Evidence-based guidelines for ulcerative colitis management

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Buenos Aires, August 14, 2014
Consensus guidelines for managing acute severe ulcerative colitis in children

A joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN

Management of pediatric ulcerative colitis

Joint ESPGHAN and ECCO evidence-based consensus guidelines
Making the right diagnosis: is it ulcerative colitis

Assessing disease activity

Optimizing medical treatment of UC
  - Acute severe UC
  - Mild to moderately severe UC
OUTLINE

- Making the right diagnosis: is it ulcerative colitis?
- Assessing disease activity
- Optimizing medical treatment of active UC
- Optimizing maintenance therapy
Inflammatory bowel disease

Ulcerative Colitis  Crohn Diseases

A SPECTRUM of related disorders
Labeling less important than anticipated treatment responsiveness
Controversial issues in classification of colonic IBD

- **Rectal sparing**
  - May be relative rectal sparing in UC
  - Normal rectal histology = CD

- **Histologic gastritis**
  - Non-specific gastritis common in UC
  - Only antral granulomata diagnostic of CD

- **Histologic ileitis**
  - In severe pancolitis, ileal inflammation may be observed (histologically focal acute)

Paediatric working group report
How consistently do paediatric IBD experts apply “Labels” of CD/UC/IBD-U?

<table>
<thead>
<tr>
<th>Type of IBD</th>
<th># Cases</th>
<th>Kappa (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD, UC or IBDU</td>
<td>50 (all study cases)</td>
<td>0.60 (0.58-0.63)</td>
</tr>
</tbody>
</table>

Inter-relater reliability

Sherlock M et al, CCFA conference 2010
Making the right diagnosis: Potential consequences of “mis-labeling”

- 5-ASA, which when optimized is effective maintenance therapy in “UC” is not given (because of CD label)
- Methotrexate maintenance therapy is prescribed for a patient, who truly has “UC” (because of CD label)
- “Curative” colectomy is deferred for too long in a “UC” patient with chronic steroid dependency and consequent growth impairment (because of CD label)
OUTLINE

- Making the right diagnosis: is it ulcerative colitis
- Assessing disease activity
- Optimizing medical treatment of active UC
- Optimizing maintenance therapy
Assessing activity in UC

- Usually easier than in Crohn’s disease

- Sequence of increasing activity….blood in loose stools…..blood in more loose stools…more blood in more loose stools….lots of blood in lots of loose stools and pain
# Pediatric UC Activity Index (PUCAI)

<table>
<thead>
<tr>
<th>ITEM</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Abdominal pain</strong></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>0</td>
</tr>
<tr>
<td>Pain can be ignored</td>
<td>5</td>
</tr>
<tr>
<td>Pain cannot be ignored</td>
<td>10</td>
</tr>
<tr>
<td><strong>2. Rectal bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Small amount only in &lt; 50% of stools</td>
<td>10</td>
</tr>
<tr>
<td>Small amount with most stools</td>
<td>20</td>
</tr>
<tr>
<td>Large amount (&gt;50% of the stool content)</td>
<td>30</td>
</tr>
<tr>
<td><strong>3. Stool consistency of most stools</strong></td>
<td></td>
</tr>
<tr>
<td>Formed</td>
<td>0</td>
</tr>
<tr>
<td>Partially formed</td>
<td>5</td>
</tr>
<tr>
<td>Completely unformed</td>
<td>10</td>
</tr>
<tr>
<td><strong>4. Number of stools per 24 hours</strong></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td>3-5</td>
<td>5</td>
</tr>
<tr>
<td>6-8</td>
<td>10</td>
</tr>
<tr>
<td>&gt;8</td>
<td>15</td>
</tr>
<tr>
<td><strong>5. Nocturnal bowel movement (any diarrhea episode causing wakening)</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td><strong>6. Activity level</strong></td>
<td></td>
</tr>
<tr>
<td>No limitation of activity</td>
<td>0</td>
</tr>
<tr>
<td>Occasional limitation of activity</td>
<td>5</td>
</tr>
<tr>
<td>Severe restricted activity</td>
<td>10</td>
</tr>
<tr>
<td><strong>SUM OF PUCAI (0-85)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Remission: <10  
Mild: 10-30  
Moderate: 35-60  
Severe: 65-85  

Turner D et al; Gastroenterology 2007;133:423-432  
Recognize acute severe ulcerative colitis!

- Frequent bloody diarrhea, nocturnal stools, abdominal pain ++

- An IBD emergency
Select initial treatment according to disease activity

- **Hospitalized Acute Severe**: 15%
  - Intravenous steroids

- **Non Hospitalized Moderate to Severe**: 20%
  - Out-patient steroids

- **Non Hospitalized Mild**: 35%
  - 5-ASA

- **Non Hospitalized**: 30%
Induction therapy is chosen with maintenance strategy in mind

- 5-ASA ……… 5-ASA maintenance

- Steroids …… 5-ASA maintenance ….?or thiopurine maintenance

- Anti-TNF …… scheduled anti-TNF maintenance ? + concomitant immunemodulator
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- Optimizing maintenance therapy
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Corticosteroid dosing in acute severe UC

- Intravenous methylprednisolone, 1 to 1.5 mg/kg/day, is recommended to a maximum of 60 mg given in one or two divided daily doses [EL2, RG B]

Practice points

a. Methylprednisolone is preferred over hydrocortisone because it has fewer mineralocorticoid effects.

Am J Gastroenterol 2011; 141: 1566-1571
Avoid prolonged IV corticosteroid therapy if ineffective

- Recognize early the patient who will not respond to IV steroids
- Prepare to introduce second line therapy in timely fashion
Short term steroid failure rate in children
The OSCI multi-centre study

29%

37/128

2006-2008

Turner D et al, Gastroenterology 2010; 138: 2282 -229
“Get set…go” Criteria: Day 3

PUCAI > 45
- Screen for 2nd line therapy
- Consult surgeons
- Consult stoma therapist
- Repeat blood tests
PPV = 43%

PUCAI 35-45
NPV = 95%

PUCAI < 35
- Consider switching to oral prednisone and discharge
NPV = 98%

Daily PUCAI assessment to day 5

Pucaid et al. Am J Gastroenterol 2011
“Get set….go” Criteria: Day 5

- Repeat blood tests
- Daily PUCAI assessment

**PUCAI>65**
- PUCAI>65: PPV=82%
- PUCAI>70: PPV=87-100%
- Start second line medical therapy

**PUCAI 40-65**
- NPV ~80%

**PUCAI<35**
- Consider switching to oral prednisone and discharge

*Turner D et al. Am J Gastroenterol 2011*
Treatment of steroid-refractory UC

• Infliximab: preferred in most centers because of better toxicity profile + ability to continue as maintenance therapy

• Calcineurin inhibitors

• Colectomy
Management of ulcerative colitis: ECCO/ESPGHAN guidelines

Turner D et al, JPGN 2012

- Infliximab is indicated in steroid refractory disease
OUTLINE

● Making the right diagnosis: is it ulcerative colitis

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● Optimizing medical treatment of UC
  – Acute severe UC
  – Mild to moderately severe UC

● Optimizing maintenance therapy
High dose oral 5-ASA is the first line therapy for both induction and maintenance of remission in children without acute severe colitis.
Combined oral and enema 5-ASA vs oral 5-ASA alone in extensive mild-moderate UC

Predicting Response to Standardized Pediatric Colitis Therapy
Aims of PROTECT

- Define rates of week 52 steroid free remission with 5-ASA as sole maintenance therapy in patients receiving standardized induction therapy with 5-ASA/corticosteroids.

- Test predictors of week 52 Steroid Free Remission.

- Identify biologic pathways associated with initial response and week 52 Steroid Free Remission.
## Initial Therapy By Disease Activity Assessment (PUCAI)

<table>
<thead>
<tr>
<th>Baseline PUCAI</th>
<th>Pentasa</th>
<th>Oral Steroids</th>
<th>IV Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (n=67)</td>
<td>58 (86.6%)</td>
<td>6 (9.0%)</td>
<td>2 (3.0%)</td>
</tr>
<tr>
<td>Moderate (n=123)</td>
<td>39 (31.7%)</td>
<td>60 (48.8%)</td>
<td>22 (17.9%)</td>
</tr>
<tr>
<td>Severe (n=82)</td>
<td>2 (2.4%)</td>
<td>22 (26.8%)</td>
<td>57 (69.5%)</td>
</tr>
</tbody>
</table>
5-aminosalicylic acid

- **Dosing in children with ulcerative colitis**
  - 50 - 75 mg/kg/day in NIH-funded PROTECT study in new onset pediatric UC
Thiopurines are recommended for maintaining remission in children with: frequent relapses (2-3 relapses per year); steroid-dependent disease, despite the use of maximal 5-ASA treatment; after most acute severe colitis cases.

Turner D et al, JPGN 2012
Does adding 5-ASA to azathioprine improve outcomes in UC?

- **No difference:**
  - Time to relapse
  - Discontinuation of treatment
  - UCDAI score
  - IBDQ score

- **Combination therapy:**
  - More adverse events*
  - Increased costs
  - Reduced compliance

*pain, diarrhea, transient leukopenia, infection

Mantzaris GJ. Am J Gastroenterol 2004;99:1122-8

**Figure 2.** Kaplan-Meier estimates for time to relapse or discontinuation of treatment for patients treated with AZA monotherapy or AZA and olsalazine (OLS).
Azathioprine metabolism and 5-ASA

Dubinsky MC. Gastroenterology 2002;122:904-15
Management of ulcerative colitis: 
ECCO/ESPGHAN guidelines

Turner D et al, JPGN 2012

- Infliximab should be considered for treatment of children with persistently active, or steroid-dependent UC when maintenance of steroid-free remission is not achieved by 5-ASA and thiopurines
Moderate UC Algorithm: Accelerated Step Care

- **Moderate**
- **Prednisone**
  - Steroid dependent
    - AZA x 12–16 weeks
  - First or second flare-up
    - IFX 0, 2, 6 +/- Immunomodulators

Infliximab in ambulatory pediatric patients with UC: Study Design

**Visits**

- **Week 0**: All subjects (n=60)
  - Infliximab 5 mg/kg q8w

- **Week 2**:
  - Responders (n=45)
  - Non-responders (n=15)

- **Week 6**:
  - Responders: Infliximab 5 mg/kg q8w (n=22)
  - Non-responders: No further infliximab (n=15)

- **Week 8**: Evaluation at week 54

- **Week 14**
  - LOR ≤ 8Wk: Infliximab 10 mg/kg q8w (n=6)
  - LOR > 8Wk: Infliximab 5 mg/kg q8w (n=6)

- **Week 22**
  - LOR ≤ 8Wk: Infliximab 10 mg/kg q8w (n=8)

- **Week 30**
  - LOR > 8Wk: Infliximab 5 mg/kg q8w (n=6)

- **Week 38**
- **Week 46**

*Infusions

LOR = loss of response

PedUC: Hyams et al., DDW2011. Abstract 747
Response, Remission and Mucosal Healing at Week 8

(95% C.I.: 62.1%-84.5%)

Percent of patients

Response: 44/60
Remission (Mayo): 24/60
Remission (PUCAI): 17/51
Mucosal healing: 41/60

Steroid-Free Remission† at Week 16

†Total Mayo score ≤ 2, with no individual subscore > 1, and no steroids

IFX+Azathioprine in Ambulatory UC

Primary endpoint

**Steroid-Free Remission† at Week 16**

- **AZA (N=76)**: n=18
- **IFX (N=77)**: n=17
- **IFX/AZA (N=78)**: n=31

- p=0.813
- p=0.032
- p=0.017

Panaccione et al. Gastroenterology 2013
TROUTH LEVELS PREDICT CLINICAL OUTCOME

Seow C H et al. Gut 2010;59:49-54
Summary: important take-home messages

- Diagnose UC appropriately
- Assess disease activity accurately
- Optimized 5-ASA is effective maintenance therapy
- Thiopurines or infliximab or combination in UC which is steroid dependent despite optimized 5-ASA
- Infliximab for steroid-refractory UC
- Therapeutic drug monitoring with biologics is important