SERUM gASCA, ANTI-L AND SMOKING STATUS ARE ASSOCIATED WITH A CROHN'S DISEASE-LIKE PHENOTYPE AFTER PELVIC POUCH SURGERY FOR ULCERATIVE COLITIS

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Introduction

- 8-30% of patients with UC will require a colectomy due to medically-refractory disease or dysplasia

- IPAA (ileal pouch-anal anastomosis), after colectomy is the surgical procedure of choice following colectomy for UC

Background

- Inflammation is not seen in the terminal ileum in UC with the exception of backwash ileitis
- However, following IPAA, *de novo* inflammation (pouchitis) of the ileal reservoir occurs frequently in UC
- Features of CD, such as pre-pouch ileitis and perianal/fistulizing disease, may develop after IPAA in those with established UC
- Pouchitis and CD-like features that develop in individuals with confirmed UC prior to IPAA represents a unique *human* model to study factors that lead to ileal inflammation

Background

- Pouchitis develops in up to 50% of individuals and CD-like features in up to 15% of individuals with IPAA for confirmed UC

- The etiology of intestinal inflammation that develops in the ileum after IPAA surgery for UC is unknown and may represent:
  - recurrence of UC
  - development of CD
  - a unique form of IBD

- That significant inflammation of the ileal pouch develops in UC & not familial adenomatous polyposis (FAP) underscores the importance of inherited predisposition in the etiology of intestinal inflammation

Aisenberg *et al*. Am J Gastro 2004

Definition of Pouchitis

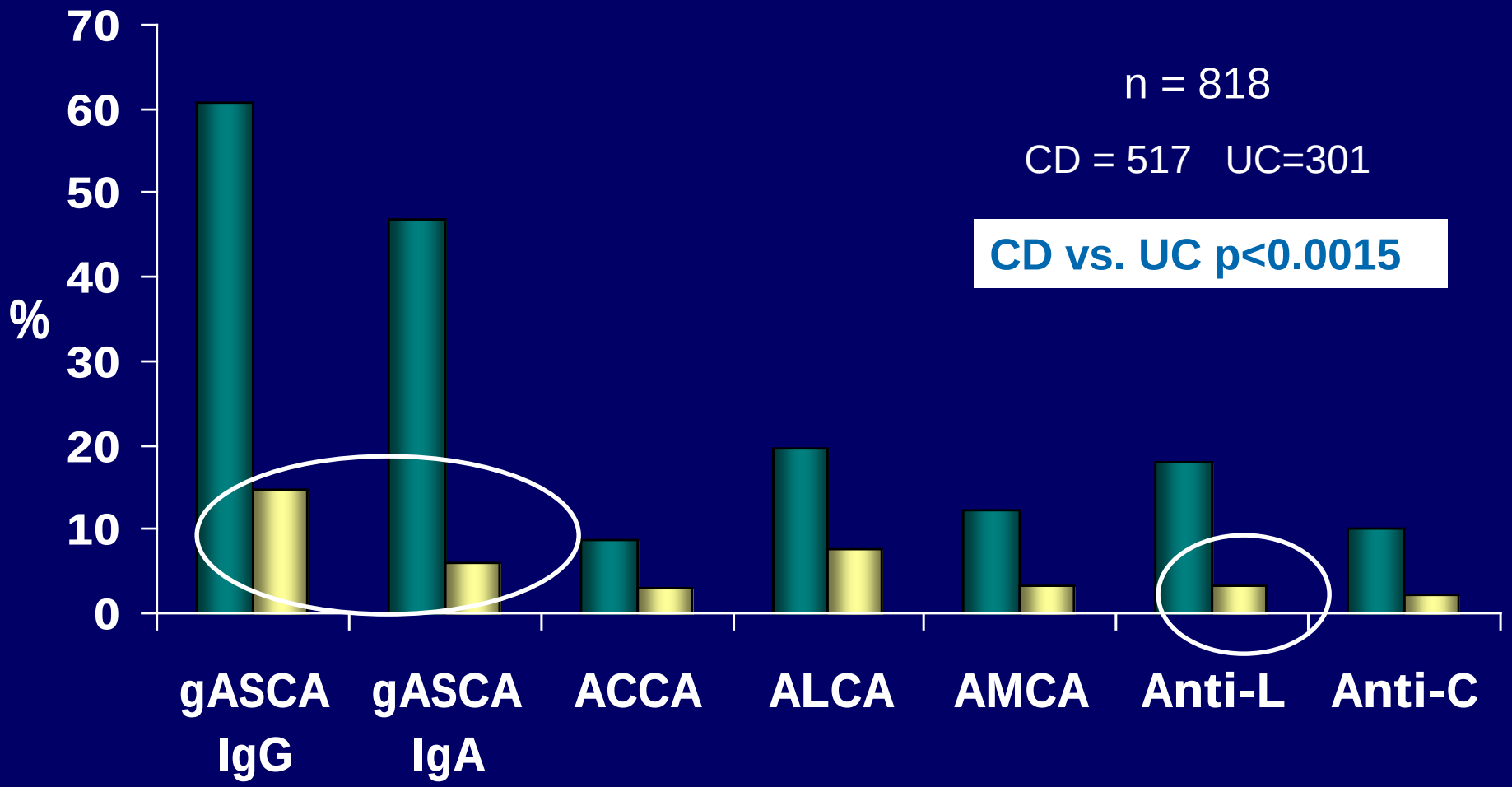
- No universally accepted diagnostic criteria
- Classification is based on clinical symptoms, endoscopy, and/or histology
- Symptoms:
  - Watery, frequent diarrhea
  - Urgency
  - Incontinence
  - Abdominal cramping
  - Malaise
  - Occasionally, rectal bleeding and fever

Shen B *et al.* Gastro 2001

Serum Biomarkers Associated with IBD

Antibody	Antigen	Non-IBD (%)	CD (%)	UC (%)
ASCA	Saccharomyces cerevisiae	5%	55–65%	5-15%
pANCA	Histone H_1, bacterial antigen?	<5%	2–25%	50–65%
Anti-OmpC	E. Coli	<5%	40–50%	2%
Anti - I2	Pseudomonas fluorescens	5-10%	54%	10%
Anti-Flagellin	cBIR	8-10%	~50%	6%

Anti-Glycan Antibodies: CD vs. UC



Seow et al. Am J Gastro (in press)

Methods

- Search of MSH pelvic pouch database for:
  - Patients with UC who underwent IPAA with at least one year of follow up following ileostomy closure
  - Pre-colectomy diagnosis of CD was excluded by chart review; review of endoscopic reports/histology and review of colectomy pathology (Dr. R. Riddell)
- Patients contacted by letter & telephone with consent forms
- Patients consenting to participate underwent interview, clinical chart review and blood sample collection (DNA, serum)

Methods: Patient Classification

Group 1 – No Pouchitis/Limited Acute Pouchitis:

- No symptoms or dx of pouchitis by patient self-report; AND
- No evidence of pouchitis in medical record; OR
- "Acute" pouchitis (≤3 episodes/yr and responsive to short course of antibiotics)

Group 2 – Chronic Relapsing Pouchitis:

- Self-report and chart review evidence of ≥4 episodes/yr; AND
- Antibiotic/medication-dependent; OR
- Antibiotic/medication-refractory

Shen B *et al.* CGH 2008

Methods: Patient Classification

Group 3 – CD-like Phenotype:

- Inflammation/ulceration in the pre-pouch ileum (afferent limb) or small bowel on endoscopy/imaging in the absence of NSAID use; OR

- Non-surgery related perianal fistula (≥1 year after ileostomy closure)

Shen B *et al.* CGH 2008

Methods: Serological Assessment

- Anti-Glycan antibody panel tested on all available serum samples (Glycominds, Israel)

  - gASCA - Anti *Saccharomyces cerevisiae*
  - ACCA – Anti Chitobioside Carbohydrate
  - ALCA – Anti Laminaribioside Carbohydrate
  - AMCA – Anti Mannobioside Carbohydrate
  - anti-L – Anti Laminarin
  - anti-C – Anti Chitin

Results

1670 IPAA pts in MSH database

↓

424 patients recruited & consented

↓

69 excluded

colectomy pathology suggestive of CD;
post-IPAA insufficient clinical follow up

↓

355 pts with clinical data only

↓ 52 pts without serology data

303 pts with clinical & serologic data

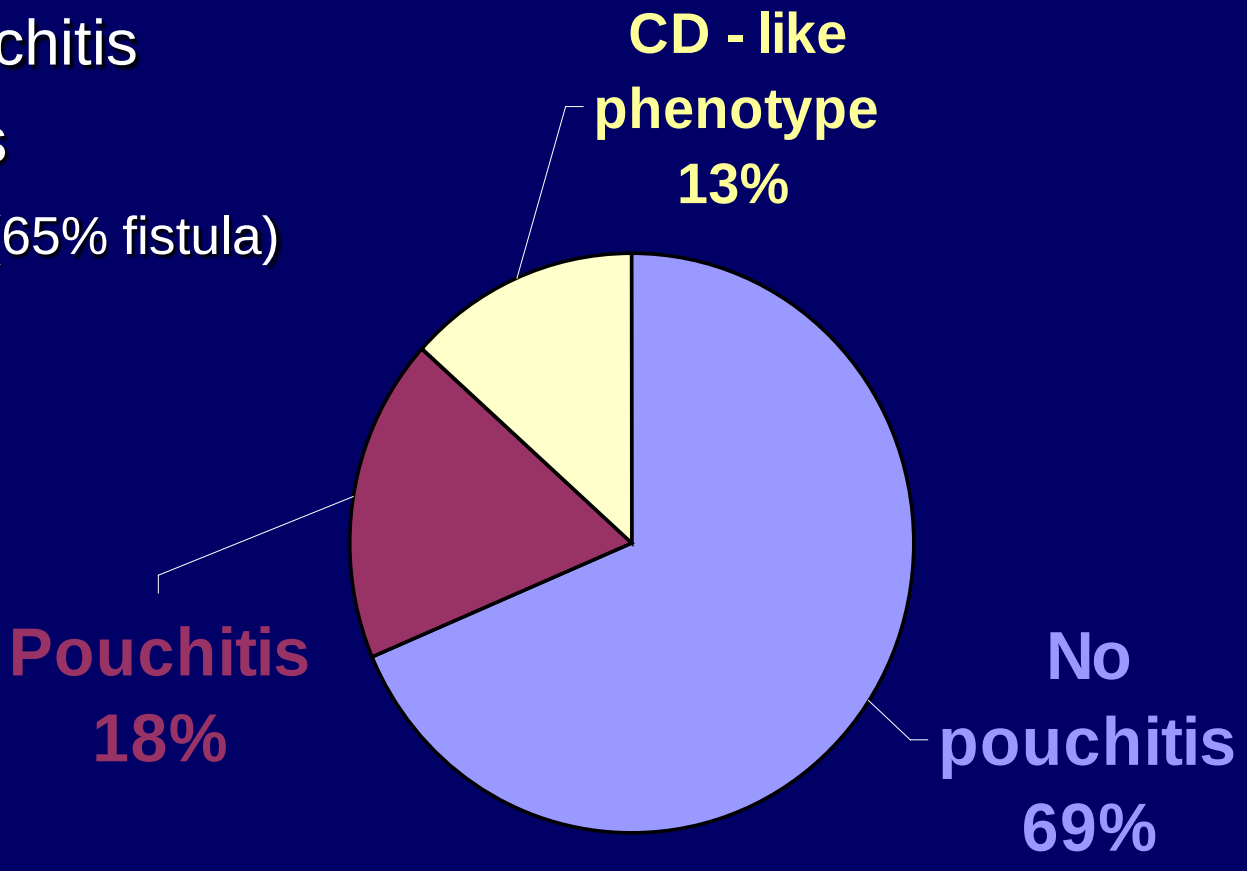
Results

- 355 patients:

  (1) 246 no pouchitis

  (2) 64 pouchitis

  (3) 45 CD-like (65% fistula)



Disease Characteristics by Group

	No Pouchitis (n=246)	Pouchitis (n=64)	CD-like (n=45)	P-value
Mean Age (yrs) at UC Dx	31	29	28	0.23
Mean Duration Dx (yrs) pre-op	6.4	7.2	5.7	0.08
Mean Age (yrs) at IPAA	38	36	34	0.19
Caucasian (%)	86	75	81	0.08
Ashkenazi Jew (%)	**7**	**19**	**14**	**0.01**
Family Hx UC (%)	10	9	4	0.46
Family Hx CD (%)	5	2	4	0.50
Backwash Ileitis (%)	1	0	2.5	0.51

Variables Significantly Associated with Outcome after IPAA

	No Pouchitis (n=246)	Pouchitis (n=64)	CD-like (n=45)	P-value
Pouch Failure (%)	1	6	26	<0.0001
Current Smokers (%)	4	6	24	<0.0001
Never Smoked (%)	52	45	31	0.04
Axial Arthritis (%)	5	5	18	0.004
Pouch F/U (yrs)	9	9	12	0.01

Serology and Outcome after IPAA

	No Pouchitis (n=208)	Pouchitis (n=56)	CD-like (n=40)	P-value
Colectomy to serum draw (yrs)	9.4	9.3	12.4	0.08
gASCA (%)	**19**	**16**	**40**	**0.006**
Anti-L (%)	**4**	**2**	**13**	**0.04**
AMCA (%)	<1	2	3	0.40
Anti-C (%)	2	2	5	0.58
ALCA (%)	17	21	23	0.63
ACCA (%)	12	9	8	0.68

Conclusions

- ASCA, anti-L and smoking are associated with a CD-like phenotype after IPAA for UC
- These features, typically related to CD, are associated with development of a CD-like phenotype after surgery for UC
- These data suggest that either:
  - ASCA and anti-L become positive after IPAA for UC due to the development of a microbial environment in the pouch similar to that found in Crohn's disease; OR,
  - ASCA and anti-L are positive prior to IPAA for UC and represent markers for a subset of UC at risk for a CD-like phenotype
- Future Directions:
  - Analysis of other serum markers (pANCA, anti-OmpC, anti-flagellin) and genetic markers is in progress