that typically used in clinical practice, and no long-term effectiveness or harms data being available.

Recommendation 4: In adults with CIC who fail or are intolerant to OTC therapies, the panel suggests the use of lactulose over management without lactulose (conditional recommendation, very low certainty of evidence).

Implementation considerations

- Bloating and flatulence are dose-dependent and common side effects, which may limit its use in clinical practice.

Lactulose

Summary of the evidence. Two RCTs studied the efficacy of lactulose syrup for the treatment of CIC in elderly participants (48,49). One multicenter study performed in the Netherlands included 103 participants who were regularly taking laxatives for the treatment of chronic constipation (49). The initial dose of 15 mL of either 50% lactulose syrup or 50% glucose syrup was administered daily for a total of 3 weeks. The daily dose was reduced by half after 3 consecutive days with defecation, but if no defecation occurred for more than 48 hours, the dose was doubled. If defecation occurred on 3 consecutive days with the doubled dose, the dose was reduced back to 15 mL (49). The second study, conducted in the United States, included 55 constipated participants (48). Participants received 30 mL daily of either 50% lactulose syrup or 50% glucose syrup, taken at bedtime for 12 weeks (48).

Benefits and harms. Based on one study, lactulose may have little to no effect on SBMs per week (MD 0.35, CI −0.91 to 1.61). A second study, however, showed that lactulose may be associated with a large increase in global relief (RR 2.42, CI 1.29–4.54, in absolute terms, 473 more per 1,000, CI 97 more to 1,000 more). Across the 2 studies, there was a higher rate of individuals taking lactulose who met the responder definition (defined as >1 SBM from baseline in 1 study and lack of need of other laxatives in other study) compared with placebo. Lactulose was associated with 267 more per 1,000 (from 108 more to 471 more) responders. The studies did not report on CSBMs per week, diarrhea, serious adverse events, quality of life, or stool form.

Certainty in evidence of effects. The certainty of evidence for SBMs was very low because of risk of bias (unclear methods of randomization and blinding) and imprecision. The certainty of evidence for global relief and responder rate was low because of concerns for risk of bias and imprecision. The overall certainty of evidence for lactulose was very low.

Discussion

Lactulose is β-galactosido-fructose, a synthetic disaccharide not digested in the small intestine that exerts an osmotic laxative effect in the colon to promote peristalsis. It is approved by the FDA in the United States for the treatment of constipation at a dose of 10–20 g (15–30 mL or 1–2 packets) daily and is widely available in other countries. The dose may be increased to 40 g (60 mL or 2–4 packets) daily if needed. There were significant limitations in the 2 RCTs of lactulose; both trials were conducted over 40 years ago, included relatively small numbers of elderly participants, and did not report the diagnostic criteria for constipation (48,49). In the US study, most participants were women living in a nursing home and medical facility and the mean age was in the mid-80s (48). Bowel movement frequency and the severity of symptoms improved to a greater degree in the lactulose group compared with the glucose group. Interestingly, the most dramatic finding was the decrease in impactions and need for enemas in individuals receiving lactulose. The other study from the Netherlands did not report demographics of the patient population.

There were minimal data on adverse events from the 2 published studies (48,49); however, bloating and flatulence (which are dose-dependent) are considered very common side effects of lactulose in clinical practice, which limit its use. Some brands of lactulose may be expensive, although generic lactulose is generally low cost. Lactulose can be considered if symptoms of CIC have failed to improve with fiber and OTC laxatives, and individuals do not experience significant bloating or abdominal pain with lactulose use. The use of lactulose in mildly constipated, noninsulin-dependent patients with diabetes mellitus type 2 may not lead to increase in blood sugar levels (50).

STIMULANT LAXATIVES

Recommendation 5: In adults with CIC, the panel recommends the use of bisacodyl or sodium picosulfate (SPS) short term or as rescue therapy over management without bisacodyl or SPS (strong recommendation, moderate certainty of evidence).

Implementation considerations

- Short-term use is defined as daily use for 4 weeks or less. While long-term use is probably appropriate, data are needed to better understand tolerance and side effects.
- This is a good option for occasional use or rescue therapy in combination with other pharmacological agents for CIC.
- The most common side effects are abdominal pain, cramping and diarrhea. The panel suggests starting at a lower dose and increasing the dose as tolerated.

Summary of evidence. The panel considered studies that evaluated bisacodyl and SPS, which are mechanistically related, for the management of CIC. Of note, SPS tablets/drops are not available for use in the United States; however, they are approved for use in Europe. In the United States, SPS is available in combination with other laxatives and used for bowel preparation before colonoscopy. Given their common mechanism of action and limited number of trials on these drugs in treatment of CIC, the data from available trials were pooled in calculations of estimates of effect. A total of 2 studies were included. One of these studies was a multicenter randomized double-blinded placebo-controlled trial in the United Kingdom where recruited participants were assigned in a 2:1 ratio to bisacodyl (n = 247) vs placebo (n = 121) and treated for 4 weeks (51). The other study examined effects of SPS in a multicenter double-blinded placebo-controlled RCT conducted in Germany, and participants were randomized in a 2:1 ratio to SPS (n = 229) or placebo (n = 133) and treated for 4 weeks (52).

Benefits and harms. Based on meta-analyzed data from 2 studies, SPS likely leads to a large increase in CSBMs per week (MD 2.54, 95% CI 1.07–4.01) and SBMs per week (MD 4.04, 95% CI 2.37–5.71) and improved the consistency of stool on the Bristol Stool Form Scale (53) (MD 2.4 points higher, 95% CI