Overview and Treatment of IBD

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Disclosures

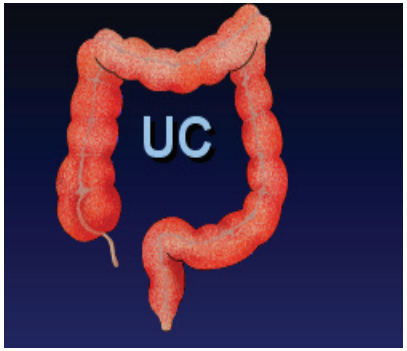
- No disclosures

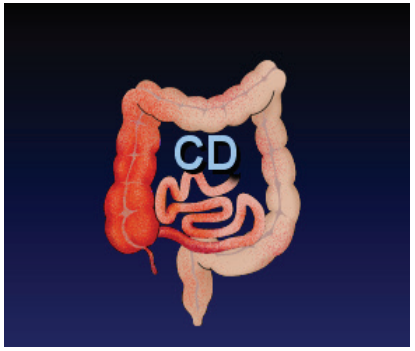
Learning Objectives

- Types of IBD
- Differences between pediatric and adult IBD
- Pathogenesis
- Genetics
- Treatment overview

What is IBD

- Chronic inflammation of the gut
- Driven by gut bacteria
- Associated by dysregulation of immune system
- Types of IBD
  - Ulcerative colitis(UC)
  - Crohn's disease (CD)
  - Indeterminate colitis (IBD-U)





Rectal Bleeding

Diarrhea

Urgency/tenesmus

Abdominal pain

Anemia

Weight loss

Fevers

Arthritis

Skin lesions

Extraintestinal

Abdominal Pain

Weight loss

Growth failure

Anemia

Diarrhea

Perianal disease

Fevers

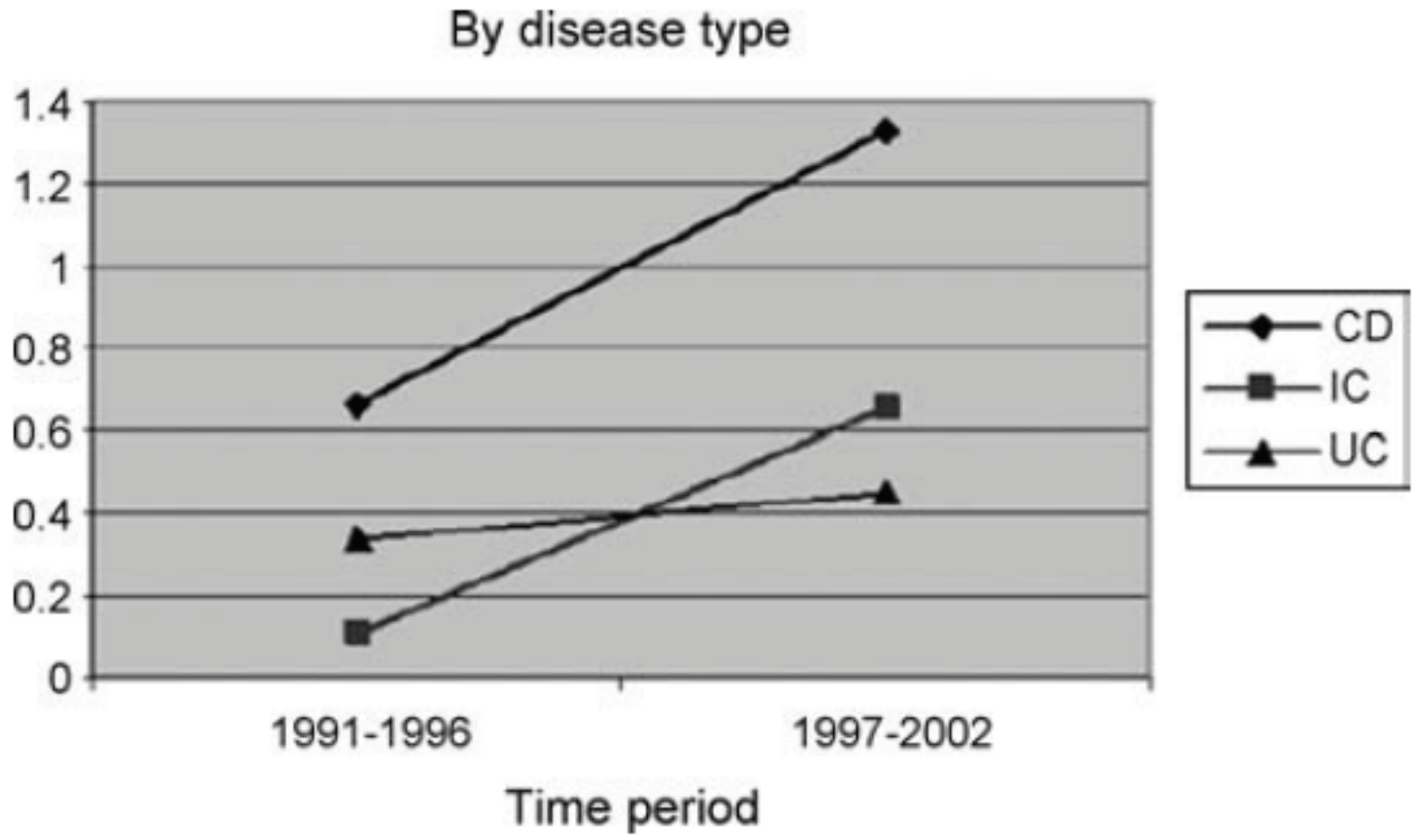
Arthritis

Skin lesions

Extraintestinal

Rheum Dis Clin N Am (2013)

Increasing Incidence of CD in Children



JPGN;2010:50(1)

Classification of IBD

- Type of IBD
- Age of onset
- Disease location
- Disease behavior

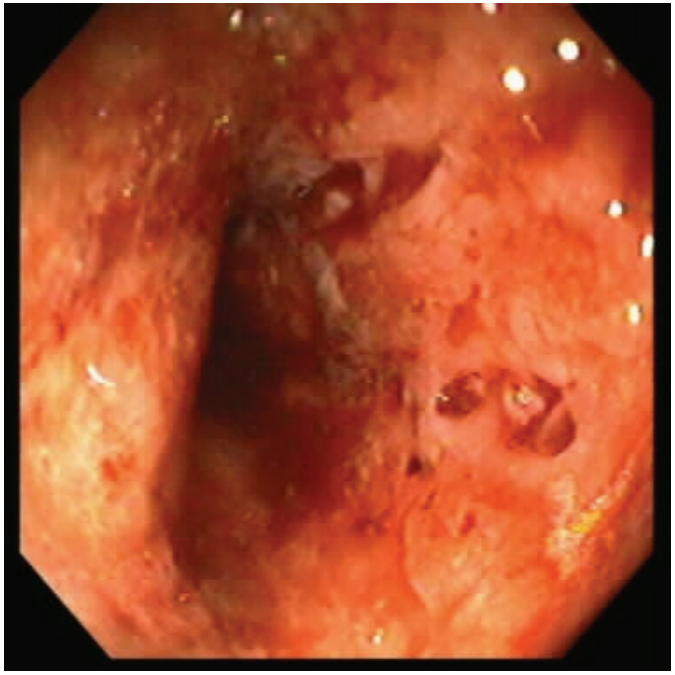
Inflamm Bowel Dis:2011;17(6)

Features Suggestive of CD

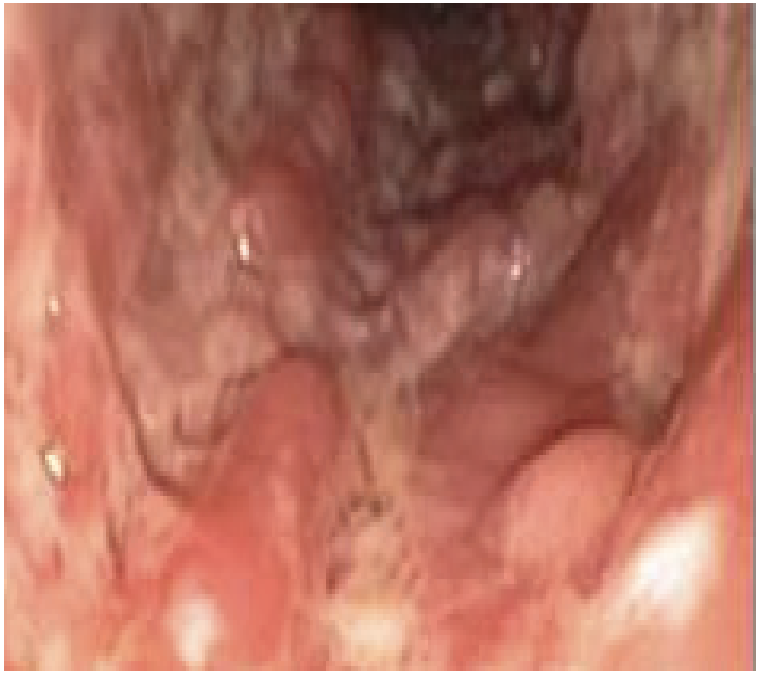
- Perianal disease
- Microscopic normal appearing skip lesions
- Microscopic rectal sparing
- Stenosis/cobblestoning/linear ulcers in ileum
- Macroscopic ileitis with normal cecum
- Granuloma remote from ruptured crypt
- Ulcers/cobblestoning of UGI tract

Inflamm Bowel Dis:2011;17(6)

Crohn's Vs. Ulcerative colitis

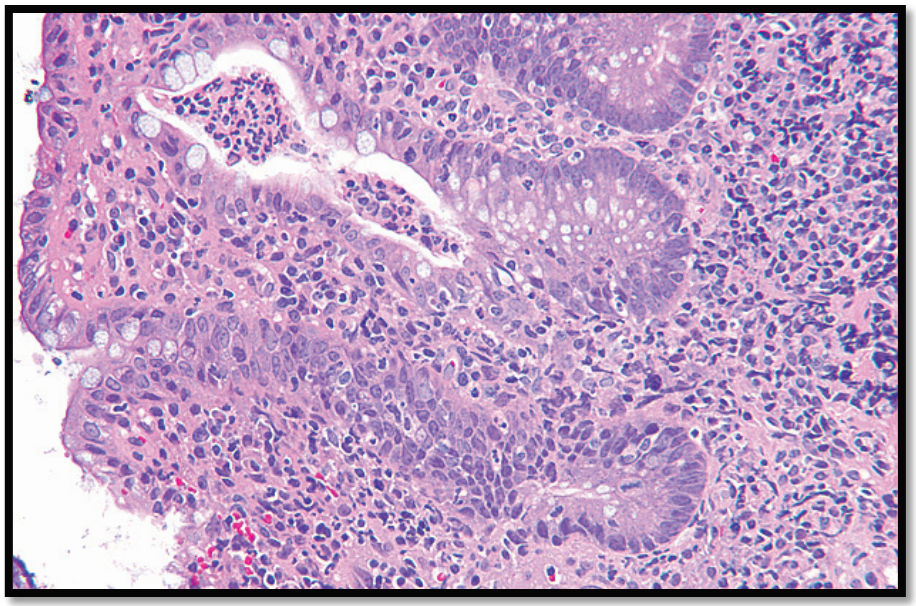


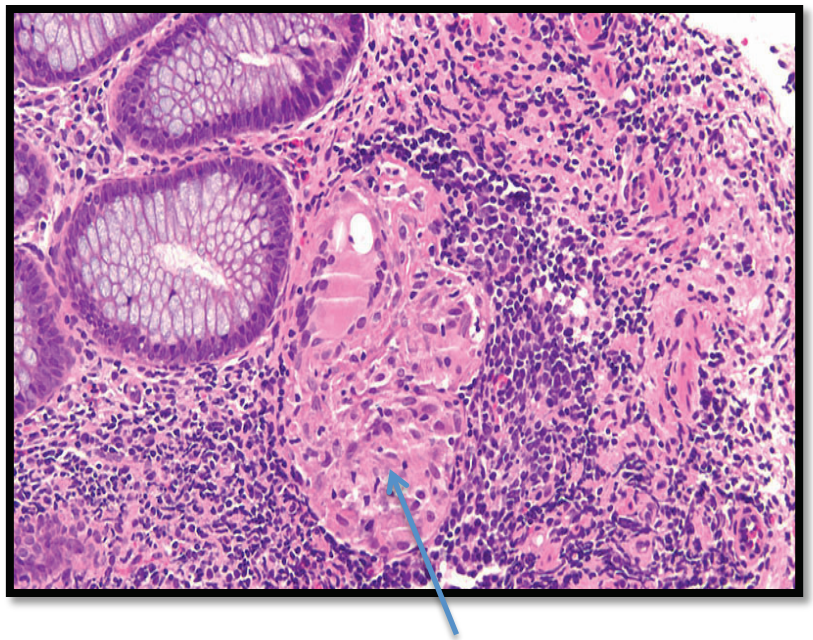
Ulcerative colitis



Crohn's colitis

Histopathology





Epitheloid granuloma

Ulcerative colitis

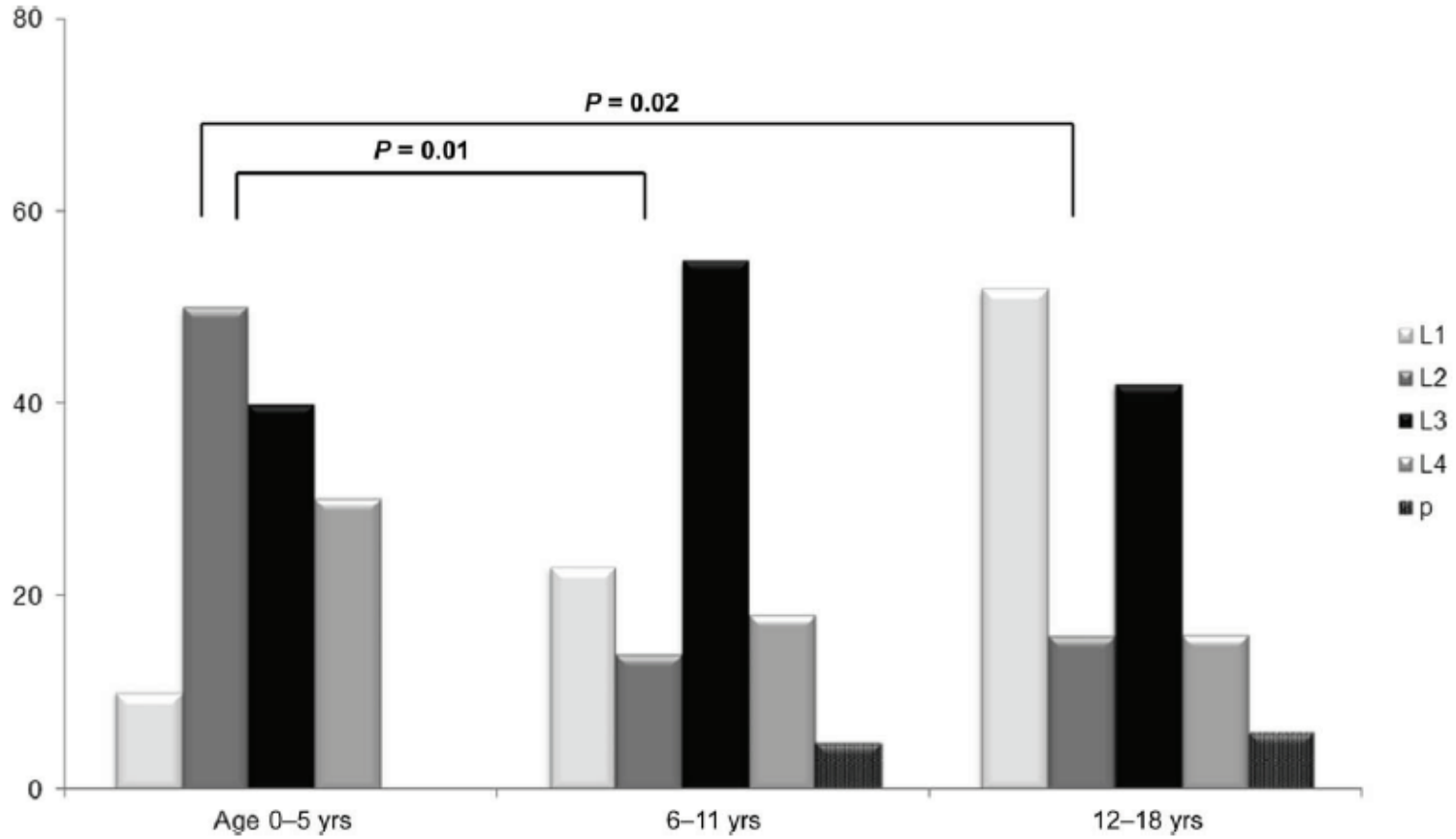
Crohn's disease

Pediatric IBD

- About **25%** have onset before 18 years
  - **0-5 years**: 11%
  - **6-11 years**: 39%
  - **12-18 years**: 50%
- Crohn's disease more likely than Ulcerative colitis
- **Very early onset IBD**
  - Crohn's Disease
    - **Predominantly colonic disease**
    - Disease extension more common
    - Complicated disease behavior
  - Ulcerative colitis
    - **Pancolitis**
    - Higher chances of disease extension

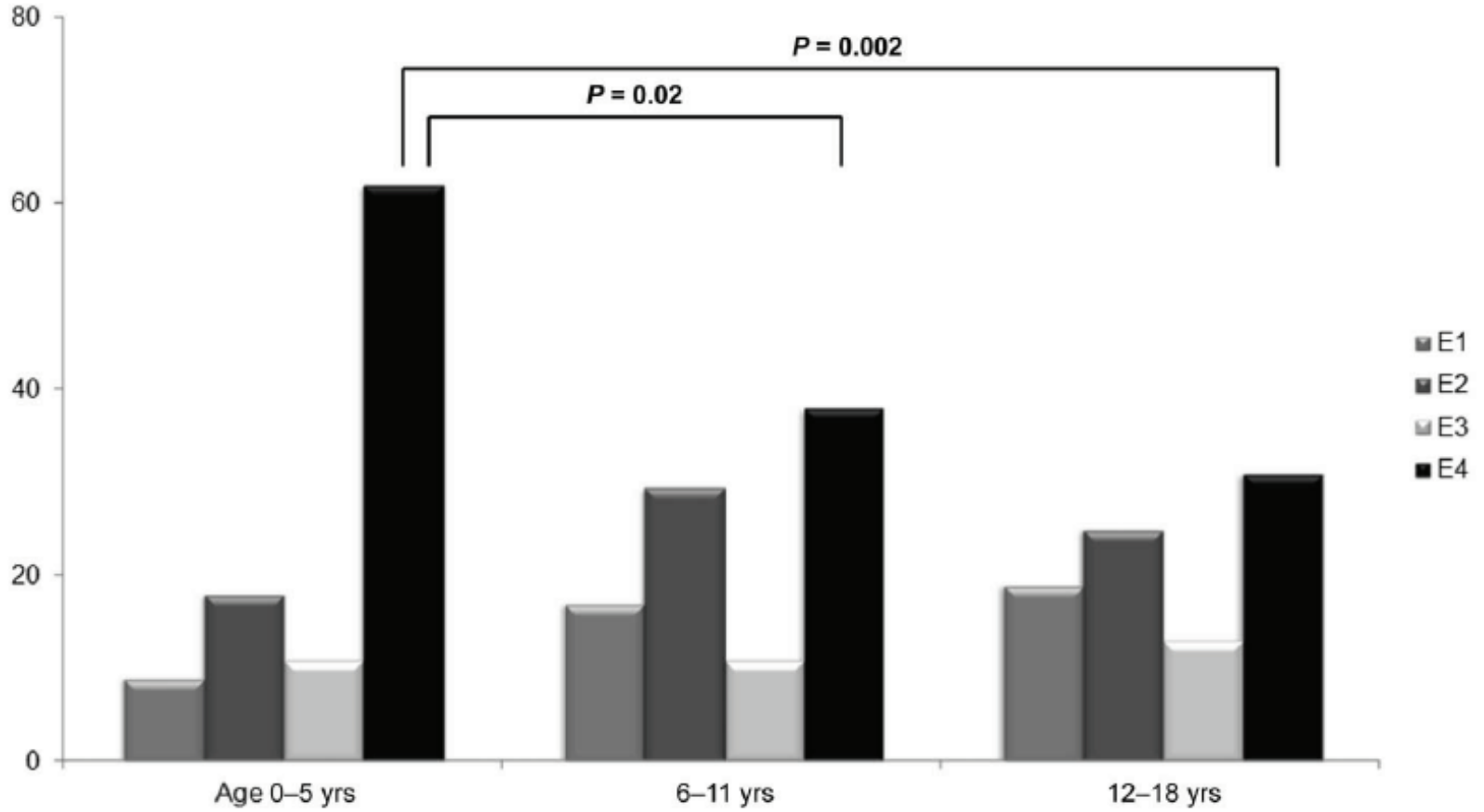
Inflamm Bowel Dis: April 2014 Nat.rev. Gastroenterol. Hepatol ;2014:11:88

Disease Location at Diagnosis by Paris Classification in Children-CD



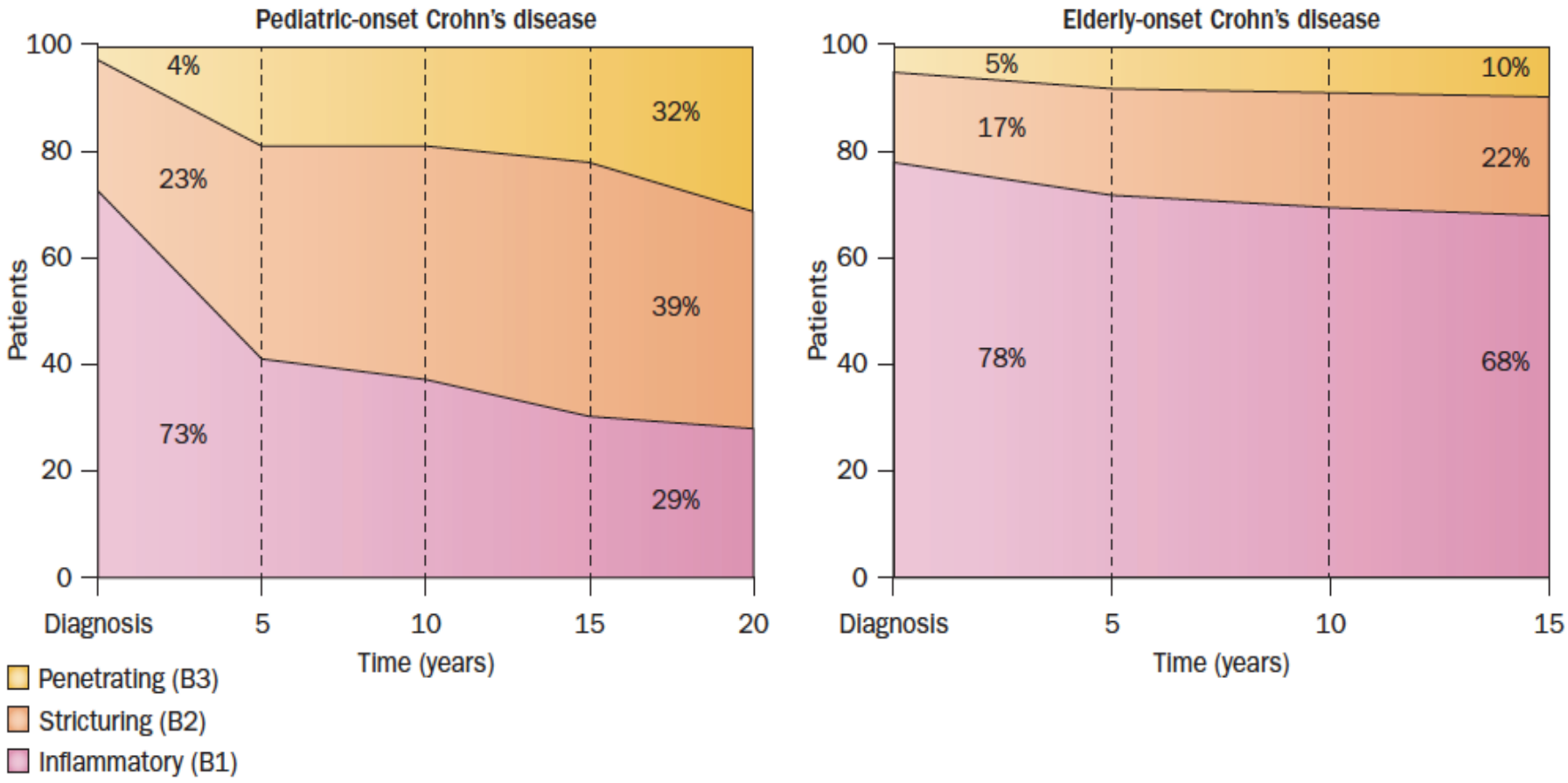
Inflamm Bowel Dis: April 2014

Disease Location at Diagnosis by Paris Classification in Children-UC



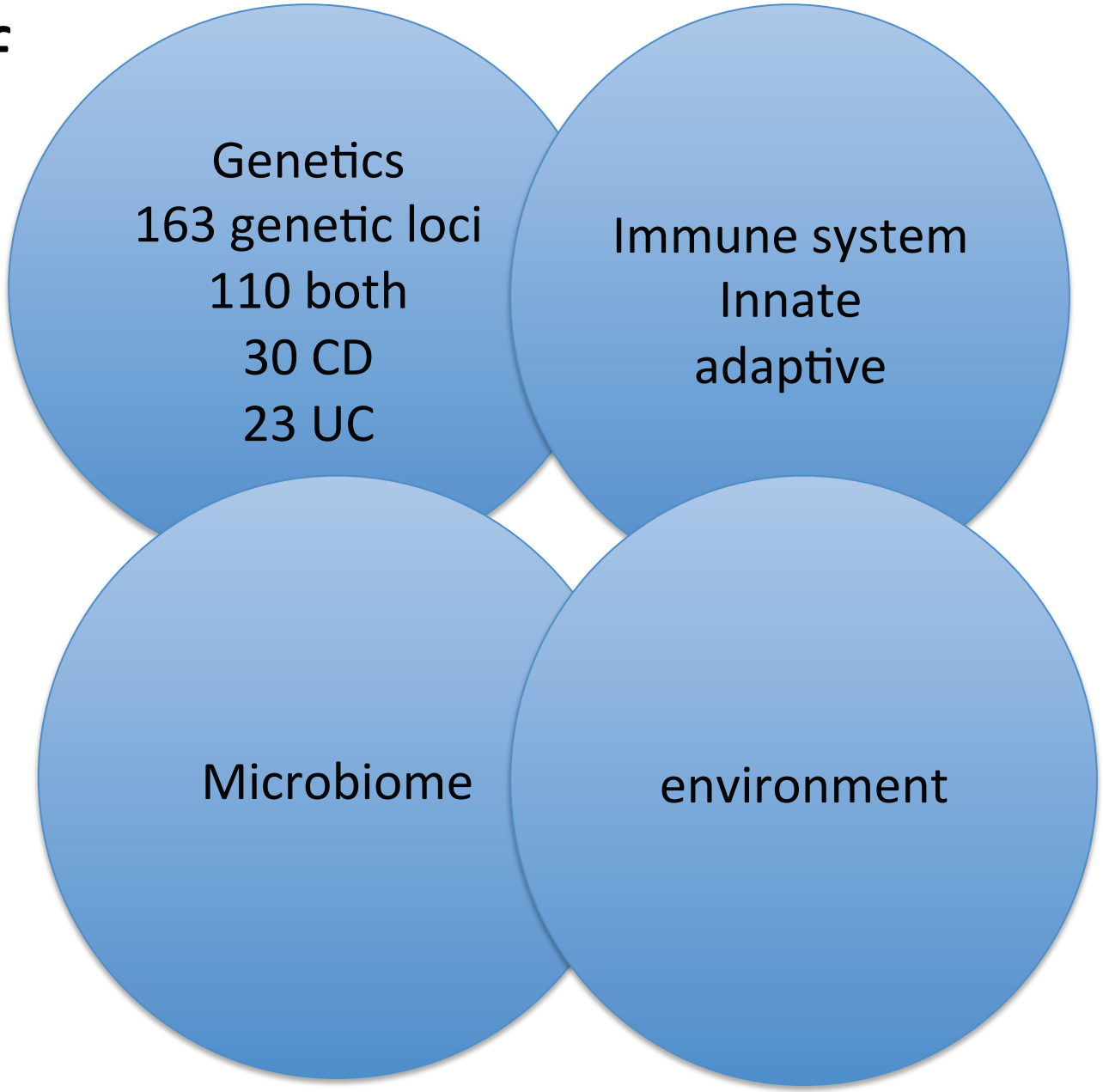
Inflamm Bowel Dis: April 2014

Difference in Disease Behavior in Children vs. Adults

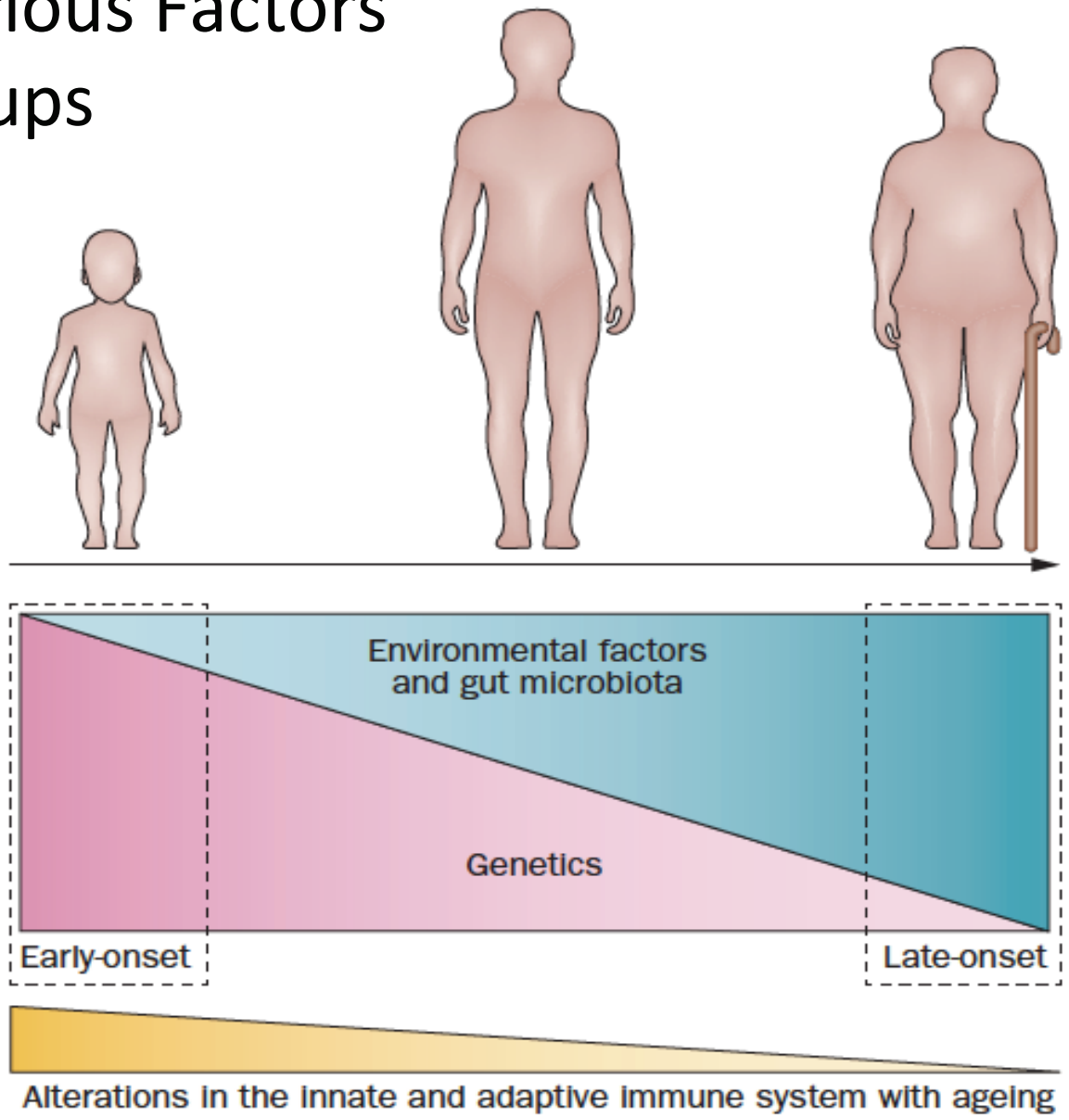


Nat.rev. Gastroenterol. Hepatol ;2014:11:88

Etiology of IBD

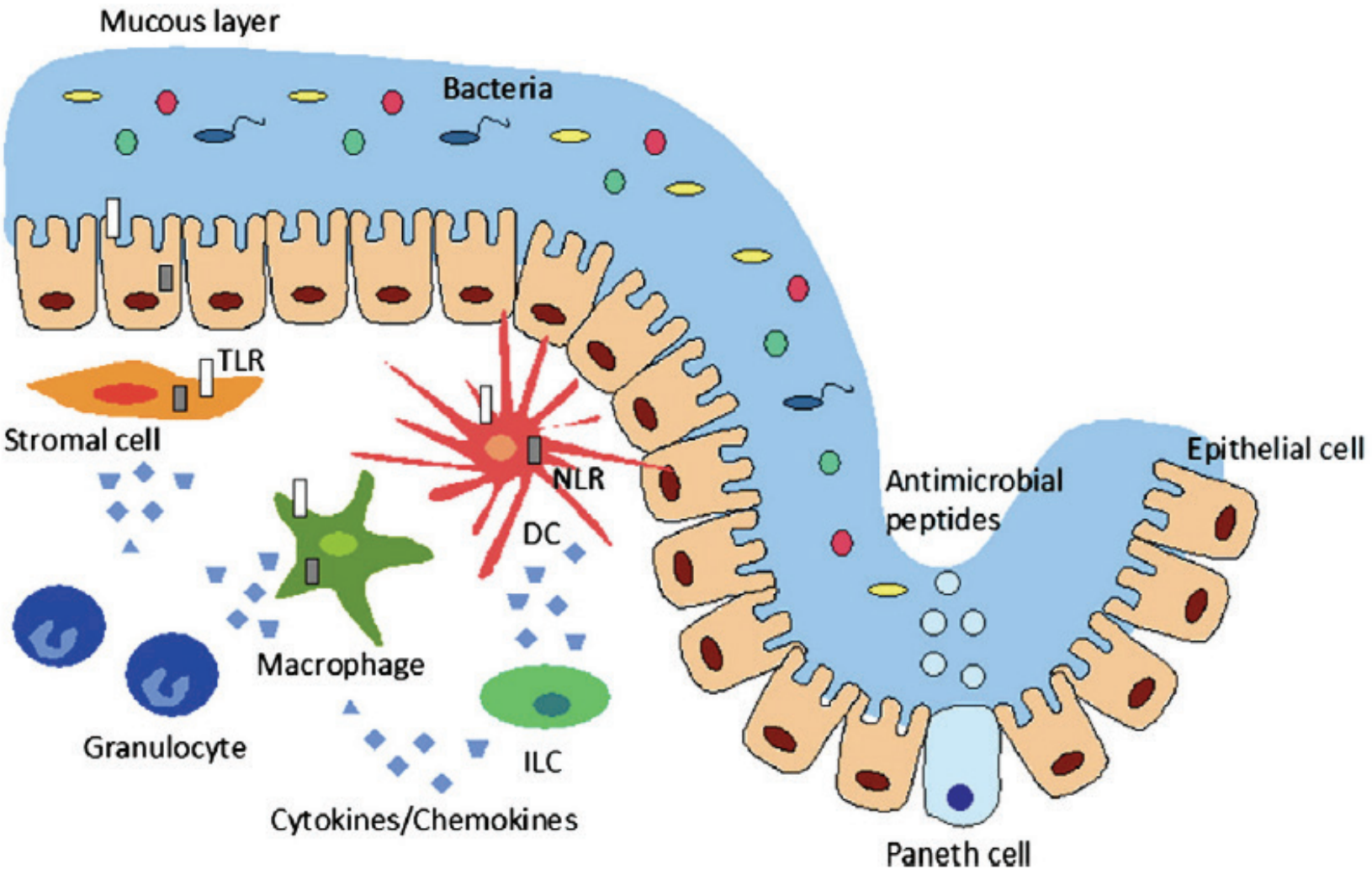


Influence of Various Factors Across Age Groups



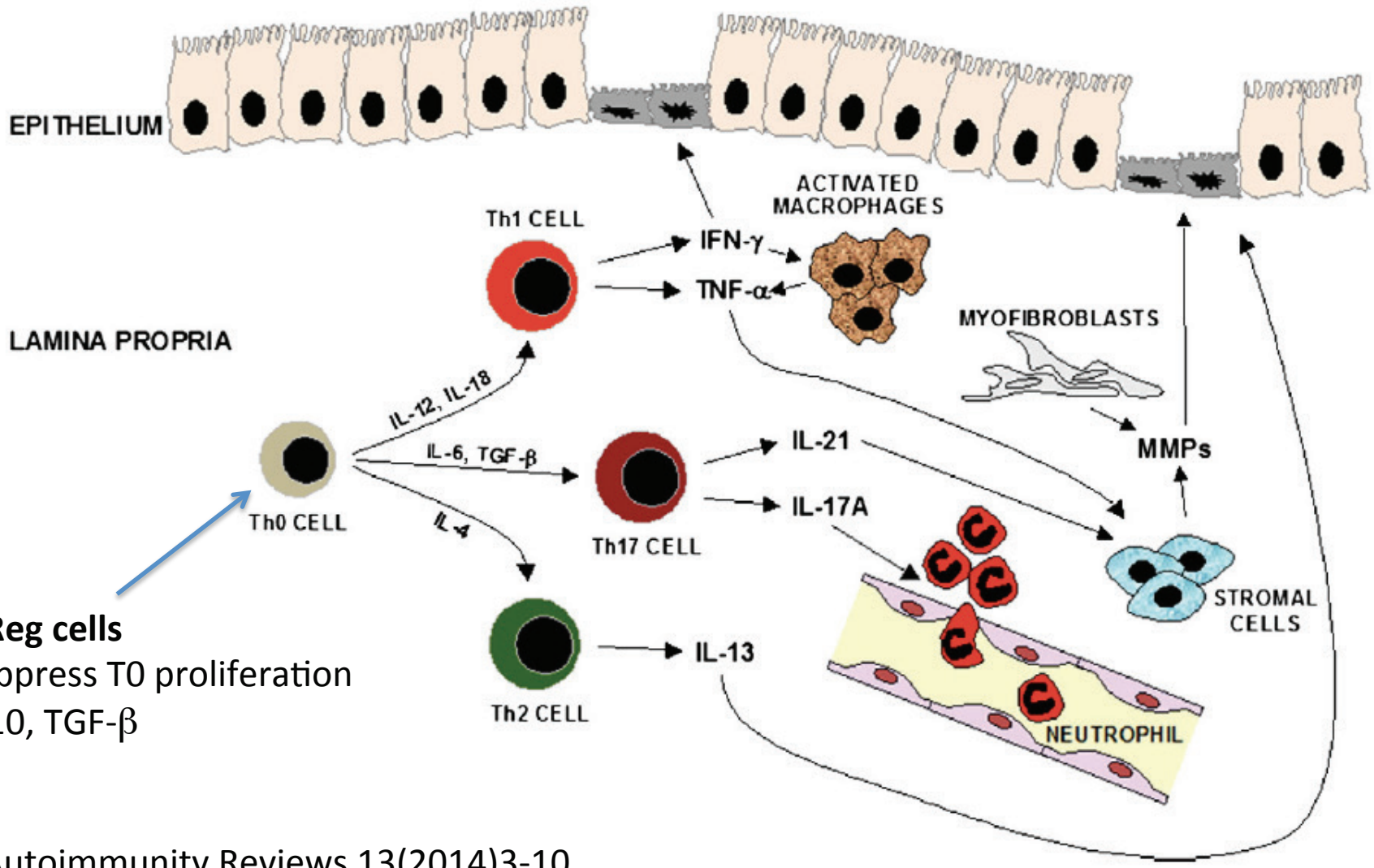
Nat.rev. Gastroenterol. Hepatol ;2014:11:88

Innate Immunity of Gut



Autoimmunity Reviews 13(2014)3-10

Adaptive Immunity



T Reg cells
Suppress T0 proliferation
Il-10, TGF-β

Autoimmunity Reviews 13(2014)3-10

Genetic Factors

- Non-Mendelian
- Genetic epidemiology studies
  - 8-10 fold increased risk of IBD
    - F/H for UC or CD
  - Ashkenazi Jews have greater risk for IBD
  - Greater contribution to CD vs. UC
  - Twin studies

	UC	CD
Monozygotic	15.4%	30.3%
Dizygotic	3.9%	3.6%

Gastroenterology 2011;140

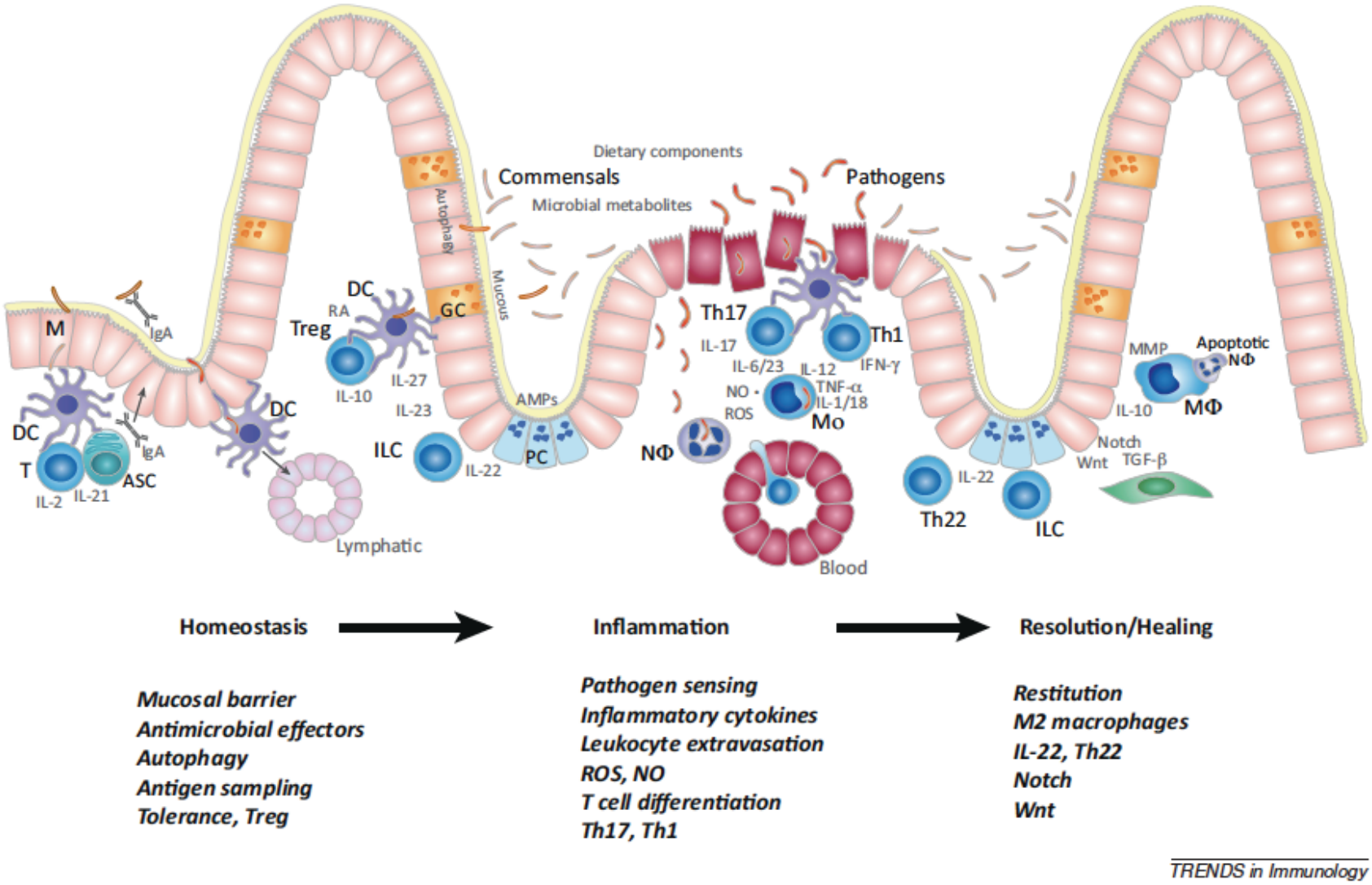
Genetic Influence

IBD susceptibility genes: *TNFRSF18, TNFRSF4, TNFRSF9, IL23R, IL12RB2, RORC, UBQLN4, RIT1, MSTO1, CD48, SLAMF1, ITLN1, CD244, F11R, USF1, FCGR2A, FCGR2B, FCGR3A, FCGR3B, HSPA6, FCGR2A, C1orf53, IL24, PIGR, IL20, IL19, MAPKAPK2, IL10, FAIM3, ADCY3, FOSL2, BRE, RELA, FOSL1, REL, C2orf74, KIAA1841, AHSA2, SPRED2, IL18RAP, IL1R2, IL18R1, IL1R1, IL1RL1, IL1RL2, IFIH1, STAT1, STAT4, SLC11A1, CXCR1, CXCR2, PNKD, ARPC2, SLC11A1, TMBIM1, GPR35, MST1R, UCN2, GPX1, PFKFB4, IP6K2, BSN, MST1, IP6K1, USP4, IL8, CXCL1, PHACTR2, CCR6, RPS6KA2, ZPBP, SMURF1, EPO, TRIB1, JAK2, NFIL3, TNFSF8, TNFSF15, CARD9, PMPCA, SDCCAG3, INPP5E, IL2RA, IL15RA, MAP3K8, CREM, CISD1, IPMK, TSPAN14, C10orf58, NKX2-3, LSP1, TNNI2, CNTF, CD6, CD5, PTGDR2, RPS6KA4, TRPT1, CCDC88B, FLRT1, RELA, FOSL1, CTSW, SNX32, CXCR5, LOH12CR1, MUC19, IFNG, IL26, IL22, IFNG, GPR183, ZFP36L1, FOS, MLH3, GALC, GPR65, SMAD3, CRTC3, LITAF, SOCS1, RMI2, PRKCB, RABEP2, IL27, EIF3C, SULT1A1, SULT1A2, NUPR1, IRF8, CCL13, CCL11, CCL2, IKZF3, ZPBP2, GSDMB, ORMDL3, GSDMA, STAT5B, STAT3, STAT5A, TUBD1, RPS6KB1, SMAD7CXCL6, CXCL3, PF4, CXCL5, CXCL2, PF4AV1, IL2, IL21, DAP, PTGER4, ERAP2, ERAP1, LNPEP, IL13, CSF2, IRF1, IL4, IL5, IL3, SLC22A4, PDLIM4, SLC22A5, SPRY4, NDFIP1, TNIP1, IRGM, ZNF300P1, IL12B, DOK3, TRAF3IP2, FYN, REV3L, TNFAIP3,, CD226, TYK2, PPAN-P2RY11, ICAM1, CEBPG, NLRP7, NLRP2, KIR2DL1, DNMT3B, MMP9, CD40, CEBPB, ZNF831, TNFRSF6B, LIME1, SLC2A4RG, ZGPAT, ICOSLG, MAPK1, YDJC, UBE2L3, RIMBP3, CCDC116, LIF, OSM, MTMR3, ATF4, TAB1*
Crohn's disease susceptibility genes: *PTPN22, ADAM30, TNFSF18, FASLG, UCN, SP140, ATG16l1, TXK, TEC, SLC10A4, IL31RA, IL6ST, CPEB4m HLA-C, PSORS1C1, CREB5, JAZF1, RIPK2, LACC1, SPRED1, RASGRP1, NOD2, LGALS9, NOS2, GPx4, DBP, SPHK2, IZUMO1, FUT2, IFNGR2, IFNAR2, IL10RB, IFNAR1, GART, TMEM50B*
Ulcerative colitis susceptibility genes: *TNFRSF14, MMEL1, RFTN2, PLC1, PRKCD, ITIH4, NFKB1, MANBA, SLC9A3, HLA-DRB1, HLA-DQA1, HLA-DQB1, CARD11, GNA12, DLD, IRF5, TNPO3, JRKL, MAML2, FAM55A, FAM55D, ITPKA, NDUFAF1, ITGAL, ZFP90, CALM3, PROCR, UQCC, CEP250, ADA, HNF4A*

163 Loci, 110 shared between UC and CD, 30 specific for CD, 23 specific for UC

Nat. Rev. Gastroenterol. Hepatol. March 2014

Genetic factors in IBD



Trends in Immunology Aug 2013;Vol 34:8

IBD with Mendelian patterns

- IL-10 receptor mutations
- X-Linked Chronic granulomatous disease
- Glycogen storage disease

Very Early onset IBD (≤6 years)

- Consider Immunodeficiency
  - IL-10 and IL-10 receptor
  - X-Linked inhibitor of apoptosis deficiency
  - FOX P3 mutations-IPEX
  - TTC7A deficiency
  - NADPH oxidase

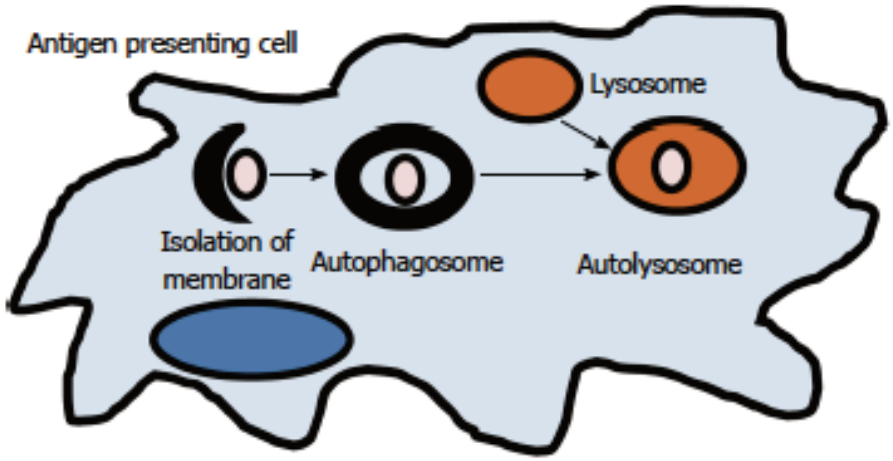
NOD 2 Mutations

- First genetic association with CD
  - Homozygotes, compound heterozygotes : 17.1 fold
  - Heterozygotes : 2.4 fold
- European but not in Asians
- Protective for UC
- Ileal, stricturing disease
- Pathogen recognition intracellular receptor
  - NF-kβ and MAP kinase signaling
  - Decrease levels of defensins
  - Role in autophagy pathway

Gastroenterology 2011;140:1704

Autophagy Pathway

- **ATG 16 L1**
- **IRGM**
- **LRRK2**



- **Autophagy** Involved in
- Cellular homeostatic function
- Protection against invading organisms
- Links to adaptive immunity: antigen presentation

Gastroenterology 2011;140:1704

IL-23 mutations

- AA change Arg 381Gln in IL-23 receptor
- Glutamine present in 14% healthy individuals
- Reduces risk for both CD and UC by nearly 3-fold
- Also associated with ankylosing spondylitis and psoriasis

Gastroenterology 2011;140:1704

Environmental Factors

- **Diet**
  - Increased risk
    - **processed, simple sugars, red meat, cow milk allergy, polyunsaturated fatty acids**
  - Decreased risk
    - **long term fruit intake: CD**
    - **Vegetable intake : UC**
- **Smoking**
- **Drugs**
  - **Antibiotics**
  - **Oral contraceptives**
  - **Non-steroidal**
- Physical activity
- Appendectomy
- Hygiene hypothesis

Curr Gastroenterol Rep;2013:15:326, Up to Date , Google images

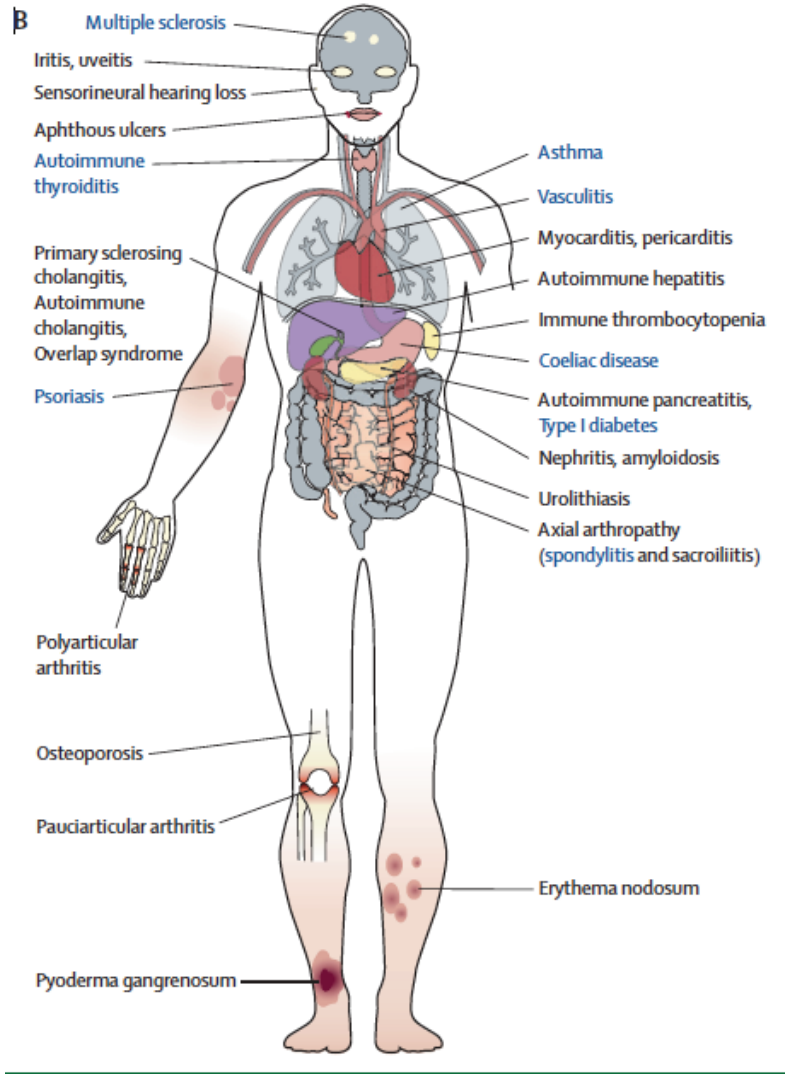
Microbiome

- **Normal human gut microbiome**
  - >90% Bacteroides & Firmicutes
  - Fungi and virus
- **IBD**
  - Decreased fecal diversity, esp. Firmicutes
  - Increased bacterial density in mucus layer
  - Increased Enterobacteriaceae
- **UC**
  - Decreased Bacteroides
  - Increased Fusobacterium
- **CD**
  - Decreased Firmicutes
  - Increased Adherent invasive E.Coli (AIEC) in TI

Gastroenterology 2014, google images

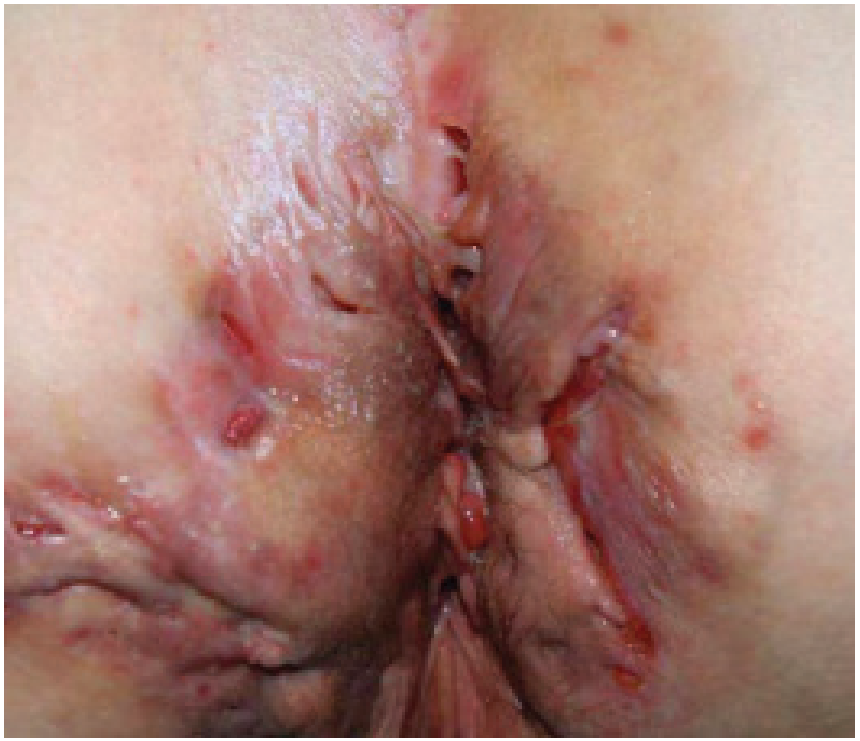
Extra Intestinal Manifestations

- Cutaneous
- Musculoskeletal
- Hepatobiliary
- Ocular
- Growth and puberty

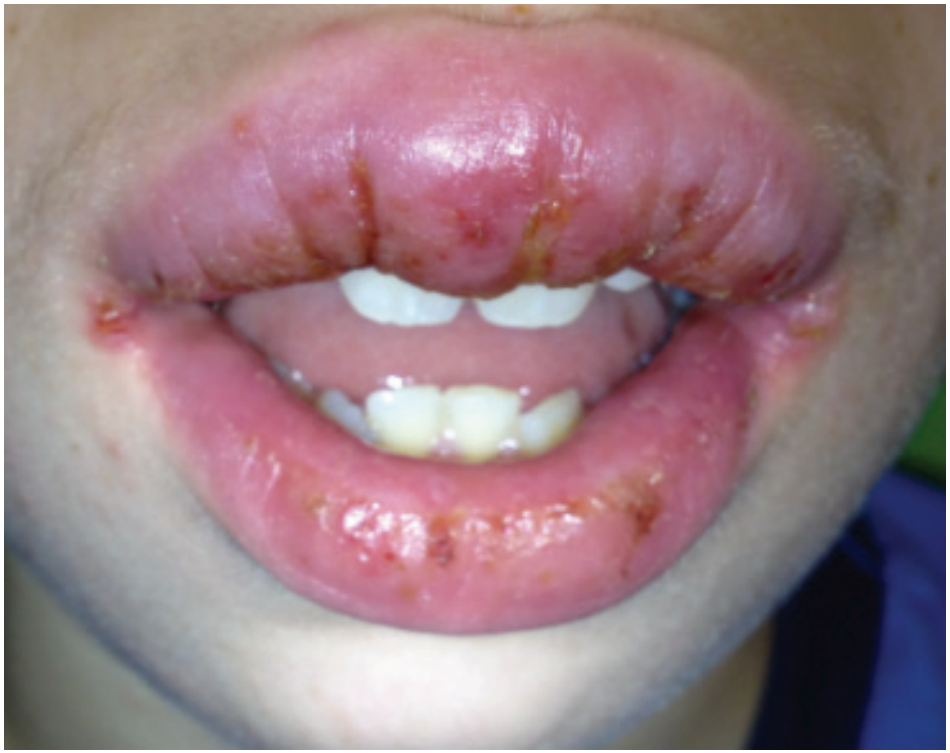


Lancet 2012;380:1590

Same Histological Features

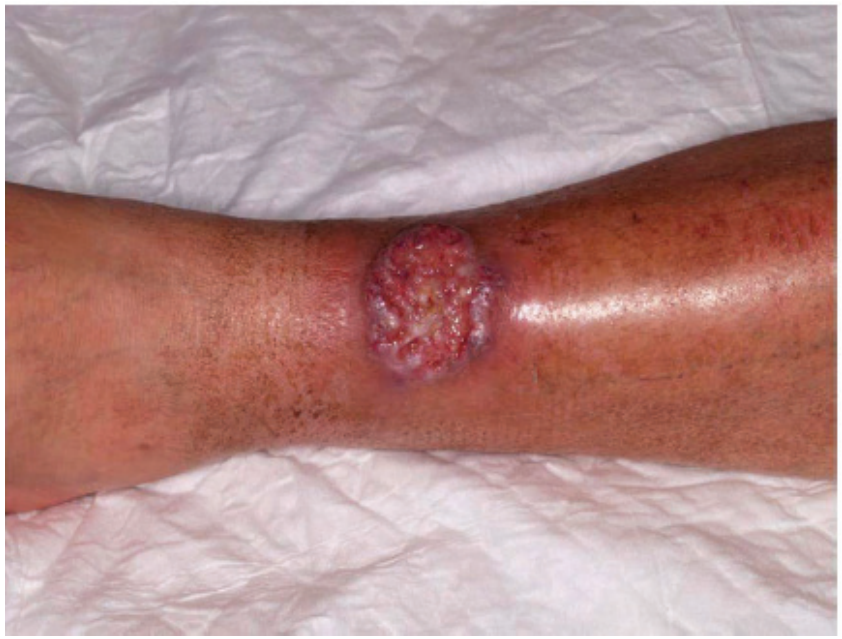


Perianal Crohn's Disease

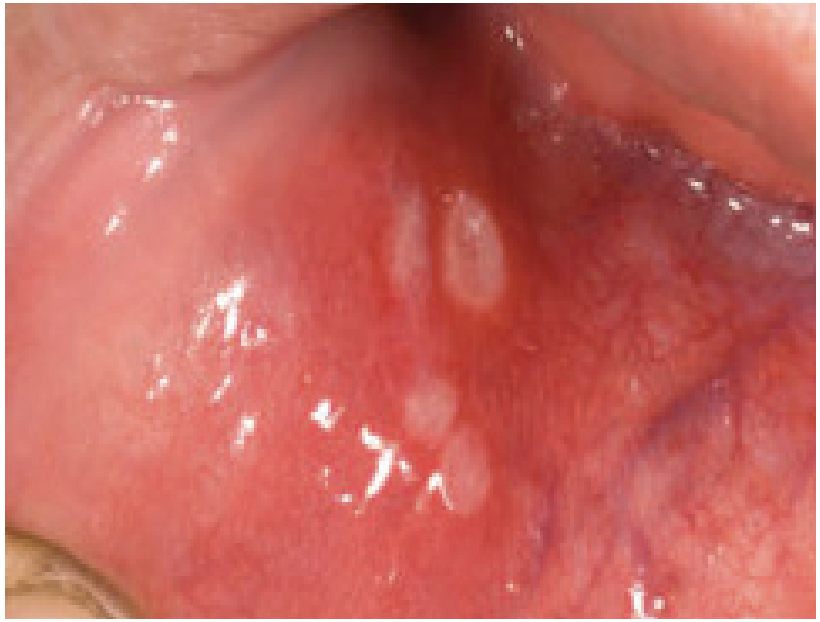


Orofacial Crohn's disease

Reactive Manifestations

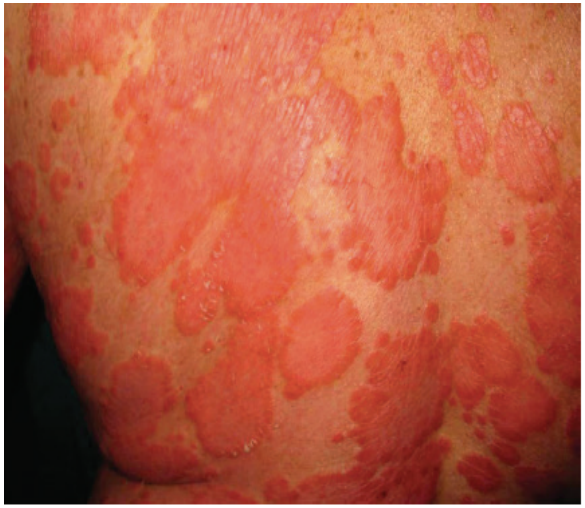


Pyoderma gangrenosum

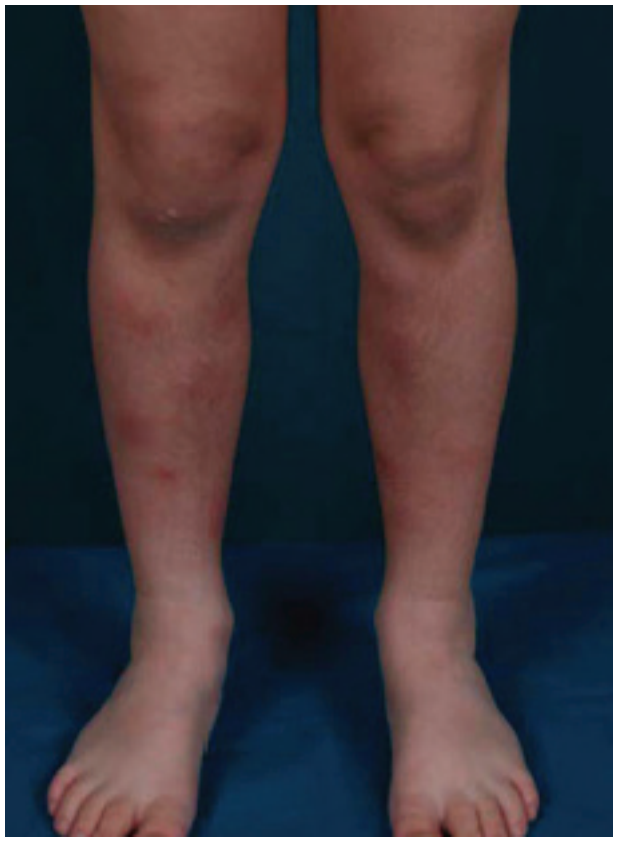


Apthous stomatitis

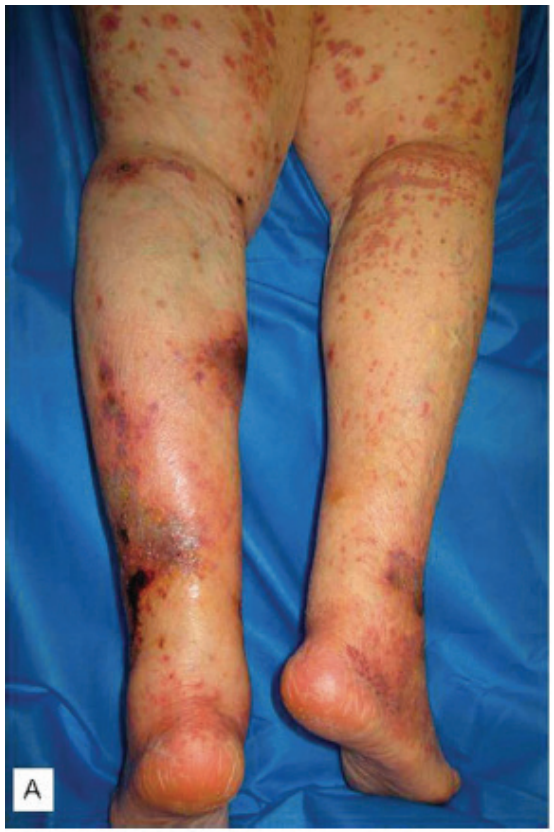
Associated with IBD



Psoriasis



Erythema nodosum



Vasculitis

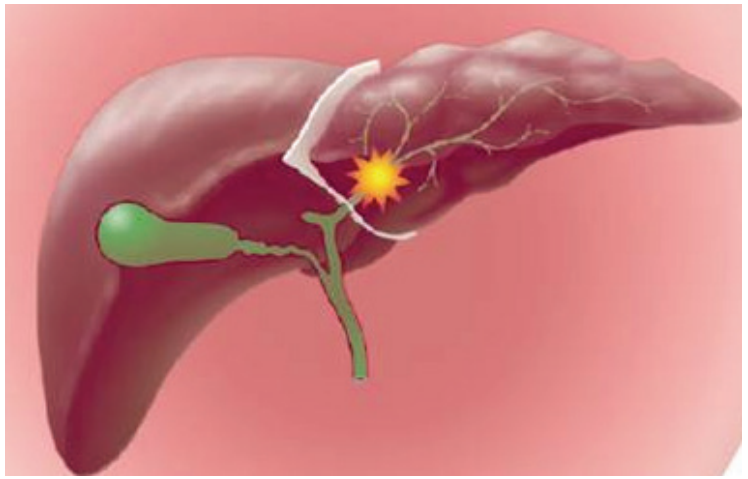
Musculoskeletal

- Peripheral arthritis
  - Type I: Oligoarticular large joint
  - Type II: bilateral, symmetrical, small joint
- Arthralgia
- Back pain
  - Ankylosing spondylitis
  - Inflammatory back pain
  - Isolated sacroiliitis

Autoimmunity Reviews 13 (2014) 20–23

Hepatobiliary Manifestations

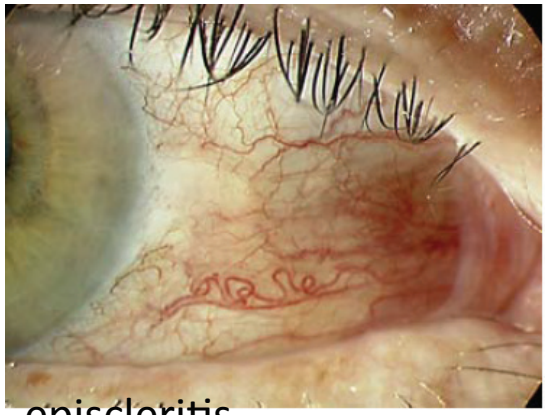
- Primary sclerosing cholangitis
- Overlap syndrome
- Autoimmune hepatitis
- IgG4 cholangiopathy
- Granulomatous hepatitis
- Liver abscess
- Portal vein thrombosis



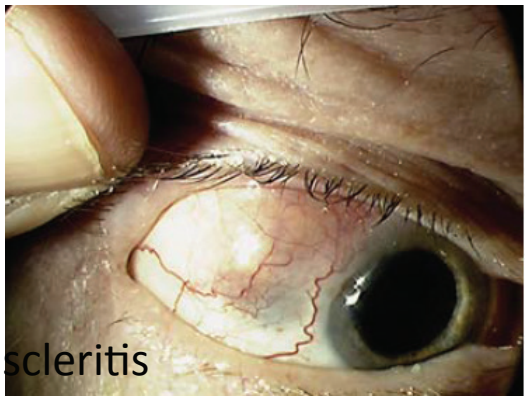
World J Gastroenterol 2013 November 14; 19(42): 7327-7340

Ocular Manifestations

- Anterior segment
  - Episcleritis
    - Redness, pain, photophobia, tearing
  - Scleritis
    - More severe pain
  - Uveitis
    - Pain, blurred vision, photophobia
  - Corneal
    - Rare: avoid refractory surgery with IBD



episcleritis

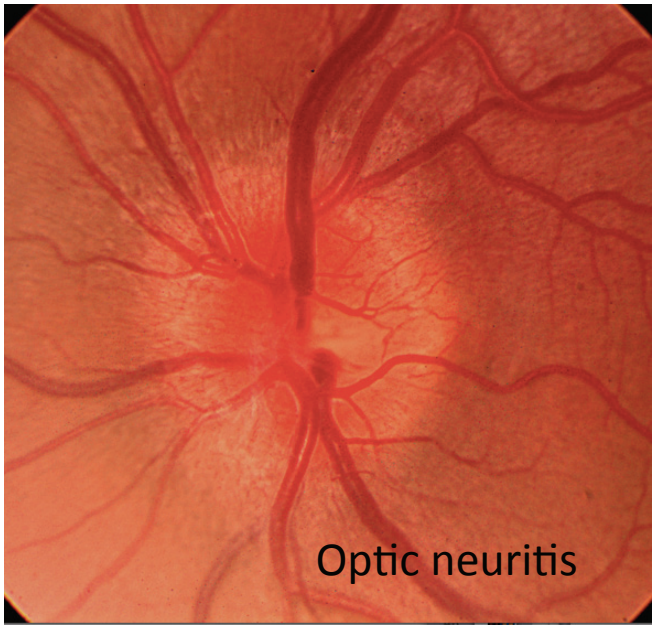


scleritis

Dig Dis 2013;31:229–232

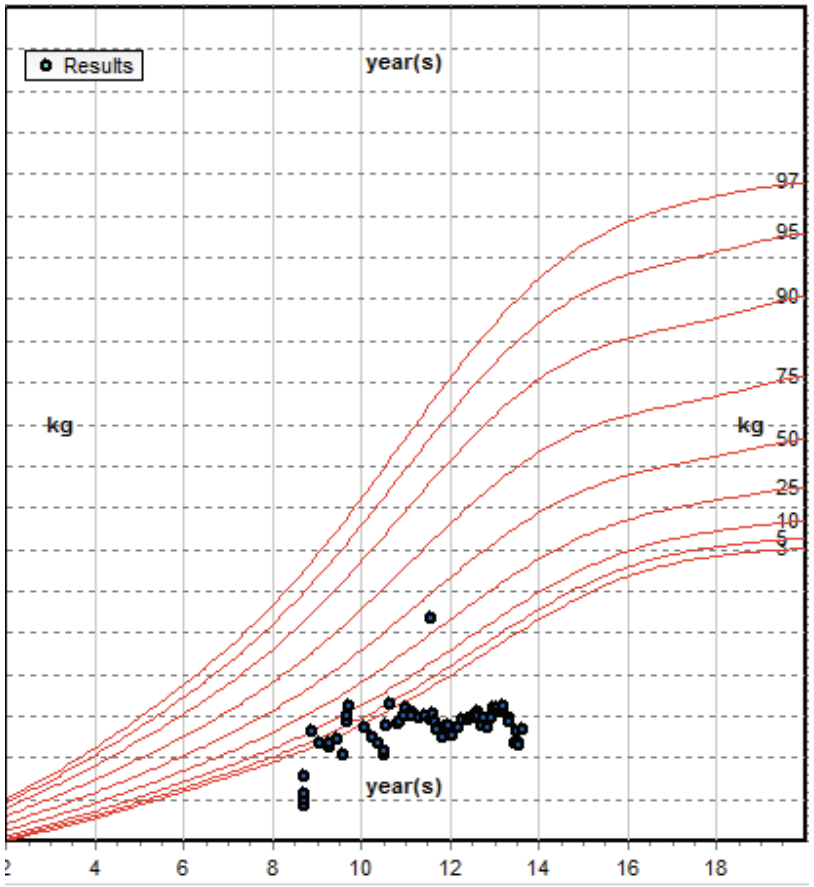
Ocular Manifestations

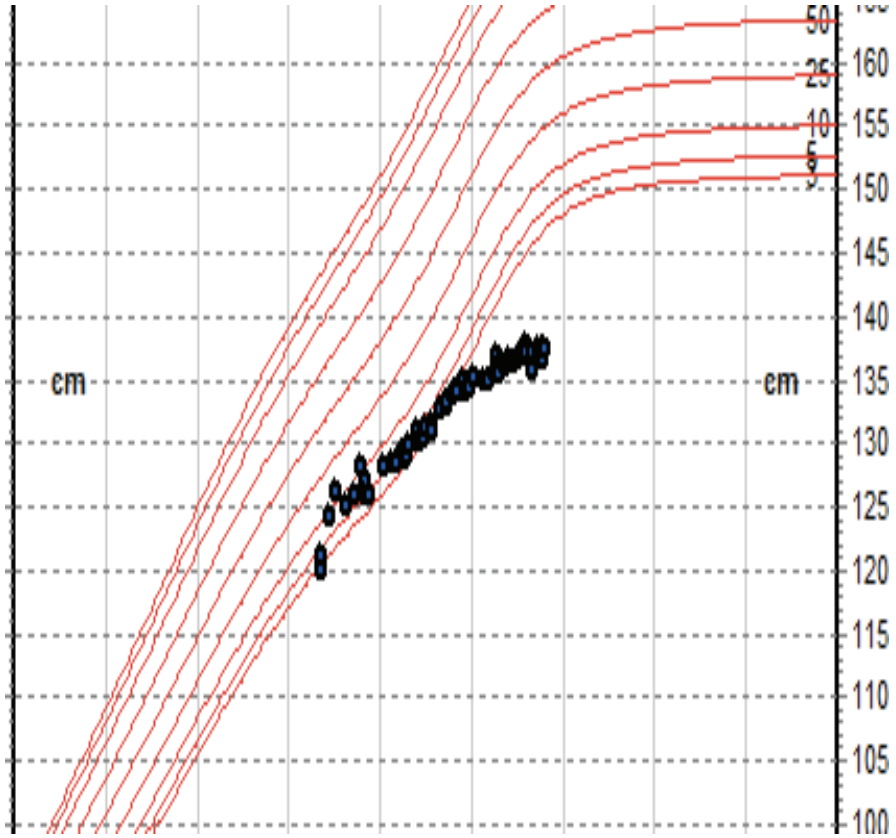
- Posterior segment
  - Vitritis, papillitis, retinitis
- Treatment related
  - Optic neuritis: TNF-α ab
  - Dry eye: 5 ASA



Dig Dis 2013;31:229–232

Growth Delay





Management of Pediatric IBD

- Medical therapy
- Optimization of nutrition and growth
- Diagnosis and treatment of complications
- Surgical therapy
- Other Aspects
  - Coping and education
  - Monitoring disease activity
  - Vaccination
  - Cancer screening

Medical therapy

- Induction of remission
  - Steroids
  - 5-ASA for mild to moderate colitis
  - Diet
  - Immunomodulators
  - Biologicals
- Maintenance
  - Immunomodulators
  - Biologicals
  - 5-ASA

Medical therapy of Crohn's

Steroids

- Systemic
- Topical
- Important principles
  - Need an exit strategy
  - Not a maintenance drug
  - Long term use may lose effectiveness
  - Not a benign drug: infections, growth, osteoporosis
  - Does not cause healing

Enteral Nutrition (EN)

- In children efficacy similar to steroids
- Mechanism of action is not clear
  - Alteration of gut Microbiota, gut rest
- Improves weight and BMI, not linear growth
- Advantages
  - Mucosal healing, no drug side effects, improves weight and BMI
- Disadvantages
  - Compliance, not as effective for colonic disease
- Modified protocol
  - 80-90% formula, some food allowed
  - 65% remission and 87% response

Inflamm Bowel Dis. 2013;19

Biologicals

- Anti TNF-α antibodies
  - Infliximab
  - Adalimumab
  - Certolizumab: Not approved in children
  - Golimumab: Not approved in Children
- Integrin inhibitors
  - Natalizumab
  - Vedolizumab (pending FDA approval in USA)
- Anti IL-12/IL-23
  - Ustikinemab: Not FDA approved for IBD

Anti-TNF Antibodies

- **Mechanism of action**
  - Binds TNF (soluble and membrane bound)
  - Promotes apoptosis of activated lymphocytes
  - Cytotoxity: antibody mediated, complement mediated
- **Infliximab**
  - REACH: 88% response, 58% remission at 10wk
    - Week 54: 63.5% response and 55.8% remission
- **Adalimumab**: humanized IgG1 antibody
  - Remission: TNF naive : 57% 26 wk., 45 %: 1 year
    - Previous Infliximab: 20% wk. 26, 18% at 1 year

Gastroenterology 2012:143, Gastroenterology 2007

Alpha Integrin Inhibitors

- **Natalizumab**
  - α-4 Integrin inhibitor
  - Only 1 study in children with CD:
    - response 55%, remission 29%
  - Main concern is
    - **Progressive multifocal leukoencephalopathy**
- **Vedolizumab** (not yet approved in USA)
  - Specific for gut

JPGN: 2007(44)185

Immunomodulators (IM)

- **Mercaptopurine**
  - Children seem to have a better response
  - Single prospective pediatric study showed 91% long term response Vs. 53% in placebo
  - In clinical practice results are not as good
  - Still considered a useful drug
- **Methotrexate**
  - Increased use by pediatric gastroenterologists
    - (1st line) especially in young boys
  - About 30% maintain long term response
  - Favored for dual immunosuppression

GASTROENTEROLOGY 2013;145:1459–1463

AGA

American Gastroenterological Association Institute Guideline on the Use of Thiopurines, Methotrexate, and Anti–TNF-α Biologic Drugs for the Induction and Maintenance of Remission in Inflammatory Crohn's Disease

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- Induction of remission
  - Immunomodulators, steroids and biologicals are all more effective than placebo
- Maintenance
  - Immunomodulators, biologicals are more effective than placebo
  - Combination of immunomodulator/biological as effective as biological alone

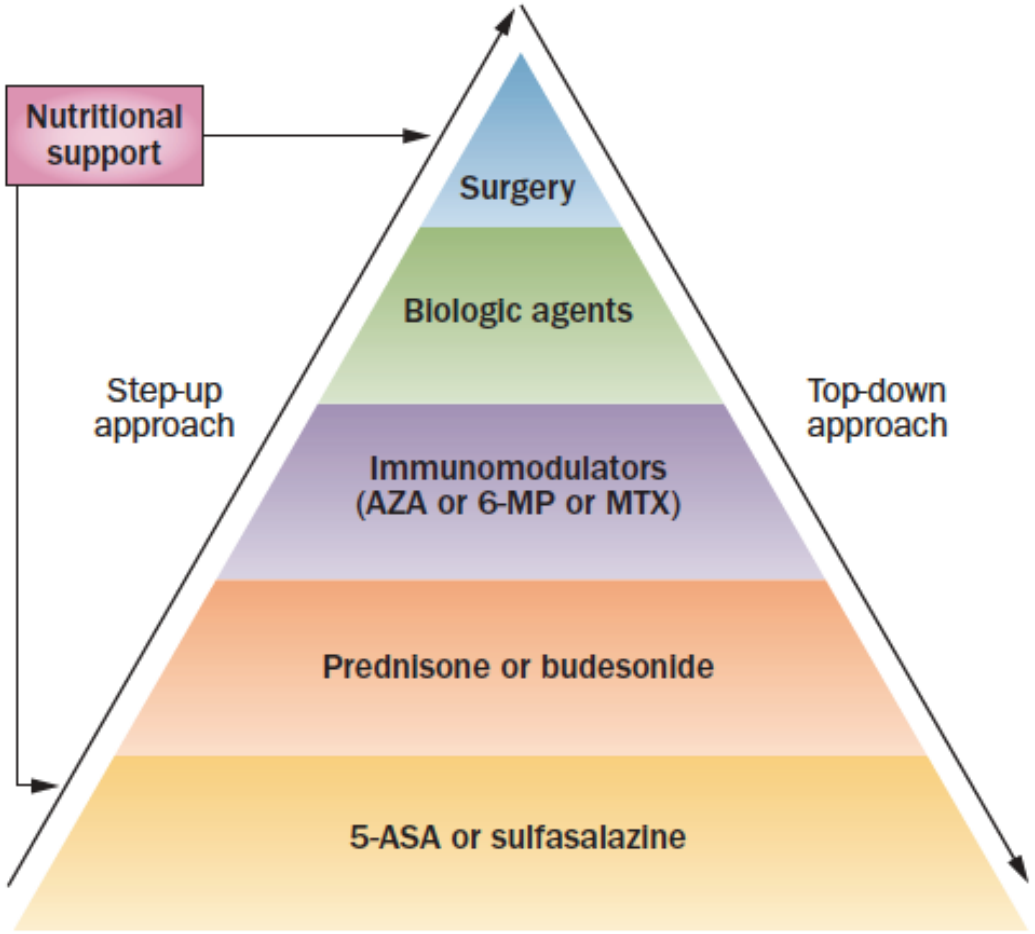
Risks

- Infections
  - Thiopurines and anti-TNF have a low risk
  - Opportunistic infections
    - Anti-TNF
  - Viral infections
    - Thiopurines & Methotrexate
- **Serious infections**
  - **CS > Immunomodulators and anti-TNF**
- **Overall risk: High in Inadequately treated IBD**
- **Lymphoma: Combination > Thiopurine alone**

New concepts in treatment of IBD

Reversal of Therapeutic Pyramid for Pediatric IBD

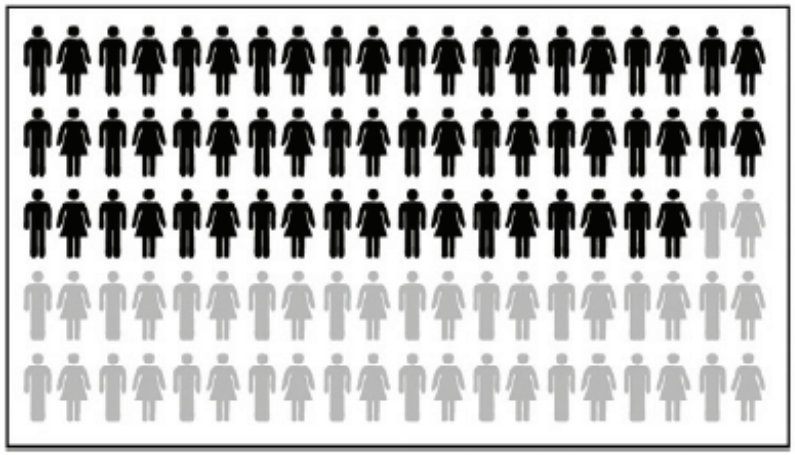
? Deep remission=less complications



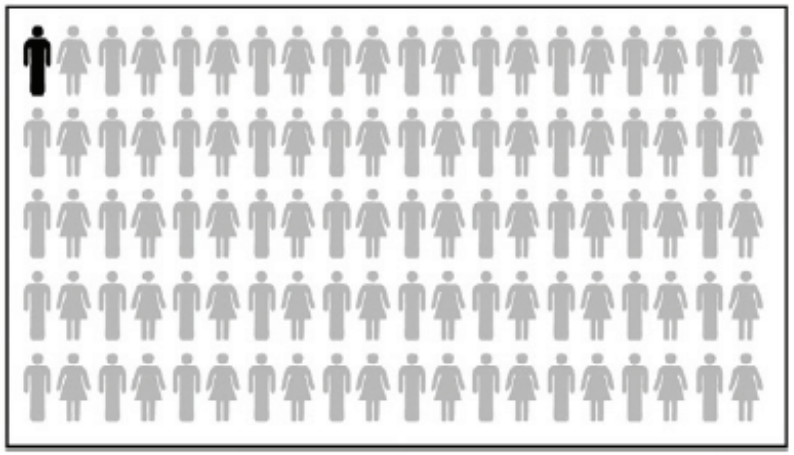
Nat. Rev. Gastroenterol. Hepatol. **11**, 99–108 (2014)

Risk of sub-optimal therapy>risk of side effects
How to deliver the message effectively?

Benefit = 58%
58 in every 100 people who take this medicine will experience benefit Y



Risk = 1%
1 in every 100 people who take this medicine will experience adverse event X

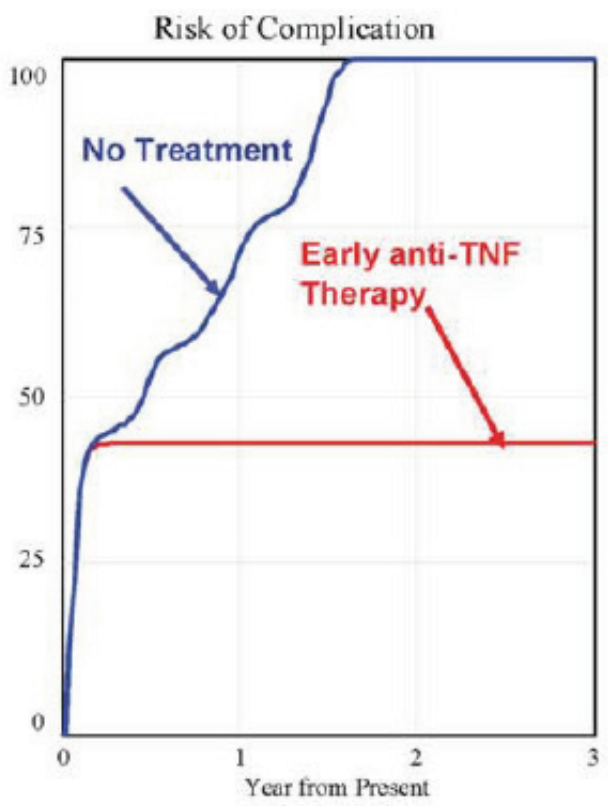


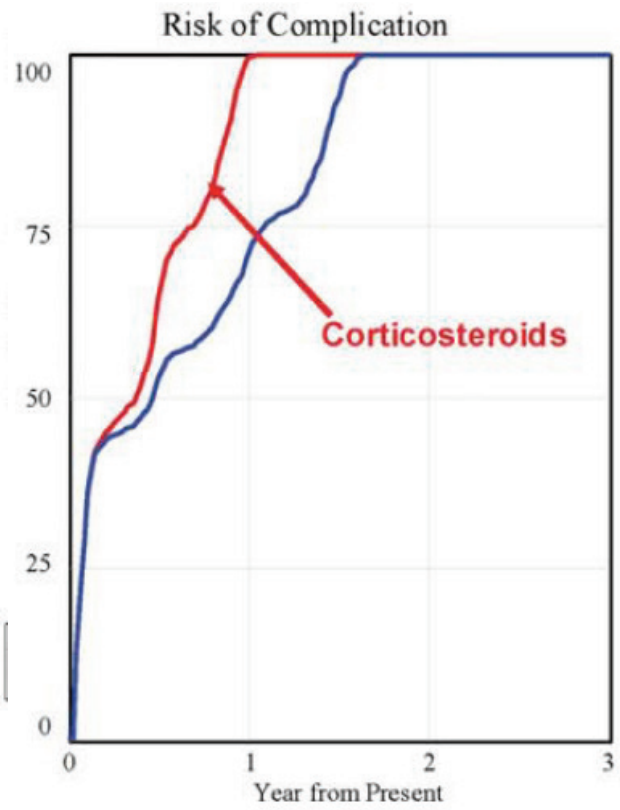
Journal of Crohn's and Colitis (2014)

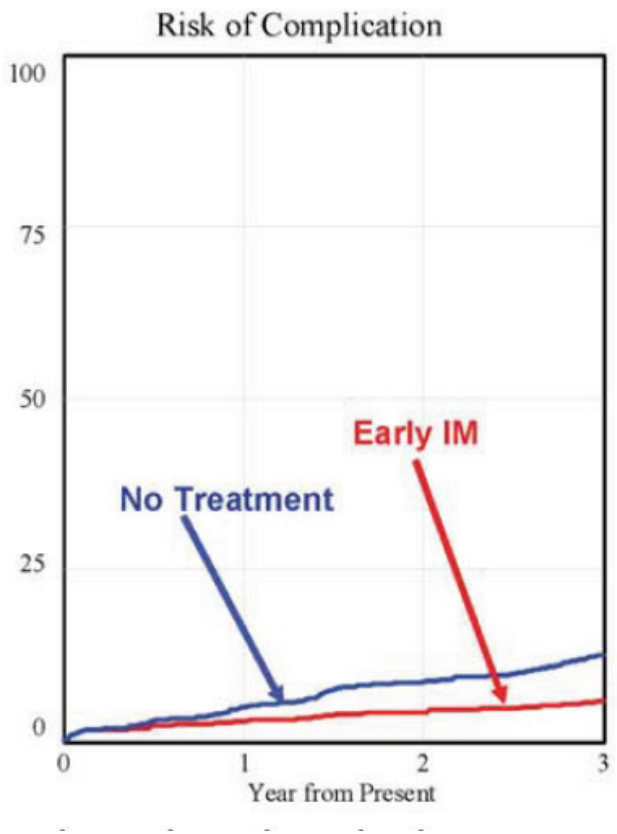
Reduced complication
With early TNF in a
High risk patient

Increased complication
With early steroid in a
High risk patient

Marginal benefit in a
Low risk patient with early
Immunomodulators



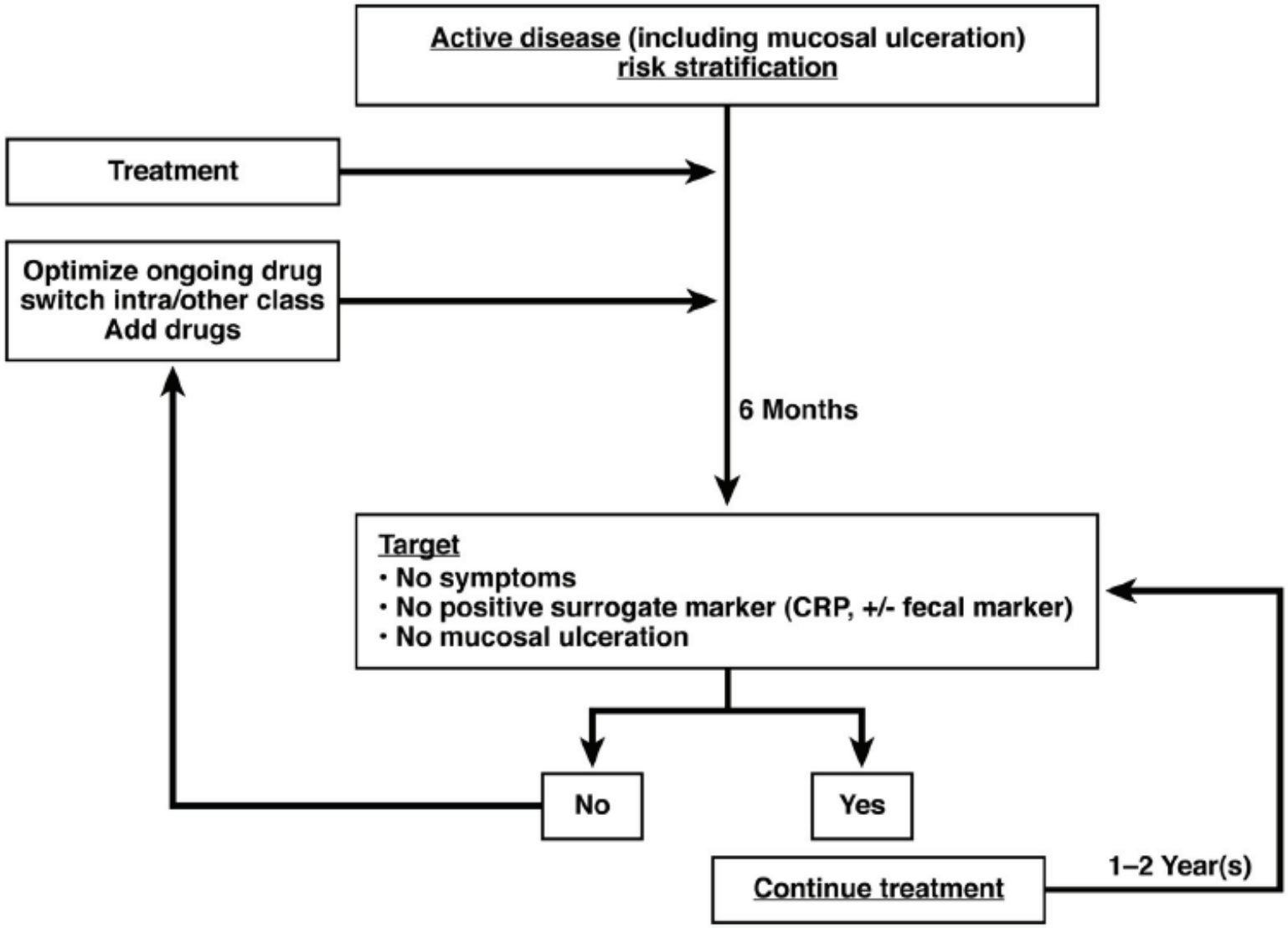




Hazard ratio: Increase risk with female gender, perianal or extensive small bowel disease, Older age at diagnosis, high serum antibodies

Inflamm Bowel Dis. Jan 2011(17)

Treat to Target: A new paradigm



Clinical Gastroenterology and Hepatology 2014;■:■–■

Quality Improvement in IBD

- **American Gastroenterology Association**
  - Accountability measures for physician quality reporting system
- **Crohn's and Colitis Foundation of America (CCFA)**
  - Top ten recommendations for high quality care
- **Pediatric improvecarenow Collaborative network**
  - Demonstrated improvement in disease activity

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CCFA: Quality Process Indicators

- **Treatment**
  - PPD before anti-TNF therapy
  - Prednisone >10 mg for 16 weeks: steroid sparing medications
  - Hospitalized without improvement for severe colitis on IV steroids for 3 days
    - Flex sig to R/O CMV + surgical consultation
  - Worsening diarrhea: check C.Diff
  - TPMT testing: before Mercaptopurine/Azathiopurine
- **Surveillance**
  - Every 1-3 years in patients with UC or crohn's colitis
  - Low-grade dysplasia: repeat surveillance in 6 months/or proctocolectomy
- **Health care maintenance**
  - IBD patients on immunosuppressive
    - Annual inactivated influenza, avoid live viral vaccine
    - Pneumococcal vaccine with booster every 5 years
  - CD with H/O smoking: recommend cessation, referral annually

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CCFA: Quality Outcome Indicators

- Corticosteroid use
  - Steroid free remission for a 12-month period
  - Patients on steroids beyond 112 days after diagnosis
- Number of days lost: school/work due to IBD
- Number of days hospitalized/year due to IBD
- Number of ED visits/year due to IBD
- Proportion of patients (POP) with malnutrition
- POP with anemia
- POP with normal disease-targeted health-related quality of life
- POP taking narcotics
- POP with nocturnal stools/bowel leakage
- POP with encopresis

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Special Considerations in Children

- Pediatric IBD:
  - severe phenotype
  - Higher risk of complications
- Goals: deep remission
  - Likely to decrease long term consequences
- Linear Growth
- Balance risk of side-effects with efficacy

Essential Principals

- Assessment of disease
- Avoid radiation when possible
- Monitor response
  - Symptoms
  - Laboratory markers: hemoglobin, albumin, CRP, sedimentation rate
  - Fecal calprotectin
  - Complications

Initial Work-up

- Stool studies
  - Clostridium Difficile, culture, ova/parasites
- Screen for tuberculosis
- Blood work
  - Blood counts, liver enzymes , albumin, sedimentation rate, C reactive protein
  - Immunoglobulins, celiac antibodies
  - Immunization status and antibody levels to vaccines
- Endoscopy and colonoscopy with biopsies
- Small bowel radiography
  - MR enterography preferred

Initial Treatment for Crohn's Disease

- **Perianal disease, deep ulcers and extensive small bowel disease: Use early TNF-α ab**
- Mild-mod colitis ± terminal ileum
  - Systemic steroids + IM
- Upper GI tract: mild-moderate
  - Acid suppression + IM ± steroids
- Limited mild ileocecal disease
  - Budesonide + monitor
  - No role of 5-ASA

Complicated Crohn's Disease

- Perianal Fistula: Seton placement+ biological/IM + Antibiotics
- Abscess
  - drain if possible
  - IV antibiotics (3-6 weeks)
  - parenteral nutrition ± EN
  - Then evaluate and consider surgery
- Small bowel obstruction
  - Stabilize patient
  - Early surgery better than steroids

Crohn's disease presenting as Growth Failure/ short stature

- Evaluate extent of disease
- **Consider early biologicals**
  - Age close to puberty
  - Inflammatory extensive disease
- **Consider early surgery**
  - Localized disease/stricture

Colitis Severity PUCAI(pediatric)

- Abdominal pain
  - No pain 0, can be ignored 5, cannot be ignored 10
- Rectal bleeding
  - None 0, small in <50%: 10, in >50%:20, blood>50%:30
- Stool consistency
  - Formed:0, partially formed:5, completely unformed:10
- Number of stools/24 hours
  - 0-2:5, 3-5:5, 6-8:10, >8: 15
- Nocturnal : No: 0, yes: 10
- Activity level: No limitation:0, occasional: 5, severe:10

Inactive <10, mild: 10-34, moderate 35-64, severe> 65

Gastroenterology 2007 Aug;133(2):423

Ulcerative Colitis

Newly diagnosed mild-moderate colitis

- Can start with 5-ASA
- Mod-severe colitis : Higher dose (100mg/kg)
- Oral and topical agents in distal disease
- Steroids if no improvement in 1-2 weeks
- Add IM if steroid dependent
- Biological if steroid unresponsive/dependent

Severe Ulcerative Colitis

Hospitalized patient on IV steroids

(1-2 mg/kg, maximum dose 60 mg/day)

- Rule out infections, Clostridium difficile
- Monitor for complications: albumin, toxic megacolon, anemia, electrolytes, dehydration, nutrition, infection
- **Day 3: PUCAI > 45** (moderate-severe colitis)
  - Consider flex sig to R/O infections, CMV, give PPD
- **Day 5: PUCAI>65** (severe colitis)
  - Consider TNF-α ab or calcineurin inhibitors
  - consult surgery

Monitoring During Maintenance Phase

- Every 3 months
  - Blood counts, urea, creatinine, ESR, CRP, liver enz
- Every 1 year
  - Vit D25(OH), B12, Folic acid
- Fecal calprotectin periodically, suspected flare
- On IM (desirable)
  - Optimize Mercaptopurine with 6TG and 6MMP levels
- On Biologicals (Still not standard of care)
  - Trough and antibody levels:
- Surveillance colonoscopy: 7-8 years after diagnosis

Conclusions

- Pathogenesis of IBD is evolving
- Pediatric IBD is often more severe and progressive
- Very early onset (Less than 2 years) may be a monogenic disease and require different treatment considerations
- Treatment approach in IBD is changing
  - Early aggressive approach
  - Risk stratification
  - Mucosal healing and deep remission
  - Drug optimization
  - Evaluation of effectiveness of therapy
  - Incorporate quality control and effectiveness measures

Acknowledgements

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Thank You