Severe ulcerative colitis: The pediatric perspective

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The Hebrew University of Jerusalem
ISRAEL
Acute severe pediatric UC

- Pediatric definition
- Epidemiology
- Use of corticosteroids
- Outcome
- Second line therapy
- Pediatric radiography and TMC
Case JM

- 11 year old boy (39 kg), diagnosed with UC 4 months earlier, presented to ER due to a flare

- 10 days of 8 bloody diarrhea/d (1 nocturnal) with moderate abdominal cramping, but no fever, and no vomiting

- No benefit to 1 week of prednisone

- Mild abdominal tenderness, but no peritoneal signs
# Truelove and Witts classification

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Criteria</th>
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</table>
| **Remission**    | 1 – 2 stools/day without blood  
No fever  
No tachycardia  
Haemoglobin normal or returning to normal  
ESR normal or returning to normal  
Gaining weight |
| **Mild**         | ≤ 4 stools/day with no more than small amounts of macroscopic blood  
No fever  
No tachycardia  
Anaemia not severe  
ESR ≤ 30 |
| **Moderate**     | Intermediate between severe and mild |
| **Severe**       | ≥ 6 stools/day with macroscopic blood  
Fever > 37.5°C or ≥ 37.8°C 2/4 days  
HR > 90/minute  
Hb ≤ 75%  
ESR > 30 |
Severe UC - definitions

Mild-moderate colitis

Severe colitis
## The PUCAI

<table>
<thead>
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<th>ITEM</th>
<th>POINTS</th>
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<td>Pain can be ignored</td>
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<td><strong>2. Rectal bleeding</strong></td>
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<td>Small amount only in &lt; 50% of stools</td>
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<td>Small amount with most stools</td>
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<td>Large amount (&gt;50% of the stool content)</td>
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<td>0-2</td>
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<td>&gt;8</td>
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**SUM OF PUCAI (0-85)**

Turner et al; Gastroenterology 2007;133:423-432
PUCAI cutoffs (n=205)

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<th>Definition</th>
<th>AUC of ROC</th>
<th>Sens/Spec</th>
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<td>Severe: &gt;65</td>
<td>0.97 (0.95-0.99)</td>
<td>96%/91%</td>
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<td>Mod: 35-60</td>
<td>0.97 (0.95-0.99)</td>
<td>96%/91%</td>
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<td>Mild: 10-30</td>
<td>0.98 (0.97-0.99)</td>
<td>89%/94%</td>
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<tr>
<td>None: &lt;10</td>
<td>0.99 (0.99-1)</td>
<td>95%/99%</td>
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Turner D et al; Gastroenterology 2007;133:423-432
Turner D et al; Inflam Bowel Dis 2009; In press
How common are severe attacks in pediatric UC?
Population-based analysis of severe pediatric UC


Admission rate: 28% (55/196)

Total admission burden: 1.6/100,000/yr

Pediatric UC differs from adults

**Pediatric onset**
- Left-sided 26%
- Proctitis 13%
- Extensive 62%

**Adult onset**
- Left sided 34%
- Proctitis 33%
- Extensive 33%

HSC Toronto
1990-99; n=197
2004-2006; n=205

Moum et al, Am J Gastro 1999; n=399

AM Griffiths & TD Walters
Turner; Gastroenterology 2007
Case JM

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- Mild abdominal tenderness, but no peritoneal signs
Heterogeneity - controlled meta-regression of methylprednisolone equivalent versus colectomy rate

Turner D et al; Clin Gastroenterol Hepatol 2007;5:103-110
Glucocorticoid bioassay

- 50 children with severe UC
- Serum for GBA on 3rd steroid days

*Turner D & Kolho KL et al; In preparation*
# North American survey of IV steroid dosing in severe pediatric UC

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<th>Site</th>
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<td>MP</td>
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<td>40-60 mg/d</td>
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<tr>
<td>Canada</td>
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<td>1-2 mg/kg %1-2</td>
<td>40-60 mg/d</td>
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Personal communications
So....what dose?

- 1-1.5 mg/kg/day up to 40-60mg daily
- Rapid tapering to 1mg up to 40mg
What is the outcome of standard therapy?
Short term outcome in cohort studies of severe pediatric UC (n=293)

- Infliximab (the OSCI study): 34% (95% CI 27-41%)
- Failure rate
- Colectomy rate

- Turner 2009: N=128
- Turner 2008: N=99
- Barabino 2002: N=20
- Gold 1995: N=11
- Werlin 1977: N=13
JM: 3 days passed on IVCS....

- 8→5 bloody stools, one nocturnal
- Still abdominal pain, less tender
- Fever up to 37.8, no vomiting

- CRP 44.2 mg/L
- Albumin 43→40 g/L
- Hb 144→130 g/L

- WHAT’S NEXT?
Can we predict steroid failure in children?

AKA, when to introduce 2\textsuperscript{nd} line therapy?
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*Turner D et al; Clin Gastroenterol Hepatol 2007*
Adult clinical prediction rules all at the 3rd day of IVCS

- Travis (i.e. the Oxford index)
  - Stool frequency>8/d OR 3-8/day with CRP>45 mg/dL
  - PPV of 85%

- The fulminant colitis index (i.e. Lindgren)
  - CRP (mg/L) X0.14+No of stools/day
  - PPV of 70%

- Ho’s score

- Seo index

Travis et al, Gut 1996
Lindgren et al, Eur J Gastroenterol Hepatol 1998; Jarnerot et al, Gastroenterology 2005
Ho et al, Aliment Pharmacol Ther 2004
PREDICTION

“get set....go!”

Turner  D et al NASPGHAN annual meeting, 2008
Area under the curve

Day 3:
- PUCAI: 0.82 (0.75-0.90)
- Lindgren: 0.78 (0.69-0.86)
- Seo: 0.70 (0.60-0.80)
- Calprotectin: 0.65 (0.5-0.81)

Day 5:
- PUCAI: 0.82 (0.72-0.91)
- Lindgren: 0.80 (0.69-0.90)
- Seo: 0.71 (0.60-0.83)

N=128 of which 37 failed (29%)
N=92 of which 33 failed (35%)
Prediction

• PUCAI>45 on day 3- start planning...

  – Sens=92 (95%CI 79-98)
  – Spec=50 (44-52)
  – NPV=94 (84-98)
  – PPV=43 (37-45)
  – LR=0.16

  ▪ OR=11.1 (3-49); P<0.0001

Turner D et al NASPGHAN annual meeting, 2008
**“get set....go!” criteria: DAY 5**

- PUCAI>70 on day 5 - **EXECUTE!**
  - Sens=33 (23-36)
  - Spec= 100 (94-100)
  - NPV=87 (68-97)
  - PPV=100 (65-100)
  - NPV=75 (71-76)
  - +LR=42.7

<table>
<thead>
<tr>
<th>Failure</th>
<th>PUCAI&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

- **OR=64 (5->1000); P<0.0001**

Turner D et al NASPGHAN annual meeting, 2008*
Days to salvage Rx during the first year post discharge

# at risk: PUCAI≤45 48 19 16 16 11
   PUCAI>45 80 26 24 20 12

P<0.001
How to interpret abdominal X-ray in children?
Transverse colonic width at admission

![Graph showing Transverse colon width at admission with responders and non-responders]

Turner et al. Gut 2008; 57:331-338
Pediatric TMC
1:2 matched case-control study

<table>
<thead>
<tr>
<th>Clinical / Laboratory Sign</th>
<th>Toxic Megacolon (n=10)</th>
<th>UC w/o TMC (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>90%</td>
<td>25%</td>
<td>$P = 0.005$</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>80%</td>
<td>5%</td>
<td>$P = 0.0001$</td>
</tr>
<tr>
<td>Dehydration</td>
<td>40%</td>
<td>0%</td>
<td>$P = 0.015$</td>
</tr>
<tr>
<td>Electrolyte Disturbance</td>
<td>100%</td>
<td>25%</td>
<td>$P = 0.0002$</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>80%</td>
<td>70%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Anemia</td>
<td>90%</td>
<td>75%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Altered LOC</td>
<td>0%</td>
<td>0%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10%</td>
<td>0%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Benchimol et al. Am J Gastroenterol 2008;103:1524-1531
Do we have good alternatives to colectomy?
Outcome of cyclosporine in severe pediatric UC (n=84)

- Short term success
- Long term success

79% (95%CI 74-84%)
Tacrolimus in children

- Open label uncontrolled study
- 7 days IVCS failure
- N=14 (one dropout)


69% response at discharge
38% response at 1yr
The OSCI study

Short term colectomy rate: 11 (9%)

- 91 response
  - 8 colectomy

- 33 infliximab
  - 25 response

- 3 colectomy

- 1 cyclo
  - 1 response

1 year colectomy rate: 23 (18%)

- 3 colectomy
  - 7 infliximab
    - 5 response
    - 2 colectomy

- 7 colectomy

- 0 colectomy

*Turner D et al NASPGHAN annual meeting, 2008*
Outcome of infliximab in severe pediatric UC (n=101)

77% (95% CI 68-84%)
Colectomy: pediatric considerations

Pros
- Many future treatment years with toxic medical therapy
- Quality of life

Cons
- Crohn’s common phenotype <5yo, is colitis (avoid a pouch until later in life?)
- Infertility
- Poor self image with stoma and frequent stools/pad
Long-Term Evolution of Disease Behavior in CD

Patients at risk
N = 2002 552 229 95 37

Months
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240

% Cumulative Probability
0 10 20 30 40 50 60 70 80 90 100

Penetrating

Inflammatory

Stricturing

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Conclusions

• Children are not little adults in regards with:
  Epidemiology, symptoms, prediction rule, definitions and radiography.
  - Unique age-related considerations over management.

• Children are little adults in regards with:
  Treatment effect, and outcome of steroid therapy
  (tradeoff of more severe disease VS. shorter disease duration and more effort to avoid second line therapy)
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