Management of Difficult Constipation

Elyanne M. Ratcliffe, MD, FRCPC
Louis Liu, MD, PhD, FRCPC

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Financial Interest Disclosure:
Elyanne M. Ratcliffe

No relevant financial relationships with any commercial interests

(over the past 24 months)
Financial Interest Disclosure: Louis Liu

Relevant relationships with commercial entities over the last 48 months

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
</tr>
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<tbody>
<tr>
<td>Takeda Canada Inc.</td>
<td>Speaker bureau, advisory board</td>
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<tr>
<td>AbbVie</td>
<td>Speaker bureau, advisory board</td>
</tr>
<tr>
<td>Allergan Canada</td>
<td>Speaker bureau, advisory board, consultant</td>
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<tr>
<td>Lupin Pharma Canada</td>
<td>Advisory board</td>
</tr>
</tbody>
</table>
### CanMEDS Roles Covered

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Expert</td>
<td>(as Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. Medical Expert is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.)</td>
</tr>
<tr>
<td>Communicator</td>
<td>(as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</td>
</tr>
<tr>
<td>Collaborator</td>
<td>(as Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</td>
</tr>
<tr>
<td>Leader</td>
<td>(as Leaders, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)</td>
</tr>
<tr>
<td>Health Advocate</td>
<td>(as Health Advocates, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)</td>
</tr>
<tr>
<td>Scholar</td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</td>
</tr>
<tr>
<td>Professional</td>
<td>(as Professionals, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)</td>
</tr>
</tbody>
</table>
Learning Objectives

By the end of this session, the attendees will be able to:

1. Identify the different etiologies of constipation between children and adults
2. Apply the evidence for current therapies to manage constipation in children and adults
Difficult Constipation - Pediatrics

Elyanne M. Ratcliffe, MD, FRCPC
Associate Professor and Head, Division of Gastroenterology and Nutrition
Department of Pediatrics, McMaster University

Image courtesy of Dr. Bob Issenman
Difficult Constipation - Pediatrics

- Functional Constipation
- Congenital Anomaly
Pediatric Case

• 5 year old girl
• Daily liquid “stool accidents” (3-4x/day)
• Hard stool; refuses to use toilet; hides in room to pass bowel movement in underwear
• Investigations:
  – Normal TSH, negative celiac screen
  – Lower GI contrast study: severe fecal loading; no evidence of transition point to suggest Hirschsprung’s disease
Functional Constipation
Rome IV Diagnostic Criteria

H3a. Diagnostic Criteria for Functional Constipation
Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:

(1) 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
(2) At least 1 episode of fecal incontinence per week
(3) History of retentive posturing or excessive volitional stool retention
(4) History of painful or hard bowel movements
(5) Presence of a large fecal mass in the rectum
(6) History of large diameter stools that can obstruct the toilet

After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.
Approach to Functional Constipation

- Education
- Diary
- Toilet training
- Oral medication
- Manage fecal impaction
Management – What is the Evidence?

Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

M.M. Tabbers, C. DiLorenzo, M.Y. Berger, C. Faure, M.W. Langendam, S. Nurko, A. Staiano, Y. Vandenplas, and M.A. Benninga

• Evidence does not support:
  – Fibre supplements
  – Extra fluid intake
  – Pre- or probiotics
  – Behavioural therapy

• No RCTs to support:
  – Physical activity
  – Multidisciplinary treatment
  – Alternative medicine
Pharmacological Management

**Fecal disimpaction**
- High-dose PEG +/- electrolytes daily for 3-6 days
- Enema once daily if PEG not available

**Maintenance**
- PEG +/- electrolytes; dose adjusted to clinical response
- Addition of enemas not recommended
- Lactulose if PEG not available

**Additional or second line treatment**
- Milk of magnesia, mineral oil, stimulant laxatives
- No RCTs in children for: prucalopride, lubiprostone, linaclotide

Tabbers JPN 2014
Pharmacological Management

Oral Prucalopride in Children With Functional Constipation

*Harland S. Winter, †Carlo Di Lorenzo, ‡Marc A. Benninga, §Mark A. Gilger, ¶Gregory L. Kearns, ¶Paul E. Hyman, ¶Lieve Vandeplasche, ¶Jannie Ausma, and ¶Mieke Hoppenbrouwers

Methods: A single oral dose of 0.03 mg/kg prucalopride was administered to 38 children to characterize prucalopride pharmacokinetics (NCT01674166). Thereafter, 37 children entered an open-label extension period in which 0.01 to 0.03 mg/kg of prucalopride was administered once per day for 8 weeks to investigate efficacy, safety, and tolerability (NCT01670669).

JPGN • Volume 57, Number 2, August 2013

Prucalopride Is No More Effective Than Placebo for Children With Functional Constipation

Suzanne M. Mugie, Bartosz Korczowski, Piroska Bodó, Alexandra Green, René Kerstens, Jannie Ausma, Magnus Ruth, Amy Levine, and Marc A. Benninga

Efficacy and safety were assessed in 213 children (106 prucalopride, 107 placebo) Children < 50 kg given 0.04 mg/kg oral solution; Children > 50 kg were given a 2 mg tablet; once daily for 8 weeks

Gastroenterology 2014;147:1285–1295
Pharmacological Management

Multicentre randomized placebo-controlled trial with lubiprostone in children is currently being carried out in Europe and North America (NCT02042183).

Currently recruiting participants in a safety and efficacy study of a range of linaclotide doses administered orally to children aged 7-17 years, with irritable bowel syndrome with constipation (NCT02559817).
Differential Diagnoses

- Celiac disease
- Hypothyroidism
- Congenital anomalies

Tabbers JPGN 2014
Congenital Anomalies

- **Hirschsprung’s disease**
  - Delayed passage of meconium
  - Anorectal manometry; rectal biopsy

- **Anorectal malformations**
  - Inspection of perianal region; associated congenital anomalies
  - Barium enema

- **Spinal malformations**
  - Exam of lumbosacral region
  - MRI

- **Pseudoobstruction syndrome**
  - Family history; associated anomalies
  - Abdominal ultrasound; colonic manometry
Intractable Constipation

- Anterograde continence enema (ACE)
  - No RCTs; 6 open retrospective studies
  - Option when maximal conventional therapy not successful
  - Potential complications: granulation tissue, leakage, dislodgement, skin infection, stoma stenosis

Tabbers JPN 2014
Future Directions

- Multidisciplinary/Translational Research
- Multicentre Research/Clinical Pathological Correlations
- Multidisciplinary Team/Transdisciplinary Collaboration
Management of Difficult Constipation in Adult

http://www.qmedicine.co.in/top%20health%20topics/C/Constipation%20in%20Adults.html

Louis W.C. Liu
MD, PhD, FRCP(C)

Head of Gastroenterology, University Health Network and Sinai Health System
Director of Motility Unit, University Health Network
Learning Objectives

By the end of this session, the attendances will be able to:

1. identify the different etiologies of constipation between children and adults
2. apply the evidence for current therapies to manage constipation in children and adults
Case

• 37 yr-old healthy female, constipated since teenage years starting in high school.
• Tried various laxatives, all worked initially and then stopped working.
• Now using stimulant laxatives prn, often 6 to 8 tablets required “to go” with un-predictable response and caused abdominal pain.
• Tried to increase “fiber” intake but get cramps and bloating
• Referred to GI for refractory constipation and bloating
Constipation means more than infrequent BM

n = 1128 (60% university students, 32% hospital employees, 8% medical students)

Chronic Constipation Treatment Algorithm
Louis Liu, Chris Andrews, David Armstrong, Alain Bitton, Brian Bressler, John Marshall
Contributing faculty members involved in the development of the algorithm

History & Physical Including Careful Perineal / Rectal Examination

Assess Alarm Features
- Alarm Features Identified
- No Alarm Features Identified

Optimize Management of Secondary Causes

Specialist Assessment Recommended (Refer)

Constipation Persists
Constipation

Red Flags for Organic Causes

- > 50 yr, recent onset in symptoms
- Acute severe symptoms
- Rectal bleeding
- Fever or wt loss
- Unremitting or nocturnal symptoms
- Abnormal blood test
  - Fe def anemia
  - Positive family hx
  - IBD, CRC
  - Abnormal physical exam
    - Abd mass
    - skin/joints

PPV 98-100%, NPV 68-76%
Utility of Digital Rectal Examination

- In trained examiners, DRE
  - Has a high PPV to identify DD in patients with constipation\(^1,2\) and probably in FI\(^2\)
  - Is poor in identifying abnormal sphincter tone\(^1,2\)

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1. Tantiphlachiva K et al. Clin Gastro Hep 2010
2. Soh, JS et al. The diagnostic value of a digital rectal examination compared with high-resolution anorectal manometry in patients with chronic constipation and fecal incontinence. AJG Aug 2015; 110:1197–1204
Basic Investigations

- Screening Blood work TSH, Calcium, renal function, CBC, and screen for diabetes
- Abdominal flat plate often enough to see how much stool in the colon and if the colon looks dilated
She is worried about a blockage and wants to have a colonoscopy.  

What would you do?
Colonoscopy is not recommended as a routine investigation for constipation

4. Avoid performing a colonoscopy for constipation in those under the age of 50 years without family history of colon cancer or alarm features.

Constipation is a common problem and systematic review data suggests this is not an accurate symptom in diagnosing organic disease. If the patient is also under the age of 50 and does not have a family history of colon cancer and there are no alarm features such as anemia or weight loss, then the risk of colorectal cancer is very low and the risks of colonoscopy usually outweigh the benefits in these patients.

http://www.choosingwiselycanada.org/recommendations/gastroenterology-2/
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History & Physical Including Careful Perineal / Rectal Examination

- Assess Alarm Features
  - Alarm Features Identified
  - No Alarm Features Identified
  - Specialist Assessment Recommended (Refer)

Optimize Management of Secondary Causes

- Constipation Persists

Type of Constipation?

1. Glycerine suppository
2. Stimulant laxatives (e.g. bisacodyl)
3. Enema

Rescue Therapy

- Constipation symptoms predominant
- Functional abdominal pain predominant

Specialist Assessment for Consideration of Anorectal Manometry, Defecography and Biofeedback Therapy

- Linaclotide or Prucalopride
- Eight to twelve-week trial prior to reassessment for maintenance or consideration of referral for specialist assessment

Additional Agents:
- Options as in slow transit*
  - (e.g. stimulant, osmotic laxative)

Additional Therapy:
- Pharmacological
  - eg. TCA, SSRI, SNRL antispasmodic
- Non-Pharmacological
  - eg. Medication, Relaxation, Hypnosis

Fibre Supplements
- Osmotic Laxatives
- Prosecretory Agents
  - e.g. Linaclotide

Consideration of Anorectal Manometry, Defecography and Biofeedback Therapy

- Specialist Assessment Recommended (Refer)

Patient Education and Management of Expectations

- Assess for Complex or Complicating Features

Alarm Features Identified

- No Alarm Features Identified
- Specialist Assessment Recommended (Refer)

Tse Y et al CJGH 2017, in press
Conceptual approach to constipation

POOR INTAKE
WATER/FIBER

LOSS OF PERISTALTIC CONTRACTIONS
“PUMP FAILURE”

OUTLET PROBLEMS
“FAILURE SPHINCTER RELAXATION”

Quigley, EM., Ther Adv Gastroenterol (2011) 5(1) 23-30
Bristol Stool Chart

- designed to classify stool consistency into seven categories
- Types 1 and 2 indicate slow transit constipation

Lewis SJ, Heaton KW. *Scan J Gastroenterol* 1997;32(9):920–924
FBDs are a Continuum in Clinical Practice

Pain is an important therapeutic target to manage

Symptom-based criteria for CIC and IBS-C overlap and transition between diagnosis overtime

Chronic Constipation Treatment Algorithm

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Contributing faculty members involved in the development of the algorithm

Type of Constipation?

- Lifestyle Modifications (e.g., Dietary Fibre, Fluid, Exercise)
  - Inadequate Fibre Intake
  - CIC/Slow Transit
  - IBS-C
    - Constipation symptoms predominant
    - Functional abdominal pain predominant
  - Pelvic Floor Dyssynergic Defecation

History & Physical Including Careful Perineal / Rectal Examination

Assess Alarm Features

- Alarm Features Identified
- No Alarm Features Identified
- Specialist Assessment Recommended (Refer)

Optimize Management of Secondary Causes

- Constipation Persists

Assess for Complex or Complicating Features

Patient Education and Management of Expectations

Tse Y et al CJGH 2017, in press
# ACG Monograph on the Management of CIC – Abbreviated Table

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Trials</th>
<th>No. of Patients</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
</tr>
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<tbody>
<tr>
<td>Fiber</td>
<td>3</td>
<td>293</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>PEG</td>
<td>4</td>
<td>573</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Lactulose</td>
<td>2</td>
<td>148</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Stimulant Laxatives</td>
<td>2</td>
<td>735</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Prucalopride</td>
<td>8</td>
<td>3140</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Linaclotide</td>
<td>3</td>
<td>1582</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>4</td>
<td>651</td>
<td>Strong</td>
<td>High</td>
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</table>

Grading of Recommendations Assessment, Development and Evaluation (GRADE)
Quality of Evidence Grading: High, Moderate, Low or Very Low
Recommendations: Strong or Weak
Polyethylene Glycol for IBS-C: Results from an RCT

ACG Task Force Recommendation:
There is no evidence that PEG improves overall symptoms and pain in patients with IBS
Recommendation: weak; Quality of evidence: very low

Percent Change from Baseline in Abdominal Bloating by Week in CIC

Significant improvements noted at week 1 and sustained thereafter
(p<0.05 vs. placebo for all time points)

### ACG Monograph on the Management of IBS-C – Abbreviated Table

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Trials</th>
<th>No</th>
<th>NNT</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialized diet</td>
<td>3</td>
<td>203</td>
<td>NA</td>
<td>Weak</td>
<td>Very Low</td>
</tr>
<tr>
<td>Psyllium, not bran</td>
<td>7</td>
<td>499</td>
<td>7 (4-25)</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>Probiotics</td>
<td>23</td>
<td>2575</td>
<td>7 (4-12.5)</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>23</td>
<td>2154</td>
<td>5 (4-9)</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Peppermint Oil</td>
<td>5</td>
<td>482</td>
<td>3 (2-4)</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>17</td>
<td>1084</td>
<td>4 (3-6)</td>
<td>Weak</td>
<td>High</td>
</tr>
<tr>
<td><strong>Linaclotide</strong></td>
<td>3</td>
<td>2028</td>
<td>6 (5-8)</td>
<td><strong>Strong</strong></td>
<td><strong>High</strong></td>
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<tr>
<td>Lubiprostone</td>
<td>3</td>
<td>1366</td>
<td>12.5 (8-25)</td>
<td><strong>Strong</strong></td>
<td><strong>Moderate</strong></td>
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<tr>
<td>PEG</td>
<td>2</td>
<td>166</td>
<td>NA</td>
<td>Weak</td>
<td>Very Low</td>
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- **Quality of Evidence Grading:** High, Moderate, Low or Very Low
- **Recommendation Grading:** Strong or Weak

*Grading of Recommendations Assessment, Development and Evaluation (GRADE)*  
*Ford et al. Am J Gastroenterol 2014; 109:S2-S26*
Weekly CSBMs and abdominal pain responses in linaclotide group

Complete Spontaneous Bowel Movement (CSBM) – A spontaneous bowel movement that gives a sense of complete evacuation

Diet and IBS symptoms

• Low FODMAP diet is better than typical Austrian diet\textsuperscript{1}
• Low FODMAP diet is no different from the convention IBS diet\textsuperscript{2}

\textsuperscript{1} Halmos, E. P., Power, V. A., Shepherd, S. J., Gibson, P. R., & Muir, J. G. (2014). A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology, 146(1), 67-75.e5
\textsuperscript{2} Böhn, L., Störsrud, S., Liljebo, T., Collin, L., Lindfors, P., Törnblom, H. et al. (2015). Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology, 149(6), 1399-1407.e2
Probiotic reduces IBS symptoms

- Meta-analysis included 21 trials – improves overall abdominal symptoms and QoL, but not individual abdominal symptoms
- No significant improvement in abdominal pain


Figure extracted from the ROME IV slide deck, 2016
Sustained Release Peppermint Oil Improves IBS Symptoms

Enteric coated delayed release (IBgard®)

Percent reduction from baseline in total IBS Symptom Score (average of frequency and intensity of 8 IBS symptoms)
Chronic Constipation Treatment Algorithm
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Contributing faculty members involved in the development of the algorithm

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  - Specialist Assessment Recommended (Refer)
- No Alarm Features Identified

Optimize Management of Secondary Causes

- Constipation Persists

Type of Constipation?

Lifestyle Modifications (e.g., Dietary Fibre, Fluid, Exercise)

- Inadequate Fibre Intake
  - Fibre Supplements
  - Osmotic Laxatives (e.g. Milk of Magnesia, Lactulose or PEG titrate to efficacy and tolerability +/- fibre supplements)
  - Eight-week trial at a reasonable dose prior to reassessment of maintenance or escalation to step-up therapies

- pelvic floor dyssynergic defecation

- CIC/Slow Transit
  - Osmotic Laxatives
  - Prosecretory or Prokinetic Agents

- IBS-C
  - Prosecretory Agents (e.g. Linacotide)
  - Additional Agents: Options as in slow transit (e.g. stimulant, osmotics/laxatives)

- rescue therapy
  - Glycerine suppository
  - Stimulant laxatives (e.g. bisacodyl)
  - Enema

- specialist assessment recommended (refer)

Unsatisfactory Response or Intolerant to Side Effects

- Specialist Assessment Recommended (Refer)

Patient Education and Management of Expectations

Assess for Complex or Complicating Features

Tse Y et al CJGH 2017, in press
Overcoming the challenges in managing difficult constipation

• Validate and educate
  – Normal variation of bowel function
  – Ensure adequate and appropriate trials of treatment agents

• Manage expectations

• Empower and engage patients

• Choose therapy targets predominant symptoms
  – Align patients’ belief and acceptance

• Patient-physician relationship
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