2014: ACG-FDA Public Forum

American College of Gastroenterology
&
U.S. Food and Drug Administration

Toward Improving the Quality of Colonoscopy: Evidenced-Based State of the Art in Bowel Preparation

Sponsored by the ACG FDA Related Matters Committee
**Agenda & Speakers**

**Moderators:**
Lawrence Cohen, MD, FACG  Robert Fiorentino, MD (FDA)

**Topics:**

- The FDA perspective on bowel preparation registration trials (Robert Fiorentino, MD)

- What is the evidence for an optimal dosing scheme and bowel preparation formulation? (Paul Moayyedi, MD)

- What are the immediate and delayed safety issues surrounding over the counter and prescription bowel preparations? (Philip Schoenfeld, MD)

- What are the optimal endpoints for assessing bowel preparation in clinical practice or trials? (Douglas Rex, MD)

Open Forum Discussion
Outline

• Case Studies: Safety
  – Visicol / Osmoprep (phosphate nephropathy)
  – HalfLytely (ischemic colitis)

• General Efficacy Remarks
  – Shared Goals
  – Endpoint Selection
  – Noninferiority design considerations
  – Choice of Regimen
    – *(day before, same day or split dose?)*
  – “Combination Rule”
FDA Approved Bowel Cleansing Products

Oral Sodium Phosphate Preps
- Visicol (2000)
- OsmoPrep (2006)

Polyethylene Glycol Preps
- GoLYTELY (4L) (1984)
- Colyte (4L) (1984)
- OCL Solution (4L) (1986)
- NuLYTELY (4L) (1991)

Sulfate Salt Preps
- SUPREP (2010)

Others (Combinations)
- Prepopik (2012)
- Suclear (2013)
In September 2003, Desmeules et al published a case report of acute phosphate nephropathy followed by persistent renal insufficiency in a 71-year-old woman who took 90 mL of an OSP solution as a cathartic.

In November 2005, Markowitz et al published a case series study describing 21 biopsy-proven cases of acute phosphate nephropathy in patients who took OSP and had no history of hypercalcemia or superimposed renal pathology.

- 18 patients were diagnosed with acute renal failure within 2 months of colonoscopy, and all were diagnosed within 5 months.

FDA review of the above literature and the FDA Adverse Event Reporting System (AERS) revealed 10 additional unique cases of renal failure associated with use of OSP solution and 10 cases of renal failure associated with use of OSP tablets.
Case Study: Sodium Phosphate Preps

- In 2006, FDA took steps to include information regarding the risk of acute phosphate nephropathy associated with the use of OSP products for bowel cleansing to the WARNINGS section of the existing prescription labeling for Visicol, as well as OsmoPrep.

- In 2006, the Agency issued an FDA Alert on OSP products for bowel cleansing (2006 FDA Alert), which included information for healthcare professionals and patients, and a science background paper (links provided below).

For more information:
Case Study: Sodium Phosphate Preps

• In 2008, FDA conducted a new analysis of the AERS reports involving OSP-associated acute phosphate nephropathy, as well as a review of the recent medical literature
  – Between 2006 to 2008 there were 20 reported cases of kidney injury associated with the use of OsmoPrep, 3 were biopsy-proven cases of acute phosphate nephropathy.
  – The onset of kidney injury in these cases varied, occurring in some within several hours of use of these products and in other cases up to 21 days after use.

• This review demonstrated that acute phosphate nephropathy could lead to serious kidney injury, requiring dialysis or kidney transplant, and in rare instances, death.

• FDA determined that, “taking steps to ensure that healthcare providers and their patients are better informed about the risk of OSP-associated acute phosphate nephropathy might help to decrease the number of these adverse events.”
Case Study: Sodium Phosphate Preps

• This information resulted in:
  – A determination that OSP oral solution for bowel cleansing are prescription products and not available over the counter (laxatives still OTC)
  – A Boxed Warning within the Osmoprep and Visicol labels
  – The Development of and distribution of a Medication Guide and a Communication Plan
  – Postmarketing clinical trials needed to evaluate safety
    • Randomized, controlled clinical trial evaluating the risk of developing acute kidney injury, comparing patients undergoing bowel cleansing using prescription OSP products to patients undergoing bowel cleansing using PEG-containing products.
Case Study: HalfLytely

- HalfLytely/Bisacodyl Bowel Prep Kit was originally developed to reduce the prep volume (2L) compared to standard bowel preparations (4L).
- HalfLytely was approved in 2004 with a bisacodyl dose of 20 mg.
- Following this approval, several reports of ischemic colitis were received.
- In May 2006, HalfLytely labeling was revised to include reports of ischemic colitis (IC).
- IC reports were suspected to be related to the dose of bisacodyl (20 mg) included in the original kit.
- The dose of bisacodyl was reduced from 20 mg to 10 mg in 2007. Data demonstrated similar efficacy between HalfLytely with 20 mg bisacodyl and HalfLytely with 10 mg bisacodyl.

Case Study: HalfLytely

- Although the risk of ischemic colitis is low (about 1 in 100,000 for the HalfLytely and bisacodyl 20mg prep) it appeared to be reduced by the dose reduction to 10 mg based on post-market reporting.
- In the approval letter for the HalfLytely and Bisacodyl (10 mg) Bowel Prep Kit the FDA requested that additional studies be performed to evaluate lower doses of bisacodyl.
- A trial compared HalfLytely with 5 mg of bisacodyl to the approved HalfLytely with 10 mg of bisacodyl.
- After the marketing of the HalfLytely and Bisacodyl (10 mg) Bowel Prep Kit, 3 cases of ischemic colitis were reported.
- Ultimately, the dose of Bisacodyl in the Bowel Prep Kit was reduced to 5mg.

Communicating Safety

• Oral sodium phosphate products for colon cleansing now have boxed warnings

• Prescription bowel prep labels contain similar Warnings & Precautions
  – Serious Fluid and Serum Chemistry Abnormalities
  – Cardiac Arrhythmias
  – Seizures
  – Use in Patients with Renal Impairment
  – Ischemic Colitis
More Recent Trials...

• Assess renal and hemodynamic safety
  – Orthostatic BP measurements on the day of colonoscopy
  – More distal renal function assessment timepoints post colonoscopy

• Assess risk factors for renal injury
  – Antihypertensive drugs / discontinuation
  – IV fluids other therapies peri-colonoscopy
Efficacy: Consider Our Goals

✓ Excellent visualization of the mucosa
✓ Adequate visualization of all segments (e.g., ascending colon)
✓ Appropriate timing of administration prior to endoscopy
✓ Ease for patient (i.e., completion of prep)
Efficacy Considerations

• There isn’t a universally accepted endpoint model to assess efficacy. Why not?
  – Trial proposals reviewed on a case-by-case basis
  – Typically see multiple outcome scales and definitions of study success for each prep
  – Various approaches used to evaluate colonic segments (e.g., ascending colon)
  – Evaluation of bowel preps could benefit from a standardized approach
Efficacy Considerations

• Non-inferiority “creep”
  – Important to maintain efficacy of products over time, especially if goal is to have the “lowest volume prep”

• Various clinical programs evaluating day before colonoscopy, day of colonoscopy or split dose regimens, and various combos
  – Recent split dose regimens have been labeled as the Preferred Regimen
“Combination Rule”

• Various combination of osmotic agents (PEG, salts) with or without laxatives are possible, each having a contribution to the bowel cleansing

• Regulations (21 CFR 300.50) require that:

Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.
“Combination Rule”

• E.g., the combination should be better than the components alone
• How do you demonstrate that each component of a bowel prep makes a contribution to the claimed effect?
• Burden of proof rests with the sponsor
• *Imagine all the combinations possible…*
Wrap Up

• We need to be vigilant to the safety of preps given the history of these products
• Common goal: maximize the rate of excellent preps (positive public health impact)
• Maintain excellence across new products and dosing regimens
• Don’t sacrifice these for convenience only
• Plenty of opportunity for standardization of endpoints and trial designs
Thank You!
What is the evidence for an optimal dosing scheme and bowel preparation formulation?

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Co-Editor in Chief of American Journal of Gastroenterology
Director, Division of Gastroenterology
Richard Hunt/AstraZeneca Chair
McMaster University, Hamilton Ontario, Canada
Disclosures

• No relevant financial declaration
Introduction

• Type of bowel preparation
  – 4 liter PEG
  – 2 liter PEG
  – Sodium picosulfate
  – Oral sulfate solutions
• Previous day versus split dose
• Same day versus split dose
• How GRADE assessment can guide future RCTs
Information evaluated

• Previous systematic reviews of RCTs
• RCTs identified by Medline search
• Meta-analyses
Optimizing Adequacy of Bowel Cleansing for Colonoscopy: Recommendations From the US Multi-Society Task Force on Colorectal Cancer

David A. Johnson¹, Alan N. Barkun², Larry S. Cohen¹, Jason A. Dominick², Yena Kaltenbach², Myrta Martel², Douglas J. Robertson²,⁶, C. Richard Hollyweg⁵, Frances M. Glaros⁵, David A. Lieberman⁴, Theodore S. Levin⁴ and Douglas K. Rex⁴


Colonoscopy is the second leading cause of cancer-related deaths in the United States (1). Colonoscopy can prevent CRC by the detection and removal of precancerous lesions. In addition to CRC screening and surveillance, colonoscopy is used widely for the diagnostic evaluation of symptoms and other positive CRC screening tests. Regardless of indication, the success of colonoscopy is linked closely to the adequacy of preprocedure bowel cleansing. Unfortunately, up to 20-25% of all colonoscopies are reported to have an inadequate bowel preparation (2,3). The reasons for this range from patient-related variables such as compliance with preparation instructions and a variety of medical conditions that make bowel cleansing more difficult to unit-specific factors (eg, extended wait times after scheduling of colonoscopy) (4). Adverse consequences of ineffective bowel preparation include lower adenoma detection rates, longer procedural times, lower colon inspection rates, increased iatrogenic risk, and shorter intervals between examinations (3.5-7).

Bowel preparation formulations intended for precolonoscopy cleansing are assessed based on their efficacy, safety, and tolerability. Lack of specific organ toxicity is considered to be a prerequisite for bowel preparations. Between cleansing efficacy and tolerability, however, the consequences of inadequate cleansing suggest that efficacy should be a higher priority than tolerability. Consequently, the choice of a bowel cleansing regimen should be based on cleansing efficacy first and patient tolerability second. However, efficacy and tolerability are closely interrelated. For example, a cleansing agent that is poorly tolerated and thus not fully ingested may not achieve an adequate cleansing.

The goals of this consensus document are to provide expert, evidence-based recommendations for clinicians to optimize colonoscopy preparation quality and patient safety. Recommendations are provided using the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) scoring system, which weights the strength of the recommendation and the quality of the evidence (6).

METHODS

Search Strategy

Computerized medical literature searches were conducted from January 1960 (first year of approval of polyethylene glycol-electrolyte lavage solution [PEG-ELS]) based on the Food and Drug Administration [FDA]; up to August 2013 using MEDLINE, PubMed EMBASE, Scopus, CENTRAL, and ISI Web of Knowledge. We used a highly sensitive search strategy to identify reports of randomized controlled trials (6) with a combination of medical subject headings adapted to each database and text words related to colonoscopy and gastrointestinal agents, bowel preparation, generic name, and brand name. The complete search terms are available in Appendix A. Inclusive searches and cross-referencing also were performed using "similar articles" function. Hand searches of articles were identified after an initial search. We included all fully published adult human studies in English or French.

A systematic review of published articles and abstracts presented at national meetings was performed to collect and select the evidence. A meta-analysis and consensus agreement were used to analyze the evidence. Expert consensus was used to formulate the recommendations. The GRADE system was used to rate the strength of the recommendations. The guideline was reviewed by committees of and approved by the governing boards of the member societies of the Multi-Society Task Force on Colonoscopy (American College of Gastroenterology, American Gastroenterological Association, and American Society of Gastrointestinal Endoscopy).

Johnson DA et al. AJG 2014; 109: 1528-45
4 liter versus 2 liter PEG

• High volume (≥ 3 l) vs. low volume (< 3 l)
• 28 trials
• 7208 ITT patients
• No difference in bowel cleanliness
• OR = 1.03 (95% CI = 0.80 to 1.32)

Johnson DA et al. AJG 2014; 109: 1528-45
PEG versus sodium picosulfate

- Sodium picosulfate versus PEG solutions
- 11 trials
- 3097 ITT patients
- No difference in bowel cleansing
- OR = 0.92 (95% CI = 0.63 to 1.36)

Johnson DA et al. AJG 2014; 109: 1528-45
Oral sulfate solution versus PEG

• Oral sulfate solutions versus PEG
• 2 trials (different PEG regimens)
• 923 ITT patients
• No difference
• OR = 1.12 (95% CI = 0.77 to 1.62)

Johnson DA et al. AJG 2014; 109: 1528-45
Split dose versus day before

- **PEG solutions**
  - 8 trials, 1990 ITT patients
  - Split improved cleanliness
  - OR = 4.38; 95% CI = 1.88 to 10.21

- **Sodium picolsulfate**
  - One trial, 250 ITT patients
  - Split dose improved cleanliness
  - OR 3.54; 95% CI = 1.95 to 6.45

Johnson DA et al. AJG 2014; 109: 1528-45
Split dose versus same day

• No RCTs
• One RCT same day 4 l PEG versus day before
• 136 patients
• Same day superior
• OR = 2.63 (1.31 to 5.27)

Varughese S et al. AJG 2010; 105: 2368-74
Summary of what the evidence tells us

• Can be reasonably confident
  – 4 l PEG, 2 l PEG, sodium picosulfate similar efficacy
  – Split dose better than previous day preparations (PEG)

• Need more data to be confident
  – Oral sulfate solution
  – Same day preparations for afternoon colonoscopy
Evidence Based Medicine
Gordon Guyatt

“Evidence based Medicine” ACP Journal Club 1991
• Grades the quality of evidence
• Gives a strength of recommendation
• Systematic transparent approach
• Developed by a Working Group since 2000
• Endorsed by over 90 organizations worldwide
Quality of the evidence

- High
  - further research unlikely to change effect estimate
- Moderate
  - more research likely to change effect estimate
- Low
  - more research very likely to change effect estimate
- Very low
  - Any effect estimate very uncertain
Strength of recommendation

• Strong recommendation
  – Applies to most patients most of the time

• Weak recommendation
  – Applies only to some patients
It’s Complicated
FDA-APPROVED PREPARATIONS

Recommendations

1. Selection of a bowel-cleansing regimen should take into consideration the patient's medical history, medications, and, when available, the adequacy of bowel preparation reported from prior colonoscopies (Strong recommendation, moderate-quality evidence).

2. A split-dose regimen of 4l PEG-ELS provides high-quality bowel cleansing (Strong recommendation, high-quality evidence).

3. In healthy nonconstipated individuals, a 4-L PEG-ELS formulation produces a bowel-cleansing quality that is not superior to a lower-volume PEG formulation (Strong recommendation, high-quality evidence).
# Confidence assessment criteria
(quality of the evidence)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Confidence in estimates</th>
<th>Lower if</th>
<th>Higher if</th>
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<tbody>
<tr>
<td>Randomised trial</td>
<td>High</td>
<td>Risk of bias</td>
<td>Large effect</td>
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<td>-1 Serious</td>
<td>+1 Large</td>
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<td>-2 Very serious</td>
<td>+2 Very large</td>
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<td></td>
<td></td>
<td>Inconsistency</td>
<td>Dose response</td>
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<td>-1 Serious</td>
<td>+1 Evidence of a gradient</td>
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<td>-2 Very serious</td>
<td>All plausible confounding</td>
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<td>Indirectness</td>
<td>+1 Would reduce a demonstrated effect or</td>
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<td>Observational study</td>
<td>Low</td>
<td></td>
<td>+1 Would suggest a spurious effect when results show no effect</td>
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<td>Very low</td>
<td>Publication bias</td>
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<td>-1 Likely</td>
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<td>-2 Very likely</td>
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Individual quality criteria

- Method of randomization
- Concealment of allocation
- Masking

Confidence in 2L vs 4L PEG data

• 24 trials for 2L vs 4L
• In ALL trials patients were not blinded
• Not the fault of the investigators
• Patients should be unblinded to assess tolerance
• Nevertheless ALL trials are at high risk of bias
Quality of 2L vs 4L data

- Only 6/24 (25%) met minimal standards for randomization and concealment of allocation
- 0/24 met highest standards for randomization and concealment of allocation
### Confidence assessment criteria (quality of the evidence)

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<td>Moderate</td>
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<tr>
<td></td>
<td></td>
<td>-2 Very likely</td>
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A grading system needs to be outcome-centric

Old system

GRADE

Outcome #1
Outcome #2
Outcome #3

Quality
Quality
Quality
Systematic review

Guideline development

Formulate question
Select outcomes
Rate importance
Outcomes across studies
Create evidence profile with GRADEpro
Rate quality of evidence for each outcome

RCT start high, obs. data start low

High
Moderate
Low
Very low

Summary of findings & estimate of effect for each outcome

Grade down
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up
1. Large effect
2. Dose response
3. Confounders

Summary of findings & estimate of effect for each outcome

Grade down
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up
1. Large effect
2. Dose response
3. Confounders

PICO
Outcome Critical
Outcome Critical
Outcome Important
Outcome Less important

By considering:
- Quality of evidence
- Balance benefits/harms
- Values and preferences

Revise if necessary by considering:
- Resource use (cost)

Formulate recommendations:
- For or against (direction)
- Strong or weak (strength)

By considering:
- Quality of evidence
- Balance benefits/harms
- Values and preferences

Revise if necessary by considering:
- Resource use (cost)

Guideline development

Overall quality of evidence across outcomes based on lowest quality of critical outcomes

- “We recommend using...”
- “We suggest using...”
- “We recommend against using...”
- “We suggest against using...”
Patient perspective critical

• Clinician perspective
  – Bowel cleanliness

• Patient perspective
  – Reduce cancer risk > high risk ADR > ADR
  – Tolerable
  – Safe
# Trials of 4L vs. 2L PEG

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. trials</th>
<th>No. patients</th>
<th>No. validated</th>
</tr>
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<tbody>
<tr>
<td>Bowel cleanliness</td>
<td>23</td>
<td>5533</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>Tolerability</td>
<td>13</td>
<td>3299</td>
<td>0</td>
</tr>
<tr>
<td>Safety (electrolyte)</td>
<td>6</td>
<td>1325</td>
<td>N/A</td>
</tr>
<tr>
<td>Polyp detection</td>
<td>5</td>
<td>987</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*McMaster University*
Bowel cleanliness

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>2L PEG Events</th>
<th>4L PEG Events</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Day before for 4L vs 2L</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Adams 1994</td>
<td>131</td>
<td>191</td>
<td>128</td>
<td>191</td>
</tr>
<tr>
<td>Gentile 2011</td>
<td>30</td>
<td>60</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>McKenna 2012</td>
<td>54</td>
<td>66</td>
<td>59</td>
<td>70</td>
</tr>
<tr>
<td>Porchon 2013</td>
<td>177</td>
<td>210</td>
<td>172</td>
<td>205</td>
</tr>
<tr>
<td>Pomone 2011</td>
<td>37</td>
<td>72</td>
<td>30</td>
<td>72</td>
</tr>
<tr>
<td>Samarasekera 2012</td>
<td>19</td>
<td>60</td>
<td>11</td>
<td>57</td>
</tr>
<tr>
<td>Sharma 2008</td>
<td>76</td>
<td>91</td>
<td>46</td>
<td>59</td>
</tr>
<tr>
<td>Valiente 2012</td>
<td>143</td>
<td>189</td>
<td>128</td>
<td>170</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>919</td>
<td>884</td>
<td>32.8%</td>
<td>1.04 (0.99, 1.10)</td>
</tr>
<tr>
<td>Total events</td>
<td>607</td>
<td>604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.00$, $Ch^2 = 6.77$, df = 7 ($P = 0.45$); $I^2 = 0$%</td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 1.62$ ($P = 0.11$)</td>
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</tbody>
</table>

1.2.2 Split dose 4L vs 2L | | | | |
| Corporaal 2010 | 135 | 149 | 151 | 158 | 7.1% | 0.95 (0.89, 1.01) | |
| Ell 2008 | 156 | 180 | 162 | 179 | 6.9% | 0.96 (0.89, 1.03) | |
| Hjerkern 2011 | 35 | 213 | 49 | 101 | 1.9% | 0.34 (0.24, 0.49) | |
| Samarasekera 2012 | 41 | 54 | 42 | 51 | 4.1% | 0.92 (0.76, 1.12) | |
| Subtotal (95% CI) | 596 | 489 | 20.0% | 0.79 (0.64, 0.99) | |
| Total events | 367 | 404 | | | |
| Heterogeneity: $I^2 = 0.04$, $Ch^2 = 46.25$, df = 3 ($P < 0.00001$); $I^2 = 94$% |
| Test for overall effect: $Z = 2.02$ ($P = 0.04$) |

1.2.3 Day before 4L vs same day 2L | | | | |
| Abur 2009 | 22 | 39 | 44 | 81 | 2.1% | 1.04 (0.74, 1.46) | |
| DiPalma 2003 | 81 | 100 | 86 | 100 | 5.7% | 0.94 (0.83, 1.07) | |
| Park 2010 | 55 | 95 | 40 | 95 | 2.6% | 1.38 (1.03, 1.84) | |
| Subtotal (95% CI) | 234 | 276 | 10.4% | 1.08 (0.83, 1.42) | |
| Total events | 158 | 170 | | | |
| Heterogeneity: $I^2 = 0.04$, $Ch^2 = 7.04$, df = 2 ($P = 0.03$); $I^2 = 72$% |
| Test for overall effect: $Z = 0.59$ ($P = 0.55$) |

1.2.4 Split dose 4L vs same day 2L | | | | |
| Cesaro 2011 | 35 | 50 | 24 | 51 | 2.1% | 1.49 (1.06, 2.10) | |
| Park 2010 | 55 | 95 | 61 | 95 | 3.5% | 0.90 (0.72, 1.13) | |
| Seo 2011 | 72 | 103 | 75 | 102 | 4.6% | 0.95 (0.80, 1.12) | |
| Subtotal (95% CI) | 248 | 248 | 10.2% | 1.04 (0.82, 1.34) | |
| Total events | 162 | 160 | | | |
| Heterogeneity: $I^2 = 0.03$, $Ch^2 = 6.33$, df = 2 ($P = 0.04$); $I^2 = 68$% |
| Test for overall effect: $Z = 0.35$ ($P = 0.73$) |

1.2.5 Complex regimen | | | | |
| Maapasmaki 2011 | 145 | 244 | 144 | 246 | 5.1% | 1.02 (0.88, 1.18) | |
| Hoppertz-Haus 2005 | 40 | 71 | 62 | 76 | 3.5% | 0.69 (0.55, 0.87) | |
| Jansen 2011 | 149 | 183 | 141 | 182 | 6.1% | 1.02 (0.92, 1.14) | |
| Kao 2011 | 174 | 214 | 170 | 218 | 6.4% | 1.04 (0.95, 1.15) | |
| Mathus-Vliegen 2013 | 78 | 100 | 90 | 100 | 5.7% | 0.87 (0.77, 0.98) | |
| Subtotal (95% CI) | 817 | 822 | 26.8% | 0.94 (0.84, 1.05) | |
| Total events | 586 | 607 | | | |
| Heterogeneity: $I^2 = 0.01$, $Ch^2 = 15.05$, df = 4 ($P = 0.005$); $I^2 = 73$% |
| Test for overall effect: $Z = 1.05$ ($P = 0.29$) |
| Total events | 2814 | 2719 | 100.0% | 0.98 (0.92, 1.04) | |
| Heterogeneity: $I^2 = 0.01$, $Ch^2 = 74.02$, df = 22 ($P < 0.00001$); $I^2 = 70$% |
| Test for overall effect: $Z = 0.70$ ($P = 0.48$) | |
| Test for subgroup differences: $Ch^2 = 7.72$, df = 4 ($P = 0.10$); $I^2 = 48.2$% |  |  |  |  |
## Tolerability

### 1.1.1 Adjectival scale

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>2L PEG Events</th>
<th>Total</th>
<th>4L PEG Events</th>
<th>Total</th>
<th>Weight</th>
<th>M−H, Random, 95% CI</th>
<th>Risk Ratio M−H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 1994</td>
<td>93</td>
<td>191</td>
<td>60</td>
<td>191</td>
<td>6.0%</td>
<td>1.55 [1.20, 2.00]</td>
<td></td>
</tr>
<tr>
<td>Di Palma 2003</td>
<td>70</td>
<td>100</td>
<td>49</td>
<td>100</td>
<td>6.3%</td>
<td>1.43 [1.13, 1.81]</td>
<td></td>
</tr>
<tr>
<td>Enestvedt 2011</td>
<td>71</td>
<td>87</td>
<td>83</td>
<td>103</td>
<td>8.1%</td>
<td>1.01 [0.88, 1.16]</td>
<td></td>
</tr>
<tr>
<td>Haapamaki 2011</td>
<td>181</td>
<td>244</td>
<td>146</td>
<td>246</td>
<td>8.3%</td>
<td>1.25 [1.10, 1.42]</td>
<td></td>
</tr>
<tr>
<td>Valiante 2012</td>
<td>138</td>
<td>169</td>
<td>126</td>
<td>170</td>
<td>8.5%</td>
<td>1.10 [0.98, 1.23]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>791</strong></td>
<td></td>
<td><strong>810</strong></td>
<td></td>
<td><strong>37.3%</strong></td>
<td><strong>1.22 [1.06, 1.41]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>553</td>
<td></td>
<td>464</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.02; \chi^2 = 15.86, \text{df} = 4 (P = 0.003); l^2 = 75\% 
Test for overall effect: \( Z = 2.74 (P = 0.006) \)

### 1.1.2 Willingness to have same preparation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>2L PEG Events</th>
<th>Total</th>
<th>4L PEG Events</th>
<th>Total</th>
<th>Weight</th>
<th>M−H, Random, 95% CI</th>
<th>Risk Ratio M−H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesaro 2011</td>
<td>47</td>
<td>52</td>
<td>25</td>
<td>51</td>
<td>5.3%</td>
<td>1.84 [1.37, 2.47]</td>
<td></td>
</tr>
<tr>
<td>Enestvedt 2011</td>
<td>83</td>
<td>87</td>
<td>85</td>
<td>103</td>
<td>8.8%</td>
<td>1.16 [1.05, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Kao 2011</td>
<td>105</td>
<td>210</td>
<td>67</td>
<td>210</td>
<td>6.2%</td>
<td>1.57 [1.23, 1.99]</td>
<td></td>
</tr>
<tr>
<td>Ker 2006</td>
<td>113</td>
<td>150</td>
<td>92</td>
<td>150</td>
<td>7.8%</td>
<td>1.23 [1.05, 1.44]</td>
<td></td>
</tr>
<tr>
<td>Mathus−Vliegen 2013</td>
<td>95</td>
<td>100</td>
<td>56</td>
<td>100</td>
<td>7.4%</td>
<td>1.70 [1.42, 2.03]</td>
<td></td>
</tr>
<tr>
<td>McKenna 2012</td>
<td>62</td>
<td>66</td>
<td>51</td>
<td>70</td>
<td>7.8%</td>
<td>1.29 [1.10, 1.51]</td>
<td></td>
</tr>
<tr>
<td>Park 2010</td>
<td>68</td>
<td>95</td>
<td>38</td>
<td>95</td>
<td>5.6%</td>
<td>1.79 [1.36, 2.36]</td>
<td></td>
</tr>
<tr>
<td>Pontone 2011</td>
<td>47</td>
<td>72</td>
<td>53</td>
<td>72</td>
<td>6.6%</td>
<td>0.89 [0.71, 1.10]</td>
<td></td>
</tr>
<tr>
<td>Seo 2013</td>
<td>84</td>
<td>103</td>
<td>60</td>
<td>102</td>
<td>7.2%</td>
<td>1.39 [1.15, 1.67]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>935</strong></td>
<td></td>
<td><strong>953</strong></td>
<td></td>
<td><strong>62.7%</strong></td>
<td><strong>1.37 [1.19, 1.58]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>704</td>
<td></td>
<td>527</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.04; \chi^2 = 43.18, \text{df} = 8 (P < 0.00001); l^2 = 81\% 
Test for overall effect: \( Z = 4.37 (P < 0.0001) \)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>2L PEG Events</th>
<th>Total</th>
<th>4L PEG Events</th>
<th>Total</th>
<th>Weight</th>
<th>M−H, Random, 95% CI</th>
<th>Risk Ratio M−H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 1994</td>
<td>1257</td>
<td>1726</td>
<td>1763</td>
<td>100.0%</td>
<td>1.31</td>
<td>1.31 [1.19, 1.45]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1257</td>
<td></td>
<td>991</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.03; \chi^2 = 63.70, \text{df} = 13 (P < 0.00001); l^2 = 80\% 
Test for overall effect: \( Z = 5.28 (P < 0.00001) \)
Test for subgroup differences: \( \chi^2 = 1.31, \text{df} = 1 (P = 0.25) \), \( l^2 = 23.6\% \)
Funnel plot of tolerability trials

Egger test – p = 0.02
### Confidence assessment criteria

#### Tolerability of 2L vs. 4L

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Confidence in estimates</th>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised trial</td>
<td>High</td>
<td>Risk of bias</td>
<td>Large effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 Large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+2 Very large</td>
</tr>
<tr>
<td>Observational study</td>
<td>Moderate</td>
<td>Inconsistency</td>
<td>Dose response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 Evidence of a gradient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>All plausible confounding</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Indirectness</td>
<td>+1 Would reduce a demonstrated effect or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 Would suggest a spurious effect when results show no effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very low</td>
<td>Imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very likely</td>
<td></td>
</tr>
</tbody>
</table>
Polyp detection rates: 2L vs. 4L PEG

### NNT = 14 (95%CI = 8 to 100)
Conclusions

• Use PEG or sodium picosalicx
• Data on oral sulfate solution modest
• Split dose preparations (especially PEG)
• End points to date have been clinician focused
• More effort in making end points patient focused
• More rigorous appraisal of confidence in the estimate of effect.
Tired

True

Dangerous habits

Tired
Safety Issues Surrounding Over-the-Counter and Prescription Bowel Preparations

Philip Schoenfeld, MD, MSEd, MSc (Epi)
Professor of Medicine
Director, Training Program in GI Epidemiology
U. of Michigan School of Medicine
Disclosures

• Consultant, Advisory Board Member and Speaker’s Bureau: Salix Pharmaceuticals, Ironwood Pharmaceuticals, Forest Laboratories

• Partner, EBMed, LLC,
only Alan was prepared to acknowledge the elephant in the room..
Miralax – Gatorade Bowel Prep

238 gram Bottle of MiraLAX

64 oz. Bottle of Gatorade

plus 10-20mg bisacodyl
Advantages of Miralax-Gatorade

- Low volume
- Palatable
- Inexpensive

... may lead to improved compliance with bowel preparation regimen?
Increasing Popularity of Miralax-Gatorade Combination

- Survey of random sample of ACG members in US in 2010-11

- Asked about use of split-dose, liberal diet (low residue on day before procedure), and use of Miralax-based preparations.

- 30% of sample responded to survey (288/999)

- 60% (170/283) used split-dose

- 37% (106/283) used miralax-based preps. Among these physicians, 82% (87/106) combined it with gatorade. Data based on survey from 2010-11.

OR = 3.40 (2.28-5.06) for Excellent/Good Bowel Cleansing with split-dose 4l Golytely vs split-dose MiraLax-Gatorade

this is the same as OR for getting Excellent/Good Bowel Cleansing with 4l of Golytely split-dose vs 4l Golytely as pm single dose (OR =3.47; 1.96-6.14)

For Enestvedt RCT, rate of excellent or good prep by Boston Bowel Prep Score was 83% (85/103) vs 68% (59/87)
Retrospective Endoscopic Database Analysis: PEG-3350 + Gatorade + Bisacodyl vs. 4-L GoLYTELY

n = 778 patients referred for CRC screening

Similarities between Miralax-Gatorade & Fleets Phospho-Soda

• Low volume
• Palatable
• No prescription needed*

*Cost for M-G plus dulcolax and 4L generic PEG is quite similar at approximately $15 for both.
Similarities between Miralax-Gatorade & Fleets Phospho-Soda

- Low volume
- Palatable
- No prescription needed*

- Hyperosmolar
- Not FDA approved
- Minimal safety data

*Cost for M-G plus dulcolax and 4L generic PEG is quite similar at approximately $15 for both.
Similarities between Miralax-Gatorade & Fleets Phospho-Soda

- Low volume
- Palatable
- No prescription needed

- Hyperosmolar
- Not FDA approved
- Minimal safety data

- Commonly used at 14X approved FDA-dose (for constipation) when used as bowel preparation
Electrolytes in Sports Drinks May Be Insufficient

Although sports drinks can aid in rehydrating and replacing electrolytes lost during sweating as a result of physical exertion, the electrolyte load may be insufficient for patients undergoing a purgative regimen for colonoscopy.

<table>
<thead>
<tr>
<th></th>
<th>Sports drink, g/2 L*</th>
<th>PEG + ELS, g/2 L</th>
<th>Ratio (PEG + ELS:Sports drink)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>0.88</td>
<td>8.35</td>
<td>9:1</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.24</td>
<td>1.06</td>
<td>4:1</td>
</tr>
<tr>
<td>Chloride</td>
<td>0.72</td>
<td>4.23</td>
<td>6:1</td>
</tr>
</tbody>
</table>

PEG + ELS = polyethylene glycol electrolyte lavage solution.
*Traditional Gatorade®.
First case report of severe hyponatremia with M-G prep

- 73-year-old-woman
- Severe hyponatremia (Na+ = 117 mmol/l)
- Hospitalized after generalized tonic-clonic seizure


* All purgative products have been associated with hyponatremia and seizure. See full prescribing information for complete details.

MiraLAX is a registered trademark of Schering-Plough Healthcare Products, Inc.
Hyponatremia may develop with any colonoscopy preparation as a result of vomiting, diarrhea, renal disease, or inappropriate secretion of ADH (SIADH)
Physiological bases for potential hyponatremia
OTC PEG-3350 + sports drink prep

- Diarrheal fluid & Na loss without adequate Na replacement
- Excessive ADH secretion & water retention
- Free water consumption & absorption
- Pre-existing CKD or CHF

POTENTIAL ACUTE (SUDDEN) HYPONATREMIA
Hypovolemia from diarrhea leads to ADH stimulation. Possible Mechanism: SIADH

- DRUGS
  - Thiazide diuretics
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Angiotensin converting enzyme inhibitors (ACEs)
  - Opiate derivatives
  - Selective serotonin re-uptake inhibitors (SSRIs)
  - Tricyclic antidepressants
  - Antipsychotics

- NAUSEA & VOMITING

- VOLUME DEPLETION

ADH is released into the blood from the posterior lobe of the pituitary. This causes the kidneys to conserve water, which can result in fluid overload and hyponatremia.
Three Cases of Severe Hyponatremia (< 130 mEq/l) with MiraLAX-Gatorade Use at UM in Summer 2010
Three Cases of Severe Hyponatremia (< 130 mEq/l) with MiraLAX-Gatorade Use at UM in Summer 2010
Methods

- Monitor for new adverse events in currently marketed drugs.
- Voluntary reporting.
- Physician/Nurse/Pharmacist
- Patients

U.S. Department of Health and Human Services
MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program

<table>
<thead>
<tr>
<th>A. PATIENT INFORMATION</th>
<th>Section A - Help</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient Identifier</td>
<td></td>
</tr>
<tr>
<td>2. Age at Time of Event or Date of Birth:</td>
<td></td>
</tr>
<tr>
<td>3. Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>4. Weight</td>
<td></td>
</tr>
<tr>
<td>lb</td>
<td></td>
</tr>
<tr>
<td>or kg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR</th>
<th>Section B - Help</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check all that apply:</td>
<td></td>
</tr>
<tr>
<td>1. Adverse Event</td>
<td></td>
</tr>
<tr>
<td>Product Problem (e.g., defects/malfunctions)</td>
<td></td>
</tr>
<tr>
<td>Product Use Error</td>
<td></td>
</tr>
<tr>
<td>Problem with Different Manufacturer of Same Medicine</td>
<td></td>
</tr>
<tr>
<td>2. Outcomes Attributed to Adverse Event (Check all that apply):</td>
<td></td>
</tr>
<tr>
<td>Death:</td>
<td></td>
</tr>
<tr>
<td>Life-threatening</td>
<td></td>
</tr>
<tr>
<td>Congenital Anomaly/Birth Defect</td>
<td></td>
</tr>
<tr>
<td>Hospitalization - initial or proloned</td>
<td></td>
</tr>
<tr>
<td>Other Serious (Important Medical Events)</td>
<td></td>
</tr>
<tr>
<td>Required Intervention to Prevent Permanent Impairment/Damage (Devices)</td>
<td></td>
</tr>
</tbody>
</table>

For VOLUNTARY reporting of adverse events, product problems and product use errors
Results

- **14 identified cases by May 15 2011
- All outpatient colonoscopies
- Age: range 35-76 y/o
- Gender: 12:2 - Female: Male ratio
- No sig PMHx = 6; Htn = 3; Hypothyroid = 2, No Data = 3
- Symptomatic Presentation: Nausea, Vomiting, Syncope
- 29% (4/14) hospitalized in ICU setting
- Lowest reported Na (range): 117 – 128 mEQ/mL

... but it isn’t all bad news

• RCT of pm only M-G (n=66) vs 2L PEG-ELS (MoviPrep®) (n=70) with serum electrolytes on day of colonoscopy
  – Serum Na+: 138.8(+/- 2.4) mmol/L vs 139.3 (+/- 2.4) mmol/L; p =0.13

• RCT of 222 patients randomized to split dose M-G (n = 54); pm only M-G (n = 60); split-dose 4L GoLytely (n=51); pm only 4L GoLytely (n = 57)
  – Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  – No significant differences in mean change in electrolytes from baseline in any group. Range of change in sodium: -0.37 (pm only M-G) to +0.02 (pm only GoLytely)

• RCT of 389 patients randomized to split dose M-G (n=180) vs split dose PEG-ELS (MoviPrep®) (n= 184)
  – Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  – Hyponatremia: M-G = 3.9% (7/180) vs PEG-ELS 2.2% (4/184); OR = 1.8; 0.5-8.6; p=0.38

... but it isn’t all bad news

• RCT of pm only M-G (n=66) vs 2L PEG-ELS (MoviPrep®) (n=70) with serum electrolytes on day of colonoscopy¹
  – Serum Na+: 138.8(±2.4) mmol/L vs 139.3 (±2.4) mmol/L; p =0.13

• RCT of 222 patients randomized to split dose M-G (n = 54); pm only M-G (n = 60); split-dose 4L GoLytely (n=51); pm only 4L GoLytely (n = 57)²
  – Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  – No significant differences in mean change in electrolytes from baseline in any group. Range of change in sodium: -0.37 (pm only M-G) to +0.02 (pm only GoLyely)

• RCT of 389 patients randomized to split dose M-G (n=180) vs split dose PEG-ELS (MoviPrep®) (n= 184)³
  – Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  – Incidence of hyponatremia: M-G = 3.9% (7/180) vs PEG-ELS 2.2% (4/184); OR = 1.8; 0.5-8.6; p=0.38

...But is this sample size large enough to identify a significant difference in rare serious adverse event?

Increased Risk of Severe Hyponatremia with Miralax-Gatorade vs Iso-osmolar PEG solution

- IRB-approved retrospective database study
- Linked UM colonoscopy scheduling records to UM Emergency Dept records
- Identified individuals who presented to ED during the 24 hours prior to scheduled colonoscopy.

Schoenfeld P, Elliott E. Am J Gastroenterol 2011; 106: A1525
Increased Risk of Severe Hyponatremia with Miralax-Gatorade vs Standard Bowel Preparation

• Among 8413 colonoscopies performed in 2009, 5 patients were hospitalized for severe hyponatremia:

  0.13% (3/2304) of M-G pts vs 0.032% (2/6109) of PEG pts

  odds ratio = 3.98; 95% CI: 0.66-23.8; p = 0.10.

• All patients presented with a combination of N/V, pre-syncope, mental status changes, or abd pain.

Schoenfeld P, Elliott E. Am J Gastroenterol 2011; 106: A1525
... and it isn’t just OTC products

- **Prepopik®**: sodium picosulfate, mag oxide, & anhydrous citric acid) Hyperosmolar, FDA-approved.
  - Rex et al. Split-dose Prepopik® superior to pm only Half-lytely® for bowel cleansing. ¹,²
  - Hyponatremia more common with Prepopik®:
    - 3.7%(11/298) vs 1% (3/295)
    - OR =3.73 (95% CI: 1.03-13.5;p =0.045)

... But this is asymptomatic hyponatremia! What about clinically important hyponatremia?

Risk of Hospitalization with Hyponatremia with PrepOpik®

- Population-based retrospective cohort study in Canada. Looked for hospitalization with hyponatremia within 30 days of prescription date.

- Risk of hyponatremia higher with sodium picosulfate bowel preparation (10mg sodium picosulfate, 3.5gm mag oxide & 12g citric acid per sachet) vs PEG bowel preparations:
  - 0.09% (93/99,237) vs 0.04% (20/48,595);
  - adjusted RR = 2.4 (1.5-3.9);
  - absolute risk difference 0.05 (95% CI: 0.04-0.06);
  - NNH = 1903 (95% CI: 1645-2257)

Conclusions

- Hospitalization due to severe hyponatremia has occurred with Miralax-Gatorade Bowel Prep and has been associated with Prepopik®

- Caution should be used in recommending a non-FDA approved prep with limited safety data.

- Possible association between these bowel preps and severe hyponatremia requires confirmation through further research.

- Remember: complications have been reported with all bowel preparations. No single bowel preparation is universally safe!
The Clinician and Patient Perspective on Endpoints for Bowel Cleansing Studies

Douglas K Rex MD, MACG
Indiana University Health
Indianapolis, IN
Disclosures

- Past consultant to, research support from, and speaker’s bureau member for Braintree and Ferring (no current or recent association)

- Braintree sponsors the ASGE colonoscopy “Tip of the Week” – all funding is to the ASGE
Efficacy

Safety

Tolerability
Safety, Efficacy, Tolerability Interaction

- **Safety**
  - Safety from direct organ toxicity is a pre-requisite
  - Safety from cancer and from repeated procedures (cost, risk) depends on efficacy

- **Efficacy**
  - Is the key to the primary purpose (cancer prevention) – it outranks tolerability (informed patients agree with this – and have)

- **Tolerability**
  - Poor tolerability is unsafe because it reduces willingness to be screened and surveyed
Bowel preparation science

- Greatest achievement of the past two decades:
  - Split-dosing adds more to efficacy than any effect of switching from one preparation to another

- Most incorrect conclusion:
  - Non-inferiority equals equivalence
Split-Dosing Provides More Satisfactory Results Than Traditional Dosing (cont)

Group A = 4 L of PEG on the night before the procedure; Group B = 2 L of PEG on the evening before and 2 L on the morning of the procedure.

Half-lytely
Efficacy Results

- Quality of cleansing was not significantly different between groups ($P = 0.16$)

Complete Bowel Preps (%)

<table>
<thead>
<tr>
<th>Adequacy of Preparation</th>
<th>4 L PEG-ELS (n = 93)</th>
<th>2 L PEG-ELS + bisacodyl (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Rates of inadequate preparation in clinical reports

- Rates of 20-40%
- References:
  - Froehlich GIE 2005;61:378-84
  - Harewood GIE 2003;58:76-9
  - Ness AJG 2001;96:1797-802
  - Borg CGH 2009;7:670-5
  - Hendry Colorectal Dis 2007;9:745-8
Recent changes in bowel preparation guidelines

- Split-dosing preferred
- USMSTF (ACG, ASGE, AGA) and ACG/ASGE quality task force have both adopted the following recommendation:
  - Clinicians in practice should achieve adequate rates of bowel preparation in ≥ 85% of outpatient examinations on a per physician basis
    • Consequences of 20-40% rates of inadequate preparation are too great a burden (1% rule)
Adequate vs inadequate

- MSTF operational definition: if the preparation allows identification of lesions > 5 mm in size then the preparation is ADEQUATE
  - Not a bowel preparation scale
  - Made-up operational definition based on the biology of colon polyps

- ADEQUATE for WHAT?
  - Adequate to follow the screening and surveillance intervals recommended in MSTF guidelines
Patient perspective on cleansing endpoints

- Patient should care first about the quality of the preparation after completion of intra-procedural cleansing
  - Affects the quality of mucosal inspection (effect is considerably less than the effect of the operator)
  - Affects the interval before the next examination
  - Patients will assume safety (rightly so)
  - Tolerability is very important to patients (they may NOT understand that efficacy is even more important)
The judging point

- The judging point is the point in time when the prep is graded (and adequacy determined).
- From the patient and clinicians’ perspective the judging point comes after completion of the intraprocedural cleansing.
  - i.e.: at the judging point patients and clinicians don’t care at all about fluid or other material that was removed.
Clinician perspective on cleansing endpoints

- Same as the patient’s with one key difference:
- Efficiency: clinicians do not want to expend great effort to reach the judging point
  - If the work required to move marginal preps to adequate preps is excessive clinicians will abandon or modify a prep or abandon intraprocedural cleansing
  - This aspect of bowel cleansing efficacy is not captured by the clinical judging point
Intraprocedural work

- 525 patients
- Mean procedure time: 24.1 minutes
- Mean washing and suctioning time (4.1 minutes (17% of all procedural time)
- Adequacy conversion rate by intraprocedural cleaning: 90% to 96%

- MacPhail et al GIE doi10.1016/j.gie.2014.05.002
The clinician and efficacy:

- 2 things to care about:
  - How often did we fail? (prep inadequate)
  - How much work did it take to achieve the level of adequacy?
Bowel preparation scales

- Aronchick
  - Aronchick GIE 2004; 60: 1037-8
- Ottawa
  - Rostom GIE 2004; 59: 482-6
- Boston
  - Calderwood GIE; 2010; 72;686-92
- Chicago
  - Gerard; Clinical Translational Gastroenterology (2013) 4, e43; doi:10.1038/ctg.2013.16
## Bowel preparation scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Validated</th>
<th>Considers retained fluid</th>
<th>Predicts an adequate preparation</th>
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<tbody>
<tr>
<td>Aronchick</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Boston</td>
<td>Yes</td>
<td>No</td>
<td>Score of ≥ 2 in each segment</td>
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<tr>
<td>“Modified Chicago”</td>
<td>Yes</td>
<td>No</td>
<td>Score of ≥ 25 defines a preparation that allows ≥ 95% of mucosa to be seen</td>
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Boston Bowel Preparation Scale

- Right, transverse and left colon segments
  - 0 = unprepared colon segment with stool that cannot be cleared
  - 1 = portion of mucosa in segment seen after cleaning, but other areas not seen because of retained material
  - 2 = minor residual material after cleaning, but mucosa of segment generally well seen
  - 3 = entire mucosa of segment seen well after cleaning

- Total score ranges from 0 to 9
Chicago Bowel Preparation Scale

- **Cleaning scores**
  - 0 = unprepared colon segment with stool that cannot be cleaned (> 15% of the mucosa not seen)
  - 5 = portion of mucosa in segment seen after cleaning; but up to 15% of the mucosa not seen
  - 10 = minor residual material after cleaning, but mucosa of the segment generally well seen
  - 11 = entire mucosa of segment well seen after washing
  - 12 = entire mucosa of segment well seen before washing (suctioning of liquid allowed)

- **Fluid scale (not shown here)**
  - [Gerard Clin Trans Gastroenterol (2013) 4, e43;doi:10.1038/ctg.2013.16](http://dx.doi.org/10.1038/ctg.2013.16)
Correlation with adequate preparation

- **Boston BPS**
  - Overall score $\geq 6$ or score $\geq 2$ in each segment predicts doctors will follow screening and surveillance guideline
    - Calderwood GIE; 2014; 80:269-76

- **Chicago BPS**
  - Score of 25-36 predicts adequate preparation ($\geq 95\%$ of mucosa seen) by definition
    - Gerard Clin Trans Gastroenterol (2013) 4, e43; doi:10.1038/ctg.2013.16
## Bowl preparation scales

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Should bowel prep studies have an ADR endpoint?

- No
What else should clinician’s care about?

- Why do patients fail bowel preparation regimens?
  - Medical factors
  - Patient factors
Medical factors

- Chronic constipation
- Opioids, tricyclics
- Obesity
- Diabetes mellitus
- Previous colon resection
- Previous incomplete colonoscopy
Patient factors

- Poor health literacy
  - Medicaid insurance
  - English not first language
    • Solution: navigation

- Low patient activation
  • Possible solution: education
Endoscopists frequently don’t adjust for predictors

- Use high volume aggressive preparations in all patients?
  - Patients are dissatisfied and go elsewhere

- Use low volume well-tolerated preparations in all patients?
  - Higher rates of inadequate preparation

- Why not adjust the dose for predictors?
  - Deceived by non-inferiority studies
  - Offering multiple preparations increases costs
  - Adjustment requires costly closed access or phone triage
A clinician’s recommendations to the FDA

- Safety is a presumed requisite
- Discourage evening-before regimens from further testing
- Encourage testing in hard to prepare populations
- Encourage use of efficacy scales that get at endpoints relevant to patients and clinicians
  - Should reflect rates of inadequacy
  - Should reflect clinical judging point
  - Should reflect the work required to reach the judging point
- Place greater value on tolerability
Key research questions for investigators:

- What scale in clinical trials best reflects important outcomes re: efficacy?
  - Adequacy rate
  - Work to achieve adequacy
- What preparations are best tolerated? Most likely to be repeated? i.e. studies with these factors as primary endpoints
- What preparations are most effective in difficult to prepare patients?
Open Forum Q & A
Questions?

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