

## DIFFICULT DIARRHEAS: Bile Salts and Diarrhea-Connected or Not

Lawrence R. Schiller, MD  
Digestive Health Associates of Texas  
Baylor University Medical Center  
Dallas, Texas

### Main Points:

1. The role of bile acid malabsorption in the pathogenesis of diarrhea is established for ileal resection or disease.
  - a. The concentration of bile acid in the colon is critical; it must be high enough to inhibit fluid and electrolyte absorption (>3—5 mmol/L). Thus if the extent of resection or disease is too great (typically >100 cm), the colon will be flooded with fluid and the luminal concentration of bile acid will be too low to affect absorption in the colon.
  - b. The mechanisms by which bile acids inhibit absorption or stimulate secretion in the colon are not fully appreciated. Dihydroxy bile acids with both hydroxyl groups in the alpha position have this effect; trihydroxy bile acids do not. Cyclic AMP levels in the mucosa rise, but this effect may be indirect and due to release of prostaglandins and other factors. Direct effects may be due to alterations in the basolateral membrane of the colonocytes.
  - c. Bile acid binders are effective therapy for diarrhea due to small ileal resection or limited ileal disease.
2. Bile acid malabsorption is likely to play a role in diarrhea seen in post-cholecystectomy diarrhea, and post-vagotomy diarrhea.
3. The impact of bile acid malabsorption is unproven in microscopic colitis, postinfective diarrhea, and idiopathic diarrhea.
  - a. Some studies demonstrate bile acid malabsorption in these settings, but it is unclear whether this is a primary cause of diarrhea or secondary to it.
  - b. Trials of bile acid binders show mixed results, but may be helpful in some patients.
4. Currently there is no test for bile acid malabsorption licensed for clinical use in the United States.

- a. Measurements of exogenous radiolabeled bile acid excretion or endogenous bile acid excretion give similar results in research studies.
  - b. In Europe, whole body retention of the radiolabeled bile acid, SeHCAT, has been used to predict responsiveness to bile acid binders. Discrepant results may be due to the fact that this test may be affected by motility alterations and does not necessarily reflect intracolonic bile acid concentrations.
5. Empiric trials of bile acid binders should use a substantial dose of the chosen agent and should quantitate stool output before and after the trial so that the result of the trial can be judged objectively.

References and Suggested Reading:

1. Meihoff WE, Kern F jr. Bile salt malabsorption in regional ileitis, ileal resection and mannitol-induced diarrhea. J Clin Invest 1968;47:261-7.
2. Hofmann AF, Poley JR. Cholestyramine treatment of diarrhea associated with ileal resection. New Engl J Med 1969;281:397-402.
3. Binder HJ, Rawlins CL. Effect of conjugated dihydroxy bile salts on electrolyte transport in the rat colon. J Clin Invest 1973;52:1460-6.
4. Thaysen EH, Pedersen L. Idiopathic bile acid catharsis. Gut 1976;17:965-70.
5. McJunkin B, Fromm H, Sarva RP, Amin P. Factors in the mechanism of diarrhea in bile-acid malabsorption--fecal pH a key determinant. Gastroenterology 1981;80:1454-64.
6. Field M. Bile salt-induced diarrhea: the cellular mechanism. J Clin Invest 1993;92:2091.
7. Thaysen EH. Idiopathic bile acid diarrhoea reconsidered. Scand J Gastroenterol 1985;20:452-6.
8. Fromm H, Malavolti M. Bile acid-induced diarrhoea. Clin Gastroenterol 1986;15:567-82.
9. Robb BW, Matthews JB. Bile salt diarrhea. Curr Gastroenterol Rep 2005;7:379-83.
10. Westergaard H. Bile acid malabsorption. Curr Treat Options Gastroenterol 2007;10:28-33.

11. Sciarretta G, Furno A, Mazzoni M, Malaguti P. Post-cholecystectomy diarrhea: evidence of bile acid malabsorption assessed by SeHCAT test. *Am J Gastroenterol* 1992;87:1852-4.
12. Sauter GH, Moussavian AC, Meyer G, Steitz HO, Parhofer KG, Jungst D. Bowel habits and bile acid malabsorption in the months after cholecystectomy. *Am J Gastroenterol* 2002;97:1732-5.
13. Ung KA, Gillberg R, Kilander A, Abrahamsson H. Role of bile acids and bile acid binding agents in patients with collagenous colitis. *Gut* 2000;46:170-5.
14. Ung KA, Kilander A, Nilsson O, Abrahamsson H. Long-term course in collagenous colitis and the impact of bile acid malabsorption and bile acid sequestrants on histopathology and clinical features. *Scand J Gastroenterol* 2001;36:601-9.
15. Fernandez-Banares F, Esteve M, Salas A, Forne TM, Espinos JC, Martin-Comin J, Viver JM. Bile acid malabsorption in microscopic colitis and in previously unexplained functional chronic diarrhea. *Dig Dis Sci* 2001;46:2231-8.
16. Sciarretta G, Bonazzi L, Monti M, Furno A, Mazzoni M, Mazzetti M, Gritti F, Malaguti P. Bile acid malabsorption in AIDS-associated chronic diarrhea: a prospective 1-year study. *Am J Gastroenterol* 1994;89:379-81.
17. Niaz SK, Sandrasegaran K, Renny FH, Jones BJ. Postinfective diarrhea and bile acid malabsorption. *J R Coll Physicians Lond* 1997;31:53-6.
18. Schiller LR, Hogan RB, Morawski SG, Santa Ana CA, Bern MJ, Norgaard RP, Bo-Linn GW, Fordtran JS. Studies of the prevalence and significance of radiolabeled bile acid malabsorption in a group of patients with idiopathic chronic diarrhea. *Gastroenterology* 1987;92:151-60.
19. Schiller LR, Bilhartz LE, Santa Ana CA, Fordtran JS. Comparison of endogenous and radiolabeled bile acid excretion in patients with idiopathic chronic diarrhea. *Gastroenterology* 1990;98:1036-43.
20. Merrick MV, Eastwood MA, Ford MJ. Is bile acid malabsorption underdiagnosed? An evaluation of accuracy of diagnosis by measurement of SeHCAT retention. *Br Med J (Clin Res Ed)* 1985;290:665-8.
21. Williams AJ, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption—a review of clinical presentation, diagnosis, and response to treatment. *Gut* 1991;32:1004-6.

22. Ford GA, Preece JD, Davies IH, Wilkinson SP. Use of the SeHCAT test in the investigation of diarrhoea. *Postgrad Med J* 1992;68:272-6.
23. Eusafzai S. Bile acid malabsorption in patients with chronic diarrhea. *Scand J Gastroenterol* 1993;28:865-8.
24. Hofmann AF. Progress in idiopathic bile acid malabsorption. *Gut* 1998;43:738-9.
25. Sinha L, Liston R, Testa HJ, Moriarty KJ. Idiopathic bile acid malabsorption: qualitative and quantitative clinical features and response to cholestyramine. *Aliment Pharmacol Ther* 1998;12:839-44.
26. Ung KA, Kilander AF, Lindgren A, Abrahamsson H. Impact of bile acid malabsorption on steatorrhea and symptoms in patients with chronic diarrhoea. *Eur J Gastroenterol Hepatol* 2000;12:541-7.
27. Smith MJ, Cherian P, Raju GS, Dawson BF, Mahon S, Bardhan KD. Bile acid malabsorption in persistent diarrhoea. *J R Coll Physicians Lond* 2000;34:448-51.
28. Wildt S, Norby Rasmussen S, Lysgard Madsen J, Rumessen JJ. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. *Scand J Gastroenterol* 2003;38:826-30.
29. Bajor A, Kilander A, Fae A, Galman C, Jonsson O, Ohman L, Rudling M, Sjovall H, Stotzer PO, Ung KA. Normal or increased bile acid uptake in isolated mucosa from patients with bile acid malabsorption. *Eur J Gastroenterol Hepatol* 2006;18:397-403.
30. Montagnani M, Abrahamsson A, Galman C, Eggertsen G, Marschall HU, Ravaioli E, Einarsson C, Dawson PA. Analysis of ileal sodium/bile acid cotransporter and related nuclear receptor genes in a family with multiple cases of idiopathic bile acid malabsorption. *World J Gastroenterol* 2006;12:7710-4.
31. Balesaria S, Pell RJ, Abbott LJ, Tasleem A, Chavele KM, Barley NF, Khair U, Simon A, Moriarty KJ, Brydon WG, Walters JR. Exploring possible mechanisms for primary bile acid malabsorption: evidence for different regulation of ileal bile acid transporter transcripts in chronic diarrhoea. *Eur J Gastroenterol Hepatol* 2008;20:413-22.
32. Sadik R, Abrahamsson H, Ung KA, Stotzer PO. Accelerated regional bowel transit and overweight shown in idiopathic bile acid malabsorption. *Am J Gastroenterol* 2004;99:711-8.

33. Possel P, Sortsoe Jensen H, Qvist P, Arveschoug A. Prognosis of adult-onset idiopathic bile acid malabsorption. *Scand J Gastroenterol* 1999;34:587-90.