PREMATURITY

Apnea of Prematurity
Necrotizing Enterocolitis
Retinopathy of Prematurity
Intra-ventricular Hemorrhage
Bronchopulmonary Dysplasia
Patent-Ductus Arteriosus
Definition of Apnea

Cessation of breathing ≥ 15 seconds or less if accompanied by:

Bradycardia
Significant hypoxemia
Cyanosis
Causes of Apnea in the Neonate

Drugs
Intracranial Pathology
Prematurity
Reflux
Thermal Instability
Infection-sepsis, meningitis
Metabolic Disorders
Impaired Oxygenation
Types of Apnea of Prematurity

Central (40% of apneic episodes): means no respiratory effort
Obstructive (10%): Airway closure
Mixed (50%)
Treatment

Supplemental oxygen
Gentle tactile stimulation
Temperature control
CPAP (continuous positive airway pressure)/ventilation (positive pressure)
Methylxanthines
Theophylline/Caffeine

Used when frequent episodes
Prolonged duration
Severe in nature
Not controlled by nonpharmacologic means
Methylxanthine Mechanism of Action

Stimulate the adrenal medullary center
Increase receptor responsiveness to carbon dioxide
Adenosine receptor blockade may be the central effects
Peripherally-increase diaphragmatic contractility, decrease diaphragmatic fatigue, and improve resp. muscle contraction. Also, increase catecholamine release and metabolic rate.
Dosing of Theophylline and Caffeine

Theophylline: 6mg/kg loading dose then 1-2mg/kg IV q8hr (q12-6hrs); Levels desired usually 6-12mcg/ml.

Caffeine Citrate: 20mg/kg (10mg/kg caffeine) then 5-10mg/kg (2.5-5mg/kg caffeine); Levels desired are usually 5-20mcg/ml.
Toxicities of Theophylline

- Tachycardia
- Irritability
- Reflux
- Emesis
- Feeding intolerance
- Seizures
- Sodium and/or potassium wasting
Caffeine Advantages

Wide therapeutic window
Less toxicities associated with it; therefore, tolerated better
Longer half-life so less fluctuation in level
Monitor levels less frequently
Some patients who do not respond to theophylline may respond to caffeine
Doxapram

May stimulate peripheral chemoreceptors
May increase ventilation
May increase blood pressure (normally with slightly higher doses); Other adverse effects: GI problems, CNS problems (jitteriness, irritability, seizures, disturbed sleep)

Dose: LD: 2.5 to 3mg/kg over 15-30 minutes; 1mg/kg/hr; may increase by 0.5mg/kg/hr to a maximum of 2.5mg/kg/hr.
Retinopathy of Prematurity

Stage I-V
The stages represent changes in the vascularization of the blood vessels to the eyes.
Stage V is complete retinal detachment
Retinopathy of Prematurity (Continued)

Incidence: 12-29% of 24-27 week premature infants get >stage III retinopathy
2-20% of 28-31 week premature infants get >3 stage III retinopathy

Long term problems: (in <1000gm birthweight infants) blindness 3.4%, severe visual handicap 2.5%, slight visual impairment 8.5%, normal vision in 85.6%
Pathogenesis of ROP

Premature birth exposes the infants to larger amounts of oxygen which is normally regulated intrauterine is one hypothesis. Other possible risk factors include light, hypercarbia, acidosis, and lack of vitamin E.
Treatment of ROP

Cryotherapy
Laser therapy
Intra-ventricular Hemorrhage (IVH)

Grade I-IV

Thought to occur due to immature development of the blood vessels in the brain and their susceptibility to hypoxic injury or changes in blood pressure or hypercarbia.

Grade I is confined to the germinal matrix.

Grade III is an intraventricular hemorrhage with ventricular dilatation. (Grade II is without dil.)

Grade IV is any of the above with an assoc. intraparenchymal hemorrhage.
Outcome

Infants with grade I or II IVH have similar outcomes to preterm infants without IVH. May have deficits in reading or other learning problems. Small percent have major disabilities. Grade III or IV are at a high risk for major handicaps as well as other less severe handicaps. More likely to develop posthemorrhagic hydrocephalus and seizures.
Prevention and Treatment

Most risk factors are associated with altering cerebral flow or blood pressure. Avoid risk factors such as pneumothorax, hypotension, hypertension, asphyxia, hyperosmolar substances, coagulation problems, hyperglycemia, PDA, seizures. Many drugs have been studied but a good treatment strategy remains to be defined. Indomethacin has been the most promising.
Indomethacin

May decrease production of prostaglandins which are known to vasodilate.

Dose studied was low-dose: 0.1mg/kg 6 to 12 hours after birth and then 0.1mg/kg q24 hrs for 2 more doses.

Seemed to reduce incidence of IVH in 600-1250 gram neonates.
Necrotizing Enterocolitis (NEC)

Intestinal necrosis occurring most commonly in premature infants.

Symptoms include abdominal distension, emesis, metabolic acidosis, apnea, temperature instability, blood in stools, and retention of feedings.

May progress to perforation (free air on abdominal radiograph) and sepsis.

Some institutions use a staging system-IA/IB-IIA/IIIB
Causes of NEC

Exact cause is uncertain; thought to be multifactorial
Thought to be due to intestinal bacteria in an injured intestinal mucosa.
Numerous factors can cause injury- toxins, infection, malnutrition, hyperosmolar substances, rapid advancement of feeds etc.
The intestinal mucosa is more prone to injury due to increased permeability, and decreased immune system.
Treatment of NEC

Bowel rest-Normally 7-14 days dependent on severity
IV antibiotics
Resuscitation as needed (inotropes, fluids)
Surgery
Bronchopulmonary Dysplasia (BPD)

Definition: Chronic lung disease (CLD) in an infant that results in the need for continued oxygen at the time of discharge or cannot be discharged at term age because of continued oxygen.

Also defined as CLD associated with supplemental oxygen dependency at 28 days of life and/or at 36 weeks’ postconceptional age, clinical signs of respiratory distress, abnormal chest radiograph, and a history of oxygen requirement in the first week of life for a minimum of 3 days.
Etiology of BPD

Prematurity/Lung immaturity
Oxygen Toxicity
Barotrauma
Inflammation
Surfactant deficiency
Other factors-Nutrition
Symptoms of BPD

Rales and rhonchi
Cough
Airway hyperactivity
Hypoxemia
Tachypnea with shallow breathing and retractions
Wheezeing
Increased mucous productions
PREVENTION OF BPD

• Antenatal: Treat maternal infections, treat causes of preterm labor, stop preterm labor (tocolytics), and glucocorticoid administration (Betamethasone)

• Surfactant—Survanta or Curosurf or Infasurf—reduces RDS but not BPD

• Avoidance of oxygen toxicity and barotrauma and volutrauma

• Optimize nutrition.

• Vitamin A administration?
Surfactants

Exosurf (Colfosceril palmitate)-synthetic; contains no SP-A, SP-B, or SP-C (apoproteins that enhance spreadability), synthetic lecithin-no longer available

Survanta(Beractant)-from bovine lung, add synthetic lecithin, contains SP-C (99%), SP-B (most important protein) removed with cholesterol during extraction process.
Surfactants

Infasurf (calfactant)-newborn calves’ lungs; no synthetic lecithin, 40% SP-B, 60% SP-C

Curosurf (poractant)-pigs’ lungs; no synthetic lecithin, 30% SP-B, 70% SP-C

Lucinactant (Surfaxin) – synthetic surfactant that contains sinapultide, a peptide to mimic SP-B.

INVESTIGATIONAL
Vitamin A deficiency causes similar changes as BPD. If vitamin A deficient, may have decreased lung healing, loss of lung cilia, increased infection risk, and decreased alveoli.

Preterm infants are deficient in vitamin A since it accumulates in the third trimester via placental passage.

IM administration in studies; various dosage schemes
Early Postnatal Steroids

Hydrocortisone 1mg/kg divided q12hrs x 12 days showed decreased BPD at 36 weeks (29% vs 59%); small study

Dexamethasone also has been studied. Reduces pulmonary inflammation and decreases BPD. Increased toxicity-infection and intestinal perforation.

Cortisol deficiency is common in preterm infants. Low cortisol levels have been associated with BPD.
MANAGEMENT & DRUG THERAPY OF BPD

Mechanical ventilation
Supplemental oxygen
Restrict fluids- to prevent congestive heart failure and pulmonary edema
Hypercaloric feeds since have increased needs and fluids are restricted
Diuretics-Furosemide/chlorothiazide/spironolactone
Bronchodilators-systemic and inhaled
Corticosteroids
Treatment of any respiratory infections
Treatment Strategies: Respiratory Support

Mechanical ventilation and oxygen supplementation
Extubation to NCPAP or oxygen hood if feasible
Same as for prevention using mechanical ventilation
Treatment Strategies: Systemic Glucocorticoids

Many differences in dosing, duration, and time of onset of therapy in studies. Due to short and long-term adverse effects noted on follow-up studies, the AAP no longer recommends.

Generally dexamethasone 0.25mg/kg q12h for 2-3 days then tapered over 3-42 days had been studied.

If used, lower dose and shorter duration. Waiting until >28 days postnatal age is used by some.
Systemic Glucocorticoids (Cont)

Adverse effects: hypertension, hyperglycemia, GI bleeding, increased risk of infection

Other adverse effects - hypertrophic cardiomyopathy - benign reversible and association with neurodevelopmental delay - permanent, irreversible.

- Because of the neurodevelopmental sequelae now used more selectively for shorter courses and lower doses if it is needed.
Treatment Strategies: Inhaled Corticosteroids

Decreased inflammatory mediators

One study did not demonstrate a reduced incidence of BPD with inhaled steroid use.

Decision to use is somewhat arbitrary; use is normally to help reduce need for systemic steroids.

May reduce oxygen requirements and duration of mechanical ventilation.

May improve lung mechanics.

Less adverse effects: bronchospasm, tongue hypertrophy, oral candidiasis
Treatment Strategies: Methylxanthines

Theophylline or Caffeine to assist in extubation and prevent reintubation.

For premature infants <1000 grams, one intubation is prevented for every 2 patients treated. Optimal dosing is varying; however, theophylline levels of up to 16 mcg/ml (or even 20 mcg/ml) have been suggested and levels of 8-40 mcg/ml for caffeine.

Adverse effects: tachycardia (HR>180), agitation, feeding intolerance, rarely, arrhythmias or seizures.
Treatment Strategies: 

**Bronchodilators**

Used extensively due to increased airway resistance, airway hyperactivity, and decreased lung compliance.

Only 50% of patients with severe BPD will respond.

Side-effects may limit use (esp. CV –tachycardia, hypertension)

B-agonists and ipratropium are effective alone or in combination.

May use albuterol (acute setting)
Treatment Strategies: Diuretics

Used to reduce pulmonary edema. May use furosemide, thiazide diuretic, or combination of the diuretic plus spironolactone.
Furosemide

Short-term benefits in a neonate with BPD and pulmonary edema
Pulmonary vasodilation through prostaglandin synthesis
Improves lung compliance and oxygenation
Decreases airway resistance through possible bronchodilator effect
1-4mg/kg 1-2 times daily (oral); 1-2mg/kg/dose q12-24 hrs (IV)
Adverse Effects: dehydration, electrolyte disorders, hypercalciuria, renal stone formation
Thiazide diuretics

Chlorothiazide or hydrochlorothiazide
Improve lung compliance and decrease oxygen requirements.

Adverse Effects: electrolyte imbalances; hypercalciuria, hyperuricemia, hyperglycemia, hypokalemia, hypomagnesium
May give with spironolactone.
RSV prophylaxis

Synagis®-Palivizumab- 15mg/kg IM q month during RSV season. Murine monoclonal antibody to RSV. Approved for less than 24 months of age children with CLD if at onset of RSV season had been on oxygen within 6 months. Also labeled to prevent RSV in ≤ 35 week premature infants. AAP generally recommends for ≤ 32 weeks (If RSV season begins: if < 6 months of age and between 29-32 weeks gestational age at birth, or <1 year of age and <29 weeks gestational age at birth). Also being recommended for children < 2 years of age with hemodynamically significant heart disease.
Summary of BPD

BPD is less common due to the advent of exogenous surfactant availability.
Infants with BPD are more prone to respiratory infections, especially the first year of life.
The use of bronchodilators, steroids, and diuretics may be used.
Some institutions use vitamin A to help prevent BPD.
Kawasaki Disease

Acute, vasculitic syndrome mainly affecting children <5 years of age. Relatively uncommon in <3 months of age (1.67%). 7.6 cases per 100,000 children in the US. Has been reported in all ethnic groups. Precise cause of disease is unknown but is thought to be of infectious etiology.
Diagnostic Criteria

Fever (at least 5 consecutive days)
Rash
Bilateral conjunctivitis
Mucous membrane changes (erythema and cracking of lips, strawberry tongue)
Extremity changes (swollen hands and feet w/erythema; desquamation)
Cervical lymphadenopathy (least common in US)

Need 4 out of the 5 top major clinical findings to fit the American Heart Association’s diagnostic criteria
Other Clinical Findings

Vomiting
Diarrhea
Abdominal Pain
Arthritis
Arthralgia
Extreme Irritability
Laboratory findings for KD that may be noted

- Increased WBC
- Thrombocytosis
- Anemia
- Increase erythrocyte sedimentation rate
- Increased C-reactive protein
- Hypoalbuminemia
- Low total and HDL-cholesterol
- Sterile pyuria
- Cerebrospinal fluid pleocytosis
The Rare Age Groups

>8 years old-<10% of cases may present with arthritic complaints or GI symptoms

Infants<6 months of age may have subtle or limited findings

Some patients have atypical findings that do not fit the American Heart Association’s diagnostic criteria.

Need to consider Kawasaki Disease in anyone with unexplained, prolonged fever
Atypical or incomplete KD

Children who fail to meet the strict criteria of classic Kawasaki disease.
They have normally laboratory values consistent with classic Kawasaki disease: maximal ESR, elevated C-reactive protein (CRP), high neutrophil cell and platelet counts, and no other explanation for their illness.
Acute and Longterm Cardiac Problems

Acute changes: Acute obstruction (due to thrombosis or stenosis of vessel from inflammation/fibrosis) or coronary aneurysms can lead to myocardial infarction or sudden death.

Coronary Aneurysm or dilatation; these may regress
Treatment of KD

IVIG- 2gm/kg over 12 hours
Aspirin-80-100mg/kg/day div. into 4 doses until afebrile.
Thrombolytics if needed
IVIG

Administration
Monitoring
Adverse Effects
Salicylate Toxicity

Tinnitus
Hearing loss
Headache
Dizziness
Sweating
Mental confusion
Tachycardia
Renal failure
Tremor
Metabolic acidosis
Seizures or coma
Longterm Therapy of KD

Aspirin - decrease to 3-5mg/kg/day after acute phase for 6-8 weeks

Warfarin

Dipyridamole
Thrombosis in KD

Small thrombi - oral anticoagulant
Obstruction - may lead to MI or sudden death; may use thrombolytic therapy.
Post-thrombolytic therapy - (heparin)warfarin + aspirin
Summary of Kawasaki Disease

Characteristics

Standard treatment

Patients that are missed
Idiopathic Thrombocytopenic Purpura (ITP)-Children

Peak incidence occurs between ages 2-4 years of age. (Some articles say 5 is peak age).
Acute onset and spontaneous resolution in several weeks to months normally in younger children
Chronic ITP has an insidious onset and affects older children, more often females, but often resolves spontaneously during childhood.
It is not possible to predict which acute ITP will become chronic ITP.
Incidence: 3-10 cases/100,000 subjects <16 years or approximately 5,000 new cases/year in the US.
Definition of ITP

Diagnosis relies on the exclusion of other causes of thrombocytopenia since there is no gold standard diagnostic test. Clinical presentation, complete blood count, and examination of peripheral smear are usually done.

Autoimmune disease characterized by low platelet counts (<30,000mcg/ml) due to increased platelet destruction with no other significant hematologic abnormalities.

Normally divided into acute and chronic form based on duration of thrombocytopenia
Differential Diagnosis of ITP

Common causes of thrombocytopenia include pregnancy, drug induced (heparin, quinidine, quinine, and sulfonamides), viral infections (HIV, mono, hepatitis).

Other diseases that appear like ITP-myelodysplasia, congenital thrombocytopenias, HUS, chronic disseminated intravascular coagulation

Thrombocytopenia associated with other disorders: autoimmune disease(eg lupus), lymphoproliferative disorders (eg, chronic lymphocytic leukemia, non-Hodgkin lymphoma)

Falsely low platelet count
Bone Marrow Aspiration

Controversial

American Society of Hematology guidelines state not required if <60 years of age if typical presentation but necessary before splenectomy.

Atypical features—additional cytopenias, protracted fever, bone/joint pain, etc. may have BM done.

Patients without response may have BM

In children, BM not necessary in children who will be observed or IVIG will be given (or anti-D immune globulin).

Many pediatric hematologists will do a bone marrow if corticosteroids will be started to rule-out acute leukemias.
Mechanism of ITP

Thought to be due to viral infection causing formation of antigen-antibody complexes. The complexes bind to platelets which then are removed more readily by the reticuloendothelial system.
Treatment of ITP

Treatment is controversial

Treatment is generally not needed if platelet count is $>30,000$ cells/mm$^3$

Treatment is given if $<20,000$ with moderate mucous membrane bleeding or if $<10,000$ with minor purpura

Spontaneous, severe bleeding risk is low if $>30,000$ platelet count.

Sometimes children at risk of falling (i.e. toddlers) may be treated without signs of bleeding.
Intravenous Gamma Globulin (IVIG)

Thought to work by preventing phagocytosis of the antibody-coated platelets or eliminate immune complexes or microbial antigens.

IVIG – 0.8gm/kg x1, 1gm/kg x 2d or 0.4gm/kg x 5 days. Infusion is at a slow rate to decrease adverse effects while infusing.

Platelets normally rise within 24 hrs of dose. Peaks at 5-10 days after giving.

Adverse Effects: Flushing, chills, anaphylaxis, myalgias, hypotension, diaphoresis, nausea, fever, and headache. May pre-medicate with diphenhydramine and acetaminophen to help with adverse effects.
Anti-D Immune Globulin

Leads to removal of sensitized red blood cells by the spleen allowing the antibody-coated platelets to survive. Patients should be Rh+ to work.

Patients should not have had a splenectomy.

Patients may experience hemolysis.

Infusion time is over 10-15 minutes.

New doses being studied- 50-75 mcg/kg. This results in a quicker response. If hemoglobin <10 g/dL, a lower dose (25-45mcg/kg) may be used initially.

Adverse reactions; in approximately 4%-fever, chills, nausea, headache; body ache; drop in hemoglobin has been significant in some patients.
Steroids

Thought to inhibit platelet phagocytosis and increase capillary integrity to decrease risk of hemorrhage.

Varying dosage schemes: 4-8mg/kg per day for 7 days followed by taper until day 21. Methylprednisolone 30-50 mg/kg for 3-7 days has also been used.

Onset with IV is similar to IVIG/high-dose Anti-D immune globulin; oral onset is slower.

Adverse effects: mood swings, GI upset, weight gain
Emergency Cases

IVIG-1g/kg/day x 2-3 days plus the following 2:

IV corticosteroids-30mg/kg/day (max: 1g/day for 2-3 days.

Platelet transfusions-intermittent or continuous; normally 2-3 times the usual amount.

Antifibrinolytic therapy such as aminocaproic acid may reduce mucosal bleeding. Factor VIIa should be considered.

May extend IVIG to 5 days if continued bleeding and continuous platelet infusion may be done.
Chronic ITP in children

Approximately 10-25% of children with ITP relapse.

Chronic ITP is thrombocytopenia for greater than 6 months.

Splenectomy is deferred as long as possible since 1/3 will have spontaneous remission and only 5% will require therapy 1 year after diagnosis. Normally do if >1yr from diagnosis with symptomatic and severe thrombocytopenia.

Anti-D immune globulin or IVIG or steroids (but not long-term)
Splenectomy

Response generally within days.
Children: 70-80% attain complete remission
Steroids or IVIG or anti-D may be given prior to surgery to maintain hemostasis during surgery.
Increased risk of bacterial sepsis.
Dependent on immunization history-immunize with haemophilus influenzae type b, pneumococcal vaccine, meningococcal vaccine.
Chronic Refractory ITP in Children

Azathioprine-2-3mg/kg/day orally to maintain mild neutropenia (alone or in combination with prednisone)

Vincristine-0.02mg/kg (max: 2mg) or Vinblastine-0.1mg/kg (max:10mg) at 5 to seven day intervals for maximum of 3 times.

Cyclophosphamide-1.5gm/m² IV q4 wks

Cyclosporine

Combination chemotherapy
Adverse Effects

Vinca Alkaloids-neuropathy (numbness, paresthesia, headache), leukopenia (vinblastine)

Azathioprine-hepatotoxicity, carcinogenicity, neutropenia

Cyclophosphamide-marrow suppression, hemorrhagic cystitis, alopecia, infertility
Education

Parents should be advised not to give their child any drugs with effects on platelets such as aspirin or non-steroidal anti-inflammatory drugs. They will also be instructed to monitor their child’s physical activities to prevent trauma.
Summary of ITP

When to treat
What to use