Recurrent Infections

BREATHE Conference
Allergy & Asthma Specialists
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Disclosure

I have no commercial conflict of interest in any of the information I am providing.
Frequent / recurrent infections

• Chief Complaint
  – “Always sick”
  – Recurrent infections
    • Ear
    • Sinusitis
    • Bronchitis
    • Pneumonia
    • Abscesses
    • Sepsis
    • Meningitis
Frequent / recurrent infections

- Normal: 50%
- Atopic: 30%
- Chronic Disease: 10%
- Immunodeficiency: 10%

Frequent / recurrent infections are most common in Normal individuals.
Frequent infections: 
*Normal vs. abnormal*

- Normal (50%)
  - Frequency:
    - Average: 4-8 URI / yr
    - Upper end: 10-12 / yr (daycare)
  - Duration:
    - Mean = 8 day (14 days or more still normal)

🌟 10 colds X 14 days => 140 days  🌟

*Still can be normal …*
Frequent / recurrent infections

• Atopic (30%)
  – Asthma
  – Allergic rhinitis
    • Normal growth & development
    • Classic physical findings
Frequent / recurrent infections

• Chronic Disease (10%)
  – Cystic fibrosis
  – GER
  – Congenital heart disease
  – Aspiration
  – Neurologic / hypotonia
  – Structural problems
    • Eustachian tube dysfunction
    • Tonsillar / adenoid hypertrophy
Frequent / recurrent infections

• Immunodeficiency (10%)
  – ≥ 6 new infections in 12 months
  – ≥ 2 serious sinus infections or pna / 1 yr
  – ≥ 2 episodes sepsis / meningitis
  – > 2 months of antibiotic no effect
  – Need for iv antibiotics to clear infection
  – Weight or growth issues
Frequent / recurrent infections

- Other red-flag features
  - Poor wound healing
  - Chronic diarrhea
  - Unexplained bronchiectasis
  - Family history
    - Childhood death
    - Autoimmunity
    - Malignancy
    - Consanguinity
The immune system

**INNATE**
- Present from birth
- First line of defense
- Recognizes microbes via: pattern recognition receptors

**ADAPTIVE**
- Continuous refinement & adjustment
- Receptors are unique
The immune system

• Innate
  – Physical barriers
  – Epithelial cell & phagocyte enzymes
  – Phagocytes
  – Surface/phagocyte granule antimicrobial peptides
  – Inflammation related serum proteins
    • Complement, CRP, lectins, MBL, ficolins
The immune system

• Innate
  – Detecting microbes, first-line defense
  – Activation/instruction of adaptive response
  – Regulate inflammation
  – Maintain homeostasis
The immune system

• Adaptive
  – Antigen specific immunity
  – Humoral
    • Extracellular organisms
    • Antibody production
  – Cellular
    • Intracellular organisms (virus; some bacteria)
    • Cancer surveillance
# The immune system

## INNATE
- Phagocytes
  - Neutrophils
  - Monocytes / macrophages
- NK cells

## ADAPTIVE
- T cells
- B cells
  - Antibody
The immune system

Innate immunity (rapid response)
- Dendritic cell
- Mast cell
- Macrophage
- Natural killer cell
- Complement protein
- Basophil
- Eosinophil
- Granulocytes
- Neutrophil

Adaptive immunity (slow response)
- B cell
- γδ T cell
- Natural killer T cell
- Antibodies
- CD4+ T cell
- CD8+ T cell

Nature Reviews | Cancer
Humoral immunity
Cellular immunity
Complement System
Primary Immunodeficiency

- Antibody deficiencies (B cell): 65%
- Combined T&B cell deficiencies: 15%
- Cellular (T cell) deficiencies: 10%
- Phagocytic deficiencies: 5%
- Complement/other innate deficiencies: 5%

- 1 / 2,000 live births
- 1 / 10,000 overall
Humoral immune deficiency

- Defect in antibody production
  - Primary B cell problem
  - B/T cell communication problem
  - Cellular immunity usually “ok”

Clinical:
- URI, LRTI
- AOM, sinusitis, pneumonia
- Diarrhea
- Autoimmune issues
Humoral immune deficiency

- Organisms
  - Encapsulated bacteria
    - Strep pneumo, H. flu
- Labs
  - IgG, A, M, +/- IgG subclasses
  - Antibody titers
    - Diptheria
    - Tetanus
    - Pneumococcal
  - Lymphocyte enumeration
Humoral immune deficiency

- X-linked agammaglobulinemia
- Common variable (CVID)
- Transient hypogammaglobulinemia of infancy
- IgA deficiency
- Selective Ab defect
- Hyper IgM syndrome
Cellular defects

- Opportunistic infections
- Viruses, bacteria, fungus
- Less common
- Lymphopenia
- Lymphocyte function may be impaired
Combined defects

• Uncommon overall
• Severe clinical presentation
• Failure to thrive
• Diarrhea
• Eczema
• Sick, Sick, Sick
• Low lymphocyte counts
Phagocytic defect

• Recurrent abscess varying sites
  – Lungs, skin, lymph nodes, bone, liver
• Bacteria & fungus
• Not enough phagocytes
• Phagocytes not working
• Phagocytes can’t reach the site
Phagocytic defect

• Chronic granulomatous disease
  – DHR- NAPDH oxidase activity
• Leukocyte adhesion defect
  – Delayed separation of umbilical cord
  – Sinopulmonary, skin, poor wound healing
  – Test for cell receptors
  – High neutrophil #
Cases
15 month old boy
“frequent infections”

• Full term, healthy baby
• Since 7 mo (daycare since 6mo)
  – Chronic runny nose
  – 6 ear infections - had tubes placed
  – 2 pneumonias (+CXR)
    • Hospitalized 1x for related bacteremia
  – Growth & Development intact
  – No eczema/rash
  – Persistent loose stools
15 month old boy
“frequent infections”

• Meds:
  – cetirizine 2.5mg daily “allergies”
  – Pulmicort 0.5mg daily, Xopenex PRN

• Immunizations: UTD

• Fhx:
  – 1st born child
  – No allergies, asthma, atopic dermatitis
  – Maternal Great Uncle, Uncle died as children of infection
15 month old boy
“frequent infections”
15 month old boy
“frequent infections”

• Differential Diagnosis
  – Eustachian tube dysfunction
  – Allergic rhinitis
  – Asthma
  – Enlarged adenoids
  – Reflux
  – Immunodeficiency
15 month old boy
“frequent infections”

- Workup
  - Skin testing: NEGATIVE
  - Lateral neck: “NORMAL”
  - Milk scan: NORMAL
  - Labs
15 month old boy
“frequent infections”

• Workup
  – Labs
    • CBC $\rightarrow ok$
    • IgG $\rightarrow 60$
    • IgA $\rightarrow <2$
    • IgM $\rightarrow 20$
    • Non-protective diptheria, tetanus, pneumococcal titers
    • Flow cytometry – lymphocyte enumeration
      – Absent B-cells
15 month old boy “frequent infections”

• Diagnosis (after gene testing)
  
  *Bruton’s Agammaglobulinemia (XLA)*
  
  • Defect: Bruton’s tyrosine kinase
  • Abnormality in B-cell development …
  • No mature B-cells
  • (T cells ok)
  • Low/absent antibodies
  • Needs gamma globulin replacement
A similar story with a different outcome…
2 year old girl
“frequent infections”

• Full term, healthy baby
• Since 9 mo (daycare starting at 12mo)
  – Chronic runny nose, snoring
  – 6 ear infections – had tubes placed
  – Pneumonia x 1 (clinical dx)
  – Growth & Development intact
  – No eczema/rash
  – No GI symptoms
2 year old girl
“frequent infections”

• Meds:
  – cetirizine 2.5mg daily “allergies”
• Immunizations: UTD
• Fhx:
  – 3rd child
  – + allergies, asthma in Mom & sibs
2 year old girl
“frequent infections”

- Differential Diagnosis
  - Eustachian tube dysfunction
  - Allergic rhinitis
  - Asthma
  - Enlarged adenoids
  - Reflux
  - Immunodeficiency
2 year old girl
“frequent infections”

• Workup
  – Skin testing: NEGATIVE
  – Lateral neck: “NORMAL”
  – Milk scan: NORMAL
  – Labs
2 year old girl
“frequent infections”

• Workup
  – Labs
    • CBC → ok
    • IgG → 215 (low for age)
    • IgA → 5 (low for age)
    • IgM → OK
    • Protective diptheria, tetanus, pneumococcal titers (prevnar serotypes)
    • Flow cytometry – lymphocyte enumeration
      – Normal B-cells
2 year old girl
“frequent infections”

• Clinical course
  – 1-2 more ear infections
  – Frequent URI’s
  – Some response to Pneumovax
  – Repeat labs at age 3 years –
    • Immunoglobulins improving
2 year old girl
“frequent infections”

• Diagnosis

*Transient Hypogammaglobulinemia of Infancy*

• Temporary failure of the young immune system to produce sufficient antibody
  – IgG (with/without other low isotypes)

• Diagnosis of exclusion

• Low levels can persist beyond infancy & still ultimately recover.

• Most do not need gamma globulin
A young adult …
A 29 year old man
sinus disease & cough

- 3-4 sinus infections / year
- CXR documented pna x 3
- 6 months of diarrhea
- 10lb weight loss in 6 months
A 29 year old man
sinus disease & cough

- IgG = 200
- IgA = <5
- IgM = 40
- Poor antibody response
  - Protein & polysaccharide
- Normal T/B cell #'s
- Stool culture + Giardia
A 29 year old man

sinus disease & cough
A 29 year old man sinus disease & cough

• Diagnosis

**Common variable immunodeficiency**

- Generally 20-30’s
- Maybe bimodal: 1-5yrs; 18-25yrs
- Presentation varies
  • Infection (sinopulmonary)
  • Chronic lung disease
  • Autoimmune disease
  • GI/liver disease
  • Enlarged spleen
  • Risk of malignancy
A 29 year old man
sinus disease & cough

**CVID**
- Low IgG, with low IgA &/or IgM
- Poor antibody response

- Organisms:
  - S. pneumo, H. flu, Mycoplasma
  - Enterovirus, fungal, giardia
Questions ?