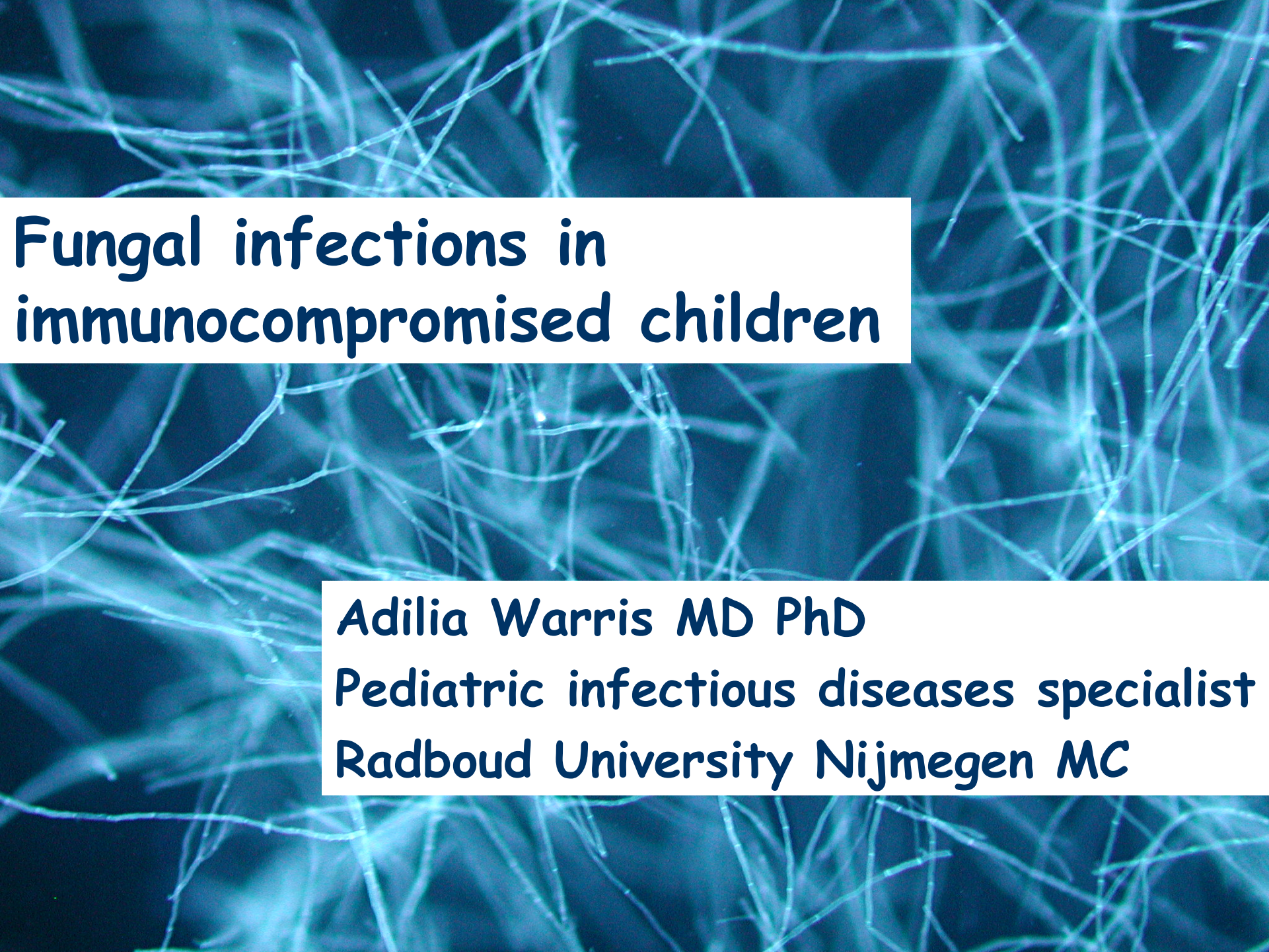
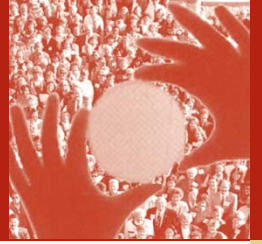


Fungal infections in immunocompromised children

Adilia Warris MD PhD
Pediatric infectious diseases specialist
Radboud University Nijmegen MC

Epidemiology of pediatric IA



- 6 tertiary care medical centers US, 2000-05
- proven IA 78%, probable 22%
- 139 pediatric patients
  - ✓ hematologic malignancy 63%
  - ✓ inherited immunodeficiency 12%
  - ✓ solid organ transplant 12%
- etiology:
  - ✓ A. fumigatus 53%
  - ✓ A. flavus 16%
  - ✓ A. niger & A. terreus 5% (each)
  - ✓ A. nidulans 1%
- outcome:
  - ✓ 53% deceased (70% due to IA or with active IA)

Burgos, Pediatrics 2008

Neutrophil disorders

- Primary defects in neutrophil function are not common, but
  - ✓ Require aggressive and specific management
  - ✓ Lifelong prophylaxis in many cases

- Phagocytic cells are cornerstone of the innate immune system

PID & risk of IFI

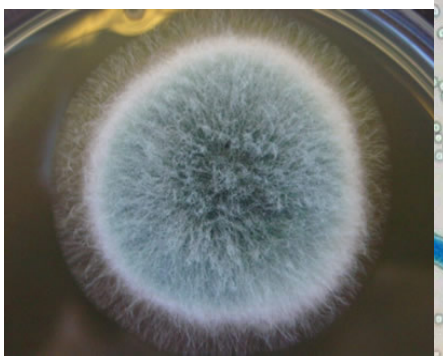
Immune deficit	Clinical disorders	Fungal infections
Humoral	XLA, AR-agammaglobulinemia, CVID, IgA-deficiency	very unlikely
Cellular	SCID, diGeorge, hyper-IgM, Wiskott-Aldrich	sporadic, variable (*Candida*, *Aspergillus*, *Crypto*, dimorphic)
Phagocytic	CGD, MPO, LAD, congenital neutropenia	*Aspergillus* frequent in CGD, variable (*Candida*, *Aspergillus*, dimorphic)
Complement	deficiencies specific factors or MBL	very unlikely
Others	hyper-IgE syndrome, CMC, defects IFNγ/IL12	*Aspergillus* in HIES, variable (*Candida*, *Aspergillus*, *Crypto*) superficial in CMC

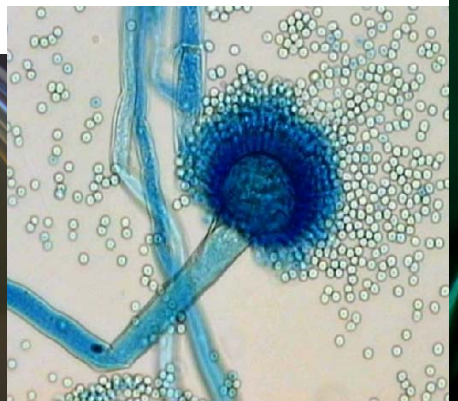
reviewed by Antachopoulos, Eur J Ped 2007

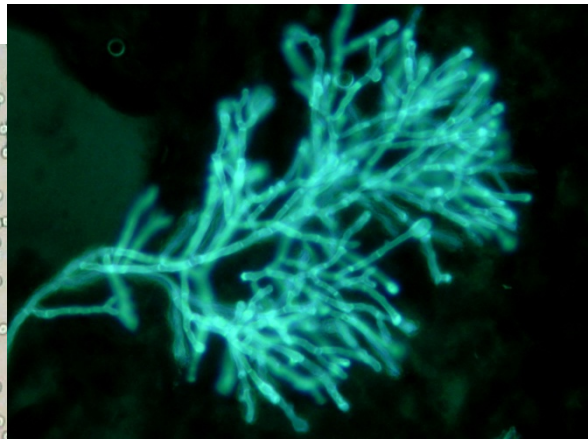
PID & Invasive Aspergillosis

- Chronic granulomatous disease
  - ✓ Lifetime incidence IA 25-40%
  - ✓ Most common cause of death (~35%)

- Hyper-IgE syndrome
  - ✓ Occasionally observation of IA
  - ✓ Important cause of death







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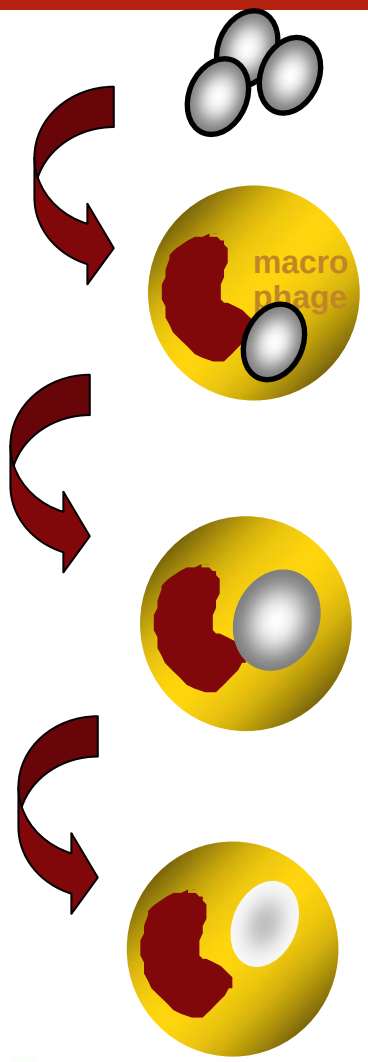
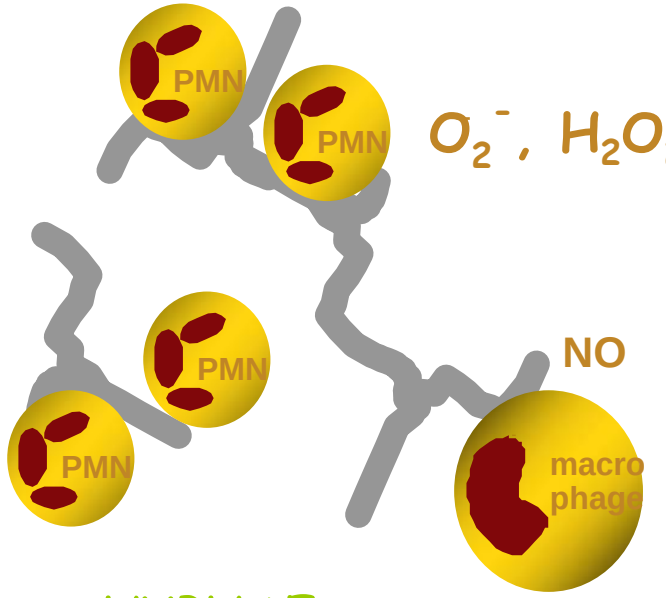
Host response to fungal infections



CONIDIA

recognition TLRs, dectin1, MR, CR

phagocytosis



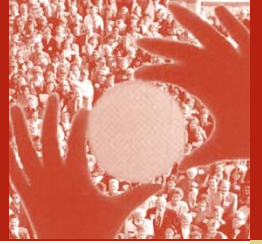
O_2^-, H_2O_2, HOCl

non-oxidative mechanisms:
defensins
lactoferrin
calprotectin
cationic proteins

HYPHAE

cytokines:
IFNγ, IL-12, IL-18, IL-17

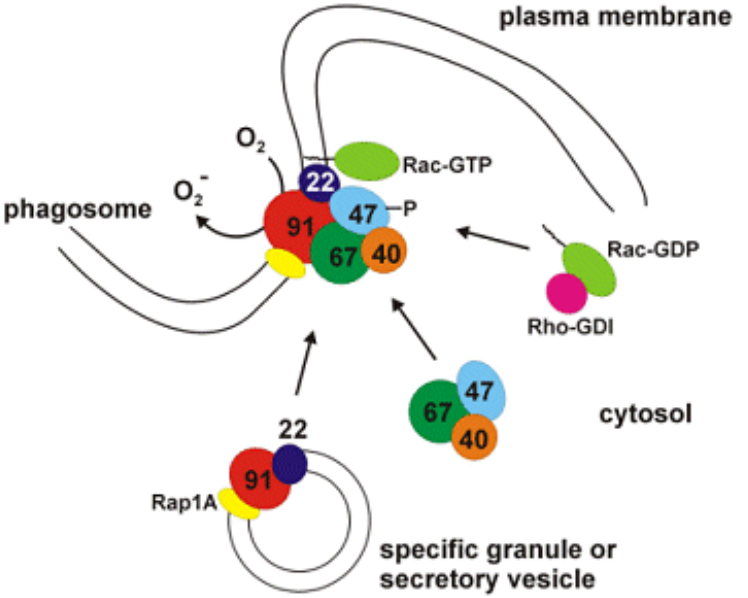
Intracellular killing



- Reactive oxygen intermediates
  - ✓ O_2 is reduced to $\cdot O_2^-$ by NADPH
    - hydroxyl radicals (•OH) and
    - hydrogen peroxide (H_2O_2) by superoxide dismutase
- Lysosomal enzymes
  - ✓ Defensins, lactoferrin
  - ✓ activity pH-dependent
- Meyloperoxidase (MPO) from lysosomes
  - ✓ Fusion fagosome + lysosome
  - ✓ H_2O_2 + chloride > hypochloriet (HOCl) by MPO

Chronic granulomatous disease

- XL (65%) and AR inheritance
- Defect in NADPH-oxidase complex
- Diminished oxidative response
- Life-threatening bacterial and fungal infections
- Exuberant inflammatory responses -> granuloma formation
- 1: 200.000



CGD and fungal infections

Combined US & European data

- 2nd most common infection caused by *Aspergillus* spp.
- invasive aspergillosis main cause of death (~35%)
- *Aspergillus* spp. main cause of pneumonia (20-41%)
- *Aspergillus* spp. main cause of osteomyelitis (~35%)
- *Aspergillus* spp. main cause of brain infections (38%)
- *Candida* spp. mainly as cause of lymphadenitis, meningitis and bloodstream infections
- *Candida* spp. less common cause of death (~6%)

van den Berg, PlosOne 2009
Winkelstein et al, Medicine 2000

Mould infection as presenting symptom in CGD

Multiple case-reports:

- Gastrointestinal zygomycosis due to *Rhizopus microsporus var. rhizopodiformis* in 10-month-old boy
- Chronic *Fusarium* infection in adult patient
- Disseminated intracranial aspergillosis in 8-year-old boy
- Invasive pulmonary aspergillosis in male neonate of 1 month of age
- Splenic abscesses caused by *Paecilomyces variottii* in a 21-month-old child

Dekkers, Med Mycol 2008; Wang, Diagn Microb Inf Dis 2005; Mouy, Arch Ped 1995; Alsultan, Ped Blood Cancer 2006; Mansoory, CID 2003

A. nidulans and CGD

- 25 reported patients
- 90% XL-CGD
- 75% lung invasion with direct spread to adjacent chest structures
- 20% bone infections
  - ✓ vertebrae 45%
  - ✓ ribs 37.5%

Henriet et al, submitted

A. nidulans and CGD

- *Emericella nidulans* (teleomorph)
- other species of *Emericella* rarely identified as agents of infections in humans
- Species not encountered in other groups of immunocompromised patiënt
- Increased virulence as shown by more easily dissemination to adjacent structures
- Associated with increased mortality when compared to *A. fumigatus* (50% vs. 5-10%)

Dotis, Int J Inf Dis 2004
Segal, Medicine 1998

Emericella spp. in CGD

E.nidulans	Lung biopsy	Proven IA	*E.quadrilineata*	NIH, Bethesda
E.nidulans	Lung biopsy	Proven IA	*E.quadrilineata*	NIH, Bethesda
E.quadrilineata	BAL-fluid	Probable IA	*E.quadrilineata*	Nijmegen, NL
E.nidulans	Bone tissue	Proven IA	*E.rugulosa*	Thessaloniki, Greece
E.nidulans	Brain tissue	Proven IA	*E.nidulans var. echinulata*	
E.nidulans	Tissue	Proven IA	*E.nidulans var. echinulata*	Nijmegen, NL

Verweij et al, EID 2008

Susceptibilities of *Emericella* spp.

drug	*E. nidulans* (n=12)	*E. quadrilineata* (n=12)	significance
Amphotericin B	2.5	0.5	P < 0.05
Itraconazole	0.07	0.13	NS
Voriconazole	0.26	0.39	P < 0.05
Posaconazole	0.25	0.22	P < 0.05
Caspofungin*	0.01	1.83	P < 0.05

Verweij et al, EID 2008

Antifungal prophylaxis & CGD

- R,DB,PC,MC-study: IFN-γ prophylaxis
  - ✓128 CGD-patients, median 15 years of age
    87% antibacterial prophylaxis
    50 ug/m^2 s.c. 3x/week for 12 mo

- Results:
  - ✓1 (IFN-γ) versus 4 (placebo) patients with IPA (0.38 vs 1.1 cases/patient year)
  - ✓in vitro no augmentation of superoxide production
  - ✓augmenting oxygen-independent pathways

Gallin, NEJM 1991;324:509-16

Antifungal prophylaxis & CGD

R,DB,PC,CO-study: itraconazole prophylaxis

39 CGD-patients > 5 years of age

antibacterial prophylaxis

34 patients on IFN-γ therapy

Exclusion: antifungal therapy < 3 mo.

fungal infection < 12 mo.

daily use of prednisone

Gallin, NEJM 2003;348:2416-22

Antifungal prophylaxis & CGD

R,DB,PC,CO-study; 39 patients > 5 y

	Itraconazole	Placebo
Courses	61	63
Days	20,000	21,253
IFI (P=0.10)	1	7
SFI (P=0.06)	0	5
AE	3	0

Gallin, NEJM 2003;348:2416-22

Antifungal prophylaxis & CGD

- Long-term antifungal prophylaxis may lead to the development of infections caused by azole-induced resistant moulds as well as primarily non-susceptible moulds

Warris, NEJM 2002;347:2173-4

Verweij, NEJM 2003;349:1190-1

Antifungal drugs and CGD

- extra effect in lowering fungal infections by using both IFNγ and itraconazole?
- overall infection rate: 0.6-0.8 / patient year
- severe infection rate: 0.2-0.4 / patient year

- follow-up studies:
  - ✓ 1970s all deaths < 10 years of age
  - ✓ 1980s 50% mortality < 10 years of age
  - ✓ 1990s 50% alive > 20 years of age
  - ✓ 2000: survival rate > 20 years is not changing

Martire, Clin Imm 2007; Marcanio, CID 2004; Liese, J Ped 2000
Cale, Clin Exp Imm 2000; Weening, Eur J Ped 1995

Therapeutic options

- increased number of antifungals
  - ✓ more important to know which fungus causes the infection
  - ✓ analyse susceptibility pattern
  - ✓ prevent empiric therapy, especially after itra prophylaxis
  - ✓ *A. fumigatus* and *A. nidulans* most frequent
    - 1st choice: voriconazole
    - alternatives:
      - posaconazole
      - combination therapy: vori + echinocandin
      - in mice: cAmB + micafungin increased survival

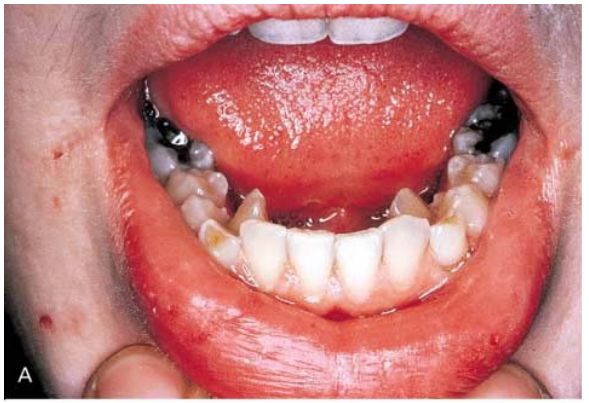
Segal, CID 2005; Walsh, PIDJ 2002
Herbrecht, NEJM 2002; Dennis AAC 2006

Hyper-IgE syndrome

- AD and AR form
- characterized by:
  - ✓ recurrent and often severe pulmonary infections
  - ✓ eczema
  - ✓ staphylococcal abscesses
  - ✓ mucocutaneous candidiasis
  - ✓ various connective tissue, skeletal and vascular abnormalities (AD)
    - facial characteristics
    - retention of primary teeth

phagocytic defect?

Hyper-IgE syndrome



- clinical epidemiology (30 pts):
  - ✓ Staphylococcal abscesses 87%
  - ✓ Recurrent pneumonia 87%
  - ✓ Lung cysts 77%
  - ✓ Mucocutaneous candidiasis 83%
- fungal infections:
  - ✓ pulmonary cyst chronically colonized with aspergillus and died of a mycotic (*A. fumigatus*) aneurysm of the brain
  - ✓ femoral osteomyelitis caused by yeast
  - ✓ lymphatic and visceral candidiasis
  - ✓ invasive esophageal *Cryptococcus neoformans* infection

Holland, NEJM 1999

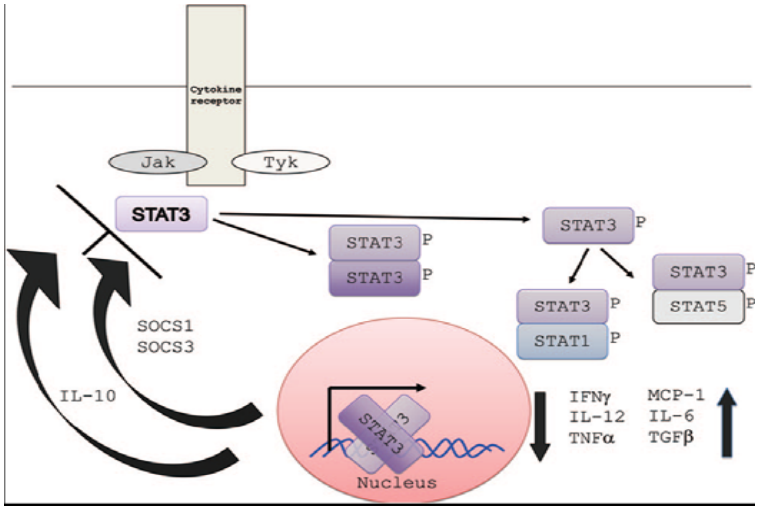
Hyper-IgE syndrome

- functional immunologic defects:
  - ✓ defective granulocyte chemotaxis
  - ✓ abnormalities T-cel subgroups
  - ✓ defective antibody production
  - ✓ decreased production and responsiveness to IFNy and IL-4

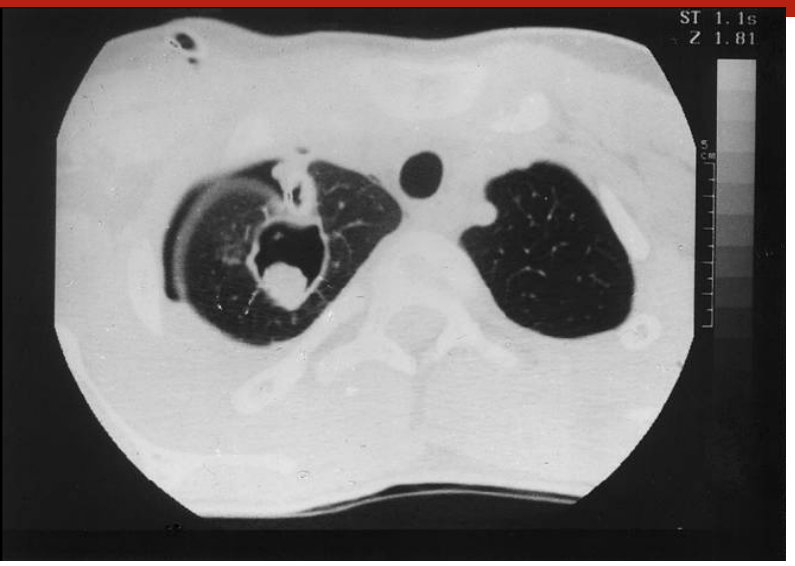
Holland, NEJM 1999

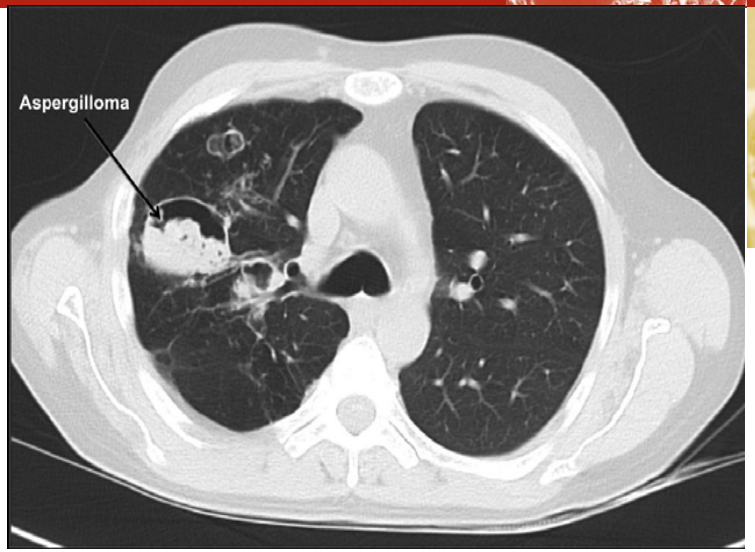
Hyper-IgE syndrome

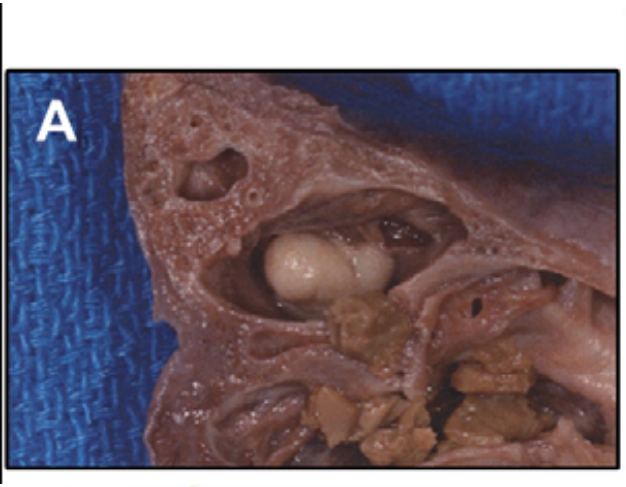
- Mutations in STAT3 responsible for AD-HIES
- STAT3 major signal transducer in many divers pathways
- STAT3 deficiency:
  - ✓ disturbed cytokine regulation
  - ✓ absence of IL-17
  - ✓ excessive and inadequate inflammation leading to pneumatoceles

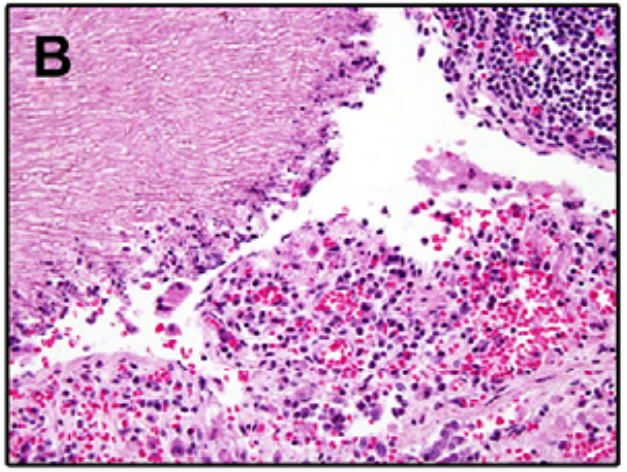


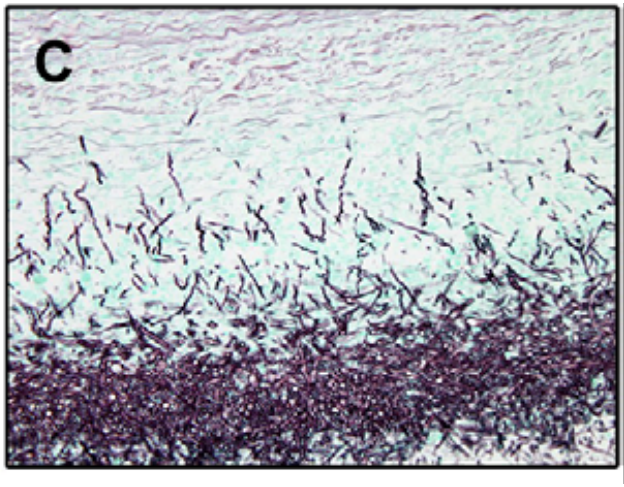
Hyper-IgE syndrome











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Freeman, J Allergy Clin Immunol 2009

Hyper-IgE syndrome

	Lung cyst	McC	age at first pneumonia	age at first known fungal infection	age at first known pseudomonas infection	age at death	lung resection
1	YES	YES	3	NA	23	29	LLL at 4 y followed by left pneumectomy at 15 y
2	YES	YES	7	AF+AN at 23 y	23	24	no
3	YES	YES	12	AF at 37 y	36	40	no
4	YES	YES	2	AF at 18 y	18	24	RLL at 23 y
5	YES	YES	<10	AF at 27 y	27	29	RUL at 28 y
6	YES	YES	18	AF at 31 y	NA	32	LLL at 31 y

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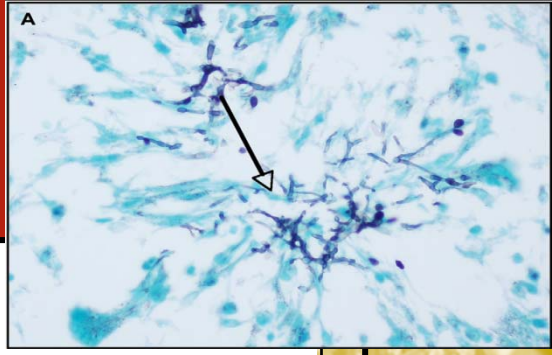
Freeman, J Allergy Clin Immunol 2009

Hyper-IgE syndrome



Patient (age at death)	cause of death	PA: lung
1 (29 y)	acute pulmonary hemorrhage	Cavitary; multi-lobular pneumonia (PSEU) with diffuse hemorrhage
2 (24 y)	prolonged course	Multi-lobular pneumonia; culture with *Scedosporium* (+ brain & kidneys)
3 (40 y)	acute pulmonary hemorrhage	Cavitary with local vascular invasion by *Aspergillus*
4 (24 y)	progressive pneumonia	Multi-lobular pneumonia (PSEU, AF) with intra-alveolar hemorrhage, emphysematous changes
5 (29 y)	multiple CNS bleeds	Cavitary with local vascular invasion by *Aspergillus* (+ brain)
6 (32 y)	pneumonia	Cavitary with local vascular invasion by *Aspergillus*; PJP outside cavity with acute/chronic inflammation

Freeman, J Allergy Clin Immunol 2009

Antifungal prophylaxis & HIES

- Antifungal prophylaxis
  - ✓ when to start?
  - ✓ does it prevent kolonisation of cavities?
- IFN-γ prophylaxis
  - ✓ in vitro studies promising results
  - ✓ but mixed clinically results

Conclusions

- Invasive aspergillosis in CGD and HIES patients
  - ✓ important with respect to survival
  - ✓ will azole prophylaxis increase survival rates?

- *Aspergillus nidulans*
  - ✓ The exclusive role in CGD patients
  - ✓ Studies are warranted to analyse why this fungus is a problem

- Antifungal prophylaxis
  - ✓ Be aware of changing etiology and resistence problems

- Therapeutic options
  - ✓ Be sure to know the fungus you are dealing with
  - ✓ Targeted therapy possible nowadays