PERNICIOUS ANEMIA

TERM DEFINITION

Autoimmune-mediated destruction of gastric parietal cells, leading to atrophic gastritis, reduced production of intrinsic factor, decreased vitamin B12 absorption, ineffective erythropoiesis (i.e., anemia and other cytopenias), and/or defective myelin synthesis (i.e., neuropathy).

VITAMIN B12*

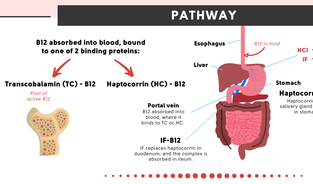
ABSORPTION

- **A water-soluble vitamin**
- **Restricted to food of animal origin**
- **Absorption depends on:**
  - Gastric acid pH
  - Binding to intrinsic factor
- **1%-5% absorbed passively**

FUNCTION

- **Cofactor for only 2 enzymes:**
  - Methionine synthase
  - L-methylmalonyl-coenzyme A mutase
- **Necessary for:**
  - DNA/RNA synthesis
  - Myelination of CNS

PATHWAY



Upon ingestion, vitamin B12 (B12) is released from food and bound to salivary haptocorrin (HC), which protects B12 from stomach acid (HCl) as it is transported to the small intestine. In the upper small intestine, HC is degraded by intestinal enzymes, thereby allowing B12 to associate with intrinsic factor (IF) produced by gastric parietal cells. In the ileum, B12-IF complex then binds to a specific receptor known as cubam on the ileal mucosa and is internalized; B12 is subsequently released into circulation. After absorption, B12 is released to the portal blood and is bound to either transcobalamin (TC) or HC (previously referred to as transcobalamin I, transcobalamin III or R-binder).

** The terms vitamin B12 and cobalamin are generally used interchangeably.*

CLINICAL PEARLS

Pernicious anemia is synonymous with chronic atrophic gastritis and is associated with increased risk of gastric cancer.

Severity of neurological findings inversely correlates with severity of blood findings.

About 1% of B12 absorption occurs passively without need for intrinsic factor = rationale for oral B12 therapy.

DIAGNOSIS

CONSIDER

Consider the diagnosis in a patient with:

- Macrocytic anemia
- Neurological findings suggesting demyelination
- Low vitamin B12 levels
  - Standard cutoff < 200 ng/L
- Elevated methylmalonic acid levels

CONFIRM

Confirm the diagnosis in a patient with:

- Presence of anti-intrinsic factor (though not 100% sensitive)
- Diagnosis of chronic atrophic gastritis, including histology and anti-parietal cell antibodies

OTHER FINDINGS

Other findings consistent with vitamin B12 deficiency:

- CBC - cytopenias
- Peripheral smear, showing presence of:
  - Macro-ovalocytes
  - Fragmented red cells (in severe cases)
  - Hypersegmented neutrophils
- Hemolytic indices

PARAMETER	ANTI-IF ANTIBODIES	ANTI-PARIETAL CELL ANTIBODIES
Antibody target	Intrinsic factor	Gastric enzyme H^+/K^+ ATPase on gastric parietal cells
Sensitivity	40%-60%	80%-90%, especially during early stages of disease
Specificity	98%-99%	About 80%

DIFFERENTIAL DIAGNOSIS
of Vitamin B12 Deficiency

- **Impaired gastrointestinal absorption of vitamin B12:**
  - Atrophic gastritis (pernicious anemia)
  - Gastrectomy (deficiency in intrinsic factor, hypo- or achlorhydria)
  - Bariatric surgery (hypo- or achlorhydria)
  - Helicobacter pylori gastritis (hypo- or achlorhydria)
  - Long-term proton pump inhibitor therapy (hypo- or achlorhydria)
  - Intestinal causes of impaired absorption:
    - Blind loop syndrome
    - Ileal disease or resection
    - Fish tapeworm from eating uncooked fish
  - Pancreatic insufficiency (lack of vitamin B12 release from haptocorrin complex due to inadequate pancreatic enzyme activity)
- **Decreased intake of vitamin B12:**
  - Malnutrition
  - Vegan diet (About 50% of vegans have B12 deficiency)
  - Vegetarian diet (About 7% have B12 deficiency)
  - Infants - breastfeeding in infants with vitamin B12-deficient mothers
- **Inherited causes** of defective vitamin B12 absorption or metabolism
- **Increased demands** (pregnancy)

TREATMENT

TREATMENT PRINCIPLES

- **Replace vitamin B12**
- **2 phases:**
  - Initial
  - Maintenance
- **Treat lifelong**
- **Multiple routes:**
  - Oral
  - Intramuscular
  - Intranasal
  - Sublingual

TREATMENT PROTOCOLS

Treatment protocols vary — one example:

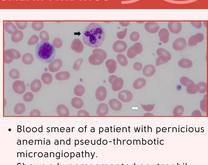
- 1,000 mcg IM/day or every other day for 1 week
- 1,000 mcg IM weekly injections up to 8 weeks
- 1,000 mcg IM every 3-4 weeks or 1,000-2,000 mcg/day orally (maintenance)

ROUTE	ADVANTAGES	DISADVANTAGES	COMMENTS
Parenteral vitamin B12	Avoids potential problems with compliance or absorption.	Requires visit to medical office.	Generally preferred as initial therapy in patients with significant neurologic symptoms.
Oral vitamin B12	May be as effective as parenteral vitamin B12 in patients with normal absorption; less painful and usually lower cost than injection.	May not be appropriate if absorption problematic.	High-dose tablets of 1,000 mcg expected to deliver about 5-40 mcg of vitamin B12 assuming oral dose absorption rate of 0.5-4%.
Intranasal vitamin B12	Easy to use.	N/A	Initial dose: 1 spray (500 mcg) in 1 nostril once weekly; administer ≥ 1 hour before or ≥ 1 hour after ingestion of hot foods or liquids.

PROXIMATE MECHANISMS

- Autoimmune destruction of parietal cells in the stomach.
- Parietal cell antibodies target the gastric enzyme H^+/K^+-ATPase proton pump in parietal cells.
- Loss of intrinsic factor leads to reduced vitamin B12 absorption in the terminal ileum.

PERIPHERAL SMEAR FINDINGS



- Blood smear of a patient with pernicious anemia and pseudo-thrombotic microangiopathy.
- Shows a hypersegmented neutrophil (black arrow) and a schistocyte (white arrow).
- This picture is consistent with severe vitamin B12 deficiency.

HISTORY OF MEDICINE

- **1800-1875:** Cases of probable pernicous anemia (PA) reported.
- **1880:** Paul Ehrlich invented staining of blood and identified megaloblasts in blood in PA.
- **1887:** Association between PA and spinal cord lesions was described
- **1921:** Megaloblasts noted in the bone marrow in PA.
- **1923:** Hyper-segmented neutrophils in peripheral blood in PA were described.
- **1923:** George Hoyt Whipple & George Richard Minot started a regimen that included 100–240 g of liver and beef muscle, and noted improvement in symptoms and increase in reticulocytes in some patients with PA.
- **1930:** William Castle shows that gastric juice contains an intrinsic factor that reacts with an extrinsic factor in beef muscle (which would be shown to be vitamin B12).
- **1934:** Nobel Prize in medicine and physiology was awarded to Whipple, Minot, and William Murphy.
- **1948:** Isolation of a red crystalline substance termed vitamin B12 and subsequently renamed cobalamin.

NOTES

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