What is the best way to evaluate acute diarrhea?

EVIDENCE-BASED ANSWER Limited evidence delineates the relative probabilities of causes of acute diarrhea, typically defined as a diarrheal disease lasting 14 days or fewer, in the developed world. Viruses (rotavirus, Norwalk, and other enteric viruses) are responsible for most cases. Stool culture helps to identify bacterial causes (*Salmonella*, *Shigella*, enterotoxic *Escherichia coli*), especially in patients with fever and bloody stool. A modified 3-day rule (eg, performing only *Clostridium difficile* toxin tests on low-risk patients who have been hospitalized for 3 or more days) leads to a more rational use of stool cultures without missing cases of clinically significant disease. (Grade of recommendation: D, based on limited studies, reliance on expert opinion, and consensus.)

EVIDENCE SUMMARY More than 2 million cases of infectious diarrhea are documented in the United States annually. Infectious diarrhea is the second leading cause of morbidity and mortality worldwide. Published data have focused on the etiology of diarrhea in the developing world, and more commonly on the clinical evaluation and treatment of patients with diarrhea and dehydration.

While most research on acute diarrhea focuses on infectious causes, noninfectious causes should also be considered (eg, drug-induced diarrhea, inflammatory bowel disease).[1] Viral causes are most common; in children, viruses are responsible for 70% to 80% of cases of diarrhea.[2] A prospective study of 147 US children with acute, mild diarrhea demonstrated that rectal swabs yielded a positive test for an infectious agent in 60.5% of cases (Table).[3]

A case-control study of stool cultures for rotavirus in adult patients found that 14% of 683 with diarrhea and 5% of 1115 without diarrhea shed rotavirus.[4] A recent systematic review found no published studies about the likelihood of specific diagnoses in children presenting to the hospital with diarrhea.[5]

Some evidence supports a structured diagnostic strategy for hospitalized patients with acute diarrhea. Using retrospective reviews, Bauer and colleagues[6] developed a prediction rule for cases of infectious diarrhea. The "modified 3-day rule" recommends stool cultures for patients with diarrhea beginning more than 3 days after hospitalization only when they fall into 1 of the following groups: patients older than 65 years with permanently altered organ function, those with HIV or neutropenia, those hospitalized during suspected nosocomial outbreaks, and those suspected of nondiarrheal manifestations of enteric infection.[6] When the modified rule was applied prospectively, only 2 cases were missed. Both patients were at risk for immunosuppression, although they did not strictly meet the modified criteria. Neither required treatment.[6]

RECOMMENDATIONS FROM OTHERS The Infectious Diseases Society of America's practice guidelines for the evaluation and treatment of acute diarrhea recommends that stool culture for bacteria (including enterotoxic *E coli*) should be considered in patients with community- or travel-acquired diarrhea, especially when fever or bloody stool is present. In hospitalized patients, only toxin tests for *C difficile* are recommended. Testing for acute parasitic diseases should be reserved only for patients whose symptoms persist after 7 days.[1]

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Clinical Commentary by Les Hall, MD, at http://www.fpin.org.

TABLE 1

Etiologic agents in US children with acute diarrhea

Infectious agent	Percent
Rotavirus	29.3%
Giardia lamblia	15%
Pathogenic *Escherichia coli*	15%
Multiple agents	10%

Data from Caeiro JP, Mathewson JJ, Smith MA, Jiang ZD, Kaplan MA, Dupont HL. Etiology of outpatient pediatric nondysenteric diarrhea: a multicenter study in the United States. Pediatr Infect Dis J 1999; 18:94–7.

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Are any oral iron formulations better tolerated than ferrous sulfate?

EVIDENCE-BASED ANSWER Ferrous salt preparations (ferrous sulfate, ferrous gluconate, and ferrous fumarate) are equally tolerable. (Grade of recommendation: A, based on randomized controlled trial.) Controlled-release iron preparations cause less nausea and epigastric pain than conventional ferrous sulfate (grade of recommendation: A, based on randomized controlled trials), although the discontinuation rates between the 2 iron formulations were similar. Ferrous sulfate remains the standard first-line treatment of iron-deficiency anemia given its general tolerability, effectiveness, and low cost.

EVIDENCE SUMMARY A randomized, double-blinded, placebo-controlled study in 1496 subjects examined side-effect rates of 3 iron salt formulations using equal dosages of elemental iron (Table).[1] Gastrointestinal (GI) side-effect rates were not significantly different. The side-effect rate in the ferrous sulfate group (23%) was significantly different from that of the placebo group (14%); thus, for every 11 patients treated with ferrous sulfate, 1 patient would have GI side effects attributable to the iron salt (number needed to harm [NNH] = 11).

Two formulations—controlled-release iron preparations and polysaccharide–iron complexes—decrease the amount of iron presented to the proximal GI tract. Three large randomized trials assessed tolerability of controlled-release iron preparations compared with ferrous sulfate.[2–4] The only double-blinded study found a lower rate of nausea and epigastric pain in the controlled-release iron formulation among 1376 blood donors receiving 200 mg/day elemental iron (3.3% vs 6.4%, $P < .05$, NNH = ~32).[2] A nonblinded randomized trial of 543 nonanemic adult patients taking 50 mg/day elemental iron also found a lower rate of stomach-related side effects in the controlled-release group (12.2% vs 27.2%, $P < .001$, NNH = ~7).[3] However, none of the 3 studies showed a difference in the discontinuation rates between the 2 iron formulations. Comparative constipation rates among the trials were conflicting.

Two small, nonblinded, randomized trials of polysaccharide–iron complexes reported conflicting results. A study of 159 subjects found fewer subjects discontinuing the polysaccharide–iron complex taken with meals than ferrous sulfate taken on an empty stomach.[5] A study of 60 subjects taking both preparations on an empty stomach found no difference in side-effect rates.[6] Two small, randomized, blinded studies found no difference in rates of GI side effects between carbonyl iron and ferrous sulfate.[7,8]

RECOMMENDATIONS FROM OTHERS *Wintrobe's Clinical Hematology*[9] and *Williams Hematology*[10] recommend ferrous sulfate as the standard oral iron preparation, and assert that claims of improved tolerability of one oral iron preparation over another have not been substantiated.

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TABLE

Representative average wholesale prices* for various iron supplement formulations

Iron supplement group	Generic or brand name	Dosage	Cost of 1-month course
Ferrous salts	Ferrous sulfate (generic)	Tablet: 325 mg po tid	$0.63 to $5.11 (90 tabs)
	Ferrous fumarate (generic)	Tablet: 300 mg (99 mg iron) po bid	$1.80 (60 tabs)
	Ferrous gluconate (generic)	Tablet: 325 mg (36 mg iron) po tid	$2.70 to $5.00 (90 tabs)
Controlled-release	Slow FE (Novartis)	Tablet: 160 mg (50 mg iron) po tid	$18.92 (90 tabs)
	Ferro-Grad-500 (Abbott)	Tablet: 105 mg iron po bid	$31.84 (60 tabs)
Polysaccharide–iron complex	Niferex-150 (Schwarz Pharma)	Capsule: 150 mg iron po qd	$10.50 (30 caps)
Carbonyl iron	Feosol (SmithKline Beecham)	Tablet: 50 mg iron po tid	$18.38 (90 tabs)

*2001 Drug Topics, Red Book. Daily dosages given here deliver 150 to 210 mg of elemental iron and are for comparison of average costs. Actual dosage should be adjusted according to the calculated need for iron replacement and the results of laboratory monitoring.

How effective are pharmacologic agents for alcoholism?

EVIDENCE-BASED ANSWER Naltrexone (ReVia) and nalmefene (Revex) are the most effective agents for treating alcoholism. Acamprosate is effective but not available in the United States. Serotonergic agents, selective serotonin reuptake inhibitors (SSRIs), and lithium work best in patients with alcoholism and comorbid depression, anxiety, or bipolar disorder. Disulfiram (Antabuse) decreases drink frequency, but is no better than placebo for other outcomes. Greater effectiveness is achieved when pharmacologic agents are combined with either counseling or Alcoholics Anonymous programs. (Grade of recommendation: B, based on multiple randomized controlled studies with short and incomplete follow-up of patients.)

EVIDENCE SUMMARY Naltrexone (50 mg qd), nalmefene (10–80 mg qd), and acamprosate (dose based on patient weight) are all superior to placebo and other agents such as the SSRIs, disulfiram, and serotonergic agents in reducing relapse rates and the phenomena of craving and in increasing abstinence rates.[1–5] For example, naltrexone reduces relapse rates by one half to two thirds.[4,6] However, these outcomes apply only to patients who completed the study protocol; noncompleters accounted for up to more than 50% of study participants. When compared with placebo, nalmefene taken for 3 to 24 months significantly reduced relapse without affecting abstinence rates or cravings.[3] When compared with placebo, disulfiram failed to significantly increase abstinence rates or decrease relapse rates or cravings.[2]

In European studies, acamprosate taken for 3 to 24 months significantly increased abstinence rates, but did not significantly decrease relapse or cravings as compared with placebo.[3] Fifteen studies evaluating serotonergic agents, lithium, and SSRIs (including citalopram, viqualine, fluoxetine, and others) taken for 2 to 12 weeks have shown promise for increasing abstinence rates and decreasing cravings in alcoholic patients with coexisting psychiatric conditions such as depression, anxiety, and bipolar disorder.[2,7,8] Studies combining pharmacologic intervention with Alcoholics Anonymous's 12-step program or psychological interventions showed the most significant effects on decreasing cravings and relapse rates and increasing abstinence rates.[2,3,6,9–12]

RECOMMENDATIONS FROM OTHERS According to the American Society of Addiction Medicine, patients who comply with a combination of medication, education, and counseling have favorable short-term and long-term benefits.[1] Naltraxone and acamprosate effectively reduce cravings and increase abstinence.

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Literature search performed by Joan Nashelsky, MLS.

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TABLE

Grade of recommendation based on the evidence

Agent	Decreased cravings at 6 & 12 months	Increased abstinence rates at 6 & 12 months	Decreased relapse rates at 6 & 12 months	Comorbidities: alcoholism with anxiety, depression, or bipolar disorder
Naltrexone	B	B	B	D
Nalmefene	C	C	B	D
Serotonergics	D	D	D	B
SSRIs	D	D	D	B
Disulfiram	C	C	C	D
Lithium	D	D	D	B
Acamprosate	B	B	C	D

Based on the Oxford Center for Evidence-based Medicine Levels of Evidence (May 2001).