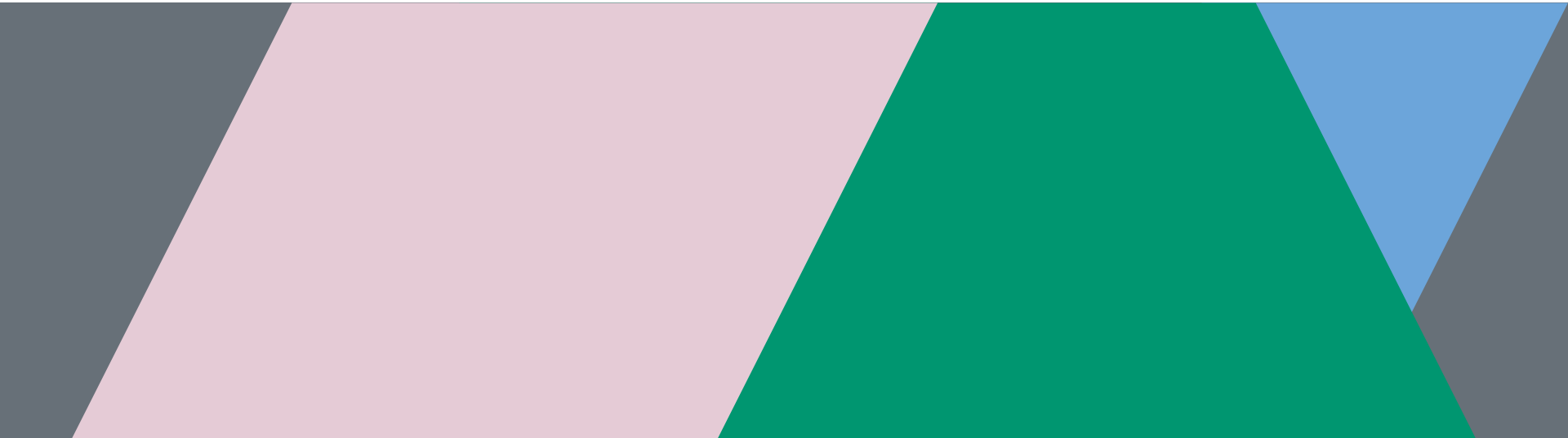
INSELGRUPPE

Bible Class – Micronutrients

6.4.2022 Niklas Krupka



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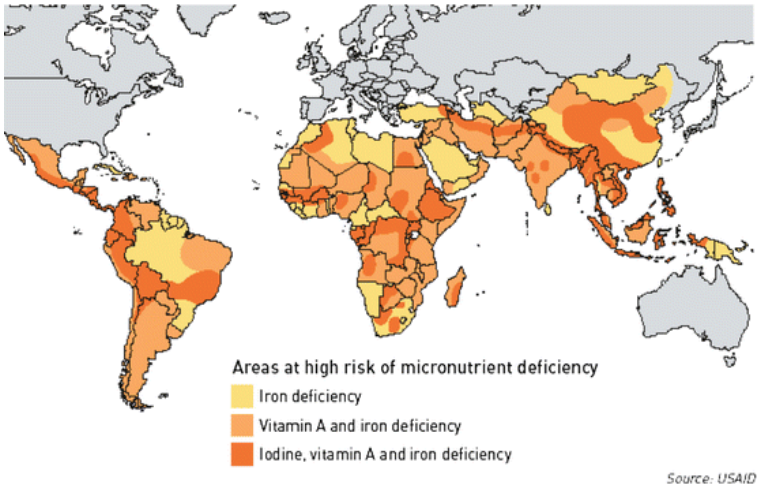
Background

Why do we need to know about MN deficiencies



Prevalence of retinol deficiency

- Micronutrient deficiencies are extremely common worldwide and a significant public health problem
- ~12% of deaths <5y are attributed to deficiencies in **iron**, **iodine**, **retinol** or **zinc**

Ramakrishna J et al. 10.1007/978-1-4614-7918-5_23
Ahmed T et al. Ann Nutr Metab. 2012;61 Suppl 1:8-17.

MN deficiencies are common in our patient population

Table 2. Disease specific vitamins and in trace elements deficiencies.

	Disease	Micronutrients at Risk
→	Alcoholism	Zn Vitamins A, D, E, K, B12, B9, B6, B1, B2, C
→	Anemia	Fe, Cu, Co Vitamins B12, B9
	Cardiomyopathies/ Heart failure	Se, Fe Vitamin B1, D [?]
→	Inflammatory bowel diseases	Se, Zn Vitamins B12, A, D, E, K
→	Liver diseases	Se, Zn Vitamins B12, A, D, E
→	Obesity and Bariatric surgery	Cu, Zn, Fe Vitamins A, D, E, K, B1, B9, B12, C
	Kidney diseases (chronic & acute)	Chronic: Vitamins K, D Acute: B1, Fe, Se, Zn, Cu

[?]: means uncertainty as to deficiency.

Berger MM et al. J Clin Med. 2019 Jun 28;8(7):931.

MN deficiencies are common in IBD patients

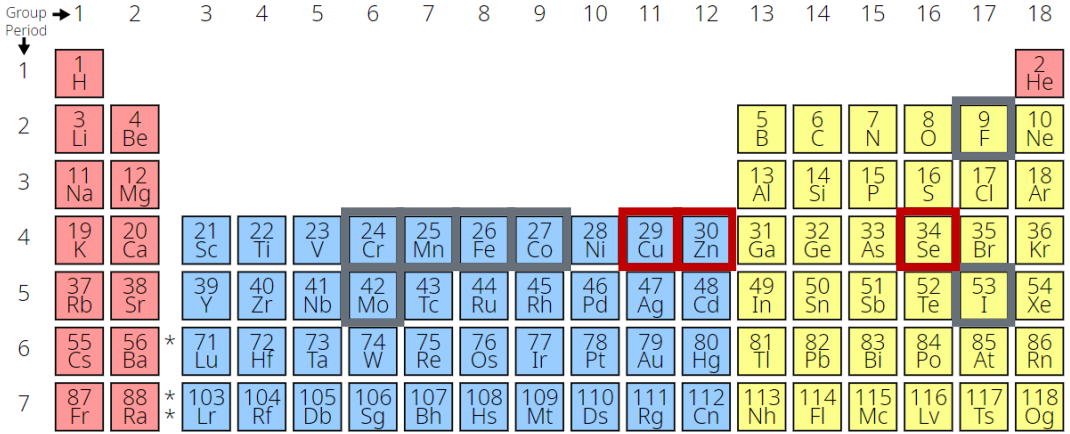
Laboratory evidence of nutritional deficiencies reported in adults with inflammatory bowel disease

Deficiencies	Percent
Common	
Anemia	60 to 80
Iron deficiency	39 to 81
Vitamin D deficiency	75
Vitamin B12 deficiency*	20 to 60
Zinc deficiency	40 to 50

Similarly high rates in CeD, SBS, bariatric patients

Source: Uptodate

Micronutrients – Trace elements



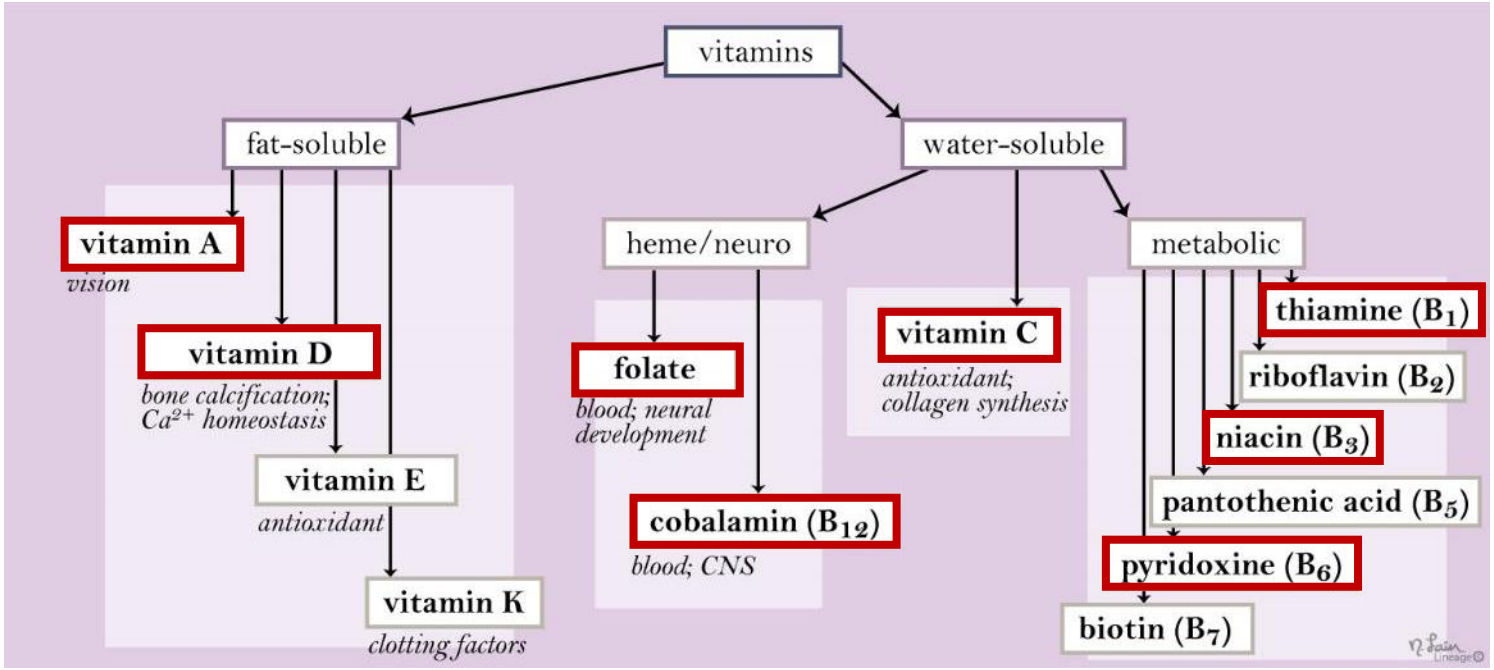
We will cover

- Copper
- Selenium
- Zinc

We will not cover

- Iron → Important, but everyone knows a lot about iron
- Cobalt → Covered in Vitamin B12
- Fluoride/Iodine → More a public health issue
- Cr/Mo/Mn → Relatively uncommon

Micronutriens – Vitamins



Deficiencies of B_2, B_5, B_7 and E are rare (in CH) and will not be covered

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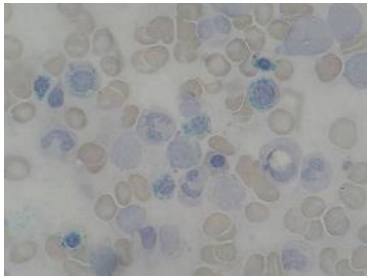
Trace elements

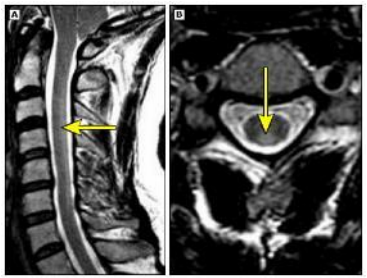
- Copper
- Selenium
- Zinc

Copper

Function	Cofactor in redox reaction, multiple cupro-enzymes
Absorption	Mainly stomach and duodenum
Assay	Serum copper
At risk	Burns, bariatric surgery, **jejunal tubes**, CeD, excessive Zn intake (competition)
Deficiency	**Anemia, neutropenia**, hair/skin depigmentation, delayed wound healing, **myeloneuropathy**, osteoporosis,

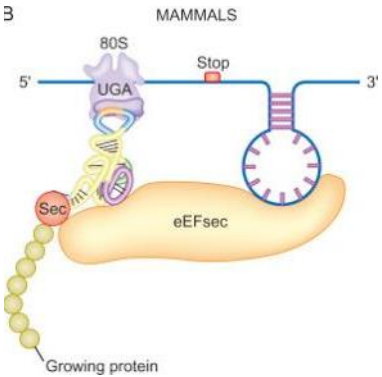


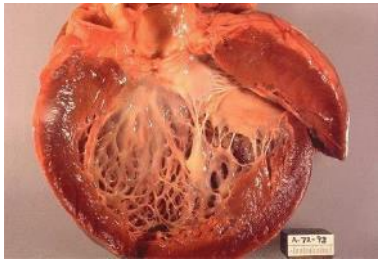
Ring sideroblast



Selenium

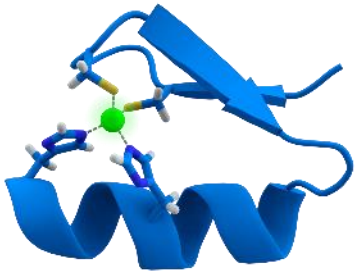
Function	Required for the synthesis of selenocysteine used in >30 **selenoproteins**. If cells lack selenium, these proteins are truncated and thus not functional
Absorption	Duodenum, colon
Assay	Plasma selenium
At risk	Geography-dependent (soil), long PN, bariatric surgery
Deficiency	**Keshan** cardiomyopathy (Coxsackie virus), impaired immunity to viral infections, myopathy, skin/nail effects

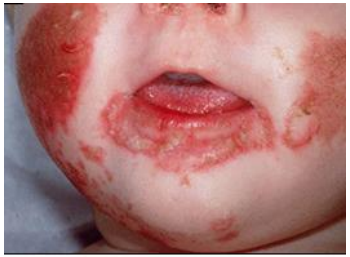




Zinc

Function	Part of >300 metalloenzymes (e.g. polymerases → growth and tissue repair)
Absorption	Jejunum, storage in muscle & bone
Assay	Plasma zinc
At risk	SBS, bariatric surgery, chronic pancreatitis, IBD, cirrhosis
Deficiency	Alopecia, **vesicular skin rash**, **impaired wound healing**, **immune deficiency**, growth impairment, diarrhea, impaired taste
Treatment	Zinc gluconate 15–30 mg/d





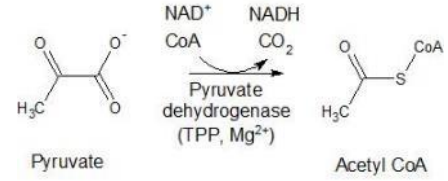
Acrodermatitis enteropathica

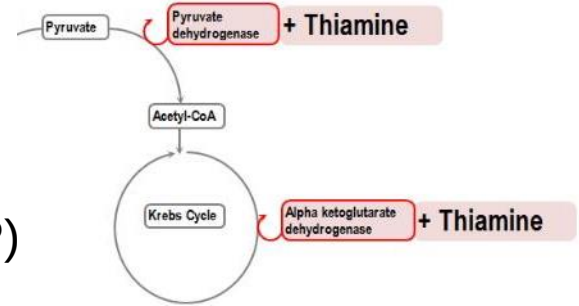
Water-soluble vitamins

- Thiamine (B_1)
- Niacin (B_3)
- Pyridoxin (B_6)
- Folate (B_9)
- Cobalamin (B_{12})
- Ascorbic acid (C)

Thiamine (B_1)

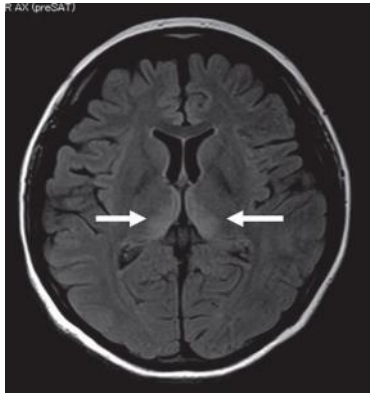
Function	Cofactor for enzymes for energy metabolism (ATP), synthesis of essential cellular molecules & nucleic acids. Highest needs of thiamine during **periods of high metabolic demand**
Absorption	Inhibited by alcohol consumption, storage highly limited (<20d)
Assay	Whole-blood thiamine diphosphate (ThDP)
At risk	Geographic, **alcoholism**, malnutrition (refeeding)



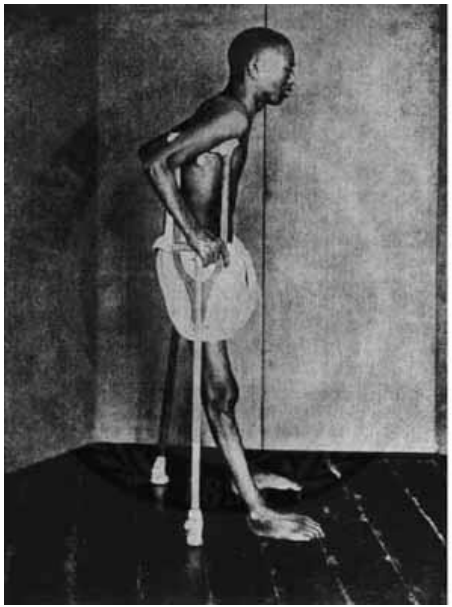


Thiamine deficiency – Wernicke encephalopathy

Presentation	Classic triad: **confusion**, **oculomotor dysfunction**, **gait ataxia** (only in 30%!)
Pathophysiology	Hemorrhagic necrosis in midline brain structures
Diagnosis	Clinical suspicion: symptoms, history
Management	Immediately give thiamine, whenever WE is a differential diagnosis
Prevention	WE can be triggered by glucose infusion in patients with unknown thiamine deficiency → **Always give thiamine before glucose in patients at risk**



Thiamine deficiency – Beriberi syndrome



Dry beriberi	Wet beriberi
• Peripheral neuropathy • Muscle weakness • Gait ataxia • Parasthesias • Wernicke's Encephalopathy	• High output heart failure • Heart hypertrophy especially of the right ventricle • Tachycardia or bradycardia • Dyspnea/ respiratory distress • Edema in lower extremities; oliguria • Lactic acidosis

Image: sciencephoto.com

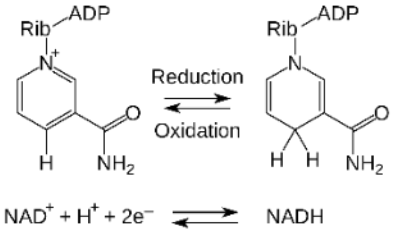
Thiamine substitution

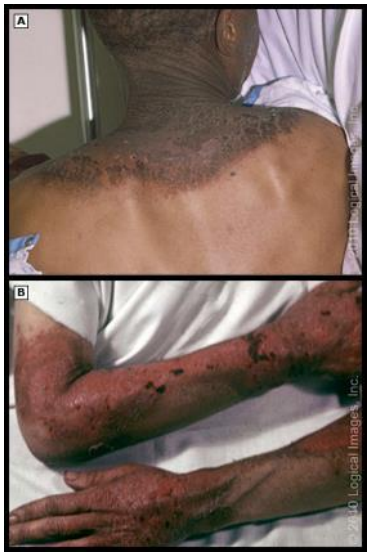
Table 8
Recommended thiamine treatment doses (adapted from [329,346,347]).

Clinical situation	Dose
Mild deficiency – outpatients	10 mg/day thiamin for a week, followed by 3–5 mg/daily for at least 6 weeks [348]
Chronic diuretic therapy	Suggestion: 50 mg a day, by mouth
→ At risk for deficiency	100 mg, 3 times a day, IV
High suspicion or proven deficiency	200 mg, 3 times a day, IV
Encephalopathy of uncertain etiology including Wernicke encephalopathy	500 mg, 3 times a day, IV [347]
Maintenance dose in proven deficiency	50–100 mg/day, orally
→ Refeeding syndrome	300 mg IV before initiating nutrition therapy, 200–300 mg IV daily for at least 3 more days
Continuous renal replacement therapy	100 mg/day
→ Hospitalized patients-critical illness	100–300 mg/day [345,349–351]

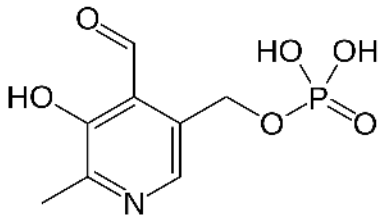
Niacin (B_3)

Function	Used for the coenzyme NAD (multiple roles!). Niacin can be synthesized from tryptophane
Assay	No reliable biomarker available
At risk	Malnutrition (e.g. corn-based diet), alcoholism, chronic diarrhea, carcinoid syndrome, chemotherapy
Deficiency	**Pellagra** (**D**ermatitis**, D**iarrhea**, D**ementia**)**
Toxicity	Flushing, hepatotoxicity





Pyridoxin (B_6)



Function	Used in the biologically active form pyridoxal phosphate (PLP). Coenzyme for >160 reactions (e.g. transamination)
Assay	Plasma PLP is a good biomarker
At risk	Alcoholism, dialysis, critical illness, alcoholic hepatitis, INH therapy
Deficiency	Seborrheic dermatitis, stomatitis, glossitis, anemia (relatively non-specific)

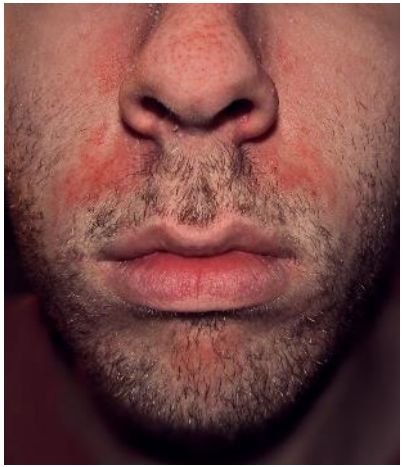
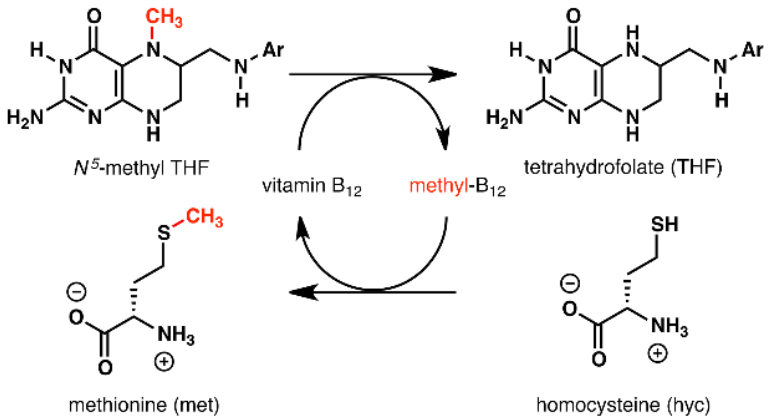


Image: Wikipedia

Folate (B_9)

Function	Required for DNA & RNA synthesis (purines), transfer of single-carbon groups
Absorption	Duodenum and jejunum
Deficiency	Similar in folate and B_{12} deficiency (will be discussed later)



Who is at risk for folate deficiency?

Table 9
Causes of Folate deficiency [471,473].

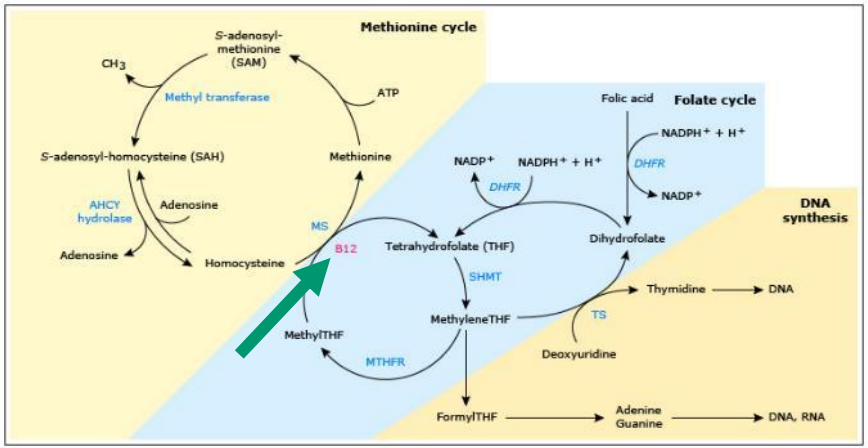
Cause	Example
Inadequate dietary intake	Alcohol abuse
	Poverty poor nutrition
Intestinal malabsorption	Inflammatory bowel disease
	Celiac disease
	Post-bariatric operations, post-gastrectomy
	Chronic intestinal failure
Increased needs	Physiological or pathophysiological states with high cell turnover:
	Pregnancy and lactation
	Inflammatory and neoplastic diseases
	Renal dialysis
	Increased hematopoiesis (e.g. chronic hemolytic anemia)
	Exfoliative dermatological conditions
Antifolate drug intake	Sulfasalazine
	Methotrexate
	Anticonvulsants
	Metformin
	Chemotherapy drugs

Assays for folate status

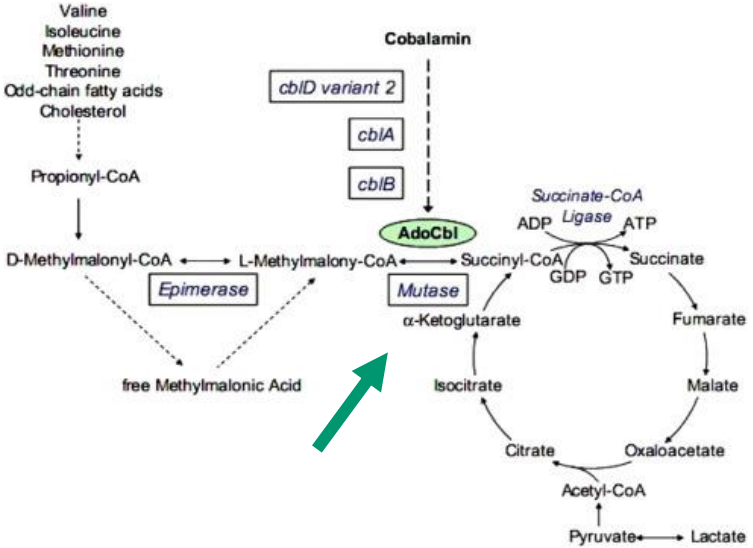
Serum/plasma folate	RBC folate	Plasma homocysteine
Reflects recent intake	Reflects status during the preceding 3 months	Elevated in folate deficiency (but also in B2, B6, B12 deficiency)

Cobalamin (B_{12}) – Function

DNA synthesis



AA / FA degradation



uptodate.com

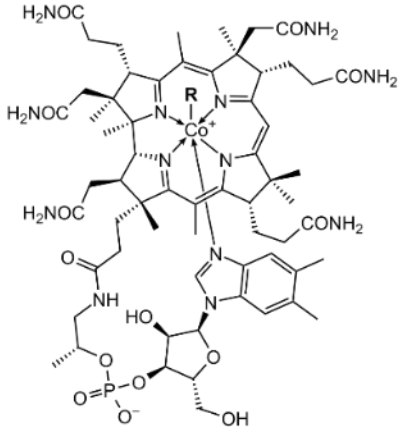
Ghoraba DA et al., Meta Gene. 2015;3:71-88.

Cobalamin (B_{12}) – Absorption

Absorption of this chemically complex molecule is not trivial

Interruption of any step can lead to deficiency

Storage ~1–3y



R = 5'-deoxyadenosyl, CH_3, OH, CN

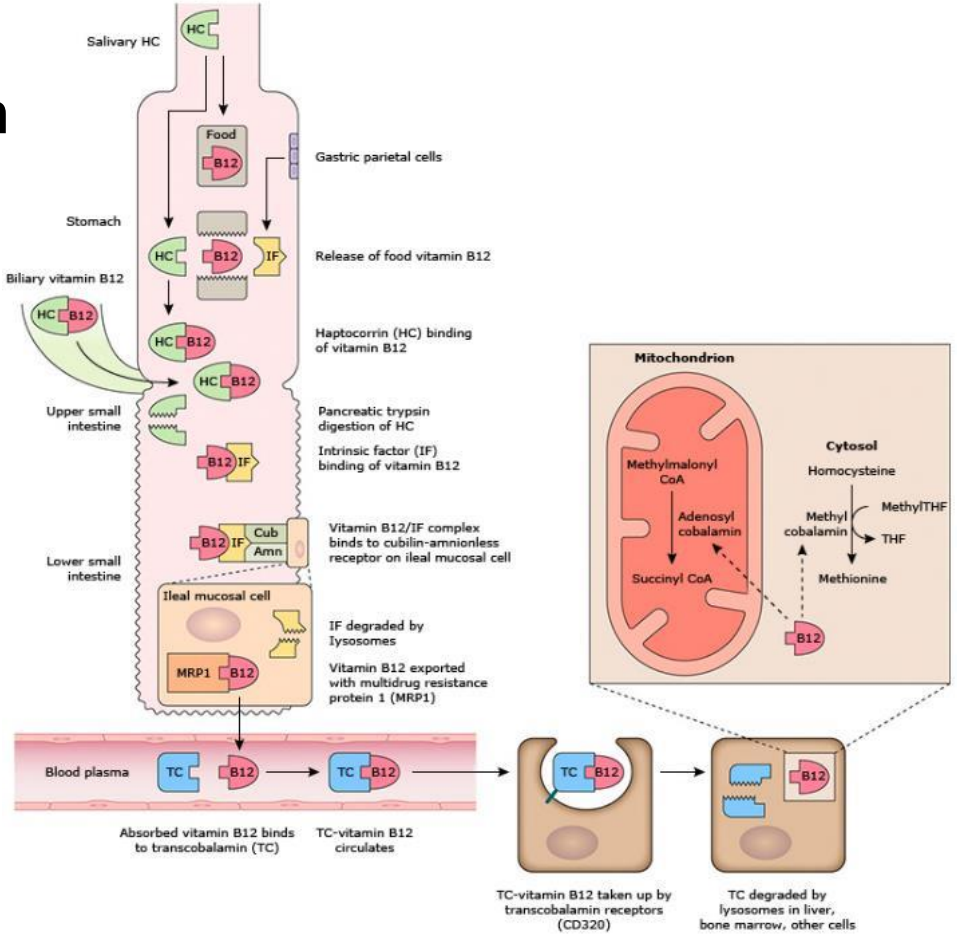


Image: uptodate.com

Causes of cobalamin deficiency

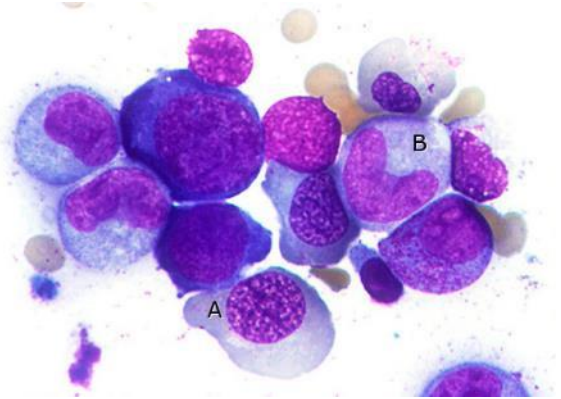
Table 12.1 The Causes of Vitamin B_{12} Deficiency

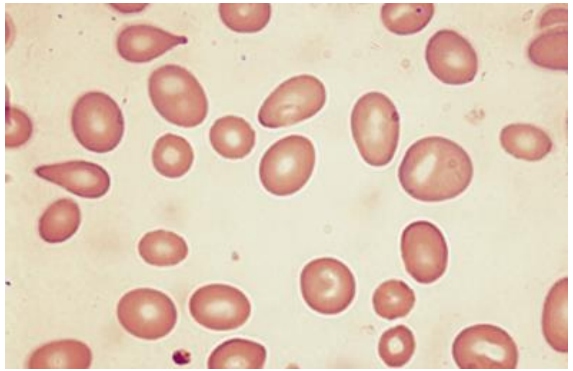
Deficit	Origin
Restricted intake	Malnutrition Reduced intake of food of animal origin Breastfed infants of vitamin B_{12} deficient mothers
Impaired gastric absorption	Atrophic gastritis with achlorhydria Gastrectomy Zollinger-Ellison syndrome
Loss or inactivity of intrinsic factor	Pernicious anemia
Pancreatic insufficiency	Insufficient trypsin to release of haptocorrin bound vitamin B_{12}
Impaired ileal absorption of vitamin B_{12}-intrinsic factor complex	Ileal resection Ileal disease, e.g., Crohn's Inflammatory bowel disease and tuberculous ileitis Tropical sprue Luminal disturbances: chronic pancreatic disease and gastrinoma Parasites: giardiasis, bacterial overgrowth, and fish tapeworm Blind loop syndrome
Increased requirement	Hemolysis HIV infection Pregnancy
Acquired	Alcohol *(impedes absorption as consequence of gastritis)* Nitrous oxide *(irreversibly binds to cobalt atom in vitamin B_{12} and deactivates it)* Proton pump inhibitors *(reduce gastric acid production)* H_2 receptor antagonists *(reduce gastric acid production)* Metformin *(impedes absorption)* Colchicine *(reduces IF-B12 receptors)* Slow K *(impedes absorption)* Cholestyramine *(decreases gastric absorption)*

Cobalamin deficiency

Table 10
Clinical symptoms of vitamin B12 deficiency [492,493,498,502–504].

	Clinical manifestation
Hematolgical (Same for folate deficiency)	Macrocytosis, Reticulocytosis Anaemia- pallor, fatigue, weakness, shortness of breath, tachycardia Thrombocytopenia, Leucopenia, Pancytopenia
Neurological	Peripheral neuropathy, paresthesia Sensory loss of extremities, Tingling, Numbness, Vertigo Demyelisation of corticospinal tract and dorsal columns- ataxia
Neuropsychiatric	Irritability, Mood-disorders/mood-swings, Psychosis, Depression
Cognitive	Confusion, Memory impairment, Cognitive decline, Dementia
non-specific	Glossitis, Malaise, Fatigue, Weakness





Relatively high prevalence (10–30%)

Images: uptodate.com

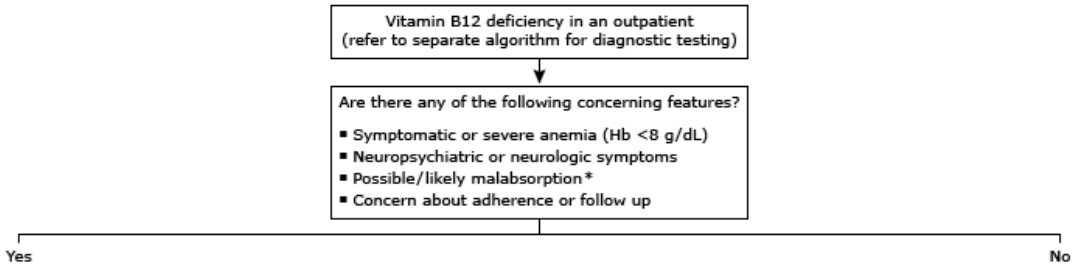
Assays for cobalamin status

Serum cobalamin	Holo-TC	Methylmalonic acid (MMA)
Total levels	Biologically active fraction	Elevated in B12 deficiency

No clear gold standard, both can be performed

2nd line assay
(not performed in-house)

Cobalamin substitution



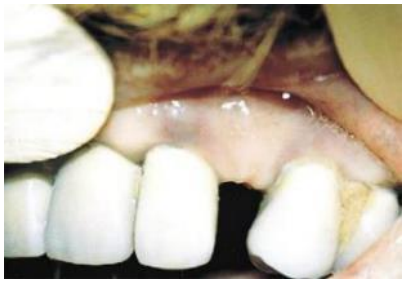
always i.m./i.v.

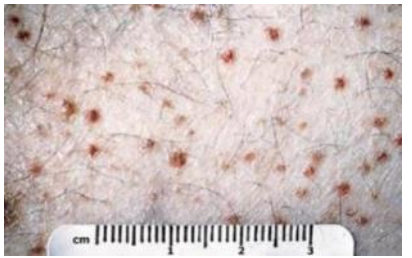
Oral supplementation possible

Source: uptodate.com

Ascorbic acid (Vitamin C)

Functions	Electron donation, radical scavenger Cofactor for: neurotransmitters, prostaglandins, peptide hormones, collagen
Absorption	Distal small intestine
Assay	Plasma AA (light sensitive!)
At risk	Sepsis, burns, trauma, bariatric surgery, alcoholism
Deficiency	**Scurvy** (weakness, gum disease, myalgias, skin changes, mood changes)
Treatment	1g/d AA for at least one week





perifollicular hyperkeratotic papules

Fat-soluble vitamins

- Vitamin A
- Vitamin D

Vitamin A – Functions

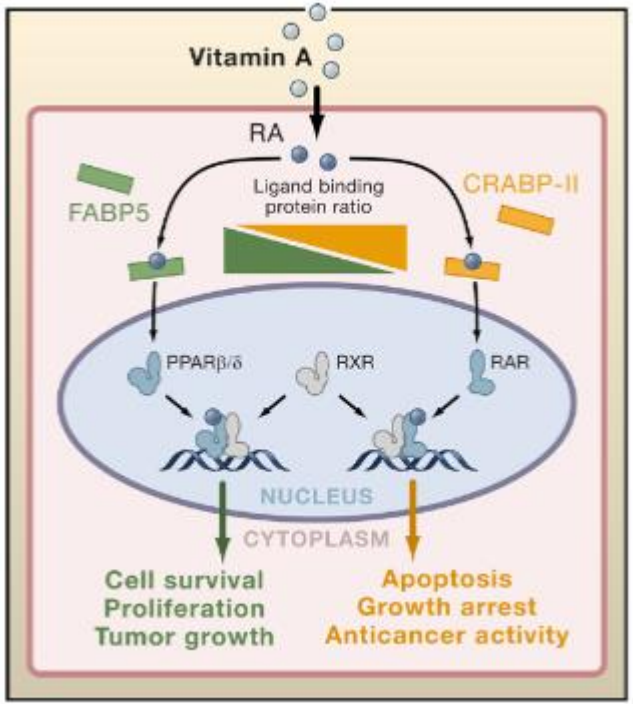
Retinal

Essential factor in rod cells and cone cells (eye)

Retinoic acid

Hormone that regulates >500 genes, particularly: immunity

Nuclear Receptors: RAR, RXR, PPAR-γ

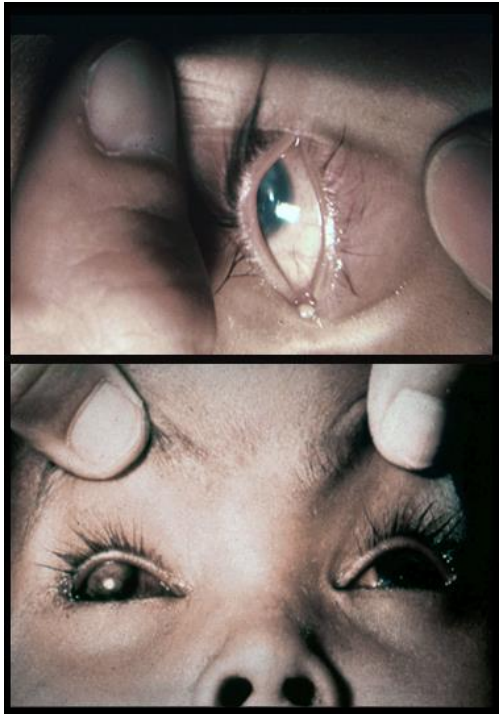


Michalik L, Wahli W. Cell. 2007 May 18;129(4):649-51.

Vitamin A deficiency (VAD)

Liver storage last for ~6 months

At risk patients	Liver disease, alcoholism, SBS, CD
Presentation	Night blindness, Bitot spots, xerophtalmia, skin problems
Treatment	3300–3500 IU per day Beware: toxicity

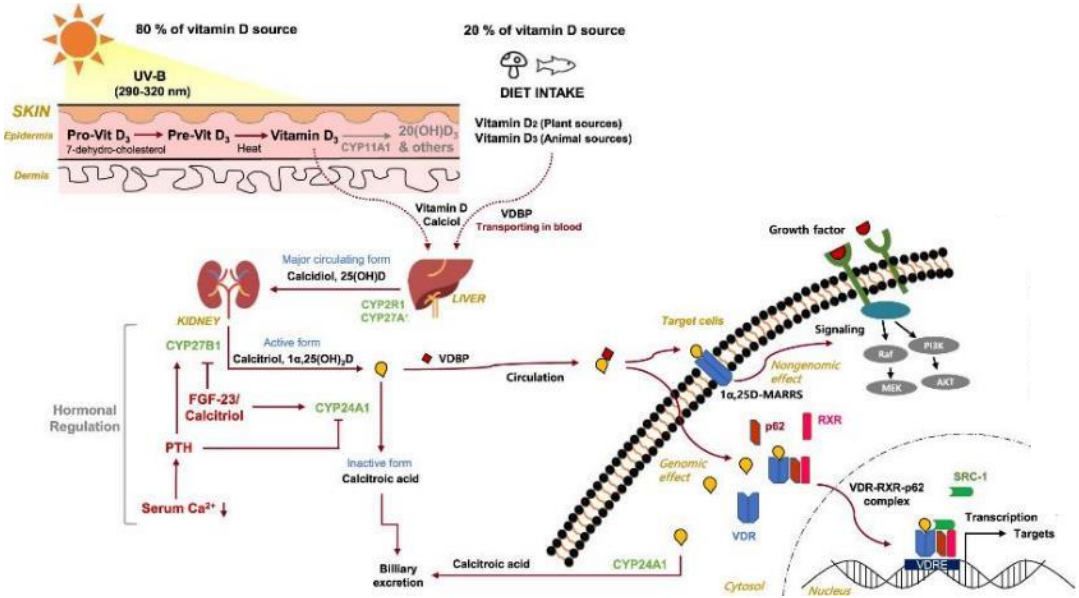


Cornea xerosis

Vitamin D – Functions

Vitamin D is not a classic vitamin but a steroid hormone precursor

3% of the mouse or human genome is regulated by VDR



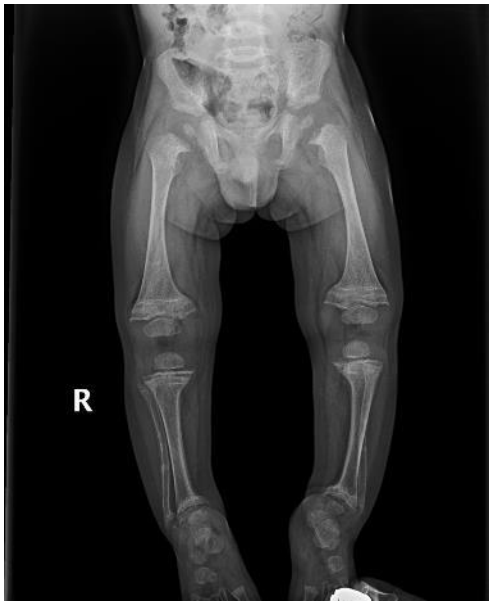
Roles in

- Bone homeostasis
- Muscle function
- Cancer
- Immunity

Jeon SM, Shin EA. Exp Mol Med. 2018;50(4):1-14.

Vitamin D – Deficiency and treatment

Requirement	600–800 IU/d, more in patients at risk (upper limit 10000 IU)
Prevalence	Vitamin D deficiency (<50 nmol/L) in 40% of Europeans
Biomarkers	25-OHD
Treatment	Physiological complementation or high-dose regimen (50000 IU; evidence low)



Rickets

Source: Radiopaedia

General remarks and synopsis

General remarks on assays of MN

Many of our patients with MN deficiency have some degree of inflammation (i.e. CRP >20 mg/L)

Decreased in inflammation:
- Selenium, Zinc
- Pyridoxin (PLP), Vitamin C
- Vitamin A, Vitamin D

Increased in inflammation
- Copper, Ferritin
- Cobalamin

Unaffected by inflammation:
- Thiamine (ThDP), Folate

INSELGRUPPE

Prevention of MN deficiencies

"Something from the supplement cart?"

Zusammensetzung

Vitamine	Pro Brausetablette	In %*
Vitamin B1	3,3 mg	300%
Vitamin B2	4 mg	286%
Vitamin B6	4 mg	286%
Vitamin B12	3 µg	120%
Vitamin C	180 mg	225%
Vitamin D	5 µg	100%
Vitamin E	12 mg	100%
Vitamin K	20 µg	27%
Biotin	145 µg	290%
Folsäure	430 µg	215%
Niacin	45 mg	281%
Pantothensäure	17 mg	283%

Mineralstoffe

Eisen	8 mg	57%
Calcium	120 mg	15%
Jod	150 µg	100%
Kupfer	1 mg	100%
Magnesium	80 mg	21%
Mangan	500 µg	25%
Molybdän	50 µg	100%
Selen	55 µg	100%
Zink	4,4 mg	44%

Indication

- Patients at risk for malnutrition

Beware

- Multivitamin preparations usually contain little thiamin, Fe, Zn, B_{12}
- These need to be supplemented separately

Conclusion

- MN deficiencies common in the global south, but also in our patient populations (chronic inflammation, malabsorption, bariatric surgery, alcoholism)
- Some MN deficiencies are easy to detect (e.g. iron),
  some require high index of suspicion (e.g. niacin)
- Plasma concentrations of most MN depends on inflammation
  → always check CRP and interpret accordingly
- Many MN deficiencies can be prevented by supplementing multivitamin preparations in patients at risk
- Some MN deficiencies require separate supplementation (e.g. Zn, Fe, B_{12})

INSELGRUPPE

Multiple-choice questions

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Multiple choice question 1

A 37 year-old man presents to your clinic for further workup of sudden onset of secretory diarrhea with ten to twelve watery bowel movements day and night. With a job as an executive, he finds himself increasingly fatigued, with occasional lapses in focus and confusion; he finds he is unable to follow conversations. Current medications are ibuprofen 400mg as needed for joint pain of headaches. His past medical, social and family history are negative. On physical exam he appears dehydrated and with normal vital signs. Physical exam is remarkable for two light purple, macular and scaling lesions on his forehead and left forearm. You order a stool culture and osmolytes; C. diff. PCD; ova and parasites, and stool stain; sedimentation rate; CRP; CBC; comprehensive metabolic panel; and 24h urine collection.

Which additional test would support your suspicion?

A. Niacin
B. Thiamine
C. Riboflavin
D. Pyridoxine
E. Folic acid

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Multiple choice question 1

A 37 year-old man presents to your clinic for further workup of sudden onset of secretory **diarrhea** with ten to twelve watery bowel movements day and night. With a job as an executive, he finds himself increasingly fatigued, with occasional lapses in focus and **confusion**; he finds he is unable to follow conversations. Current medications are ibuprofen 400mg as needed for joint pain of headaches. His past medical, social and family history are negative. On physical exam he appears dehydrated and with normal vital signs. Physical exam is remarkable for two light purple, **macular and scaling lesions** on his forehead and left forearm. You order a stool culture and osmolytes; C. diff. PCD; ova and parasites, and stool stain; sedimentation rate; CRP; CBC; comprehensive metabolic panel; and 24h urine collection.

Which additional test would support your suspicion?

A. Niacin → Pellagra
B. Thiamine
C. Riboflavin
D. Pyridoxine
E. Folic acid

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Multiple choice question 2

Chronic use of which of these medications can potentially contribute to Vitamin B_{12} deficiency?

A. Cholestyramine
B. Sulfasalazine
C. Omeprazole
D. Penicillamine
E. Isoniazid

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Multiple choice question 2

Chronic use of which of these medications can potentially contribute to Vitamin B_{12} deficiency?

A. (Cholestyramine) → Questionable
~~B. Sulfasalazine~~ → Folate
C. Omeprazole
~~D. Penicillamine~~ → Zinc
~~E. Isoniazid~~ → Pyridoxin (B_6)

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Multiple choice question 3

A 29-year-old woman with fistulizing Crohn's disease who had multiple resections of small bowel in the past has been on total parenteral nutrition (TPN) for the last 2 months. She continues to have watery diarrhea and some discharge from an enterocutaneous fistula despite not taking anything by mouth. She presented to your clinic and complains of impaired taste, hair loss, skin rash and difficult vision at night in the last 2 weeks. In the physical exam you note several erythematous and vesicular lesions on her elbows and hands. Basic blood tests are as follows:

WBC	9000/uL
Hb	110 g/L
MCV	88 fL
Electrolytes	normal
Albumin	32 g/L

What would be your next step in the management of her recent manifestations?

A. Check plasma zinc level
B. Empiric zinc supplementation
C. Check blood niacin level
D. Empiric niacin supplementation
E. Empiric copper supplementation

Multiple choice question 3

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WBC	9000/uL
Hb	110 g/L
MCV	88 fL
Electrolytes	normal
Albumin	32 g/L

What would be your next step in the management of her recent manifestations?

~~A. Check plasma zinc level~~ → unreliable in inflammation

B. Empiric zinc supplementation

~~C. Check blood niacin level~~ → No good assay

~~D. Empiric niacin supplementation~~ → Rare in CD

~~E. Empiric copper supplementation~~ → Good idea, but 1) rare in CD 2) no hematologic abnormalities present

Multiple choice question 4

A 62-year-old man presents to your office 3 months after Roux-en-Y gastric bypass. He is brought in by his wife, who has to help him transfer from the care and the waiting room because he is having trouble walking. He appears sluggish and does not participate in the conversation. She relates that ever since discharge from his surgery he has been vomiting nearly every day, and over the past couple of weeks he has become more sluggish, more forgetful, and has begun to act bizarrely (e.g., putting his shoes in the freezer). He has not been taking any of his prescribed medications. On physical exam, you note nystagmus.

In addition to IV fluids, which of the following is the most appropriate management?

A. Urgent CT scan of head
B. Upper endoscopy
C. IV chromium
D. IV thiamine
E. IV selenium

Multiple choice question 4

A 62-year-old man presents to your office 3 months after Roux-en-Y gastric **bypass**. He is brought in by his wife, who has to help him transfer from the care and the waiting room because he is having **trouble walking**. He appears sluggish and does not participate in the conversation. She relates that ever since discharge from his surgery he has been vomiting nearly every day, and over the past couple of weeks he has become more sluggish, more forgetful, and has begun to **act bizarrely** (e.g., putting his shoes in the freezer). He has not been taking any of his prescribed medications. On physical exam, you note **nystagmus**.

In addition to IV fluids, which of the following is the most appropriate management?

A. Urgent CT scan of head
B. Upper endoscopy
C. IV chromium
D. IV thiamine → Wernicke encephalopathy
E. IV selenium