

# Anemia

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# Signs/Symptoms of Anemia

- Fatigue
- Low Hemoglobin/Hematocrit
  - Elderly often can feel normal despite levels below normal
  - WHO (men <14, women <12.3)
- Dizziness/Falls
- Skin pallor
- Weak
- Confusion

# Classic Causes of Anemia

- Blood loss
  - Anticoagulants, antiplatelets, NSAIDs
- Iron
- B12
- Folic Acid
- Chronic Disease (esp. CKD)
- Chemotherapy

# B12 Deficiency Causes

- PPI
- Metformin
- ETOH
- Intrinsic Factor - pernicious

# Drug Causes – Folic Acid Deficiency

- Methotrexate
- Trimethoprim
- Phenytoin

# Treatment of Anemia

- Transfusion
- ESA (i.e. darbepoetin)
- B12
- Iron
- Folic Acid
- No treatment (if asymptomatic)

# Mechanisms of Supplements

- Iron is a key component of hemoglobin, the protein that carries oxygen in red blood cells; with no iron, hemoglobin is not produced correctly, leading to red blood cells that are smaller and paler (microcytic, hypochromic)
- Vitamin B12 acts as a cofactor in DNA replication. Deficiency causes impaired nuclear maturation while cytoplasm continues to grow, producing large, immature red blood cells known as megaloblasts
- Folic acid is essential for DNA synthesis and cell division during red blood cell production; deficiency leads to defective DNA synthesis and megaloblastic anemia

# Megaloblastic Versus Microcytic

- B12/FA
  - Megaloblastic
  - MCV > 100
    - Homocysteine
    - MMA
- Iron
  - Microcytic
  - MCV < 80
  - Ferritin
- \*Elderly often present with mixed type of anemias and normal MCV

# Pernicious Anemia

- Lack of intrinsic factor
- Poor oral B12 absorption
- B12 toxicity rare
- B12 shots
  - For replacement, most will do 1,000 mcg weekly until deficiency is corrected and then do once monthly maintenance

# Vitamin B12 (Cyanocobalamin)

- Supplementation well tolerated
- Minimal to no risk of over supplementation
- A level of 300 pg/mL or greater is typically considered an adequate concentration
- Blood levels of homocysteine and methylmalonic acid in addition to B12 may be monitored
  - Elevations in homocysteine may indicate B12 or folic acid deficiency
  - Methylmalonic acid elevations may indicate B12 deficiency

# Folic Acid

- RDA – 400 mcg/day (for adults) – more for pregnant/breastfeeding
- Oral supplemental dose – 1-5 mg per day
- Minimal to no risk of over supplementation
- Common in alcohol use disorder
- Normal levels: > 4 ng/mL (9.1 nmol/L)

# Oral Iron

- Ferrous sulfate, gluconate, fumarate
- Constipation, stomach upset (dose and elemental iron content dependent), black stools
- Binding interactions can lower drug concentrations of levothyroxine, quinolones, and tetracycline antibiotics
- Vitamin C (acidic environment) may aid absorption
- PPIs, H2 blockers, and antacids may cause a reduction in iron absorption
- Target ferritin levels are not well defined and may vary based upon clinician experience and clinical response (100 ng/mL is considered adequate stores)
- Avoid dosing more than once per day; every other day dosing may have similar absorption with better tolerability

# IV Iron

- Indications
  - Patients who cannot tolerate oral
  - Gastric surgery or other patients who may have challenges absorbing oral iron
  - Severe and ongoing blood loss
  - Absorption/GI disorders that may impair absorption of oral iron preparations (i.e. celiac disease)
- Disadvantages
  - More upfront expense
  - Anaphylaxis/allergic reaction risk (less common now with newer preparations)
  - Iron dextran has highest risk of anaphylaxis reaction (requires test dose)
  - IV infusion

# ESA Pearls

- Erythropoietin Stimulating Agents (ESA's)
  - Epoetin alfa (Epogen), darbepoetin alfa (Aranesp)
  - Stimulates erythropoiesis by the same mechanism as the body's own erythropoietin
  - Boxed warning for cardiovascular events like stroke, MI, and blood clots (do not target hemoglobin levels higher than 11g/dL because of this risk in CKD)
  - Less frequent dosing with Aranesp, but may be more expensive
  - Injection only
- Iron supplementation is typically necessary with ESA use

# Acute Blood Loss

- Blood Transfusion (PRBC)– way to quickly raise hemoglobin
- Risks are rare but significant
  - Allergic reaction
  - Donor matching
  - Iron overload with too many infusions

# DVT/PE

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# Deep Vein Thrombosis

- Deep Vein Thrombosis (DVT) symptoms
  - Redness, swelling, pain in leg
  - One sided
  - Warmth at site
  - Detected by ultrasound
- D-Dimer elevation may be helpful in guiding diagnosis

# Pulmonary Embolism

- Pulmonary embolism (PE) symptoms
  - Shortness of breath
  - Chest pain
  - Light headed
  - Cough potentially with blood

# Risk Factors for DVT/PE

- Patient history
- Hypercoagulable Disorders (i.e. Factor 5 Leiden)
- Immobility
- Atrial Fibrillation
- Medications
- Smoking
- Cancer

# Medications – Increased Risk of DVT/PE

- Estrogen therapy/oral contraceptives
- SERMs
- Megestrol
- Testosterone
- Tranexamic acid

# Important Considerations DVT/PE Treatment

- Drug Selection
  - DOACs preferred for most
  - Warfarin
  - LMWH
  - Heparin
- Contraindications
  - Heparin induced thrombocytopenia
  - Derived from pork products
  - Injection
- Warfarin/DOACs/Heparin Products – See separate presentations

# Length of Anticoagulation

- Known cause
  - Shorter duration
- Risk Factors
  - Longer term likely necessary
- First Episode (usually 3-6 months)
  - 3 months if provoked (i.e. surgery)
  - 3 months if high risk of bleed and unprovoked first episode
    - Continue longer with lower risk of bleed

# Fibrinolytic Therapy

- Use typically limited to extensive, severe cases
- tPA (alteplase), Tenecteplase
- Bleeding risk (be aware of patients who may have or have recently had internal bleeding, also use with caution in patients who may have had recent head trauma) with all fibrinolytics
- Avoid use in active internal bleeding, recent head trauma, intracranial or spinal surgery, severe uncontrolled hypertension

# Oncology – Generalized Chemotherapy Agents

# Anthracyclines

- Doxorubicin (Adriamycin), daunorubicin (Cerubidine)
- Mechanism of Action: Inhibits DNA/RNA synthesis by inhibiting topoisomerase 2; leads to blockade of intercalation of DNA base pairs
- Cardiotoxicity
  - Beta-blockers or dexrazoxane may be used to help prevent this
  - Typically due to exposure (more exposure, more risk)
- N/V (\*one of the highest risk agents in combo with cyclophosphamide)
- Stomatitis, neutropenia, anemia, and hair loss

# Taxanes

- Paclitaxel (Taxol), Docetaxel (Taxotere)
- Mechanism of Action: Stimulates tubulin dimers, interferes with G2 mitotic phase and prevents cell replication by inhibiting microtubule disassembly
- Neutropenia (\*one of the highest risk agents)
- N/V, Change in taste
- Hypersensitivity reaction – pretreat with corticosteroids, Benadryl, and H2 blockers
- Neuropathy (\*one of the highest risk agents for this adverse effect)

# Cyclophosphamide (Cytoxan)

- Mechanism of Action: Prevents DNA cross-linking which ultimately prevents proliferation and growth of cells
- Prodrug
- N/V/D – High risk with Anthracyclines
- Bladder damage (most common cause of bladder cystitis)
  - Fluids and Mesna may help prevent
- Lung/heart toxicity possible usually with higher doses
- Appetite suppression, and hair loss (common side effect)

# Platinum Compounds

- Mechanism of Action: Blocks DNA synthesis and alters the natural double helix of DNA to inhibit cell growth
- Carboplatin (Paraplatin), Cisplatin (Platinol)
- Neutropenia, hair loss, CNS changes, N/V/D, neuropathy
- Cisplatin is considered one of the highest emetogenic drugs
  - Carboplatin is considered slightly less, but still relatively high

# Bevacizumab (Avastin)

- Mechanism of Action; monoclonal antibody that binds to vascular endothelial growth factor (VEGF) – this binding ultimately prevents growth and formation of vasculature
- Add on option to cisplatin for recurrent, metastatic or advanced disease
- Boxed warning – GI perforation
- Hypertension, fatigue, GI upset, pancytopenia

# 5-fluorouracil (Adrucil)

- Mechanism of Action: pyrimidine antimetabolite that is incorporated into RNA and terminates extending of the strand and stops cell growth
- Stomatitis, photosensitivity, diarrhea, hand-foot syndrome
- Neutropenia, myelosuppression
- Dihydropyrimidine dehydrogenase deficiency – patients at risk of reduced clearance and more likely to have toxicity
- Leucovorin (Wellcovorin)
  - Combined with 5-FU
  - Also used for high dose methotrexate rescue

# Irinotecan (Camptosar)

- Boxed warning for diarrhea
- Myelosuppression
- Moderate emetogenic agent

# Capecitabine (Xeloda)

- Warfarin interaction risk
- Hand-foot syndrome
- Hepatotoxicity
  - Elevated bilirubin
- Dihydropyrimidine dehydrogenase deficiency – patients at risk of reduced clearance and more likely to have toxicity

# Acute and Chronic Kidney Disease

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# Signs of Kidney Failure

- Rise in serum creatinine
  - Generally 30%
- Rise in Blood urea nitrogen
  - Both are removed by the kidney
  - In renal disease, both accumulate
- Hyperkalemia/cardiac changes

## Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ if female})$$

# Acute Renal Failure

- Prerenal
  - Inadequate perfusion
- Post renal
  - Blockage (stones, BPH)
- Intrinsic
  - Infection
  - Toxic agents
  - May be marked by elevated protein in the urine

# Acute Kidney (Injury) Disease - Prerenal

- Reversible
- Common causes
  - Reduced blood flow to kidney
  - Caused by
    - Dehydration
    - Significant acute blood loss
    - Severe N/V/D
- Medications
  - ACE/ARB
  - NSAIDs
  - Diuretics
  - SGLT-2 Inhibitors

# Intrinsic and Postrenal

- Intrinsic AKI
  - Damage to the functional units of the kidney (nephrons)
  - Caused by infection, toxic agents, drugs
  - Drug Induced Causes: aminoglycosides, vancomycin, chemotherapy, amphotericin B
- Postrenal AKI
  - Caused by obstruction (i.e. stone, BPH, tumor)
  - Drugs that can form crystals/stones – acyclovir, indinavir, methotrexate, sulfa, topiramate

# Treatment of ARF

- Supportive care
- Prerenal
  - Volume replacement with dehydration
- Intrinsic
  - Remove offending agent
  - Inflammation
    - Steroids
- Post renal
  - Remove blockage

# Supportive Care in ARF

- No medications to “treat” acute renal failure
- Dialysis is used in emergency situation to filter blood where normal function can't expeditiously be restored
- Treat underlying cause if possible
  - I.e. infection -> antibiotics, dehydration -> fluid replacement, drug induced -> stop drug etc.
- Fluid overload
  - Loop diuretics

# Supportive Care In ARF

- Correct imbalances caused by acute renal failure
  - I.e. hyperkalemia
    - In emergency (EKG changes and/or  $K^+ >6.5$ ), IV insulin and calcium utilized to bring down elevated  $K^+$ 
      - Insulin stimulates cellular uptake of several ions including potassium, thus reducing blood concentration
      - Glucose given as well to avoid hypoglycemia
    - GI cation exchangers – i.e. - Sodium Polystyrene Sulfonate (SPS, Kayexalate)
      - Lowers potassium by binding up potassium in the large intestine
      - GI side effects
  - Severe acidosis
    - Consider sodium bicarbonate

# Chronic Kidney Disease

- Slow loss or reduction in kidney function over time (years)
- “Creatinine creep” – slow rise in creatinine over time is an indicator of chronic kidney disease
  - Normal creatinine 0.8-1.2 mg/dL (may vary slightly based upon lab)
  - Creatinine is a byproduct of muscle breakdown that is cleared by the kidney
  - Creatinine may be reduced and falsely indicate good renal function in patients with reduced muscle mass (i.e. ALS, muscular dystrophy, MS, older age)

# Chronic Kidney Disease

- Estimated glomerular filtration rate (eGFR)
  - eGFR of  $<60$  mL/min for three months is considered chronic kidney disease (or albuminuria of 30 mg/day or more)
- Blood urea nitrogen (BUN)
  - Not as consistent of a marker as creatinine
  - Elevation in BUN to Creatinine ratio may be a significant sign that renal failure is due to a prerenal cause (i.e. dehydration)
  - Normal 7-20 mg/dL
- Kidney function generally declines with age

## GFR categories in CKD

Category	GFR ml/min/1.73 m <sup>2</sup>	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

\*Relative to young adult level.

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

# Albuminuria

- Albuminuria
  - Albumin (protein) in the urine is indicative of damage to the kidney, most often caused by chronic hyperglycemia, and/or hypertension
  - Mild/normal - <30mg/day
  - Moderate – 30-300mg/day (historically called microalbuminuria)
  - Severe - >300 mg/day (historically called macroalbuminuria)

# Problem: Dosing Medications

- Many drugs are dosed by CrCl
- Lab reports GFR
- Keep an eye on changes in kidney function
  - Drugs can accumulate
  - Cause toxicity

# Incredible # of Medications Dose Adjusted

- Chronic medications
  - Use common sense
  - Check levels (i.e. digoxin)
  - Start low go slow
  - Should you change dose if no side effects
    - Gabapentin
    - Antibiotics
    - Allopurinol