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In their comprehensive review of *Clostridium difficile*-associated diarrhea (CDAD), Susan Poutanen and Andrew Simor[1] refer to the use of anion-binding resins (colestipol or cholestyramine). It is important to highlight the timing of administration of these agents in relation to other oral therapeutic agents (metronidazole or vancomycin). In addition to binding the toxin and spores of *C. difficile*, the binding agents may also bind orally administered therapeutic agents to various degrees, thereby negating their effect. Ideally, resin binders should be given either an hour before or 4 to 6 hours after administration of the oral antibiotics[2] to avoid this problem. However, in clinical practice, especially in hospitals, I have found that the binders and other agents are often given simultaneously; many of the patients have recurrent disease, are described as being resistant to metronidazole (an otherwise rare situation) and are subsequently given oral vancomycin, which is more costly. I believe that this is a common cause of iatrogenic resistance to oral metronidazole.

There are no studies of this phenomenon (i.e., no evidence in this era of evidenced-based and "evidence-made"[3] medicine), but on the basis of a theoretical understanding of the pathophysiology of CDAD, I often administer 10 to 14 days of oral metronidazole followed by 5 to 7 days of oral cholestyramine (to bind the remaining spores in the gut) and have observed a very low rate of recurrence. It is time to prospectively evaluate this simple strategy of sequential therapy in the management of CDAD in a randomized trial.

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[The authors respond to Dr. Parmar:]

We agree with Malvinder Parmar that the role of anion-binding resins in the treatment of CDAD needs to be studied further. Anion-binding resins, such as cholestyramine and colestipol, have been shown to bind *C. difficile* toxins[1] and have consequently been proposed as potentially useful in the treatment of CDAD, as we mentioned in our review.[2] Parmar also suggests that anion-binding resins may also bind *C. difficile* spores, but to the best of our knowledge, this phenomenon has not been described in published reports. Small numbers of mostly anecdotal reports of success and failure with the use of anion-binding resins in the treatment of CDAD have been published (summarized by Ariano and associates[3]), but no large randomized controlled trials have been completed to definitively determine the role of resins. Anion-binding resins have been shown to bind vancomycin[1,4] and theoretically may bind other antibiotics such as metronidazole, although we are not aware of any published data specifically describing this. Given the possibility of antibiotic binding by resins, some authors have suggested not using anion-binding resins in the treatment of CDAD,[5] whereas others recommend using them only if administered at different times from metronidazole or vancomycin.[6] As Parmar suggests, more study is needed to address the optimal indication and timing of anion-binding resins in the treatment of CDAD.

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Cobalamin deficiency in elderly patients

Emmanuel Andrès and colleagues,[1] in their comprehensive review of diagnosis and treatment of vitamin B_{12} (cobalamin) deficiency, fail to consider 2 elements relevant to the Canadian experience.

First, because Canada's flour supply is fortified with folic acid,[2] plasma homocysteine level (determined primarily by folate status) is much less effective in the diagnostic work-up of suspected cobalamin deficiency.[3] In a large population-based study, we established the

test properties of total plasma homocysteine for the diagnosis of cobalamin deficiency among 692 adults in Ontario, after exclusion of people with renal impairment or folate deficiency (red cell folate less than 215 nmol/L).[2] A homocysteine value of 15 µmol/L or more did not discriminate between cobalamin concentrations below and above 120 pmol/L (positive and negative predictive values 7.4% and 97.2%, respectively), nor did it discriminate "indeterminate" cobalamin levels between 120 and 150 pmol/L (positive and negative predictive values 6.3% and 94.0%, respectively).[2]

Second, the diagnostic algorithm for cobalamin deficiency proposed by Andres and colleagues (Fig. 3 in their article[1]) is unnecessarily complex, especially for seniors, in whom cobalamin malabsorption is commonly found because of age-related atrophic gastritis.[4] Although serum methylmalonic acid (MMA) may have a place in a diagnostic algorithm, this indicator of cobalamin insufficiency is falsely elevated in the presence of modest renal impairment[5] with advancing age. Furthermore, serum MMA is commonly elevated in elderly North Americans,[6] but lowering it through vitamin B_{12} supplementation does not appear to affect blood hemoglobin concentration, neurological disability score or quality of life.[7] Like homocysteine, MMA has not been fully validated as a routine clinical test of cobalamin deficiency,[8] especially in the face of increased folate fortification,[2] and MMA testing is not routinely available in Canadian centres and community laboratories.

We propose a simpler and more direct diagnostic approach in elderly patients (Fig. 1), with 2 options for serum cobalamin concentrations in the "grey zone" of 150 to 200 pmol/L. Option A involves testing for serum holotranscobalamin — the complex formed by cobalamin and its transport protein, transcobalamin — the physiologically active form of vitamin B_{12} that is transported into cells.[9] This inexpensive, simple radioimmunoassay-based test, which will become more readily available in Canada, displayed a sensitivity of 100% and a specificity of 89% for cobalamin deficiency in one study.[9] Option B involves initial treatment with parenteral cobalamin according to the dosing schedule outlined by Andrès and colleagues,[1] with assessment of the clinical response after 3 months. High-dose oral cobalamin (e.g., 1000 µg/day) can be used thereafter, as described by Andrès and colleagues.[1] A therapeutic re-

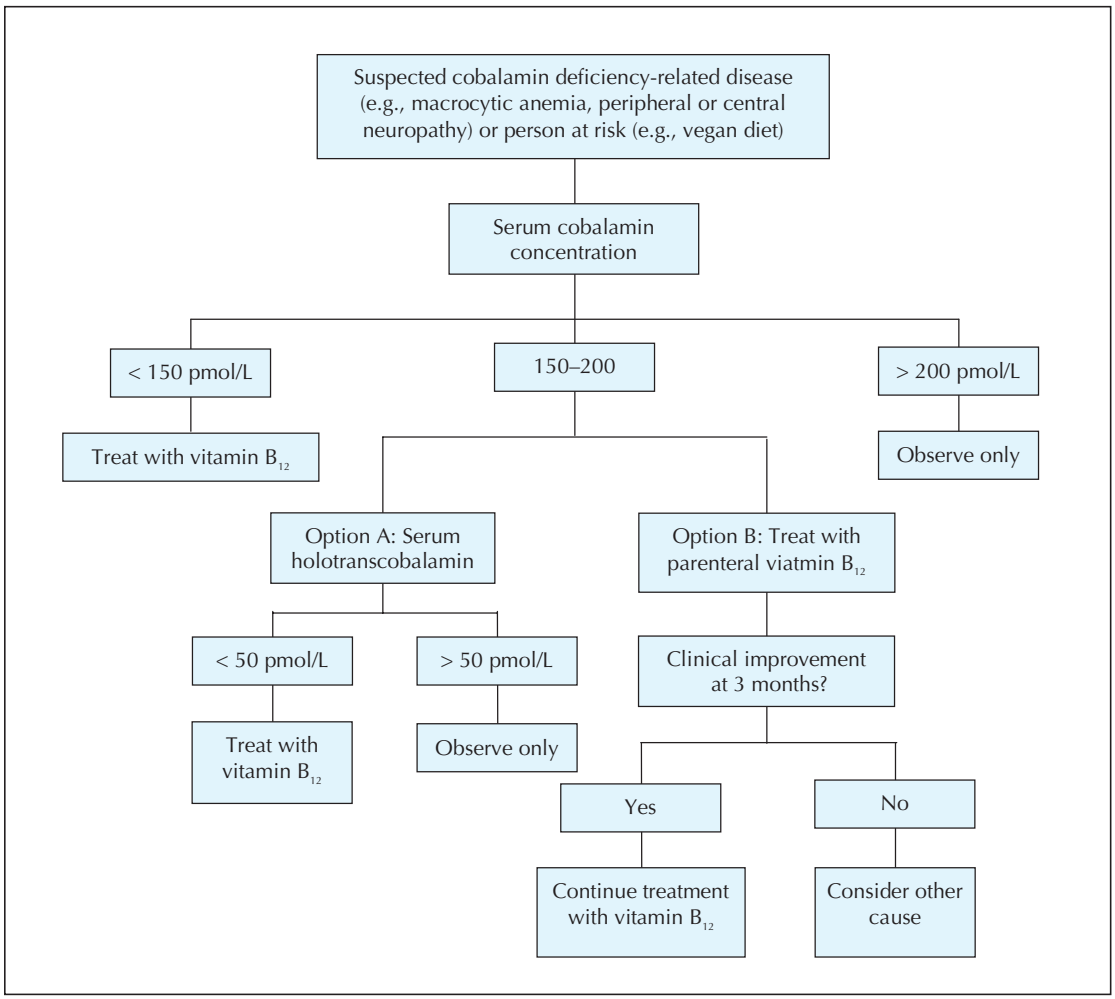

Fig. 1: Diagnostic approach to suspected cobalamin deficiency in elderly patients.

sponse validates not only the diagnosis, but also the treatment, which is otherwise safe and inexpensive.

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Emmanuel Andrès and colleagues[1] state that the classic treatment for deficiency of vitamin B_{12} is injections of crystalline vitamin B_{12} and that an oral treatment has "recently" been devised. However, oral treatment of pernicious anemia was described in 1926 by George Minot and William Murphy.[2] Indeed, in 1934, they (along with George Whipple) received the Nobel Prize for this work. Not until 1948 did Karl Folkers and his coworkers at Merck succeed in purifying crystalline vitamin B_{12}.[3]

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In a recent review, Emmanuel Andrès and colleagues[1] recommend parenteral or oral administration of cobalamin as the treatment of choice for food-cobalamin malabsorption syndrome. The authors mention hypochlorhydria as a factor in this problem but do not recommend hydrochloric acid (HCl) and pepsin therapy as a potential treatment.

In a study of 5 patients with hypochlorhydria, all of the patients had decreased urinary excretion of protein-bound cobalamin.[2] After receiving supplemental HCl, pepsin, gastric intrinsic factor or some combination of these, 4 of the 5 patients showed improvement in protein-bound cobalamin absorption. Another study examined the effect of water, cranberry juice (pH 2.5–2.6) or a 0.1N HCl solution (pH 1.2) on the absorption of protein-bound cobalamin in 3 groups of elderly subjects: healthy individuals, subjects pretreated with omeprazole to simulate the hypochlorhydria of atrophic gastritis and patients with diagnosed atrophic gastritis.[3] Administration of diluted HCl increased the absorption of protein-bound cobalamin in all 3 groups, and this difference was statistically significant for both the omeprazole-treated and healthy subjects ($p < 0.001$). The authors noted that this improvement might have been the result of the acid's ability to augment the release of cobalamin from protein.

Maintaining adequate gastric pH ensures a sufficient sterilizing barrier against enteric pathogens, allows for proper absorption of micronutrients, preserves normal intestinal permeability and prevents hypergastrinemia.[4,5] High gastric pH (as occurs in atrophic gastritis) is also associated with the development of gastric malignant tumours;[6] therefore, maintaining adequate gastric pH might be a preventive measure. Supplemental HCl has been shown to reduce (acidify) gastric pH in subjects with simulated hypochlorhydria.[7] The method of administration has been described by several investigators.[5,8-10] Patients usually start with one 5- to 10-grain (325- to 650-mg) capsule of betaine or glutamic acid hydrochloride with each meal; pepsin is sometimes added to these capsules to improve absorption. Patients are instructed to increase the dosage by one 5- to 10-grain capsule with each meal, sometimes working up to 60–80 grains with every meal. Patients are advised against this therapy if they are also receiving nonsteroidal anti-inflammatory medications or corticosteroids, if they have active peptic ulcer disease, if they have abdominal pain, or if they experience abdominal pain or burning with this treatment. Patients are also instructed to use fewer capsules with smaller meals and more capsules at larger meals.

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