

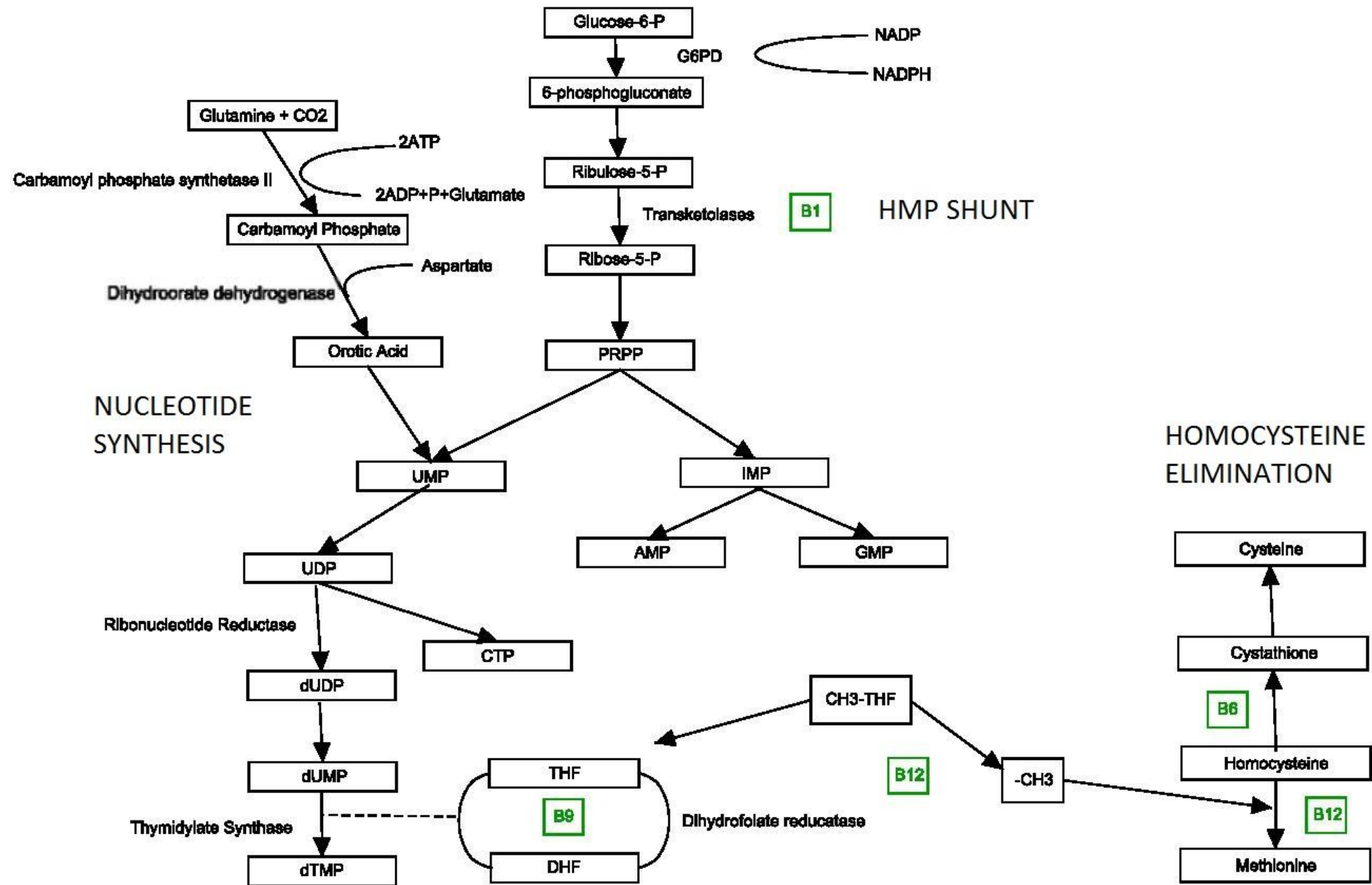
BIOCHEMISTRY PATHWAY SERIES FOR STEP ONE

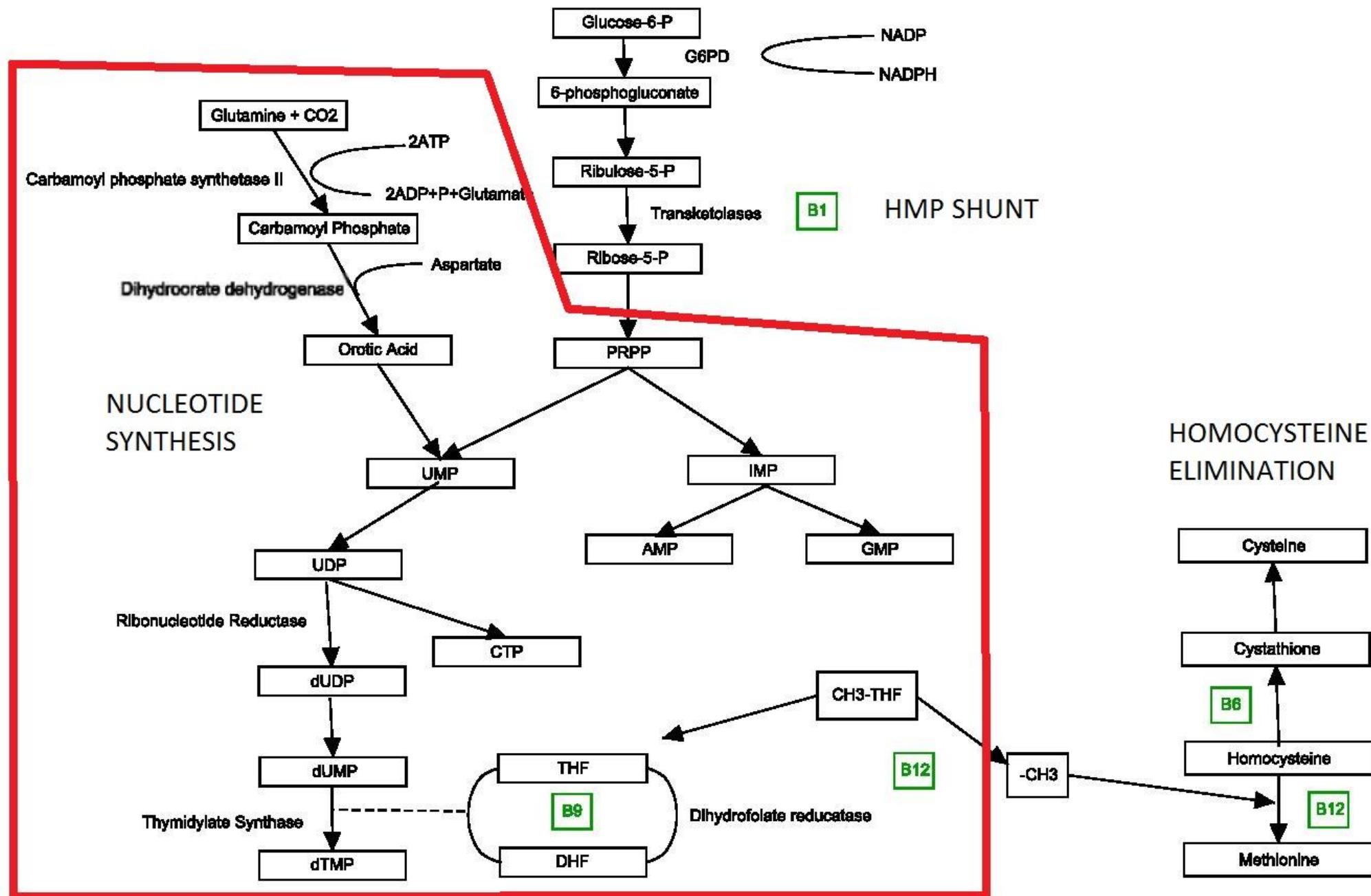
For each pathway:

- Where do we start?
- Where do we end?
- What are the goals of the pathway?
- What key enzymes will get us from start to end, and what do they need to function?
- Key disorders related to these pathways
- How do they all come together?

Nucleotide Synthesis

- **Start** with Glutamine, Aspartate, and CO₂ **end** with purines and pyrimidines
- **Goal** is to synthesize purines and pyrimidines to make DNA
- Key enzymes: UMP Synthase, Ribonucleotide Reductase
- Disorders: Hereditary orotic aciduria, Chemotherapy agents
- Fits into pathways for folate, B12, HMP shunt





Why target this pathway with drugs?

- This fundamental point of this pathway is to make DNA for cells that are replicating
- Targeting this pathway prevents cells that are replicating the most (and therefore need the most DNA) from doing to
- When do we want cells that are replicating rapidly to stop replicating?
 - 1) Cancer – tumor cells have rapid turnover
 - 2) Autoimmune conditions – stop WBC's that are attacking the body from replicating
 - 3) Bacteria

A note on patterns

You need nucleotides for DNA synthesis – no nucleotides, no DNA. The nucleus needs DNA in order to “mature” relative to cytoplasm.

What does this all mean? Regardless of how you do it (enzyme deficiency, vitamin deficiency, drugs, etc), if you can't make nucleotides properly, cells with high turnover will not mature properly – for red blood cells this means BIG CELLS, which shows up as increased mean corpuscular volume (MCV)

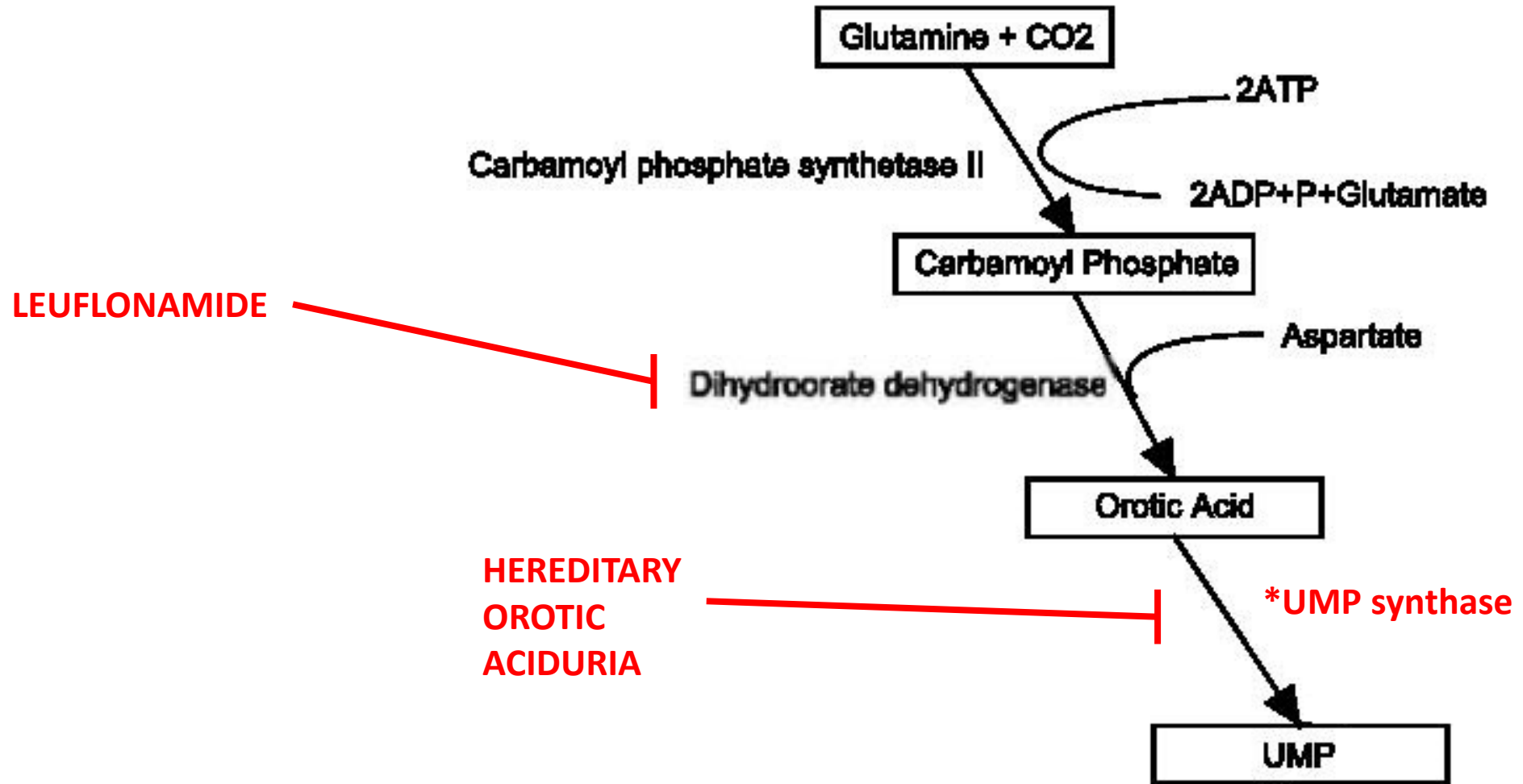
Moral of the story: messing up any part of this pathway will give you INCREASED MCV

BREAKING DOWN THE PATHWAY

When thinking about approaching this pathway, it is best to think about it in three parts: one gets you to **UMP** from amino acids, one makes **purines (A,G)**, and the last uses **UMP** to make **pyrimidines (C,T)**

Each part of the pathway is associated with different disorders, and is targeted by different drugs— this is how to think about this pathway for boards

Part 1: Making UMP



Reference: Leuflonamide

LEUFLOXAMIDE

Indications: Rheumatoid Arthritis

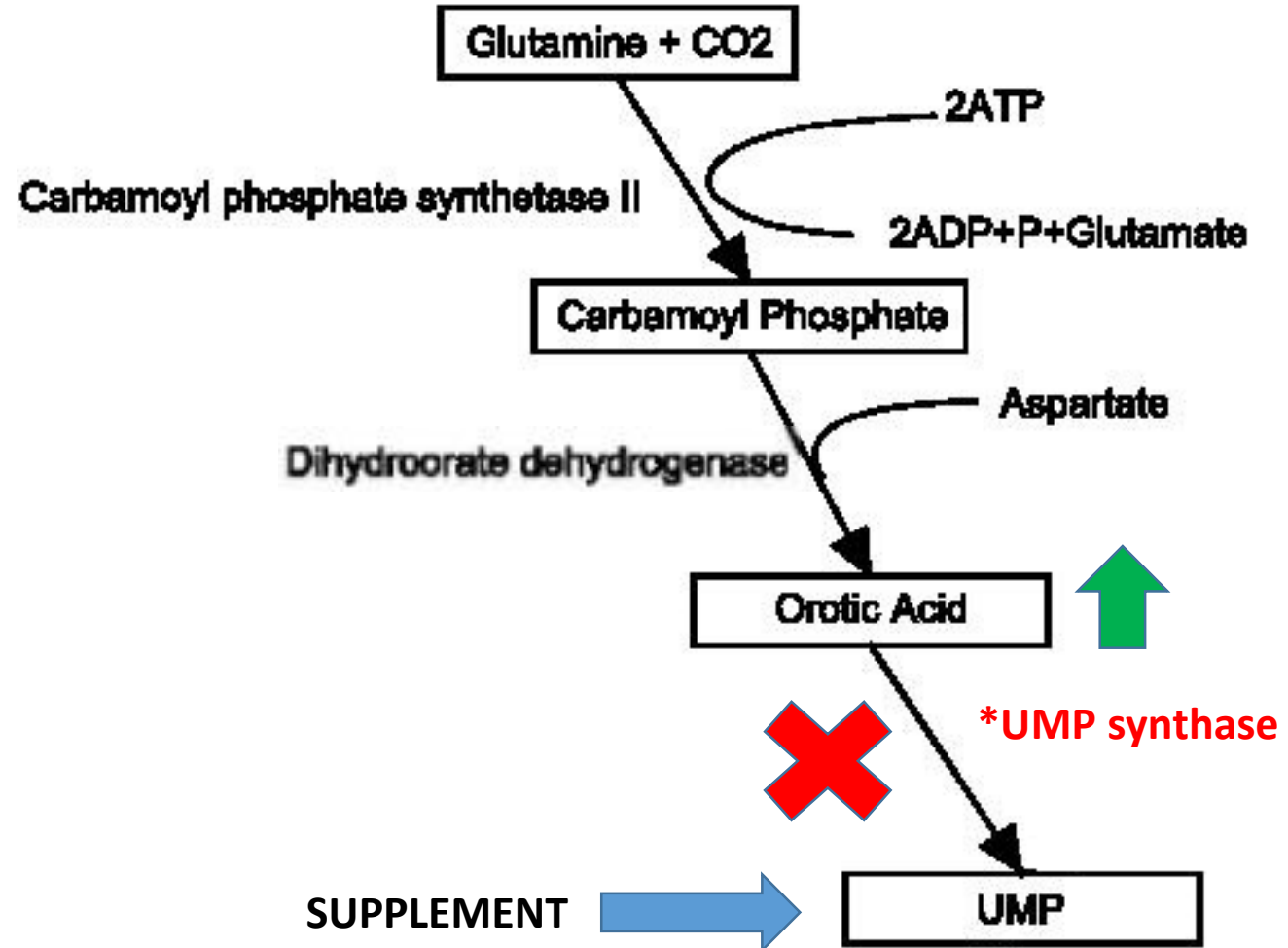
Adverse Effects: Liver damage, Lung disease, Immunosuppression

Hereditary Orotic Aciduria

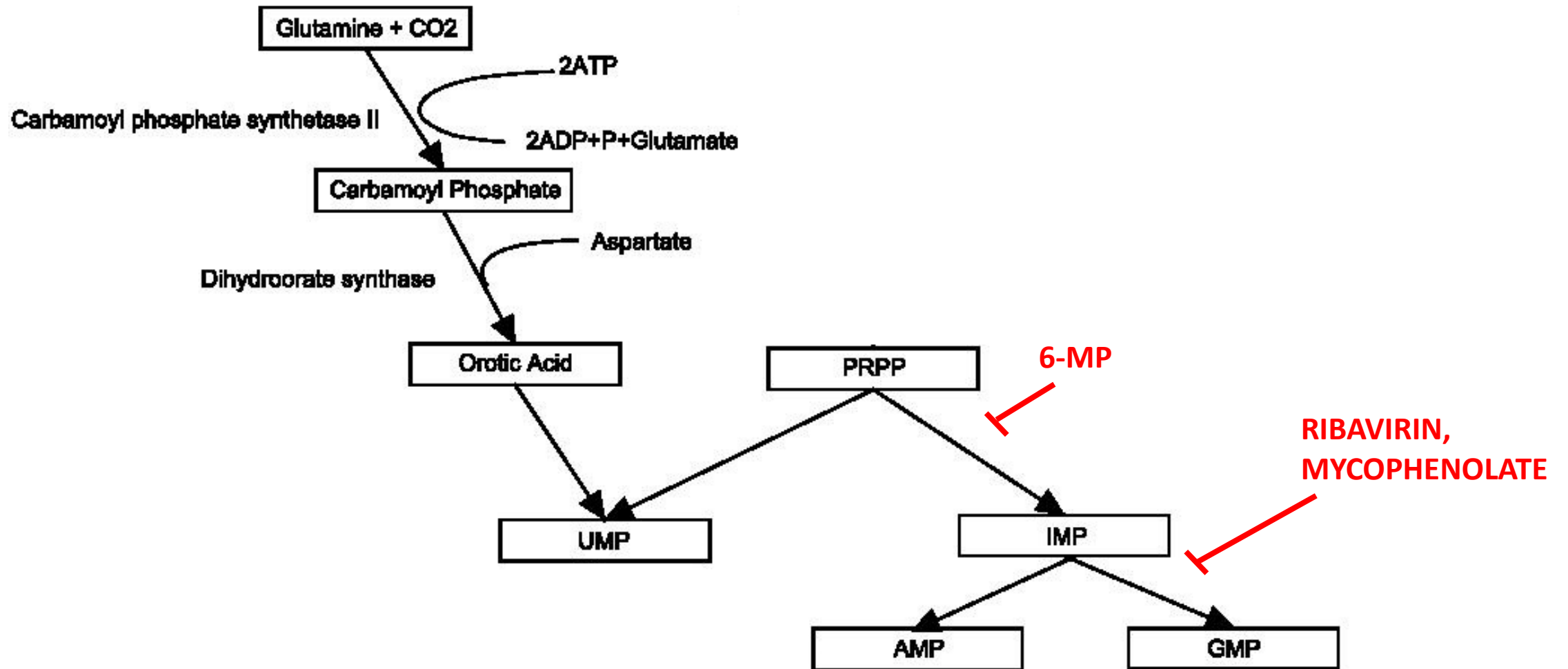
- Rare, autosomal recessive condition with a loss of function mutation in UMP Synthase (last step in UMP synthesis)
- Results in: Mental retardation, Developmental delay, **increased MCV**, and **excretion of high levels of orotic acid in the urine**
- Can be treated by giving uridine, bypassing the missing enzyme
- Will show up on boards as a child with failure to thrive, developmental delay and high levels of orotic acid in the urine
- Will usually ask about enzyme deficiency, or treatment

Hereditary Orotic Aciduria

- Infant or young child
- Failure to thrive
- Mental/physical developmental delay
- High orotic acid in urine



Part 2: Making Purines



Reference: Drugs targeting Purine Synthesis

6-MP

Indications: Acute Lymphocytic Leukemia, Chrons, Ulcerative Colitis

Adverse Effects: Diarrhea, N/V, hair loss

Ribavirin

Indications: Hep C, RSV

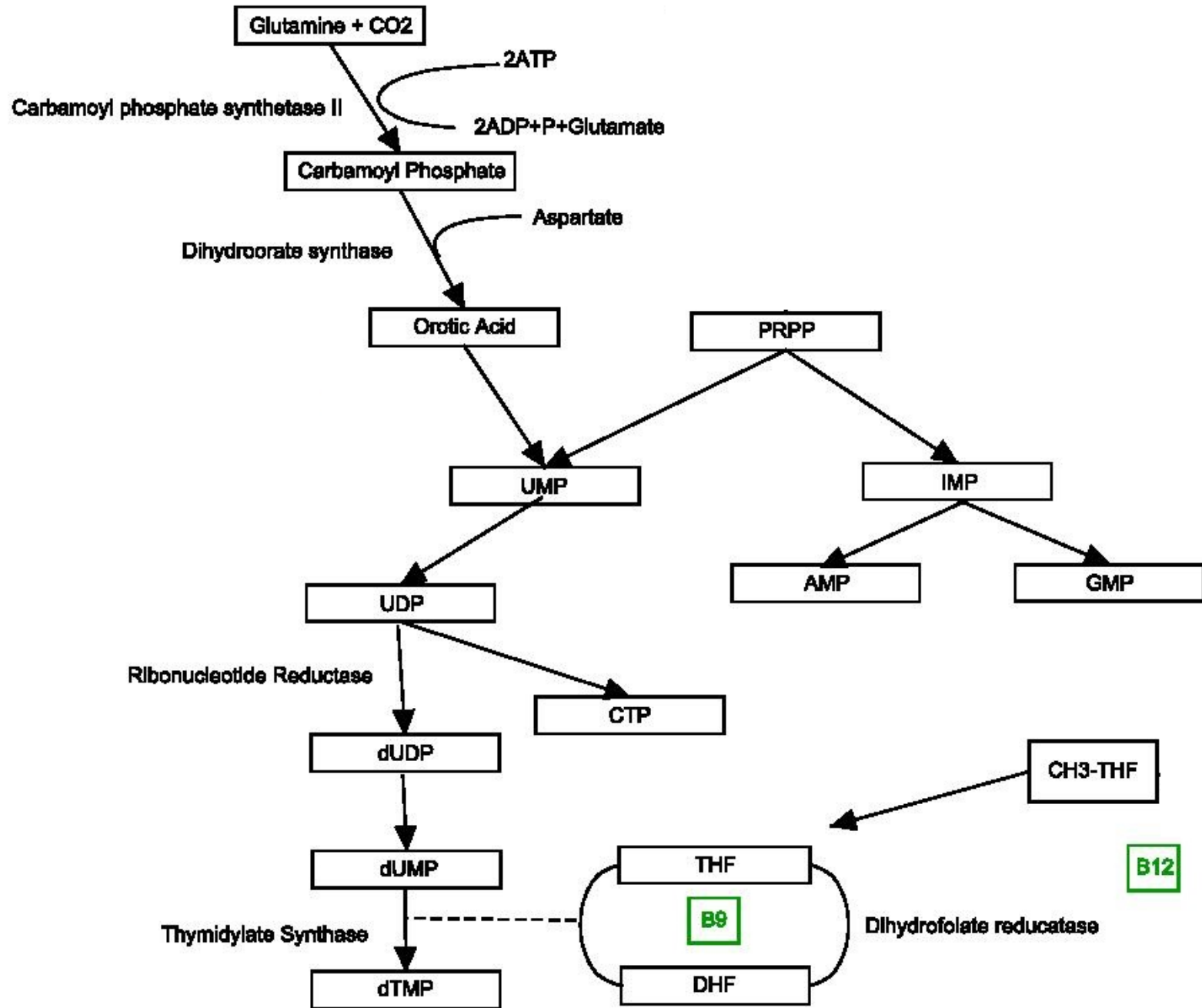
Adverse Effects: Hemolytic anemia, teratogenic

LEUFLONAMIDE

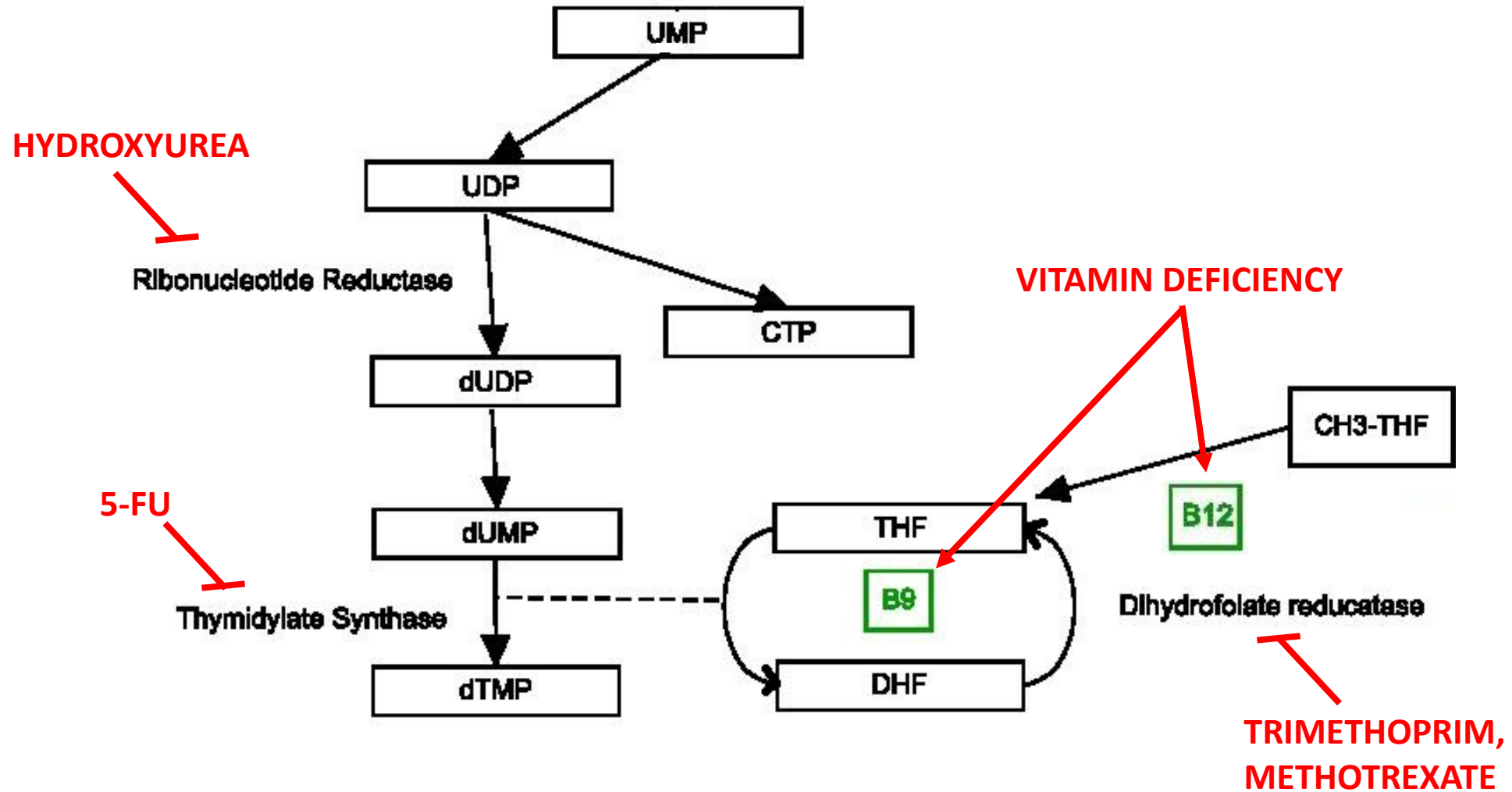
Indications: Prevention of organ transplant rejection

Adverse Effects: Diarrhea, N/V, Immunosuppression, pulmonary fibrosis (rare)

Part 3: Making Pyrimidines



Part 3: Making pyrimidines



Reference: Drugs targeting Pyrimidine Synthesis

Hydroxyurea

Indications: Melanoma, CML, sickle cell

Adverse Effects: Diarrhea, N/V, severe myelosuppression

Hydroxyurea

Indications: Colon cancer, pancreatic cancer, basal cell carcinoma

Adverse Effects: Myelosuppression

Trimethoprim

Indications: Antibiotic – used for UTI's, salmonella, shigella, pneumocystis pneumonia

Adverse Effects: Megaloblastic anemia, leukopenia, granulocytopenia

Methotrexate

Indications: Leukemias, lymphomas, sarcomas, ectopic pregnancy, medical abortion, RA, psoriasis, IBD, vasculitis

Adverse Effects: mouth ulcers, hepatotoxicity, mucositis, pulmonary fibrosis

B12 and Folate

