High Dose Vitamin B12 vs. Injected B12

1. Can high dose oral vitamin B12 replace injected B12?

Question submitted by:
Robert Dickson,
Hamilton, Ontario

The short answer is no. However, it is important to know the mechanisms of vitamin B12 absorption and the evidence for use of these two routes of therapy. Typically, absorption of vitamin B12 (cobalamin) requires a series of steps including binding of intrinsic factor leading to the complex of cobalamin with intrinsic factor binding to a receptor on the terminal ileum. However, a very small (yet potentially useful) amount of cobalamin (1%) is absorbed by simple diffusion across the entire intestinal tract without the need for intrinsic factor. Thus, at pharmacologic doses of oral vitamin B12, there will be some amount of cobalamin absorption even in the absence of an intrinsic factor.

There is limited evidence to inform whether or not high dose oral vitamin B12 is as effective as intramuscular injections. Two small prospective, randomized, controlled trials have been conducted comparing these two modalities, and surprisingly, two meta-analyses on these two trials have been published. The conclusion in these meta-analyses demonstrate that high-dose oral vitamin B12 could be as effective as intramuscular vitamin B12. However, the conclusions are based on a limited number of participants in each trial, relatively short follow-up periods, and primarily the response to the use of serum vitamin B12 levels. Serum vitamin B12 levels measure the total amount of cobalamin bound to different proteins, namely transcobalamin I, II and III. Only vitamin B12 bound to transcobalamin II is physiologically active and may not be reflected in the total serum vitamin B12 levels. Further, in the studies, there is no clear indication if certain patients, such as those with pernicious anemia, were less likely to respond to oral supplementation. Given the available evidence, we would recommend that either oral or intramuscular vitamin B12 be used initially for proven clinical vitamin B12 deficiency. If oral vitamin B12 is used initially and there is a lack of response (based on haemoglobin and neurologic response) after four to six months, then a switch to intramuscular vitamin B12 should be considered. Consider an initial parenteral dose in patients with neurological signs and symptoms of B12 deficiency. It is also interesting to note that many patients report increased energy after parenteral B12 administration, even in the absence of B12 deficiency. I have not yet noted very many patients reporting this with oral B12 replacement.

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Answered by:
Dr. Cyrus Hsia and
Dr. Kang Howson-Jan

Child with Recurrent UTIs

2.

In a child with recurrent UTIs (> four-years-old), and normal ULs and VCUG would you consider prophylactic antibiotics?

Question submitted by:
Dr. M.I. Ravaliaxx
Twillin Gate, Newfoundland

The question of how to approach an otherwise healthy child who has a normal ultrasound and VCUG, but has had recurrent urinary tract infections (UTIs) remains controversial. There are a number of under-powered studies that have failed to show any benefits, while more recent, larger studies have shown a reduction in the number of recurrences of UTIs, but there has been no evidence of a change in renal scarring and an increase in the incidence of bacterial resistance. Until more evidence is available, it would be reasonable in this case to use 6 to 12 months of prophylactic therapy (conventionally low-dose co-trimoxazole) for children with recurrent urinary tract infections, even in the absence of abnormalities in diagnostic imaging.

Answered by:
Dr. Michael Rieder

Oral Cimetidine in Wart Treatment

3.

Is there any benefit to using oral cimetidine in addition to other therapy in wart treatment?

Question submitted by:
Dr. Paul L. Kordish
Heidelberg, Ontario

The role of cimetidine in the treatment of warts is hotly debated. In short, the benefit of its use seems no better than placebo for adults, but a slight benefit has been noted in younger patients.[1] There are some studies showing some effect when combined with levamasole (an immunomodulator and antihelminthic).[2]

In my experience, the practical benefits are slim, if any, but can be an avenue to pursue when conventional therapies are not practical, as in generalized verrucae.

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Answered by:
Dr. Scott Murray

Risk of GI Bleeding with SSRI Use

4.

What is the risk of GI bleeding with the use of SSRIs?

Question submitted by:
Dr. Sheila Fergusson
Kelowna, British Columbia

There is emerging evidence that selective serotonin reuptake inhibitors (SSRI) may be associated with abnormal bleeding including upper gastrointestinal (GI) bleeding. The hypothesis for a SSRI-induced GI bleed is that serotonin is critical for maintaining platelet haemostatic function and aggregation. SSRIs may inhibit platelets from engaging in serotonin reuptake by leading to a depletion of serotonin and impaired platelet aggregation. These patients have a greater risk of experiencing GI bleeding. However, the medical evidence for SSRIs as a cause of GI bleeding is weak. Most of the information supporting this claim is from case reports, observational studies and retrospective studies. These studies are confounding and highly susceptible to bias. A meta-analysis was conducted of these weak studies that showed that the odds ratio of an upper GI bleed was 2.36 while taking an SSRI.[1] This demonstrates a weak relationship between SSRIs and upper GI bleeding. More evidence is required before these agents can be definitively associated with upper GI bleeding.

Reference:
1. Loke YK, Trivedi AN, Singh S, *et al*: Meta-analysis: Gastrointestinal Bleeding Due to Interaction Between Selective Serotonin Uptake Inhibitors and Non-steroidal Anti-inflammatory Drugs. Aliment Pharmacol Ther. 2008 Jan 1;27(1):31-40.

Answered by:
Dr. Jerry McGrath

Can Thrombocytosis Cause Hyperkalemia?

5.

Can thrombocytosis cause hyperkalemia?

Question submitted by:
Dr. Jeffrey Hesselson,
North Battleford,
Saskatchewan

Thrombocytosis, and indeed any situation causing an elevation of any of the peripheral blood cells, can cause a pseudo-hyperkalemia. Collection of blood samples in nonanticoagulated tubes, which is the routine for any serum biochemistry, will result in a certain amount of hemolysis when the blood clots. The intracellular potassium is released into the supernatant serum, resulting in an increased potassium level. A similar phenomenon occurs with serum lactate dehydrogenase, as well. If there is any concern about the potassium level, I would recommend an electrocardiogram and determination of the plasma potassium by measuring the electrolytes in an anticoagulated sample.

Answered by:
Dr. Cyrus Hsia and
Dr. Kang Howson-Jan

Pros and Cons of Menstrual Suppression

6.

What are the pros and cons of menstrual suppression?

Question submitted by:
Dr. Greg Baran
Kingston, Ontario

Menstrual suppression refers to the prevention of monthly menses. Pregnancy and lactation are physiologic forms of menstrual suppression. More recently, women are choosing to suppress their menses through hormonal methods such as the continuous use of the oral contraceptive pill, intramuscular progesterone injections, the progesterone intrauterine device (IUD), and the vaginal ring. The benefits of menstrual suppression include the lack of menses at inopportune times, potential cost saving associated with monthly period products, and the physiologic effects of preventing hormonal surges that contribute to dysmenorrhea and endometriosis. Menstrual supression is safe and does not impact upon future fertility. The disadvantages of menstrual suppression include unpredictable sporadic spotting especially at the onset of use, and consequently, resulting uncertainty regarding possible pregnancy. Depending upon the menstrual suppression contraceptive method, the costs may be greater than the alternative.

Answered by:
Dr. Cathy Popadiuk

High Blood Pressure in an Otherwise Healthy Elderly Patient

7.

Should a 93-year-old female, living independantly, not having been previously hospitalized, who is asymptomatic, and has a BP of 240/80 be treated, and if so, with what?

Question submitted by:
Dr. Dan Buie
Victoria, British Columbia

In someone who has previously had normal blood pressure, or in someone who has relatively well-controlled hypertension, a presentation with such high systolic blood pressure is rather unusual. One should consider ruling out any secondary causes (*e.g.* endocrine causes or renal artery stenosis, *etc.*)

Clinical trials of hypertension in the elderly have consistently demonstrated benefit from antihypertensive therapy, including for patients over the age of 80. Points to consider when choosing the hypertensive medications and goals of therapy in the elderly include:

1) Lower initial doses (approximately half of that given to younger patients) to minimize the potential side effects
2) Reduction in blood pressure should be gradual to minmize the risk of ischemic symptoms, particularly among patients with postural hypotension
3) It is the attained BP, not the particular drug that is the primary determinant of outcome

In general, three classes of drugs are considered first-line therapy for the treatment of hypertension among elderly patients: low-dose thiazide diuretics (*e.g.*, 12.5 to 25 mg/day of chlorthalidone), long-acting calcium channel blockers (most often dihydropyridines) and ACE inhibitors or angiotensin II receptor blockers.

Answered by:
Dr. Chi-Ming Chow

Caffeine Intake in Children

8. How much caffeine could be toxic in children?

Question submitted by:
Dr. Edwin Jordan
Slave Lake, Alberta

The question of caffeine toxicity in children is interesting, as one would think that children would have little exposure to caffeine. In fact, caffeine has been used in some groups of children on a regular basis, most notably among premature infants for the treatment of neonatal apnoea. That being said, this is for therapeutic use in a closely monitored, in-patient setting. Caffeine exposure for most children is via carbonated soft drinks, such as colas, or chocolate.

Health Canada has recently addressed this issue and has recommended that children receive no more than 2.5 mg/kg per day of caffeine. Given the average weight of children, this would translate to children aged 4 to 6 years receiving no more than 45 mg of caffeine, while for children ages 7 to 9 the maximum caffeine exposure should be no more than 65 mg, and for children aged 10 to 12 years, maximum exposure would be 85 mg. Translating this into practical terms, the average 355 (12 oz) can of cola has between 35 and 45 mg of caffeine, while chocolate has between 7 and 19 mg of caffeine per 28 grams (one ounce), dark chocolate having slightly more. Many conventional chocolate bars contain about 45 g (one and a half ounces).

Thus, in addition to avoiding excessive sugar, other reasons to use moderation with respect to soft drinks and chocolate is to keep caffeine consumption reasonable. It should be noted that the guidelines have been developed for children, aged four-years and older, and for smaller children, there are a number of reasons, caffeine content-including, that in soft drinks and chocolate, should be moderate.

Answered by:
Dr. Michael Rieder

C. Difficile Rate of Colonization

9. What is the rate of colonization of normal persons with *C. difficile*?

Question submitted by:
Dr. Jane Purvis
Peterborough, Ontario

The problem is in defining "normal" people. Studies have been done on general community populations, demonstrating carriage rates of around 1 or 2%. However, if one screens people without Gastrointestinal (GI) symptoms when entering the hospital over 8% may test positive for this bacteria in their stool. This latter group is presumably a population that has more underlying disease and perhaps more contact with health care institutions. Some studies show that after taking antibiotics, transient carriage rates may be up to 50%. On the other hand, many healthy people are very resistant to colonization. In studies with a non-toxigenic strain, many volunteers failed to become colonized despite ingestion of large quantities of C. difficile. Thus, there is no simple answer to this question. Studies looking at household carriers and transmission in the community are ongoing, and results should be available soon.

Answered by:
Dr. Michael Libman

Effectiveness of Probiotics for IBS

10. What is the effectiveness of probiotics in irritable bowel syndrome (IBS)?

Question submitted by:
Dr. Ngoc-Lan Nguyen
Montréal, Québec

Several short-term studies of probiotics in irritable bowel syndrome (IBS) have been published, and none have provided clear evidence as to the potential role of pro-biotic treatment. The probiotic *Bifidobacterium infantis* was significantly more effective than placebo in a controlled trial of 362 patients with IBS.[1] *Lactobacillus GG* or placebo is compared in 25 patients with IBS in a crossover trial.[2] No significant differences were observed in symptom scores for pain, urgency or bloating.

There was, however, a trend toward reduction in the number of unformed stools in patients with diarrhea predominant symptoms. Another study randomized 77 patients with IBS to *Lactobacillus salivarius* or *Bifidobacterium infantis* or placebo.[3] Symptoms were significantly improved in the group receiving *Bifidobacterium*. *Lactobacillus plantarum* was studied in 60 patients with IBS for four weeks.[4] Flatulence was significantly reduced in the probiotic group compared with placebo. There was no difference in abdominal pain.

Better overall gastrointestinal function was maintained at 12 months in the probiotic group compared with placebo, but there was no difference in bloating.

Another study with *Lactobacillus plantarum* and *Bifidocterium breve* compared to placebo found pain and severity scores decreased significantly in the probiotic group after 14 days of treatment.[5]

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Answered by:
Dr. Jerry McGrath

Fertility Drugs and Breast Cancer; Is There a Connection?

11. What is your opinion regarding the question of whether fertility drugs increase a woman's risk of contracting breast cancer?

Question submitted by:
Dr. Danielle Fisch
Canton de Hatley, Québec

Breast cancer risk is increased with prolonged exposure to, and higher levels of, endogenous estrogen. Women with early menarche and late menopause are thus at higher risk due to prolonged exposure to these hormones. Infertility as a risk factor has been studied in the context of anovulatory disorders. With fewer ovulations, there may be a slightly decreased risk of breast cancer. When this is controlled for factors such as parity and age at first birth, other studies suggest no protective effect and a possible slight increased risk. When considering the role of fertility drugs in this context, there does not appear to be an increased risk of breast cancer, but the studies are small. Furthermore, in a recent large population based study from Sweden, there was no increased risk of breast cancer in women undergoing IVF and taking fertility drugs.[1] In general, at present, there is no clear association between fertility drugs and an increased risk of breast cancer.

Reference:
1. Källén B, Finnström O, Lindam A, *et al*: Malignancies Among Women Who Gave Birth After In Vitro Fertilization. Oxford University Press. Oxford Journals 2010; 253:258

Answered by:
Dr. Cathy Popadiuk

Most Efficacious Typhoid Vaccine

12.

What is the most efficacious typhoid vaccine available?

Question submitted by:
Dr. J. Molson
Kingston, Ontario

There are two types of typhoid vaccines available in Canada: an intramuscular purified polysaccharide antigen vaccine, and an oral live attenuated bacterial vaccine. Unfortunately, there is no head-to-head comparative data available for these vaccines. In fact, there is very little data on their efficacy in travellers altogether, since the major trials for all these vaccines studied only residents of endemic areas. In these areas, vaccine efficacy for both types of vaccine was only about 60% overall. It may be better in travellers, who are generally older adults that are in good health, and who have relatively mild exposures, but this is entirely speculatuve. Serologic data suggests that the interval before a booster dose is needed is a couple of years longer for the live vaccine. Otherwise, the overall adverse event rate and cost is similar for both of these products. There is no obvious difference in safety or efficacy among different formulations of the injectable vaccine. The live vaccine does require the patient to have a certain organizational capacity, as it must be kept refrigerated in the house, and doses are taken on alternate days.

Answered by:
Dr. Michael Libman

Slide and Fixative Method for Paps

13.

Our local hospital still uses the slide and fixative method for Paps, but most clinics are using the liquid-based cytology. What is best?

Question submitted by:
Dr. J. Molson
Kingston, Ontario

Liquid-based cytology (LBC) is a new method for specimen collection and slide preparation of Pap smears. Numerous studies and reviews suggest there are no significant differences in diagnostic accuracy, sensitivity, and predictive values between the methods for detecting cervical pre-cancers. LBC, however, is better in that it decreases the number of unsatisfactory, un-interpretable slides that would otherwise require a repeat. Collection in a liquid medium also allows reflex HPV testing on the original specimen. This obviates the need for a second sample to determine whether colposcopy is required, thus reducing patient anxiety. Furthermore, LBC specimens are prepared from spun down samples, eliminating debris and blood, so Pap smears can be performed during menses, allowing greater flexibility for women and physicians.

Answered by:
Dr. Cathy Popadiuk

What Can Help Patients with Lipodermatosclerosis?

14.

What can you do to help lipodermatosclerosis?

Question submitted by:
Dr. Catherine McCuaig
Westmount, Québec

Lipodermatosclerosis is the indurated fibrous change that results from venous disease and stasis in the lower leg. It leaves skin hard and bound down. It tends to be prone to ulceration. Management is aimed at the underlying venous congestion and swelling. Edema can be decreased by diuresis, increased calf muscle activity (leg-muscle pump) and elevation. Underlying congestive heart failure, obesity and varicose vein pathology should be addressed. From a practical management standpoint, the prime therapeutic intervention is compression. Adequate compression systems – either through stockings, or leg wraps – should be instituted to limit further tissue damage from venous distension.

Answered by:
Dr. Scott Murray

What Is the Prognosis for CLL?

15. What is the prognosis for chronic lymphocytic leukemia (CLL) now? How is this best managed?

CLL prognosis has dramatically changed over recent years with the advent of newer cytogenetic and molecular studies. However, the traditional staging systems of Rai and Binet are still very relevant and useful for prognosis. Please see the table below.

Question submitted by:
Dr. S. McCutcheon
Sussex, New Brunswick

Rai Staging System

Risk	Stage	Clinical Features	Median Survival (months)
Low	0	Lymphocytosis	> 120
Intermediate	I	Lymphocytosis with lymphadenopathy	108
	II	Lymphocytosis with hepato- and/or spleno-megaly	94
High	III	Lymphocytosis with anemia (Hb < 110 g/L)	60
	IV	Lymphocytosis with thrombocytopenia (plt < 100 x 10^9/L)	60

Binet Staging System

Stage	Clinical Features	Median Survival (months)
A	Lymphocytosis AND < 3 lymphoid areas involved	> 120
B	Lymphocytosis AND ≥ 3 lymphoid areas involved	84
C	Lymphocytosis with anemia (Hb < 100 g/L), thrombocytopenia (plt < 100 x 10^9/L), or both	60

Lymphoid areas – cervical, axillary, inguinofemoral, spleen, liver

As CLL is not a curable disease, management is aimed solely at improving quality of life and treating symptoms. Treatment is initiated for constitutional symptoms (also known as "B" symptoms), symptomatic lymphadenopathy, splenomegaly, progressive anemia, thrombocytopenia and other associated complications. The constitutional symptoms consist of unexplained, persistent fevers, drenching night sweats, or unexplained weight loss of more than 10% of baseline weight over a six-month-period. Hence, asymptomatic patients with CLL, regardless of their stage or prognosis, do not require treatment and should only be monitored.

Answered by:
Dr. Cyrus Hsia and
Dr. Kang Howson-Jan

What to do with Keratoacanthomas

16.

Must keratoacanthomas be excised?

Question submitted by:
Dr. Janna Bentley
Kelowna, British Columbia

Keratoacanthomas are felt to be a varient of well differentiated squamous cell cancer. They behave in a benign manner, but tend to grow very quickly, often at an alarming rate. On occasion they can even spontaneously resolve. The best management is full excision, allowing for a full view of the lesion architecture to the pathologist, and making the histologic diagnosis possible. If in a difficult area, or if unusually large, some lesions may respond to intralesional fluorouracil, bleomycin or methotrexate. Cryotherapy will sometimes work as well. Widespread keratoacanthomas may respond to systemic retinoids, such as isotretinoin, or acetretin.

Answered by:
Dr. Scott Murray

Severe Panic Attacks in a Pregnant Woman

17. I have a 30-year-old pregnant patient (12 weeks), who suffers from severe panic attacks and anxiety. How should I treat this patient?

Question submitted by:
Dr. Abdul Elghamari
Etobicoke, Ontario

When deciding whether to treat severe panic attacks and anxiety during pregnancy, the risks to the fetus, resulting from individual treatment must be weighed against the potential benefits to both the mother and the fetus. In pregnant women suffering from panic disorders, it has been observed that there may be increased rates of cleft/lip palate, other congenital abnormalities, prematurity, and low birth weight. It is also thought that untreated panic disorder may result in changes to the infant's neurophysiology (*e.g.*, elevated cortisol levels or sleep disruptions).[1] In order to make a decision regarding treatment, the safety of potential medications should be assessed.

Benzodiazepines are commonly used to treat and prevent anxiety or panic attacks. However, their use in pregnant women is often not recommended, as they are classified as a pregnancy risk factor D. This means that there is positive evidence of human fetal risk based on adverse reaction data from investigative or marketing experience post-marketing surveillance or from human studies. Specifically, benzodiazepines freely cross the placenta and accumulate in the fetal circulation. This may, in turn, be associated with increased risk of congenital malformations following first-trimester exposure. Post-partum, infants may experience hypotonia, lethargy, withdrawl and sucking difficulties.[2]

Selective serotonin reuptake inhibitors (SSRIs) are also commonly used for treating anxiety disorders, including panic disorder. However, the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy must also be carefully weighed, as the literature lacks a great deal of evidence to support their safety in pregnancy.[3] As such, the safety of SSRIs in pregnancy is still the subject of much debate. Sertraline is the SSRI most frequently recommended as it holds a pregnancy risk category C and is considered one of the preferred antidepressants to use while breastfeeding. Sertraline is classified as category C due to adverse effects that were observed in animal studies only. Sertraline has been shown to cross the human placenta, and some post-marketing reports of neonates exposed to sertraline late in the third-trimester have shown that these infants have developed discontinuation syndrome and complications requiring prolonged hospitalizations and respiratory support.[2] Also, there is some debate that increasing serotonin in the first trimester may increase risk in the neonate of autism spectrum disorders." The babies have also been shown to be at risk for developing a drug discontinuation syndrome immediately after birth. However, these potential effects are temporary, usually disappearing after two to four weeks of life without treatment.[4,5] Therefore, these potential short-term effects of sertraline use must be weighed against the potential serious long-term effects that could result from leaving panic disorder untreated.

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Answered by:
Professor Joel Lamoure

Contributor:
Professor Jessica Stovel