Future Directions in IBD: Treatments & Approaches

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APRIL 29, 2018
Why do pharmaceuticals dominate IBD therapy discussions?

- “Evidence-Based Medicine”
  - Strongest evidence is large, blinded, randomized, placebo-controlled clinical trial
    - Hard to blind, randomize, or make placebo for non-pharmaceutical interventions (e.g., surgery, diet, THC...)
  - Safety mechanisms make such clinical trials expensive

- Money
  - Global biopharmaceuticals market to exceed $340 billion by 2023

- Improving technology
  - Safety and efficacy of pharmaceuticals rapidly improving
IBD Drugs: Current

**Small Molecules**
- Steroids
  - Prednisone
  - Solu Medrol
  - Budesonide
- 5’ASA’s
  - Sulfasalazine
  - Mesalamine
  - Balsalazide
- IMM’s
  - Azathioprine
  - 6-MP
  - Methotrexate

**Biologicals**
- Anti-TNF’s
  - Infliximab
  - Adalimumab
  - Certolizumab Pegol
  - Golimumab
- Anti-Integrins
  - Natalizumab
  - Vedolizumab
- Anti-IL-12/23
  - Ustekinumab
# IBD Drugs: Current & Future

## Small Molecules
- **Steroids**
  - Prednisone
  - Solu Medrol
  - Budesonide
- **5'ASA’s**
  - Sulfasalazine
  - Mesalamine
  - Balsalazide
- **IMM’s**
  - Azathioprine
  - 6-MP
  - Methotrexate

## Biologicals
- **Anti-TNF’s**
  - Infliximab
  - Adalimumab
  - Certolizumab
  - Golimumab
- **Anti-Integrins**
  - Natalizumab
  - Vedolizumab
  - Etrolizumab
  - PF-00547659
- **Anti-IL-12/23**
  - Ustekinumab
  - Briakinumab
  - Brazikumab
  - Guselkumab
  - Risankizumab
  - Mirikizumab

## Other Classes
- **Jakinibs**
  - Tofacitinib
  - Filgotinib
  - Upadacitinib
- **S1P1 Agonists**
  - Ozanimod
  - Etrasimod
How New IBD Drugs Generally Work

Block immune cell communication
- Biologicals:
  - Block signals (cytokines) outside cells from interacting with receptors on cell surface
- Small Molecules (Jakinibs):
  - Block cell surface receptor signals (kinases) inside cells

Block immune cell migration
- Biologicals:
  - Block receptors (integrins) on circulating cells from recruiting them from blood to tissue
- Small molecules (S1P1’s):
  - Trap immune cells in lymph nodes
Blocking immune cell communication (cytokines)

Outside immune cell

Biologics:
- Anti-TNF, anti-IL (infliximab, ustekinumab…)

Inside immune cell

Small Molecules:
- Jakinib (tofacitinib…)

Blocking immune cell migration: Anti-integrins (biologics)
Blocking immune cell migration: S1P1 agonists (small molecules)

- Activate the S1P1 Receptor, used by lymphocytes to “smell” their way out of a lymph node
Blocking immune cell migration: S1P1 agonists (small molecules)

- S1P1 receptor gets down-regulated, and lymphocytes get trapped in lymph nodes, so they cannot go to inflamed tissues.
## Small Molecules versus Biologics

<table>
<thead>
<tr>
<th><strong>Small Molecules</strong></th>
<th><strong>Biologics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros:</strong></td>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>Cheap</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Fast</td>
<td>Short half life</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Allergies rare</td>
<td></td>
</tr>
<tr>
<td><strong>Pros:</strong></td>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>Specific</td>
<td>Expensive</td>
</tr>
<tr>
<td>Long half life</td>
<td>Slow</td>
</tr>
<tr>
<td></td>
<td>IV or shots</td>
</tr>
<tr>
<td></td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>
Small molecules are much less complex than biologicals.
Small molecules can be pills
Biologicals are proteins.
If you eat them, they are food.
Small molecules are much cheaper than biologicals.

IBD drugs by price

Estimated Annual Cost for 70 kg Patient

Steroids: prednisone, budesonide
Immunomodulators: azathioprine, 6-MP, MTX (PO), MTX (SQ), sulfasalazine, balsalazine
5’ASA’s: Lialda, Asacol, Delizcol, Apriso, Pentasa
Biologicals: Infliximab*, Adalimumab, Certolizumab, Golimumab, Natalizumab*, Vedolizumab*, Ustekinumab

All prices per GoodRx.com or WellRx.com, 9/3/17, and *exclude infusion center costs*
Biologic drugs require complex staged culture in sterile bioreactors

1 Cell line
Specific human genes are inserted into bacterial or mammalian cells to create a unique master cell line that yields the target antibody (biologics drug substance). This master cell bank is frozen for storage.

4a Purification
The antibody is separated from the biomass (cells, culture medium and waste products) leading to a pure solution. The centrifugation, purification and concentration steps are specific to each desired antibody.

2 Culture
For production, cells are removed from the master cell bank, cultured in a liquid growth medium and transferred to larger vessels as the cells multiply.

4b Conjugation
Additional steps for antibody-drug conjugates: The antibody is combined with a highly potent small molecule and again purified and concentrated.

3 Fermentation
The cell culture is transferred to progressively larger bioreactors. Special nutrient medium is added. Its unique composition is optimised for each cell line and enables production of the desired antibody.

5 Formulation, filling and packaging
The drug substance is formulated into a stable dosage form (sterile liquid or powder), filled into vials or syringes, and packed for shipping.
Small molecules do not
Current small molecules are less effective than biologics

Crohn’s: SONIC
Colombel et. al., N Engl J Med 2010;362:1383-95

Corticosteroid-free Clinical Remission at Wk 26

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients (%)</th>
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<tr>
<td>Azathioprine Monotherapy</td>
<td>30.0</td>
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<tr>
<td>Infliximab Monotherapy</td>
<td>44.4</td>
</tr>
<tr>
<td>Infliximab-Azathioprine</td>
<td>56.8</td>
</tr>
</tbody>
</table>

P-values:
- Azathioprine vs. Infliximab Monotherapy: P=0.006
- Infliximab vs. Infliximab-Azathioprine: P=0.02
- Azathioprine vs. Infliximab-Azathioprine: P<0.001

c. 15%
Biologic drug efficacy wanes over time

Loss Of Response to Infliximab

- **Infliximab Dose:**
  - 10 mg/kg (n=112)
  - 5 mg/kg (n=113)
  - 0 mg/kg (n=110)

Loss Of Response to Adalimumab
(CHARM trial, Colombel, J.F., Gastro 2007, 132:52.)

- **Adalimumab Dose:**
  - 40 mg weekly (n=157)
  - 40 mg every 2 wks (n=172)
  - none (n=170)

Crohn’s Disease Clinical Trials:
Biologic drug efficacy wanes over time: Why?

- Rapid protein drug clearance?
  - Inflammation gobbles up proteins?
  - Protein is lost in diarrhea?
- Immune reaction (antibodies) to protein drug?
  - Immune system recognizes protein as foreign
  - Antibodies block or clear drug?
- Drug target is too specific?
  - Disease mechanism “escapes” blockade by using a different mechanism?
“Life finds a way”
**Receptors sharing γ-chain**
- IL-2, IL-4, IL-7, IL-9, IL-15, IL-21

**Type I IFNR**
- IFN-α/β/ω/ε
- IL-10

**Receptors sharing gp130 subunit**
- IL-6, IL-13, IL-31*, G-CSF, etc.

**Type II IFNR**
- IFN-γ

**IL-12R family sharing p40 subunit**
- IL-12, IL-23

**Hormone receptors**
- GM-CSF, EPO
- IL-3, IL-5

**FUNCTION**
- Growth & maturation of lymphoid cells
- Differentiation & homeostasis of T cells, NK
- B cell class switching
- Inflammation
- Allergy
- Antiviral
- Inflammation
- Anti-tumor
- Naïve T cell differentiation
- T cell homeostasis
- Inflammation
- Granulopoiesis
- Pruritus
- Allergy
- Antiviral
- Inflammation
- Innate immunity
- Differentiation & proliferation of Th17
- Inflammation
- Erythropoiesis
- Myelopoiesis
- Megakaryocyte & platelet production
- Growth
- Mammary development

*currently only reported to use JAK1/JAK2*
Ustekinumab
Tofacitinib safety profile

Tofacitinib is effective induction therapy for UC

Remission at week 8

Mucosal Healing at week 8

Independent but identical phase III induction trials

Tofacitinib is effective maintenance therapy for UC

Remission at week 52

- Difference, 29.5 percentage points
- Difference, 23.2 percentage points
- OCTAVE Sustain

Mucosal Healing at week 52

- Difference, 32.6 percentage points
- Difference, 24.2 percentage points


Coming this June for UC?
Tofacitinib week 4 benefit in Crohn’s (phase II) less impressive

![Graph showing the response and remission rates for Placebo, Tofa 1mg, Tofa 5mg, and Tofa 15mg.]

Sandborn WJ et al., Clinical Gastroenterology and Hepatology 2014;12:1485–1493
Filgotinib benefit in Crohn’s induction phase II was more impressive

Vermeire S et. al., Lancet Vol 389 January 21, 2017
Upadacitinib also worked in Crohn’s induction phase II (CELEST)

<table>
<thead>
<tr>
<th>Week 16</th>
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</thead>
<tbody>
<tr>
<td>Response</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

Now recruiting phase III for Crohn’s, Phase II for UC

Ozanimod showed efficacy for UC induction in phase II (TOUCHSTONE)

Ozanimod showed efficacy for UC maintenance in phase II (TOUCHSTONE).

Now recruiting phase III for UC, Phase II for Crohn’s.

Etrasimod showed efficacy for UC induction in phase II (OASIS)

Etrasimod showed efficacy for UC induction in phase II (OASIS)

Week 12, UC

- Clinical + Endoscopic remission
- Clinical remission
- Endoscopic improvement

Placebo  Etrasimod 2 mg

p=0.004  P<0.001  p=0.003

Arena Pharmaceuticals press release, March 19, 2018
Entirely new pills for IBD are coming

**Jakinibs**
- Tofacitinib (Xeljanz)
  - UC only, June 2018
- Filgotinib
  - UC & Crohn’s, phase III
- Upadacitinib
  - Crohn’s phase III
  - UC phase II

**S1P1 Agonists**
- Ozanimod
  - UC phase III
  - Crohn’s phase II
- Etrasimod
  - UC phase II data just out
  - Not yet recruiting phase III
Newer versions of current biologics are coming

**Anti-integrins**
Similar to vedolizumab:
- Etrolizumab
  - Anti-integrin β7
    - Blocks α4β7 (like vedolizumab) plus αEβ7
- PF-00547659
  - Anti-addressin MADCAM1
    - Receptor for integrin α4β7

**Anti-IL-23**
Similar to ustekinumab:
- Brazikumab
- Briakinumab
- Guselkumab
- Risankizumab
- Mirikizumab
Clinical decision making: needs predictive biomarkers for guidance
Patients with high baseline integrin alpha E expression in colon biopsies responded better to integrin beta 7 blockade than those without.
Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study. Sands et. al., Gastroenterology. 2017 Jul;153(1):77-86.

aka Brazikumab, AMG139

Only people with a high blood level of IL-22 responded more to brazikumab than to placebo
What is not coming:

- Mongersen (SMAD7 antisense RNA pill)
  - Phase III trials failed to show anything like phase II successes
- IL-6 therapies (tocilizumab, etc)
  - Trials canceled due to bowel perforations
- IL-17 therapies (sekukinumab, brodalumab)
  - Actually made Crohn’s worse than placebo did
- CTLA4 therapy (abatacept)
  - Actually made UC worse than placebo
What is new besides drugs?

- Diet:
  - Autoimmune Protocol (AIP: basically Paleo) diet
  - Specific Carbohydrate Diet (SCD)
  - Partial Enteral Nutrition (PEN)
  - Curcumin

- Fecal transplant
  - Colonoscopic vs enema vs feeding tube delivery
  - Single vs multiple (pooled) donor(s)
  - Single vs multiple treatments
“The AIP dietary intervention consisted of a 6-week elimination phase (staged elimination of grains, legumes, nightshades, dairy, eggs, coffee, alcohol, nuts and seeds, refined/processed sugars, oils, and food additives) followed by a 5-week maintenance phase (during which no food group reintroduction was allowed)”
Nutritional Therapy in Pediatric Crohn Disease: The Specific Carbohydrate Diet

David L. Suskind, Ghassan Wahbeh, Nila Gregory, Heather Vendettuoli, and Dennis Christie

JPGN • Volume 58, Number 1, January 2014
Lack of Mucosal Healing From Modified Specific Carbohydrate Diet in Pediatric Patients With Crohn Disease


*JPJGN* • Volume 65, Number 3, September 2017
"The patients entered clinical remission on 4–12 weeks of EEN and were subsequently maintained on PEN (50% of total calories as polymeric diet, usually Modulen IBD) as a supplementary diet."

"The route of administration was oral, but if not tolerated, nasogastric feeding was used instead"

"Children with CD who refused EN served as the control group"
Curcumin: extract of Turmeric

- Augments mesalamine benefit in mild to moderate UC
- 3 grams curcumin/day for 1 month
- Enough to turn stool yellow, alter body odor
  - Blinding thus in question
Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial

World J Gastrointest Pharmacol Ther 2017 May 6; 8(2): 147-154

# Systematic Review and Meta-analysis: Fecal Microbiota Transplantation for Treatment of Active Ulcerative Colitis

**Neeraj Narula, MD, FRCPC,* Zain Kassam, MD, MPH,† Yuhong Yuan, PhD,* Jean-Frederic Colombel, MD,‡ Cyriel Ponsioen, MD, PhD,§ Walter Reinisch, MD,* and Paul Moayyedi, MBChB, PhD, MPH***

*Inflamm Bowel Dis • Volume 23, Number 10, October 2017*

<table>
<thead>
<tr>
<th>First Author and Year</th>
<th>Country</th>
<th>Intervention Description</th>
<th>Placebo Description</th>
<th>No. Patients</th>
<th>Concomitant Medication</th>
<th>Time of Evaluation of Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costello 2017</td>
<td>Australia</td>
<td>Anaerobically prepared, pooled donor stool (3–4 donors); administered by means of colonoscopy at time 0, then 2 enemas at day 7</td>
<td>Aerobically prepared, autologous stool; administered by means of colonoscopy at time 0, then 2 enemas at day 7</td>
<td>38</td>
<td>Stable maintenance medication (5-ASA, thiopurines, MTX, anti-TNF, vedolizumab), prednisolone ≤20 mg/d with mandatory wean</td>
<td>Week 8</td>
</tr>
<tr>
<td>Moayyedi 2015</td>
<td>Canada</td>
<td>Single donor FMT; administered through weekly enema</td>
<td>Water retention enema</td>
<td>38</td>
<td>Stable maintenance medication (5-ASA, thiopurines, MTX, anti-TNF, steroids)</td>
<td>Week 7</td>
</tr>
<tr>
<td>Paramsothy 2017</td>
<td>Australia</td>
<td>Pooled donor stool (3–7 donors); administered by means of colonoscopy at time 0, then 5 enemas per wk for 8 weeks</td>
<td>Saline + odorant + food colouring in enema</td>
<td>41</td>
<td>Stable maintenance medication (5-ASA, thiopurines, MTX), prednisolone ≤20 mg/d with mandatory wean</td>
<td>Week 8</td>
</tr>
<tr>
<td>Rossen 2015</td>
<td>The Netherlands</td>
<td>Fresh single-donor FMT; administered through nasoduodenal tube at time 0 then at week 3</td>
<td>Autologous stool administered through nasoduodenal tube</td>
<td>23</td>
<td>Stable maintenance medication (5-ASA, thiopurines), prednisolone ≤10 mg/d</td>
<td>Week 12</td>
</tr>
</tbody>
</table>

*5-ASA, 5-aminosalicylates; MTX, methotrexate; TNF, tumor necrosis factor.*
### FIGURE 3. Forrest plot of all studies reporting clinical remission.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costello 2017</td>
<td>19</td>
<td>38</td>
<td>29</td>
<td>35</td>
<td>23.6%</td>
<td>0.60 [0.42, 0.86]</td>
</tr>
<tr>
<td>Moayyedi 2015</td>
<td>23</td>
<td>38</td>
<td>28</td>
<td>37</td>
<td>27.5%</td>
<td>0.80 [0.58, 1.10]</td>
</tr>
<tr>
<td>Paramsothy 2017</td>
<td>23</td>
<td>41</td>
<td>32</td>
<td>40</td>
<td>27.8%</td>
<td>0.70 [0.51, 0.96]</td>
</tr>
<tr>
<td>Rossen 2015</td>
<td>16</td>
<td>23</td>
<td>17</td>
<td>25</td>
<td>21.1%</td>
<td>1.02 [0.70, 1.50]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>140</strong></td>
<td><strong>106</strong></td>
<td><strong>137</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.76 [0.62, 0.93]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>81</td>
<td></td>
<td>106</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.01; Chi² = 4.36, df = 3 (P = 0.23); I² = 31%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.64 (P = 0.008)</td>
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</tbody>
</table>

### FIGURE 4. Forrest plot of all studies reporting endoscopic remission.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costello 2017</td>
<td>17</td>
<td>38</td>
<td>29</td>
<td>35</td>
<td>16.0%</td>
<td>0.54 [0.37, 0.79]</td>
</tr>
<tr>
<td>Moayyedi 2015</td>
<td>29</td>
<td>38</td>
<td>34</td>
<td>37</td>
<td>26.2%</td>
<td>0.83 [0.68, 1.02]</td>
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<tr>
<td>Paramsothy 2017</td>
<td>36</td>
<td>41</td>
<td>37</td>
<td>40</td>
<td>29.7%</td>
<td>0.95 [0.82, 1.10]</td>
</tr>
<tr>
<td>Rossen 2015</td>
<td>21</td>
<td>23</td>
<td>23</td>
<td>25</td>
<td>28.1%</td>
<td>0.99 [0.84, 1.18]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>140</strong></td>
<td><strong>123</strong></td>
<td><strong>137</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.85 [0.69, 1.05]</strong></td>
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<tr>
<td>Total events</td>
<td>103</td>
<td></td>
<td>123</td>
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<tr>
<td>Heterogeneity: Tau² = 0.03; Chi² = 12.86, df = 3 (P = 0.005); I² = 77%</td>
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<td>Test for overall effect: Z = 1.54 (P = 0.12)</td>
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</table>

### FIGURE 5. Forrest plot of all studies reporting serious adverse events.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td>Costello 2017</td>
<td>3</td>
<td>38</td>
<td>2</td>
<td>35</td>
<td>29.6%</td>
<td>1.38 [0.25, 7.79]</td>
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<tr>
<td>Moayyedi 2015</td>
<td>3</td>
<td>38</td>
<td>2</td>
<td>37</td>
<td>29.5%</td>
<td>1.46 [0.26, 8.25]</td>
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<tr>
<td>Paramsothy 2017</td>
<td>2</td>
<td>41</td>
<td>1</td>
<td>40</td>
<td>15.9%</td>
<td>1.95 [0.18, 20.68]</td>
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<tr>
<td>Rossen 2015</td>
<td>2</td>
<td>23</td>
<td>2</td>
<td>25</td>
<td>25.1%</td>
<td>1.09 [0.17, 7.10]</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>140</strong></td>
<td><strong>137</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>1.40 [0.55, 3.58]</strong></td>
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<tr>
<td>Total events</td>
<td>10</td>
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<td>7</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 3 (P = 0.99); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 0.70 (P = 0.49)</td>
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</tbody>
</table>
Conclusions:

- New oral agents for IBS are promising:
  - Jakinibs (tofacitinib, etc.)
  - S1P1 agonists (ozanimod, etc.)

- New biologic (not oral) agents may have predictive biomarkers:
  - Colon (biopsy) integrin alpha E for etrolizumab
  - Serum (blood) IL-22 for brazikumab

- Diet remains hard to study
  - Small studies, subjective outcomes
  - No placebo groups/blinding

- Growing interest in fecal transplant/microbiome
  - Unclear if pooled or single donor is better
  - Need for frequent, repeated transplants—how?
    - Colonoscopy unfeasible for frequent use
    - Enemas? Encapsulated “stool pills”?