An 82 yo woman is evaluated for fatigue. Lab eval reveals a hemoglobin of 8 with an MCV of 114. B12 level is 90 (NL > 200). Folate level is normal. Urine methylmalonic acid level is high. What would you recommend for this patient?

A) Schilling test
B) Oral B12 1000 mcg a day
C) Blood transfusion, then IM B12 monthly
D) IM B12 load, then monthly B12 injections

Conventional Wisdom
“Since the defect is one of absorption, replacement should be administered parenterally, specifically in the form of intramuscular cyanocobalamin (if intramuscular administration is contraindicated or refused, cobalamin deficiency can be managed by oral replacement therapy, at doses of 300 to 1000 mcg daily, it is an expensive mode of treatment which requires close medical supervision to avoid relapse).”


The Source of the Problem
“In the management of a disease for which parenteral therapy with Vitamin B₁₂ is a completely adequate and wholly reliable form of therapy, it is unwise to employ a type of treatment which is, at best, unpredictably effective.”


Oral Replacement of Vitamin B₁₂
Problems with early studies

- Used low doses 6 - 150 mcg
- Often with intrinsic factor (animal)
- Antibodies often developed to IF
Oral Treatment of Pernicious Anemia with Vitamin B$_{12}$

- 27 patients with pernicious anemia treated with 300 mcg of B$_{12}$ po daily
- Clinical response excellent in all (normalization of Hb/HCT)
- Follow up at one year, all in clinical remission
- Serum B$_{12}$ levels rose from 90 to 321 and were maintained


Oral Treatment of Pernicious Anemia with B$_{12}$

- 33 patients with PA received 1000 mcg B$_{12}$ orally each week
- No clinical or hematologic relapse in any patient (follow-up up to 6 1/2 years)
- Serum B$_{12}$ levels remained low (mean value < 100 micro mcg/ml)
- Conclusion - 1000 mcg/wk leads to clinical remission, but low serum levels.

Arch Int Med 1960. 106: 280-292

Oral treatment of Pernicious Anemia with Vitamin B$_{12}$

- 64 patients with established B$_{12}$ deficiency from three Swedish Medical Centers
- Received 500 or 1000 mcg of oral B$_{12}$ each day
- All 64 had normal serum B$_{12}$ levels on therapy
- No patient developed neurological abnormalities or hematologic abnormalities due to B$_{12}$ deficiency on therapy


Treatment of B$_{12}$ deficiency with oral Cobalamin

- 38 newly diagnosed B$_{12}$ deficient patients randomly assigned to receive IM Cobalamin (1 mg 9x in 3 mo) or 2 mg orally daily
- B$_{12}$ levels and Methylmalonic acid levels were measured before and after treatment
- IM B$_{12}$ group
  - Serum B$_{12}$ 95 pg/ml $\rightarrow$ 325 pg/ml
  - Methylmalonic acid 3,850 nmol/l $\rightarrow$ 265 nmol/l
- Oral B$_{12}$ group
  - Serum B$_{12}$ 93 pg/ml $\rightarrow$ 1,005* pg/ml
  - Methylmalonic acid 3,850 nmol/l $\rightarrow$ 169 nmol/l

*p < .0005 comparing oral vs. IM. Blood 1998; 92(4):1191-1198

Oral Replacement of Pernicious Anemia with Vitamin B$_{12}$

Conclusions
- Both IF dependant and independent absorption occurs
- 1.2 - 1.5% of the dose is absorbed in patients with PA (IF independent)
- Doses of 500 - 1000 mcg allow for safety zone
- Long term outcome is excellent
- Cost is low

Vitamin B$_{12}$ Replacement Cost (US $)

- 1000 mcg tablets $5.02/100 tablets
- Hydroxycobalamin injection $7.37
  - 1000 mcg/ml (30 doses)
- Visiting nurse visit $75.00
- Clinic charge $15.00
Conventional Wisdom is Improving!

- "Because the defect is nearly always malabsorption, patients are generally given parenteral treatment, specifically in the form of IM cyanocobalamin. Parenteral treatment begins with 1000 mcg cobalamin a week for 8 weeks, then 1000 mcg a month for life. However, cobalamin deficiency can also be managed very effectively by oral replacement therapy with 2 mg of B12 a day"
- Harrison's 15th edition 2001

A 30 yo woman cuts her finger on a glass jar. She goes to the ER and needs to have sutures on her right ring finger. What would you recommend for anesthesia to prepare the patient for repair?

A) Bupivacaine
B) Lidocaine (Xylocaine) 1%
C) Lidocaine (Xylocaine )1% with Epinephrine
D) Lidocaine (Xylocaine) 2%
E) Saline

Conventional Wisdom

Epinephrine should never be used in an end-arterial field, e.g., digits, pinna, nose, penis.


Can Epinephrine be Used in Digital Blocks?

- 60 digital block procedures, 31 randomized to Lidocaine with epi and 29 to Lidocaine
- Lidocaine with epi- one patient needed additional anesthesia, Lidocaine 5 needed additional
- Digital tourniquet needed in 9/31 patients with Lidocaine with epi, 20/29 Lidocaine alone p<.002
- Two patients with complications after Lidocaine, none with Lidocaine and epi

Plast Reconstr Surg 2001;107:393

Epinephrine Use in the Fingers and Hand

- To examine prospectively the incidence of digital infarction and phentolamine rescue in a large series of patients who received epinephrine in their fingers and hands.
- From 2002-2004 9 hand surgeons prospectively recorded each consecutive case of hand and finger epinephrine injection.

Epinephrine Use in the Finger and Hand

- 3,110 consecutive cases of elective injection of low dose epinephrine in the hands and fingers. There were no cases of digital tissue loss. Phentolamine was never required to reverse vasoconstriction

Epinephrine for Digital Blocks?

- No reported cases of finger gangrene due to epinephrine use
- Most textbooks discourage use for digits, nose, earlobe

A 29 yo woman presents for evaluation. She reports that she has frequent headaches over the past 12 months that include pressure pain on her forehead, under her eyes and over her cheeks. She usually has nasal congestion as well. She has not had any fevers or purulent nasal discharge. What is the most likely problem?

A) Cluster headaches
B) Migraine headaches
C) Sinus headaches
D) Tension headaches

"Sinus" Headaches Are Usually Migraine Headaches

- 2991 patients screened who reported at least 6 headaches during the previous 6 months self diagnosed or physician diagnosed as sinus headaches
- 88% of these patients met IHS criteria for migraine HA (80%) or migrainous criteria (8%). Most common sx patients reported were sinus pressure (84%), sinus pain (82%) and nasal congestion (63%)

- Arch Intern Med 2004;164 (16): 1769-1772

Sinus, Allergy and Migraine Study

- 100 patients recruited who believed they had sinus headaches. All received a detail history and PE and given headache diagnosis based on HIS criteria
- Final diagnosis were as follows: Migraine with or without aura 52%, probable migraine 23%, chronic migraine with medication overuse HA 11%, nonclassifiable HA 9%. 76% of migraine patients reported pain in the distribution of the 2nd division of the trigeminal nerve and 62% experienced bilateral forehead and maxillary pain with their HA’s.

- Headache 2007;47:213-224

Treatment of Sinus Headache as Migraine: The Diagnostic Utility of Triptans

- To determine the response rate to triptans in alleviating "sinus headache" in patients with endoscopy and CT negative sinus exams
- Prospective study of patients with physician or patient self diagnosed sinus headaches with negative workup all treated with triptans
- 54 patients enrolled, 38 completed follow up. 31 patients (92%) had significant reduction in headache pain with triptan use, 35 (92%) had a response to migraine directed therapy.

- Laryngoscope 2006;Dec: 2235-2239.
Tip Offs That a Headache is Not of Sinus Origin

- Absence of fever
- Absence of purulent drainage
- Chronicity

A 60 yo man comes to clinic following an episode of diverticulitis. He was treated with a course of amoxicillin clavulanate and improved. He asks what is the best way to prevent a recurrence?

A) Chronic antibiotics
B) Avoid nuts and popcorn
C) Regular laxative use
D) How would I know?

Nuts, Corn and Popcorn and Diverticular Disease

- Participants: The study included 47,228 men aged 40 to 75 years who at baseline were free of diverticulosis or its complications, cancer, and inflammatory bowel disease and returned a food-frequency questionnaire.
- During 18 years of follow-up, there were 801 incident cases of diverticulitis and 383 incident cases of diverticular bleeding

There was an inverse association between nut and popcorn consumption and the risk of diverticulitis. Multivariate HR was .80 for nuts, and 0.72 (95% confidence interval, 0.56-0.92; P for trend=.007) for popcorn.

In conclusion, no evidence that eating nuts, or popcorn increase the risk of diverticular disease

JAMA 2008;300(8):907-914

47 M obese with type 2 diabetes has been on metformin for the last 2 years with good effect, HbA1c 6.8, and with exercise has been able to lose 5-10 pounds. His last 2 blood tests show creatinine levels of 1.5 and 1.6. What do you recommend?

A) Continue with metformin
B) Stop metformin, start sulfonylurea
C) Stop metformin, begin glargine
D) Stop metformin, begin Rosiglitazone

A 60 yo man develops shortness of breath and is diagnosed with CHF (echo shows EF of 30%). He is treated with an ACE inhibitor and furosemide with good clinical response. He has elevated glucose at presentation and over the next month is diagnosed with DM (HBA1C 8.4). What would you recommend for treatment of his DM?

A) Metformin
B) Rosiglitazone
C) Glyburide
D) Insulin
Metformin Package Insert

- Lactic acidosis risk of 0.03 cases/1000, with a fatality rate of 0.015/1000
- Discontinuation if Cr >1.5 in men and >1.4 in women, and advises against initiation in people > 80 years of age unless they have a normal creatinine clearance
- Other contraindications include congestive heart failure requiring medical management, acute or chronic metabolic acidosis, and acute presentations of dehydration, hypotension, and sepsis

Cochrane Review

- 206 studies
- 47,800 person-year of exposure to metformin, and 38,200 patient-years in the non-metformin comparison group
- no cases of fatal or non-fatal lactic acidosis in either group
- 96% of studies allowed for at least one high risk group to be included
- Cochrane Database Syst. Rev.; 2005 Jul 20;(3)

Incidence of Lactic Acidosis in Metformin Users (1)

- Patients with a metformin prescription from 1980-1995 in Saskatchewan Health administrative database.
- 11,797 patients with 22,296 person years of exposure. Two patients had a hospital diagnosis for lactic acidosis (rate 9 /100,000)
- Rate of lactic acidosis in diabetic patients not on metformin 9.7 /100,000 (2).
  1. Diabetes Care 1999 Jun: 22(6) 925-7

Safety of Metformin in Heart Failure

- Medline search from 1966-2007 looking for studies and case reports of lactic acidosis in metformin users with CHF
- No case studies were found where lactic acidosis occurred in patients with CHF as the only risk. Two large retrospective studies showed metformin did not increase the risk of lactic acidosis in CHF patients
  1. Ann Pharmacotherapy 2007; 41:642-646

Does Metformin Improve Outcomes in Patients With Type 2 DM and CHF?

- 12,272 new users or oral diabetes agents between 1991-1996 reviewed. 1,833 had CHF
- Of these patients treated for DM with CHF, 208 received metformin monotherapy, 773 were given sulfonylurea monotherapy and 852 received combination therapy.
- Fewer deaths occurred in patients receiving metformin monotherapy (52% receiving sulfonylurea’s died, 33% receiving metformin monotherapy died, 31% receiving combination therapy died)

- A 34 yo woman presents with a recurrent pyelonephritis. Urine cultures show resistance to Ciprofloxacin and TMP/sulfa. Organism is sensitive to Cephalexin, Cefixime, and Nitrofurantoin. She has a history of penicillin allergy. What do you recommend
  A) Cephalexin
  B) Cefixime
  C) Nitrofurantoin
Is There Cross Reactivity Between Penicillins and Cephalosporins?

- Retrospective cohort study
- 3,375,162 patients who received a PCN, 506,679 received a subsequent cephalosporin. unadjusted risk ratio for those receiving a cephalosporin who had a prior PCN allergic compared with those who had no prior response was 10. absolute risk of anaphylaxis after a cephalosporin was .001% (1/3920).
- The unadjusted risk ration for sulfonamide antibiotic after PCN allergy was 7.2
- American J of Med 2006;119: 354

Cephalosporin Allergy

- Cephalosporin skin allergy 1-3 %, severe skin reactions less than with PCN
- Rate of allergic reaction to cephalosporins in patients with PCN allergy is 6-8%
- In patients with hx of PCN allergy and negative skin tests rate of cephalosporin allergy 1%

A 59 y.o. male is admitted to the ICU with a myocardial infarction. He is discharged after 5 days on enalapril, atenolol, simvastatin and aspirin. At a 3 month follow-up he is noted to have marked anhedonia, complaints of insomnia, feelings of worthlessness and psychomotor retardation.

What would you do?
- a) Stop the enalapril
- b) Stop the atenolol
- c) Stop the simvastatin
- d) Begin a TCA
- e) Begin a SSRI

Cognitive function in patients on B-blockers

42 patients enrolled in a:
- Randomized, double-blind, controlled crossover trial (Atenolol/Propranolol)
- 9 different tests of cognitive function tested with no difference in 7 tests, one test enhanced by B-blockers, one worsened
- Beck depression inventory not effected by B-blockers use
- J Gen Intern Med 1990; 5: 310-318

Is depression more common in new users of B-blockers?

- Harvard community health plan population tracking occurrence of depression in new users of Propanolol (704), other B-blockers (587), ACE (976), Ca channel blockers (742) and diuretics (773).
- Follow-up period 6 months
- Rates of depression:
  - B-blockers 20.2/1000 p-y
  - Non B-blockers 25.2/1000 p-y
- J Clin Epi 1996; 49(7); 809-15

Is depression more common in B-blocker users? (Part 2)

- Pharmacoepidemiologic database - Odense University Denmark
- Exposure histories of 11,244 antidepressant users, looking at order of prescription (was B-blocker prescribed before antidepressant?)
- No increased rate of antidepressant prescribing after B-blockers
- Epi 1996; 7: 478-484
Beta blockers And Depression After MI
- 127 non beta blocker users and 254 beta blocker users were studied post MI for depression
- They were assessed using Beck Depression Inventory at baseline, 3, 6 and 12 months post MI
- No significant differences were found between non-beta-blocker users and beta-blocker users on the presence of depressive symptoms
- J Am Coll Card 2006; 48 (11):2209 - 14

Depression and B-blockers
- Original concerns were based on case series, not controlled trials or epidemiologic data
- Still controversial, but if an effect exists, it is small
- Must weigh benefit of B-blocker continuation against theoretical possibility of it causing depression

A 34 yo woman burns her left arm when hot grease spills on it. She presents for treatment. She has a 4cm X 6cm partial thickness burn involving the left forearm. What treatment would you recommend?
A) Hydrocolloid dressing (Duoderm)
B) Silver sulfadiazine (Silvadene)
C) Honey
D) Biobrane

Honey vs Silvadene for Treatment of Burns
- 50 patients with superficial burns randomized to honey (25 patients) or Silvadene (25 pts)
- In the honey treated patients epithelialization occurred in 84% by 7 days and 100% by 21 days. In Silvadene treated patients epithelialization occurred in 72% by 7 days and 84% by 21 days (p<.05)
- Evidence of wound infection in 0 patients treated with honey at 21 days and 5 patients treated with Silvadene at 21 days. Burns 1998; 24:157-161

Honey vs Silvadene in Treatment of Burns
- 104 patients with partial thickness burns randomly assigned to honey or silver sulfadiazine (52 in each group)
- In the honey treated group 45 patients were healed by 15 days, where it took 40 days to have a similar number (47) healed in the SSD group p<.001.

Efficacy of Honey in Inhibiting Pseudomonas Aeruginosa From Infected Burns
- 17 strains of Pseudomonas Aeruginosa isolated from infected burns were tested for sensitivity to 2 kinds of honey (pasture honey and manuka honey)
- All strains showed sensitivity to the honeys with MIC below 10%, and MBC of 9% (compared to 19% for artificial honey)
Hydrocolloid Dressing (Duoderm) vs Silver Sulfadiazine (Silvadene)

- 42 patients with second-degree burns randomized to treatment with hydrocolloid dressing (22) or silver sulfadiazine (20)
- Pain and itch less in hydrocolloid treated patients
- Less time for dressing changes, less interference with daily activities and quicker healing with hydrocolloid (p< .01)


A 49 yo with type 1 DM is evaluated for increasing dyspnea. He has a history of CAD, CHF and renal insufficiency. His current meds are furosemide, carvedilol, simvastatin and aspirin. Chest x-ray shows pleural effusions.
BP 140/80 p-60. Urea 38 Cr 3.4 K 4.3
What would you recommend?
A) Amlodipine
B) Enalapril
C) Nitrates
D) Nitrates + Hydralazine

Use of ACEI in Patients With Renal Insufficiency

- Retrospective study of 20,902 medicare patients with LVEF < 40%
- Outcome measures: 1 year survival for patients who did or did not receive an ACEI at hospital discharge
- Receipt of ACEI associated with 37% lower mortality for patients with Cr> 3.0, 16% lower mortality for patients with Cr<3.0.


ACEI and Renal Insufficiency

- Randomized control trial of Benazepril vs placebo in patients with CRI
- Dose escalation to 20 mg Benazepril, followup to 3 ½ years. Endpoints doubling of Cr, ESRD or death
- 94/422 patients excluded in the initial phase of study, mostly due to cough (72)
- 41% of patients on Benazepril vs 60% on placebo reached a primary endpoint during the 3.4 years of the study
- Risk reduction 19%, NNT for 3.4 years was 5.3

NEJM 2006; 354:131-140

A 57 yo woman comes to clinic to discuss worsening hot flashes. She has tried natural products without benefit. She is healthy with no major medical problems. No past surgical Hx. FH of breast cancer in her mother (diagnosed last year).
What would you recommend?
A) Estrogen + Progesterone
B) Estrogen
C) Vanlafaxine
D) Tamoxifen
E) Raloxifene

What Did The WHI Tell Us?

A) The risk of coronary disease, breast cancer and endometrial cancer is higher in women taking estrogen + progestin
B) The risk of coronary disease, breast cancer and premature mortality is higher in woman taking estrogen + progestin
C) The risk of coronary disease, breast cancer and premature death is not elevated in women who receive estrogen only
WHI: The Facts

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WHI: Estrogen Only

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Estrogen Therapy and Coronary Artery Calcifications in Post Menopausal Women

- Women who had received a hysterectomy randomized to conjugated estrogen vs placebo
- 1079 received a CT to evaluate for coronary artery calcification
- Agatson calcium score 83 for those receiving estrogen vs 123 for those receiving placebo (p=.02)
- The risk of extensive calcification (score > 300) was 40% less in those receiving estrogen

Questions or Comments
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