# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*

2020 INFECTIOUS DISEASE BOARD REVIEW

**Host Defense: Where the Rubber of Immunology Hits the Road of Life**

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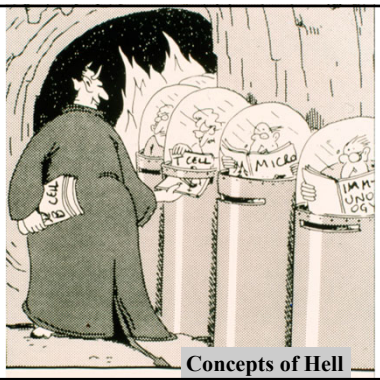
**Disclosures of Financial Relationships with Relevant Commercial Interests**

- None




Concepts of Hell

## Host Immune Defense

Humoral
- Complement
- Mannose binding lectin
- Antibody

Cellular
- Neutrophils
- Monocytes
- Lymphocytes (NK, T, B)
- Other (erythrocytes, platelets)

## Basic Principles

Patients with impaired inflammation:
- may be unable to tell you they are sick (feel fine)
- are often sicker than they look
- often have more extensive disease than is apparent
- may require longer treatment than normals
- may have unusual infections

## Who's Got a Problem?

Abnormal frequency of infections
- recurrent *Neisseria* bacteremia
- recurrent pneumonia

Abnormal presentation of infections
- necrotic cutaneous ulcers (not anthrax)
- *Aspergillus* pneumonia

Specific unusual infections
- *Pneumocystis jiroveci*
- *Burkholderia cepacia*
- *Nontuberculous mycobacteria*

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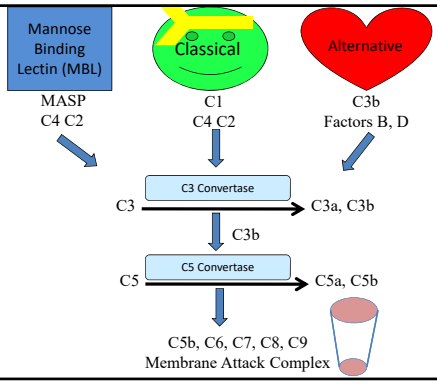



## Complement Deficiencies

Classical Pathway (C1-C9) (AR)
- Antibody *de*pendent bacterial lysis
- Deficiency leads to recurrent bacteremia and meningitis

Alternative Pathway (Factors I, H, Properdin, C3) (Properdin X-linked, others AR)
- Antibody *in*dependent bacterial lysis
- More severe than classical defects

Mannose Binding Lectin (MBL) Pathway
- Very modest IF ANY defect, mild effect in infancy

## Complement Defects

C5-C9 Defects
- recurrent *Neisseria* bacteremia and meningitis
- average age of onset 17 y, milder CNS sequelae
- high rates of relapse and reinfection

C1-C4 Defects
- Autoimmune disease (SLE, DLE) more common

**Dx-** $CH_{50}$ (Classical), $AH_{50}$ (Alternative)

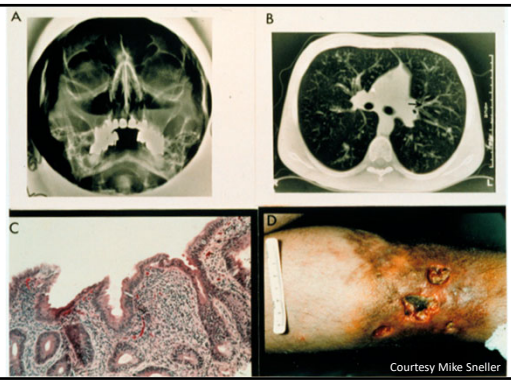
**Rx-** treat infections, prophylaxis if needed, hypervaccination?

## Antibody Deficiencies

IgA Deficiency (AR)
- common (1/700 adults)
- probably not a pathologic condition *per se*
- frequently associated with other deficits, such as common variable immunodeficiency (CVID), Ig subclass deficiencies

Dx- low IgA

Rx- none




## Common Variable Immunodeficiency (CVID)

- recurrent sino-pulmonary bacterial infections
- chronic enteric infections with *G. lamblia, Campylobacter, Salmonella, Shigella*
- severe echoviral meningitis/encephalitis/myositis

Dx- ↓ IgG (total and subclasses 1,3 or 2,4), IgA, IgM, isohemagglutinins, DTH, response to new or recall immunization
↑ autoimmunity and cancer

Rx- treat infections, Ig replacement

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47 year old woman

Recurrent episodes of bronchitis, recently more exacerbations. Tired.

One episode of documented bacterial pneumonia and sinusitis.

Immunoglobulin levels:

IgG 500 (normal 523-1482)

IgA <10 (normal 51-375)

IgM 165 (normal 37-200)

Next step?

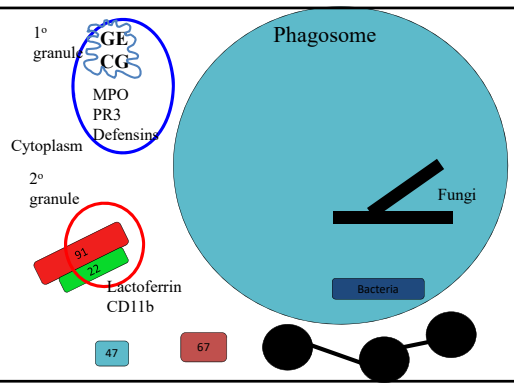
a) IgG subclasses and titers against tetanus and pneumococcus. If low consider IVIG

b) Repeat IgG levels. If low, consider IVIG.

c) Skin tests for DTH. If anergic, consider IVIG.

d) Titers against tetanus and pneumococcus, immunize, and repeat. If low, consider IVIG.

e) Check MBL levels. If low, consider IVIG.




52 year old man

referred from his Family Practitioner.

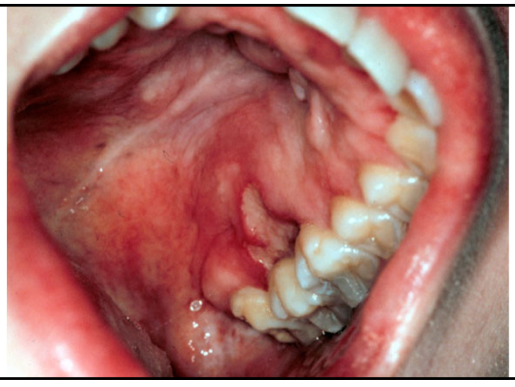
Recurrent digital and oral ulcers occurring every month or so for the last 4 months.

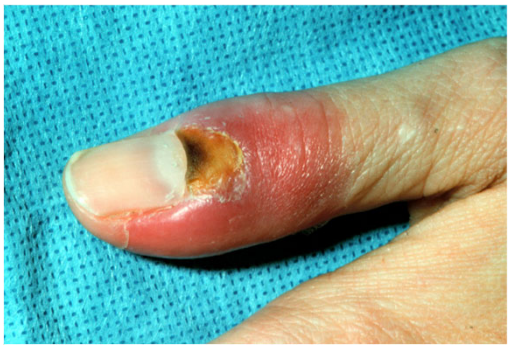
One CBC showed an ANC of 100, but on repeat several days later was normal.

Previous health good.

Took "some antibiotic for a cold a few months ago".

Spleen tip felt.





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## Cyclic or Acute Neutropenia

-drug induced (chemoRx, sulfa, nucleosides, clozapine)

-hereditary **cyclic** and chronic neutropenia (AD) due to neutrophil elastase (ELA2) mutations. Childhood.

- digital, oral, perineal infections, usually self-healing with recovery of counts, bacteremia uncommon
- relatively low baseline PMN count with valleys of profound neutropenia, about every 3-4 weeks

**Dx-** molecular; demonstration of periodicity, family history.

**Rx-** G-CSF lifts both nadir and baseline

## Acquired Neutropenia in Adults

-Drugs, lupus, etc.

-acquired cyclic neutropenia

(Large Granular Lymphocytosis, LGL)

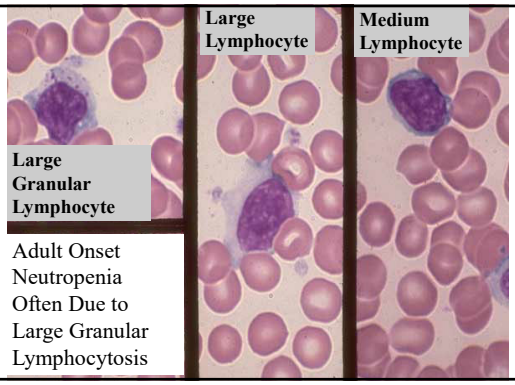
splenomegaly, often associated with rheumatoid arthritis (Felty Syndrome)

**Dx-** clonal CD3+/8+/57+ lymphs (LGL)

(Gain of Function mutations in STAT3)

**Rx-** treatment of the abnormal clone is curative (cyclosporine, MTX, steroids)

G-CSF may lift both nadir and baseline




Adult Onset Neutropenia Often Due to Large Granular Lymphocytosis

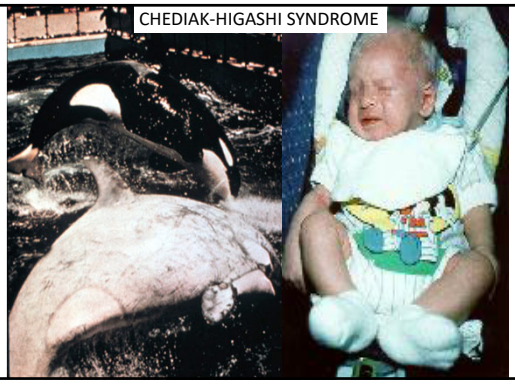
## Myeloperoxidase (MPO) deficiency (AR)

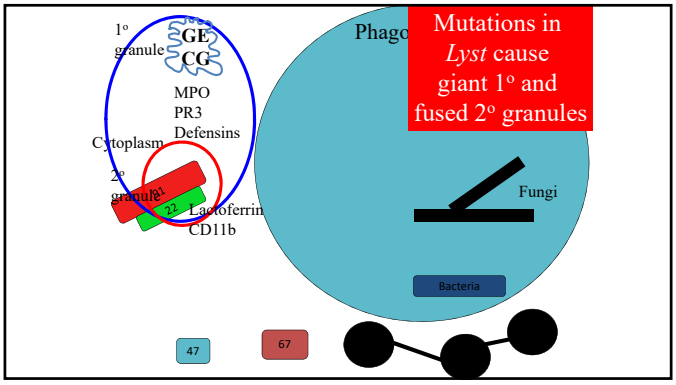
most common neutrophil disorder (1/2000)

- not a pathologic condition *per se*
- failure of $H_2O_2$ -----MPO-----> HOCl
- compensated by increased $H_2O_2$ production
- appears to need another condition to potentiate, such as diabetes mellitus

**Dx-** absence of peroxidase positive granules due to mutations in *MPO* gene

**Rx-** treat invasive infections (*Candida*), no specific therapy



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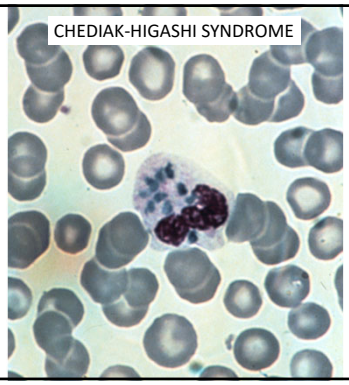
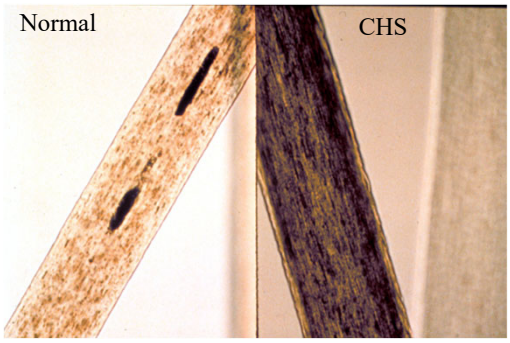
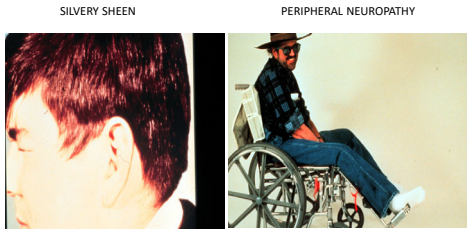



## Chediak-Higashi Syndrome (AR)

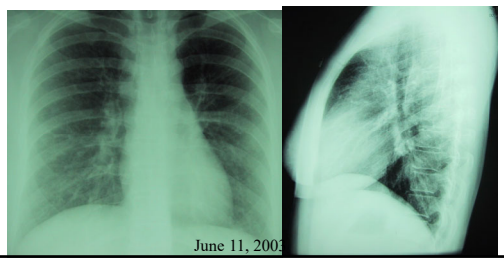
recurrent cutaneous, sino-pulmonary infections
- GNR, staph, strep, no fungi
- mild neutropenia (intramedullary destruction)

partial oculocutaneous albinism,
mental retardation, neuropathy (late),
lymphoma or HLH-like "accelerated phase" (late)

**Dx-** giant blue granules; killing and chemotactic defects due to mutations in *CHS1*, encodes LYST
**Rx-** prophylaxis, treatment of infections, BMT

## 23 yo woman; athletic coach

Previously healthy; short of breath 4 hours after 3 mile run




## ER presentation

Recent weekend with friends in NYC
Anxious, chest pressure, febrile
acute mononucleosis?

PMH
Respiratory infections in infancy
Cat scratch disease 8 yo: resolved with antibiotics

Family History
1 brother with two episodes Cat scratch cervical nodes
2 sibs well

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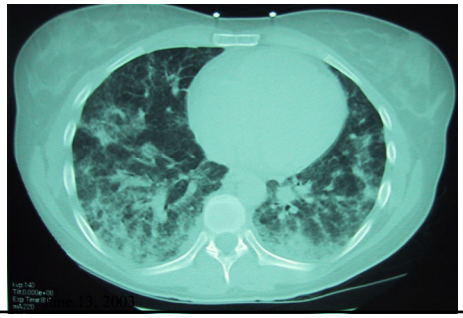
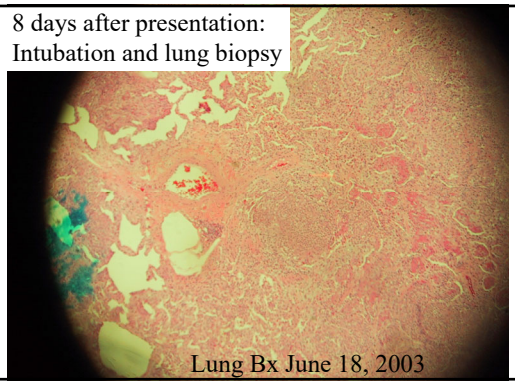
2 days later, hypoxia and fever



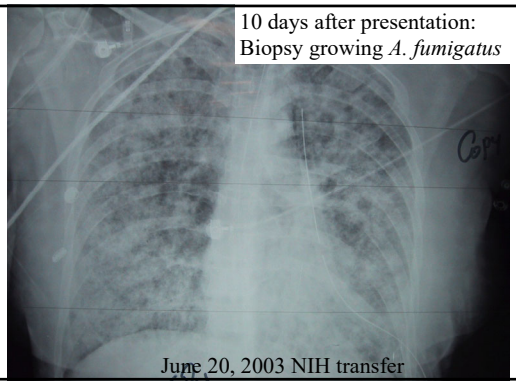
## Hospital Course

- Progressive dyspnea, fever, leukocytosis
- Refractory to antibiotics and steroids
- Bronchoscopy uninformative
- Visually Assisted Thoracoscopic Surgery (VATS)
  necrotizing granulomata and hyphae

8 days after presentation:
Intubation and lung biopsy




10 days after presentation:
Biopsy growing *A. fumigatus*




## Differential Diagnosis?

Invasive aspergillosis in an <u>otherwise normal host</u>

a) Allergic bronchopulmonary aspergillosis

b) Cystic fibrosis

c) Lymphocyte dysfunction (SCID)

d) Phagocyte defect

e) Acute HIV

## What is so special about phagocytes?

neutrophils, monocytes, macrophages, eosinophils, basophils

Preformed cytoplasmic granules with stored enzymes

Normal humans make how many neutrophils/d?
$10^{11}$

Half life of neutrophils in the circulation?
7 hours

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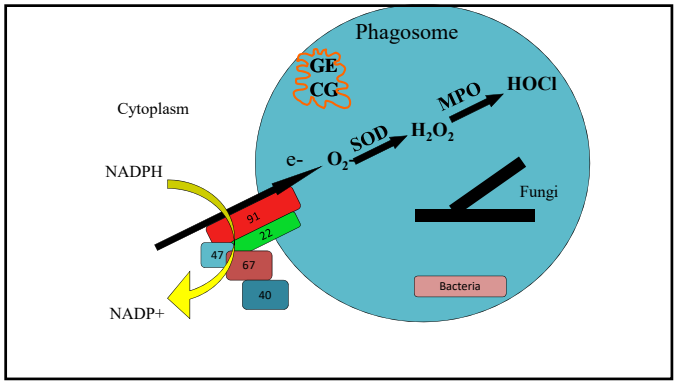
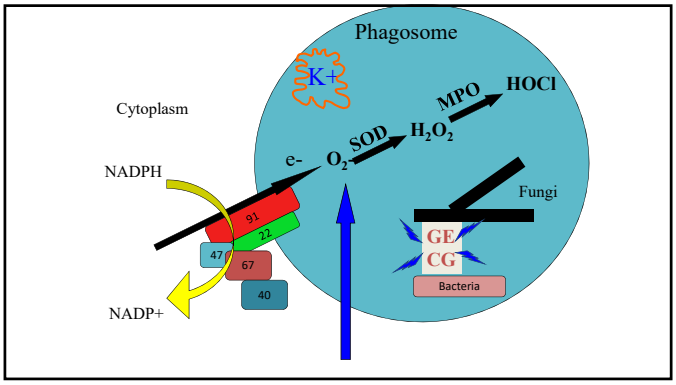
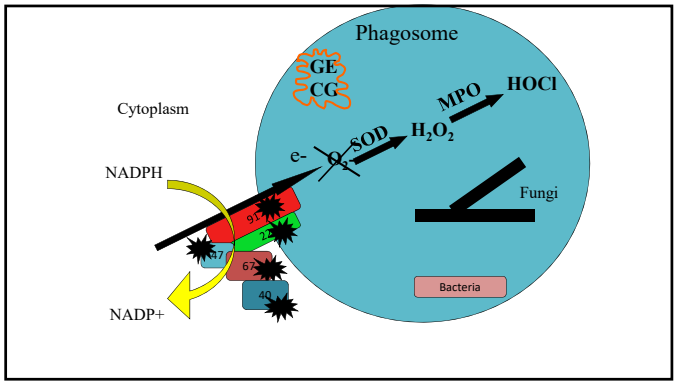



## Chronic Granulomatous Disease

(X, AR)

frequency 1/100,000 - 1/200,000 live births

- presentation usually in childhood, but more adult cases being recognized

recurrent life-threatening infections

catalase-positive bacteria, fungi

tissue granuloma formation

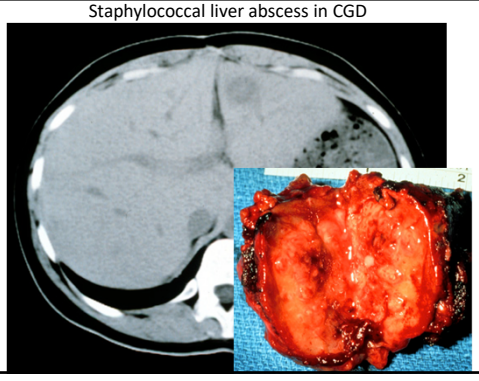
- **infections**: lung, liver, lymph nodes, skin, bone
- **Bacteremia:** uncommon but bad

## Infections in CGD

| | |
|---|---|
| *S. aureus* | (liver, lymph nodes, osteo) |
| *S. marsescens* | (skin, lung, lymph nodes) |
| *B. cepacia* | (pneumonia, bacteremia) |
| *Nocardia* spp. | (pneumonia, brain, liver) |
| *Aspergillus* spp. | (lung, esp. miliary, spine) |
| *Salmonella* | (enteric, bacteremia) |
| *BCG* | (local/regional infections) |

*Chromobacterium violaceum* *(warm brackish water, soil, e.g., Disney World)*
*Francisella philomiragia* *(brackish water, Chesapeake Bay, Sounds)*
*Burkholderia gladioli* *(causes onion rot)*
*Granulibacter bethesdensis* *(necrotizing LN, hard to grow, likes CYE)*
*Paecilomyces* spp.

Staphylococcal liver abscess in CGD



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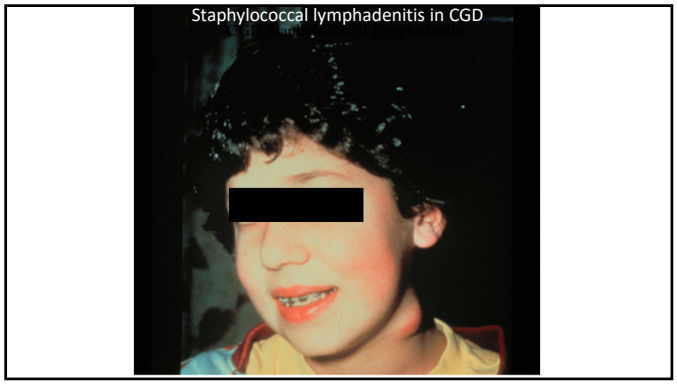


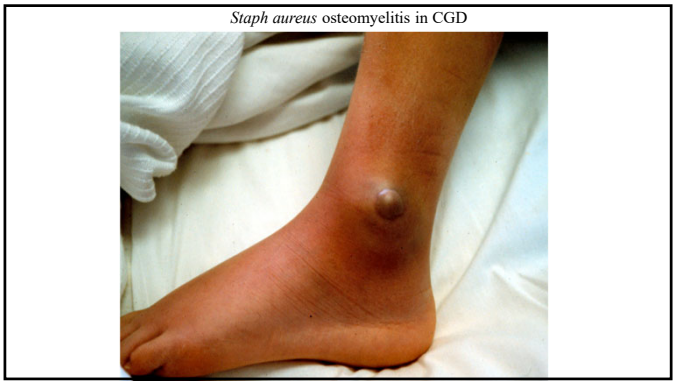


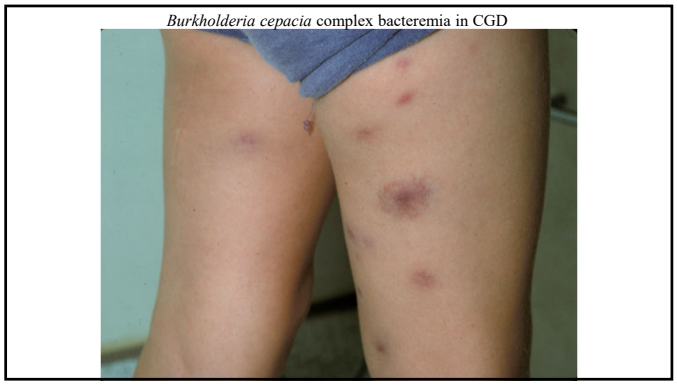


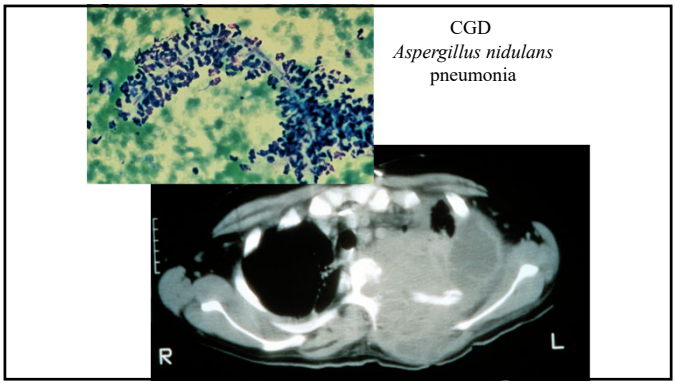


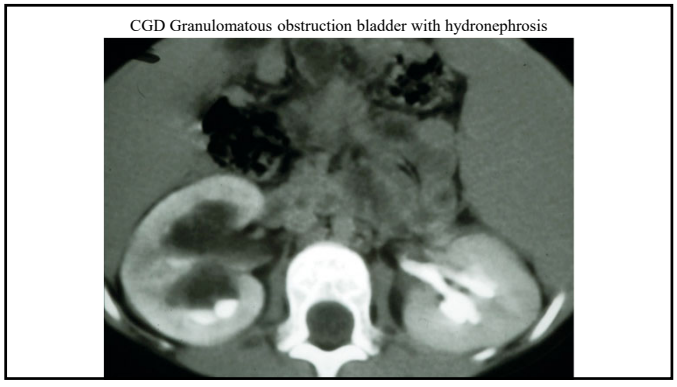


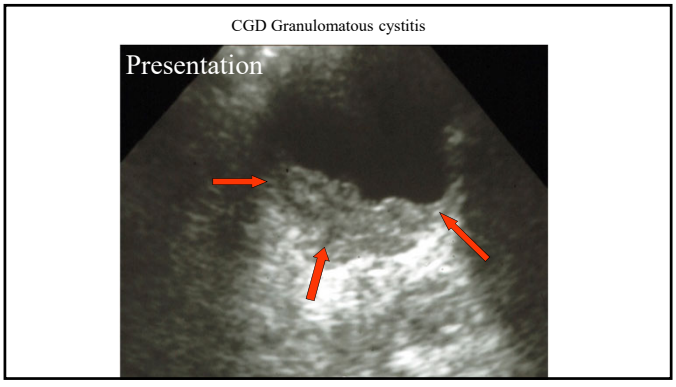

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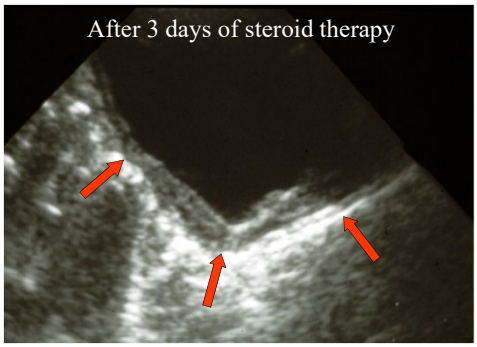
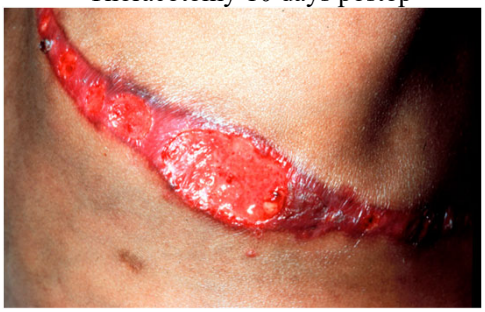
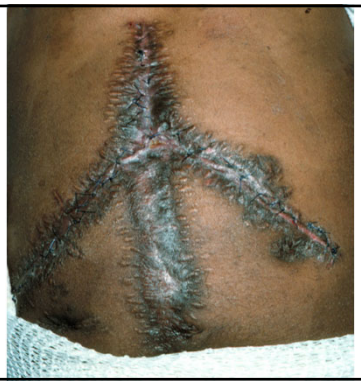



Thoracotomy 10 days postop

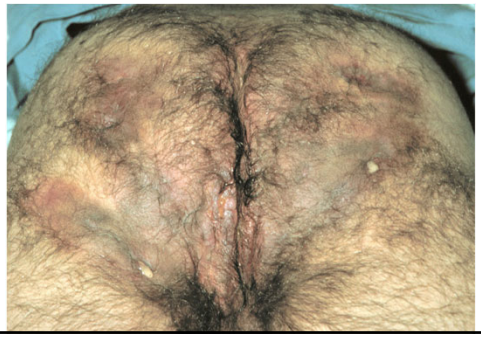


CGD granulomatous wound dehiscence



CGD granulomatous esophageal obstruction

CGD Inflammatory Bowel Disease



## Chronic Granulomatous Disease

frequency 1/100,000 - 1/200,000

- presentation usually in childhood, but more adult cases being recognized

failure to produce superoxide and its metabolites

**Dx-** PMN dihydrorhodamine 123 oxidation (DHR),
PMN nitroblue tetrazolium reduction (NBT)
(MPO Deficiency gives a FALSE ABNORMAL DHR)
BE CAREFUL ABOUT THE LAB!!!!

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## CGD Genetics

X-linked, chr. Xp21 (70% of cases)
- carrier females are mosaic (Lyonization)
- 1/2 of offspring of carrier Mom will receive the gene
  - about 1/3 of carriers are sporadic, from sperm
- X-linked male: all daughters carriers, no sons affected

autosomal recessive (30% of cases)
- 1/2000 carry the gene for the most common AR form
  - bad luck happens

## CGD Management and Treatment

90% overall long-term survival

follow ESR, radiographs

prophylactic antibiotics and antifungals

TMP/SMX, itraconazole

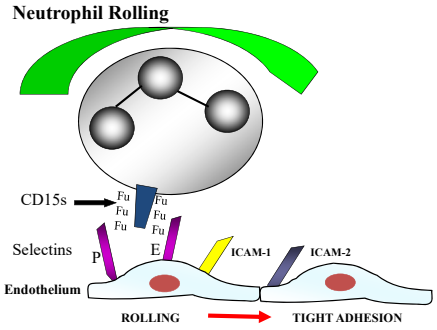
prophylactic interferon gamma

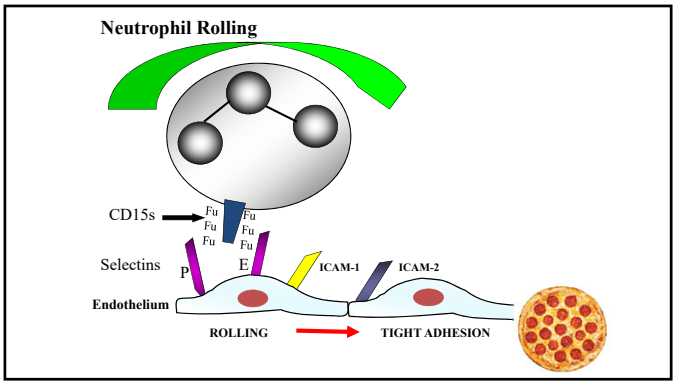
50 µg/m2 subcutaneously three times weekly

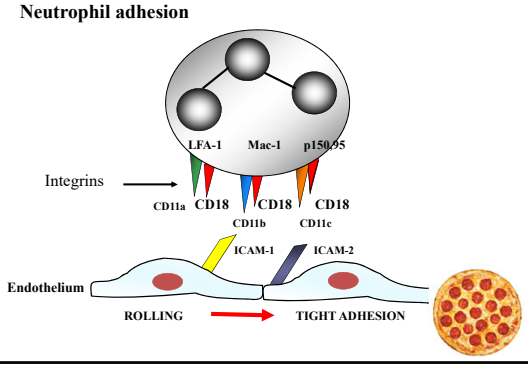
aggressive search for and treatment of infections

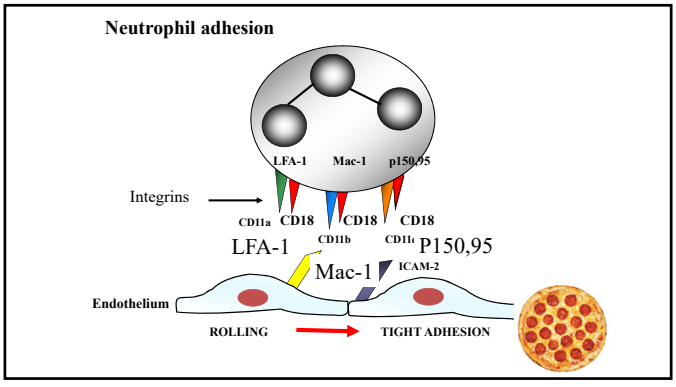
BMT

(gene therapy)



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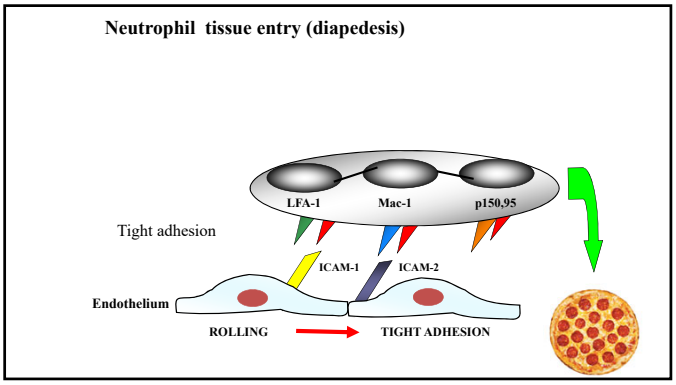
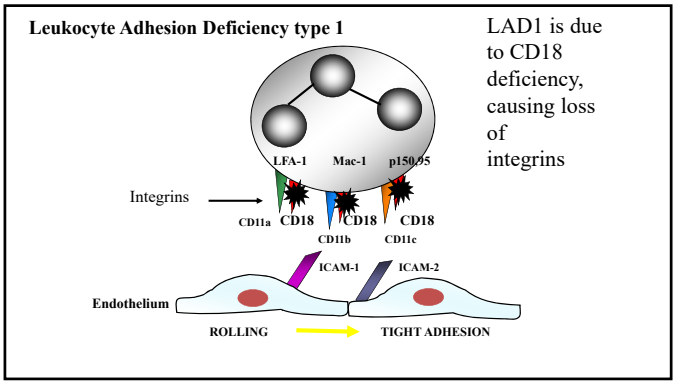



## Leukocyte Adhesion Deficiency Type 1 (AR)

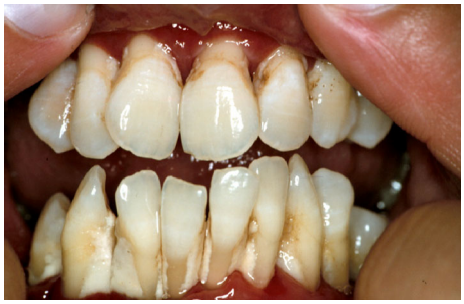
Recurrent necrotizing infections: skin, perineum, lung, gut

Enteric GNR, GPC, NOT fungi or *Candida*

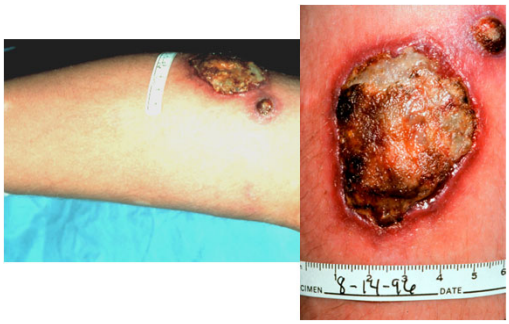
baseline leukocytosis, further WBC increase to infection

rare, consanguinity common

Almost universal tooth loss in LAD1 by adulthood



Impaired wound healing in LAD1



## Leukocyte Adhesion Deficiency I

Delayed umbilical stump separation
dystrophic, "cigarette paper" scars
gingivitis with tooth loss, alveolar ridge resorption
Biopsies: no neutrophils at sites of infection,
rare monocytes and eosinophils
Severe and moderate forms of disease

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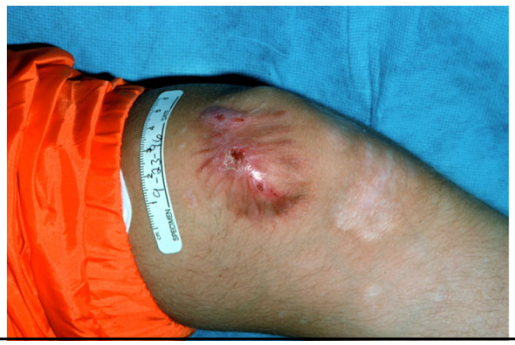
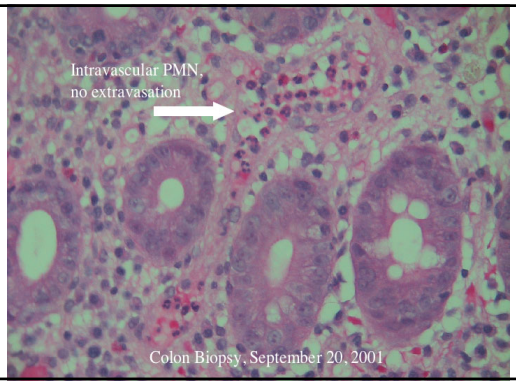
*Speaker: Steven Holland, MD*

Cigarette paper scarring






## Leukocyte Adhesion Deficiency 1

Mutations in CD18, obligatory chain of integrins
Binds to intercellular adhesion molecules (ICAMs)
also serve as receptors for C3bi

**Dx-** FACS for CD18,
Complement dependent opsonization
**Rx-** treatment of infections, BMT

## 19 year old boy with Pneumonia

Admission WBC 43,000, looked OK.
Ceftriaxone, good response.
Medical student: WBC never <11,000/mcl
Left shin ulcer not inflamed
Not healed in > 2 mos
She raises the possibility of
Leukocyte Adhesion Deficiency (LAD1)

## Ruling against LAD1 would be:

a) Gingivitis, tooth loss, and alveolar ridge resorption.

b) FACS showing 5% of normal expression of CD18 and CD11a-c on granulocytes.

c) He is the product of a first cousin union.

d) Extensive neutrophil infiltration in the left shin ulcer.

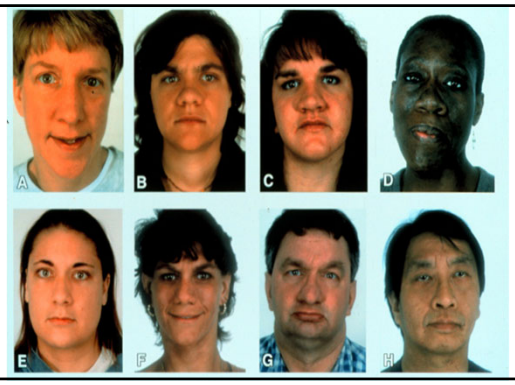
e) Multiple dystrophic scars over the legs from previous ulcers

## 27 year old woman with boils

Referred from her internist for recurrent boils with *S. aureus*
IgE of 12,376 IU.
"Bronchitis and sinusitis at least once a year"
Persistent eczema requiring topical steroids.
Never hospitalized but having "more trouble" lately.

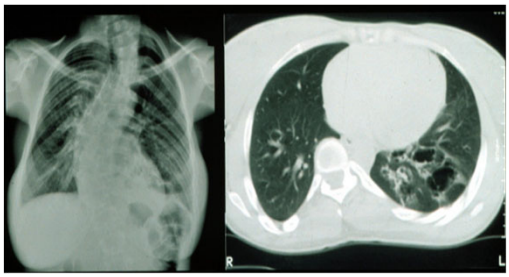
# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*



## HIE (Job's) Syndrome History and Exam

| | |
|---|---|
| Eczema | 100% |
| Facies | 100% (≥16y) |
| Boils | 87% |
| Pneumonia | 87% |
| Mucocutaneous Candidiasis | 83% |
| Pulmonary Cysts | 77% |
| Scoliosis | 76% (≥ 16y) |
| Delayed dental deciduation | 72% |
| Coronary artery aneurysms | 65% |
| Pathologic fractures | 57% |



## Pulmonary Pathogens in HIE

Primary pathogens:

*Staphylococcus aureus*

*Streptococcus pneumoniae*

*Hemophilus influenzae*

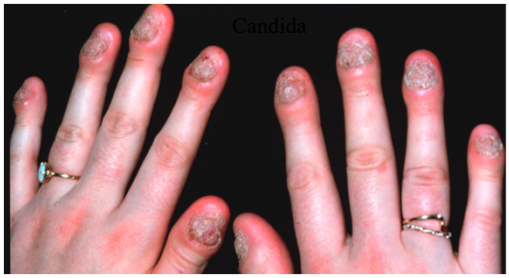
Secondary pathogens:

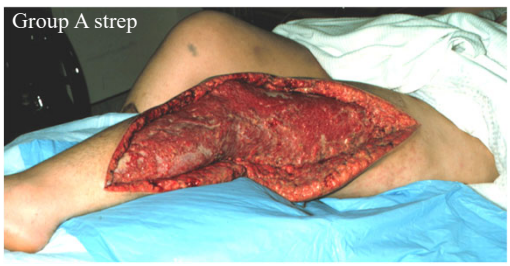
*Pseudomonas aeruginosa*

*Aspergillus fumigatus*

Others:

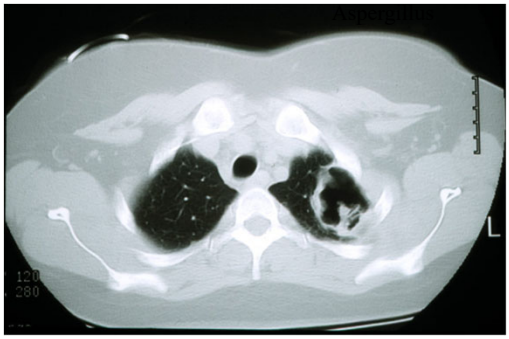
*Pneumocystis jiroveci, M. avium* complex

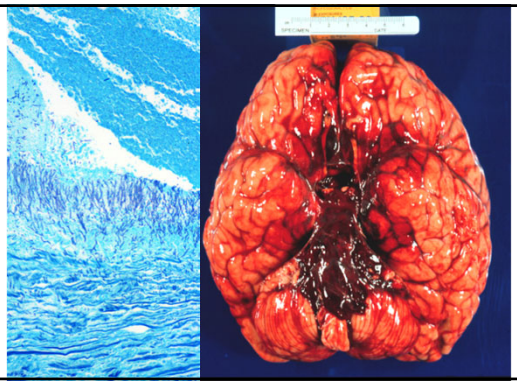


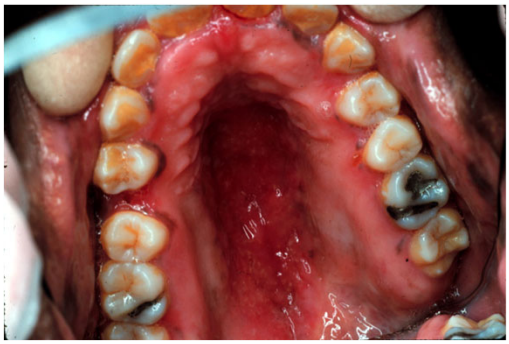



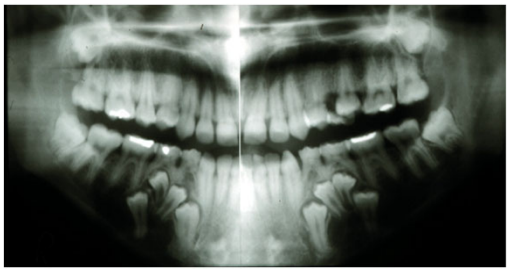
# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*









## HIE Laboratory Findings

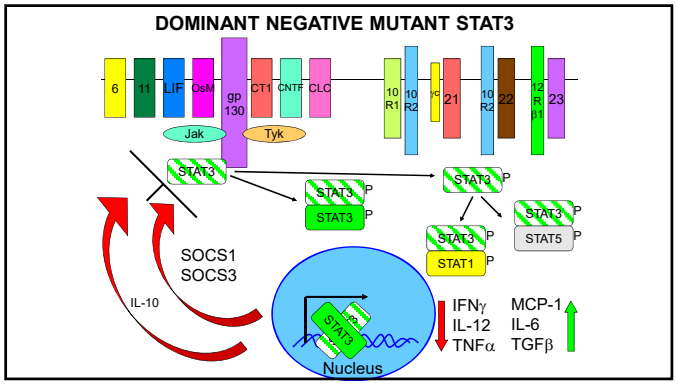
| | |
|---|---|
| Hyper IgE | 97% >2000 IU/ml |
| Eosinophilia | 93% >2SD above mean |

No correlation between IgE and eosinophilia

IgE values declined into the normal range in 17%

# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*




## Hyper IgE Recurrent Infection (Job's)

recurrent sinopulmonary infections *S. aureus, S. pneumo, H. flu*
post-infectious pulmonary cyst formation
recurrent *S. aureus* skin abscesses
characteristic facies, eczema, scoliosis, fractures
very elevated IgE (>2000 IU), eosinophilia

**DDx-** atopic dermatitis is a close mimic
HIE: onset of rash near birth, pneumonia, lung cysts, skeletal
Mutations in STAT3
**Rx-** treatment of infections, prophylactic antibiotics, antifungals.
BMT

## DOCK8 Deficiency

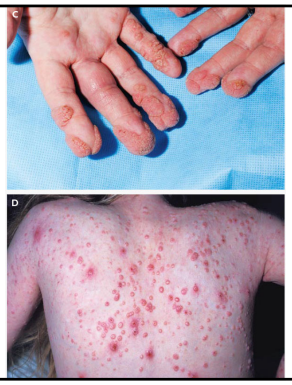
Autosomal Recessive
Eczema, allergies, asthma, high IgE
*Staph, Strep, H. flu, Acinetobacter, Pseudomonas*

*Candida, Cryptococcus, Histoplasma*

HPV, HSV, molluscum

Squamous cell carcinomas, lymphoma

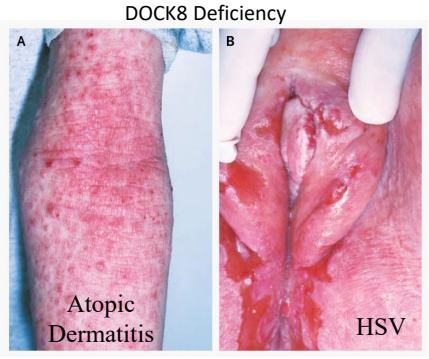
## DOCK8 Deficiency



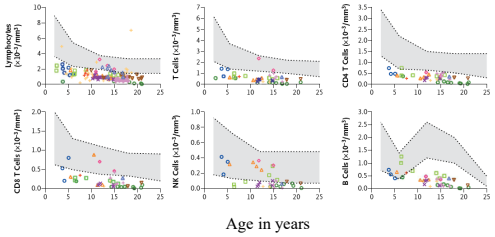
HPV

Molluscum contagiosum

## DOCK8 Deficiency



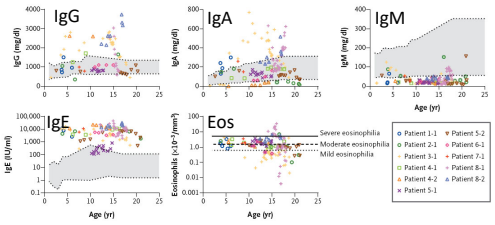

## DOCK8: Lymphopenia is common and somewhat progressive



# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*

DOCK8: IgE and eosinophils are high, IgM is low




## DOCK8 vs. STAT3 Hyper IgEs

| | DOCK8 (Recessive) | STAT3 (Dominant) |
|---|---|---|
| Pneumonia | + | +++ |
| Pneumatoceles | - | +++ |
| Retained teeth | - | +++ |
| Fractures | - | +++ |
| Viral infections | +++ | - |
| Fungal infections | + | ++ |
| Allergies | +++ | - |
| IgM | low | normal |
| eosinophils | + to +++ | + |

## 15 year old girl with recurrent infections

Infancy: eczema, recurrent pneumonias, skin infections

IgE 14,574 IU/ml

Allergist: use bed covers to avoid dust mites.

*Going over the allotted 15 minutes* you elicit points trying to establish whether she has hyper-IgE recurrent infection syndrome (Job's).

## Which one of the following is not supportive of the diagnosis of Job's:

a) Pneumatoceles
b) Scoliosis
c) Severe warts
d) Retained baby teeth
e) Recurrent fractures

## 18 year old male with lymph node

Referred from hematologist/oncologist

nodes biopsied for Hodgkin showed granulomata and grew *M. avium.*

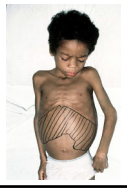
PMH recurrent salmonellosis as a child.

Sibling had tuberculosis but is now cured.

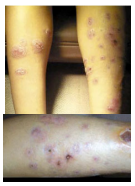
CD4+ number is normal, HIV -

## Clinical Spectrum of NTM Infections

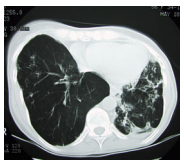
**Disseminated**
Severe, Young
IFNγ/IL-12 defects
NEMO, STAT1



**Skin**
Exposure
Inoculation

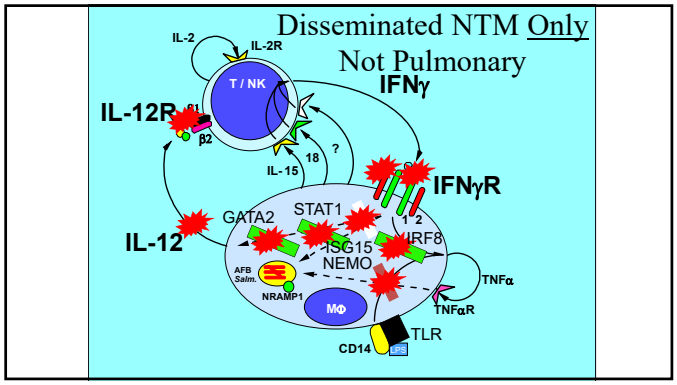


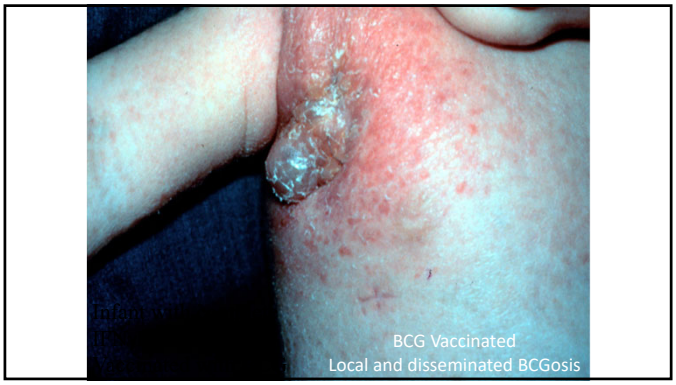
**Pulmonary**
Chronic, Older
Bronchiectasis
Cystic fibrosis (CF)
Ciliary dyskinesia (PCD)

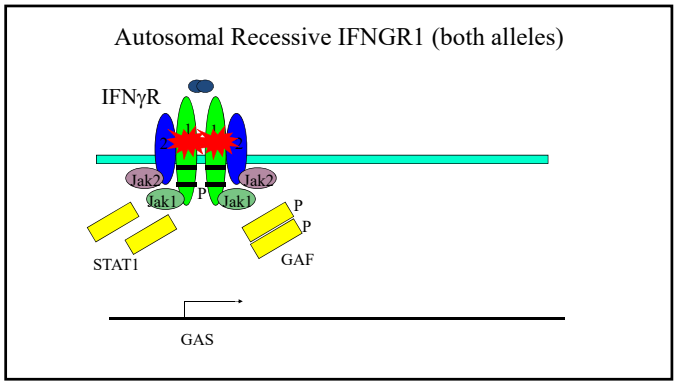


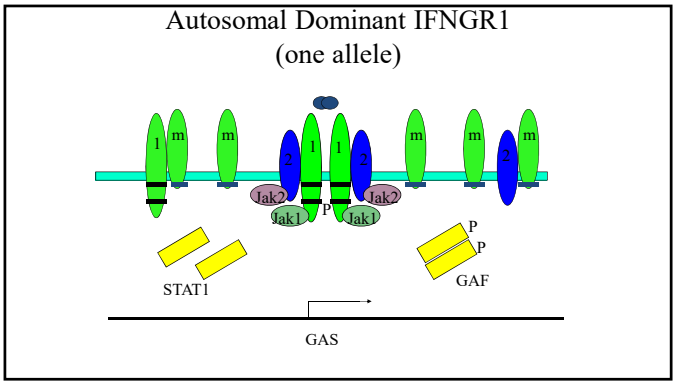
# 03 - Clinical Immunology and Host Defense

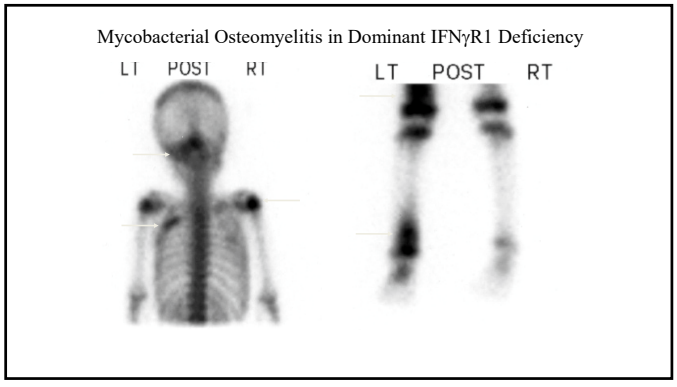
*Speaker: Steven Holland, MD*




## IFNGR1: Dominant vs. Recessive

| Characteristic | AD | AR |
|---|---|---|
| IFNγR1 display | high | none |
| IFNγ responsiveness | low | none |
| Clinical presentation | local | disseminated |
| Granulomata | present | absent |
| Osteomyelitis | 100% | rare |
| Survival | excellent | most die |

# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*

## Pathogens in human IFNγR deficiencies

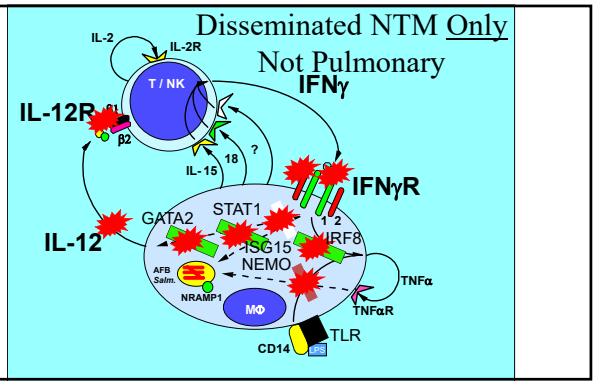
| | |
|---|---|
| *M. avium* | *Salmonella* |
| *M. intracellulare* | *Listeria* |
| *M. chelonae* | |
| *M. abscessus* | CMV |
| *M. smegmatis* | HSV |
| *M. fortuitum* | VZV |
| *M. tuberculosis* | RSV |
| *Bacille Calmette Guerin* | HHV-8 |

*Coccidioides*
*Histoplasma*

## Interferon γ Receptor Deficiencies

Absent or defective IFNγR1
- MAC and other NTM, *Salmonella*, TB, viruses
- complete defects present in childhood
- partial defects present later in life
- may be misdiagnosed as malignancy!
- NOT a cause of isolated lung disease in adults

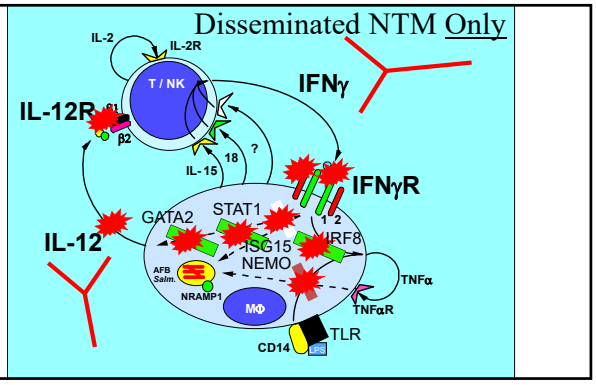
Dx- genetics, flow cytometry for IFNγR1
Rx- antimycobacterials (BMT for recessive)




## IL-12βR1 Deficiency

Similar to IFNγR defects
- disease is usually milder and later onset
- residual IFNγ production
- similar pathogens-NTM, TB, *Salmonella, cocci*

Dx- genetics, flow cytometry
Rx- antimycobacterials, IFNγ systemically




## Anti-IFNγ autoantibody syndrome

Disseminated NTM later in life
Predominantly female, mostly East Asian
NTM, TB

Dx- autoantibody detection
Rx- antimycobacterials, possibly rituximab

# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Adult-Onset Immunodeficiency in Thailand and Taiwan

Sarah K. Browne, M.D., Peter D. Burbelo, Ph.D., Ploenchan Chetchotisakd, M.D., Yupin Suputtamongkol, M.D., Sasisopin Kiertiburanakul, M.D., Pamela A. Shaw, Ph.D., Jennifer L. Kirk, B.A., Kamonwan Jutivorakool, M.D., Rifat Zaman, B.S., Li Ding, M.D., Amy P. Hsu, B.A., Smita Y. Patel, M.D., Kenneth N. Olivier, M.D., Viraphong Lulitanond, Ph.D., Piroon Mootsikapun, M.D., Siriluck Anunnatsiri, M.D., Nasikarn Angkasekwinai, M.D., Boonmee Sathapatayavongs, M.D., Po-Ren Hsueh, M.D., Chi-Chang Shieh, M.D., Ph.D., Margaret R. Brown, B.S., Wanna Thongnoppakhun, Ph.D., Reginald Claypool, R.N., Elizabeth P. Sampaio, M.D., Ph.D., Charin Thepthai, M.Sc., Duangdao Waywa, M.Sc., Camilla Dacombe, R.N., Yona Reizes, R.N., Adrian M. Zelazny, Ph.D., Paul Saleeb, M.D., Lindsey B. Rosen, B.S., Allen Mo, B.S., Michael Iadarola, Ph.D., and Steven M. Holland, M.D.

*NEJM* 2012;367:725

## 20 yo with back pain

WBC 12,000/µl, ESR 93 mm/hr, PPD12 mm

2 weeks pain over L2 and a lytic lesion

Biopsy: histiocytic malignancy, chemotherapy started

Father had similar illness, turned out to be MAC

You suspect that she has the autosomal dominant form of IFNγR1 deficiency and you need to prove it before radiation starts.

## To confirm the diagnosis, you should:

a) Show high TNFα from stimulated cells
b) Show high IL-12 from stimulated cells
c) Show high IFNγR1 on cell surfaces
d) Show high TNFαR on cell surfaces
e) Show low IFNγR1 on cell surfaces

## GATA2 Deficiency

Adolescent to adult onset
- HPV (hands, genitals, cervical, vulvar)
- disseminated NTM (mediastinal *M. kansasii*)
- pancytopenia

Labs: profound monocytopenia, low B, low NK

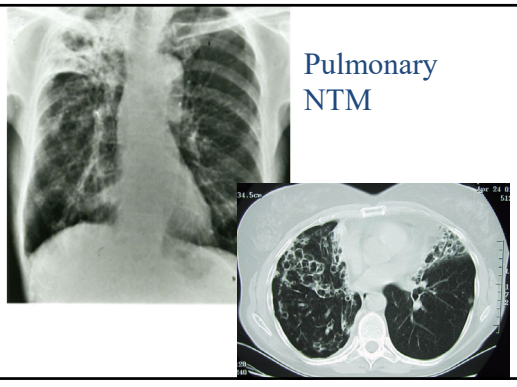
CT: subpleural blebs

Autosomal dominant

Dx: genetic, hypocellular marrow

Rx: antibiotics, BMT

Spinner et al. Blood 2014; 123:809-21



## Pulmonary NTM

## Pulmonary NTM: Adults

Female predominance
Caucasian predominance
Post menopausal
"Lady Windermere Syndrome"
tall, thin, pectus abnormalities
Association with CFTR mutations
Complex immunologic and somatic genetics

Szymanski Am J Respir Crit Care Med. 2015

# 03 - Clinical Immunology and Host Defense

*Speaker: Steven Holland, MD*

## Remember

Disseminated NTM means immunodeficiency

Corollary: Isolated Pulmonary NTM Does not

## CD4+ T-lymphocytopenia

HIV associated

autoimmune associated

idiopathic CD4+ T-lymphocytopenia (ICL)

- ≤ 300 CD4+/μl
- associated with AIDS-like infections (crypto, PCP, MAC)
  - exclude HIV infection (PCR, bDNA, p24, culture)
  - often older onset than HIV associated OI

**Dx-** determination of ICL (FACS)

Often due to an underlying defect, so LOOK

**Rx-** treat infections (follow CD4+, ?cytokines)

## Screening Laboratories

For Lymphocytes

- Ig levels
- immunization status (tetanus, pneumovax)
- CD4+ number
- Genetics (exome studies, panels)

## Screening Laboratories

phagocytes

- DHR for superoxide
- FACS (CD18, CD11a-c, IFNγR1, IL-12Rβ1)

complement

- $CH_{50}$ (classical pathway)
- $AH_{50}$ (alternative pathway)
- ELISA for individual components

Think about the gene involved!

Use Pubmed OMIM

- sequence gives a solid diagnosis

## It is the SOS

History

Physical

Imaging

Laboratories

*(talk to the lab yourself!!!)*