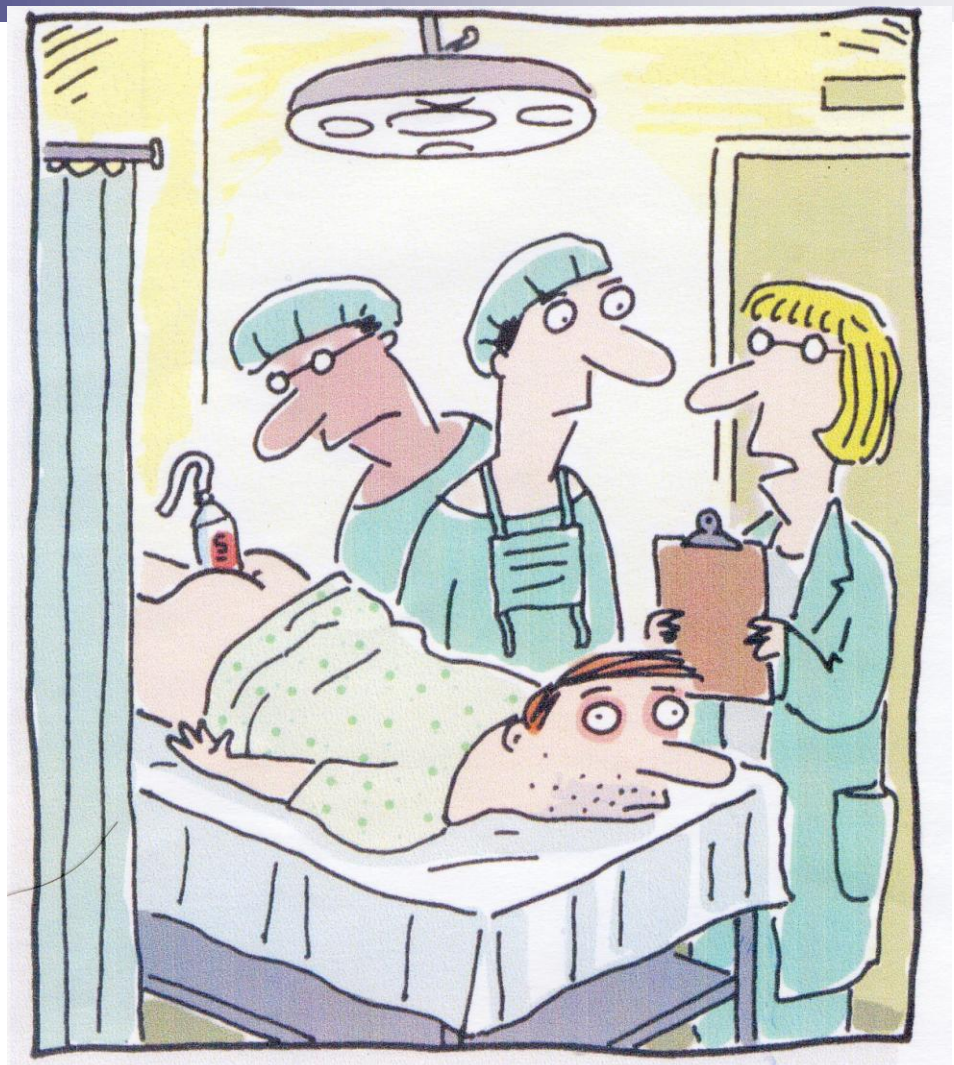
IBD in teenagers – Biological and Transition

Dr Warren Hyer
Consultant Paediatric Gastroenterologist
St Mark's Hospital
Chelsea and Westminster Hospital



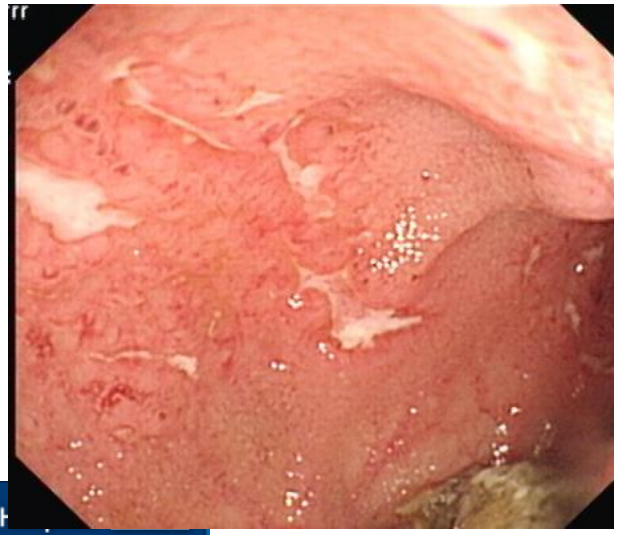
" That's correct, Doctor. He claims
that the instructions said
to squeeze toothpaste from bottom."

Conflict of Interest

- None to declare
- Fee for presentation

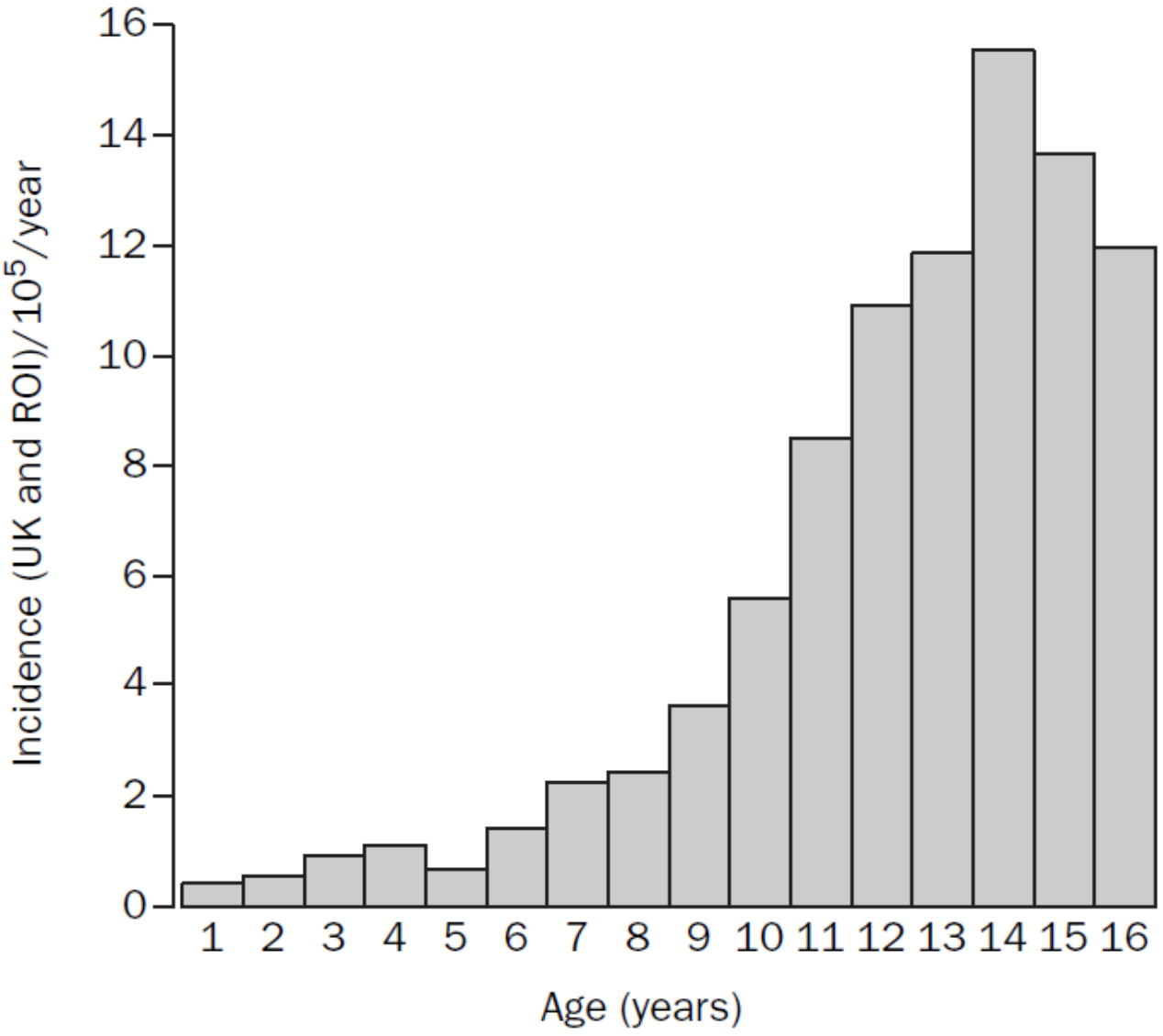
Plan for the next 25 mins

- The size of the case load
- Need for early immunosuppression
- Timing of biological therapies
- Transition of care



Specific issues:

- Disease is more extensive
- Higher requirements for immunosuppression
- Avoidance of steroids
- Bone mineralisation
- Growth implications
- Earlier need for surgery



Incidence of childhood inflammatory bowel disease in the UK and ROI during 1998 and 1999

All figures are incidence per 100 000 children (95% CI) aged younger than 16 years.

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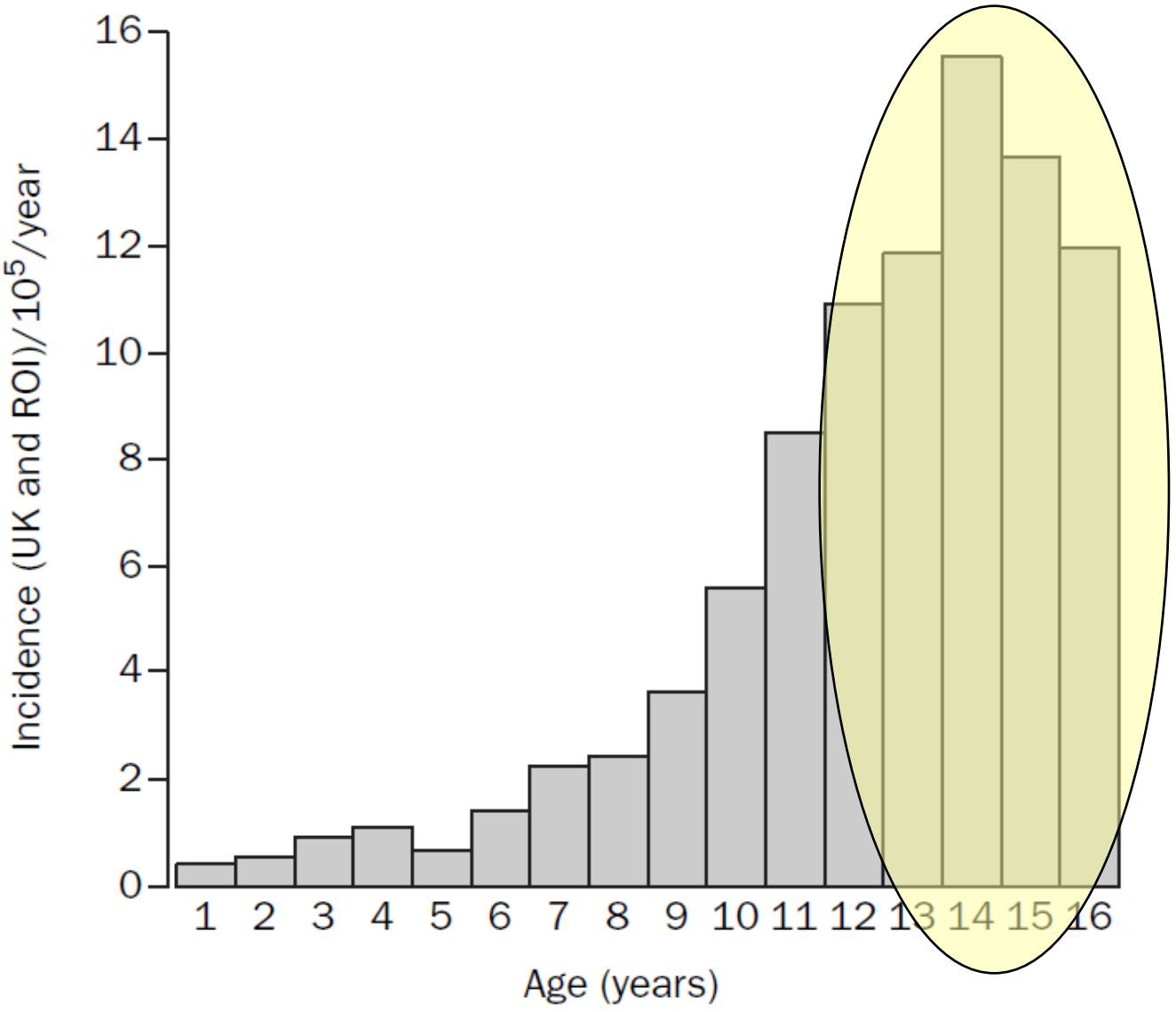

Incidence of childhood inflammatory bowel disease in the UK and ROI during 1998 and 1999

All figures are incidence per 100 000 children (95% CI) aged younger than 16 years.

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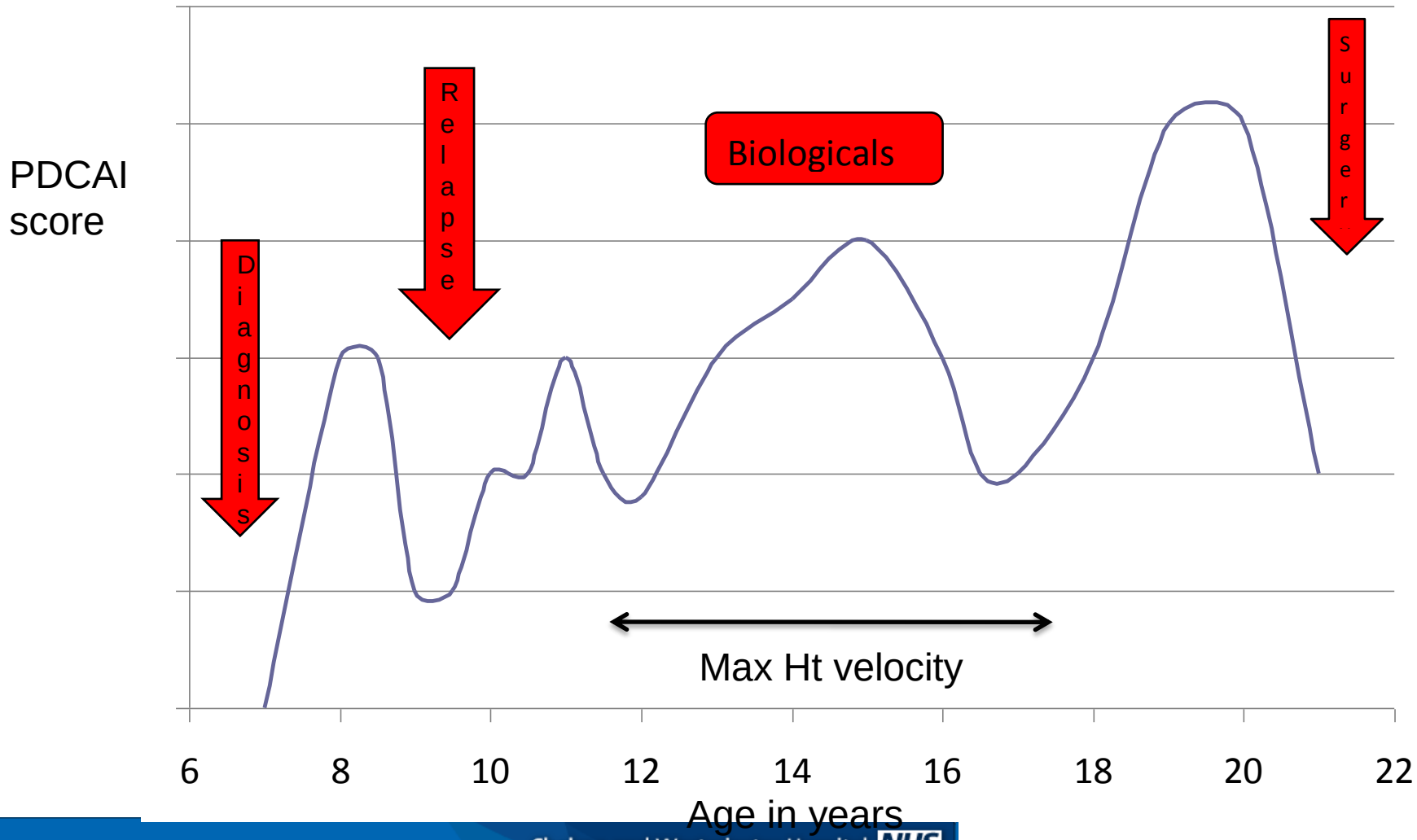
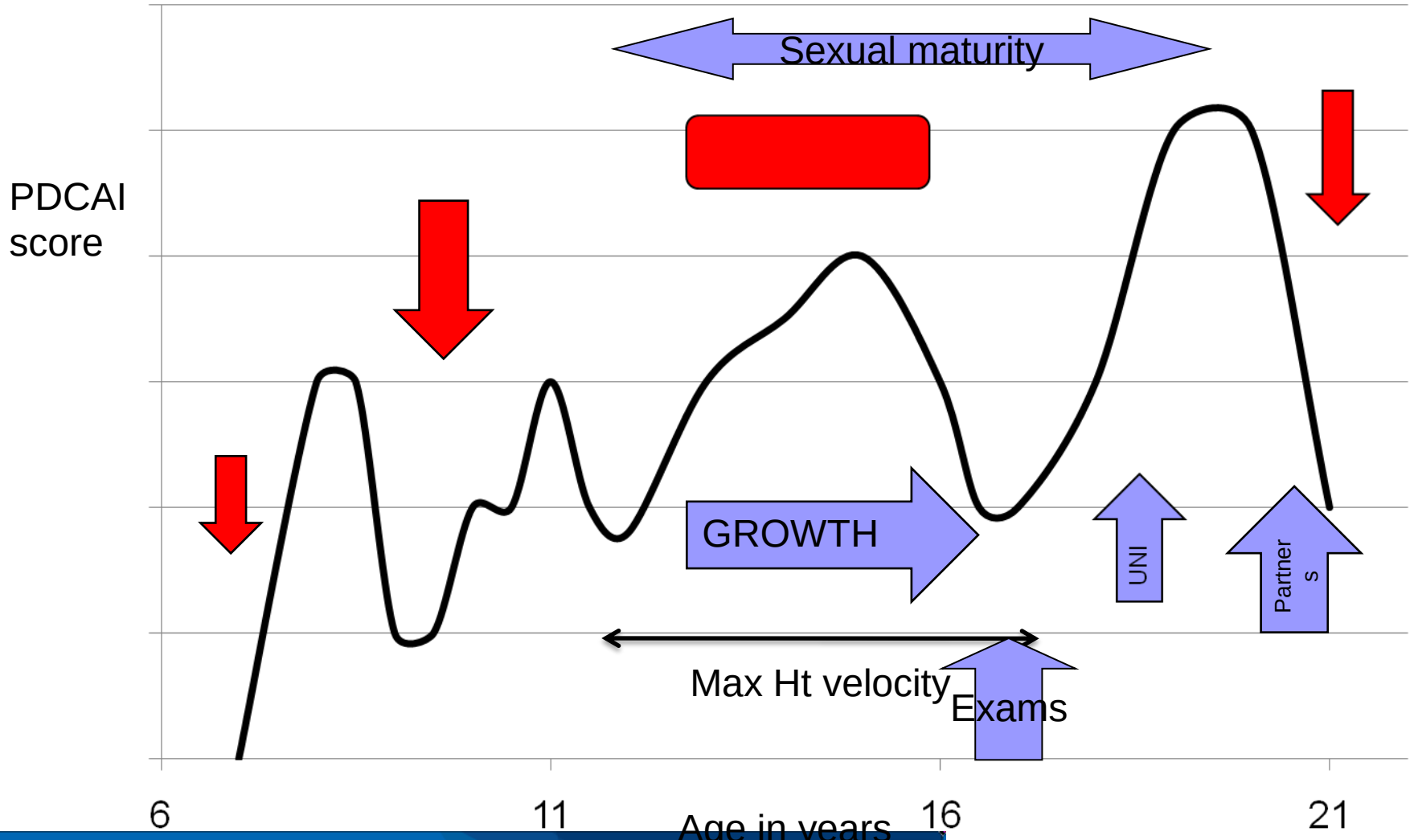
Population studies

- Trebling incidence over 50 years
- Prevalence1-2 per 1000
- Incidence = 1.5 per 10,000 per year
- OR 5 for first degree relative
- Perhaps protection
  - Rural
  - vegetables

The adolescent IBD course



Major life events



Why the obsession with mucosal healing

- 19% of IBD children fail to achieve their final height losing up to 8cms
- Earlier disease leads to earlier surgery, fistula disease and strictures
- Paediatric disease is more severe and refractory to treatment.
- Bone health
- Inflammation leads to GH resistance

Invited Review

The Role of Pro-Inflammatory Cytokines in Inflammatory Bowel Disease Growth Retardation

*S.C. Wong, *†V.E. MacRae, ‡P. McGrogan, and *S.F. Ahmed

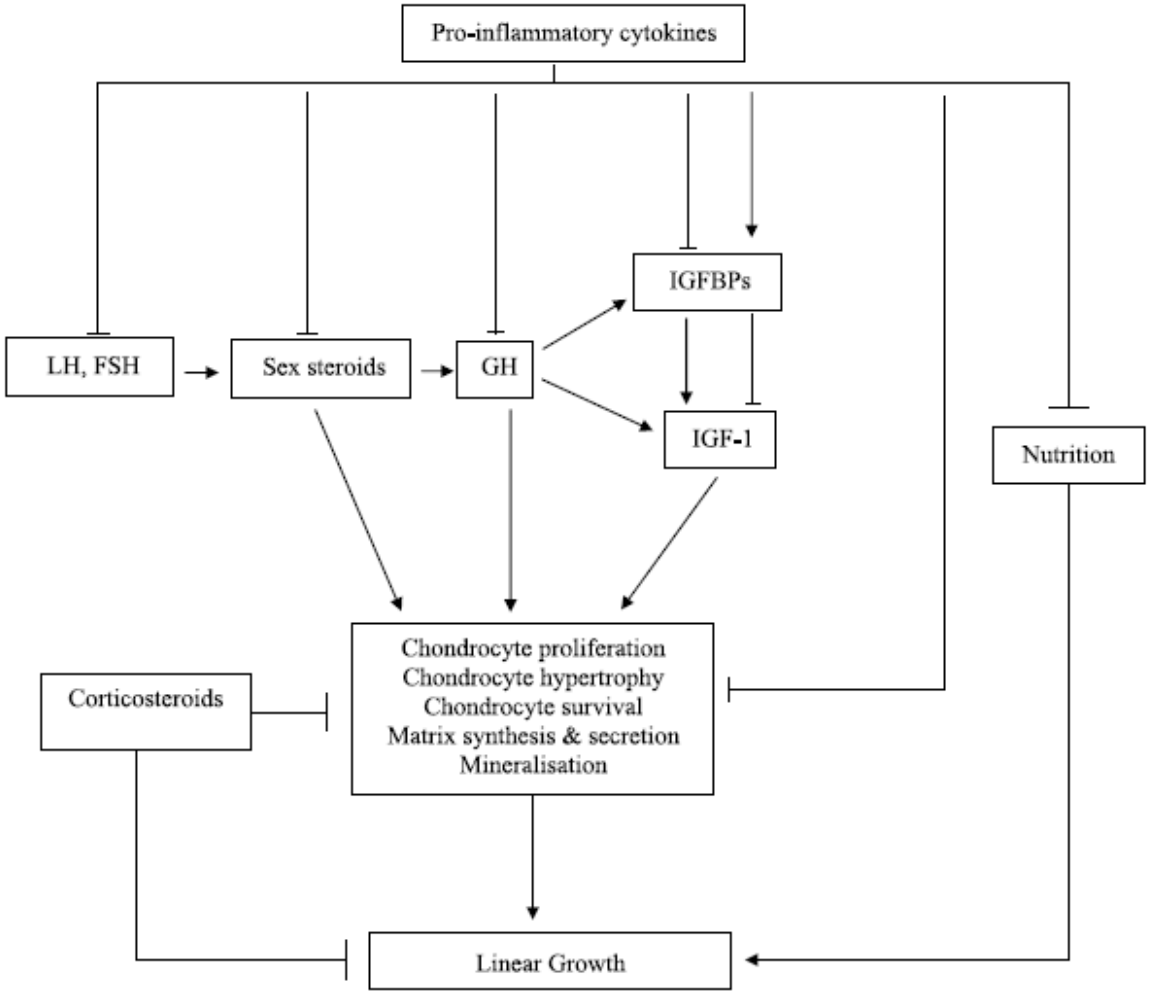


FIG. 1. Mechanisms of growth failure in chronic inflammatory disease.

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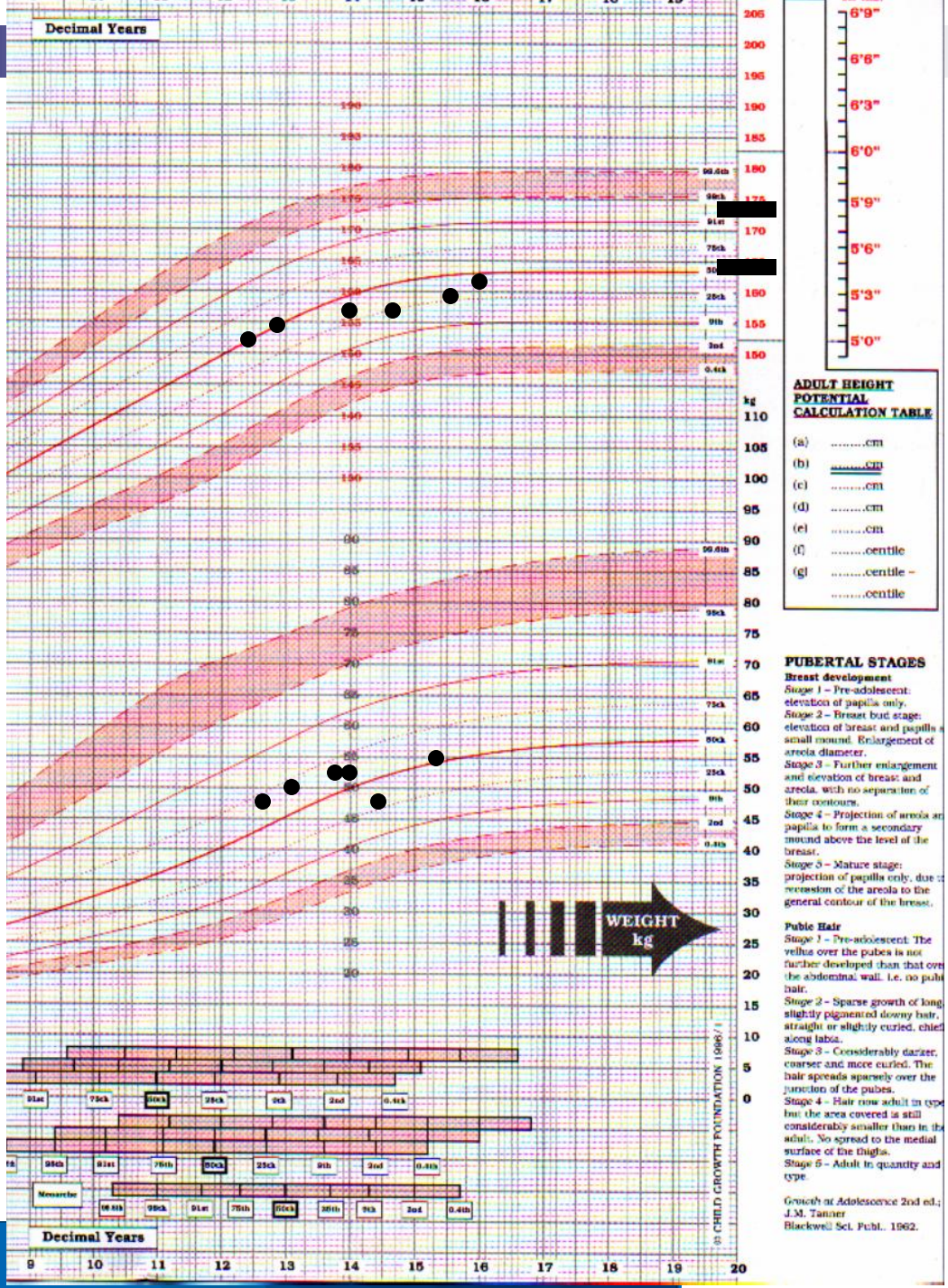
See Crohns as a disease of growth



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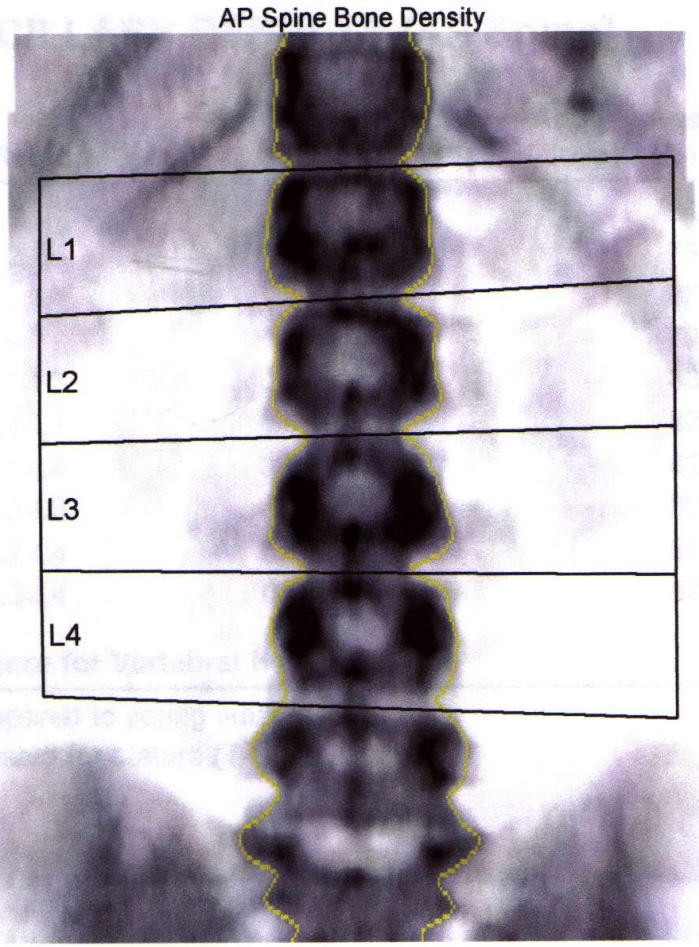

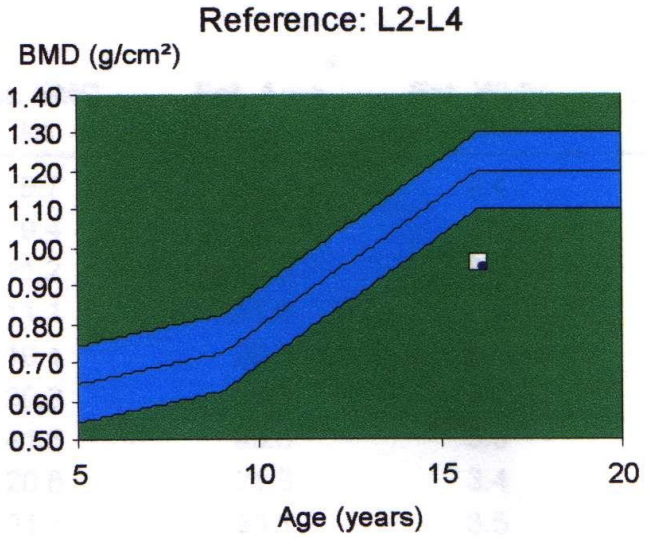

Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	Young-Adult[2] T-Score	Age-Matched[3] (%)	Age-Matched[3] Z-Score
L1	0.951	-	-	84	-1.8
L2	0.898	-	-	75	-3.0
L3	1.031	-	-	86	-1.7
L4	0.948	-	-	79	-2.5
L2-L4	0.959	-	-	80	-2.4

Do Bones Crack Under the Effects of Inflammatory Bowel Disease in Children?

Francisco A. Sylvester

Connecticut Children's Medical Center, Hartford, CT, University of Connecticut School of Medicine, Farmington, CT

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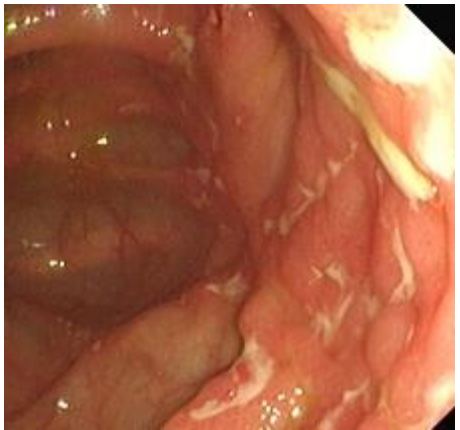
Conclusion 1

- Adolescents have a different disease course to adults
- Therapies must be directed at mucosal healing and not disease suppression
- Special attention should be paid growth



Specific issues:

- Disease is more extensive
- Higher requirements for immunosuppression
- Avoidance of steroids
- Bone mineralisation
- Growth implications
- Earlier need for surgery

The 21st century – treatment options for children

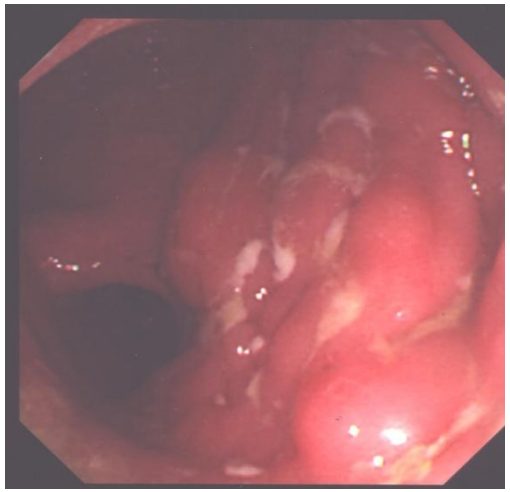
Cyclosporin, tacrolimus

Colectomy with IPAA

Steroids / budesonide steroid naive

Enteral nutrition

Adalimumab



Gastrostomy feeding

Endocrine augmentation

Azathioprine

Stricturoplasty

ASA products

Laparoscopic hemicolectomy

6MP or methotrexate

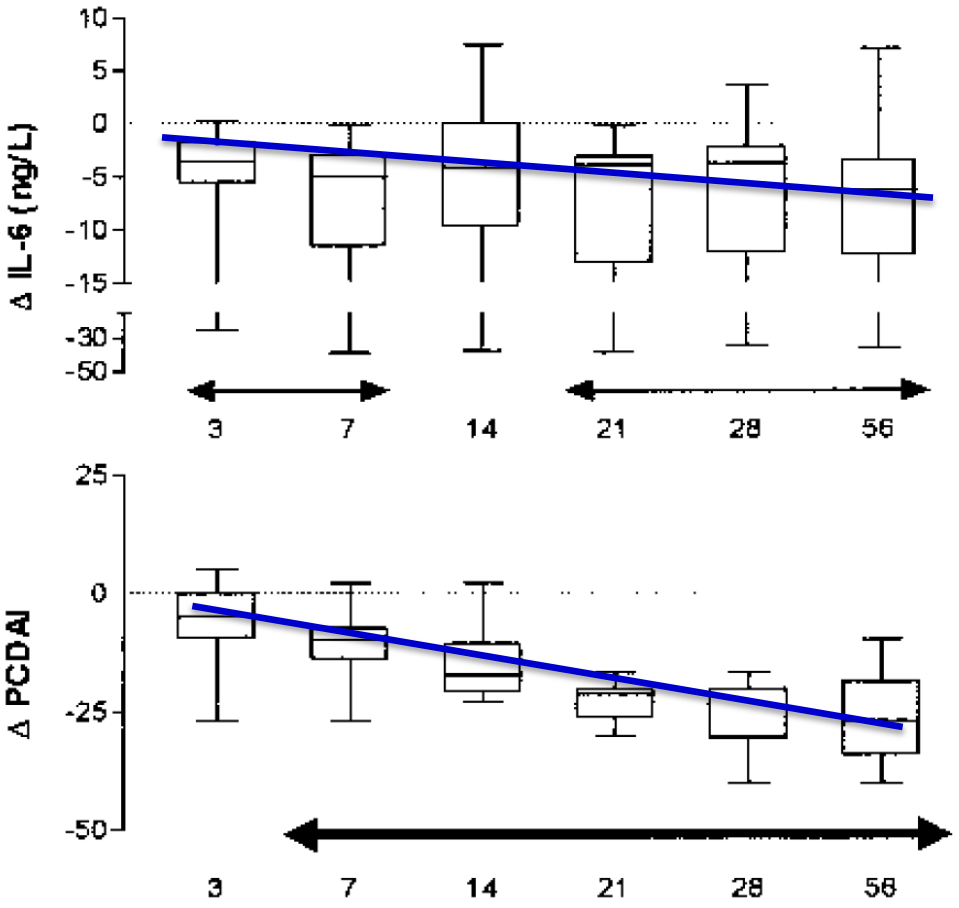
Infliximab

How to achieve mucosal healing

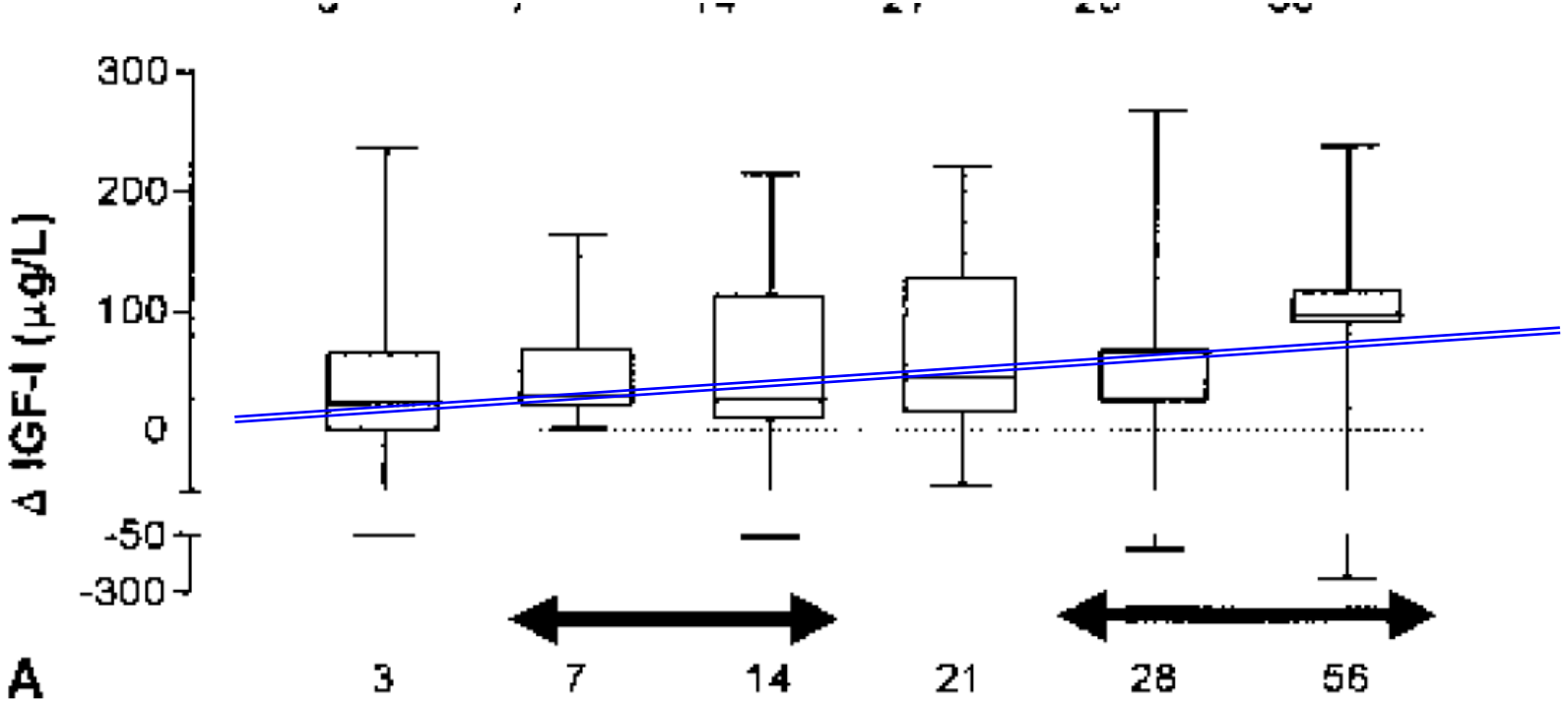
- Steroids vs. enteral nutrition
- But what is the difference

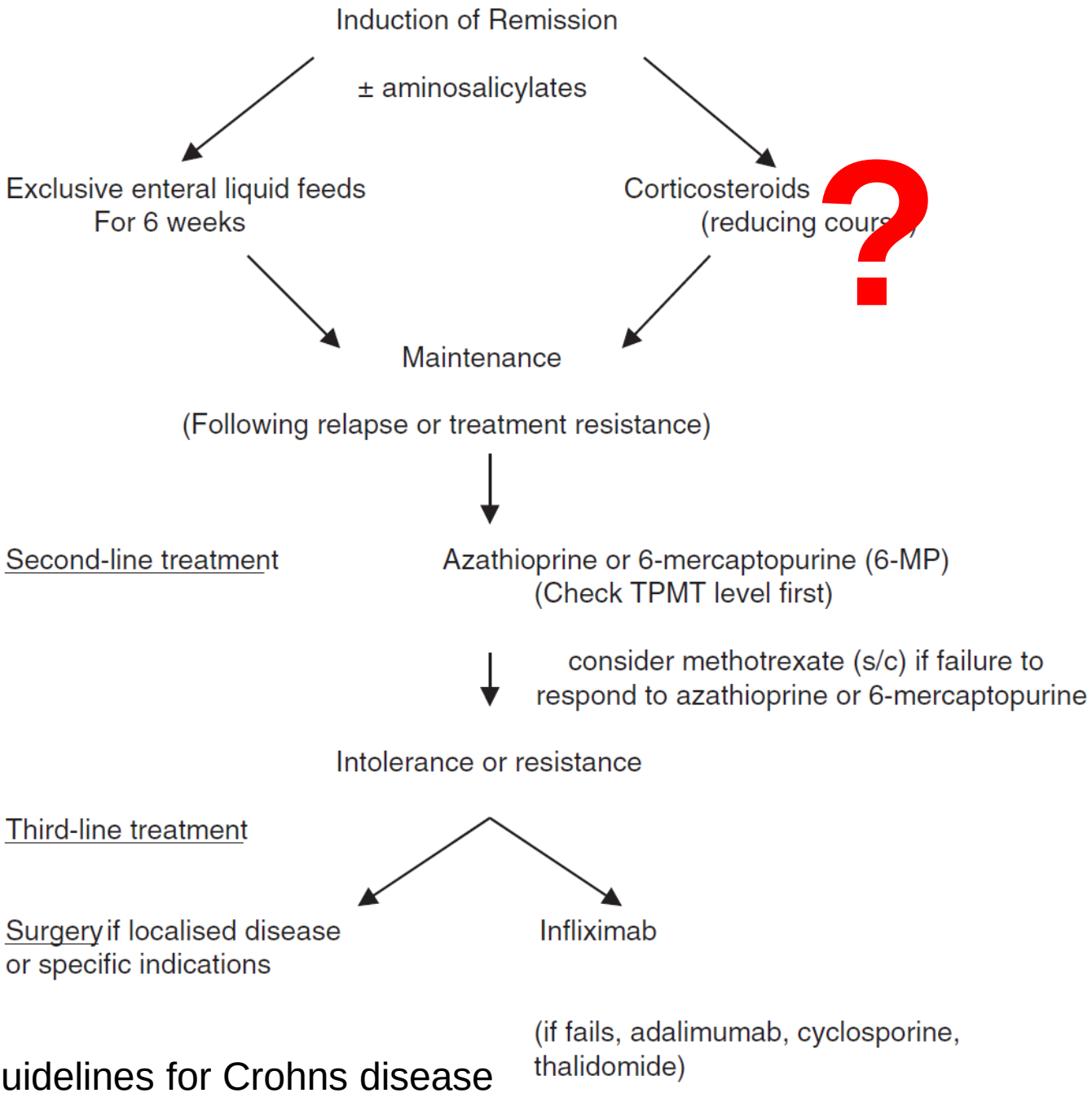
Height velocity impairment

- Height velocity impairment secondary to body nitrogen diverted to inflammation
- Enteral nutrition impacts on inflammation and reverses impact on height



IGF1 levels on enteral nutrition





BSPGHAN guidelines for Crohns disease

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Why early azathioprine?

- multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease*
- James Markowitz, Kathy Grancher, and The Pediatric 6MP Collaborative Group.

- Early azathioprine leads to shorter courses of steroids
- Relapse 9% in the 6 MP group
- 47% relapsed in the control group – but then 53% did not relapse and did not need azathioprine.

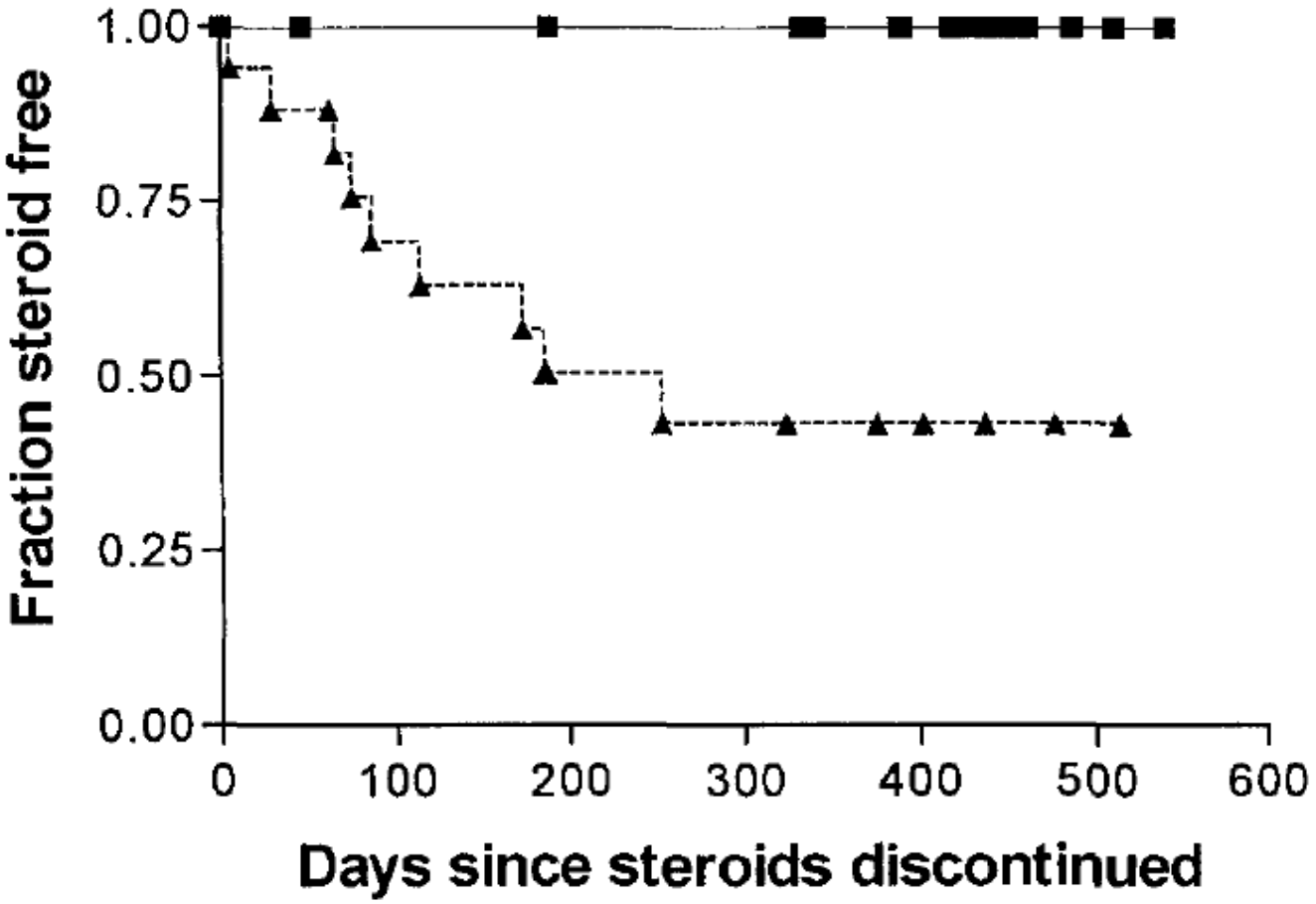


Figure 1. Time (days) off of corticosteroid treatment after initial discontinuation, depicted as a Kaplan–Meier survival curve. ■, 6-MP; ▲, controls. $P < 0.0001$.

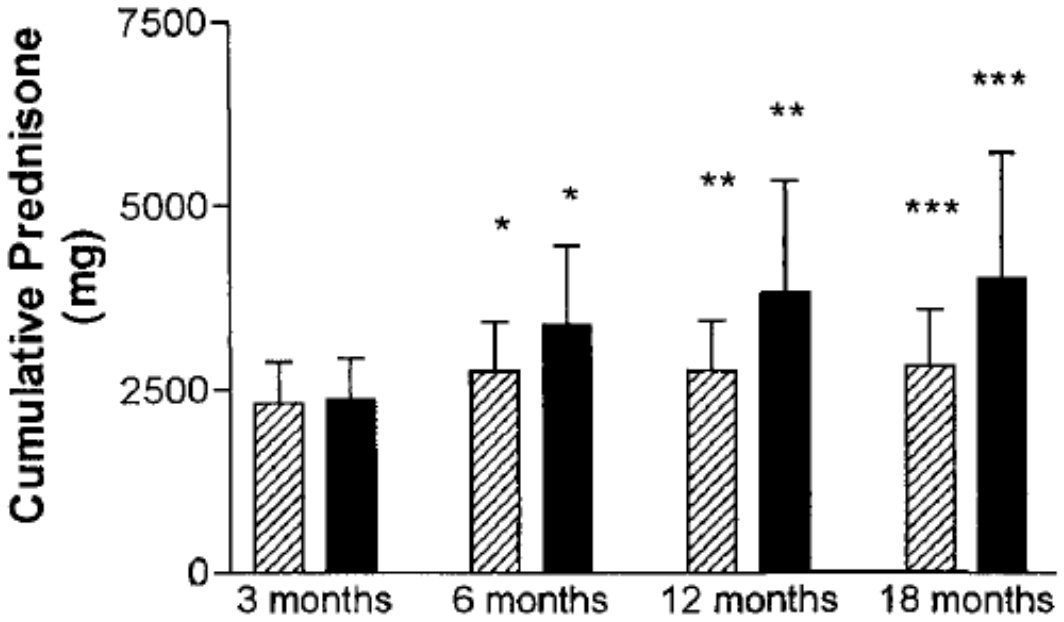
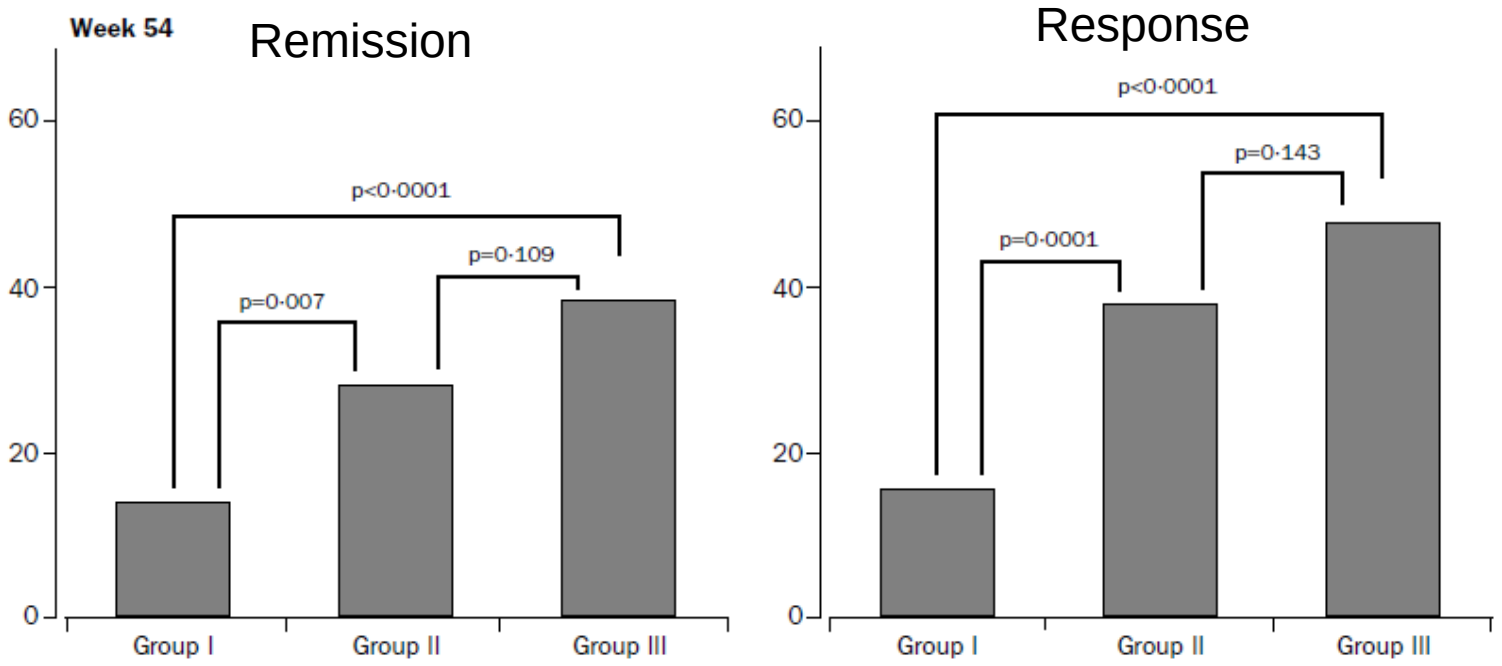


Figure 3. Cumulative prednisone dose (mean ± SD) actually taken by subjects in both groups from day of entry into the study until completion of the 18-month treatment period or until withdrawal. ▨, 6-MP (n = 27); ■, controls (n = 28). *$P < 0.03$; **$P < 0.007$; ***$P < 0.008$.

Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial

*Stephen B Hanauer, Brian G Feagan, Gary R Lichtenstein, Lloyd F Mayer, S Schreiber, Jean Frederic Colombel, Daniel Rachmilewitz, Douglas C Wolf, Allan Olson, Weihang Bao, Paul Rutgeerts, and the ACCENT I Study Group**



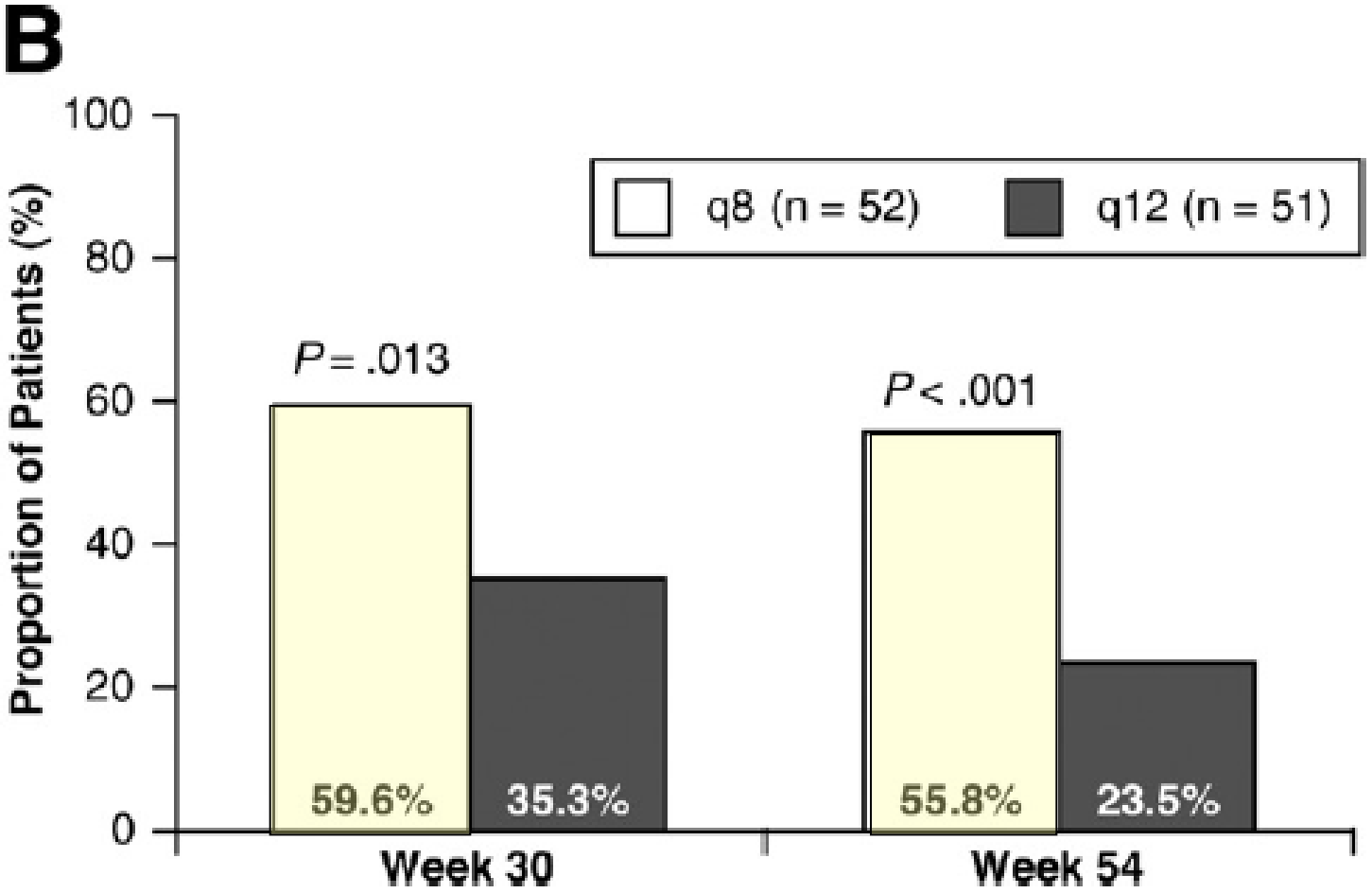
gure 2: **Clinical response and clinical remission for week-2 responders**
inical response=reduction in CDAI to ⩾70 points and ⩾25% from baseline. Clinical remission=CDAI <150 points.

Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-Severe Crohn's Disease in Children

Hyams J, Kugathasan S, et al. Induction and maintenance of infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;132:863–73.

- Multicentre, randomised, open label – REACH study
  - Age 6-17
  - Off steroids
  - 5mg/kg 0,2,6 weeks.
    - Then randomised to 8 weekly or 12 weekly
    - n=112

Number of patients in clinical remission on IFX at week 30 and 54



- 92/112 responded to induction
- If 8 weekly: 56% were in clinical remission at week 54.
- If 12 weekly: 23% were in clinical remission at week 54.

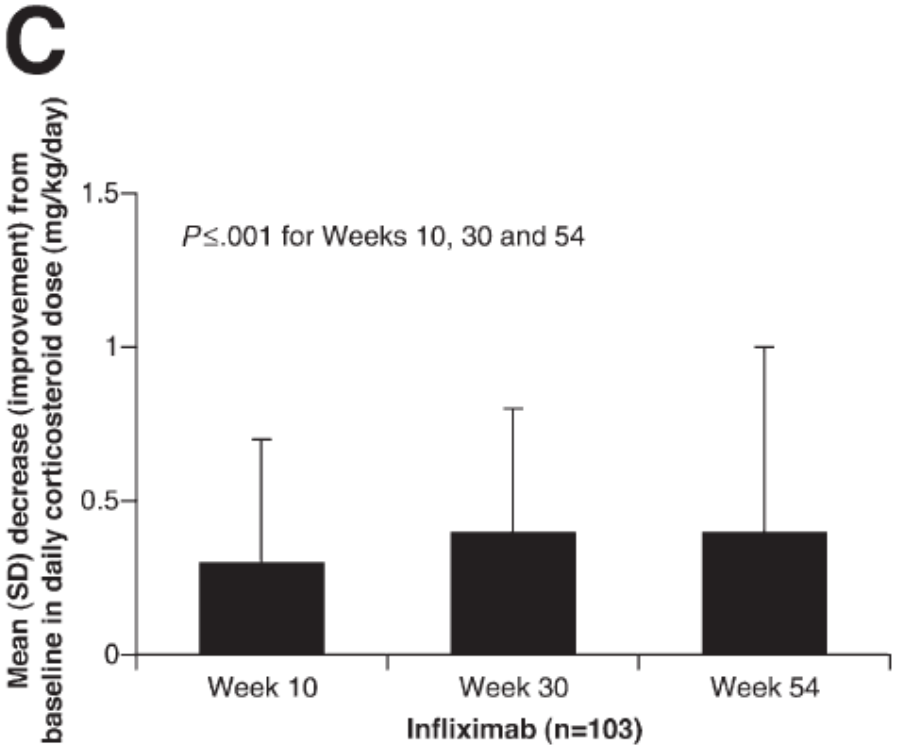
- Able to discontinue steroids
- Improvement in height SDS scores
- 7 children had serious infections

8 weekly maintenance

Safe and effective

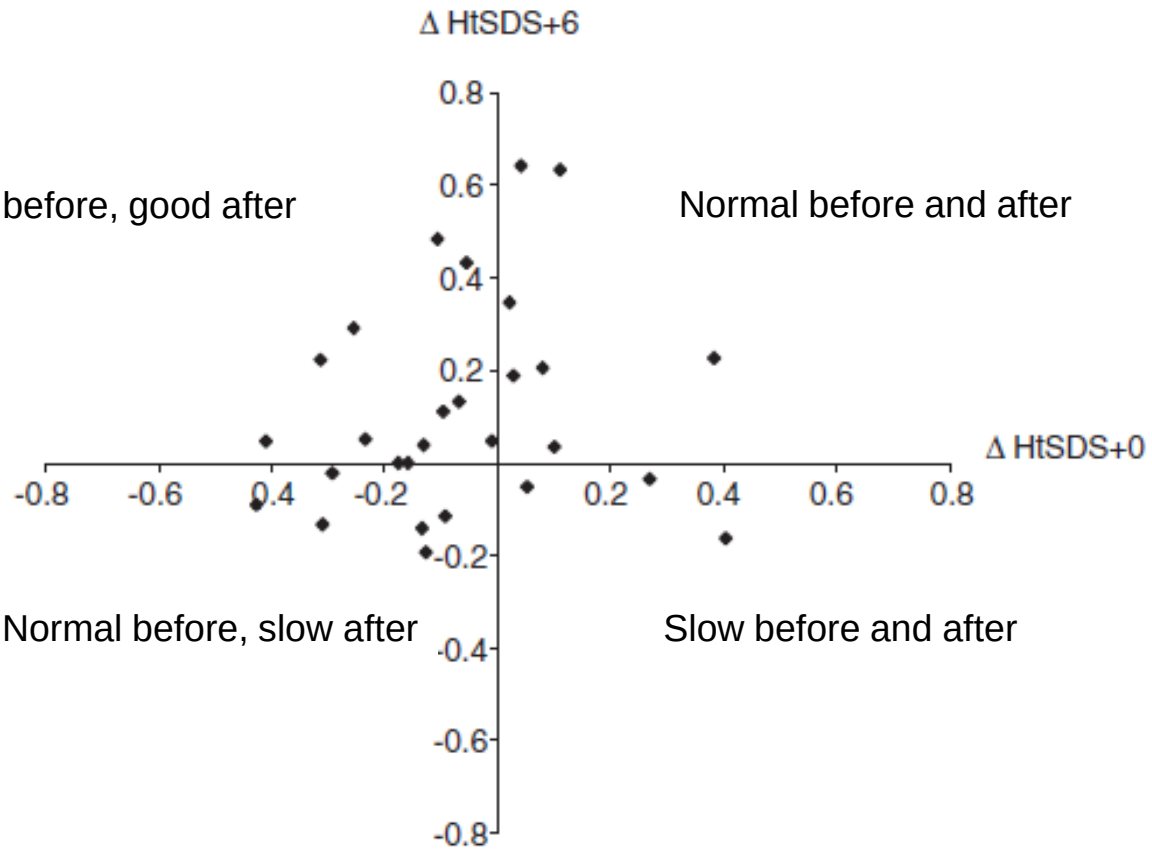
Bone health – can IFX decrease steroid use?

- Risk of 3 months of steroids or > 2mg/kg

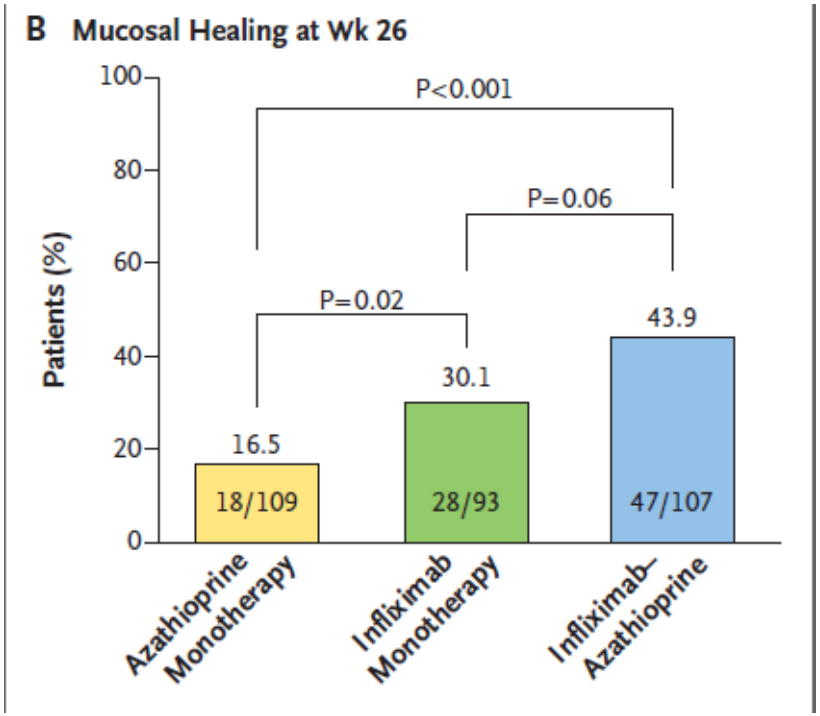


Improvement in Growth of Children With Crohn Disease Following Anti-TNF-α Therapy Can Be Independent of Pubertal Progress and Glucocorticoid Reduction

*Malik, *S.C. Wong, †J. Bishop, †K. Hassan, †P. McGrogan, *S.F. Ahmed, and †R.K. Russell*



The more medicines you give, the better you respond – Sonic trial



No of serious infections was “lower” in the blue group

2005

Case Report

Adalimumab, a Novel Anti-Tumor Necrosis Factor-α Antibody in a Child with Refractory Crohn's Disease

*Sameera Mian and †Howard Baron

*Department of Pediatrics, the University of Nevada School of Medicine, and †Pediatric Gastroenterology and Nutrition Associates, Las Vegas, Nevada

Safety and Efficacy of Adalimumab in Pediatric Patients With Crohn Disease

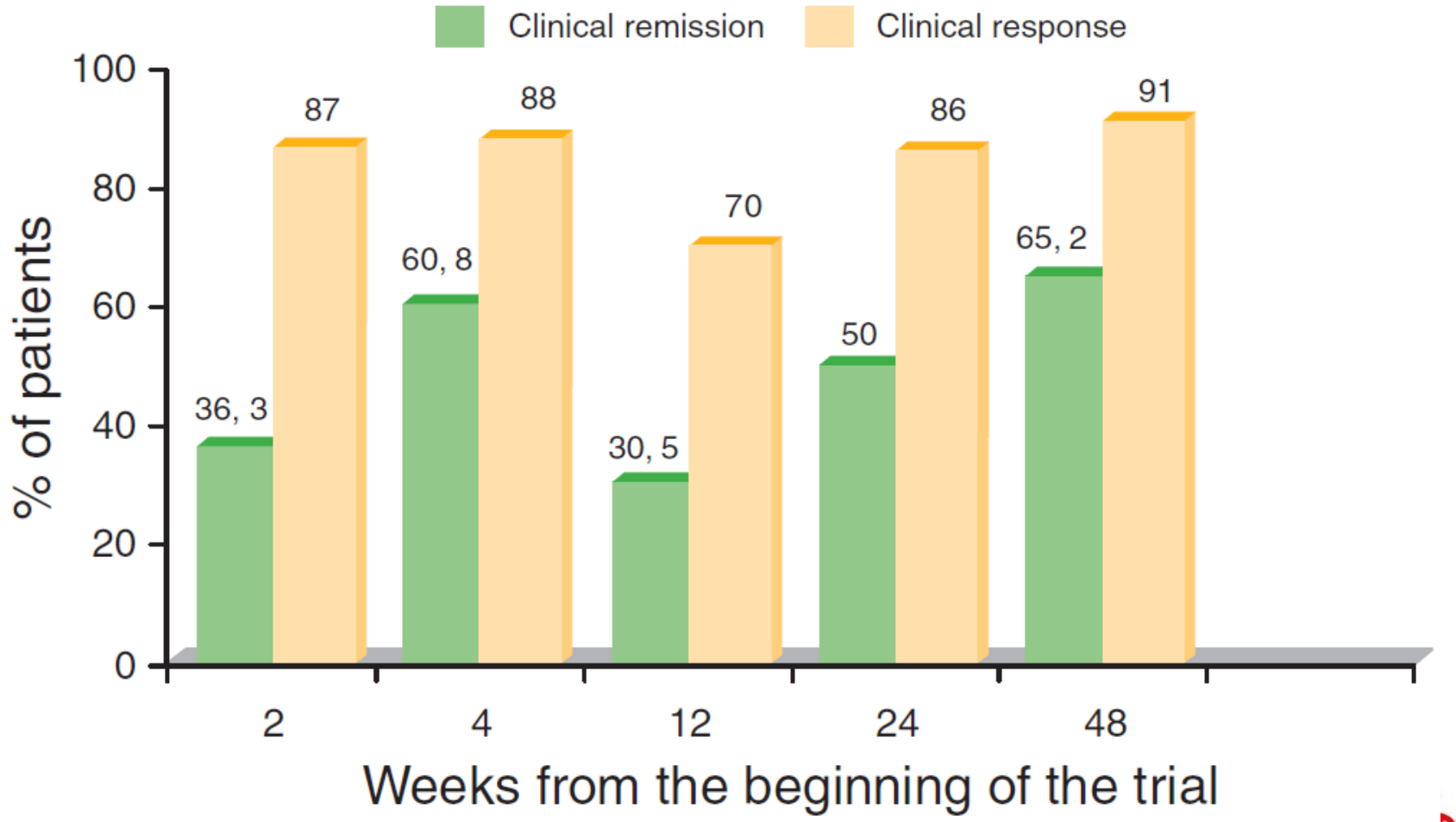
*Matthew J. Wyneski, †Alex Green, *Marsha Kay, *Robert Wyllie, and *Lori Mahajan

*Department of Pediatric Gastroenterology and Nutrition, Children's Hospital, Cleveland Clinic, and †Department of Pediatrics MetroHealth Medical Center, Cleveland, OH

N=15, no serious adverse responses

Efficacy of Adalimumab in Moderate-to-Severe Pediatric Crohn's Disease

Franca Viola, MD[1], Fortunata Civitelli, MD[1], Giovanni Di Nardo, MD[1], Maria Beatrice Barbato, MD[1], Osvaldo Borrelli, MD[1], Salvatore Oliva, MD[1], Francesca Conte, MD[1] and Salvatore Cucchiara, MD, PhD[1]



N=23

Journal of Pediatric Gastroenterology and Nutrition
44:165–167 © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Editorial

Infliximab Use and Hepatosplenic T Cell Lymphoma: Questions to Be Asked and Lessons Learned

*Joel R. Rosh, and †Maria Oliva-Hemker

*Division of Pediatric Gastroenterology, Goryeb Children's Hospital/Atlantic Health, Morristown, NJ, and †Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, Baltimore, MD

- 15 paediatric cases reported by 2009
- TREAT registry
  - Risk increases with use of narcotics, steroids and other immunosuppression
  - Malignancy risk – same in treated group as untreated : - 0.5 per 100 patient years

Annals of Internal Medicine | ARTICLE

Adalimumab Induction Therapy for Crohn Disease Previously Treated with Infliximab

A Randomized Trial

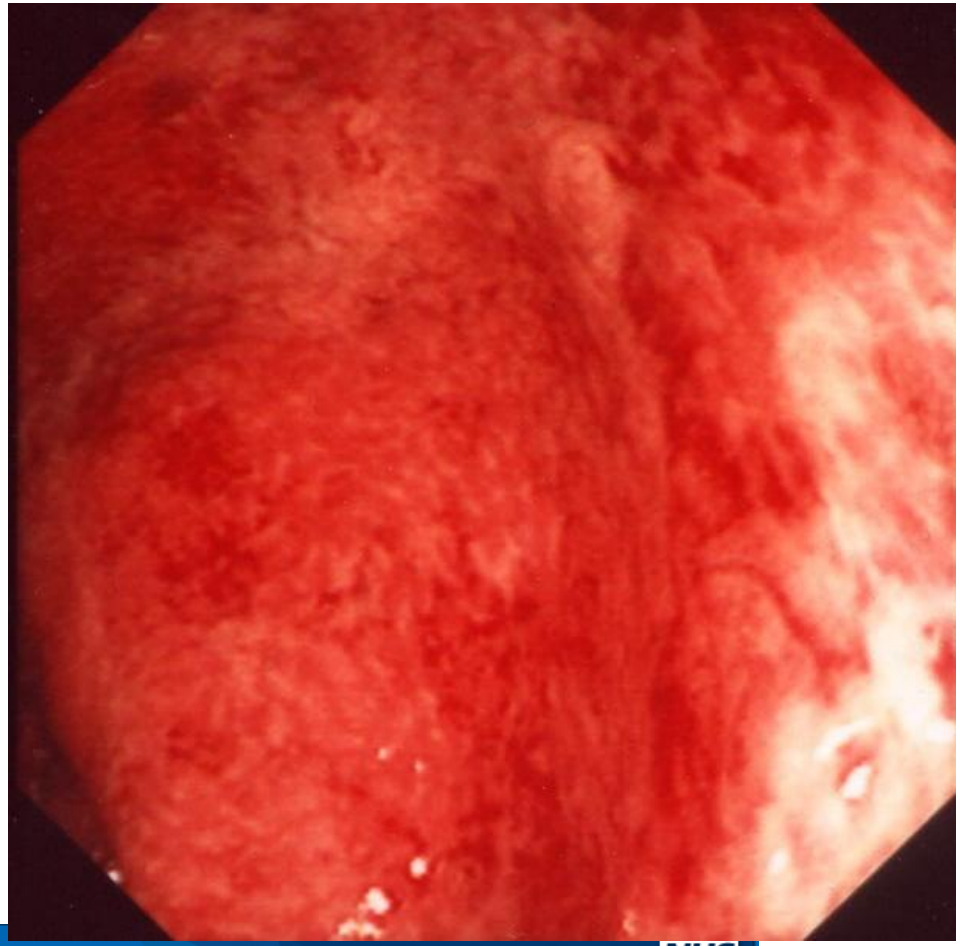
William J. Sandborn, MD; Paul Rutgeerts, MD, PhD; Robert Enns, MD; Stephen B. Hanauer, MD; Jean-Frédéric Colombel, MD; Remo Panaccione, MD; Geert D'Haens, MD; Ju Li, PhD; Marie R. Rosenfeld, BA; Jeffrey D. Kent, MD; and Paul F. Pollack, MD

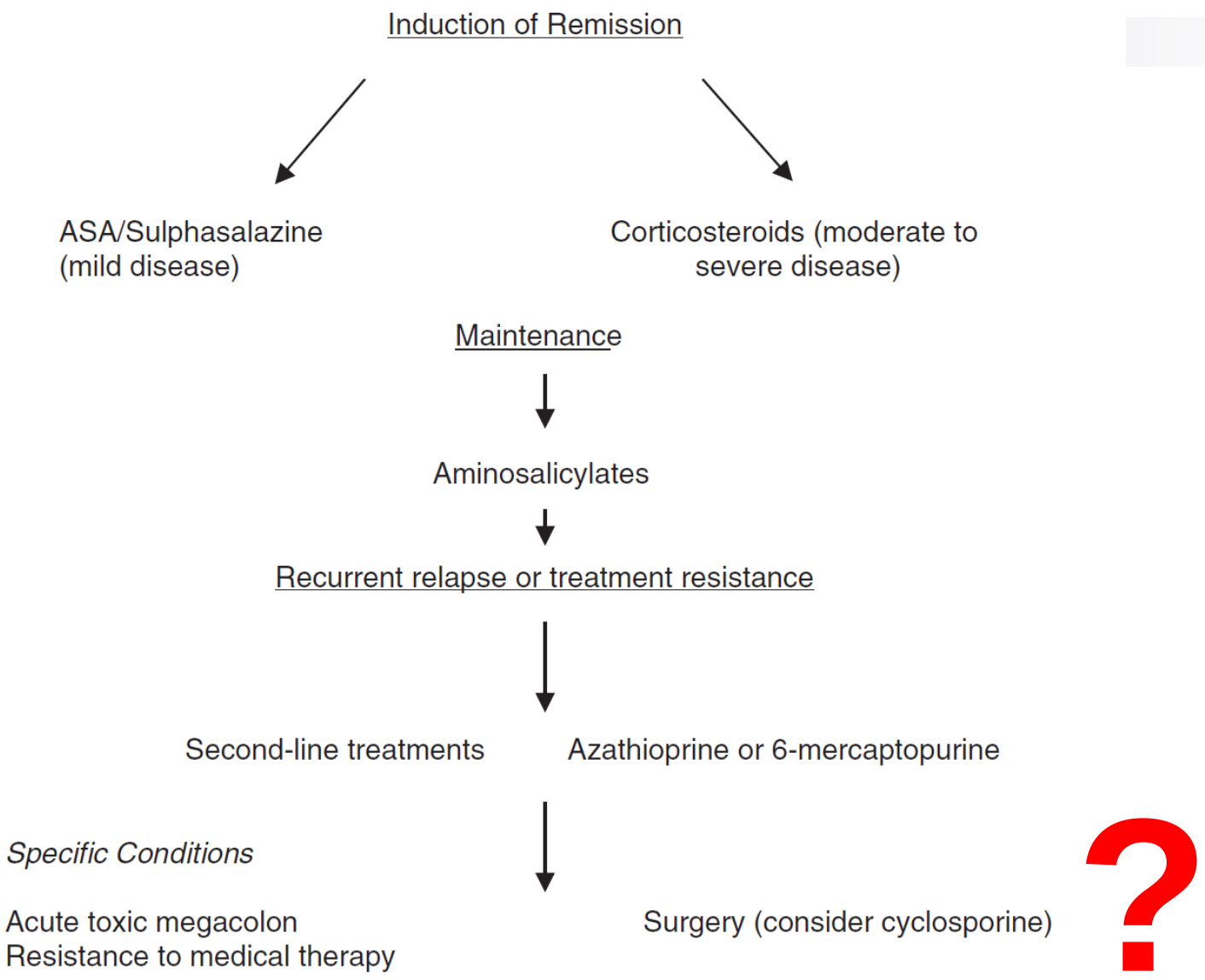
- Adults with loss of response to infliximab
- 21% entered remission after ADA
- 7% entered remission on placebo
- Only a 4 week study

Conclusion 2

- Biologicals have a role in CD
- There are trials of use in children
- They are presently reserved for refractory disease
- Their response may be improved if used earlier?

Does the same apply for UC?





BSPGHAN guidelines for Ulcerative colitis

For fulminant UC (in adults)

GASTROENTEROLOGY 2005;128:1805–1811

CLINICAL–ALIMENTARY TRACT

Infliximab as Rescue Therapy in Severe to Moderately Severe Ulcerative Colitis: A Randomized, Placebo-Controlled Study

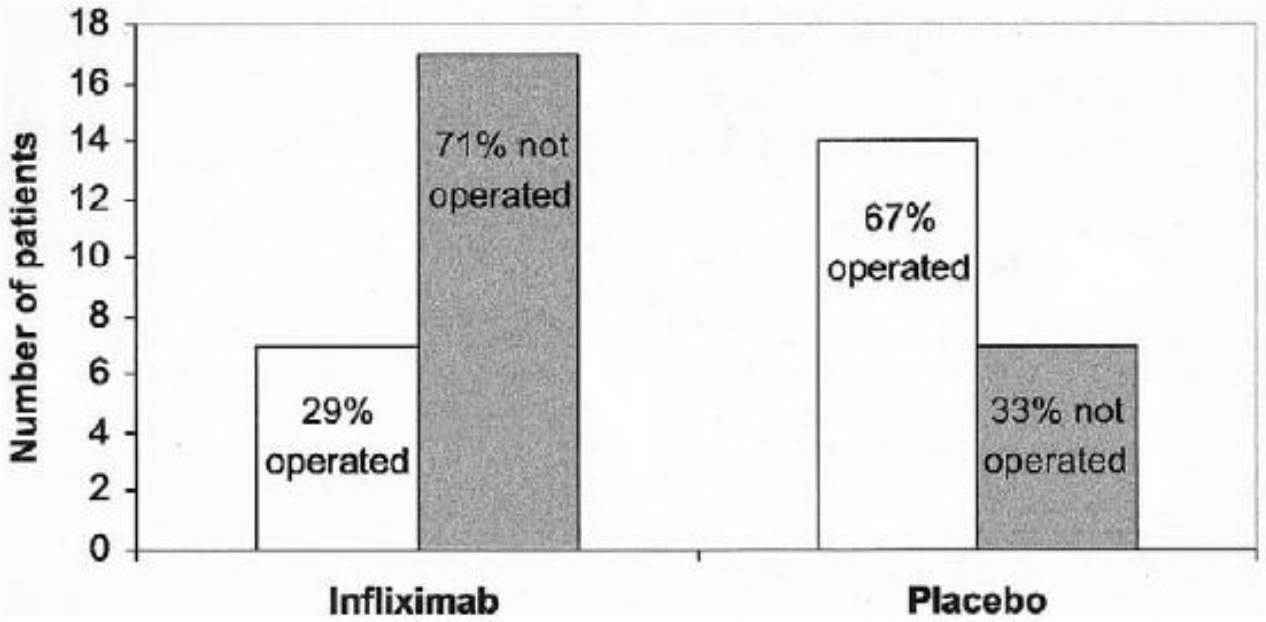


Figure 1. Proportion of surgical/nonsurgical patients in the infliximab and placebo groups.

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ORIGINAL ARTICLE

Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis

Paul Rutgeerts, M.D., Ph.D., William J. Sandborn, M.D., Brian G. Feagan, M.D.,

Only 50% on 6MP

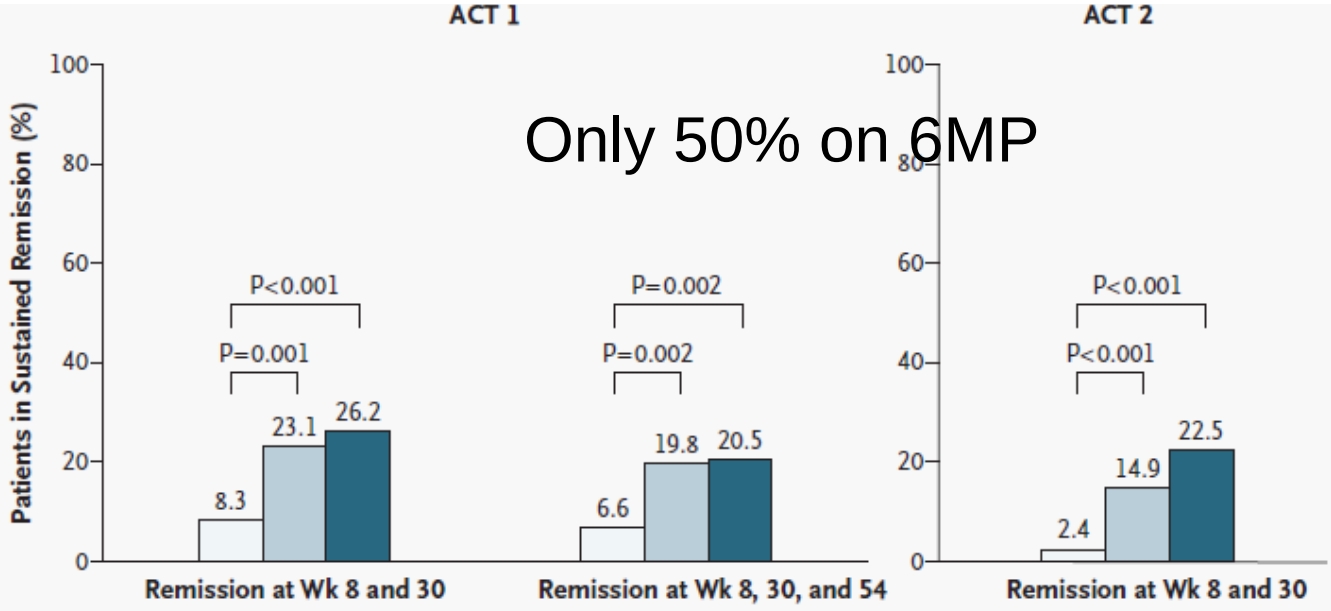


Figure 3. Proportion of Patients with a Sustained Clinical Response (Panel A) and in Sustained Clinical Remission (Panel B) in ACT 1 and ACT 2.

Translating into paediatric practice

A RANDOMIZED, MULTICENTER, OPEN-LABEL PHASE 3 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INFLIXIMAB IN PEDIATRIC PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

J. Hyams1, L. Damaraju2,M. Blank2, J. Johanns2, C. Guzzo2,

60 patients enrolled
40% remission by week 10
28% in remission by week 54
37% off steroids by week 54

Data superior to ACT 1 – but ? patients not as ill?

Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial

Walter Reinisch,[1] William J Sandborn,[2] Daniel W Hommes,[3] Geert D'Haens,[4]

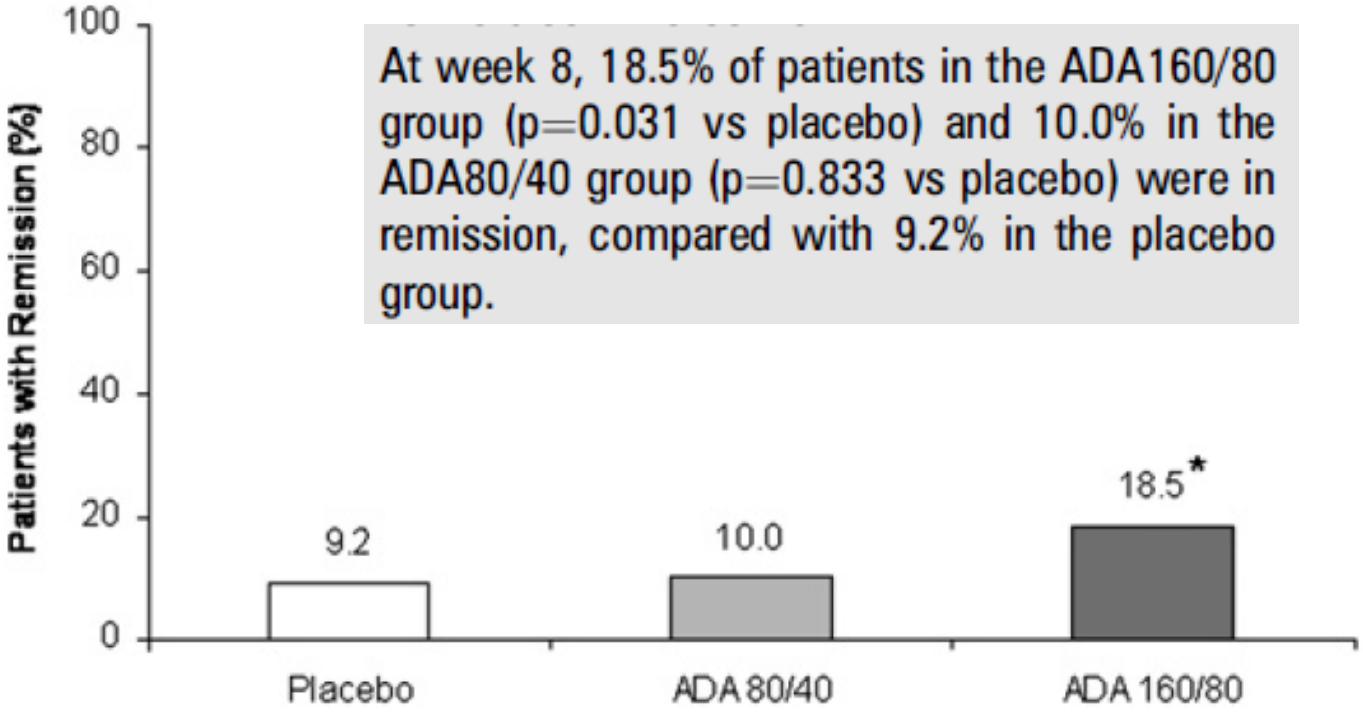


Figure 3 Clinical remission at week 8 in the ITT-A3 population (non-responder imputation). N=130 for each group. *p=0.031 versus placebo

Conclusion 3

- Role of biologicals is being defined in UC
- Role for fulminant disease
- ? Less effective than in CD
- ? More effective in children
  - Is this effect real?

- Patient needs
  - Be normal
  - Be pain free
  - Not have bowel prep
  - No needles
  - No hospital admissions
  - Have energy and be well
  - Smoke and have sex

- Doctors need
  - Achieve mucosal healing
  - Reassess and endoscopy
  - Regular and frequent follow up
  - Increase medical therapies
  - Introduce to lots of professionals
  - Prevent smoking
  - Prevent pregnancy

- Patient needs
  - Be normal
  - Be pain free
  - No
  - No
  - No
    adr
  - Ha
    we
  - Sm

- Doctors need
  - Achieve mucosal healing
  - Prevent pregnancy

ent

The Parents agenda

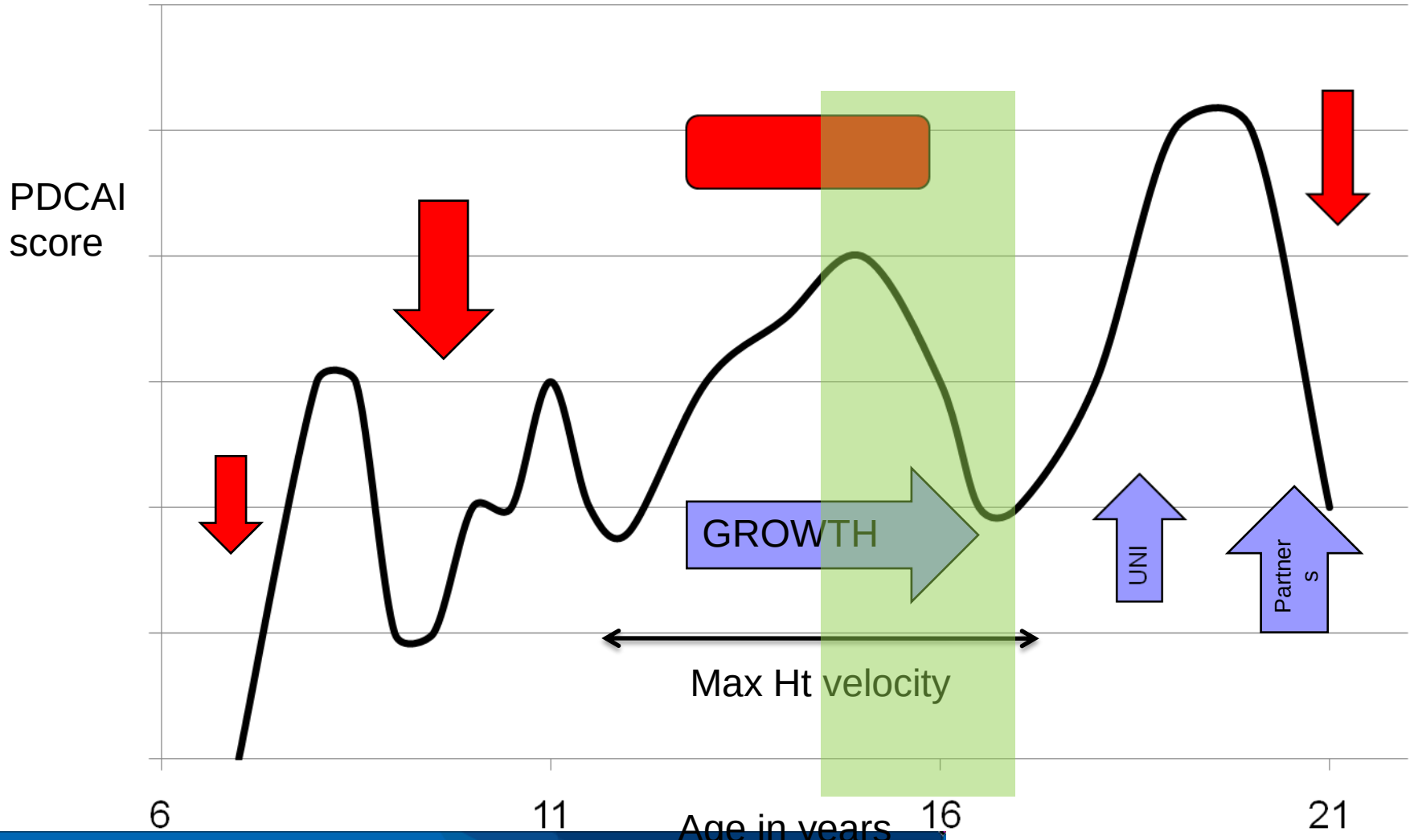
Cure
Education
Quality of life
Guilt
Implications for children and siblings
Risk to career choices

- Patient needs
  - B
  - B
  - N
  - N
  - N
    a
  - H
    w
  - S
- Doctors need
  - Achieve mucosal

Transition

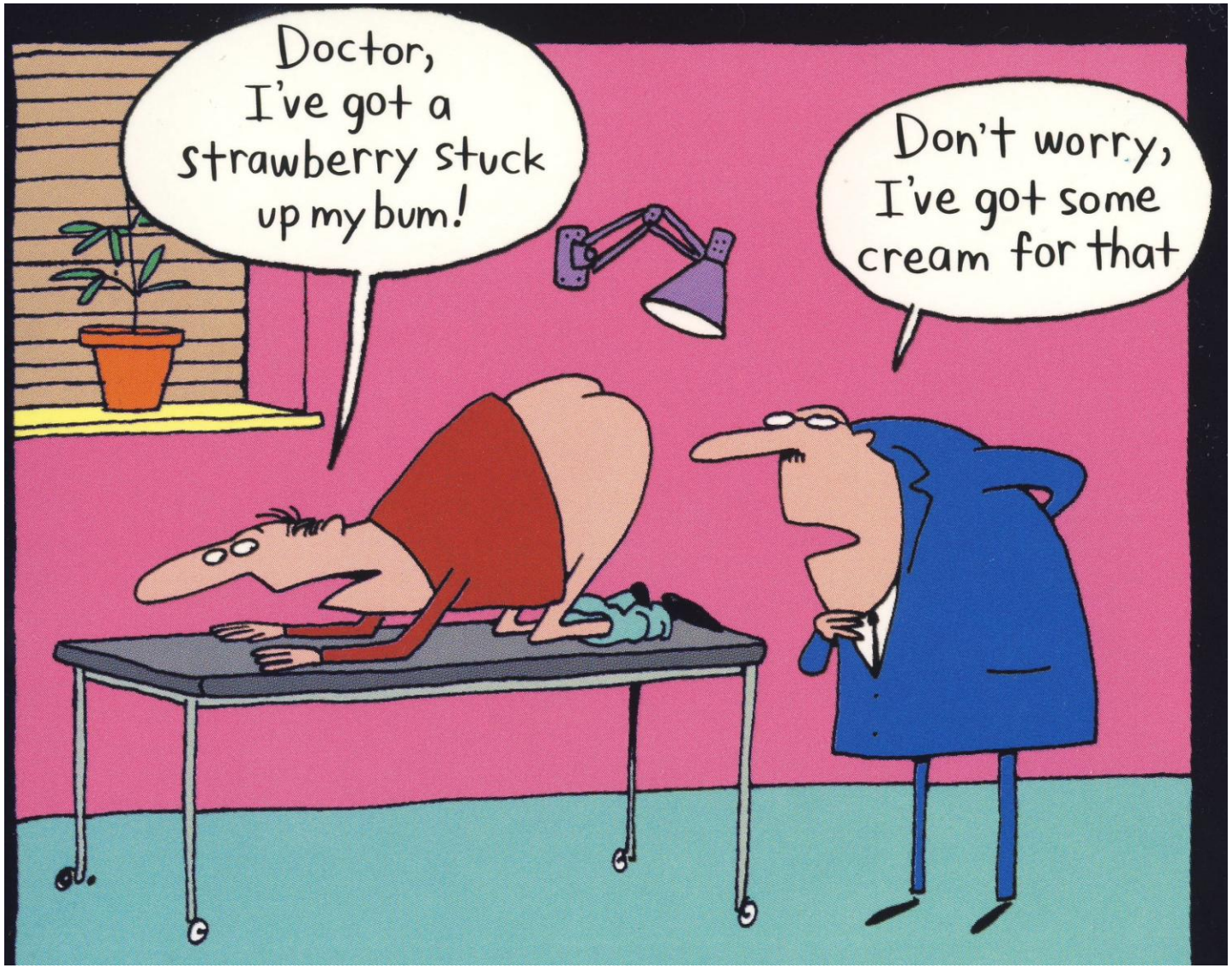
Change of team
Change of ethos
Change in set up of clinics
Absence of parents at consultation
Unfamiliar and changing doctors
Change in endoscopy
Move away from nutrition towards steroids

Major life events



Conclusions

Biological therapies work
Which biological, and when – NICE
Risks of therapies are small
More medicines – better response
Complexity necessitates transition clinics


Doctor, I've got a strawberry stuck up my bum!
Don't worry, I've got some cream for that