Enteral Nutrition in Pediatric Crohn’s Disease

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Multi-factorial Pathogenesis of IBD

- Genes
- Mucosal Immune System
- Environment
Age of Onset of IBD

Loftus, *Gastroenterology* 2003; 124:abstract 278
How Common is IBD in Children?

• Impact in children:
  – 25% of IBD diagnosed at pediatric age

• Incidence and prevalence:
  – An estimated 1.5 million people (all ages) in the United States currently have IBD
  – 7-10 children out of 100,000 develop IBD in any given year in the United States
  – Estimated 50,000 children are presently believed to be suffering from IBD

Barton et al, Gut 1989; 30:618-22
Kugathasan et al, J Pediatr 2003; 143:525-31
Markowitz, Inflamm Bowel Dis 2004; 10:599-605
Pediatric Crohn’s Disease

• Usually moderate-severe at presentation

• Evaluation of natural history in children involves more than clinical symptoms (eg, growth, QOL)

• Biological behavior (phenotype) and genetic background affect course and response to therapy

• All Crohn’s disease is not alike; Crohn’s diseases
Therapeutic Goals in Pediatric IBD

• Short-term
  – Control symptoms

• Long-term
  – Prevent relapse
  – Reduce complications
  – Restore normal growth and development

• Universal
  – Heal the gastrointestinal mucosa
  – Improve patient quality of life
  – IMPROVE THE NATURAL HISTORY
Medical Therapies for Pediatric IBD

• Induction of remission: Steroids, Anti-TNFα
• Maintenance of remission: 6-MP/AZA, MTX, Anti-TNFα
• Mucosal healing: Anti-TNFα > 6-MP/AZA/MTX
• Improvement in growth: Anti-TNFα

AZA=azathioprine; 6-MP=6 mercaptopurine; MTX=methotrexate
“But doctor - can’t we treat this with diet, all my friends say so...”
Rationale For Nutritional Therapy

- Increased caloric intake—improved BMI
- Anti-inflammatory properties
- Modification of gut microflora

BMI=body mass index
Fell, J Parenteral Enteral Nutr 2005; 29:S126-8
Exclusive Enteral Nutrition: Primary Treatment of Active CD

- Therapeutic efficacy
  - In adults: > 50%
  - In children: 50% to 75%

- Value of elemental vs. polymeric diets

- Controversy regarding influence of anatomic location:
  - colon vs. small intestine

Meta-analysis: Exclusive Enteral Nutrition in Pediatric CD

- 5 prospective randomized clinical trials comparing exclusive enteral nutrition vs. steroids in children
  - Study population of 166
  - Interventions
    - Elemental, semi-elemental, polymeric x 4 – 8 weeks (exclusive)
    - OR
    - Prednisone/prednisolone 1 – 2 mg/kg/day x 1 – 3 weeks & then taper

Seidman et al. *Gastroenterology* (abstract) 1986
Tomas et al. *JPGN* 1993
Seidman et al. *AGA* abstract 1993
Ruuska et al. *JPGN* 1994
Borrelli et al. *Clin Gastro Hepato* 2006
Enteral Nutrition vs Prednisone

Relative Risk (95% CI)

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Corticosteroids  EEN

Corticosteroids in the Treatment of Pediatric IBD

- Very effective short-term
- Psychosocial problems common
  - depression, anxiety, memory loss, loss of concentration, irritability, sleep disturbances
- Adverse effects on growth, bone metabolism

A stunted, cushingoid child without gastrointestinal symptoms is not a success story
Polymeric Formula Induces Remission

Study Design: • Open-label, 8-week trial (n=29)
  • Polymeric diet was sole source of nutrition

Results: • Clinical remission: 79%
  • Mean weight gain: 3.2 kg
  • Improved endoscopic and histologic scores
  • ↓ mucosal inflammatory cytokines
  • Relapse: 39% relapse (by 10 months after stopping formula)

Polymeric Diet vs. Steroids for Induction

- Methods (n=37)
  - Prospective 10 week randomized, open-label trial
  - Polymeric formula (n=18) or steroids (n=19)
  - Primary outcomes at 10 weeks
    - Clinical remission (PCDAI \leq 10)
    - Mucosal healing
      - Decrease in both endoscopic and histologic scores by > 50% when compared to baseline

Polymeric Diet vs. Steroids for Induction

- Clinical Improvement
  - Enteral Nutrition (n=19)
  - Corticosteroids (n=18)
  - P<0.05

- Healing of GI tract
  - Enteral Nutrition (n=19)
  - Corticosteroids (n=18)
Cochrane Review: Effect of Protein Type

- 7 trial meta-analysis
- 113 patients elemental
- 109 patients polymeric
- No difference between groups
  - (OR 1.37; 95% CI 0.80—2.35;  p = 0.24)

Does Disease Location Affect EN?

- Two year retrospective
- 27 prescribed exclusive enteral nutrition: 24 completed course
- ITT analysis at 8 weeks
- New CD remission rates
  - 12/15 (80%; PCDAI 37→7)
- Chronic CD
  - 7/12 (58%; PCDAI 34→15.5)

Australian Retrospective: Effect of Disease Location

Glasgow Prospective: Effect of Disease Phenotype

- 114 patients over 3 year period (2004-2007)
- 8 weeks of exclusive enteral nutrition for active disease
- 52% oral; 48% NG (polymeric vs. elemental)
- Disease location and behavior (Vienna)
  - 73% inflammatory
  - 45% upper (L4)
  - 26% ileocolon (L3)
  - 17% colon (L2)

Glasgow Prospective: Effect of Disease Phenotype

• 80% remission at 8 weeks

• Significant improvement of BMI

• No difference by:
  – Type of exclusive enteral nutrition
  – Disease behavior or location

BMI = body mass index
• **Induction:**
  – Exclusive enteral nutrition (elemental or polymeric)
    • Duration: 4 – 12 weeks

• **Maintenance therapy:** (either)
  – Nutritional therapy:
    – Repeat 4 week cycle of exclusive enteral nutrition every 3 – 4 months

  OR

  – Medical therapy:
    – 6-MP/AZA/MTX after induction with nutritional therapy
Enteral Nutrition For Maintenance in CD

• Inclusion
  – Patients in remission at the beginning of trial
    (CDAI<150)

• Methods (prospective study)
  – 50% of caloric needs via overnight NG with elemental
    exclusive enteral nutrition for 1 year (n=20)
    OR
  – Normal diet (n=20)
Proportion in remission was higher in the enteral nutrition group ($P=0.01$)

$P=0.01$ by the log-rank test
Endoscopic Assessment

Severity of mucosal inflammation was graded 0-3

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<th>Enteral Nutrition Group</th>
<th>Normal Diet</th>
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<td>At Entry</td>
<td>0.95±0.22</td>
<td>0.85±0.22</td>
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<td>At 6 months</td>
<td>1.05±0.24</td>
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<tr>
<td>At 12 months</td>
<td>1.25±0.25</td>
<td>2.00±0.26</td>
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Conclusion: Endoscopic inflammation was significantly higher in the normal diet group at 12 months*

Methods: (prospective, control study)

- S/P Resection for ileal or ileocolonic CD

- Patients received either:
  - 50% of caloric needs from overnight NG with elemental exclusive enteral nutrition for 1 year (n=20)
  - Normal diet (n=20)

Prevention of Post-op Recurrence with Enteral Nutrition for CD

Rates of Recurrence

Exclusive Enteral Nutrition and the Gut Microbiome: Possible Mechanism of Action?

- Stool from active CD and controls
- Bacterial diversity by PCR
- Active exclusive enteral nutrition vs 4 months after exclusive enteral nutrition
- Controls: stable profile
- Exclusive enteral nutrition:
  - Decreased diversity
  - If lost Bacteroides → best clinical outcome
  - Changes persisted at 4 months

Summary: Enteral Nutrition as Therapy in CD

- Shown to induce remission
- Shown to maintain remission
- Shown to yield mucosal healing
- Improved growth
- Post-op prophylaxis
- ? Tolerability—enhanced with polymeric
Conclusions: Our Patients are Correct!

• Enteral nutrition is a valid treatment option
• Polymeric as effective as elemental
• Effect independent of disease location
• Partial enteral nutrition may be a valid adjunct
• Mechanism still to be fully established
  – Altered gut microbiota?