magnesium deficiency based on physiologic principles as listed in the Table, but none provide data on the relative frequency of the various causes in the general population or specific subgroups.[6–9]

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CLINICAL COMMENTARY

We need to know when magnesium replacement improves patient outcomes

Treating the underlying cause of hypomagnesemia makes sense. However, even though clinicians often treat "the numbers," it is not clear that magnesium replacement therapy is beneficial in the absence of symptoms caused by the hypomagnesemia. For example, hypomagnesemia is common for patients with acute myocardial infarction, but magnesium replacement therapy has not been shown to improve outcomes in 2 large randomized trials, the Fourth International Study of Infarct Survival (ISIS 4)[14] and Magnesium in Coronaries (MAGIC).[15] We need better-designed randomized trials to know for what clinical conditions magnesium replacement leads to improved patient-oriented outcomes.

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What are effective therapies for *Clostridium difficile*–associated diarrhea?

EVIDENCE-BASED ANSWER

Oral metronidazole and oral vancomycin are equally effective treatments for *Clostridium difficile*–associated diarrhea (CDAD) (strength of recommendation [SOR]: **A**, based on randomized trials). Oral vancomycin is considerably more expensive and may select for colonization with vancomycin-resistant enterococci, leading the American College of Gastroenterology to recommend oral metronidazole as preferred therapy (SOR: **C**, expert opinion). They recommend therapy with vancomycin for those who are pregnant, breast feeding, less than 10

TABLE

Medical treatment of *C difficile*–associated diarrhea

Indication	Treatment
First episode of *C difficile*–associated diarrhea (SOR: **A**; SOR: **C** for preference over vancomycin)	Metronidazole, 500 mg orally 3 times daily for 10 days
First episode, allergy, or intolerance to metronidazole, pregnant, breast feeding, or age <10 years (SOR: **A**; SOR: **C** for preference over metronidazole)	Vancomycin, 125 mg orally 4 times daily for 10 days
Unable to take oral medication (SOR: **C**)	Metronidazole 500 mg IV 4 times daily
First recurrence (SOR: **C**)	As for first episode or Option #1 below
Second or greater recurrence: Option #1 (SOR: **B**, single RCT)	Metronidazole or vancomycin, plus *S boulardii* (500 mg twice daily [3 x 10^{10} CFUs])
Option #2 (SOR: **C**)	Vancomycin or metronidazole plus rifampin 300 mg oral twice daily for 10 days
Option #3 (SOR: **C**)	Vancomycin tapered dose: 125 mg orally 4 times daily for 7 days 125 mg orally twice daily for 7 days 125 mg orally once daily for 7 days 125 mg orally every other day for 7 days 125 mg orally every 3 days for 14 days
Option #4 (SOR: **C**)	Vancomycin plus cholestyramine 4 g twice daily for 10 days

years old, nonresponders to metronidazole, critically ill, or allergic or intolerant to metronidazole (SOR: **C**, expert opinion).

Treat first recurrences the same as primary infection. In persons with recurrent infection, addition of the probiotic agent *Saccharomyces boulardii* reduces the risk of further recurrences (SOR: **B**, single RCT). Little other evidence exists to guide therapy for subsequent recurrences.

EVIDENCE SUMMARY

Two randomized controlled trials have compared the efficacy of oral metronidazole and oral vancomycin for treatment of CDAD.[1,2] Both studies demonstrated statistically equivalent cure rates exceeding 90%, with relapse rates of 10% to 20% for each drug. These small trials lacked the power to detect small but potentially significant differences in treatment response.

No published data exist indicating that vancomycin is more effective than metronidazole in any clinical setting. A dose-range study showed that 125 mg of oral vancomycin 4 times a day is as effective as higher doses.[3] Patients who cannot take medication by mouth should receive intravenous metronidazole, 500 mg 4 times per day. Unlike vancomycin, metronidazole achieves potentially effective concentrations in the intestinal lumen following intravenous administration.[4]

Treatment of first recurrences of infection with metronidazole or vancomycin produces response rates similar to treatment of initial

CONTINUED

For those with recurrent infection, addition of *S boulardii* decreased the absolute risk of relapse by 30%

infections.[5] A minority of patients suffers multiple relapses of infection, and there are few data to guide therapy in this setting.

A randomized, double-blinded, placebo-controlled study evaluated the impact of adding the probiotic agent *Saccharomyces boulardii* to either metronidazole or vancomycin.[6] For persons with recurrent infection, addition of *S boulardii* led to a 30% decrease in the absolute risk of relapse (64% relapse vs 34%; number needed to treat=3; $P<.05$). There was also a nonsignificant trend toward reduced recurrences in the treatment of primary infections. The 2 minor side effects noted with this treatment were dry mouth (number needed to harm [NNH]=11) and constipation (NNH=9). *S boulardii* capsules are available from health food stores and via the Internet. Several published case series describe various additional approaches to therapy of recurrent CDAD (**Table**).

RECOMMENDATIONS FROM OTHERS

The American College of Gastroenterology and the American College of Physicians treatment guidelines for CDAD both call for treatment with oral metronidazole 250 mg 4 times daily or 500 mg 3 times daily.[7,8] The American College of Gastroenterology recommends vancomycin (125 mg orally 4 times daily) when there is an intolerance or confirmed resistance to metronidazole, failure of response, when the patient is pregnant, breast feeding, or under 10 years of age, critically ill from colitis, or when the diarrhea could be related to *Staphylococcus aureus*. In milder cases, treatment may involve only discontinuation of antibiotics and supportive therapy with observation. Opiates and antispasmodics should be avoided. These guidelines do not recommend any treatment over another for therapy of multiple recurrences.

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CLINICAL COMMENTARY

Discontinue the offending antibiotic and treat the infection; prevent outbreaks via patient-to-patient transmission

Most cases of *Clostridium difficile*–associated diarrhea are caused by antibiotic use; it is therefore one of the most common nosocomial infections. In addition to discontinuing use of the offending antibiotic and treating the infection, it is also important to prevent further outbreaks via patient-to-patient transmission. In our hospital, once a patient is diagnosed with *C difficile*, contact precautions are instituted. If the patient is incontinent, isolation in a single room is required. If the patient is continent