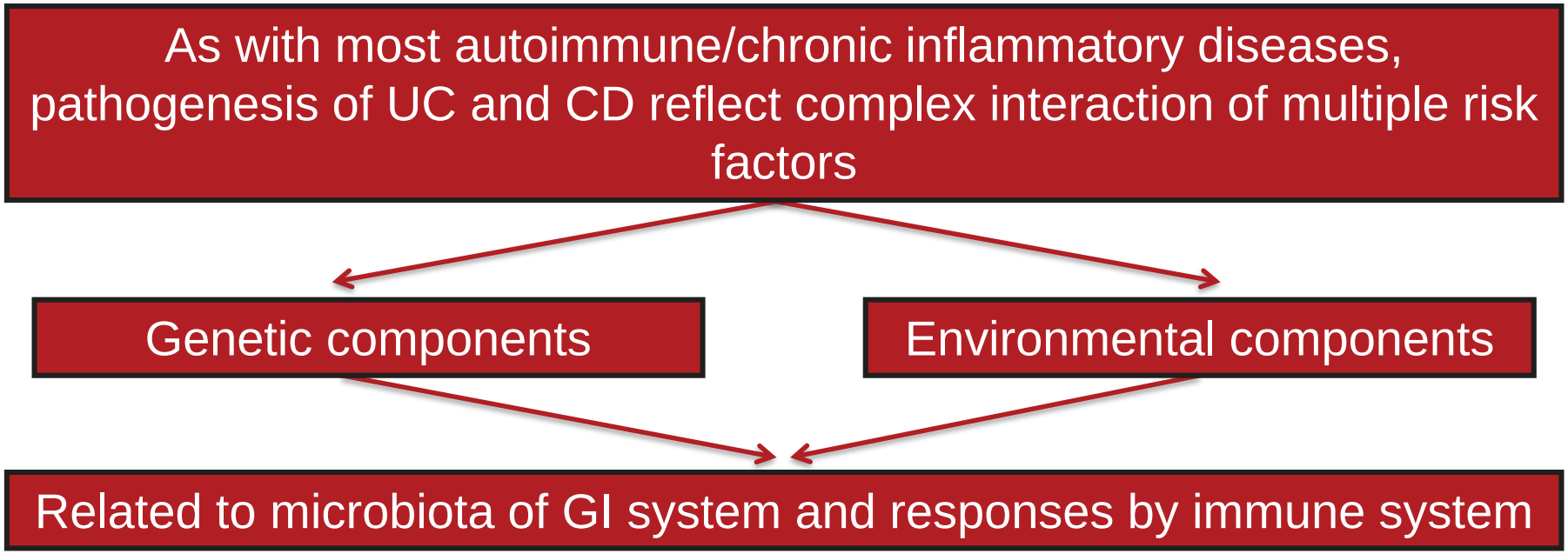
- Diarrhea
  - Often urgent
- Bloody stool
  - May lead to anemia
- Pain
  - Lower abdomen
  - Rectum

Crohn's disease (CD)

- Diarrhea
- Weight loss
  - Malabsorption
  - Limited food intake
- Pain
  - Intermittent
  - Due to obstruction through narrowed lumen

- Fever
- Fatigue
- Arthralgias

Pathogenesis of IBD



Pathogenesis of IBD

Genetic component

- Approximately 300 candidate genes identified
  - Linked to susceptibility of UC, CD, or both
  - Estimated to account for 20-25% of genetic risk
- NOD2
  - Increased risk for CD
  - Heterozygotes
    - 2- to 4-fold
  - Homozygotes
    - 15- to 40-fold

Pathogenesis of IBD

Environmental component

- Risk factors
  - Antibiotics
  - Industrialization
    - Pollution
    - Diet
    - Hygiene
- Protective factors
  - Breastfeeding
  - Smoking

Epidemiology of IBD

Generally considered to be disease of the developed world

- Prevalence of UC
  - 35-100/100,000
- Prevalence of Crohn's disease
  - 10-100/100,000

Peak age of onset

- 15 to 25 years

All-cause standardized mortality ratios

- 1.19 for ulcerative colitis
- 1.38 for Crohn's disease

Risk of colorectal cancer increased in IBD

- Cumulative probability varies with certain risk factors

Diagnostic Evaluation for IBD

Clinical evaluation

- GI and systemic manifestations
- Family history

Endoscopy and biopsy

- Localization of inflammation
- Characterization of inflammatory response in tissue

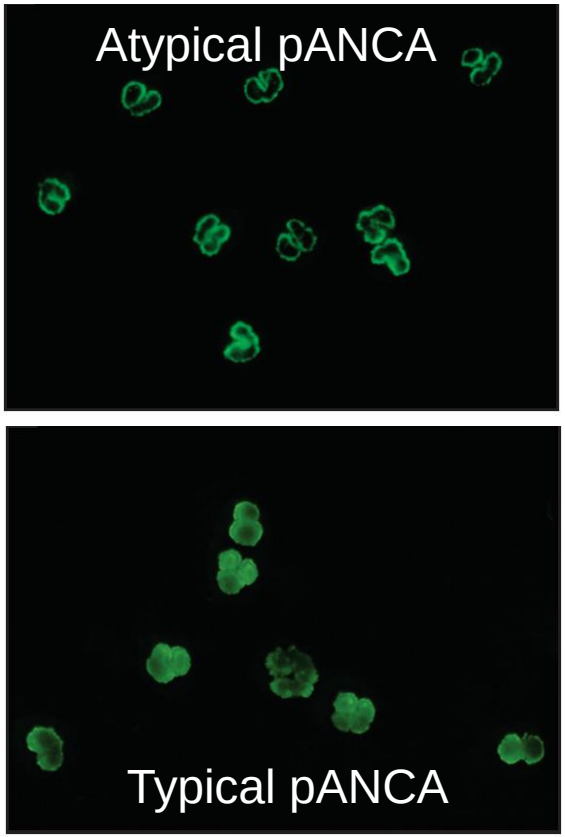
Laboratory testing

- Serology
  - Assess for presence of IBD-specific antibodies
- Stool
  - Exclude presence of infectious agent
  - Assess for GI inflammation

Serologic Testing for IBD

pANCA

- Atypical staining
  - Broad, non-homogeneous rim-like staining of the nuclear periphery
  - Associated with IBD
  - Specific antigen is unknown
- Typical staining
  - Perinuclear staining with nuclear extension
  - Associated with small-vessel vasculitis
  - Specific antigen is myeloperoxidase



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Serologic Testing for IBD

Saccharomyces cerevisiae antibodies

- Specific for cell-wall mannan in yeast
  - Generically referred to as anti-glycan antibodies
  - Other anti-glycan antibodies associated with IBD
- Antibodies specific for other microbial proteins
  - Anti-OmpC
  - Anti-CBir1
  - Anti-A4-Fla2

Serologic Testing for IBD

General interpretation of IBD serology

	pANCA	*S. Cerevisiae* Ab
Ulcerative colitis	Positive	Negative
Crohn's disease	Negative	Positive

Prevalence of IBD serology

	pANCA	*S. Cerevisiae* Ab
Ulcerative colitis	60-70%	10-15%
Crohn's disease	10-15%	60-70%

Mitsuyama K, Niwa M, Takedatsu H, Yamasaki H, Kuwaki K, Yoshioka S, et al. Antibody markers in the diagnosis of inflammatory bowel disease. World J Gastroenterol 2016;22:1304-10.

Serologic Testing for IBD

Meta-analysis of diagnostic utility of pANCA and *S. cerevisiae* antibodies in IBD

	Serology	Sensitivity	Specificity
IBD vs. non-IBD	ASCA+ and/or pANCA+	62.6%	92.6%
CD vs. UC	ASCA+ and pANCA-	55.0%	93.0%
UC vs. CD	ASCA- and pANCA+	51.3%	94.3%

Reese GE, Constantinides VA, Simillis C, Darzi AW, Orchard TR, Fazio VW, et al. Diagnostic Precision of Anti-Saccharomyces cerevisiae Antibodies and Perinuclear Antineutrophil Cytoplasmic Antibodies in Inflammatory Bowel Disease. Am J Gastroenterol 2006;101:2410-22.

Serologic Testing for IBD

Current recommendations for serology testing

- Diagnosis of UC or CD
  - Limited utility due to relatively poor sensitivity of pANCA and *S. cerevisiae* antibodies
- Differentiation between UC and CD
  - May be useful in patients for whom differential diagnosis between UC and CD is unclear
    - Approximately 10% of patients ultimately diagnosed with IBD

Stool Testing and IBD

Inflammation in GI tract associated with neutrophil migration

- Proteins from neutrophils accumulate in feces and are excreted from the body

Neutrophil proteins

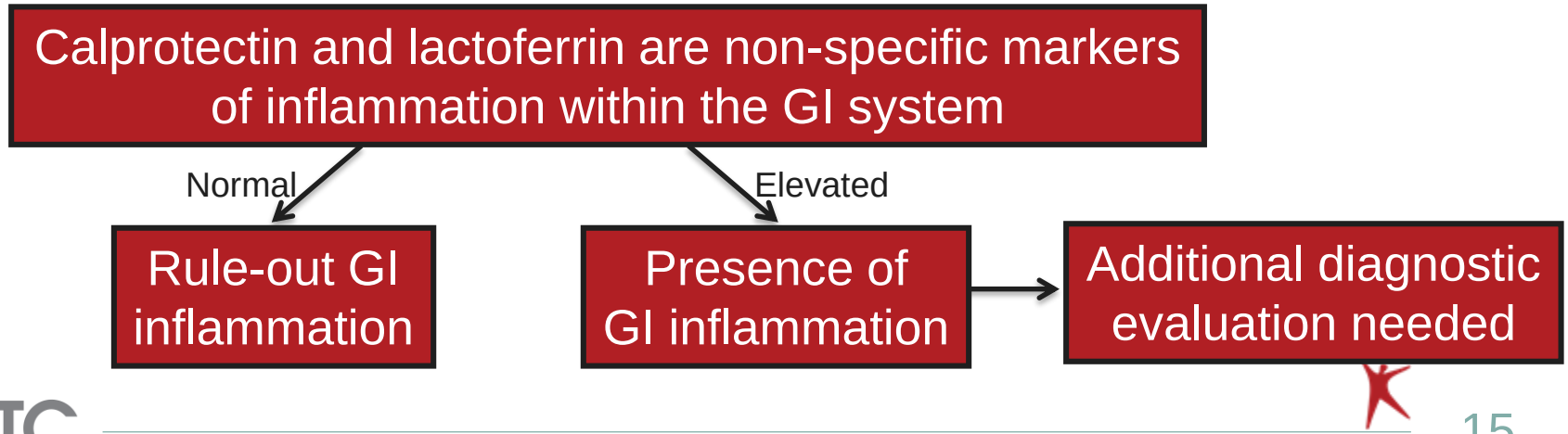
- Calprotectin
  - Calcium-binding protein
- Lactoferrin
  - Fe-binding glycoprotein

Stool Testing and IBD

Neutrophils will localize to GI system as part of innate immune response

Inflammatory response may occur in

- IBD
- Celiac disease
- Infection
- Colorectal malignancy
- Use of non-steroidal anti-inflammatories (NSAIDS)



Summary and Conclusions

Ulcerative colitis and Crohn's disease are chronic inflammatory conditions that affect varying areas of the GI system

- Complex interplay between genetic and environmental triggers

Diagnosis can be challenging

- Overlapping and generally non-specific symptoms
- Although laboratory testing is available, diagnostic evaluation centers around clinical evaluation and endoscopy

Summary and Conclusions

Fecal calprotectin and lactoferrin

- Optimal screening test for detecting presence of GI inflammation
  - Normal result
    - Excludes inflammatory GI disorder
  - Elevated result
    - Indicates presence of GI inflammation
    - Further diagnostic evaluation recommended

S. Cerevisiae antibodies and pANCA serology

- Not necessary and not useful for diagnosis
- May be helpful for distinguishing between Crohn's disease and ulcerative colitis in subset of patients

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Disclosures/Potential Conflicts of Interest

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