ONCOLOGY

New Diagnosis Leukemia

1. IVF: D5 ½ or D5 ¼ NS at 1.5 - 2 x maintenance (to be started in the ER) as long as there is adequate urine output and no Cardio/Pulm reasons the pt couldn't handle increased volume
2. Labs:
    a. CBC diff, CMP, Mag, Phos, LDH, uric acid
    b. Baseline viral titers: CMV, VZV, HSV, Hepatitis panel
    c. Coags
    d. Blood culture (if pt is febrile)
    e. QuIgs (Quantitative Immunoglobulins)
3. CXR
4. Follow tumor lysis protocol (see section on tumor lysis syndrome)
5. Transfuse if indicated to keep Hb >7 and plts >10 (May need to keep higher if diagnostic procedure or central line placement planned for next day)
6. Start Cefepime 50 mg/kg/dose if pt is febrile

<u>Oncologic Emergencies</u>

Tumor lysis syndrome (TLS)

Definition: Metabolic complication of rapid cell turnover seen more frequently in pediatric oncology patients with large tumor cell burden and tumors sensitive to chemotherapy agents (Non-Hodgkin lymphoma and T-cell ALL). It is a consequence of rapid release of intracellular metabolites: uric acid, potassium and phosphate.

- TLS is more pronounced 12-72 hours after the initiation of chemotherapy
- The progressive precipitation of uric acid crystals in the distal tubules may produce obstructive uropathy, oliguria and azotemia
- Tumor lysis labs include: **Uric acid, K+, Ca+ and Phosphate.** Must also monitor Creatinine and urinalysis.
- Clinical tumor lysis syndrome includes seizures, cardiac arrhythmias and acute kidney injury (AKI)

Laboratory tumor lysis syndrome	Clinical tumor lysis syndrome
• Uric acid ≥ 8mg/dL or 25% increase from baseline • K+ ≥ 6 mEq/L or 25% increase from baseline • Phos ≥ 6.5 mg/dL or 25% increase from baseline	• AKI- Cr ≥1.5 X ULN or GFR ≤60ml/min • Cardiac arrhythmia/Sudden death • Seizure

Management:

1. General
    a. IVF : D5 ½ at 3 L/m2/day without potassium or calcium (extracellular volume expansion to increase urate excretion)
    b. Monitor I&O: Keep urine output at > 100ml/m2/hr (>4ml/kg/h for infants) and urine specific gravity < 1.010 should be established before initiation of chemotherapy

    a. Pts who develop hyperkalemia and hyperphosphatemia or have poor UO despite IVF should have a renal USG to r/o renal involvement or obstructive uropathy
  c. Laboratory: Monitor tumor lysis labs every 4-6 hrs for pts with high WBC or Q 12-24 hrs for low risk patients with low WBC and no significant hepatosplenomegaly
  d. Monitor neuro exam
2. Hyperuricemia
    a. Allopurinol 10mg/kg/dose PO divided Q 8hrs; max 800mg/day (decreases the urate production by competitive inhibition of xanthine oxidase).
        i. Decrease dose by 50% in patients with renal failure
    b. Rasburicase 0.05 mg/kg IV x 1 for pts with uric acid >11 mg/dL
        i. Contraindicated in patients with G6PD deficiency
        ii. Subsequent doses may be given if uric acid again > 8mg/dL in high risk patients
3. Hyperkalemia
    a. Calcium gluconate 100-200mg/kg IV slow infusion with EKG monitoring
    b. Sodium polystyrene sulfonate (Kayexalate) 1g/kg in 50% sorbitol PO Q 6hr; max dose 15 gr
    c. Regular insulin +D25W: 0.1 U/kg insulin (max 10 Units) + 2ml/kg (0.5g/kg) D25W IV over 30 min
    d. Albuterol (inhaled via nebulizer): Patient <25 kg give 2.5mg, if 25-50kg give 5mg, if >50 kg give 10mg.
    e. Furosemide 0.5-1mg/kg IV
    f. Sodium bicarbonate 1-2 mEq/kg IV over 5-10 mins; max dose 50 mEq
4. Hyperphosphatemia
    a. Aluminum hydroxide
        i. Children 50-150 mg/kg/day PO divided Q 4-6 hrs
        ii. Adolescents 300-600mg PO TID
        iii. Avoid in patients with renal insufficiency
    b. Sevelamer (Renagel): Administer with each meal. Dose not well established in children. Adolescent dosing is based on Phos level
        i. >5.5 and <7.5 give 800mg PO TID
        ii. ≥ 7.5 and ≤ 9 give 1200mg PO TID
        iii. ≥ 9 give 1600mg PO TID
    c. Calcium carbonate (use with caution as can increase calcium-phosphate product and risk of calcium phosphate precipitation
        i. There is increased risk of calcium phosphate precipitation when Ca x Phos > 60
5. Hypocalcemia
    a. Calcium gluconate 50-100 mg/kg IV slow infusion with EKG monitoring

Fever and Neutropenia

Definition: Fever is defined as a single <u>oral</u> temperature ≥38.3℃ (101℉) OR ≥38 ℃ (100.4℉) that is sustained for >1 hr AND absolute neutrophil count (ANC) < 0.5 x 10^9/L

Stem cell transplant patients: ANY oral temperature ≥38 ℃ (100.4℉)

- Febrile neutropenia is a life-threatening complication of cancer therapy.
- Patients with neutropenia are unable to produce and adequate inflammatory response; infection can disseminate rapidly and terminate fatally.
- Approximately 85% of bacterial infection arise from endogenous flora colonizing the GI tract (gram negative bacilli- E. Coli, Klebsiella) or skin (gram positive cocci- staph aureus, staph epi)
- Most common sites of infection are: Skin (IV/Central line sites, cellulitis), GI tract (typhlitis, stomatitis, perirectal cellulitis, enterocolitis) and lungs
- You must make and immediate assessment of the patient's hemodynamic status. Impending shock requires emergent intervention.
- Do not wait for the patient to become hypotensive, recognize the signs and symptoms of *impending* shock.
    1. Decreased perfusion: decreased urine output, clouded sensorium, cool extremities
    2. Compensation for decreased perfusion: tachycardia, ultimately hypotension

RISK ASSESSMENT CRITERIA: Pt is considered HIGH risk if ANY of the following is present:

1. Sg/Sx sepsis
    a. Chills
    b. Age-specific vital signs

Age	Heart rate	Systolic BP
1 wk- 1 mo	>180 or <100	<80
1 mo - 1 y	>180 or <90	<75
1 y - 5y	>140	<75
5y - 12 y	>130	<80
12y – 18 y	>110	<90

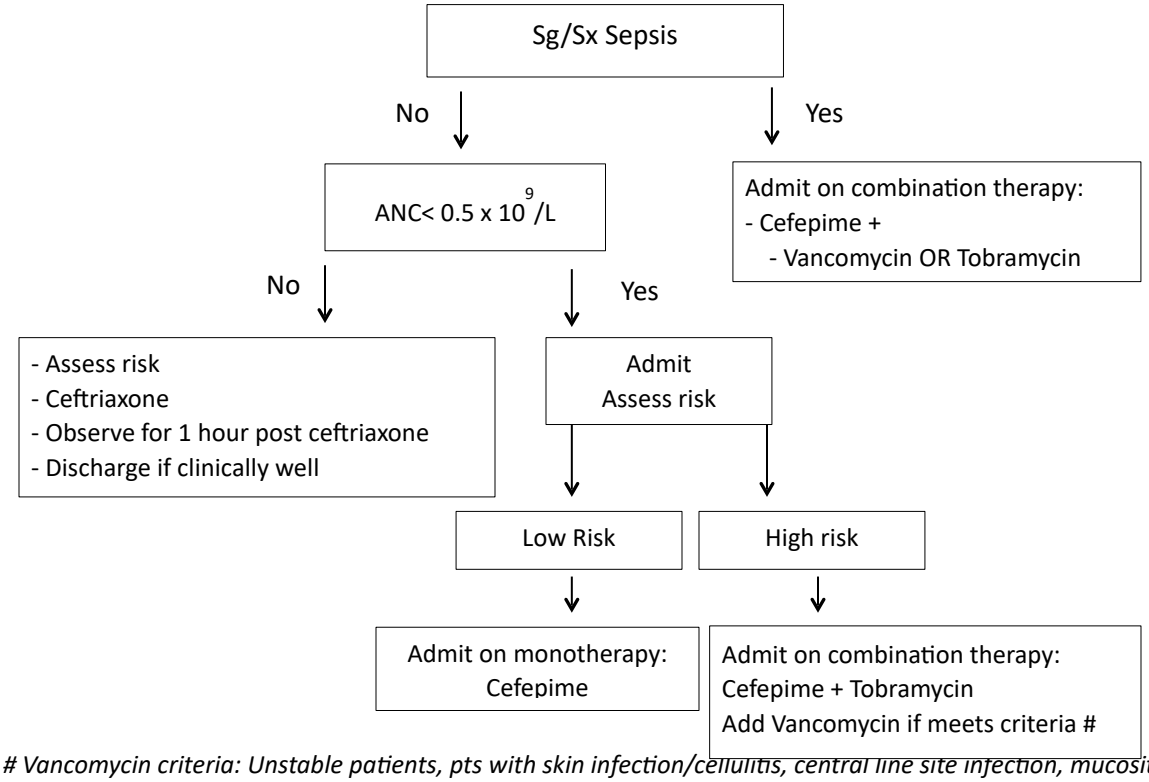
2. ANC $<0.1 \times 10^9/L$
3. Focal infection (i.e. mucositis, abdominal pain, perianal tenderness)
4. Pt receiving dexamethasone or prednisone
5. Infant ALL, ALL in induction or delayed intensification, AML
6. Stem cell transplant patients <100 days from transplant

ANC formula = WBC X (%neutrophils + % bands)
APC formula = WBC X (% neutrophils + % bands + % monocytes)

ED and Outpatient Management

1. Access central venous line, if unable, place peripheral IV and obtain blood cultures
    a. Blood Culture from central line (peripheral only if they have no central line or unable to access)

2. Examine oral, perirectal and central line areas.
3. Obtain CBC diff, CMP, T&S
4. Obtain UA/ UCx
5. CXR, stool cultures, RVP if symptoms are present
6. KUB or abdominal CT for suspected typhlitis
7. Order appropriate antibiotics (see guidelines below)
   ** Antibiotics to be given within 1 hr of arrival to Emergency Room**

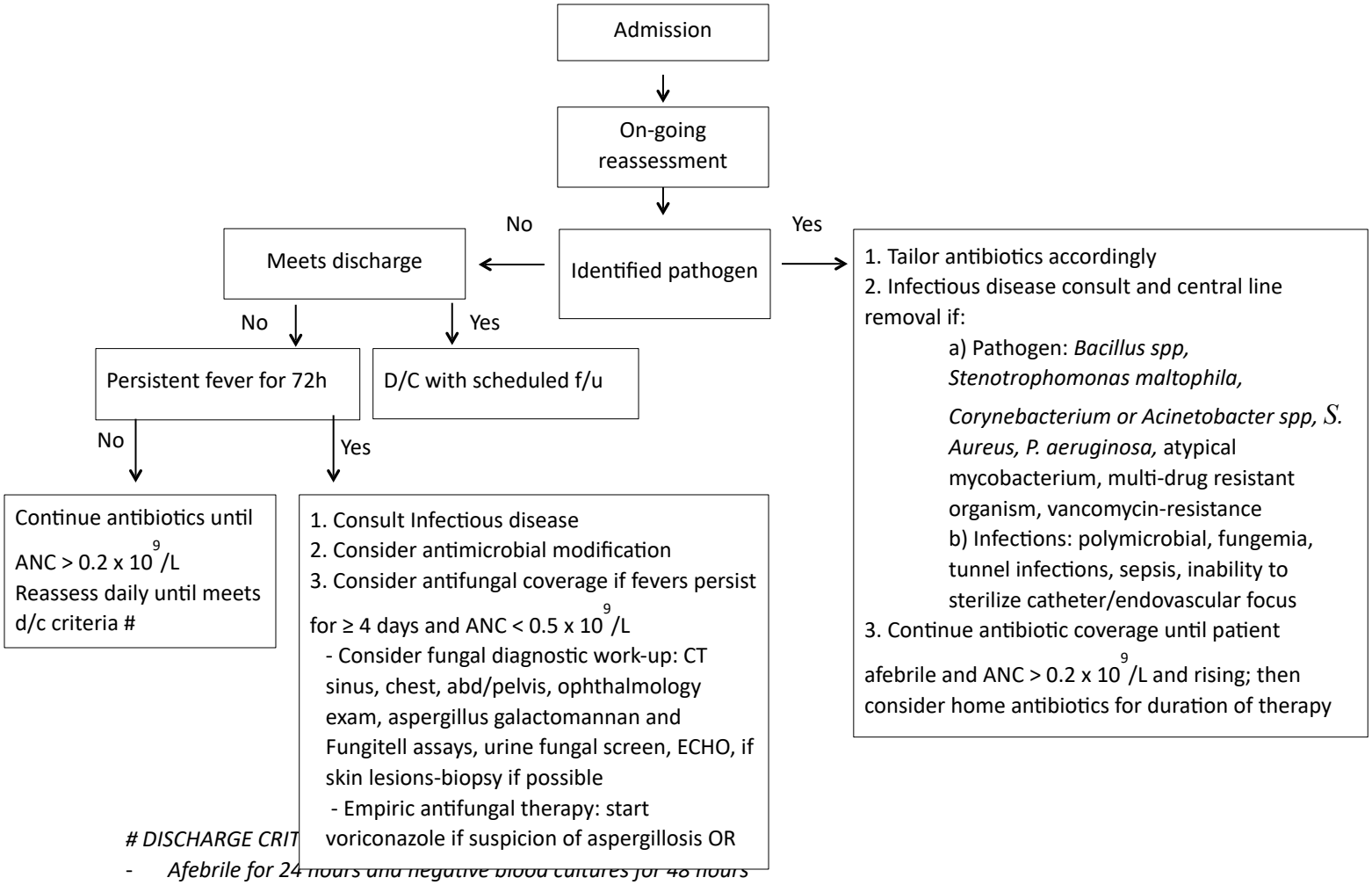


 # Vancomycin criteria: Unstable patients, pts with skin infection/cellulitis, central line site infection, mucositis, AML or recent high-dose Cytarabine administration, isolation of vancomycin-sensitive organism, previous MRSA or Streptococcus viridans.

Consider stress-dose steroids if patient has been receiving systemic steroids for ≥ 7 days or if patient presents within 4 weeks of ALL induction.

<u>Antimicrobial allergies</u>
Penicillin allergy: Cefepime + Metronidazole OR Meropenem
Cephalosporin allergy: Meropenem OR Ciprofloxacin
β-lactam allergy: Fluoroquinolones
Vancomycin allergy: Linezolid OR Daptomycin (if no lung infection)

<u>Inpatient management</u>
* Pts on oral chemotherapy admitted for concern of infection, hold oral chemo until work-up is negative



 # DISCHARGE CRIT

- *Afebrile for 24 hours and negative blood cultures for 48 hours*
- *No signs of localized or documented infection*
- *Performance status back to baseline*
- *ANC 0.2 x 10^9/L and rising*
- *24 hour caregiver whom is able to take patient's temperature, lives within 1 hour of accessible medical care, has phone access and has transportation*

Risk factors for invasive fungal infections:

- Sg/Sx of sepsis with neutropenic fever
- Prolonged fever and ANC <> 0.1 x 10^9/L
- Mucositis
- Steroids and high-dose Cytarabine
- ALL (induction, DI), AML, severe aplastic anemia
- Stem cell transplant < 100 days from transplant and active GVHD/prolonged immunosuppression
- Prolonged TPN/IL, prolonged antibiotics and previous history of invasive fungal infection

Antimicrobial doses

Medication	**Dose**
Acyclovir	250mg/m2/dose IV or PO Q 8hr

Amikacin	< 18yo: 7.5 mg/kg/dose IV Q 8hr >18yo: 7.5 mg/kg/dose IV Q 12hr
Amphotericin Liposomal	3mg/kg/dose IV once a day
Azithromycin	10mg/kg/dose once a day on day1, 5 mg/kg/dose on days 2-5 IV or PO (max 500mg/day on day1, 250mg/day for days 2-5)
Caspofungin	<40 kg: 70mg/m2/day on Day1, then 50mg/m2/day >40kg: 70mg/day on Day 1, then 50mg/day
Cefepime	50mg/kg/dose IV Q 8hr (max 2gr Q8hr)
Ceftazidime	50 mg/kg/dose IV Q 8hr (max 2gr Q8hr)
Ceftriaxone	50mg/kg/dose IV Q 12hr (max 2 gr Q12hr)
Cephalexin	25 to 50 mg/kg/day divided every 6 hr (max 2 grams /day)
Clindamycin	40mg/kg/day divided Q6-6 hrs (max 2.7g/day)
Ciprofloxacin	7.5 – 15 mg/kg/dose IV Q 12hr (max 400mg Q12hr) Ciprofloxacin 15-20 mg/kg/day divided Q12hrs (Max 800mg/ day)
Fluconazole	Prophylaxis: 3-5 mg/kg/dose IV or PO Q day (max 400mg/ day) Treatment: 6-12 mg/kg/dose IV Q day
Gentamicin	<18 yo: 1.5-2.5 mg/kg/dose >18 yo:
Linezolid	<12 yo: 10mg/kg/dose IV or PO Q 8hr (max 400mg Q8hr) >12 yo: 10mg/kg/dose IV or PO Q 12hr (max 600mg Q12hr)
Metronidazole	7.5 mg/kg/dose IV Q 6hr (max 500mg Q6hr)
Micafungin	>4 mo: 1 mg/kg/dose IV Q 24hr (max 50mg/day)
Pentamidine	PCP Prophylaxis: IV- 4mg/kg/dose IV once a month Aerosolized 300mg once a month
Piperacillin/Tazobactam	>6 mo: 100 mg/kg/dose IV Q 6hr (max 4.5 g Q6hr) Adult: 4.5 grams/dose IV Q 6hr
Tobramycin	<18yo: 1.5 -2.5 mg/kg/dose IV Q 8hr >18yo: 1 -2.5 mg/kg/dose IV Q 8hr
Trimethoprim/Sulfamethoxazole	PCP prophylaxis: 2.5 mg/kg/dose PO or IV BID on Saturday and Sunday
Vancomycin	< 50kg: 10mg/kg/dose IV Q 6hr >50kg: 1000mg/dose IV Q 12hr
Voriconazole	IV: 6mg/kg BID day 1, then 4mg/kg BID PO: >40kg: 400mg BID Day 1, then 200mg BID <40kg: 200mg BID Day1, then 100mg BID

Hyperleukocytosis
Definition: Elevated WBC >100 X 10^9/L in patients with ALL, AML or CML.

Patients are at high risk for acute complications due to rapid proliferation of leukemic blasts resulting in leukostasis and tumor lysis syndrome and blast cell lysis leading to release of anti and pro-coagulant factors.

Signs/Symptoms: Hypoxia, tachypnea, dyspnea, mental status changes, headaches, seizures, papilledema, GI bleeding, renal insufficiency, priapism, intracranial hemorrhage. Leukostasis may be asymptomatic

Risk factors: Age <1 yr, T-cell phenotype, AML M1, M4 and M5. Hyperleukocytosis occurs at lower WBC in AML (>100 x 10^9/L) vs ALL and CML (>300 x 10^9/L)

Management:
1. In ALL and AML
    a. Rapid initiation of chemotherapy
    b. Hyperhydration: D5 ½ or D5 ¼ NS at 2 X maintenance/24hrs
    c. Consider leukapheresis for WBC >400-600 X 10^9/L (if CNS or pulmonary symptoms AND as long as this doesn't delay start of chemotherapy)
    d. In pts with DIC: FFP to keep PT/PTT WNL, Vit K and Fibrinogen concentrate or Cryoprecipitate to keep fibrinogen >150mg/dL
    e. Platelet transfusion to keep plts >50 X 10^9/L if WBC > 300 – 400 X 10^9/L
    f. Symptomatic anemia: Transfuse small aliquots (5ml/kg) and keep Hb <10 g/dL
    g. Manage TLS:
        i. Allopurinol 10mg/kg/dose PO divided Q 8hrs, max 500mg/m2/day
        ii. Rasburicase if uric acid >11 mg/dL; consider second dose if repeat uric acid is >8 mg/dL
    h. Consider Hydroxyurea in patients with AML or CML
2. Acute promyelocytic leukemia
    a. Rapid initiation of ATRA (all trans retinoic acid) or ATO (arsenic trioxide)
    b. FFP to keep PT/PTT WNL
    c. Fibrinogen concentrate or Cryoprecipitate to keep fibrinogen >150mg/dL
    d. Platelet transfusion to keep plts >50 X 10^9/L
    e. APL differentiation syndrome/retinoic acid syndrome (unexplained fever, acute respiratory distress with interstitial pulmonary infiltrates, and/or a vascular capillary leak syndrome leading to acute renal failure after initiation or ATRA/ATO): Treat with IV Dexamethasone
    f. Leukocytosis with ATRA or ATO: Hydroxyurea and consider holding ATRA or ATO
3. CML
    a. Hyperhydration
    b. Hydroxyurea
    c. Consider leukapheresis
    d. Priapism: Hyperhydration, hydroxyurea, consider leukapheresis, urologic consultation for therapeutic aspiration and possible sympathomimetic therapy and pain management

BMT
Fever: Temp > 38 ℃ (100.4 ℉) x 1

Labs:
1. CBC diff
2. CMP
3. Blood culture from central line
4. Urine culture
5. CXR

Management:
1. Cefepime 50mg/kg/dose Q8 hrs (regardless of ANC)
2. Vancomycin (add Vancomycin for pts with AML and fever post high-dose Ara-C and for clinically unstable patients)
    a. <50 kg- 10-15mg/kg/dose IV Q 6hrs
    b. >50 kg- 1000mg/dose IV Q 8-12 hrs

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Etiology:
- This may be secondary to chemotherapy agents such as Cyclophosphamide, Ifosfamide and Vincristine
- Cerebral injury, hemorrhage
- Following brain surgery (DI may be present the first 3-5 days post-op with SIADH developing later)
    - Brain tumors, leukemia, lymphoma and Ewing sarcoma
    - Pulmonary disease

Signs and symptoms: Fluid retention, headache, irritability, muscle weakness, nausea, confusion and seizures.

Diagnosis: Hyponatremia, hypo osmolality, concentrated urine relative to plasma, continued urinary excretion of Na (>20mEq/L), normal renal and adrenal function, improvement of hyponatremia and urine sodium loss by fluid restriction.

Management:
Patient should be in PICU with any Na ≤ 125 mEq/L
1. Mild SIADH (NA ≥125 mEq/L: Fluid restriction (50-60% maintenance), maintenance Na intake.
2. Severe SIADH (Na = 120-125 mEq/L): Furosemide 1mg/kg IV, replacement of urine loss with hypertonic saline
3. Life-threatening SIADH (Na ≤ 120 mEq/L): Furosemide 1mg/kg IV, 200ml/m2 of 1.5 NaCl to correct Na to 120 mEq in 6-8hrs, then more slowly to normal over 24-48 hrs

Spinal cord compression
** Paraplegia for more than 24 hrs may be IRREVERSIBLE**

Etiology: Direct extension of paravertebral tumors (neuroblastoma, Ewing sarcoma, rhabdomyosarcoma), extradural lesion (metastasis, abscess), intradural lesion (primary CNS tumor, drop metastasis), hematoma in a patient with thrombocytopenia resulting from a lumbar puncture, vertebral body collapse from osteoporosis (due to prolonged steroid therapy) or vertebral body metastasis.

Signs and symptoms: Pain (central back, vague deep ache, radiating pain to the extremities, tenderness and or irritability in infants), weakness, sensory changes (sensory level, hyperesthesia), bowel and bladder involvement (generally late findings, constipation and urinary retention precede incontinence)

Diagnosis:

1. Careful and complete neurological AND general physical examination
    a. Localized back pain or radicular pain extending down the leg occurs in up to 80% of children with cord compression. Pain is almost always the first presenting symptom, with weakness and bladder/bowel dysfunction occurring later.
2. MRI (with gadolinium)
3. CT myelogram (if MRI is contraindicated)
4. Consult: Neurosurgery, Neurology and radiation oncology

Management:

1. Close monitoring with frequent neuro exams
2. Patients with rapidly progressing cord dysfunction require immediate intervention; dexamethasone 1mg/kg IV should be given even before imaging is performed
    a. Patients with suspicious findings who are stable should be started on Dexamethasone : 0.25 -0.5 mg/kg/day divided Q6hr with MRI performed within 24 hours
3. Pain relief
4. Surgical decompression
5. Radiation: if the diagnosis is known and tumor is radiosensitive
6. Chemotherapy: for chemo sensitive tumors (neuroblastoma, Ewing sarcoma, Hodgkin lymphoma, NHL)

Increased intracranial pressure
Etiology: ventricular obstruction or CSF flow obstruction

Signs and symptoms:

1. Headaches, irritability, lethargy, emesis, neck pain
2. Evaluate for Cushing triad: hypertension, bradycardia and abnormal respiratory pattern
3. Funduscopic exam for papilledema

Diagnosis:

1. CT of the head OR Rapid (Flash) MRI of the brain
2. Shunt series if pt has a VP shunt

Management:

1. Emergent Neurosurgical consult and PICU transfer
2. Limit fluids to 75% of maintenance
3. Loading dose of dexamethasone 0.5-1mg/kg IV, followed by 0.25-0.5 mg/kg every 6 hours
4. Elevate head of bed 30˚
5. Obtain: CBC diff, CMP
6. Use NS or hyperosmolar solutions for maintenance fluids
7. 3% NS 2-5 ml/kg OR Mannitol 0.25g/kg IV for temporary reduction of increased ICP

8. Acetazolamide (Diamox) 5mg/kg/dose every 6 hours to decrease CSF production
9. Intubation and hyperventilation for acute management to decrease PCO2 to 20-25 mmHg will decrease cerebral perfusion.
10. Prophylaxis with antiseizure medication should be considered

Superior vena cava syndrome and superior mediastinal syndrome

Superior vena cava syndrome refers to the signs and symptoms resulting from the compression or obstruction of the SVC caused by an anterior mediastinal mass.

Signs and symptoms: orthopnea, headache, facial swelling, dizziness or fainting, sudden pallor and exacerbation of symptoms with Valsalva maneuver.

Physical exam: plethoric, edematous face and neck, jugular venous distension, papilledema and pulsus paradoxus. Blood pressure changes, pallor and even cardiac arrest can result from postural changes.

Superior mediastinal syndrome is the combination of SVCS and tracheal compression that leads to cough, dyspnea and wheezing. Physical exam reveals decreased breath sounds, wheezing, anxiety, stridor or cyanosis.

The most common cause is non-Hodgkin lymphoma (NHL), but other malignancies such as Hodgkin lymphoma, T-cell ALL, malignant teratoma, thymoma, neuroblastoma, rhabdomyosarcoma or Ewing sarcoma may also be a cause.

Evaluation:

1. History and physical examination- typically short period of progressive symptoms.
2. CXR (AP and L): may reveal mediastinal widening, tracheal deviation and/or pleural effusion
3. CT chest
4. Tissue diagnosis with the least invasive procedures, with no sedation and local anesthesia
5. Echocardiography

Management:

1. Close monitoring in the PICU with head elevation and continuous cardiovascular and respiratory monitoring.
2. Children with impending or actual airway obstruction should receive emergent radiation therapy.
    a. Radiation is given in 1 to 2 Gy fractions for 1 to 4 days. A small area of the tumor should be shielded to prevent radiation-induced changes if a biopsy is still necessary
3. Empiric therapy for suspected malignancy may be initiated with steroids, cyclophosphamide, vincristine or anthracyclines

Pancreatitis

Pancreatitis is a rare but well-known complication of multiple chemotherapeutic agents such as:

1. Asparaginase
2. Steroids
3. Mercaptopurine (6MP)

4. Cytarabine

Signs and symptoms: Pts present with abdominal or back pain and the majority has nausea or emesis.

Evaluation:
1. History and physical exam: date of last chemotherapy, onset of symptoms, etc.
2. Laboratory tests:
    a. CMP (evaluate for hypocalcemia, renal and liver function tests to monitor multiorgan failure secondary to cytokine release from inflamed and/or necrotic pancreas)
    b. Triglycerides
    c. Amylase and lipase
3. Imaging:
    a. Consider abdominal US as primary imaging modality
    b. CT with IV contrast if there is high clinical suspicion
    c. CXR for pts with respiratory symptoms

Management:
1. Initial gut/bowel rest (NPO), but consider early oral refeeding in patients with mild pancreatitis
2. Hydration with electrolyte replacement or parenteral nutrition for prolonged gut rest
3. Analgesia (usually narcotics)
4. Antiemetics as needed
5. Broad antimicrobial coverage in patients with necrotic pancreatitis and clinical deterioration
6. Consider Octreotide

Complications: Potential complications include development of abscess, pseudocyst, necrosis or hemorrhage. Hemorrhagic pancreatitis is a medical emergency and initial management parallels that of any GI bleed.

Neutropenic enterocolitis/Typhlitis

Definition: Necrotizing enterocolitis refers to necrotizing inflammation of the small or large intestine that occurs in the setting of neutropenia. Typhlitis specifically refers to necrotizing inflammation of the cecum.

Typhlitis is usually seen with prolonged neutropenia (> 7 days) but it has been reported in patients without neutropenia. Usually develops in pts >10 yo and within 2-3 weeks of receiving intensive chemotherapy.

Factors contributing to development of neutropenic enterocolitis: prophylactic antibiotics (alter colonic flora), cytotoxic chemotherapy (disrupts bowel mucosal barrier allowing microbial/fungal invasion) and prolonged neutropenia (prevents adequate infection clearance)

Most common bacterial pathogens include: E. Coli, P. Aeruginosa and C. Difficile. Less common pathogens seen include coag-neg staph and alpha-hemolytic strep. Most common fungal pathogen is Candida spp.

Signs and symptoms: Abdominal pain, vomiting, diarrhea, GI bleeding, fever, abdominal distention, tachycardia, hypotension, sepsis and peritoneal irritation (diffuse or localized to the RLQ).

Evaluation:

1. 2 view plain AXR should first be obtained (evaluate for pneumatosis or free air- presence of free air will require immediate surgical consultation)
   ** Contrast enema is CONTAINDICATED if neutropenic enterocolitis is suspected as it may lead to PERFORATION **
2. Abdominal USG is preferred imaging for demonstrating bowel wall thickening
3. CT abdomen is the current definitive study if USG is inconclusive
   a. CT is sensitive for identifying cecal wall thickening, transmural inflammation, soft tissue masses and pneumatosis

Management:
1. Gut rest (NPO) during the acute phase of symptomatic pain
2. Nasogastric suctioning for decompression
3. Parenteral nutrition while NPO
4. Consult surgery (early consultation, even if surgery is not indicated)
5. Analgesia (narcotics)
6. Transfusion support (PRBCS, platelets and/or FFP) if necessary
7. Consideration for GCSF utilization
8. Broad antimicrobial coverage (gram negative, anaerobe and gram positive coverage)
   a. For monotherapy: Piperacillin/Tazobactam OR Imipenem/Cilastatin
   b. For dual therapy: Ceftazidime or Cefepime PLUS Metronidazole
9. Surgery only if supportive care fails to improve clinical picture

Complications: Bowel obstruction, hemorrhage, abscess or perforation

Mucositis

Mucositis is one of the most common side effects of cancer therapy. It results from damage to the mucosal lining of the GI tract due to radiation therapy and/or chemotherapy. It is a clinical condition characterized by erythema, ulceration and pain.

Lesions will heal approximately 2-4 weeks after the last dose of the offending chemotherapy agent or radiation. In immunosuppressed patients, resolution usually coincides with granulocyte recovery. The clinical course can be complicated by infection.

World Health Organization (WHO) scoring criteria for mucositis

Grade	0	1	2	3	4

Description	Normal	Soreness with or without erythema	Ulceration and erythema; patient can swallow a solid diet	Ulceration and erythema; patient cannot swallow a solid diet	Ulceration and pseudomembrane formation of such severity that alimentation is not possible

NCI CTCAE v4.0

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oral mucositis definition: a disorder characterized by inflammation of the oral mucosa	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Management:
Pain management
Mouth care
Sucralfate

Prevention:
Palifermin

Commonly used antineoplastic agents

Agents	**Toxicities**
Asparaginase	Hypersensitivity, pancreatitis

Bevacizumab	Hypertension, proteinuria, delayed wound healing, hemorrhage, thrombosis
Bleomycin	Hypersensitivity, pulmonary fibrosis/pneumonitis
Busulfan	Myelosuppression, pulmonary fibrosis with high cumulative dose, seizures
Carboplatin	Myelosuppression, nephrotoxicity, ototoxicity
Cisplatin	N/V, renal toxicity, ototoxicity, SIADH, peripheral neuropathy, Mg and Ca
Cyclophosphamide	Hemorrhagic cystitis, N/V, SIADH. Cardiotoxicity with large doses
Clofarabine	Myelosuppression, hepatotoxicity, SIRS, capillary leak
Corticosteroids	Sodium and water retention, hyperglycemia, hypertension, gastritis
Cytarabine	Fever, arthralgia, rash, nausea, emesis, myelosuppression, conjunctivitis, CNS
Dactinomycin	Skin reaction- radiation recall, stomatitis, N/V
Daunorubicin	N/V, mucositis, cumulative cardiotoxicity (>450mg/m2), hepatotoxicity
Doxorubicin	N/V, mucositis, cumulative cardiotoxicity (>450mg/m2), radiation recall, hepatotoxicity
Etoposide	N/V, hypotension, anaphylaxis
Gemcitabine	Peripheral edema, rash, N/V
Ifosfamide	Similar to cyclophosphamide, CNS toxicity, magnesium wasting
Imatinib	Edema, pleural effusion, rash
Irinotecan	Diarrhea, N/V
Lomustine	Myelosuppression, N/V
Melphalan	N/V, hypersensitivity
Mercaptopurine (6MP)	Hepatotoxicity, renal toxicity, N/V
Methotrexate	N/V, mucositis, hepatotoxicity, renal toxicity, hypersensitivity, CNS toxicity, pneumothorax
Mitoxantrone	Myelosuppression, cardiomyopathy
Paclitaxel	Neutropenia, anaphylaxis, ventricular tachycardia
Temozolomide	Myelosuppression
Thiotepa	Seizures, hyperpigmentation, skin breakdown, myelosuppression
Thioguanine (6TG)	Hepatotoxicity
Vinblastine	Myelosuppression, sensory-motor impairment
Vincristine	Peripheral neuropathy, jaw pain, constipation, hepatotoxicity
Vinorelbine	Myelosuppression, peripheral neuropathy

HEMATOLOGY

New diagnosis thrombocytopenia
Thrombocytopenia may be immune or non-immune. Immune causes generally cause increased platelet destruction and non-immune causes may cause increased destruction or decreased bone marrow production.

Evaluation:

1. Look for red flags of underlying leukemia in the H&P (fevers, decreased activity, abnormality in another cell line, splenomegaly, lymphadenopathy, bone pain, etc)
2. Evaluate for bleeding symptoms
3. Send CBC and manual diff (look for platelet morphology)
4. If there are bleeding symptoms:
    a. Coag panel
    b. VonWillebrand panel
    c. Blood type

Management:

1. If platelets >10,000 and NO bleeding symptoms- Observation only (Don't need admission, just follow up with Hematology in the next couple of days). Make sure to educate family on bleeding risks and trauma precautions
2. If therapy is warranted:
    a. IVIG 0.8-1 g/kg/day for 1-3 days (first line therapy)
    b. IV Methylprednisolone 30 mg/kg/day for 3-4 days (second line therapy)
    c. WinRho 75 micrograms/kg (ONLY for Rh + patients)

New diagnosis anemia
Definition: Reduction in Hb two standard deviations below the mean, based on age-specific norms. (Usually iron def vs hemolytic anemia vs bone marrow suppression)

Assessment: Ask for diet history, sources of blood loss, menstrual history, ethnicity, pica, medication exposure, growth/development, hyperbilirubinemia, family history of anemia, splenectomy or cholecystectomy.

Physical Exam: Evaluate for pallor, tachycardia, cardiac murmur, jaundice, hepatosplenomegaly, glossitis, tachypnea, koilonychia, angular cheilitis and signs of systemic illness.

Labs:

1. CBC diff and retic.
    a. Look at MCV, RDW and retic to look for classic iron deficiency anemia
2. Peripheral blood smear
3. Stool for occult blood
4. Urinalysis
5. Bilirubin
6. If considering bone marrow suppression: Parvo or other viral studies

Anemia may be categorized as microcytic, macrocytic or normocytic. (MCV value is age dependent). Important to look at the RETIC COUNT!
Microcytic anemia:
Low retic- Causes: *Iron deficiency*, lead poisoning, chronic disease, aluminum toxicity, cooper deficiency, protein malnutrition
Normal retic- Causes: Thalassemia trait, sideroblastic anemia
High retic- Causes: Thalassemia syndromes, Hemoglobin C disorders

Normocytic anemia:
Low retic- Causes: Chronic disease, RBC aplasia (transient erythroblastopenia of childhood, infections or drug-induced), malignancy, juvenile rheumatoid arthritis, endocrinopathies, renal failure.
Normal retic- Causes: Acute bleeding, hpersplenism, dyserythropoietic anemia II.
High retic- Causes: Hemolysis, hypersplenism, microangiopathy (HUS, TTP, DIC, Kasabach-Merrit), membranopathies (spherocytosis, elliptocytosis), enzyme disorders (G6PD, pyruvate kinase) and hemoglobinopathies.

Macrocytic anemia:
Low retic-Causes: Folate deficiency, Vit B12 deficiency, aplastic anemia, congenital bone marrow dysfunction (Diamond-Blackfan or Fanconi Sd), drug-induced, trisomy 21 and hypothyroidism
High retic- Causes: Dyserythropoietic anemia I and III, active hemolysis

<u>Iron deficiency anemia:</u>
Diagnosis:
1. CBC: hypochromia, microcytosis, low retic count, low MCHC and high RDW
2. Iron studies: Ferritin (reflection of total body iron) decreases first, low serum iron, elevated TIBC, elevated transferrin
3. Stool for occult blood
4. Calculate Mentzer index (MCV/RBC) : >13.5 suggests iron deficiency; <11.5 suggests Thalassemia minor

Management:
Iron deficiency: Start oral iron 6mg/kg/day divided BID

- Iron therapy should result in increased retic count in 2-3 days, increase Ht in 1-4 weeks, iron stores are repleted after 3 months of therapy.

<u>Hemolytic anemia:</u>
Diagnosis: Consider if reported jaundice and/or dark urine

1. Send CBC
2. Send retic count- usually elevated
    a. Corrected retic count: CRC = % retic x patient's Ht/Normal Ht
        i. CRC >1.5 suggests increase RBC production secondary to hemolysis or blood loss
3. Coombs:
    a. Direct- tests for antibodies or complement on the patient's RBCs
    b. Indirect- tests for free autoantibodies in patient's serum after RBC antibody binding sites are saturated
4. CMP, LDH and indirect bili: Elevated AST, LDH and indirect bili
5. Haptoglobin: decreased in hemolytic anemias (binds free Hb)
6. Osmotic fragility test: useful in hereditary spherocytosis
7. G6PD assay

Management:
Transfusion is RARELY indicated unless clearly symptomatic from anemia or Hb <5.
Coombs:

a. If Coombs Positive: Consider starting steroids
b. If Coombs negative: Order ektacytometry or RBC enzyme panel

Red cell aplasia:
1. Acquired
    a. TEC (transient erythroblastopenia of childhood): Occurs from 6 months to 4 years of age. Spontaneous recovery within 4-8 weeks
    b. Infectious causes: parvovirus, EBV, CMV, HHV6, HIV
    c. Exposure to radiation, drugs or chemicals
2. Congenital

Diagnosis: Low retic count. Bone marrow aspiration evaluated RBC precursors and evaluate for marrow dysfunction, neoplasm or infection. Congenital anemias usually have Macrocytosis.

Sickle cell disease
SCD refers to a group of genetic disorders that share a common feature: Hb S alone or in combination with another abnormal Hb. All children who have sickle cell anemia have a variable degree of hemolytic anemia and vaso-occlusive tissue ischemia resulting in complications.
Complications of SCD: cerebrovascular disease, pulmonary sickling (acute chest syndrome), osteonecrosis, retinopathy and nephropathy.

Fever:
Susceptibility to infection is due mostly to loss of splenic function which can result in life-threatening episodes of sepsis. *Streptococcus pneumoniae* is responsible for >80% of the morbidity in infection.
Other bacteria include: *Haemophilus influenza, Neisseria meningitides, Mycoplasma pneumoniae, Staphylococcus aureus, Salmonella sp, Escherichia coli and Streptococcus pyogenes.*
Parvovirus B19 may cause aplastic crisis.

Temp >38.5 ℃ (101 ℉)
Labs:

1. CBC diff
2. Retic count
3. BMP
4. Blood culture
5. Urinalysis and urine culture
6. CXR (always!)

Management:
- Ceftriaxone 50-75 mg/kg IV (if no or difficult IV and ill-appearing child, antibiotic should be given IM)
- For cephalosporin allergies, give Clindamycin 10 mg/kg/dose Q6-8H (max 3000 mg/day)
- Admission based on criteria below
- Patients who don't meet criteria for admission may be managed as outpatient.

Admission Criteria for pts with sickle cell and fever:

1. Any child < 12 months
    a. These patients should be followed at least for 48-72 after blood culture

2. Any child < 2 with HbSS or HbSB0Thal (higher risk of bacteremia in these genotypes)
3. History of bacteremia
4. Episode of splenic sequestration in last 3 weeks
5. T ≥104
6. WBC < 5000 or > 30,000
7. Indwelling lines (PICC, port, etc)
8. Hgb ≤ 2 g/dL below baseline in HbSS or HbSB0Thal, or Hgb ≤ 5 g/dL
9. Social situation that prevents good follow-up
10. CXR findings concerning for acute chest syndrome
11. Young children with a lower Hb/Plts with concern for splenic sequestration
12. Ill appearing or hemodynamic instability

*Consider admission for patients who have had surgical splenectomy if any of above criteria are also met

Complications of fever:

1. Pain crisis
2. Acute chest syndrome
3. Ileus

Pain/Vaso-occlusive crisis:

Bone and joints are major sites of pain in sickle cell. Back pain is a common symptom as result of vertebral infarct. Swelling and pain may occur in long bones and may be hard to differentiate from osteomyelitis.

Vaso-occlusive episodes can last for many days. Don't assume the episode is controlled when acute administration of analgesia is effective.

Outpatient management – Refer to APH Pain Management Algorithm

1. Mild Pain (score 1-3)
    a. Give PO Morphine (0.3-0.5 mg/kg) and Ibuprofen 10 mg/kg if has not received either in last 4-6 hours
    b. Apply warm packs to painful area
    c. Oral fluids
    d. Reassess Q30min
    e. If pain has resolved, discharge home. If not, transition to Moderate/Severe Pain plan.
2. Moderate/Severe Pain (score 4-10)
    a. Intranasal Fentanyl 1.5-2 mcg/kg/dose while establishing IV access
    b. Labs – CBC, retic, CMP, extra pink top
    c. After IV access is established, give IV Morphine 0.1-0.2 mg/kg/dose (max 8 mg/dose) and IV Ketorolac 0.5 mg/kg/dose (max 30 mg)
    d. Start maintenance IVF
    e. Famotidine for GI PPX
    f. Apply warm packs to painful area
    g. Reasses Q30min, repeat Morphine 0.2-0.2 mg/kg/dose (max 8 mg/dose) if pain has not improved or worsened
    h. Plan for admission if pain has not resolved after 3 doses of IV Morphine

Inpatient management:

1. Start Morphine PCA (there will be guidelines re: dosing to come, developing new pathway for pain management, evidence shows early utilization of PCAs decreases LOS and overall opioid usage)

2. IVF at 1 x Maintenance (Maintenance rate for no more than 24 hours)
3. Toradol (3-5 days max, do not order if has received in last 30 days)
4. Incentive spirometry (EZpap)!!!!
5. PT consult on Day 2 of hospitalization

Dactylitis (Hand-Foot syndrome):
Painful swelling of the hands and feet seen exclusively in infants and children <5 yo.

Diagnosis: Presents with pain, low-grade fever and diffuse non-pitting edema of the dorsum of the nads and feet which extends to the fingers. One or more extremities may be affected at one time.

Although the swelling may persist for weeks, the illness is self-limited. Occasionally there may be a precipitating factor such as hypoxia, fever, viral illness or dehydration.

Management: Analgesics, hydration and parental reassurance.

Abdominal pain:
Children with sickle cell have high incidence of cholecystitis. Also consider pancreatitis, UTI, PID and pneumonia presenting as abdominal pain.

Constipation is also a common source of abdominal pain in sickle cell patients. Consider KUB to evaluate stool burden and ALWAYS start a scheduled bowel regimen (softener + stimulant) if ordering scheduled opioids.

ACUTE CHEST SYNDROME (ACS)

- Characterized by fever **AND** new pulmonary infiltrate on CXR, +/- respiratory symptoms
- Patients can either present with ACS or develop it secondary to severe pain
- Can be triggered by pulmonary embolism, fluid overload, over-sedation from opioids, and/or hypoventilation
- Can be life-threatening
- SIGNS & SYMPTOMS
    - Cough
    - Chest pain
    - Shortness of breath
    - Hypoxemia
    - Tachypnea
    - Tachycardia
    - Decreased air movement
    - Drop in Hgb
- MANAGEMENT
    - Respiratory support as indicated by patient status, maintain SaO2 ≥ 9% or within 3% of patient's baseline
    - Antibiotics – Ceftriaxone/Clindamycin (10 day course total, can transition to PO if ready for discharge) + Azithromycin (3-5 day course depending on dosing)
    - PRBCs – simple transfusion vs exchange depending on patient status
    - IV fluids – individualize to patient, avoid fluid overload
    - Pain control, taking care to avoid over-sedation
    - Incentive spirometry 10x/hr while awake, CPT as patient tolerates
    - If patient has a history of asthma, consider scheduled Albuterol nebs
    - If patient also have components of acute asthma exacerbation, corticosteroids can be helpful but can cause rebound pain crisis when stopped. Not recommended for patients who do not have asthma

- FOLLOW-UP
    - Within 2 weeks of discharge from hospitalization
    - Consider referral to Pulmonology due to risk of pulmonary fibrosis/scarring with each ACS episode

STROKE

Stroke in sickle cell disease is an **EMERGENCY**. Acute ischemic stroke is most common in patients with sickle cell disease, however other types can occur and should not be overlooked. Also be sure to rule out infection.

****If you suspect that a patient with sickle cell disease has had a stroke, immediately notify the hematology attending on call!!****

DIAGNOSIS & MANAGEMENT

1. Imaging – *CRITICAL*
    a. Brain MRI/MRA is ideal
    b. Can do head CT if patient is not stable
2. Labs
    a. CBC
    b. Retic
    c. Quantitative Hgb S
    d. Type & screen
3. Transfusion – Goal is Hgb S < 30% (trait level), Hgb ~ 10 g/dL
    a. Exchange transfusion is preferred, especially with confirmed ischemic stroke or TIA
    b. Simple transfusion can be performed when Hgb ≤ 8.5 g/dL or if there is a delay in coordinating exchange transfusion

SPLENIC SEQUESTRATION

Splenic sequestration is a life-threatening complication of sickle cell disease, characterized by acute drop in hemoglobin and enlarged spleen on physical exam. A large volume of blood is trapped in the spleen which can lead to hypovolemic shock and death. It is seen in patients who have not auto-infarcted their spleens (HbSS/HbSB0Thal < 5 years of age, teens/young adults with HbSC/HbSB+Thal).

- SIGNS & SYMPTOMS
    - Abdominal pain and distension
    - Enlarged spleen (≥3 cm below LCM)
    - Sudden drop in counts (Hgb, platelets) with normal retic
- MANAGEMENT
    - Transfusion – Small aliquots (5 mL/kg) over 3 hours to prevent hyperviscosity
        - Spleen will auto-transfuse and release trapped cells
        - Small volumes to prevent fluid overload
    - Frequent CBCs to monitor transfusion response
    - Fluid resuscitation to maintain euvolemia
    - Serial spleen exams
- FOLLOW-UP
    - Family education on how to monitor spleen size and when to call if concerned
    - Consider surgical splenectomy WHEN STABLE if patient has had ≥ 2 episodes in 12 months (try to avoid doing before 2 years of age)
    - If under 2 yrs and a candidate for surgical splenectomy, consider putting on chronic transfusion to prevent subsequent episodes until spleen can be removed

HEPATIC SEQUESTRATION

SIGNS & SYMPTOMS

- RUQ pain
- Rapidly increasing hepatomegaly
- Failing Hct
- Transaminitis and coagulopathies can occur with intrahepatic cholestasis, which is a variant of hepatic sequestration

MANAGEMENT

- Aggressive blood volume replacement, usually simple transfusion
- As with splenic sequestration, use smaller volumes to avoid hyper-viscosity
- Monitor CBCs closely after transfusion due to risk of hyper-viscosity syndrome
- For intrahepatic cholestasis, treatment is exchange transfusion and FFP to reverse coagulopathy

PRIAPISM

Priapism is an unwanted erection in the absence of sexual desire or stimulation, high prevalence in patients with sickle cell disease (particularly HbSS). It can occur at any age, however it is a more significant clinical problem after puberty. Major/prolonged episodes (≥ 4 hours) have greater potential to cause permanent damage to penile tissue

DIAGNOSIS/SIGNS & SYMPTOMS

- Painful, unwanted erection that has not resolved
- Common precipitating factors include sexual activity, fever, and/or dehydration

MANAGEMENT

- Pain control
- Phenylephrine 30 mg Q6H
- Urology consult for possible aspiration of blood from the corpus cavernosum +/- saline irrigation, dependent upon duration of erection
- Correction of dehydration if present

APLASTIC CRISIS

- Acute drop in hemoglobin with accompanying reticulocytopenia
- Infection is most common cause, predominantly Parvovirus B19.
- Can also happen as a side effect of Hydroxyurea
- Management is transfusion support/symptom management until counts normalize, which can take 2-14 days
- If caused by Hydroxyurea, medication is held until counts normalized and restarted at lower dosing to prevent further cytopenias.

Transfusion Medicine

TRANSFUSION IN PEDIATRIC ONCOLOGY

- Parameters for transfusion: Hb ≤ 7 (or symptomatic) and platelets ≤ (or symptomatic)
    a. PRBC transfusion of 10-15 ml/kg will raise Hb by approximately 3g/dL.
        - PRBC may be administered over 2-4hrs
        - 1 unit of PRBCs is approximately 250-300ml volume
    b. Platelets: Transfuse 10ml/kg of apheresed platelets.
        - May administer over 30 mins -1 hour
        - Each unit of apheresed platelets is equivalent to approximately 6 units of platelets.
- Maintain Hb ≥ 10 for patients receiving XRT (Radiation therapy)
- If pt is having an invasive procedure (i.e. Central Line placement) keep plts ≥ 50,000
- Oncology patients should receive *LEUKOREDUCED, IRRADIATED BLOOD*
    c. Leukocyte reduction decreases alloimmunization to HLA antigens and the incidence of febrile transfusion reactions
    d. Irradiation: prevents transfusion associated GVHD in immunocompromised pts
    e. Washing: RBC may be washed, which removes plasma. This may be indicated in patients who experience recurrent allergic transfusion reactions

- Fresh Frozen Plasma
    f. FFP is plasma frozen within 8-24 hrs of collection
    g. It contains all coagulation factors
    h. Plasma components must be ABO-compatible with the recipient
    i. Recommended administration dose is 10-15 ml/kg over 2-4 hrs
        - Expected increase in 15-20% in factor levels
        - 1 Unit of FFP is 200-250 ml in volume
        - Effect of FFP lasts 6-12 hours
    j. Indications for transfusions
        - Acute bleeding or in preparation of invasive procedure in patients with elevation of PT and/or PTT (liver dysfunction, DIC, etc.)
        - Coagulation factor replacement in factor deficient patient with bleeding, when about to undergo an invasive procedure or when factor concentrates are not available
        - Replacement fluid in plasma exchange to treat TTP/HUS

- Cryoprecipitate
    k. Contains fibrinogen, Factor VIII, Von Willebrand Factor and Factor XIII
    l. Indications: Hypofibrinogenemia or dysfibrinogenemia
    m. Each units is 10-15 ml
    n. Administer as 1-2 units/10kg, this will increase fibrinogen by 60-100 mg/dL

Transfusion Reactions

Non-Hemolytic Transfusion Reaction

Febrile:

Occurs during or shortly after transfusion and is due to leukoagglutination or cytotoxic antibodies against leukocytes. Symptoms include fever, chills and diaphoresis. Prevent by giving leucocyte reduced blood products

Treatment:

1. Acetaminophen 10mg/kg PO

2. Antihistamines (Diphenhydramine 1mg/kg IV)
3. Steroids (Prednisone 2mg/kg PO or Methylprednisolone 2mg/kg IV)

Allergic:

Occurs during or shortly after transfusion and is caused by antibodies against plasma proteins. Symptoms include urticarial rash, facial and mucous membrane swelling.

Treatment:

1. Antihistamines (Diphenhydramine 1mg/kg IV)
2. Steroids (Prednisone 2mg/kg PO or Methylprednisolone 2mg/kg IV)

Anaphylaxis:

Symptoms include rash, face and mucous membrane edema and respiratory symptoms.

Treatment:

1. Airway and cardiovascular support
2. Epinephrine (1:1000) 0.01mg/kg or 0.01ml/kg IM (max dose 0.5mg)
3. Antihistamines (Diphenhydramine 1mg/kg IV)
4. Steroids (Methylprednisolone 2mg/kg IV)
5. IV Fluids

Hemolytic Transfusion Reaction

These are most commonly due to ABO incompatibility. Patient may have fever, chills, tachycardia, flushing, hypotension, shock, acute renal failure, DIC, chest, abdominal and lower back pain, nausea, emesis, hemoglobinuria. Positive labs - Coombs and indirect hyperbilirubinemia.

Treatment:

1. IVF
2. Forced diuresis (may use furosemide)
3. Steroids
4. Antihistamines
5. Treat shock
6. Treat DIC

Delayed Hemolytic Transfusion Reaction (DHTR)

DHTRs are defined as a hemolytic transfusion reaction that occurs more than 24 hours following transfusion, most commonly present 1-2 weeks after PRBC transfusion. They typically occur as a response to a foreign RBC antigen to which the recipient was previously exposed. Most common antigens are those of the Kidd or Rh system.

Lab Findings

- Increased LDH
- Increased indirect bilirubin
- Decreased haptoglobin
- Positive Coombs and DAT
- Low hemoglobin
- Increased retic count with ongoing DHTR

Treatment

- Monitor hemoglobin closely until hemolysis has ended (determined by severity of hemolysis)
- With brisk hemolysis, hydrate and monitor renal function closely
- Hyperhemolytic crisis – Seen most often in patients with sickle cell disease, rare type of DHTR where transfused RBCs **AND** patient's own RBCs are hemolyzing. Treat with IVIG and glucocorticoids.

Further Management

- Document antibody to prevent further exposure
- Extended matching (phenotype, genotype) for high risk populations (sickle cell disease)

Hemophilia

For all suspected and actual bleeds give dose of IV factor prior to any and all evaluations. Family should always have an emergency dose of their child's specific Factor VIII replacement on hand. Contact Hematologist on call upon presentation for dosing recommendations.

1. Minor Bleed – 25 units/kg of emergency Factor VIII replacement (50% dosing)
2. Major Bleed – 50 units/kg of emergency Factor VIII replacement (100% dosing)

*For any major bleeds, patient will likely need to be admitted for monitor and further Factor VIII replacement.