

# Nouveaux marqueurs biologiques dans les MICI



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- Marqueurs génétiques
- Anticorps anti-glycan et anti-bactérien
- Calprotectine fécale, lactoferrine
- CRP
- CMV dans les colites graves

# Genetics of CD

## *Results of the US-UK-Belgian meta-analysis*

- **> 30 gene loci** definitively associated with CD
- Genes involved in **immune regulation, host-bacteria interaction, auto-immunity...**
- **Common genes** with other inflammatory and auto-immune diseases
- Broad **genetic heterogeneity** of CD
- A huge number of **new tracks** to **understand** and develop **new treatments** for CD
- ...but no **diagnostic value**

# The genetic MATRIX of CD

Pat.	CARD15	IRGM	ATG16L1	ICOSLG	MUC19	STAT3	JAK2	IL23-R	TNFSF15	PTPN22	PTPN2	CDKAL1	MHC
FCOLL	0	0	1	2	0	1	0	2	2	2	0	1	1
SDESS	0	0	2	0	0	1	2	2	2	2	0	1	0
CPIRO	0	0	0	0	0	1	2	2	0	2	1	1	0
JCARP	1	1	0	2	0	1	1	2	2	2	0	2	0
INOTE	0	0	2	1	0	1	0	2	2	1	0	2	0
PAROH	0	1	1	1	0	1	1	2	1	2	0	1	1
KEBOH	1	0	2	2	0	1	2	2	2	1	0	2	0

# Clinical usefulness of genetic markers in IBD

- No marker with diagnostic value
  - The vast majority of carriers of at risk alleles for CARD15 and IL-23R will not develop CD
  - The same for IL-23R and other genetic markers in UC
- CARD15 variants are significantly associated with ileal CD
  - Almost all CARD15 variant homozygotes with CD have ileal disease
  - Carriers of CARD15 variants
    - 60% among ileal CD
    - 20% among colonic CD
    - 15% among controls
- No other clear and striking association with subphenotypes of IBD

# Circulating antibodies associated with IBD

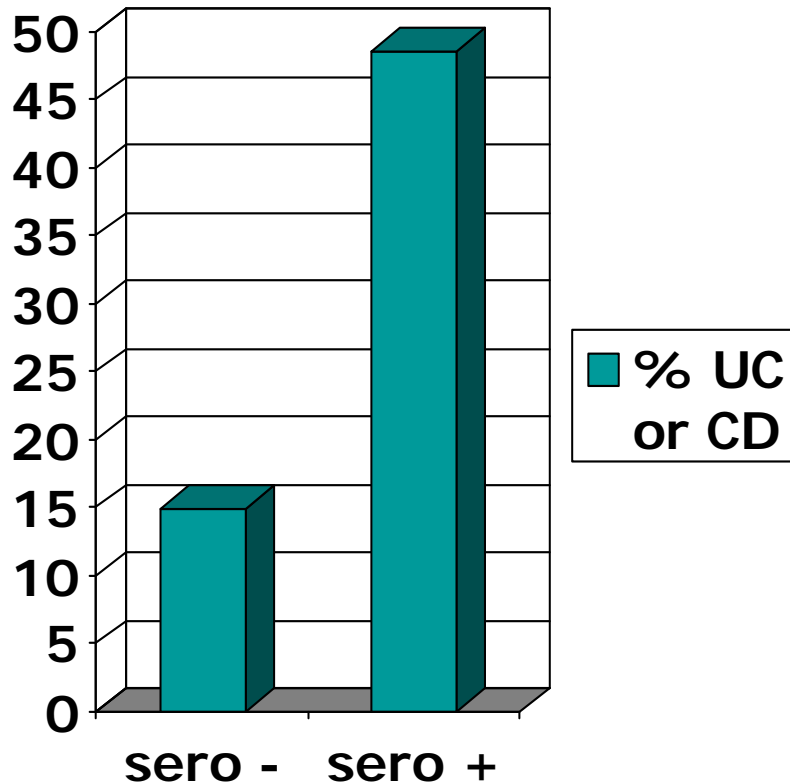
- ASCA: mannose epitopes from the yeast *saccharomyces cerevisiae*
- pANCA: unidentified nuclear lamina protein of neutrophils
- Anti-Ompc: *E. Coli* outer membrane protein C
- Anti-CBir: flagellin antigen from intestinal flora
- Anti-I2: protein from *pseudomonas fluorescens*
- ALCA: laminaribioside-laminarin from cell walls of saprophytic and pathogenic fungi and yeast, oats and algae
- ACCA: chitobioside-chitin from cell walls of bacteria and yeast
- AMCA: mannobioside

# Diagnostic value of ASCA and pANCA in IBD

- ASCA+ and pANCA- :diagnosis of CD
  - Sensitivity: 49-64%
  - Specificity: 94-97%
  - Positive predictive value: 86-96%
- ASCA- and pANCA+ :diagnosis of UC
  - Sensitivity: 44-57%
  - Specificity: 94-97%
  - Positive predictive value: 75-92.5%

*(1) Quinton et al. Gut 1998; 42: 788. (2) Peeters et al. Am J Gastroenterol 2001; 96:730. (3) Sandborn et al. Inflamm Bowel Dis 2001; 7: 192. (4) Linskens et al. Eur J Gastroenterol Hepatol 2002; 14: 1013*

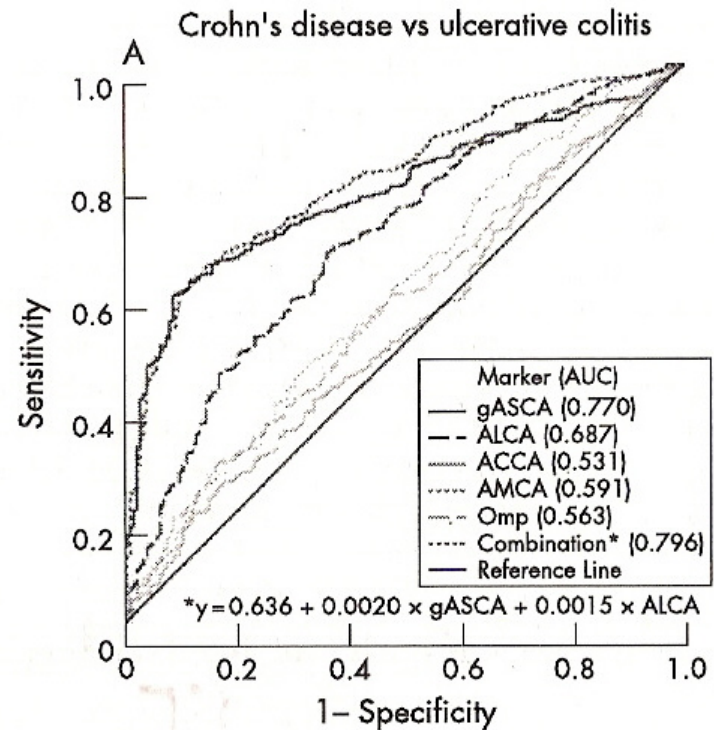
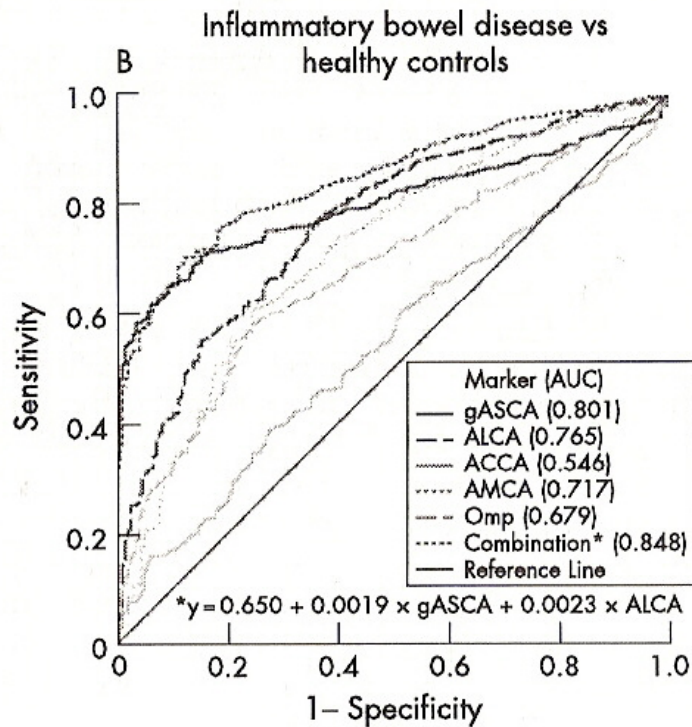
# ASCA and pANCA in indeterminate colitis



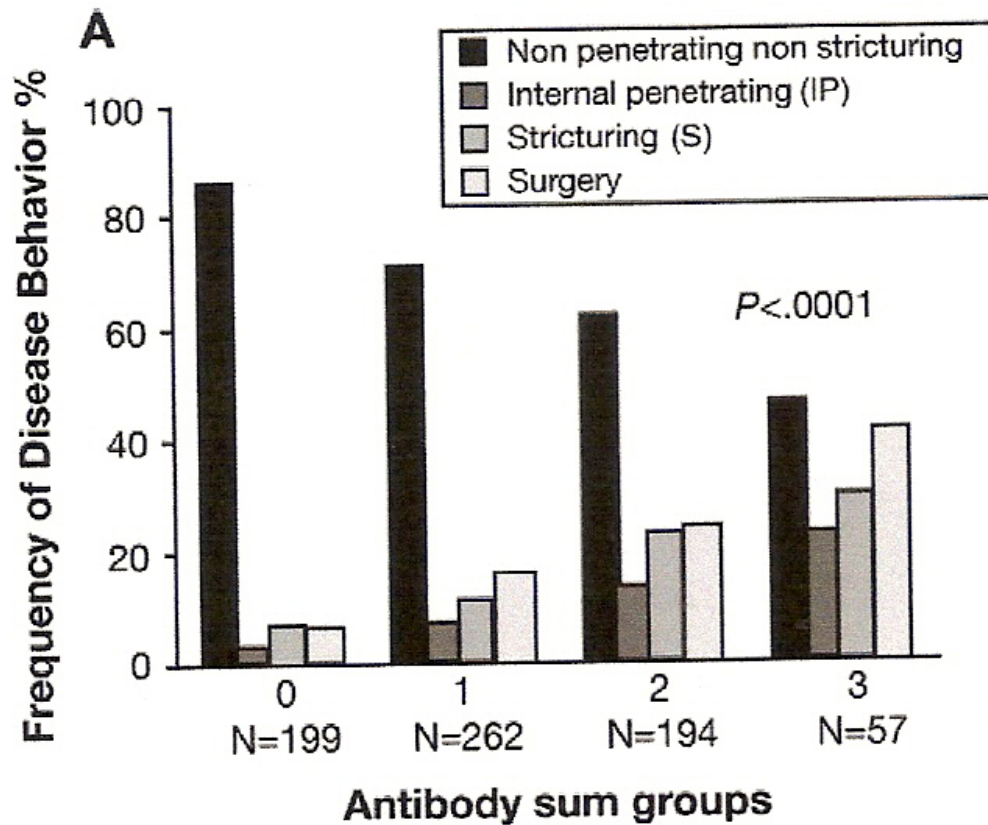
*P* < 0.001

- 97 IC patients followed up over 4 years
- 50/97 were sero+
- ASCA+/pANCA- predicts CD in 80%
- ASCA-/pANCA+ predicts UC in 63.6%

# Diagnostic yield of an antibody combination

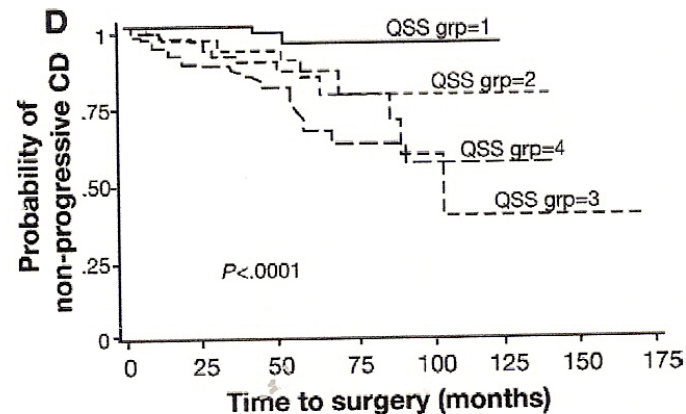
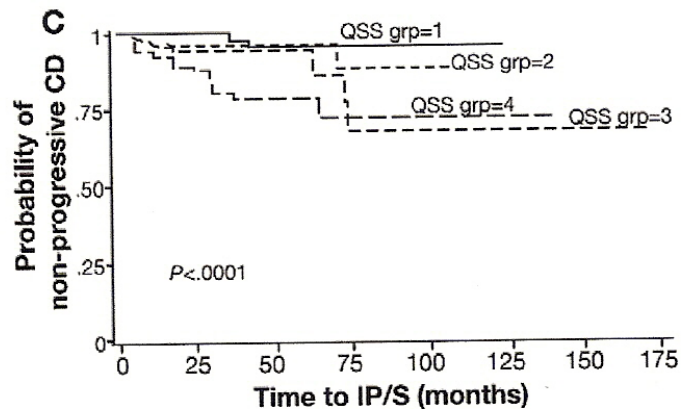
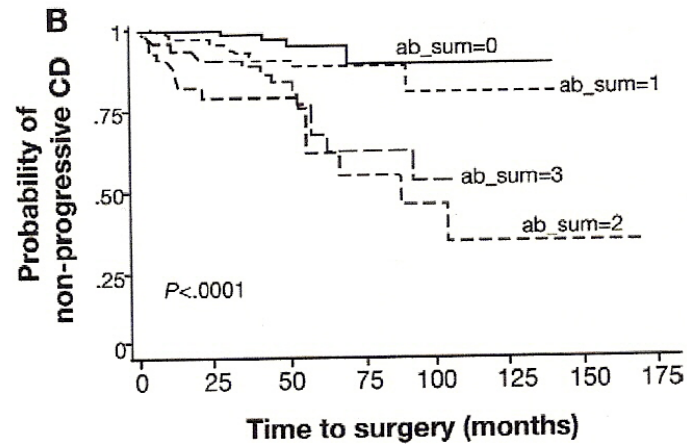
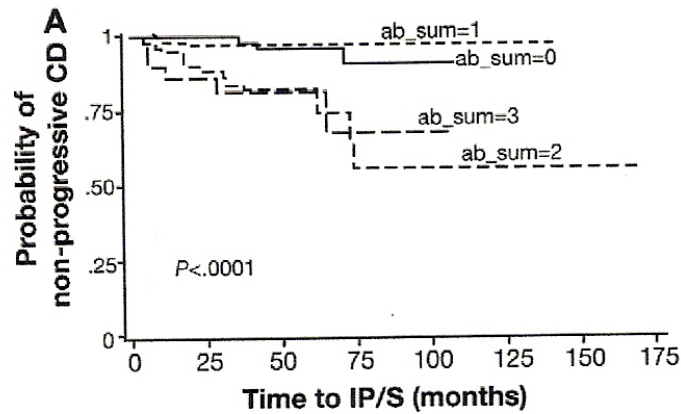


# Complicated CD is associated with the number of positive antibodies anti-CBir, anti-OmpC, ASCA



# Antibody positivity and titles are predictive of complicated CD

## anti-CBir, anti-OmpC, ASCA



# **Clinical use** of diagnostic antibodies in IBD

- No systematic use
- No clear added value of new markers over ASCA and pANCA
- Relative usefulness of ASCA and pANCA **unclassified colitis**
- Anti-bacterial and anti-glycan antibodies may help and predict **complicated CD**
- Relative usefulness of ASCA and pANCA in **IBD difficult to diagnose**

# Negative **CD serology** predicts negative small bowel WCE

- 835 patients with WCE in the University of Michigan health system
- Inclusion: clinical suspicion of CD, negative upper and lower endoscopy, serology panel and WCE
- Interpretation of WCE: normal, abnormal not CD, possible CD (erosions, mucosal breaks), probable CD (deep mucosal erosions, ulcers, strictures)- possible and probable considered +
- 67 patients, 58% with negative CD serology
- In case of negative serology, 95% negative WCE (95%CI=81-99%)
- In case of positive serology, 41% positive WCE (95%CI=23-61%)
- **Predictive value of serology for a positive WCE:**
  - **Sensit: 85%, Specif: 68%, PPV: 41%, NPV: 95%**

# Fecal calprotectin

- Correlates with fecal excretion of indium-111-labelled granulocytes in IBD

*Roseth et al. Scand J Gastroenterol 1999; 34: 50*

- Can **differentiate between IBD and IBS**

*Tibble et al. Gut 2000; 47: 506*

*Costa et al. Dig Liver Dis 2003; 35: 642*

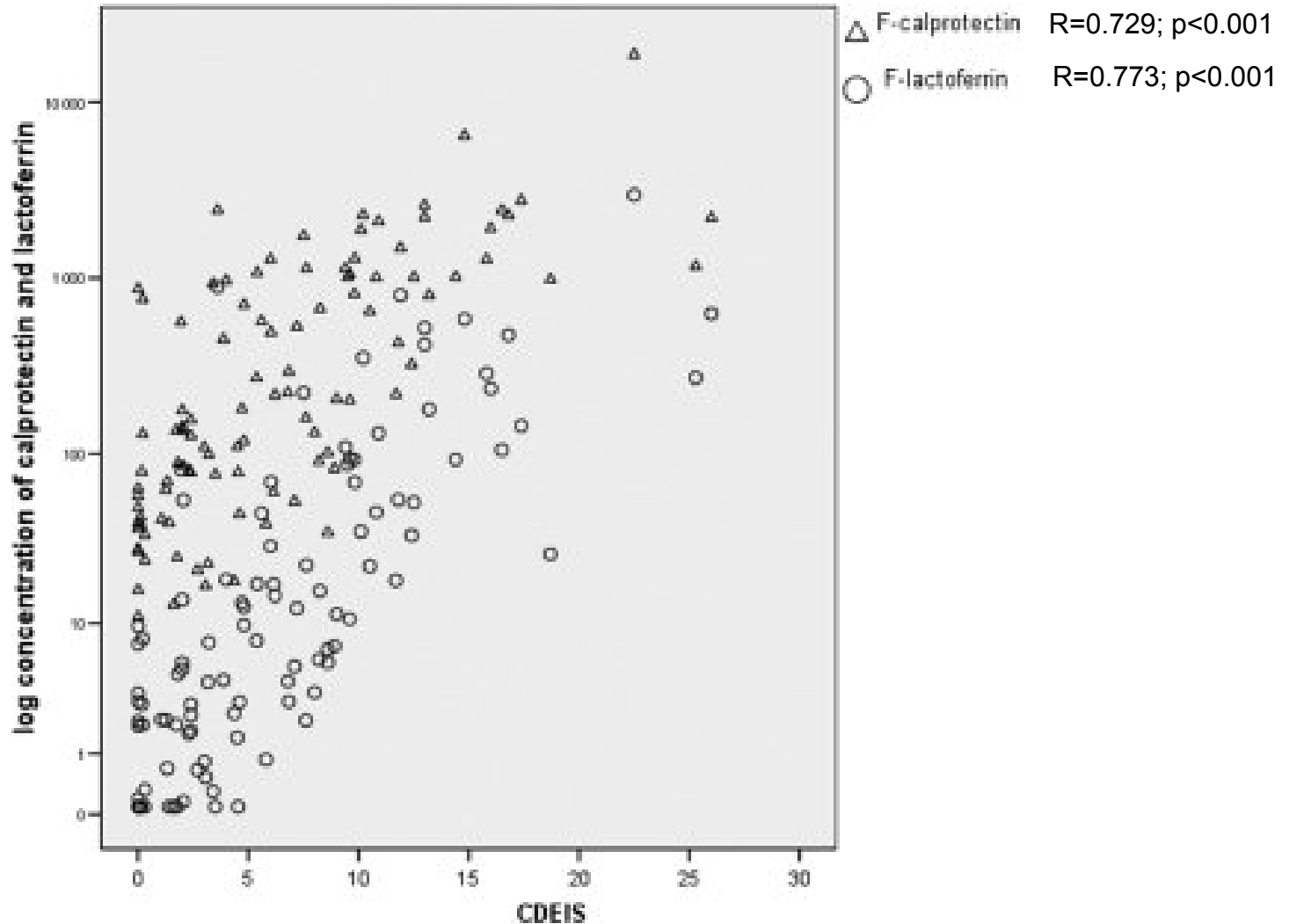
*Olafsdottir et al. Acta Paediatr 2002; 91: 45*

- Can not differentiate between IBD and colorectal cancer

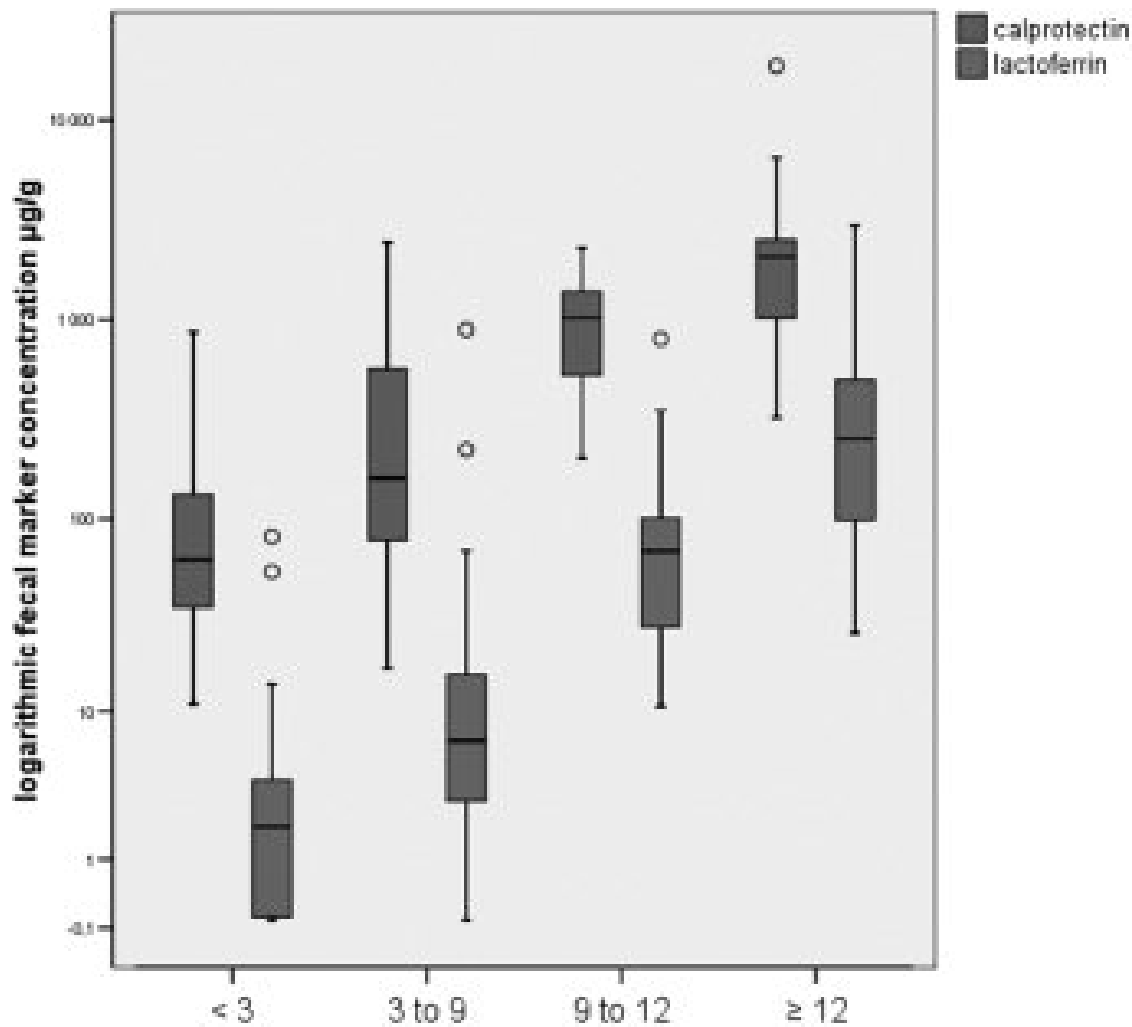
*Summerton et al. Eur J Gastroenterol Hepatol 2002; 14: 841*

*Costa et al. Dig Liver Dis 2003; 35: 642*

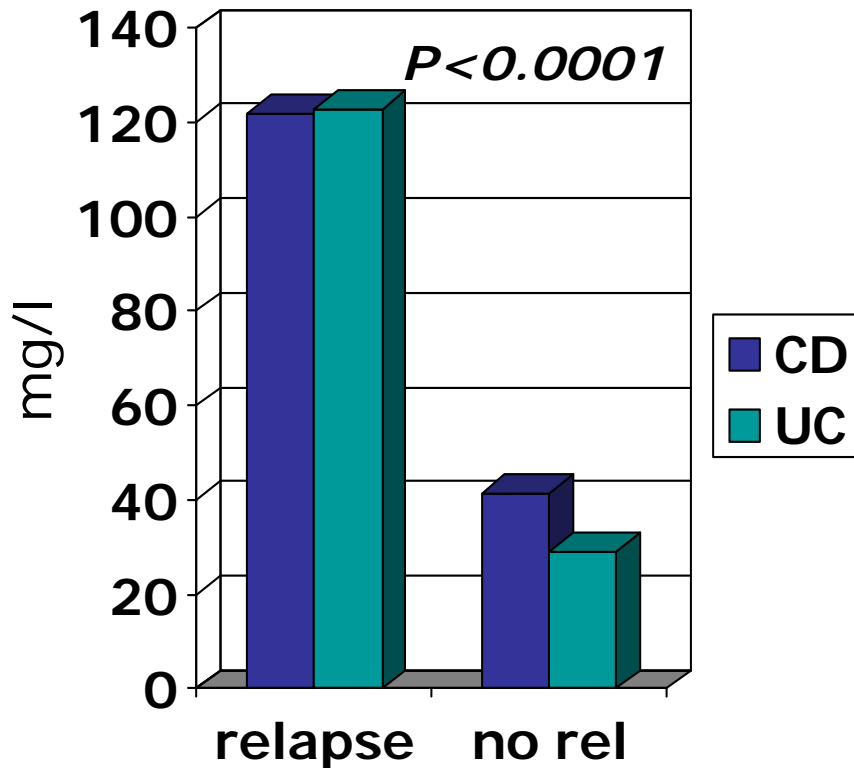
# Correlation between fecal calprotectin, lactoferrin and endoscopic activity in CD



# Fecal calprotectin and lactoferrin by CDEIS group

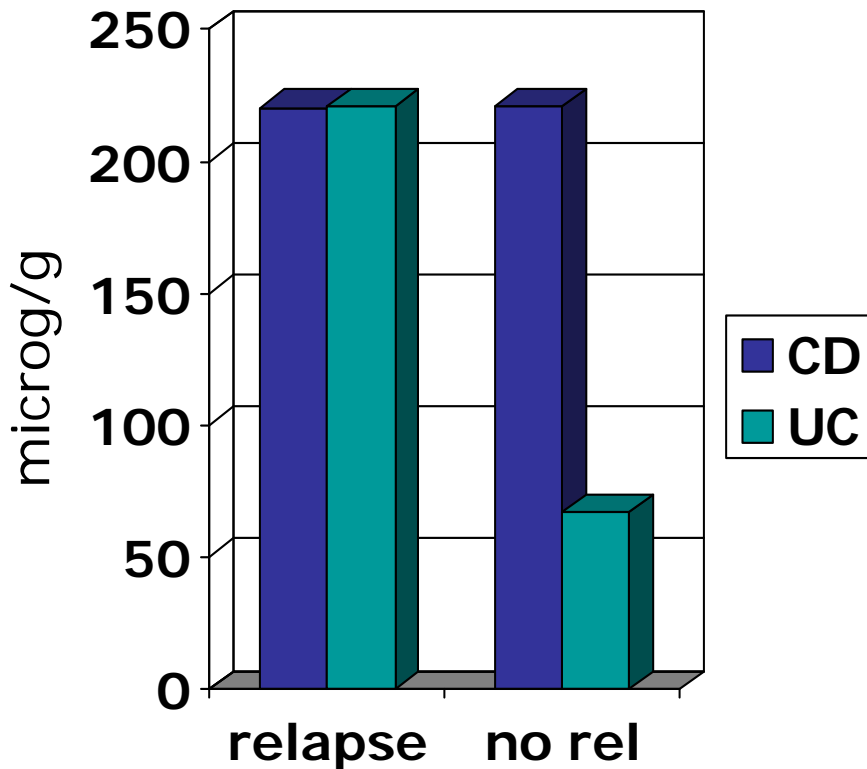


# Fecal calprotectin and prediction of relapse in IBD



- 43 CD and 37 UC in remission
- At 50 mg/l, calprotectin had a sensitivity of 90% and a specificity of 83% for relapse prediction
- Relapse predictive value of calprotectin was superior to intestinal permeability

# Fecal calprotectin can predict relapse in UC but not CD



- 38 CD and 41 UC in remission
- Above 150 microg/g, calprotectin was associated with a twofold and 14-fold increase in relapse risk in CD ( $p=0.395$ ) and UC ( $p<0.0001$ ) respectively

# Fecal calprotectin: **next step** for clinical use

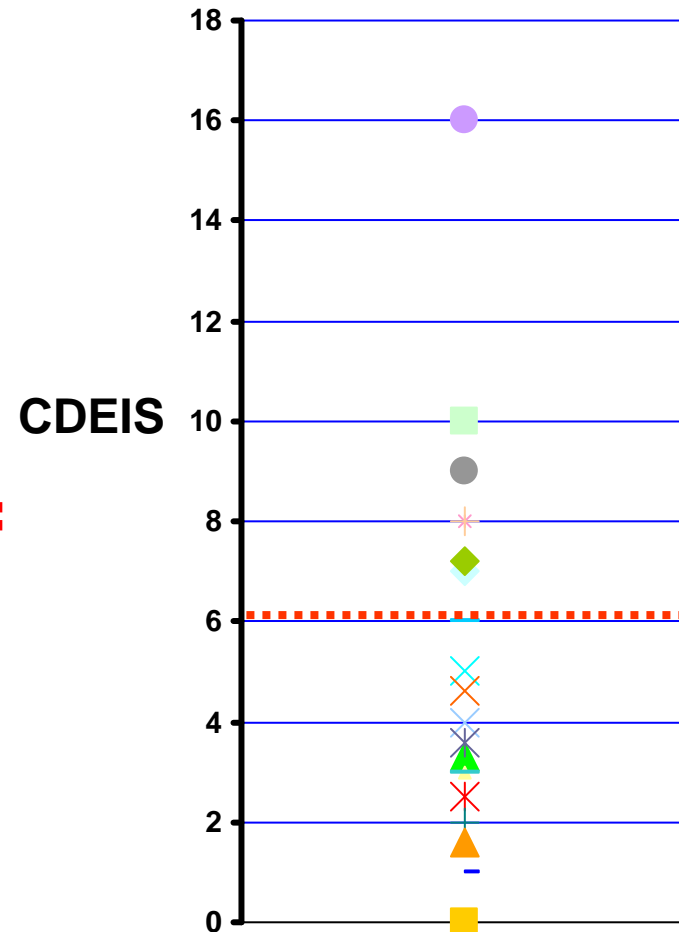
- Confirmed as a **good marker** of organic ileo-colonic disease
- Prospective studies in **UC** with adaptation of treatment according to fecal calprotectin
- In CD: study the **performance of individual variation** of fecal calprotectin in response to treatment, in parallel to clinical response and in the prediction of relapse

# Correlation between computed tomography enterography and endoscopic and biological scores in CD

- 143 CD patients: ileocolonoscopy, CRP, CT enterography
- Endoscopic score correlates with CT bowel enhancement, comb sign, fat density
- Histological inflammation correlates with bowel enhancement
- **CRP correlates with fat density** but not with bowel enhancement

# Endoscopic activity in CRP-negative clinically-active CD

- Endoscopic lesions: 91,6%
- Low endoscopic activity:
  - **median CDEIS= 3,4** (0-16)
  - only 33,3% with CDEIS  $\geq 6$



# CRP and relapse prediction in CD

- CRP predicted relapse of CD in two successive cohorts (RR=4.3 and 4.7; P=0.04 and 0.03)

*Louis et al. Eur J Gastroenterol Hepatol 1997; 9: 939*

- Elevated CRP was associated with risk of relapse after stopping azathioprine in longlasting quiescent CD (RR of relapse= 16.9 (95%CI= 2.7-104.3) if CRP > 20 mg/l)

*Lemann et al. Gastroenterology 2002; abstract DDW*

# CRP as **predictive marker** in UC

- CRP is less increased in UC than CD
- **Severe UC** is often associated with increased CRP
- On day 1 of **treatment of severe colitis with cyclosporine**, CRP > 45 mg/l (together with fever, tachycardia and severe endoscopic lesions) is associated with increased risk of colectomy
  - » Cacheux et al. *Am J Gastroenterol* 2008;103:637
- On day 3 of **treatment of severe colitis with steroids or cyclosporine**, CRP > 45 mg/l (together with > 8 stools/day) is associated with risk of colectomy
  - » Travis et al. *Gut* 1996;38:905
- High CRP **before infliximab** is predictive of colectomy (RR of colectomy = 7.2 (95% CI = 1.7-30.8) if CRP > 5 mg/l)
  - » Ferrante et al, submitted 2008

# Use of **CRP** in clinical practice in IBD

- Active CD may have **normal CRP** (mostly superficial lesions)
- Evaluate with endoscopy or CT patients with normal CRP who are **candidates for anti-TNF**
- Elevated CRP is **predictive of relapse in CD**
- High CRP before treatment or persisting after a few days of treatment is **predictive of non response and further colectomy in severe UC**

# CMV infection and severe colitis

- CMV **reactivation** (Antigenemia or blood DNA) is frequent in active UC (more than half of the sero-+ patients). There is no association with disease outcome and rarely sign of systemic illness.
  - » *Matsuoka et al. Am J Gastroenterol 2007;102:331*
- Less than 25% of patients with **CMV DNA in the colon** have inclusion bodies or antigenemia
  - » *Yoshino et al. Inflamm Bowel Dis 2007;13:1516*
- **CMV colitis** (inclusion bodies and/or positive immunohistochemistry) is essentially found in seropositive, steroid-refractory patients.
  - » *Domenech et al. Inflamm Bowel Dis 2008*
  - » *Kojima et al. Scand J gastroenterol 2006;41:706*
- Patients with CMV colitis may have **favourable outcome with conventional and without antiviral treatment**. The advantage of anti-viral treatment has not been specifically evaluated
  - » *Criscuoli et al. Di Liver Dis 2004;36:818*

# **Testing** for CMV reactivation in **severe colitis**

- In severe steroid-refractory colitis:
  - The most useful test is looking for **inclusion bodies and/or positive immunohistochemistry**
  - A preliminary test to look for **antigenemia or blood viral DNA** may help but has low positive predictive value for CMV colitis and often no particular clinical significance
  - The advantage of an anti-viral treatment in patients with active CMV colitis is not EBM but may be considered on a **case by case basis**

# Conclusions

- No indication of **genetic testing** in clinical practice
- **pANCA and ASCA** testing may help in **particular situation**
- No indication of new **anti-bacterial and glycan antibodies** in clinical practice
- **Fecal calprotectin** may be useful in the early workup of IBD suspicion. Its interest in the F-up of IBD patients remains to be proven
- **CRP** is not always elevated in active CD. High CRP is predictive of relapse in CD and poor outcome in severe UC
- Colonic biopsies looking for active **CMV** colitis may be useful in steroid-refractory colitis