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Pediatric Acute Care Review Course

Rheumatology & Immunology

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Disclosures

- No relevant financial disclosures

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Learning Objectives

- Review pediatric rheumatologic and immunologic diseases
- Discuss the diagnostic evaluation of pediatric rheumatologic and immunologic diseases
- Identify the appropriate management for pediatric rheumatologic and immunologic diseases

Immunologic Diseases

The Immune System

Innate

- Neutrophils, monocytes, macrophages, natural killer cells
- Complement system attracts cells to areas of inflammation via chemoattractants and enhance phagocytosis by opsonins
- Alerts adaptive immune system to presence of infection

Adaptive

- More specific response to antigens or foreign substances
- Lymphocytes: T cells, B cells, NK cells
  - T-lymphocyte binds with antigen and triggers response causing release of humoral mediators (including cytokines and B-cell production)
    - » Antibodies block binding of antigens to cellular receptors and neutralize microbes and microbial toxins

Immunodeficiencies - Primary

- Genetic disorders that affect components of the innate and adaptive immune systems
- Results in susceptibility to infection

Primary Immunodeficiencies

- Humoral
  - Isolated immunoglobulin
  - X-linked agammaglobulinemia
  - Common variable immunodeficiency*
  - Transient hypogammaglobulinemia of infancy
  - Hyper-IgM syndrome
- Cellular
  - 22q11.2 Deletion
- Combined antibody and cellular defects
  - SCID
  - Wiskott-Aldrich syndrome
  - Ataxia telangiectasia
- Phagocytic
  - Chronic granulomatous disease
  - Hyper-IgG syndrome
  - Leukocyte adhesion defect
- Complement
  - Early complement defect
  - Late complement defect

Primary Immunodeficiencies

- Clinical Presentation
  - Humoral: sinopulmonary or gastrointestinal infections, otitis media, cellulitis, meningitis, osteomyelitis
    - Organisms: encapsulated bacteria (*Haemophilus*, pneumococci, streptococci), parasites (*Giardia lamblia*, cryptosporidium), enterovirus
  - Combined: FTT, respiratory or gastrointestinal infections, candidal skin infections
    - Organisms: fungal (*candida* species, *pneumocystis jiroveci*), viral (CMV, EBV, RSV, parainfluenza), *mycobacterium* species

Primary Immunodeficiencies

- Clinical Presentation
  - Phagocytic: severe skin and visceral infections
    - Organisms: bacteria (*staphylococcus aureus, pseudomonas* species, S*erratia* species, *Klebsiella* species), fungal (*Candida, Nocardia, Aspergillus*)
  - Complement: meningitis, septicemia
    - Organisms: *Neisseria* meningococcal, pneumococcal

Primary Immunodeficiencies

- Evaluation
  - Immune organs: tonsils, spleen, lymph nodes
  - Infection may be accompanied by autoimmune diseases or malignancy
  - Consider associated syndromes
  - Labs
    - CBC with diff, quantitative immunoglobulins, lymphocyte subsets, total protein, albumin, antibody titers, complement activity, nitroblue tetrazolium dye test

Primary Immunodeficiencies

- Management
  - Dependent on type
  - Appropriate antimicrobials
  - CMV-negative blood products for transfusion
  - Post-exposure prophylaxis for VZV
  - Avoid live-virus vaccines

Live vaccines:
Rotavirus, MMR, varicella
oral polio, intranasal
influenza

Primary Immunodeficiencies

- Management
  - Humoral: intravenous/subcutaneous immunoglobulin, antibiotic prophylaxis, vaccines not required
  - Cellular: bone marrow transplantation (BMT)
  - Combined: strict isolation, IVIG, PJP prophylaxis, BMT
  - Phagocytic: PJP prophylaxis, recombinant gamma interferon
  - Complement: prevent infection with vaccines, prompt intervention for infection

Immunodeficiency - Secondary

Human Immunodeficiency Syndrome (HIV)

- Background
  - 36.7 million people worldwide (WHO, 2017)
  - 4.2% of new diagnoses in the US were in individuals < 19 years of age (hiv.gov, 2018)
  - It is estimated that 51% of people between 13-24 years of age do not know they have AIDS (hiv.gov, 2018)
  - Pediatric burden has shifted from infants to adolescents living longer with disease
- Etiology
  - Human RNA retrovirus; HIV-1 and HIV-2

Immunodeficiency - HIV

- Presentation
  - Infants: viral infections, growth retardation, skin rash, lymphadenopathy, hepatosplenomegaly and cytopenias
  - Older children: acute viral syndrome, fever, fatigue, headache, myalgias, arthralgias, pharyngitis, lymphadenopathy, oral and genital ulcers, nausea, diarrhea, rash, aseptic meningitis, weight loss, thrush
  - Occurs within 10 weeks of infection

Secondary Immunodeficiency - HIV

- Pathophysiology
  - Blood borne-virus; transmission via sexual intercourse, shared needles, mother-to-child (during birth, breastfeeding)
  - Failure of T-cell production and eventual immune suppression of both the cellular and humoral systems

Secondary Immunodeficiency - HIV

- Diagnosis
  - High-sensitivity ELISA (screening), positive result confirmed with Western blot assay
  - CD4 T-cell test reliably reflect current risk of opportunistic infection; < 200/µL is considered AIDS-defining
  - *Screen all adolescents at risk
    - If at high risk, screen annually

Secondary Immunodeficiency - HIV

- Management
  - Antiretroviral therapy: start before 1 year of age for best outcomes
  - Highly active antiretroviral therapy (HAART): principal method for preventing immune deterioration
  - In some cases, prophylaxis recommended for opportunistic infections
    - Pneumocystis jirovecii, toxoplasma
  - Vaccinate during periods of high CD4 counts
    - Annual influenza and pneumococcal vaccine
  - Viral levels monitored every 6 -12 months when well
  - Due to longer survival, recommendations for additional screening
    - Diabetes, osteoporosis, colon cancer, lipid monitoring
  - Referral to Special Infectious Disease team

Rheumatologic Diseases

Juvenile Idiopathic Arthritis (JIA)

- Background
  - Encompasses complex group of disorders; common feature of arthritis
  - Each subtype characterized by a different mode of presentation, disease course, and outcome
- Definition
  - Requires persistence of arthritis for > 6 weeks in a child < 16 years of age
  - No other identifiable cause of arthritis
  - Currently, 7 subtypes have been identified

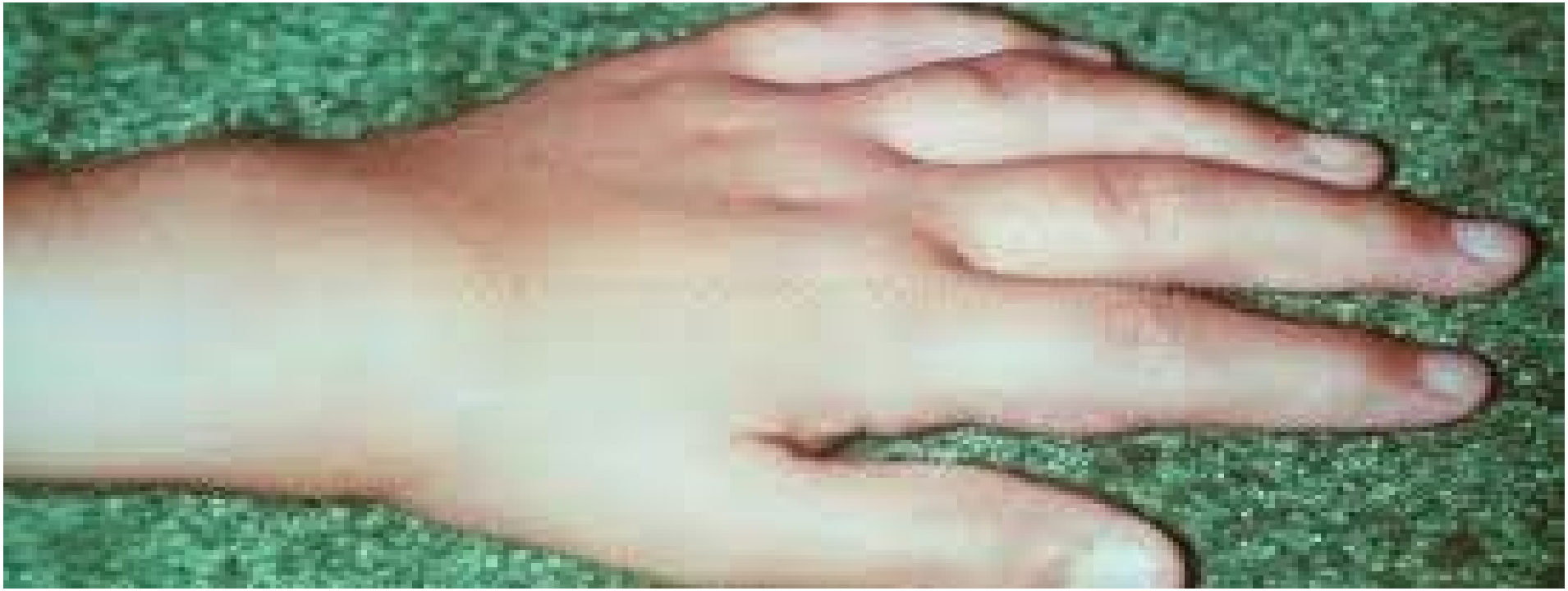
Juvenile Idiopathic Arthritis (JIA)

- Subtypes
  - Oligoarticular
  - Polyarticular (RF-negative)
  - Polyarticular (RF-positive)
  - Systemic
  - Enthesitis-related arthritis
  - Psoriatic arthritis
  - Undifferentiated

Juvenile Idiopathic Arthritis (JIA)

- Pathophysiology
  - Unclear
  - Heterogeneous disorder
  - Likely multifactorial and triggered by genetically susceptible host
- Presentation
  - Joint effusion, joint line tenderness, restricted range of movement, limitation of movement secondary to pain
  - *Common feature = arthritis
  - Some forms associated with systemic illness (e.g. fatigue, weight loss, anemia, anorexia, fever)

Juvenile Idiopathic Arthritis (JIA)



Juvenile Idiopathic Arthritis (JIA)

- Diagnostic Evaluation
  - No single test to diagnose JIA
  - Diagnosis of exclusion based on history and physical examination
  - Exam focuses on presence of joint swelling, pain, range of motion, flexibility, abnormal gait pattern, and activity limitation
  - Laboratory evaluation
    - Antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide
    - A positive ANA does not confirm diagnosis of JIA, however, may suggest risk for uveitis

Juvenile Idiopathic Arthritis (JIA)

- Complications
  - Uveitis: chronic nongranulomatous inflammation of the anterior chamber
  - Poor linear growth
  - Localized growth abnormalities:
    - Accelerated growth at ossification center → overgrowth, longer affected limb
    - Premature epiphyseal fusion → shortened affected limb
    - Temporomandibular joint → micrognathia, hypoplasia, asymmetry

Juvenile Idiopathic Arthritis (JIA)

- Management
  - Occupational and physical therapy
  - Dietary/herbal supplements
    - Calcium, vitamin D
  - Analgesics: nonsteroidal anti-inflammatory drugs
  - Anti-inflammatory medications (i.e. corticosteroids)
  - Disease-modifying anti-rheumatic drugs (DMARDs) (i.e. methotrexate)
  - Biologic agents
    - Tumor necrosis factor α inhibitors (i.e. etanercept, infliximab)
    - Interleukin inhibitors (i.e. anakinra)
  - T-cell and B-cell targeted therapy

Systemic Lupus Erythematosus (SLE)

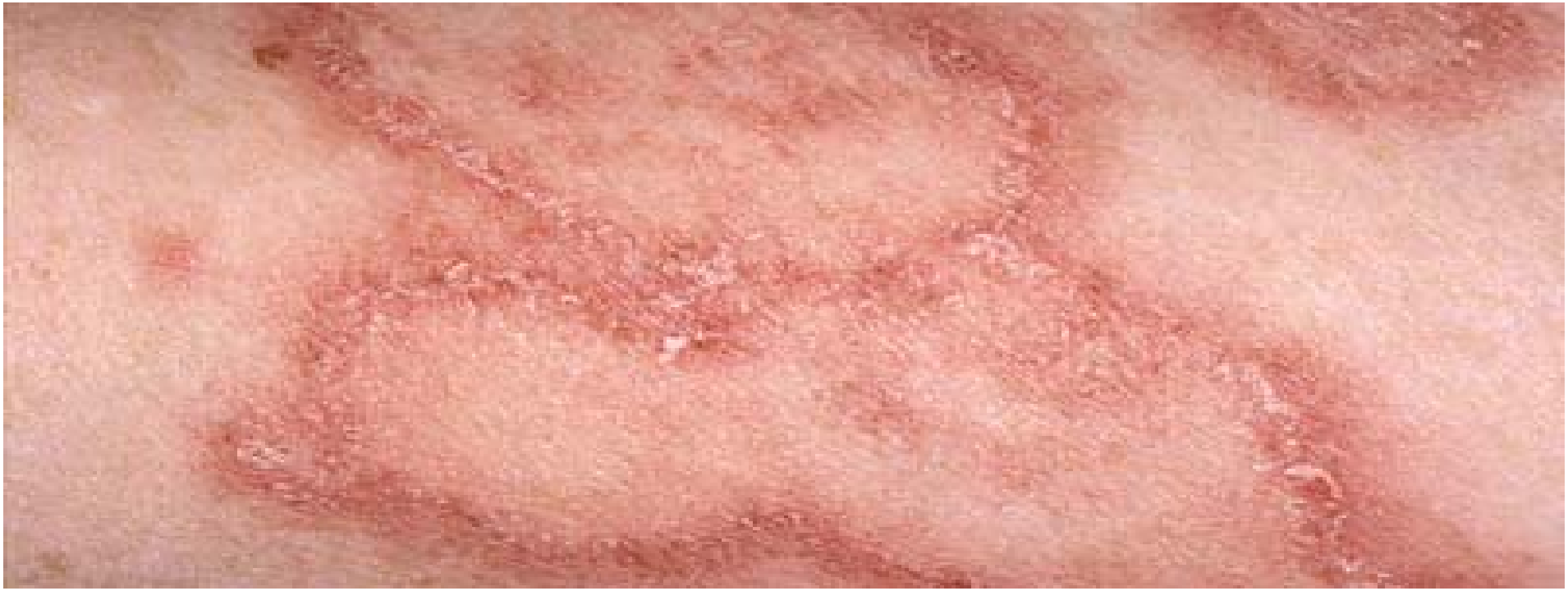
- Background
  - Chronic autoimmune disease that can involve any organ system
  - Highest incidence in females; increases with age
  - Non-whites affected more frequently and more severely
- Pathophysiology
  - HLA Class II alleles DR2 and DR3 and complement deficiencies contribute to development of disease

Systemic Lupus Erythematosus (SLE)

- Malar rash
- Presence of discoid lupus rash
- Photosensitivity
- Arthritis
- Nephritis
  - Proteinuria >0.5gm/day
  - Cellular casts
- Encephalopathy
  - Seizures
  - Psychosis
- Pleuritis or pericarditis
- Cytopenia
- Positive immunoserology
  - Positive double-stranded DNA antibodies
  - Positive anti-Smith antibodies
  - Positive antiphospholipid antibodies
  - Positive antinuclear antibody

Presence of four criteria has a 96% sensitivity and 100% specificity of childhood lupus

Systemic Lupus Erythematosus (SLE)



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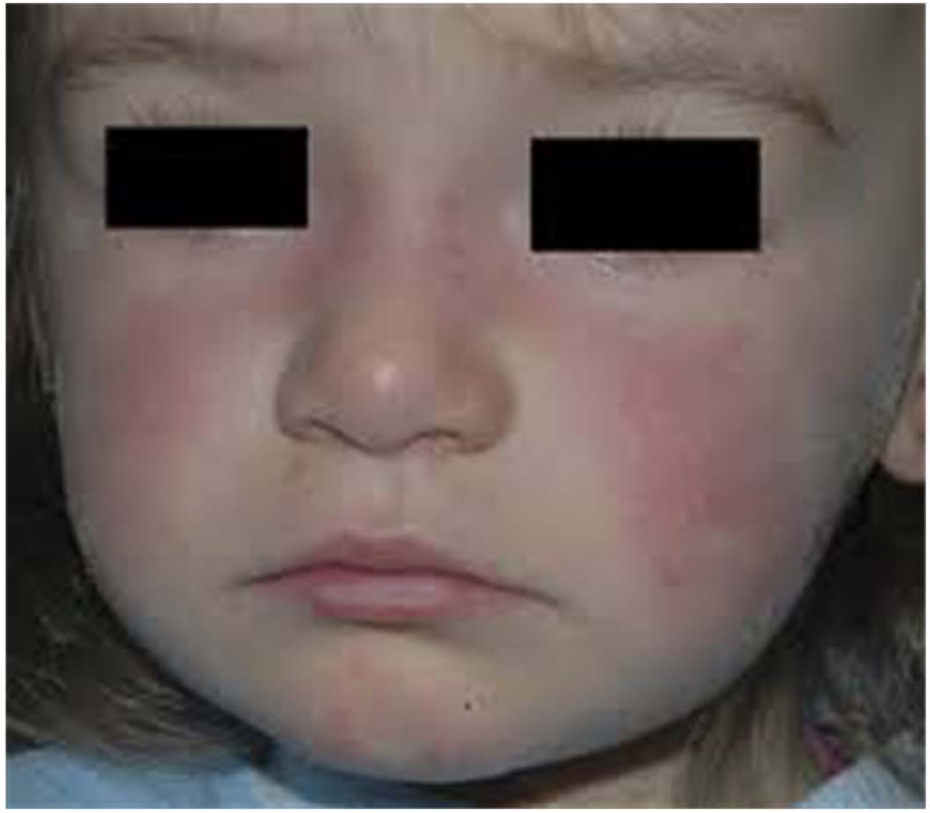


Weiss, J. E. (2012). Pediatric systemic lupus erythematosus. *Pediatrics in Review, 33*(12),

Systemic Lupus Erythematosus (SLE)

- Clinical Presentation
  - Acute or subtle
  - Constitutional symptoms: fever, lymphadenopathy, weight loss
  - Mucocutaneous: malar rash, discoid rash, ulcers
  - Musculoskeletal: arthritis, arthralgias, avascular necrosis
  - Renal: hematuria, proteinuria, glomerulonephritis, nephrotic syndrome
  - Neurologic: headaches, seizures, psychosis, cognitive dysfunction, mood disorder

Systemic Lupus Erythematosus (SLE)

- Clinical Presentation
  - Hematologic: cytopenias, thrombosis, hemolytic anemia
  - Gastrointestinal: abdominal pain, autoimmune hepatitis, pancreatitis, protein-losing enteropathy
  - Endocrine: hypothyroidism, delayed puberty, irregular menses
  - Cardiopulmonary: pericarditis, pleuritis, myocarditis, interstitial pneumonitis, pulmonary hemorrhage
  - Vascular: vasculitis, thrombotic thrombocytopenia

Systemic Lupus Erythematosus (SLE)

- Diagnostic Evaluation
  - Requires 4 of 11 diagnostic criteria *over time*
  - Laboratory evaluation
    - Autoantibodies: antinuclear antibodies, Anti-Smith antibodies
    - CBC with differential: cytopenias, hemolytic anemia
    - Serologies: SLE, autoimmune hepatitis, thyroiditis
    - Inflammatory markers: elevated ESR

Systemic Lupus Erythematosus (SLE)

- Management
  - Based on symptoms and affected organs
  - Immunosuppressants: corticosteroids, DMARDs, mycophenolate mofetil, cyclophosphamide, monoclonal antibodies
  - Immunizations: influenza, pneumococcal, meningococcal vaccines
  - Prompt recognition and intervention for infection
  - Monitor for comorbidities

Neonatal SLE

- Transient syndrome
- Passed to neonate from mother (who is often undiagnosed) via placenta
- Associated with heart block (unresolving), rash, thrombocytopenia, abnormal liver function test, and Coomb's positive hemolytic anemia

Kawasaki Disease

- Background
  - Second most common pediatric vasculitis
  - Small to medium vessel vasculitis
  - Male predominance
  - 90% of cases in children < 5 years of age
  - Etiology unknown; hypothesized infectious, immune, and genetic factors may play role
- Definition
  - Inflammation of blood vessels
  - Can lead to necrosis and arterial aneurysms; more specific to coronary artery aneurysms

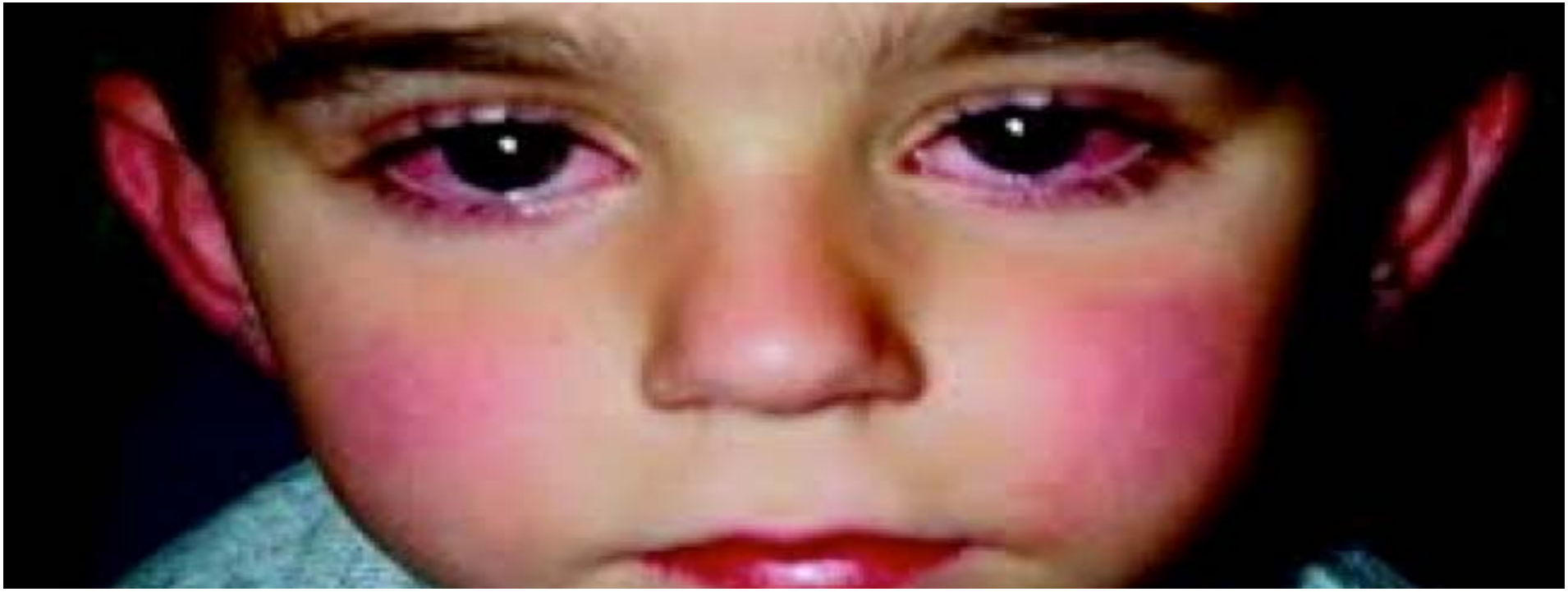
Kawasaki Disease

- Diagnostic criteria
  - Specific criteria, in addition to **fever for 5 days**, must be met for diagnosis of 'classic' (4-5 criteria). Atypical or incomplete disease (2 criteria)
    - Bilateral painless bulbar conjunctival injection (without exudate)
    - Changes to lips and oral cavity (injected oral mucosa, dry/cracked lips, strawberry tongue)
    - Polymorphorous exanthem
    - Cervical lymphadenopathy (≥ 1.5 cm, typically unilateral)
    - Changes in peripheral extremities or perineal area (e.g. palms of hands and/or soles of feet)
      - Acute: Erythema/edema
      - Convalescent: Peeling/desquamation

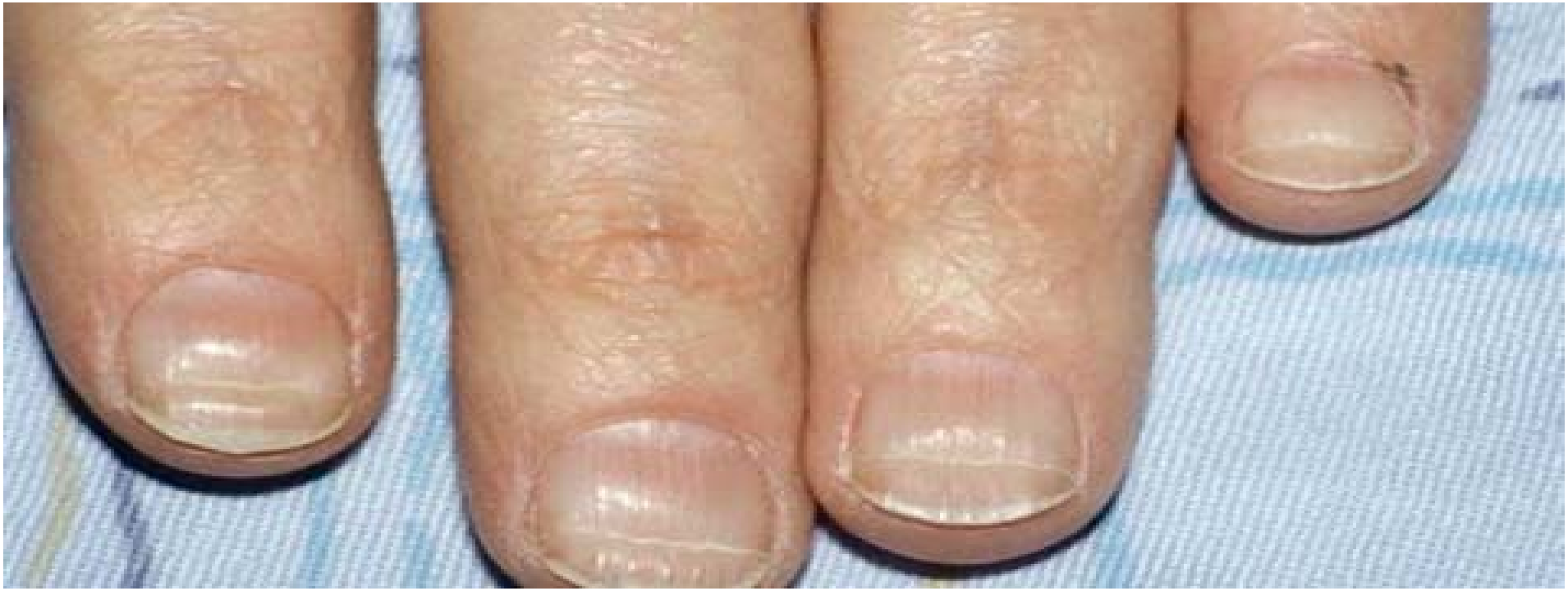
Kawasaki Disease

- Additional Symptoms
  - CV: Heart murmur, valvulitis, myocarditis, pericardial effusion, ECG changes, cardiomegaly, coronary artery aneurysms
  - Pulm: URI symptoms, infiltrate
  - GI: Abdominal pain, nausea, vomiting, diarrhea, hydrops of the gallbladder
  - Musc: Arthritis
  - GU: Dysuria, sterile pyruria, scrotal pain/swelling
  - Skin: transverse furrows of fingernails (Beau's lines)
  - Neurologic: irritability, headache, aseptic meningitis

Kawasaki Disease



Kawasaki Disease



Kawasaki Disease

- Laboratory Findings
  - CBC with leukocytosis, increased neutrophils
  - Elevated ESR, c-reactive protein, platelets, transaminases, and GGT
  - Hypoalbuminemia
  - Anemia
- Radiographic Imaging
  - ECHO: Coronary abnormalities (dilation, stenosis, aneurysms), decreased ventricular function
  - Chest radiograph: evaluate for cardiomegaly

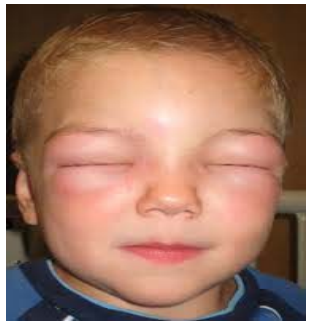
Kawasaki Disease

- Management
  - Prompt diagnosis
  - Intravenous immunoglobulin (IVIG) 2 grams/kg
  - Aspirin (ASA) 80-100 mg/kg/day; weaned with deferevescence
    - Once afebrile, antiplatelet dose of 3-5mg/kg/day
  - Long term therapy
    - Varies, based on risk level

Anaphylaxis

- Background
  - Occurs most commonly among children and adolescents
  - Incidence is on the rise
  - Fatal cases are rare
- Definition
  - Potentially life-threatening systemic reaction to an allergen or trigger
  - Primarily affects mucocutaneous, hemodynamic, and respiratory systems

Anaphylaxis



- Etiology
  - Most common triggers include food (e.g. peanuts, eggs, shellfish), medications, and insect stings
  - Occurs through a variety of mechanisms; IgE mediated, Non-IgE mediated, non-immunologic, idiopathic
  - All mechanisms are treated identically
- Presentation
  - Rapid onset: minutes to hours
  - Urticaria, angioedema, abdominal pain, emesis, wheezing, stridor, laryngeal edema, hypotension, shock

If not treated promptly, can lead to cardiovascular collapse

Anaphylaxis

- Diagnostic evaluation
  - Clinical diagnosis, based on symptoms
  - No specific laboratory testing
  - Plasma histamine levels, serum tryptase, serum IgE elevated, if measured
  - Subsequent skin testing indicated to confirm allergens/triggers

Anaphylaxis

- Clinical Criteria

  1) Acute onset with skin and/or mucosal involvement in the absence of known trigger AND at least one of the following:
     - Respiratory compromise
     - Reduced BP, symptoms of end-organ dysfunction

  2) Two or more rapidly occurring symptoms after known exposure:
     - Skin or mucosal tissue involvement
     - Respiratory compromise
     - Reduced BP, symptoms of end-organ dysfunction
     - Persistent GI symptoms

  3) Rapidly reduced BP after known exposure to an allergen

Anaphylaxis

- Management
  - ABCs
  - Discontinue exposure
  - Epinephrine administration (IM/SQ); do NOT delay if anaphylaxis is suspected
    - 0.01mg/kg of 1:1000 concentration; vastus lateralis muscle
      - Max dose 0.3mg for children
    - Repeat every 3 -5 minutes, as needed
  - Fluid bolus often needed to treat hypotension
  - Consider diphenhydramine, albuterol, methylprednisolone, ranitidine