Screening for Immune Deficiency

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Conflicts of Interest

1. Talecris/Grifols Medical Advisory Board
2. Baxter Healthcare: research funding for project on the Statewide Planning and Research Cooperative System (SPARCS) data base seeking use of IDC codes in primary immune deficiency in NYS.
3. Octapharma: research grant to dissect antibody deficiencies to guide Ig therapy
Who to screen?
Ten Warning Signs of Immunodeficiency
(two or more indicates that an evaluation is needed)

• Two or more episodes of pneumonia.
• Unexplained weight loss in adults; failure to thrive in infants.
• Recurrent deep organ or skin abscesses.
• One or more episodes of serious infections such as meningitis, sepsis, cellulitis, osteomyelitis.
• Family history in immune deficiency.

• Recurrent ear infections; need for tubes in an adult.
• Oral or cutaneous candidiasis after age one.
• Two or more months on oral antibiotics with little effect.
• Need for IV antibiotics to clear infections.
• Two or more sinus infections in one year.
Unexplained elements in the history

- Lymphadenopathy
- Splenomegaly
- History of autoimmune disease
- Serious infections
- Chronic infections
- Unexplained lung disease
- Scarring herpes zoster
- Myringotomy as an adult
- Prior diagnosis of an immune defect
- Bronchiectasis
- Family history of an immune defect
- Malabsorption
- Weight loss
- Joint pain and swelling
Additional Clinical Signs of Immunodeficiency

- History of autoimmune disease, (especially ITP and AHA)
- Bronchiectasis
- Enlarged spleen and/or lymph nodes
- Scarring herpes zoster
- Diarrhea
- Arthralgia, arthritis
- Weight loss, intermittent fever
Immune Defects in Refractory Sinusitis in Adults

- 79 patients average age 44 with 2.94 (± 2.19 SD) previous operations.
- 50.6% had at least one positive result on skin test to an aeroallergen.
- Low IgG in 14 of 78 patients (18%), low IgA in 13 of 78 (17%), and low IgM in 4 of 78 (5%).
- Common variable immunodeficiency (CVID) was diagnosed in 10% of patients, and selective IgA deficiency was found in 6%.

L. Chee et al, Laryngoscope 2001;111:233-235
Immunologic defects in pediatric patients with refractory sinusitis

- 61 children with chronic sinusitis were evaluated.
- Recurrent otitis media and asthma exacerbation were common.
- 5 had an elevated IgE level; 22 patients had positive prick tests to one or more environmental inhalants.
- 11 had low Ig levels, 6 had low Ig levels and vaccine hyporesponsiveness, and 17 had poor vaccine response only.

1994 British study of 4000 children referred for evaluation of chronic suppurative disease (excluding CF) found incidence of bronchiectasis to be 1% (40 children).

In 63% an etiology was found:
- 27% immune disorder (11)
- 17% ciliary dyskinesia (7)
- 15% congenital malformation (6)
- 5% foreign body (2)
Bronchiectasis in Adults

- 150 patients with bronchiectasis, proven by HRCT.
- Mean age = 52.7 years
- Median age at onset symptoms = 14 years
- 11 (7%) ABPA; aspiration 6; CF 4; ciliary defects 3, pan-bronchiolitis 1, congenital defect 1.
- 12 (8%) patients had humoral defects: 1 CVID, 6 isolated IgG subclass deficiency, 3 IgA deficiency, 1 IgM deficiency; 6 had antibody deficiency.

Pasteur et al, Am J.Respir Crit Care Med, 162, 1277-1284, 2000
Pulmonary signs indicate that an immune defect might be present:

- Recurrent pneumonia with low virulence organisms (H. flu, S. pneumoniae, mycoplasma, others)
- Empyema complicating pneumonia
- Unexplained Bronchiectasis
- Unexplained lung abscess
- Unexplained Obstructive lung disease
- Unexplained Restrictive lung disease
- Lymphocytic interstitial infiltrates
- Bronchospasm with repeated infections.
- Granulomatous disease with recurring infections and low immunoglobulins.
Conditions of 100 immune deficient patients

- Acute bronchitis
- Acute (maxillary) sinusitis
- Acute bronchitis
- Bacterial pneumonia
- Chronic OM
- Chronic diarrhea
- Chronic bronchitis
- Pneumonia, unclear cause
- Weight loss
- Failure to thrive
- Cellulitis
- Septicemia
- Chronic mastoiditis
- Lymphopenia
- Neutropenia
- Mycoses
- Splenomegaly
- Thrush
- FUO
- ITP
- Lymphadenitis
- Suppurative OM
- Empyema
How to approach the workup?

• Initial steps
  – Clues from the family and personal history, physical examination
  – Verify the x-ray and/or culture/pathology reports

• What is common and what is rare?
Chronic Granulomatous Disease
Common Variable immune deficiency
Complement Selective IgA deficiency
X-linked Agammaglobulinemia
Combined immunodeficiency
Mucocutaneous candidiasis
Hyper IgE syndrome
SCID
Transient hypogammaglobulinemia
DiGeorge
IgG subclass deficiency
Common Variable immune deficiency
Immunodeficiency Diagnoses: (450 patients)
Consider what cells of the immune system you will focus upon.
Immunodeficiency Diagnoses:

Antibody defects are most common
Primary Immune Deficiencies:

time of diagnosis

Infants/children

- SCID syndromes
- X Linked Agammaglobulinemia
- Hyper IgM syndromes
- Wiskott Aldrich
- Hyper IgE
- DiGeorge Syndrome
- CGD

Adolescents/Adults

- Common variable immunodeficiency
- IgG subclass deficiency
- IgA deficiency
- Complement defects
- Thymoma/agammaglobulinemia
- Mucocutaneous candidiasis
- Neutropenia
- CGD
Defects of various immune functions lead to selected illnesses

B cells / complement
- Otitis media, Mastoiditis, Maxillary sinusitis, Acute, chronic bronchitis.
- Bacterial pneumonia, Bronchiectasis, Klebsiella pneumonia, Hemophilus pneumonia, Broncho-pneumonia, Pneumococcal sepsis
- Empyema, Cellulitis, Bacterial meningitis, Aseptic meningitis, Viral meningitis

Neutrophils

Giardiasis

Staph

Osteomyelitis, Organ abcesses

T cells
- Thrush, Mycoses, Lymphopenia, Mycobacteria infection, MAC, Herpes Zoster
Laboratory Evaluation of Immunodeficiency
Initial Workup

• Get a complete history
• Get old records
• Do physical exam. Get height and weight.
• Get blood, culture and X ray results from the past.
• CBC and differential
• Serum Immunoglobulins, IgG, IgA and IgA.
• B cell function: antibody production to several antigens
• T, T cell subsets, B cell and NK cell numbers
Using IgG alone does not always document antibody deficiency.
Post pneumococcal vaccine responses for 40 patients with CVID

Again, serum IgG level is not the end of the story
For Ig replacement: the most important thing

For subjects with lower than normal serum IgG

• Do a complete workup.

• Don’t start Ig until this is done.

• Titers to a number of protein vaccines, natural exposures; antibodies to carbohydrate antigens.

• Tetanus, diphtheria, herpes zoster, measles, mumps, rubella, pneumococcal and hemophilus vaccines, isohemagglutinins, etc
Why do the full lymphocyte screen?
Flow Cytometric Evaluation:

No B Cells:

Low or absent B cells (no CD20+ cells) = XLA
Or what?

B cells = 0.2%
T cells = 95%
51 year old architect

1. Long history of sinusitis but no hospitalizations or serious infections
2. Felt poorly and fainted
3. Went to his internist who noted that the chest was dull on the left
4. Referred for chest Xray
5. A mass suspicious for a thymoma
6. Removed at MSSM
7. 8 months later, he went to an allergist about the sinusitis.

8. Allergist tested serum immune globulins:
9. \( \text{IgG} = 30 \quad \text{IgA} = 0 \quad \text{IgM} = 5 \)
10. Diagnosis?
1 kg thymoma
All had recurrent sinopulmonary infections
  *Haemophilus influenzae* (11)

CMV disease (8)
Bacteremia (7)
Oral, esophageal, mucocutaneous candidiasis (11)
Chronic diarrhea (5) with documented pathogens
Urinary tract infections (4)
*P. carinii* pneumonia (4)
Tuberculosis (2)
Kaposi sarcoma (1)
Disseminated varicella (1)
Candidemia (1)
*Clostridium perfringens* wound infection (1)
Mycoplasma arthritis (1)

Tarr et al, Medicine, 2001
Referral for Mild Hypogammaglobulinemia

- 43 year old woman with URIs and recurrent sinus infections, referred for this and IgG1 subclass deficiency. (IgG1 = 250)
- IgG = 601, IgA = 55, IgM = 43
- CBC 51% lymphocytes; 5,000
- T = 48%
- B% = 40% (normal 5-15); 1731 (75-375)
Too many B cells: B cell clonal issue, CLL: test for light chains kappa/lambda
Unusual lab data

• 51 year old man referred for unusual IgG subclass tests, done for recurrent sinusitis.

• IgG1 = 301 mg/dl; IgG2 = 1,241, IgG3 = 13; IgG4 = 1.
New referral

• 28 year old man from NC moved to NYC for business; on IVIG for CVID for 3 years.
• Had diagnosis of sinusitis prior to Ig
• He brought original lab data: IgG=67, IgA= 1,261, IgM=180 mg/dl.
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- Repeat: IgG= 1400, IgA= 59, IgM=192
What about other immune defects?
Laboratory Evaluation of Immunodeficiency
Intermediate Work-up

- T cell proliferation using non specific stimulators: mitogens phytohemagglutinin, Concanavalin A, pokeweed mitogen
- T cell proliferation using antigens such as tetanus, candida.
- More B cell functions: antibody production, before and after vaccine challenge. (tetanus, diphtheria, Hemophilus, pneumococcus, etc. Isohemagglutinins
- Neutrophil function.
- Complement pathway functions (CH50 and AH50)
- Fluorescent in situ hybridization for DiGeorge syndrome
- Flow cytometer studies for specific markers, hyper IgM syndrome, CD18 etc
SO: male with increased abdominal girth and fever

- 18 month old male with rectal abscesses at 2 months
- Admitted to hospital, increased abdo size + fever
- Sonogram - fluid in the abdomen and lesions in spleen
Confocal image of human neutrophil undergoing respiratory burst.

The bilobed nucleus (blue) is surrounded by Rac GTPase (red), and p22^phox^ (green.) The NADPH oxidase complex is assembled and activated intra-cellularly, shown as regions of yellow where Rac and p22^phox^ colocalize.
Reduction of nitro blue tetrazolium dye by neutrophils

Yellow → blue
DHR Assay to Diagnose CGD

Normal

Phox$^{47}$ deficient CGD (AR)

Phox$^{91}$ deficient CGD (X-linked)

X-linked CGD carrier

Slide from T Fleisher NIH
CD40L (CD154) Expression in HIGM1

Evaluation based on PMA/ionomycin activated CD4 T cells
One more case
Recurrent pneumonia

- Not hospitalized. Resolves with levaquin.
- Previous history of sinusitis; ENT said to be nl.
- CT showed minimal RML bronchiectasis
- PFTs: 100% function
- Infectious disease work up negative.
- Past medical history: migratory arthritis, hypertension, parathyroidectomy for hyperparathyroidism and partial thyroidectomy in 2005.
Case: recurrent pneumonia

- CBC and general lab tests nl.
- IgG 1000; IgA 165; IgM 284
- IgG subclasses 1-4 nl
- Antibody titers to pneumococci + 10/14 serotypes.
- Antibodies to tetanus, diptheria, MMR and varicella all +.
Flexible fiberoptic endoscopic evaluation with sensory testing:

- Severe post glottic edema
- Aryepiglottic folds, arytenoids: severe edema
- Ventricle: obliteration R ar
- Sensory: severe deficits due to chronic reflux
New methods for screening

- New born Screening for SCID and severe T cell defects ongoing
- Targeting likely genes
- Whole genome studies
SCID Newborn Screening

Green - States where screening is already taking place

Yellow - States that have voted to begin screening through legislation or their Newborn Screening Advisory Committees

Red - States that we are still working on
Conclusions