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ENDOCRINOLOGY 8

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Diabetes Mellitus and Diabetic Ketoacidosis

DIABETES MELLITUS

Syndrome characterized by fasting and postprandial hyperglycemia. Diabetes mellitus encompasses a heterogeneous group of disorders including type 1 diabetes mellitus, type 2 diabetes mellitus, maturity onset diabetes of the young (MODY), and secondary diabetes mellitus.

Epidemiology

- *Type 1 diabetes mellitus:* onset predominantly in childhood, but may occur at any age; prevalence: 1.9 per 1000
- *Type 2 diabetes mellitus:* most prevalent among obese; in children, onset usually in mid-puberty; more frequent in African Americans, Hispanics, Pacific Islanders, Asians, and Pima Indians
- *MODY:* autosomal dominant inheritance; onset usually between 9 and 25 years of age

Etiology

- *Type 1:* autoimmune-mediated destruction of pancreatic islets in predisposed individuals (with certain HLAs) triggered by unknown agent
- *Type 2:* insulin resistance and relative insulin deficiency
- *MODY:* genetic defects in enzymes or nuclear transcription factors involved in the regulation of insulin secretion or pancreatic islet development
- Other etiologies*:* exocrine pancreatic diseases (cystic fibrosis, pancreatectomy, hemachromatosis); other endocrinopathies (acromegaly, Cushing disease, pheochromocytoma); drug or chemical induced (glucocorticoids, beta-blockers, phenytoin, asparaginase, cyclosporine, tacrolimus, vacor, pentamidine, diazoxide, nicotinic acid, thiazides); infections (cytomegalovirus, congenital rubella); genetic syndromes (Prader-Willi syndrome, Down syndrome, Turner syndrome, Klinefelter syndrome)

Pathophysiology

- Insulin deficiency and/or impaired insulin action results in the abnormal metabolism of carbohydrate, protein, and fat.
- *Type 1:* destruction of pancreatic β cells leads to insulin deficiency. Insulin deficiency results in excessive hepatic glucose production and impaired glucose utilization in muscle and fat leading to hyperglycemia, glucosuria and osmotic diuresis. Lipolysis and impaired lipid synthesis lead to elevated lipids, cholesterol, triglycerides, and free fatty acids, which are converted into ketones. Impaired utilization of glucose, excessive caloric losses in urine, increasing catabolism, and dehydration all lead to weight loss.
- *Type 2:* insulin resistance and inadequate insulin secretion result in relative insulin deficiency. Most patients have sufficient insulin to suppress lipolysis, ketogenesis, and metabolic acidosis.

Clinical Manifestations

- *Type 1:* polyuria; polydipsia; polyphagia; weight loss; secondary enuresis; weakness, lethargy; blurry vision; occasional pyogenic skin infections and in adolescent females, monilial vaginitis; frequently presents with ketosis, ketonuria, and DKA
- *Type 2:* overweight and obese; absent or mild polyuria and weight loss; acanthosis nigricans (velvety hyperpigmented patches in skin folds of neck, axilla, arms); glucosuria; usually no ketonuria; infrequently presents with DKA; may already have long-term complications at diagnosis

Diagnosis

- Criteria for diagnosis of diabetes mellitus: random plasma glucose greater than 200 mg/dL, OR fasting plasma glucose greater than 126 mg/dL, OR 2-hour plasma glucose during oral glucose tolerance test greater than 200 mg/dL. These abnormalities must be present on 2 different days OR in the presence of symptoms of diabetes (polyuria, polydipsia, weight loss).
- Urinalysis for glucose and ketones
- HgA1c*:* reflects average blood glucose concentration of preceding 2 to 3 months; index of long-term glycemic control. Target for diabetes control varies by age. HgA1c goal is 7.5% to 9% for children younger than 5 years of age and 6% to 7% for adolescents.
- *Type 1:* low fasting insulin and C-peptide levels; often positive β-cell autoantibodies
- *Type 2:* acanthosis nigricans; normal or elevated fasting insulin and C-peptide levels; no β-cell autoantibodies
- *MODY:* diabetes in at least three generations; autosomal dominant pattern of inheritance; diabetes before age 25 in at least one family member

Management

Seek consultation from a pediatric endocrinologist. The following recommendations are general guidelines used at the authors' institution (also see Diabetic Ketoacidosis section):

Long Term

- *Type 1:* daily requirement for exogenous insulin; monitor metabolic control; attention to dietary intake
- *Type 2:* weight management; increase daily physical activity and decrease sedentary activity; decrease caloric and fat intake; most require insulin or oral hypoglycemics (metformin, acarbose)
- Normalize blood glucose and HgA1c: self-monitoring of blood glucose; HbA_{1c} every 3 months
- Monitor for long-term complications:
  - Small vessels: retinopathy (regular ophthalmologic screening); nephropathy (regular screening for hypertension and microalbuminuria); neuropathy
  - Large vessels: atherosclerosis (regular screening for hyperlipidemia); ischemic heart disease; arterial obstruction with gangrene of extremities

Management of Ketosis (without Acidosis)

- If ill or hyperglycemic (>240 mg/dL), check for ketonuria
- Encourage oral hydration: 1 ounce/hr × "age"; if blood glucose level less than 180 mg/dL, drink carbohydrate containing fluids; if blood glucose 180 to 240 mg/dL, drink half carbohydrate containing and half sugar-free fluids; if blood glucose greater than 240 mg/dL, drink sugar-free fluids
- Provide extra short-acting insulin: 10% of total daily dose of insulin SC every 2 hours until ketosis resolves
- Monitor blood glucose and ketones in urine every 2 hours
- If signs and symptoms persist or worsen, suspect diabetic ketoacidosis (DKA)

Management during Infections

- Often require additional insulin (~110% to 120% total daily dose)
- If vomiting, omit short-acting insulin and reduce total daily dose of insulin by ~50%. If unable to tolerate fluids orally, admit for IV fluids with glucose (D10%/1/2 NS), insulin infusion (0.02–0.05 U/kg/hr), and monitoring of electrolytes and glucose.

Hypoglycemic Reactions

- Due to honeymoon phase, errors in insulin dose, reduction in oral intake, or increased physical activity
- Give simple carbohydrates (like juice, sugar-containing soda, cake icing, or glucose tablets); recheck blood glucose 20 minutes later, and repeat as necessary.
- If vomiting, combative, seizing, or losing consciousness, give glucagon 1 mg IM.

Insulin

- Subcutaneous injections: rotate sites to prevent fibrosis and lipodystrophic changes (Table 8.1).

Table 8.1: Insulin Pharmacodynamics

Type	Name	Onset (hr)	Peak (hr)	Effective duration (hr)	Maximal duration (hr)
Short-acting	Regular	0.5–1.0	2–3	3–6	4–6
	Lispro (Humalog)*	0.25–0.5	1–2	2–3	3–4
	Novolog†	<0.5	1	2–3	3–5
Intermediate-acting	NPH	2–4	4–10	10–16	14–18
	Lente	3–4	4–12	12–18	16–20
Long-acting	Ultralente	6–10		18–20	20–30
	Glargine (Lantus)‡		no peak	11 to > 24	
Premixed	Insulin 70/30 (70% NPH, 30% regular)	70% same as NPH above; 30% same as regular above			
	Insulin 75/25 (75% NPH, 25% Lispro)	75% same as NPH above; 25% same as Lispro above			

* Lispro: Usually given right before meal. Useful for infants and younger children where insulin dose determined by carbohydrates ingested and given after meal.
† Novolog: Similar to Lispro.
‡ Glargine: No peak, relatively constant concentration.

- Insulin pumps: short-acting insulin given as continuous subcutaneous infusion (basal) plus boluses with meals

DIABETIC KETOACIDOSIS

Hyperglycemia, ketonemia, and acidosis due to lack of insulin

Pathophysiology

- Hyperglycemia
- Ketoacidosis: ketones cause a metabolic acidosis with a compensatory respiratory alkalosis with rapid deep breathing (Kussmaul respirations). Acetoacetate is converted to acetone, giving the breath a fruity odor.
- Dehydration: glucosuria and ketonuria cause urinary water and electrolyte loss. Weight loss and dehydration ensue.
- Impaired consciousness: from dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization; may result in coma and death
- Acute stress of trauma or infection may worsen the metabolic derangements.

Diagnostics

- Hyperglycemia
- Metabolic acidosis (pH < 7.3 and HCO_3 < 15 mEq/L)
- Ketonemia and ketonuria
- Pseudohyponatremia:

$$\text{corrected } [Na^+] = \text{measured } [Na^+] + 1.6 \times [(\text{glucose} - 100)/100]$$

- Hyperkalemia: at risk for arrhythmias; consider ECG
- If sepsis is suspected, check blood and urine cultures.
- Leukocytosis and elevated serum amylase are common.

Management

- Consult endocrinology
- Recommend intensive care unit, especially if pH less than 7.0, age younger than 5 years, blood glucose greater than 1000 mg/dL, or altered mental status
- First, replete intravascular volume. Then, correct fluid deficit, electrolyte deficit, and acid-base status as below:

Fluid Management

- Replace fluid deficit: usually about 10% dehydrated
- Provide ongoing maintenance requirements
- Replace ongoing losses from osmotic diuresis
- Replacement schedule:
  - First hour: normal saline (0.9%) 10–20 cc/kg bolus; reassess cardiovascular status and repeat as necessary to prevent hypovolemic shock.
  - Initial 16 hours: half of fluid deficit + maintenance + ongoing losses (with normal saline); usually ~ twice maintenance rate + ongoing losses
  - Over next 32 hours: half of fluid deficit + maintenance + ongoing losses (with normal saline); usually ~1.5 × maintenance rate + ongoing losses
- Strict monitoring of input and output; bladder catheterization in obtunded and comatose patients

Electrolyte Management

- Glucose: monitor blood glucose every hour. Lower glucose by ~100 mg/dL/hr. When blood glucose less than 300 mg/dL, add glucose to fluids (dextrose 5%). Goal blood glucose is 100 to 180 mg/dL.
  - Two-bag system: one bag of fluids with no dextrose and another with 10% dextrose. By varying the rate of fluid from each, one can vary the dextrose infusion rate without changing electrolytes or total volume.
- Potassium: check serum potassium periodically. Patients are initially hyperkalemic due to acidosis; however, they are total body potassium depleted and become hypokalemic as acidosis improves and insulin and glucose are given.
  - If urinary output is adequate, add potassium to fluids: If potassium is normal, consider 40 mEq/L; may need as much as 60 to 80 mEq/L
  - Consider ECG: risk for life-threatening arrhythmia
- Phosphate depleted: substitute some chloride with phosphate in fluids

Insulin Therapy

- Insulin infusion: initially 0.1 U/kg/hr; as hyperglycemia and acidosis correct, consider decreasing infusion rate; continue infusion until pH and acidosis correct
- Check electrolytes and acid-base status every 2 to 4 hours.
- Switch to subcutaneous insulin regimen when DKA has resolved and patient is tolerating oral intake. See Table 8.1.

Metabolic Acidosis

- Corrects with insulin treatment
- Bicarbonate use is controversial.

Cerebral Edema

- Incidence (in DKA): ~1%; mortality rate: 40% to 90%
- Risk factors: younger than 5 years old, newly diagnosed diabetes, high serum glucose, severe acidosis, low pCO_2, true hyponatremia on presentation
- Management: reduce fluid rate; give mannitol 10–20 g/m^2 (1 g/kg) IV every 2 to 4 hours; hyperventilate

Hypothalamic-Pituitary-Adrenal Axis

ADRENAL INSUFFICIENCY

Deficient production of cortisol caused by lesions in the hypothalamus, or pituitary or adrenal gland

Infectious Diseases 15

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Syndromes and Complexes

BITE WOUND INFECTIONS

Infections usually localized to site of bite. Rare sequelae include meningitis, brain abscess, endocarditis, and septic arthritis.

Epidemiology
- Infection follows 3% to 18% of dog bites and 28% to 80% of cat bites.
- Greatest rate of infection after bites to the hands

Etiology
- Usually polymicrobial; derived from oral flora of biting animal
- Cat and dog bite infections: *Pasteurella canis* (dog), *Pasteurella multocida* (cat), Streptococci, *Staphylococcus aureus, Moraxella* spp, *Neisseria* spp, and anaerobes
- Human bites: *Staphylococcus aureus,* viridans group Streptococci, *Streptococcus pyogenes, Eikenella corrodens, Streptococcus intermedius, Capnocytophaga* spp, *Neisseria* spp
- Pig bite: *Chryseobacterium*
- Horse/sheep bite: *Actinobacillus* spp, *Streptococcus equisimilis*
- Marine settings/fish bite: *Halomonas venusta, Vibrio* spp, *Aeromonas hydrophila, Plesiomonas shigelloides, Pseudomonas* spp, *Mycobacterium marinum*

Pathophysiology
- Infection follows direct inoculation of bacteria into tissues.
- Hematogenous dissemination may occur.

Clinical Manifestations
- Note wound type (puncture, laceration, avulsion), edema, erythema, tenderness, drainage, depth of penetration, bruising, deformity, involvement of underlying structure, sensation, regional lymphadenopathy
- Look for signs of systemic infection (e.g., fever, hypotension)
- Animal: record type of animal, health of animal, provoked or unprovoked attack; observe for signs of rabies if applicable
- Patient: history of asplenia; immunosuppression or other illnesses; last tetanus immunization

Diagnostics
- Gram stain and culture of wound if time from injury greater than 8 hours or if signs and symptoms of infection exist. Send blood cultures if fever present.
- Radiographs indicated if: penetrating injuries overlying bones or joints, suspected foreign body or fracture

Management

Immediate Management
- Examine for foreign body, irrigate with copious amounts of normal saline; debride devitalized tissue
- Suturing is controversial: leave wound open if greater than 8 hours old or a puncture wound; primary wound closure for injuries to face and when cosmetic outcome is important

- Indications for operative exploration and debridement: extensive tissue damage; involvement of metacarpophalangeal joint from clenched fist injury; cranial bites by large animals

Tetanus Prophylaxis

- Tetanus toxoid and tetanus immune globulin to all patients with two or fewer primary immunizations
- Tetanus toxoid alone to those who have completed primary immunization series but have not had a booster in 5 or more years

Rabies Prophylaxis

1. Dogs, cats, ferrets: if animal is healthy and available for 10 days observation, prophylax patient only if animal develops signs of rabies. If animal is rabid or suspected, give patient immunization and rabies immune globulin (RIG). If unknown, consult public health officials.
2. Bats, skunks, raccoons, foxes, woodchucks, and most other carnivores: regarded as rabid unless geographic area is known to be free of rabies or proven negative via laboratory tests. Patients require rabies immunization and RIG.
3. Livestock, rodents, and lagomorphs: consider individually and consult public health officials.

Antibiotic Prophylaxis

- Prophylaxis is generally recommended for: moderate to severe bite wounds, especially if edema or crush injury; puncture wounds, especially if bone, tendon sheath, or joint penetration has occurred; facial bites; hand and foot bites; genital area bites; wounds in asplenic and immunocompromised persons
- Antibiotics for prophylaxis and treatment of infection:
  - *Dog/cat/human bites:* amoxicillin-clavulanate; if penicillin allergy: trimethoprim-sulfamethoxazole plus clindamycin or third-generation cephalorsporin plus clindamycin
- Duration of treatment: prophylaxis: 3 to 5 days; treatment of infection: 10 to 14 days

BRONCHIOLITIS

Acute lower respiratory tract infection that causes inflammation of the bronchioles and results in distal airway obstruction

Epidemiology

- Children usually younger than 2 years of age
- All geographic areas; winter to early spring
- Infectious agents: Respiratory syncytial virus (RSV; 60% to 90% of cases); parainfluenza viruses types 1,2, and 3; adenovirus; influenza; rhinovirus, *Mycoplasma pneumoniae*, human metapneumovirus
- Risk factors for severe illness: age less than 3 months, gestational age less than 34 weeks, ill or toxic appearance, respiratory rate greater than 70 per minute, pulse oximetry less than 94%, atelectasis on chest x-ray, cardiac or pulmonary disease, immunodeficiency

Pathophysiology

- Necrosis of airway epithelium and ciliated lining causes mucosal inflammation. Lymphocytic infiltration of peribronchial and peribronchiolar epithelium causes edema of submucosa and adventitia.
- Impaired mucociliary clearance leads to obstruction of smaller caliber distal airways without significant alveolar involvement.
- Epithelial regeneration lags behind clinical recovery
- May also cause uncomplicated upper respiratory tract infections

Clinical Manifestations

- Incubation period ranges from 2 to 8 days. Acute illness ranges from 3 to 7 days. Recovery is gradual over 1 to 3 weeks.
- Signs and symptoms: rhinorrhea (profuse), cough, low-grade fever, lethargy, increased work of breathing, tachypnea, wheezing, cyanosis, apnea (especially in age less than 3 months)
- Auscultation: prolonged expiratory phase, wheezing, rales, rhonchi

Diagnostics
- Chest x-ray: hyperinflation, patchy atelectasis, peribronchial cuffing
- Rapid viral identification of nasapharyngeal collection: immunofluorescence or enzyme immunoassay; does not require viable virus; useful for cohorting hospitalized patients
- Viral culture: useful if rapid identification tests are negative
- Consider arterial blood gas and serum electrolytes if ill

Management
- Respiratory support: oxygen as needed; chest physiotherapy may improve clearance of secretions; consider noninvasive (continuous positive airway pressure) and invasive ventilation in those with severe respiratory distress.
- Infants with extreme tachypnea are at risk of aspiration. In these patients, consider nothing-by-mouth status and IV hydration.
- Nebulized beta-2 adrenergic agonists (albuterol, levalbuterol): insufficient evidence to support *routine* inpatient use. In moderately ill infants, consider trial doses with assessment of clinical response. May have more benefit in those with asthma history or ventilated patients. Potential exists for paradoxical effects and increased airway resistance.
- Nebulized alpha/beta adrenergic agonist (racemic epinephrine): insufficient evidence to support *routine* inpatient use. Studies show higher rate of clinical response than with beta-2 agonists but no difference in length of hospitalization. In moderately ill infants, consider trial doses with assessment of clinical response.
- Corticosteroids: studies do *not* show consistent clinical improvement with either systemic or inhaled form. Infants with strong family history of asthma *and* a previous episode of wheezing may benefit from early systemic steroid administration. Data remains controversial.
- Antivirals (Ribavarin): not routinely administered. Consider in high-risk patients (e.g., congenital heart disease)
- Infection control: transmitted primarily by direct contact with secretions and/or fomites. Use contact precautions, cohorting patients, and handwashing
- Passive immunization: either palivizumab (humanized monoclonal RSV antibody; preferred due to IM administration) or RSV-IGIV (immune globulin enriched for RSV-specific antibodies). The American Academy of Pediatrics (AAP) recommends monthly prophylaxis in following situations (see AAP policy statement for further guidance; Pediatrics 112:1442–1446):
  - Age younger than 24 months with chronic lung disease requiring medical therapy (e.g., supplemental O_2, diuretics, corticosteroids) within 6 months of RSV season
  - Infants younger than 6 months of age during start of RSV season and 1) born at younger than 32 weeks of gestation or 2) born between 32 and 35 weeks of gestation and have other risk factors (e.g., neurologic disease, daycare, exposure to tobacco smoke)
  - Patients younger than 24 months with cyanotic or hemodynamically significant acyanotic congenital heart disease (e.g., receiving medication to control congestive heart failure, moderate-severe pulmonary hypertension) (RSV-IGIV contraindicated in infants with cyanotic congenital heart disease)
  - Palivizumab does not interfere with response to vaccines. RSV-IGIV recipients should have MMR immunization deferred for 9 months after last dose of RSV-IGIV.

CELLULITIS

A primary, superficial skin infection

Etiology
- Immunocompetent children: *S. pyogenes, S. aureus, S. pneumoniae*
- Immunocompromised children: also *Pseudomonas* spp, enterobacteriaceae, *Cryptococcus neoformans*, anaerobes

Pathophysiology
- Most commonly follows local trauma (e.g., abrasions)
- Hematogenous dissemination is less common since introduction of *H. influenzae* type B vaccine.

Clinical Manifestations
- Constitutional symptoms including fever, chills, malaise
- Skin edema, warmth, erythema, and tenderness
- Red, lymphangitic streaks
- Regional lymphadenopathy
- Break in skin may be found on exam.

Diagnostics
- Culture of aspirate, skin biopsy, and blood cultures collectively yield causal organism in 25% of cases.
- Blood cultures have low yield in those treated as outpatients. Drain areas of fluctuance (especially in areas of high methicillin-resistant *S. aureus* [MRSA] prevalence).

Management
- Well-appearing children can be treated as outpatients: cephalexin or amoxicillin-clavulanate. Consider trimethoprim-sulfamethoxazole (TMP-SMX) or clindamycin in areas of high MRSA prevalence.
- Ill-appearing patients with high fever, rapid progression, or lymphangitis require hospitalization and IV antibiotics. Consider oxacillin, cefazolin, or clindamycin.
- Neonates should have gram-positive and gram-negative coverage.
- Typical duration of therapy is 7 to 10 days.

CROUP

Upper airway obstruction due to virus-induced inflammation may involve the larynx, infraglottic tissues, and trachea (laryngotracheitis).

Epidemiology
- Usually between ages 6 months and 3 years (peak at 18 months)
- Epidemics begin in late fall and peak in early winter.

Etiology
- Common: parainfluenza viruses (>65% of cases)
- Less common: respiratory syncytial virus, influenza virus A and B, adenovirus, coxsackieviruses, and measles

Pathophysiology
- Viral infection of the nasopharynx spreads to respiratory epithelium.
- Infection causes diffuse inflammation of the trachea and vocal cords.
- Inflammation of the subglottic trachea (narrowest part of child's upper airway) leads to dramatic airflow restriction.

Clinical Manifestations
- Initial rhinorrhea, pharyngitis, and low-grade fevers
- Upper airway obstruction 8 to 12 hours later
- Signs of obstruction include "barking" cough, hoarseness, inspiratory stridor, accessory muscle use, and hypoxia.
- Fever, tachypnea, restlessness, coryza

Diagnostics
- Diagnosis is made on clinical grounds.
- Neck x-rays are not required but can support the initial diagnosis.
- Only 50% of cases demonstrate abnormal neck x-ray findings. Antero-posterior view: narrowed air column in subglottic area (steeple sign). Lateral view: overdistention of the hypopharynx.

Management
- Cool mist tent or vaporizer: may reduce airway edema and facilitate clearing of secretions, but *benefits are unproven*. May increase patient anxiety leading to worsening respiratory distress.

- Corticosteriods: proven benefit for moderate to severe croup; decreases subglottic edema; improvement begins 6 to 8 hours after dose; consider dexamethasone (0.6 mg/kg orally or intramuscularly for one dose, maximum 10 mg), prednisone (1 mg/kg/day twice daily for 3 to 5 days, maximum dose 30 mg), or nebulized budesonide (2–4 mg) for one dose
- Nebulized racemic epinephrine (2.25%): consider for hypoxia or severe croup. Adrenergic effects induce vasoconstriction leading to decreased subglottic edema. Onset occurs in less than 10 minutes. Duration of effect is less than 2 hours and, therefore, requires 3- to 4-hour observation period before discharge.
- Criteria for discharge include: no stridor at rest; normal air entry, color, and level of consciousness
- Heliox therapy (70% helium, 30% oxygen mixture) for severe distress: helium improves laminar gas flow in edematous airway and decreases the mechanical work of respiratory muscles. Heliox may be effective only if the supplemental oxygen requirement is less than 30%.

ENCEPHALITIS

Inflammation of the brain

Epidemiology
- Most frequently observed in summer and early fall when enteroviruses and arboviruses are prevalent
- Commonly associated with meningitis

Differential Diagnosis
- Viruses (most common): arboviruses (West Nile, St. Louis, Eastern and Western equine, Venezuelan equine, Califonia, Powassan, and Colorado tick fever), enteroviruses, herpes simplex 1 and 2, human herpesvirus 6 and 7, varicella-zoster, influenza A and B, parainfluenza 1–3, mumps, measles, RSV, rotavirus, adenovirus, Epstein-Barr, rabies, Nipah virus
- Bacteria: *Haemophilus influenzae, Neisseria meningitidis, S. pneumoniae, Mycobacterium tuberculosis, Bartonella henselae*
- Other infections: *Mycoplasma pneumoniae*, Rocky Mountain spotted fever, ehrlichia, *Cryptococcus neoformans, Coccidioides immitis,* parasites, and helminths
- Postinfectious diseases: Guillain-Barré, Miller-Fisher, acute cerebellar ataxia
- Other: inborn error of metabolism, seizure disorder, toxin ingestion, mass lesion, subarachnoid hemorrhage, acute demyelinating disorder, acute confusional migraine

Pathophysiology
- Most commonly occurs by hematogenous spread to the brain following viremia or bacteremia
- May occur as a result of retrograde movement through the peripheral nerves (e.g., HSV and rabies)

Clinical Manifestations
- Common: fever, headache, altered mentation
- Other: behavioral or personality changes, generalized or focal seizures, hemiparesis, ataxia, movement disorders
- Neurologic abnormalities are based on areas of the brain affected: altered level of consciousness, cranial nerve palsies, ataxia, weakness
- If meningitis: nuchal rigidity, Kernig and Brudzinski signs (see Meningitis)

Diagnostics
- Clinical diagnosis is based on fever and altered mental status.
- Labs: CBC with differential, chemistry panel, liver function tests (especially if considering HSV), toxicology screen
- Lumbar puncture: Gram stain, bacterial and viral culture, protein, glucose, cell count and differential, opening pressure, polymerase chain reaction (PCR) for enterovirus and HSV
- Serologic titers and CSF PCR for arboviruses during the summer

NEUROLOGY 19

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General Principles

ACUTE WEAKNESS

Acute weakness is the acute loss of strength.

- *Bulk:* assess symmetry of muscle bulk
- *Tone:* assess by passive movement of limbs with patient relaxed; may be normal, increased (spastic or rigid), decreased
- See Table 19.1*:* Scales for strength and deep tendon reflexes

Etiology (by localization)

- *Central Nervous System (CNS)-Brain:* acute stroke, unilateral or bilateral
- *CNS–Spinal cord (anterior horn cell body):* cord infarction, cord compression, trauma, contusion, infection (e.g., enterovirus), transverse myelitis, spinal epidural abscess, syringomyelia
- *Spinal root of peripheral nerve:* acute inflammatory demyelinating polyneuropathy (Guillain-Barré)
- *Peripheral nerve (axon):* intensive care unit (ICU) neuropathy, HIV or zidovudine therapy, hereditary tyrosinemia, acute intermittent porphyria, medication-related (e.g., phenytoin, vincristine, nitrofurantoin, INH), toxins (heavy metals, glue), metabolic (uremia-mixed sensory and motor, or pure motor after dialysis), autoimmune (lupus), other vasculitis, chronic juvenile rheumatoid arthritis
- *Neuromuscular junction:* myasthenia gravis, botulism, tic paralysis, pharmacologic blockade, aminoglycoside toxicity
- *Muscle:* myositis (infectious, dermatomyositis, polymyositis), metabolic (hypocalcemia, hypokalemia, hypothyroid state), medication-related (especially steroids), ICU myopathy, familial periodic paralysis (hypo/hyperkalemic)

Clinical Manifestations

- *Central nervous system:* stroke; typically unilateral weakness in a cerebrovascular distribution; expected concomitant language, cranial nerve, or sensory changes; initial low tone then spastic; extensor plantar response ("upgoing toe") on affected side (Table 19.2)
- *Spinal cord:* acute flaccid paraparesis ("spinal shock") then spastic, bowel or bladder symptoms, incontinence, evolving spasticity, sensory level, back pain or trauma, fasciculation, fever (epidural abscess), hypotension (infarction), decreased rectal tone, extensor plantar responses ("upgoing toes")
- *Spinal root of peripheral nerve:* symmetric length-dependent weakness, often concomitant sensory disturbance, distal more than proximal weakness, areflexia, possible back pain, normal to decreased tone
- *Peripheral nerve:* weakness and sensory loss in distribution of specific nerve, in several discrete nerve distributions (mononeuritis multiplex), or diffusely in polyneuropathy (may be painful); may have decreased deep tendon reflexes (DTRs)
- *Neuromuscular junction:* hypotonia; DTRs present; no sensory loss (see Myasthenia Gravis and Botulism sections)
- *Muscle:* proximal more than distal weakness; normal tone; myalgias; normal to decreased DTRs

Table 19.1: Scales for Strength and Deep Tendon Reflexes

Strength		Deep Tendon Reflexes	
5	Full, normal strength	4+	Increased with clonus
5–	Nearly full strength	3+	Increased without clonus
4	Able to meet some resistance	2+	Normal
3	Able to overcome gravity but not resistance	1+	Diminished
2	Able to move in space but not overcome gravity	0	Absent
1	Flicker of movement but no movement in space		
0	No movement		

Table 19.2: Summary of Examination for Weakness by Localization

Examination Summary	Strength	Tone	DTRs	Sensory Loss	Fasciculations
Spinal cord	↓	↓ then ↑	↓ then ↑	+	+/–
Anterior horn cell	↓	↓	—	—	+
Spinal root	↓	↓	—	—	—
Peripheral nerve	↓	↓	↓/–	+	—
Neuromuscular junction	↓	↓	+(nl)	—	—
Muscle	↓	↓	+(nl)	—	—

DTRs, deep tendon reflexes.

Diagnostics

Imaging

- CT of head if stroke or hemorrhage is suspected
- MRI of brain if stroke is suspected
- MRI of spine if spinal cord compression, infarction, or transverse myelitis is suspected; can confirm diagnosis of Guillain-Barré syndrome

Electrophysiology (Electromyography and Nerve Conduction Velocities)

- May show evidence of anterior horn, peripheral nerve axon, neuromuscular junction, or muscle process; may show evidence of demyelination
- Remains normal until at least 1 week from onset of symptoms

Laboratory Studies

- Creatine phosphokinase (CPK) if myopathy is suspected
- Lumbar puncture if Guillain-Barré is suspected
- Lyme titers for mononeuritis multiplex
- Amino-levulinic acid for porphyria
- Muscle biopsy: as warranted based on previous workup

Management

Management will depend on clinical setting.

- *Stroke:* prompt recognition and management are important.

- *Spinal cord emergencies:* early steroids may stem evolution to compression; neurosurgical intervention may be needed; antibiotics if suspect abscess
- *Uremic neuropathy:* may respond to dialysis early in course
- *Neuromuscular weakness:* close monitoring of respiratory status; specific treatments for Guillain-Barré, botulism, myasthenia
- *With elevated CPK:* monitor for rhabdomyolysis, monitor renal function, and maintain hydration

ALTERED MENTAL STATUS

Decreased alertness or consciousness resulting from a pathologic process affecting the brain, whether an intrinsic central nervous process or diffuse metabolic derangement.

***Normal:* awake, easy to arouse and maintain alertness**

***Lethargic:* difficult to maintain alertness**

***Obtunded:* decreased alertness, responsive to pain, other stimuli**

***Stuporous:* decreased alertness, responsive only to pain**

***Comatose:* unresponsive even to pain**

Orientation to person, place, time, and medical situation

Language: fluency, comprehension, naming, and repetition

Etiology

- Metabolic derangement: low or high glucose, Na^+ or Ca^{2+}, low Mg^{2+}, thyroid dysfunction, hypoparathyroidism, hepatic or renal encephalopathy, hypotension, hypertensive encephalopathy, hyperammonemia, sepsis, hypoxemia, hypercarbia, adrenal insufficiency, inborn error of metabolism
- Toxin or overdose (e.g., CO, cyanide, acetaminophen, narcotics, benzodiazepines, barbiturates)
- Seizure: nonconvulsive seizures or post-ictal state
- Infection: meningitis, encephalitis, CNS abscess
- Increased ICP: space-occupying lesion, obstructed VP shunt, cerebral edema
- Vascular: subarachnoid, subdural, intracerebral hemorrhage; stroke; migraine
- Trauma: concussion, contusion, hemorrhage

Pathophysiology

- Dysfunction in both cerebral hemispheres, and/or the ascending reticular activating system

Clinical Manifestations

- Abnormal mental status exam, change in breathing pattern
- Possible loss of brainstem reflexes, including pupillary, corneal, vestibulo-ocular
- Vesicular lesions suggest herpes simplex virus.
- Evaluate on coma scale

Diagnostics

- Glucose, electrolytes, liver function tests, ammonia, arterial blood gas, complete blood count, thyroid function tests, toxin screen, blood culture, urine culture
- Lumbar puncture unless obvious cause identified; avoid lumbar puncture if concern for herniation (clinically or radiologically)
- Head CT, ECG, and EEG

Management

Treatment of reversible causes:

- Correct electrolyte, acid-base, ABCs, glucose disturbances
- Antibiotics; consider acyclovir
- Anticonvulsants
- Maintain normal body temperature
- Consider naloxone
- Consider specific antidotes

ATAXIA

Impaired control of coordination, movement, and balance

Etiology
- Intrinsic cerebellar disturbance
- Disturbance of input to cerebellum (from frontal lobes, posterior columns, and/or spinocerebellar tracts)
- Vestibular dysfunction

Differential Diagnosis
- Acute ataxia
  - Post-infectious cerebellitis
  - Infectious cerebellitis: usually viral
  - Drug ingestion: alcohol, phenytoin, carbamazepine, sedatives, hypnotics, phencyclidine, thallium
  - Other: head trauma, cerebellar hemorrhage, neuroblastoma (opsoclonus-myoclonus-ataxia), acute disseminated encephalomyelitis (ADEM), hydrocephalus, Miller-Fisher variant of Guillain-Barré syndrome, meningitis, labyrinthitis, seizure or post-ictal state, basilar migraine, posterior circulation stroke, conversion
- Intermittent ataxia: metabolic disorder (e.g., pyruvate dehydrogenase deficiency), acute paroxysmal vertigo
- Subacute, chronic, or progressive ataxia: brain tumor, congenital anomaly, degenerative spinocerebellar diseases (e.g., Friedreich ataxia, ataxia-telangiectasia)

Clinical Manifestations
Manifestations depend on location of the lesion:

- Cerebellar vermis: truncal ataxia
- Cerebellar hemispheres: gait veers toward involved side, dysmetria of ipsilateral extremity
- Sensory ataxia (peripheral nerve or posterior columns): abnormal sensation of light touch, proprioception, vibration, high-stepping gait, + Romberg, difficulties with fine motor movements, no dysmetria when eyes open, + dysmetria when eyes closed

Physical Exam
- *Cerebellar exam:* coordination, truncal ataxia, limb ataxia
- *Cranial nerves:* lower brainstem abnormalities raise concern for tumor or vascular insufficiency; vermis lesions cause direction-changing nystagmus; opsoclonus (concern for neuroblastoma)
- *Motor:* unilateral weakness is concerning for posterior-fossa lesions; loss of DTRs suggests sensory ataxia
- *Sensory:* afferent sensory input abnormalities are exacerbated by eye closure (not true of cerebellar ataxia).
- *Mental Status:* consider encephalitis if abnormal

Diagnostics
Radiology
- Brain imaging: CT acutely to rule out hemorrhage or space-occupying lesion; MRI best for posterior fossa and for leptomeningeal enhancement
- Body CT if concern for neuroblastoma

Laboratory
- CBC, electrolytes, toxin screen
- Lumbar puncture
- Urine VMA/HVA (if opsoclonus-myoclonus)
- Consider metabolic/genetic evaluation (especially if intermittent or progressive ataxia)

Management
- Treat underlying etiology.
- Post-infectious cerebellitis is self-limited (begins to resolve in 1 to 4 weeks). Steroids are not indicated.
- Physical and occupational therapy

BRAIN DEATH

Irreversible loss of cortical and brainstem function, including respiratory drive

- Death by Neurological Criteria protocols differs, and physicians must act in accordance with their own institution's policies.
- Does NOT apply to children younger than 7 days (41 weeks conceptional age)
- A comatose patient with intact circulatory function must be declared dead by neurologic criteria before organ donation can be pursued.

Guidelines for the Determination of Brain Death in Children
- Eliminate reversible causes of coma (e.g., opiates)
- Physical exam criteria (see below): coma, absent brainstem reflexes, apnea
- In some institutions, at least one exam must be performed by a neurology or neurosurgery attending physician.
- A second exam consistent with death by neurologic criteria at a specified time, depending on age
- Apnea test (to be performed as part of the last exam)
- Ancillary testing may be required (see below).
- Age-specific requirements:
  - *7 days to 2 months:* two exams and EEGs 48 hours apart
  - *2 months to 1 year:* two exams and EEGs 24 hours apart OR one exam and initial EEG demonstrating electrocerebral silence plus no cerebral blood flow on a radionuclide angiogram
  - *More than 1 year:* two exams 12 to 24 hours apart with other studies optional

Physical Exam
- Normal temperature and blood pressure
- Mental status = coma (unresponsive to any stimulus)
- Absent brainstem function: midposition or fully dilated pupils; no oculocephalic (doll's eye) response; no vestibulo-ocular response to (cold) caloric testing; no corneal, gag, or cough reflexes; no suck or root reflex
- Flaccid tone, no spontaneous or induced movements (except spinally mediated reflex movements)
- Persistence of this exam consistent with death by neurological criteria for appropriate length of time, as above.
- Apnea test (performed as part of the second or last exam): give 100% O_2 for 10 minutes before test. Allow hypercapnia (maximal respiratory stimulus) to develop by holding assisted ventilation. Monitor for spontaneous respirations. Monitor CO_2 level every 5 minutes, and continue to observe until pCO_2 is 60 torr or greater. Stop test if pO_2 less than 50 torr.

Diagnostics
- Workup for reversible causes of coma should be negative.
- Drug levels should not be in toxic range.
- If required, EEG must be done using special protocol and must determine electrocerebral silence to be consistent with death according to neurologic criteria.
- Radionuclide angiogram must demonstrate lack of cerebral blood flow to be consistent with death according to neurologic criteria.

Management
- If patient satisfies definition for death by neurologic causes, physician should explain to family that patient is dead.
- Consider organ donation, depending on wishes of family.

COMA

A state of profound unconsciousness from which one cannot be aroused

Glasgow Coma Score less than 8 (Table 19.3)

Etiology
- Trauma, infection, vascular, metabolic, increased intracranial pressure (ICP), seizure, toxin, or overdose

Differential Diagnosis
- Profound neuromuscular disease, severe akinetic mutism, locked-in state, catatonia

Physical Exam
- ABCs, vital signs, primary survey
- Normal aggregate Glasgow Coma Score, based on age: Birth to 6 months: 9; older than 6 to 12 months: 11; older than 1 to 2 years: 12; older than 2 to 5 years: 13; older than 5 years: 14
- Focused neurologic exam

Management
Resuscitation
- ABCs, correct glucose, electrolytes
- Control seizures, consider Naloxone and mannitol

Table 19.3: The Glasgow Coma Scale

Response	Score	Infants	Children
Ocular	4	Open spontaneously	Open spontaneously
	3	To sound	To sound
	2	To pain	To pain
	1	Not at all	Not at all
Verbal	5	Coos, babbles	Oriented
	4	Cries but consolable	Confused
	3	Cries to pain, irritable	Inappropriate words
	2	Moans to pain, inconsolable	Nonspecific sounds
	1	None	None
Motor	6	Normal spontaneous movement	Follows commands
	5	Withdraws to touch	Localizes pain
	4	Withdraws to pain	Withdraws to pain
	3	Decorticates (abnl flexion) to pain	Decorticates (abnl flexion) to pain
	2	Decerebrates (abnl extension) to pain	Decerebrates (abnl extension) to pain
	1	Flaccid	Flaccid

abnl, abnormal.

- IV fluids: normal saline at maintenance unless fluid-electrolyte disturbances
- There is no evidence to support expectant hyperventilation.

Medical Management
- Empiric broad-spectrum antibiotics (e.g., third-generation cephalosporin + acyclovir). Do not wait for neuroimaging and lumbar puncture if suspicion for infection is high.

Surgical Management
- Neurosurgical consultation
- Decompression of space-occupying lesion (hemorrhage or tumor) or shunt for acute hydrocephalus
- Ventriculostomy to monitor ICP, if indicated

CRANIAL NERVES

Problems with cranial nerve (CN) function suggest brainstem abnormalities. For localization, consider the *Rule of Fours:* CN I to IV arise at midbrain level; CN V to VIII arise at pons level; CN IX to XII arise at medulla level.

- CN I: Olfactory: smell of non-noxious scents (e.g., coffee)
- CN II: Optic: pupillary response, visual acuity, visual fields, fundus exam
- CN III: Oculomotor: eye movements: vertical and horizontal adduction
- CN IV: Trochlear: eye movements: intorsion with adduction (down and in)
- CN V: Trigeminal: facial sensation (three distributions)
- CN VI: Abducens: eye movements: abduction
- CN VII: Facial: closure of muscles of facial expression
- CN VII: Auditory: cochlear-hearing; vestibular-balance
- CN IX: Glossopharyngeal: palate elevation, phonation
- CN X: Vagus: palate elevation, phonation
- CN XI: Spinal accessory: trapezius and sternocleidomastoid strength
- CN XII: Hypoglossal: tongue symmetry, strength

Acquired Neurologic Disease

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Monophasic inflammatory demyelinating condition of the CNS resulting in scattered focal white matter greater than deep gray matter lesions

Typically occurs after viral illness and *very rarely* after vaccination (rabies, hepatitis, measles vaccines)

Epidemiology
- 70% have prodromal illness: usually upper respiratory infection or nonspecific febrile illness.
- ~90% of children recover completely.

Differential Diagnosis
- Meningitis, cerebellitis, sarcoidosis, CNS vasculitis, embolic events, acute hemorrhagic leukoencephalitis, multiple sclerosis (Table 19.4)

Pathophysiology
- Vasculitis: probably complement-mediated, with antigen-antibody complexes causing endothelial damage
- Demyelination: immune-mediated destruction of myelin

Rheumatology 28

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DERMATOMYOSITIS (Juvenile Dermatomyositis)

Most common pediatric inflammatory myopathy. Diagnostic criteria as follows (Bohan and Peter):

Definitive juvenile dermatomyositis (JDM): rash plus at least three criteria; probable JDM: rash plus two criteria

- Heliotrope rash (eyelids)
- Gottron's papules (extensor surfaces)
- Progressive symmetric proximal muscle weakness
- Elevated skeletal muscle enzymes (creatine kinase [CK], aspartate transaminase [AST], aldolase, lactate dehydrogenase [LDH])
- Electromyography consistent with myopathy
- Biopsy evidence of myositis or muscle abnormalities on MRI

Epidemiology

- Incidence: ~2 to 3 cases/million children
- Peaks at 6 years and 11 to 12 years of age; female:male = 2:1
- White predominance in the United States (71%)

Etiology

- Potential infectious triggers: group A beta-hemolytic *Streptococcus*, coxsackievirus B, parvovirus, others
- Human leukocytic antigen and tumor necrosis factor–alpha (TNF-α) alleles may predispose a child to JDM
- Molecular mimicry is suspected
- Sun exposure may trigger onset of rash

Pathophysiology

- Perivascular inflammation, mostly mononuclear cells
- Swelling and blockage of capillaries, tissue infarction, perifascicular atrophy
- Chronic inflammation ensues with fibrosis and microscopic calcification

Clinical Manifestations

- *Proximal muscle weakness* (neck flexors, shoulders, abdomen, thighs): Gower sign, difficulty climbing stairs or combing hair
- *Skin:* heliotrope rash (violaceous rash of eyelids), facial erythema, possibly in malar distribution, papulosquamous eruption on extensor surfaces, particularly over interphalangeal joints (Gottron's papules), shawl sign (erythematous rash in a shawl distribution), cutaneous calcinosis and ulceration
- *Nail folds:* capillary drop-out, vessel dilation, cuticular hypertrophy
- *Arthritis:* effusions, limited range of motion, pain, deformity
- *Mucocutaneous:* oral ulcers, gingival inflammation
- *Pulmonary:* shortness of breath, cough, crackles can be consistent with interstitial lung disease or aspiration pneumonia
- *Gastrointestinal:* dysphagia, ulceration, perforation, bleeding, constipation, diarrhea, abdominal pain

- *Other manifestations:* lipodystrophy, polyneuropathies, retinal exudates and cotton wool patches
- *Other complications:* calcinotic lesions may spontaneously drain, causing local inflammatory response and superinfection; can form exoskeleton; diabetes mellitus secondary to steroid use; rare arrhythmias and cardiomyopathy; growth failure; osteoporosis

Diagnostics
- CBC: lymphopenia, anemia
- ESR and CRP: normal or high
- Elevated muscle enzymes: creatine kinase, aldolase, AST, LDH
- Anti-nuclear antibodies: positive in 60% to 70%; rheumatoid factor: negative
- Neopterin and von Willebrand factor antigen: elevations correlate with disease activity
- Anti-RNP (may indicate systemic lupus erythematosus [SLE] overlap), anti-PM-Scl (associated with SLE or scleroderma), anti-Jo-1 (associated with interstitial lung disease)
- Urinalysis to rule out renal involvement
- MRI with T2-weighted images: localizes active disease sites
- Chest x-ray: evaluate for infiltrates
- High-resolution chest CT: evaluate for interstitial lung disease
- Modified barium swallow: detect palato-esophageal dysfunction
- Plain films: detect calcinosis
- ECG: may see arrhythmias, cardiomyopathy
- Muscle biopsy: myositis, perifascicular necrosis with degenerating and regenerating fibers
- Electromyography: fibrillations, insertional irritability
- Pulmonary function tests: often decreased secondary to respiratory muscle weakness, restrictive lung disease

Management
- Mild disease: corticosteroids (2 mg/kg/day then taper), methotrexate, +/– hydroxychloroquine
- Moderate-severe disease: add pulse corticosteroids (30 mg/kg/day, up to 1000 mg) x 3, IVIG (2 g/kg IV every 3 to 4 weeks)
- Refractory disease: cyclosporine A, cyclophosphamide, TNF-α inhibitors (etanercept, infliximab)
- Interstitial lung disease: cyclophosphamide, pulse corticosteroids
- Sunscreen: minimum sun protection factor of 15 with ultraviolet A and ultraviolet B protection
- Nutritional supplements: vitamin D and calcium
- Physical and occupational therapy
- Immunizations: no live vaccines for individuals on high dose steroids or antimetabolites. Inactivated influenza and pneumococcal vaccination are indicated. Delay MMR 11 months after last IVIG treatment if it is not contraindicated.

HENOCH-SCHÖNLEIN PURPURA

Immune complex-mediated small vessel systemic necrotizing vasculitis of undetermined etiology mainly affecting the skin, joints, gastrointestinal (GI) tract, and kidneys: 1990 American College of Rheumatology classification criteria (need two of four for disease): age younger than 20, palpable purpura, bowel angina, biopsy evidence.

Epidemiology
- Most common childhood vasculitis in the United States
- Age range commonly 2 to 12 years; peak: 4 to 7 years
- Incidence: 3 to 17/100,000
- Seasonal variation with peak incidence in winter and spring

Pathophysiology
- Small vessel vasculitis affecting capillaries and pre- and post-capillary vessels
- Mediated by immune complexes (IgA, IgG, and activated complement C3) that are deposited in end organs causing inflammation
- May be associated with antecedent respiratory infection (GABHS, mycoplasma, parvovirus, other viral pathogens)

Clinical Manifestations
- Classic triad: nonthrombocytopenic purpuric rash, arthritis, urinary sediment
- Typical symptoms:
  - *Rash:* most common presenting symptom; non-blanching, purpuric lesions developing in gravity or pressure dependent areas, usually distal to the elbows and waist. Early lesions may appear erythematous, petechial, or urticarial, evolving into hemorrhagic or ecchymotic lesions; may ulcerate; can see Koebner phenomenon
  - *Musculoskeletal:* arthralgia/arthritis are second most common manifestation; periarticular or articular pain with impaired mobility and minimal joint warmth and effusion, typically affecting the ankles, knees, elbows, wrists, digits; subcutaneous edema
  - *Gastrointestinal:* hemorrhage, intussusception, bowel perforation possible; presents with pain, vomiting, loose stool, melena, hematemesis; hepatosplenomegaly may be present
  - *Renal:* affects 20% to 60% of patients with Henoch-Schönlein purpura (HSP); increased risk in presence of bloody stool; may lead to end-stage renal disease. Manifestations include microscopic or macroscopic hematuria with or without proteinuria, hypertension, glomerulonephritis, ureteritis, urethritis, and cystitis
  - *Rare manifestations:* genitourinary: scrotal swelling/hemorrhage mimicking testicular torsion, testicular torsion (rare); CNS: headache, seizures, hemorrhage, cerebrovascular thrombosis, focal deficits, and peripheral neuropathies; pulmonary: interstitial disease, alveolar hemorrhage, and respiratory failure; cardiovascular: carditis, myocardial infarction
- Vital signs: possible low-grade fevers; hypertension due to renal disease; tachycardia due to anemia or pain
- Duration of symptoms: average 4 weeks if untreated; range: 3 days to 2 years
- Recurrence: up to 33%

Diagnostics
- White blood cells (normal to slightly elevated); hemoglobin (normal to slightly low); platelet count (normal to elevated); PT/PTT (normal)
- ESR: normal to elevated
- BUN and creatinine: elevated with renal disease
- Albumin: decreased with proteinuria and GI losses, malnutrition, and inflammation
- Urinalysis: proteinuria and/or hematuria; RBC casts
- Stool: may be Hemoccult positive
- Immunologic: elevated IgA (type 1) levels in 50%; ANCA (IgA type) may be positive; c-ANCA and p-ANCA negative
- Plain abdominal radiograph, barium studies, and ultrasound may be useful for assessment of abdominal obstruction and intussusception.
- Skin biopsy: can be diagnostic as light microscopy will show leukocytoclastic vasculitis and IgA deposition on immunofluorescence
- Renal biopsy: useful if proteinuria/hematuria is significant or does not resolve; normal to severe crescentic glomerulonephritis with immune complex deposits
- Arthrocentesis: useful to exclude infectious arthritis

Management
- Acetaminophen for analgesia; avoid NSAIDs if GI or renal involvement
- Steroids: indicated for renal involvement, abdominal and musculoskeletal pain. For severe disease, consider pulse solumedrol up to 30 mg/kg/day up to 3 days then daily treatment for 1 to 2 weeks with 2-week taper. For mild or moderate disease, consider prednisone or solumedrol 2 mg/kg/day up to 60 mg/day for 1 to 2 weeks with 2-week taper.

- Cytotoxic therapy: should be considered in patients with severe nephritis and pulmonary or CNS manifestations
- Antibiotics: may be useful in preventing relapses given that GABHS may be a common infectious trigger.
- Supportive care: severe pain may require narcotics. Severe GI involvement may require nothing-by-mouth status, nasogastric suction, and total parenteral nutrition, although response to steroids is often dramatic with prompt initiation of therapy.

JUVENILE RHEUMATOID ARTHRITIS

Chronic synovial inflammation of unknown etiology with onset before 16 years of age and leading to arthritis in one or more joints for at least 6 weeks. Type defined by symptoms in first 6 months:

- Oligoarticular: involvement of four or fewer joints (40% to 50%)
- Polyarticular: involvement of five or more joints (30% to 40%)
- Systemic: characterized by fever, rash, and arthritis (10% to 15%)

Epidemiology

- Most common chronic childhood rheumatologic disease
- Girls affected with oligo- and polyarthritis twice as often as boys
- Incidence: 10 to 15/100,000 in children less than 16 years old

Etiology

- Genetic and environmental factors suspected
- HLA associations exist
- Associated with immunodeficiencies: IgA deficiency, 22q11 del
- Possible viral trigger: for example, rubella, parvovirus B19

Differential Diagnosis of Chronic Arthritis

- *Oligoarthritis:* Lyme disease, mycobacterial infection, leukemia, bone or synovial tumor, sarcoid, spondyloarthropathies, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, pigmented villonodular synovitis, cystic fibrosis, congenital arthropathies, metabolic disorders, foreign body
- *Polyarticular arthritis:* Lyme disease, systemic lupus erythematosus and related disorders, dermatomyositis, sarcoidosis, vasculitis, spondyloarthropathies
- *Systemic onset arthritis:* septic arthritis, Lyme disease, EBV, parvovirus B19, acute rheumatic fever, leukemia, lymphoma, Langerhans cell histiocytosis, SLE, sarcoidosis, Kawasaki disease, neonatal onset multisystem inflammatory disease, periodic fever syndromes

Pathophysiology

- Synovitis with villous hypertrophy and hyperplasia
- T cell activation and recruitment into joint synovium leads to release of pro-inflammatory cytokines by multiple cell types
- Pannus formation in late disease, causing progressive erosion of cartilage and bone

Clinical Manifestations

- General: fatigue, low-grade fevers, anorexia, weight loss, failure to thrive, limp, joint swelling (may be asymptomatic), hepatosplenomegaly, pain with inactivity, evanescent urticarial rash, lymphadenopathy, morning stiffness
- Oligoarticular: usually involves knees, ankles, fingers, wrists, or elbows; systemic symptoms unusual
- Polyarticular: may involve large and small joints, spares distal interphalangeal joints
- Systemic onset: high fevers one to two times/day for at least 2 weeks, temperature often returns to normal or subnormal and is accompanied by erythematous macular rash on trunk and proximal limbs; serositis (pericarditis and/or pleuritis); pericardial tamponade may ensue.

- Musculoskeletal: swelling/effusion; limited range of motion; warm; contracture/deformity; +/– limb length discrepancies and wasting of surrounding muscles (gastrocnemius or quadriceps); cervical spine extension and rotation may be limited.
- Arthritis of temporomandibular joint may cause failure to thrive secondary to pain. Micrognathia and/or hemifacial atrophy may ensue.
- Ophthalmologic: pupil irregularities, synechiae, band keratopathy; uveitis: oligoarticular more often than polyarticular, rare in systemic onset; may lead to visual loss, cataract, glaucoma
- Macrophage activation syndrome is a potentially life threatening complication seen with systemic onset juvenile rheumatoid arthritis (JRA). Symptoms may include fever, hepatosplenomegaly, lymphadenopathy, bruising, mucosal bleeding, respiratory distress, encephalopathy, liver failure, coagulopathy, and renal involvement.
- Other complications: growth disturbances, osteoporosis, pseudoporphyria with NSAID use

Diagnostics
- ESR and CRP: normal or high in oligoarticular or polyarticular disease; high with systemic onset disease
- CBC: leukocyte count normal or high; platelets may be elevated
- Anti-nuclear antibodies: positive in 40% to 85% of oligoarticular and polyarticular disease; rarely positive in systemic onset disease; positive ANA associated with increased risk for developing uveitis
- Rheumatoid factor: positive in a minority of patients with polyarticular JRA, useful for prognostic purposes only
- Urinalysis: abnormal results may suggest alternative diagnosis
- Joint fluid aspirate: usually 2000 to 50,000 WBC/uL (but may be higher); neutrophils may predominate; glucose normal to slightly low; elevated protein
- Radiologic studies are helpful to rule out other disease processes, such as tumors, and to establish baseline for evaluation of joint erosions.
- If cervical spine range of motion limited, order cervical lateral flexion and extension spinal films to assess for atlantoaxial instability and subaxial ankylosis prior to surgery, intubation, sports participation

Management
- Oligoarticular JRA: treatment of choice is intra-articular corticosteroids for persistent joint inflammation; NSAIDs (e.g., naproxen 15–20mg/kg/day, divided twice daily); if no response then use methotrexate
- Polyarticular JRA: methotrexate, TNF-α inhibitors (e.g. etanercept, infliximab), NSAIDs, intra-articular corticosteroids
- Systemic onset JRA: corticosteroids, methotrexate, TNF-α inhibitors, cyclosporine, NSAIDs, intra-articular corticosteroids; cyclophosphamide for refractory disease
- Regular ophthalmology examinations: slit-lamp examination to diagnose silent uveitis
- Dietary evaluation: ensure adequate calcium, vitamin D
- Physical therapy: to maintain joint function
- Occupational therapy: if hands and wrists involved
- Immunizations: no live vaccines for individuals on high dose steroids or antimetabolites. Inactivated influenza and pneumococcal vaccination are indicated.

KAWASAKI DISEASE

An acute, febrile vasculitis of childhood defined by 5 days of fever and four of the following: conjunctivitis, mucous membrane changes, peripheral extremity changes, polymorphous rash, cervical adenopathy. Atypical Kawasaki disease may present with fewer than four criteria.

Epidemiology
- Incidence: United States: ~12 per 100,000; Japan: ~112 per 100,000
- ~80% of cases before 5 years of age