21/168 (12.5%) compared with 102/165 (62%) in the placebo arms had diarrhea lasting greater than 4 days. When combined, these studies achieved a 79% efficacy (relative risk: 0.21, 95% CI: 0.08–0.52) for this outcome with substantial heterogeneity (T^2=0.56; χ^{22}=10.47, d.f.=3 (P=0.01); I^2=71%). However, theoretical safety concerns raised about this product limits further recommendation (90). The one study with *S. boulardii* did not appear to confer any advantage in the primary or secondary outcomes evaluated (89).

Based on the current evidence, there are not enough studies, which would support the recommended use of any particular probiotic product for treatment in acute adult diarrhea infection. Although a statistically significant summary treatment effect was observed for *Enterococcus* LAB SF68, heterogeneity in results does not allow for generalization, theoretical safety concerns, and no recent studies with this product have been reported. Recommendations on use of probiotics in pediatric populations have recently been published (91).

A single study of polyphenol-based prebiotic has been described in the treatment of acute diarrhea in children and adults seeking treatment at community health centers in Managua, Nicaragua (92). No diarrhea case definition (e.g., frequency or duration) for inclusion was reported; however, exclusion critieria included those with high fever, vomiting, severe dehydration, and bloody stools. A remarkable treatment effect on mean time to last unformed stools among the treatment group compared with placebo was reported (prebiotic: 10.5 h vs. placebo: 54 h, P<0.0001). While important methodological and analytic detail are missing, and understanding of potential mechanism of action is lacking, this product may warrant additional investigation in a well-designed clinical trial.

While evidence supporting therapy of probiotics in treatment of acute diarrheal infection is lacking, and few studies addressing the effectiveness of probiotics in treatment of antibiotic-associated diarrhea (93), there is supporting evidence for the role of probiotics in prevention of acute diarrhea associated with antibiotic use (94). The pooled results among 63 randomized controlled trials across all population, setting, and probiotic types indicated a relative risk reduction of 0.58, with a number needed to treat of 13. Heterogeneity and gaps in reporting of the studies, design, population, and antibiotic associated class make clinical application of these results to the individual patient clinical care challenging. Future research is needed to support directed therapy and effectiveness among various patient populations, clinical indications, antibiotics, and probiotic strains, as well as further understanding the risk of adverse events associated with probiotic use for these indications.

Non-antibiotic therapies

Recommendation

7. Bismuth subsalicylates (BSSs) can be administered to control rates of passage of stool and may help travelers function better during bouts of mild to moderate illness. (Strong recommendation, high level of evidence)
8. In patients receiving antibiotics for TD, adjunctive loperamide therapy can be administered to decrease duration of diarrhea and increase chance for a cure. (Strong recommendation, moderate level of evidence)

Summary of the evidence. Medical treatment is not required in patients with non-severe, non-cholera-like diarrhea. Non-antibiotic anti-diarrheal drugs have been shown to reduce the number of stools passed in cases of diarrhea allowing the ill people to continue their planned schedule. The drugs with value in controlling symptoms with reduced rate of stooling are the antisecretory and antimotility drugs. Intestinal secretion is the major pathophysiologic mechanism leading to watery diarrhea in some forms of acute diarrheal infection including TD. The antisecretory drugs that have been evaluated and shown to have value for therapy in secretory forms of diarrhea are BSS (95), zaldaride maleate (96), and crofelemer (97). It is the salicylate part of BSS that has antisecretory anti-diarrheal properties (98). BSS will reduce the stools passed by ~40% (95). Crofelemer is a cystic fibrosis transmembrane regulator chloride-channel blocker and is effective in some forms of diarrhea including TD and AIDS-associated diarrhea (99). Zaldaride is a calmodulin-inhibiting drug that has antisecretory properties related to intracellular concentrations of calcium (100). The drug significantly shortened the stools passed in subjects studied with TD compared with placebo therapy (96,101,102). Racecadotril, a specific enkephalinase inhibitor that prevents degradation of the endogenous antisecretory peptide neurotransmitter enkephalins that inhibit cyclic nucleotide secretory pathways without effect on gut motility (103) and has been used successfully in pediatric diarrhea (104). While racecadotril was shown to be as effective as loperamide in the treatment of acute endemic diarrhea in adults (105), this antidiarrheal drug needs to be studied further in diverse forms of diarrhea. Of the strictly antisecretory, only two agents are approved for use by the Food and Drug Administration in the United States, BSS for treatment of acute diarrhea and crofelemer for HIV-associated diarrhea. The recommended dose of BSS for therapy of acute diarrhea is 30 ml (525 mg) of liquid formulation or two tablets (263 mg per tablet) chewed well each 30–60 min not to exceed eight doses in 24 h. The drug will produce black stools and black tongues from harmless bismuth sulfide salt.

The major antimotility drugs used for therapy of acute diarrhea are loperamide and diphenoxylate. Of these, the most useful drug is loperamide, which has less central opiate effects. Another limitation of diphenoxylate is that it contains atropine, which has no antidiarrheal effectiveness and may produce objectionable side effects. Loperamide works through two mechanisms, the most important being the production of segmental contraction of the gut, which slows the intraluminal movement of fluids and allows greater absorption (106). A secondary effect appears to be inhibition of calmodulin leading to reduced mucosal secretion (107). Thus, the mechanisms of antidiarrheal effect of loperamide are indirect or direct inhibition of mucosal secretion and reduction in motility. In a comparative randomized trial in patients with TD, loperamide reduced the number of diarrheal stools passed when compared with BSS (108) and loperamide was shown to shorten diarrhea in both children (109) and adults with acute diarrhea (110). The recommended dose of loperamide for therapy for adults with diarrhea is 4 mg initially followed by 2 mg after subsequently