Inflammatory Bowel Disease: Treatment

Jorge Amil Dias
Porto - PORTUGAL
jamildias@zonmail.pt
## Objectives of treatment in IBD

<table>
<thead>
<tr>
<th>Differences</th>
<th>UC</th>
<th>CD</th>
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<tbody>
<tr>
<td>Disease activity</td>
<td>Acute flares</td>
<td>Persistent inflammation activity</td>
</tr>
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<td>Treatment goals</td>
<td>Prevention of relapse and CRC</td>
<td>Prevention of strictures and penetrating complications</td>
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<tr>
<td>Immunomodulators and Biologics</td>
<td>Only when inadequate response to steroids</td>
<td>Early introduction?</td>
</tr>
<tr>
<td>Surgical outcomes</td>
<td>“Curation” of disease</td>
<td>Immediate clinical benefit</td>
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</tbody>
</table>
Paediatric vs adult-onset CD

% of pts with active disease % of pts with immunosuppressants

Pigneur B et al. Inflamm Bowel Dis, 2010
Risk of surgery in CD

- Childhood-onset CD
- Adult-onset CD

Pigneur B et al. Inflamm Bowel Dis, 2010
Frequent myths in Paediatric Ulcerative Colitis

• “U.C. is not a severe disease (≠ Crohn’s)”
• “Distal disease is usually mild”
• “U.C. is curable”
• “Mucosal healing is not important”
Extension of Ulcerative Colitis

Paediatric
- Pancolitis E3: 82.0%
- Left colitis E2: 16.4%
- Proctitis E1: 1.4%

Adults
- Pancolitis E3: 48%
- Left colitis E2: 35%
- Proctitis E1: 17%

van Limbergen et al Gastroenterology 2008
Ulcerative Colitis in a Southern European Country: a National Perspective

Francisco Portela, MD,1,2† Fernando Magro, PhD,1,3,4† Paula Lago, MD,1,5 José Cotter, MD,1,6
Isabelle Cremers, MD,1,7 João de Deus, MD,1,8 Ana Vieira, MD,1,9 Horácio Lopes, MD,1,10
Paulo Caldeira, MD,1,11 Luísa Barros, MD,1,12 Jorge Reis, MD,1,13 Laura Carvalho, MD,1,14
Raquel Gonçalves, MD,1,15 Mário J. Campos, MD,1,16 Paula Ministro, MD,1,17 Maria A. Duarte, MD,1,18
Jorge Amil, MD,1,3 Susana Rodrigues, MD,1,3 Luís Azevedo, MD,1,19 and A. Costa-Pereira, PhD,1,19
Patients <16 yrs with UC

<table>
<thead>
<tr>
<th></th>
<th>≤ 5 yrs of Dg</th>
<th></th>
<th>&gt; 5 yrs of Dg</th>
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</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (33)</td>
<td></td>
<td>28 (35)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (67)</td>
<td></td>
<td>53 (65)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With constitutional symptoms</td>
<td>9 (18)</td>
<td></td>
<td>10 (12)</td>
<td></td>
</tr>
<tr>
<td>Without constitutional symptoms</td>
<td>40 (82)</td>
<td></td>
<td>71 (88)</td>
<td></td>
</tr>
<tr>
<td><strong>Extent of disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>6 (12)</td>
<td></td>
<td>11 (14)</td>
<td></td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>17 (35)</td>
<td></td>
<td>29 (36)</td>
<td></td>
</tr>
<tr>
<td>Pancolitis</td>
<td>26 (53)</td>
<td></td>
<td>41 (51)</td>
<td></td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>12 (25)</td>
<td></td>
<td>22 (27)</td>
<td></td>
</tr>
<tr>
<td>Steroid therapy</td>
<td>30 (61)</td>
<td></td>
<td>58 (73)</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>17 (35)</td>
<td></td>
<td>15 (19)</td>
<td></td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>2 (4)</td>
<td></td>
<td>7 (9)</td>
<td></td>
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</tbody>
</table>
The Natural History of Pediatric Ulcerative Colitis: A Population-Based Cohort Study

Corinne Gower-Rousseau, MD1, Luc Dauchet, MD1, Gwénola Vernier-Massouille, MD2, Emmanuelle Tilloy, MD1, Franck Brazier, MD1, Véronique Merle, MD1, Jean-Louis Dupas, MD3, Guillaume Savoye, MD4, Mamadou Baldé, MD1, Raymond Marti, MD2, Éric Lerebours, MD4, Antoine Cortot, MD2, Jean-Louis Salomez, MD4, Dominique Turck, MD3 and Jean-Frédéric Colombel, MD2

At diagnosis

At maximal follow-up

P < 10^-4

%  

0  10  20  30  40  50  60  70  80  90  100

Proctitis  Left-sided  Extensive

Proctitis  Left-sided  Extensive

Am J Gastroenterol 2009; 104:2080–2088;
Initial activity of Ulcerative Colitis

North American Pediatric IBD Collaborative Research Group
Evolution of Ulcerative Colitis

% without colectomy

Time to colectomy

van Limbergen et al Gastroenterology 2008
Assessment of IBD

- Confirm diagnosis with full work-up
- Evaluate extension
- Extra-intestinal signs or symptoms?
- Assess activity
- Check for immunization status
Evolution of Crohn’s Disease

J Cosnes et al. Gastroenterology, 2002
Crohn’s disease – Goals of treatment

- Mucosal healing
- Maintenance of remission
- Optimize growth
- Preserve quality of life

Children have a more active disease, require more immunosuppression and have higher risk for the need of surgery
Crohn’s disease – Goals of treatment

Need for pediatricians with experience!

- Preserve quality of life

Children have a more active disease, require more immunossuppression and have higher risk for the need of surgery.
Induction of remission in CD

- Nutrition therapy is the first line treatment
- **Exclusive enteral nutrition** is the best option for luminal disease regardless of location
  - Isolated oral or perianal disease may require alternative treatment
- Polymeric diet with whole protein is adequate
- EEN promotes mucosal healing
Enteral nutrition in Crohn’s disease

Dziechciarz P et al/ Alim Pharmcol Therap, 2007
Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn’s disease

Zubin Grover · Richard Muir · Peter Lewindon
N=26

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Before EEN</th>
<th>After EEN</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weight Z score</td>
<td>-0.79</td>
<td>-0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean height Z score</td>
<td>-0.19</td>
<td>-0.005</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BMI Z score</td>
<td>-1.40</td>
<td>-0.54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean PCDAI</td>
<td>37.88</td>
<td>7.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CRP</td>
<td>44.86</td>
<td>5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean SES-CD</td>
<td>14.28</td>
<td>3.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean MRI score</td>
<td>4.69</td>
<td>2.63</td>
<td>0.01</td>
</tr>
</tbody>
</table>
How to give EEN

- No advantage of elemental over polymeric formulas
- Use oral if possible, or NG tube
- Use composition with 1-1.5kcal/kg
- Try to match individual preference of flavour
- **Exclusive** nutrition for 6-8 weeks, then taper over 2 weeks
- Water or gums allowed
- Need for motivation (doctor and patient)!
Induction of remission in CD

- Oral corticosteroids are a possible alternative
- Less expensive in the short term
- Side effects
  - Prednisone – 1 mg/kg (max 40) once daily
    - 2-4 weeks with tapering of 8-12 weeks
  - Budesonide less effective but possible option in mild luminal ileo-cecal/ascending colon disease (9-12 mg/d)
- Enemas may be used for distal disease
- Steroids must not be used for maintenance.
- Symptomatic relief but do not heal the mucosa
Induction of remission in CD

• Biologics (anti-TNFα monoclonal antibodies)
  – Infliximab, Adalimumab

• In moderate to severe disease, refractory to immunomodulators

• Best option for perianal penetrating disease
  – IFX 5 mg/kg at wk 1,2,6 then every 8 wk, iv
  – ADA
    • >40kg: 160 mg at wk 1, 80 mg at wk 2, then 40 mg every 2wk
    • <40kg: 80 mg at wk 1, 40 mg at wk 2, then 20 mg every 2wk
Induction of remission in CD

• Biologics (anti-TNFα monoclonal antibodies)

Important: Exclude TB carefully before starting biologics.

Reactivation of infection may occur.

• >40kg: 160 mg at wk 1, 80 mg at wk 2, then 40 mg every 2wk
• <40kg: 80 mg at wk 1, 40 mg at wk 2, then 20 mg every 2wk
5-ASA

- There is no evidence of benefit for induction
- May be useful in some cases with very mild disease
  - 50 mg/kg/d
Maintenance treatment

- **Thiopurines** for maintenance of remission (steroid sparing)
- Thiopurine at diagnosis in children at risk for adverse outcomes (complications, disease severity and, extent and phenotype)
  - Azathioprine 2-3 mg/kg/d
  - 6-Mercaptopurine 1-1.5 mg/kg/d
- **Methotrexate** can be used as a primary maintenance therapy or as an alternative to thiopurines.
  - 15 mg/m² (max 25mg) once a week, sc (oral?...)
  - Supplement with weekly folate (24-72h after MTX)
  - Contraindicated in pregnancy!
Use of thiupurines in Crohn’s disease

J Markowitz et al. Gastroenterology 2000
Maintenance treatment with thiopurines

• Check blood count regularly
• Stop if pancreatitis occurs and do **not** re-start
• TPMT assay (activity/genetics)?
• Effect of treatment takes up to 3 months
  – Not useful for induction of remission
• Sun protection!
Biologics for maintenance

• Scheduled maintenance should be continued after responding to induction with a biologic
• Patients with sustained remission should maintain scheduled anti-TNF therapy or switch to an immunomodulator if they were previously immunomodulator naive
• Combination with AZA may have higher risks for side effects
  – Evaluate the risk benefit on an individual basis.
  – If combination therapy is used for a first anti TNF, it should be for a limited time
• Monitor for infections!
Prolonged Duration of Response to Infliximab in Early But Not Late Pediatric Crohn’s Disease

Weeks after IFX administration

% patients without relapse

- CD <2y after dx (n=6)
- CD >2y after dx (n=8)

S Kugathasan et al. Gastroenterology 2000
Inflammation and mineral density

Inflammation is the main determinant of low bone mineral density in pediatric inflammatory bowel disease

Correlation between disease activity and BMAD in patients with CD

Effect of infliximab on bone mineral density

M Paganelli et al Inflamm Bowel Dis 2007
Onset

Diagnosis

Early disease

Late disease

Modified from: B Pariente et al. Inflamm Bowel Dis 2011
Internal penetrating disease

• Signs and symptoms
  – abdominal pain, fever, nausea and vomiting, diarrhea and fistula
  – Predominantly in the lower right quadrant

• Diagnosis
  – Blood counts and infection screen
  – Imaging of the abdomen (US, CT and MR)

• Probable agents
  – *Pseudomonas*, *Enterobacter*, *Klebsiella*, *E coli*, *Enterococcus*, *Bacteroides*, *Peptostreptococcus*
Treatment of internal penetrating disease

• Empiric **antibiotics**
  – carbapenem (imipenem or meropenem), a b-lactam/b-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (ceftazidime) **with** metronidazole
  – Vancomycin should be used empirically if the patient has had recent cephalosporin exposure, a history of previous infection, or colonization with enterococcal organisms

• **Drainage** and culture of fluid

• **Immunomodulators** (long term)

• **Biologics** (after drainage)

• **Surgery** in refractory cases

MD Pfefferkorn *et al.* JPGN, 2013
Classification of perianal fistulas
Perianal fistula evaluation and treatment

Assessment of intestinal disease
- History and physical
- Colonoscopy to evaluate rectal inflammation
- Perianal assessment
- Examine for pain, fluctuance, erythema
- Digital rectal exam for stricture

Absent: Pain, fluctuance, or stricture

- EUA+/-EU or MRI

Simple fistula no rectal inflammation
- Antibiotics
- Anti-TNFα
- Immunomodulators
  - Consider noncutting seton or fistulotomy
  - Anti-TNFα

Complex or simple fistula with rectal inflammation
- Antibiotics
- Anti-TNFα
- Immunomodulators
  - Consider noncutting seton
  - Anti-TNFα

Complex fistula no rectal inflammation
- Antibiotics
- Anti-TNFα
- Immunomodulators
  - Consider advancement flap in rectovaginal fistulae
- Anti-TNFα
Elective surgery in CD

- It is no longer a “last resource” solution
- Elective in limited segmental disease specially with growth failure.
Endoscopy in follow-up - CD

• **Before starting biologics**
  – Look for TB and CMV in mucosa

• **Objective:**
  – evaluate severity and exclude complications
  – justify change of treatment

Guidelines for the management of IBD in UK. JPGN 2010
European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. JCC 2009
Endoscopy in follow-up - CD

• 10 years after diagnosis or before transition to adult care
  – involvement of 1 or more colonic segments
  – Independently of disease activity

• objective:
  – Screen for dysplasia
  – Evaluate extension of the disease

NICE clinical guidelines, 2011
Endoscopy in follow-up - CD

• **After surgery:**
  – 1 year after ileal or ileocolonic resection
  – Even if asymptomatic
  – Evaluation and classification according to Rutgeerts score (0-4)
  – **NOTE:** check for simultaneous **calprotectin** (every 3 months after surgery)

• **Objective:**
  – Check for subclinical endoscopic relapse; indication for biologic if on AZA, in score 3-4 (Rutgeerts)
  – Reason for calprotectin: correlate with endoscopy and reliability for monitoring

ECCO, 2010
P Rutgeerts *et al.* Inflamm Bowel Dis 2008
Rutgeerts *et al.* Gastroenterology 1990
Endoscopy in follow-up - CD

• **Patients on biologics:**
  – After 5 years of treatment with clinical and biochemical remission
• **objective:**
  – Consider stopping biologics?
  – Individual basis consideration (avoid growth spur)
  – Evaluate mucosal healing

• **Patients with growth failure on apparent remission**
• **objective:**
  – Check disease activity and consider change of therapy

• **Patients on apparent remission but with ongoing subjective complains**
• **objective:**
  – Check disease activity and consider change of therapy
Induction of remission in UC

• Oral 5-ASA are recommended as first-line induction therapy for mild to moderately active pediatric

• Monotherapy with topical 5-ASA may be effective in selected children with mild to moderate proctitis (rare!)

• Combining oral 5-ASA with topical 5-ASA is more effective than oral alone

• Rectal 5-ASA is superior and should be preferred over rectal steroid therapy
Steroids to induce remission in UC

• Oral steroids are effective for inducing remission but not for maintaining remission
• Oral steroids are recommended in moderate disease or in those failing remission with optimal 5-ASA therapy
• Those with severe disease should be admitted for iv steroid therapy
  – Dose 1 mg/kg (max 40 mg) once daily
• Steroid dependency should not be tolerated
Maintenance of remission in UC

- **Thiopurines** are recommended for maintaining remission in frequently relapsing (2–3/year) or steroid-dependent disease
- Thiopurines are ineffective for induction of remission
- **5-ASA** monotherapy in children responding to steroids
- **Cyclosporine** or **tacrolimus** started during an episode of acute severe colitis should be discontinued after 4 months, bridging to thiopurines
- Insufficient to recommend methotrexate in pediatric UC
Probiotics in UC?

- Probiotics may be considered in children with mild UC intolerant to 5-ASA, or as an adjuvant therapy in those with mild residual activity despite standard therapy
Severe UC (PUCAI 65-80)

• Methylprednisolone iv
  – 1-1.5 mg/kg/d (max 60 mg) in 1-2 daily doses
  – Fewer mineralocorticoid effect than hydrocortisone

• Antibiotics if suspected infection or toxic megacolon
  – Consider *C diff* especially if recent antibiotics taken

• Stop 5-ASA

• If severe pain investigate for perforation and toxic megacolon
Severe UC

- When discussing second-line therapy, surgery must always be seriously considered.
- In patients failing iv corticosteroids, calcineurin inhibitors or infliximab is recommended.
Efficacy of 2nd line treatment: meta-analysis of pediatric studies

Success rate (95%CI)

- Cyclosporin (n=84, 7 studies)
- Tacrolimus (n=61, 3 studies)
- Infliximab (n=126, 6 studies)
Efficacy of 2nd line treatment: meta-analysis of pediatric studies

- Cyclosporin (n=84, 7 studies)
- Tacrolimus (n=61, 3 studies)
- Infliximab (n=126, 6 studies)
Surgery in UC

- Elective colectomy may be indicated in children with active or steroid-dependent UC despite maximal treatment with 5-ASA, thiopurines, and anti-TNF therapy, or colonic dysplasia.
- Restorative proctocolectomy (ileoanal pouch or ileal pouch-anal anastomosis), especially the J-pouch, is preferred over straight pull-through (ileoanal) or ileorectal anastomosis.
- Laparoscopy can be used safely.
Severe UC

- A child with PUCAI > 45 on day 3 should be prepared for second-line therapy
- PUCAI > 65 on day 5 should prompt initiation of second-line therapy
- Corticosteroids may be continued for additional 2–5 d in a child with a PUCAI of ≤ 60 and ≥ 35 points on day 5, before a decision on second-line therapy is made
- Those with PUCAI < 35 points on day 5 are unlikely to require second-line therapy

D Turner et al. ECCO-ESPGHAN consensus, AJG 2011
Initial diagnosis or flare
Evaluate severity; Teach coping techniques

Induction of remission

Mild d (PUCAI 10-35)
5-ASA max dose
Use enemas (may be enough in proctitis)

Moderate d (PUCAI 40-60)
Prednisolone 1mg/kg 1x/d (max 40mg) + 5-ASA

Severe d (PUCAI 65-80)
Admit for iv steroids

Response (7-14d)?
Yes

Add enemas and/or probiotics

Response 7-14d?
Yes
Reduce steroids in 10 weeks

No

Disease controlled

Tacro or IFX?
No

Yes

D Turner et al ECCO-ESPGHAN consensus JPGN 2012
Maintenance of remission

5-ASA in all Probiotics? Topical treatment in proctitis

If disease chronically active or recurrent (on 5-ASA), Thiopurines

If disease chronically active or recurrent (on thiopurines), IFX (or ADA)

If failure of biologics, without alternative diagnosis, colectomy

If disease chronically active or recurrent (on 5-ASA), Thiopurines

Severe d (PUCAI 65-80)

Admit for iv steroids

Response 7-14d?

No

Tacro or IFX?

Yes

Reduce steroids in 10 weeks

Moderate d (PUCAI 40-60)

Prednisolone 1mg/kg 1x/d (max 40mg) + 5-ASA

Response 7-14d?

No

Add enemas and/or probiotics

Yes

Disease controled

Mild d (PUCAI 10-35)

5-ASA max dose

Use enemas (may be enough in proctitis)

Response 7-14d?

No

Disease controled

Initial diagnosis or flare

Evaluate severity; Teach coping techniques

Induction of remission
Endoscopy in follow-up - UC

• **Before starting biologics**
  – Activity may prevent full colonoscopy (at least rectosigmoidoscopy)
  – Check for CMV in mucosa

• **Objective:**
  – Evaluate severity and exclude complications
  – Justify change of treatment

ECCO, ESPGHAN, and the Pediatric IBD Porto Group, Am J Gastroenterol 2011
European evidence-based concensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. JCC 2009
Endoscopy in follow up - UC

• 8-10 years after diagnosis or before transition to adult care
  – Left colitis and pancolitis (exclude proctitis)
  – Independentently of disease activity
  – If associated Sclerosing cholangitis it must be done earlier (1 year post diagnosis of PSC)
  – Multiple biopsies (and all suspitious lesions)
  – Chromo-endoscopy important

• objective:
  – Screen for dysplasia
  – Evaluate extension of disease

ECCO. Gut 2011
NICE clinical guideline 118, 2011,(www.nice.org.uk/guidance/CG118)
Conclusions – treatment of IBD

• Induction and maintenance therapies differ
• Use treatment adjustments wisely
• Not yet evidence for “top-down” therapy in pediatric CD, but “quick step-up” reasonable
• Avoid steroids
• Monitor growth
• Consider measures against opportuistic infection
Conclusions – Follow up

- Inflammation markers
- Fecal calprotectin
- Endoscopic control when necessary
There is nothing permanent except change!

Heraclitus