Hematology and Oncology for the Pediatric Anesthesiologist

Eric Wittkugel, MD
Conflict of Interest Statement

• I have no relevant relationships / affiliations with any proprietary entity producing health care goods or services.

• Thanks to Ann Bailey, MD, FAAP and the other previous lecturers.
Core Content Hematology/Oncology

1. Anatomy and Physiology
   a) Prenatal and postnatal development

2. Clinical Science
   a) Hematology
      (1) anemias
      (2) coagulation disorders
   b) Oncology
      (1) leukemia
      (2) neuroblastoma
      (3) retinoblastoma
      (4) sarcomas / osteosarcomas
      (5) Wilms tumor
   c) Chemotherapeutic agents and side effects
   d) Radiotherapy
   e) Bone marrow and stem cell transplants
      (1) graft versus host disease
   f) Immunologic disorders (congenital and acquired)
Neonate: Coagulation

• Coagulation and fibrinolytic factors do not cross placenta

• Vit K dependent factors (II, VII, IX, X), factors XI and XII, prekallikrein, kininogen:
  – ≤ 50% adult levels at birth, then slowly rise

• TEG, euglobulin clot lysis time, plt fxn (PFA-100) : coagulation equivalent or better than adults

• Bleeding unusual with normal vitamin K levels
Developmental Hemostasis

• Normal newborn: reduced levels of most procoagulants and anticoagulants

• Preterm infant
  – ↑ PT, PTT, ↓ anticoagulant proteins (C, S, AT-III)
  – ↑ Risk for bleeding (may contribute to IVH)

• Despite differences, healthy neonates have normal hemostasis

• Illnesses that disrupt hemostasis in neonate may predispose to hemorrhage or thrombosis
  – Sepsis, hypoxia, hypotension
### Reference Values Healthy Children

<table>
<thead>
<tr>
<th>TEST</th>
<th>28-31 WK GESTATION</th>
<th>30-36 WK GESTATION</th>
<th>FULL TERM</th>
<th>1-5 YR</th>
<th>6-10 YR</th>
<th>11-18 YR</th>
<th>ADULT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCREENING TESTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT (sec)</td>
<td>15.4 (14.6-16.9)</td>
<td>13.0 (10.6-16.2)</td>
<td>13.0 (10.1-15.9)</td>
<td>11 (10.6-11.4)</td>
<td>11.1 (10.1-12.0)</td>
<td>11.2 (10.2-12.0)</td>
<td>12 (11.0-14.0)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>108 (80-168)</td>
<td>53.6 (27.5-79.4)</td>
<td>42.9 (31.3-54.3)</td>
<td>30 (24-36)</td>
<td>31 (26-36)</td>
<td>32 (26-37)</td>
<td>33 (27-40)</td>
</tr>
<tr>
<td>Bleeding time (min)</td>
<td></td>
<td></td>
<td></td>
<td>6 (2.5-10)</td>
<td>7 (2.5-13)</td>
<td>5 (3-8)</td>
<td>4 (1-7)</td>
</tr>
</tbody>
</table>

Nelson Textbook of Pediatrics 2011
Sites of hematopoiesis

A practical approach to pediatric anesthesia, Holzman, Mancuso, Polaner 2008
## Hb at different ages

<table>
<thead>
<tr>
<th>AGE</th>
<th>Hemoglobin values (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>17</td>
</tr>
<tr>
<td>3 months</td>
<td>10-11</td>
</tr>
<tr>
<td>2 years</td>
<td>12.5</td>
</tr>
<tr>
<td>3-5 years</td>
<td>12.5-13</td>
</tr>
<tr>
<td>5-10 years</td>
<td>13-13.5</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>14.5</td>
</tr>
</tbody>
</table>
Physiologic anemia of infancy

- Normal decline in Hb over first few months
- Physiologic nadir at 8 – 12 weeks, Hb 9-10 g/dl
- ↓Fetal Hb, ↑Hb A results in more O₂ tissue delivery
- Down regulation of EPO, ↓erythropoiesis, ↓Hb
- When tissue O₂ needs > delivery, ↑EPO, ↑Hb
- Premature infants drop faster/farther
- Hb 7-9 g/dl common at 3-6 weeks of age
- In former preemies, HCT < 30 risk factor for postoperative apnea
Hb dissociation curve

Percent saturation ($\text{sO}_2$, %)

Oxygen partial pressure ($\text{pO}_2$, mmHg)

- Temp
- pH
- PCO2
- 2,3DPG
- ATP

Fetal hemoglobin
Adult hemoglobin
Hemolytic anemia

• Hereditary Spherocytosis: autosomal dominant
  – Splenectomy eliminates spherocyte destruction in spleen

• G-6-PD deficiency: X-linked
  – hemolysis with exposure to triggers
  – Avoid sulfonamides, nitrofurans, antimalarial, fava beans, toluidine blue
  – Prilocaine, lidocaine: cause methemoglobinemia; can’t use methylene blue
Thalassemias
Genetic defects in production of globin chains of Hb

http://sickle.bwh.harvard.edu/thal_inheritance.html
Thalassemias

• $\alpha$-thalassemia: 4 allele loci
  – 3 missing = severe anemia, 2 missing = mild anemia, 1 missing = clinically silent

• $\beta$-thalassemia: 2 $\beta$-globin gene loci
  – dysfunctional genes both loci= severe anemia with lifelong txns ($\beta$ thal major)
  – Hepatosplenomegaly, development delay
  – Cardiomyopathy, Fe overload
  – Thalassemic facies
  – Stem cell transplantation
Sickle cell disease

- Erythrocyte deformation, hemolysis, anemia, microvascular occlusion, recurrent ischemic injury in all organ systems
- Hb S mutation: valine instead of glutamine at 6th position in beta globin molecule
- During oxygen desaturation, Hb S polymerizes, red cell deforms, results in microvascular obstruction
- 1:396 births among US African Americans
- Most common genetic disease on newborn screening
Complications of SS disease

- Acute splenic sequestration
- Aplastic crisis
- Functional asplenia
- Vaso-occlusive crisis
- Priapism
- Stroke
- Acute chest syndrome
- ↓ Cardiac, renal function

NEJM 359: 2254, 2008
Perioperative Management

• ↑ perioperative morbidity, mortality (up to 1.1%)
• T&A, laparotomy, thoracotomy: greatest risk
• Preoperative
  – Hematology consultation
  – Hydration 1.5 x maintenance
• Preoperative transfusion
  – Simple: Hb ≥ 10
  – Aggressive: Hb ≥ 10 and Hb S < 30%
    • For high risk patients (CVA, ACS, CV and neurosurgery)
Perioperative Management

• Avoid hypoxemia, vascular stasis, ↓ BP
• Oxygenation, hydration, normothermia
• Tourniquet use controversial
• Postoperative period – highest complications
  – Postop admission, close monitoring
  – Supplemental oxygen
  – Analgesia
  – Hydration
Evaluation of perioperative bleeding

• Platelet count, PT, PTT

• If normal,
  – thrombin time to evaluate fibrinogen function
  – VWF testing (PFA as screen)
  – Further specific workup
  – Hematology consultation
Hemophilias

• X-linked recessive
  – Hemophilia A: factor 8 (1/5000 males)
  – Hemophilia B: factor 9 (1/30,000 males)

• Dx: ↑aPTT, other screening tests normal
  – Mix normal plasma + patient plasma → correct PTT
  – Specific factor 8, 9 levels

• Severity
  Severe: <1% factor levels
  Moderate: 1-5%
  Mild: 6-30%
Factor Replacement

• Mild Hemophilia A/minor surgery: 0.3mcg/kg DDAVP (release of endogenous factor from endothelial storage)

• Hemophilia A/major surgery: 100% levels, followed by 30-50% for 2 weeks
  – Factor 8: 0.5 IU/kg raises levels 1%
    • E.g., 30 kg with 20% level to start needs 80 x 30 x 0.5=1200 units
  – Factor 8: 1st generation (Recombinate)
    • half life: 8-12 hrs
  – Factor 8: 2nd generation (Kogenate-FS): no albumin
  – Factor 8: 3rd generation (Advate): no added protein
Hemophilia B replacement

• Purified factor 9: from human plasma
• Recombinant factor 9: half life 16 hrs; no albumin
• Dose for major surgery: 1-1.2 units/kg will raise 1%
  – E.g., 30 kg child for craniotomy with baseline level of 20% needs 80 x 30=2400 units to get to 100% level
VWF mediates initial events in hemostasis

- Platelets tether to endothelial injury site by binding of subendothelial VWF to GpIb protein
- Plts activated, exposing GpIIb/IIIa complex on plt surface
- Interacts with fibrinogen, VWF to create platelet aggregation
Von Willebrand Disease

- 1% population, most common hereditary bleeding disorder
- Excessive mucocutaneous bleeding
- Family history (type 1 dominant, type 3 recessive)
- PFA 100 has replaced bleeding time as screen
- Abnormal VWF labs:
  - Plasma VWF antigen (VWF:Ag)
  - Plasma VWF activity (ristocetin cofactor activity, VWF:RCo and VWF collagen binding, VWF:CB)
  - Factor VIII activity (FVIII): secondary decrease
Von Willebrand Disease

• Type 1 (80% cases): Quantitative deficiency of qualitatively normal VWF; MILD
• Type 2: qualitatively abnormal VWF
• Type 3: absence of VWF protein; SEVERE, very rare
• Treatment: ↑plasma level of VWF and factor VIII
  – DDAVP (desmopressin)-promotes release of VWF from endothelial cells, increases factor VIII levels Type 1
  – Plasma derived VWF concentrates with factor VIII
    Humate P, Alphanate (viral inactivation)
    Type 2, 3, major surgery (even with Type 1)
  – Cryoprecipitate not indicated
Thrombocytopenia

Immune Thrombocytopenic Purpura (ITP)
- Peak 1-4 years of age, often after viral infection
- Usually spontaneously resolves
- Antibodies against platelet membranes; accelerated clearance by macrophages in spleen
- Rx for plt <10k or bleeding
- Steroids, IVIG;
- Splenectomy for severe cases

http://www.ufrgs.br/imunovet/molecular_immunology/pathohomotissueimmunity.html#blood
### Age distribution of childhood cancers

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>0–4 years (%)</th>
<th>5–9 years (%)</th>
<th>10–14 years (%)</th>
<th>15–19 years (%)</th>
<th>0–19 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemias</td>
<td>36.1</td>
<td>33.4</td>
<td>21.8</td>
<td>12.4</td>
<td>25.2</td>
</tr>
<tr>
<td>Central nervous system tumors</td>
<td>16.6</td>
<td>27.7</td>
<td>19.6</td>
<td>9.5</td>
<td>16.7</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>3.9</td>
<td>12.9</td>
<td>20.6</td>
<td>25.1</td>
<td>15.5</td>
</tr>
<tr>
<td>Carcinomas and other malignant epithelial tumors</td>
<td>0.9</td>
<td>2.5</td>
<td>8.9</td>
<td>20.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Soft-tissue sarcomas</td>
<td>5.6</td>
<td>7.5</td>
<td>9.1</td>
<td>8.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Germ-cell, trophoblastic, and other gonadal tumors</td>
<td>3.3</td>
<td>2.0</td>
<td>5.3</td>
<td>13.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Malignant bone tumors</td>
<td>0.6</td>
<td>4.6</td>
<td>11.3</td>
<td>7.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Sympathetic nervous system tumors</td>
<td>14.3</td>
<td>2.7</td>
<td>1.2</td>
<td>0.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Renal tumors</td>
<td>9.7</td>
<td>5.4</td>
<td>1.1</td>
<td>0.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>6.3</td>
<td>0.5</td>
<td>0.1</td>
<td>0.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Hepatic tumors</td>
<td>2.2</td>
<td>0.4</td>
<td>0.6</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Other and unspecified malignant neoplasms</td>
<td>0.5</td>
<td>0.3</td>
<td>0.6</td>
<td>0.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

General Considerations in Pediatric Cancer

• Bone marrow suppression (from disease or therapy)
  – Anemia
  – Thrombocytopenia - bleeding
  – Neutropenia – infection risk

• Some diseases may have high cell counts with increased risk of HTN, clot, bleeding, stroke

• With treatment, can see:
  – **Tumor lysis syndrome** (esp ALL, Burkitt’s lymphoma)
  – Renal insufficiency from release of uric acid
  – Metabolic derangements (↑potassium, ↑phosphate, ↓calcium)
    • Hydration, prophylactic allopurinol, rasburicase (degrades uric acid)
  – Dexamethasone may trigger
Chemotherapy side effects and toxicity

- Steroids: adrenal suppression, increased appetite, facial swelling, HTN, mood swings, GI ulceration
- L-asparaginase: hyperglycemia, pancreatitis, liver dysfunction
- Anthracyclines (e.g. doxorubicin, daunorubicin): cardiomyopathy [should have baseline and follow-up echo]
- Bleomycin: pulmonary fibrosis (exacerbated by high FiO2)
- Cisplatin and ifosfamide: renal tubular damage, Fanconi syndrome, electrolyte wasting (magnesium)
- Methotrexate: renal failure at high doses
- Vinblastine, vincristine: peripheral neuropathy, seizure
- Ara-C: mucositis, hepatitis, N/V, neurotoxicity
Leukemia

- Single most common childhood malignancy
  - 3250 new cases / year in US
- ALL - 77% of leukemias
  - Peak age 2-3 years; more common with certain chromosomal abnormalities (trisomy 21)
  - Higher in twin of affected child
  - Presentation may be non-specific – fatigue, pallor, bruising, fever, bone or joint pain
  - Survival approaches 90%, but fatal without Rx
- AML – long-term survival 70%
- Relapse has poor prognosis
Hodgkin Lymphoma

• Often present with painless lymphadenopathy
• Usually have some degree of mediastinal involvement
• Systemic symptoms (fever, weight loss, sweats) important in staging
• Current treatment: multi-agent chemo with or without low-dose involved-field radiation
  – Prior radiation-only treatment had high long-term adverse effects including second tumors
• Prognosis: 5 year survival >95% for favorable types and ~90% for advanced disease
Non-Hodgkin lymphoma

• NHL in children is generally high grade/aggressive (while in adults is generally less aggressive)

• Types
  – Burkitt – nearly all B cell
    • Abdominal or head & neck forms
  – Lymphoblastic (80% T cell)
    • Frequently presents as mediastinal mass
  – Diffuse large B-cell
  – Anaplastic large cell (70% T cell)

• Primary modality of treatment is multiagent systemic chemotherapy with intrathecal chemotherapy
Anterior mediastinal mass

- Should be considered in newly-diagnosed lymphoma, ALL, neuroblastoma, germ cell tumor
- Majority caused by lymphoma, followed by bronchial cysts, teratoma, vascular malformation, neurogenic tumors
- Clinical presentations
  - SVC obstruction
  - Pulmonary artery compression
  - Tracheal obstruction
- Combination of airway and vascular compression can cause dyspnea and syncope
- Careful history including postural signs
Anterior mediastinal mass – strongest risk factors for perioperative complications

Clinical signs and symptoms
  Orthopnea
  Upper body edema (signs of SVCS)
  Stridor
  Wheeze

Diagnostic imaging findings
  Tracheal, bronchial, or carinal compression
  Great vessel compression, SVC obstruction
  Pulmonary artery outflow obstruction
  Ventricular dysfunction
  Pericardial effusion

Anterior mediastinal mass: Anesthetic Management

- Weigh risks, benefits, acuity
- Consider surgery under local
- Perform minimal procedure to obtain tissue
- Temporize with radiation or steroids
- General anesthesia with backup planning
  - Maintain spontaneous ventilation
  - Rigid bronchoscope with skilled endoscopist
  - Realize that compression and cardiovascular collapse can occur with an endotracheal tube in place
  - Reposition patient (lateral or prone)
  - Sternotomy and elevation of mass; possible ECMO or CPB
Smith’s Anesthesia for Infants and Children, 2011
Neuroblastoma

- Most common extracranial solid tumor in kids
- Most common age of diagnosis is 18 months
  - (85% of cases occur < 4 years)
- Derived from neural crest cells; majority present in abdomen, with 2/3 of those being from adrenal. Often presents with incidental discovery of abdominal mass.
  - Mass may compress renal vessels, causing HTN;
  - rarely may secrete catechols
- Metastases
  - Hepatic enlargement, subcutaneous nodules.
  - Bone infiltration may cause pain; “racoon eyes” if retro- or periorbital.
Neuroblastoma

• Excellent prognosis if diagnosed at early stage (also at age < 1 year); very poor prognosis if advanced stage

• Staging requires bilateral bone marrow aspirates and bx; evaluation of metastatic disease by MIBG scan

• Treatment:
  – Low-risk: surgery alone is sufficient with excellent survival
  – Intermediate-risk: induction chemotherapy followed by local control with surgery and radiation therapy
  – High-risk: induction chemotherapy followed by surgery and radiotherapy; may be followed with TBI and autologous bone marrow transplantation
Wilms Tumor

• 650 new cases / year in US
• Vast majority of renal tumors in children are Wilms
• 90% present with asymptomatic abdominal mass
• Uncommon manifestations
  – Hypertension (increased renin), abdominal pain, hematuria
  – Acquired von Willebrand like condition
• Survival > 90%
• If resectable: primary nephroureterectomy + lymph node sampling
• Chemo depending on histopathologic type and surgical stage
• Metastases most commonly to lung (80%)
• Bilateral Wilms: chemo to shrink; attempt to excise but preserve renal function
Brain tumors

• 2\textsuperscript{nd} most common type of childhood tumor (after leukemia)
• Equally divided between supratentorial and infratentorial
• Pathologic classification is made by cell of origin and degree of malignancy
• Presentation determined by location and rate of growth
  – Supratentorial may produce focal neurologic signs
  – Rapid expansion w/ cerebral edema or CSF blockage may cause increased ICP
  – Posterior fossa tumors
    • Medulloblastoma may present with ataxia and vomiting
    • Ependymoma may present with cranial nerve palsy
Retinoblastoma

- Most common pediatric intraocular malignancy (250 cases/yr)
- Often presents with leukocoria (white reflection)
- 90% of cases diagnosed < 3 years
- Mutations of RB1 tumor suppressor gene
  - Hereditary form (one constitutional, one somatic mutation) - often bilateral
  - Non-hereditary form (both somatic) – unilateral, later presentation
- Treatment depends on extent of involvement
  - Enucleation for advanced disease
  - Chemotherapy and/or radiation
Sarcomas

• Osteosarcoma – most common malignant bone tumor in children; peaks in adolescence
  – Genetic component in some, e.g. higher incidence in hereditary retinoblastoma patients; majority have no known abnormality
  – Majority receive neoadjuvant chemo followed by limb salvage surgery. 65% five-year survival with non-metastatic disease

• Ewing sarcoma – bone and soft tissues
  – In same morphologic spectrum with PNET
  – Survival improving with effective chemo; local control w/ surgery or XRT or both

• Rhabdomyosarcoma – more than half of soft tissue sarcomas in children; multiple sites (orbital, bladder/prostate, nasopharyngeal, extremity). Often requires multimodal therapy (chemo, surgery, XRT)
Radiotherapy

• May require anesthesia to allow immobilization for daily treatments
• Total dose is fractionated to allow healthy tissue the greatest chance for repair
• Newer techniques may minimize damage to surrounding tissue (precise focus, proton therapy, intensity-modulation)
• **Acute effects include mucositis, skin changes, myelosuppression**
• **Late effects reflect treated area - may include neurocognitive deficits, second cancers, cardiac effects, pulmonary fibrosis, chronic enteritis, hepatic or bladder fibrosis**
Bone marrow and stem cell transplants

- Currently utilized in leukemia, lymphoma, solid tumors, myelodysplasia, aplastic anemia, hemoglobinopathies (SS), and congenital immune and metabolic deficiencies

- May be autologous, syngeneic, or allogeneic (HLA-matched)

- Cumulative toxicity from underlying illness, complications of past therapy, transplant conditioning, complications from long-term myelosuppression, and graft-vs-host disease
Hematopoietic Stem Cell Transplantation

• Phases:
  – Conditioning regimen – high dose chemo +/- radiation to eradicate malignancy, clear marrow space, and suppress immune system
  – Infusion of stem cells
  – Engraftment

• Morbidity/mortality depend on
  – Patient age, primary disease, comorbidities
  – Histocompatibility between donor and recipient
  – Development of infection, regimen-related toxicity, and alloreactivity
Bone marrow transplant: regimen-related toxicity

- Mucositis
- Sinusoidal obstruction syndrome (veno-occlusive disease): hepatomegaly, jaundice, weight gain
- GI: hemorrhage, infection, opiate-induced abdominal pain and distention
- Pulmonary: infection, bleeding, edema, ARDS, inflammatory processes
- Cardiac: drug toxicity, hypertension
- Renal: acute renal failure; thrombotic microangiopathy
- CNS: infection, hemorrhage, encephalopathy, peripheral neuropathy
Graft-versus-host Disease

- Recognition of recipient antigens by donor T cells
- Acute GVHD (before day 100) is common (40-60%, depending on match)
  - Inflammatory dermatitis, enteritis, hepatitis, fever, thrombocytopenia, anemia
- Chronic GVHD (after day 100) (20-40%)
  - Resembles autoimmune disease with multi-organ system involvement
  - Dry mouth, skin changes, esophagitis, pulmonary dysfunction, alopecia, thrombocytopenia
Immunologic disorders:
Sites of cellular abnormalities in congenital immunodeficiencies

Nelson Essentials of Pediatrics, Sixth Edition; Figure 73-1
References

• Latham GJ, Greenberg RS. Anesthetic considerations for the pediatric oncology patient--part 2: systems-based approach to anesthesia. Paediatr Anaesth 2010; 20:396-420
• Smith’s Anesthesia for Infants and Children, 8th edition, Chapter 36 (systemic disorders)
• A practical Approach to Pediatric Anesthesia, Holzman, Mancuso, Polaner, 2008