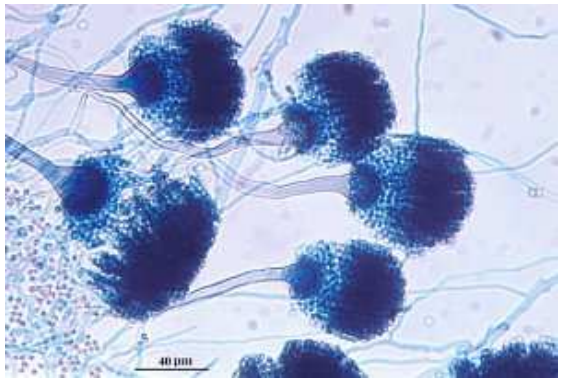
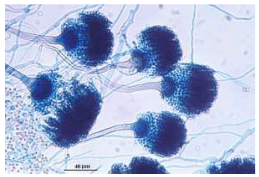


Specific Features of Aspergillosis in Paediatrics

Dr S. Blumental
Paediatric Infectious Diseases Unit
Hôpital Universitaire des Enfants Reine Fabiola
Brussels, Belgium



Why is Paediatrics different?

- Age influence overall

  newborn ≠ infant ≠ child ≠ adolescent
- Specific underlying diseases

  i.e Primary immunodeficiency or congenital syndrome
- Scarce paediatric literature

  frequent extrapolation from adults studies
- Therapeutic issues

  high variability in pharmacokinetics

  accurate drugs dosage challenging

  restricted EMA/FDA approval and reimbursement conditions

Paediatric populations at risk for Invasive Aspergillosis (IA)

Low-birthweight infants and neonates
Children with primary immunodeficiencies
Defects of phagocytic host defenses
Children with acquired immunodeficiencies
Treatment for cancer
Bone marrow failure syndromes
Allogeneic hematopoietic stem cell transplantation
Solid organ transplantation
Children with advanced HIV infection
Children receiving immunosuppressive therapy
Children with acute illnesses or trauma
Children with chronic airway diseases

Tragiannidis et al, Clin Infect Dis 2012

- **Specific features/issues of IA in paediatric Haemato-Oncology**
- **IA in primary immuno-compromised children (CGD, Job Syndrome)**
- **Primary cutaneous aspergillosis in neonates**

IA in paediatric Haemato-Oncology
Incidence

✓ **US 2000 Kids' Inpatient Database**

Retrospective review (1,9 millions records)
666 cases proven/probable IA
Malignancy in 74% IA cases

Zaoutis et al, Pediatrics 2006

Allogenic BMT	4.5%
AML	4.0%
Cong immunodeficiency	3.2%
Aplastic anemia	1.4%
ALL	0.6%
Lymphoma	0.4%
Autologous BMT	0.3%
Solid tumors	0.1%

✓ **ECIL 2011**

All proven/probable IFD
9-15% AML
4-15% allo-HSCT

Ref	Patients studied	IFD incidence	Evidence
Kobayashi et al. (Japan) 2008.	334 Hem. malignancies, HSCT and others	AML 11.7%; alloHSCT 8.1%; ALL 2.0%; sporadic in solid tumors moulds >> yeast	II retro-spective
Kaya et al. (Turkey) 2009	155 AL during intensive chemotherapy	AML 12,4; ALL 8,4 yeast >> moulds	II retro-spective
Castagnola et al. (Italy) 2010	240 AML	10% of all courses; recurrent AML: 15% moulds >> yeast	II retro-spective
Hale et al. (AUS) 2010	Acute leukemia / HSCT patients	Recurrent leukemia 21%; ALL 18.5%; alloHSCT 15.2%; AML 8.8%; yeast >> moulds	II retro-spective
Mor et al. (Israel) 2011	1047 HSCT and heme/onc patients	AML 13.6%; ALL 5.9%; alloHSCT 3.9%; autoHSCT 3.0%; solid tumors 1.6%; lymphoma 0.8% moulds >> yeast	II retro-spective

Risk factors: similar to adults

1) Underlying disease →
2) Others:

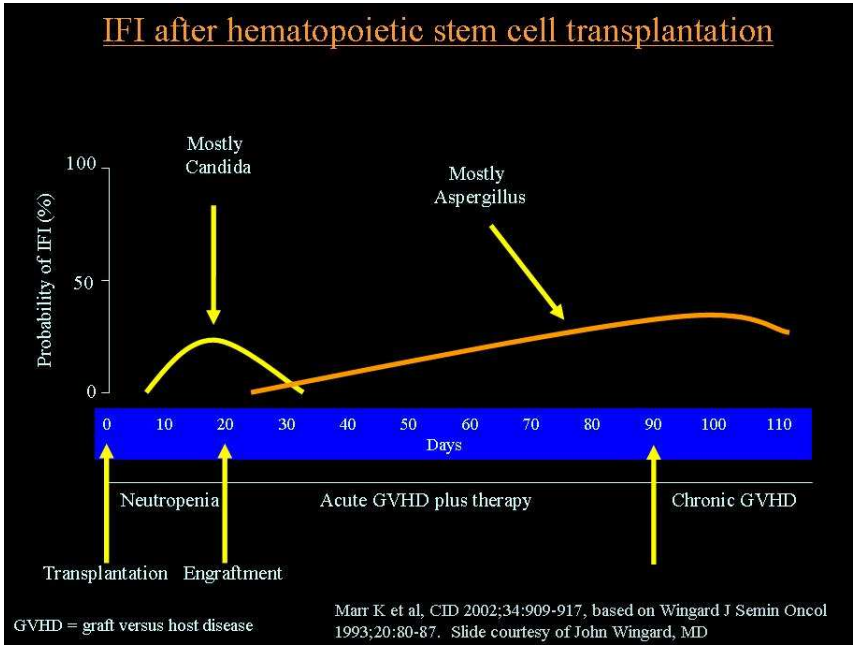
Corticosteroid Therapy	69%
Neutropenia (>3 days)	59%
Immunosuppressive Therapy	43%
Malignancy (non BMT)	38%
Allogeneic BMT	37%
GVHD	12%
Cong immunodeficiency	12%
Solid Organ Transplant	11%

Risk stratum	Patient population
High risk (≥ 10 %)	-acute myeloblastic leukemia -recurrent acute leukemia's -allogeneic HSCT
Low risk (≤5 %) *	-acute lymphoblastic leukemia ** -non-*Hodgkin* lymphoma's -autologous HSCT
Sporadic occurrence *	-pediatric solid tumors -brain tumors -*Hodgkin's* lymphoma

ECIL 2011

95% of patients had ≥ 1 of these risk factors

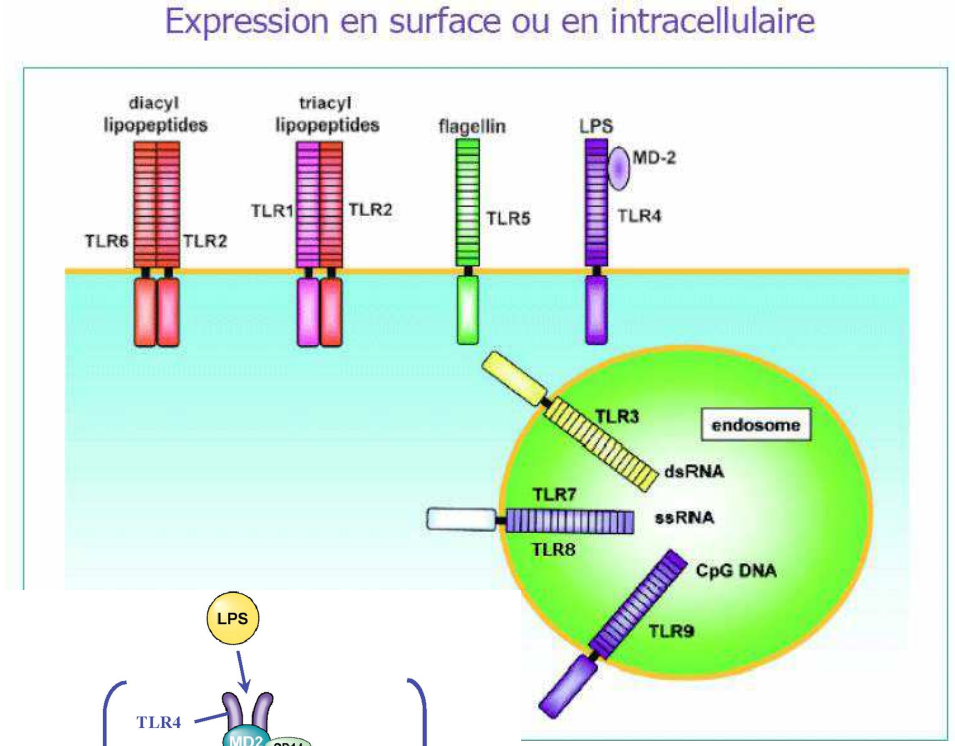
Burgos et al, Pediatrics 2007



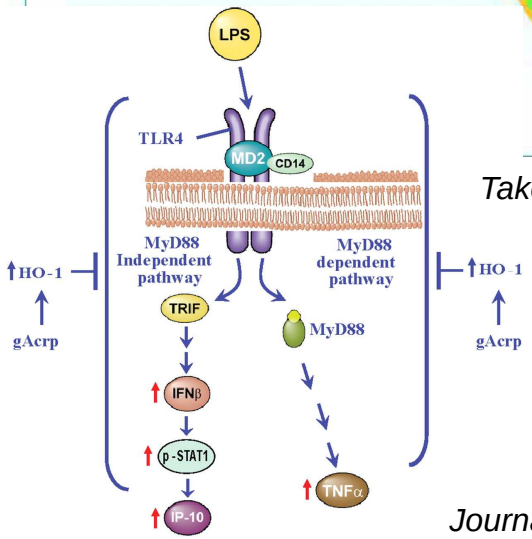
Bimodal Risk distribution

Risk factors: Genetic Polymorphism in Pattern Recognition Receptors

- Crucial components of the innate immunity system
- Single nucleotide polymorphism (SNP) could increase the risk of IA post BMT
- Donor and/or recipient
- TLR4 genetic variants (S4)
  Bochud PY et al, NEJM 2008
  Kolderhoff M et al, Transplant Infect Dis 2013
- TLR5 (stop codon)
  Grube M et al, Med Mycol 2013
- PTX3 (homozygous haplotype 2)
  Cunha C et al, NEJM 2014



Takeda et al, Int immunol 2005



Journal of Immunol 2010

IA in paediatric Haemato-Oncology
High mortality

- **Historically: fatality 69%–85%**

  Walmsley S et al, Ped infect Dis 1993
  Groll AH et al, Mycoses 1999
  Li et al, Clin infect Dis 2001

Age (yrs)	No. of patients	No. of deaths	CFR, %
≤ 20	22	15	68.2
21 - 30	27	16	59.3
31 - 40	52	31	59.6
41 - 50	57	30	52.6
51 - 60	49	29	59.2
> 60	31	17	54.8
Unreported	135	76	56.3

- **Recent Series: fatality ≈ 50 %**

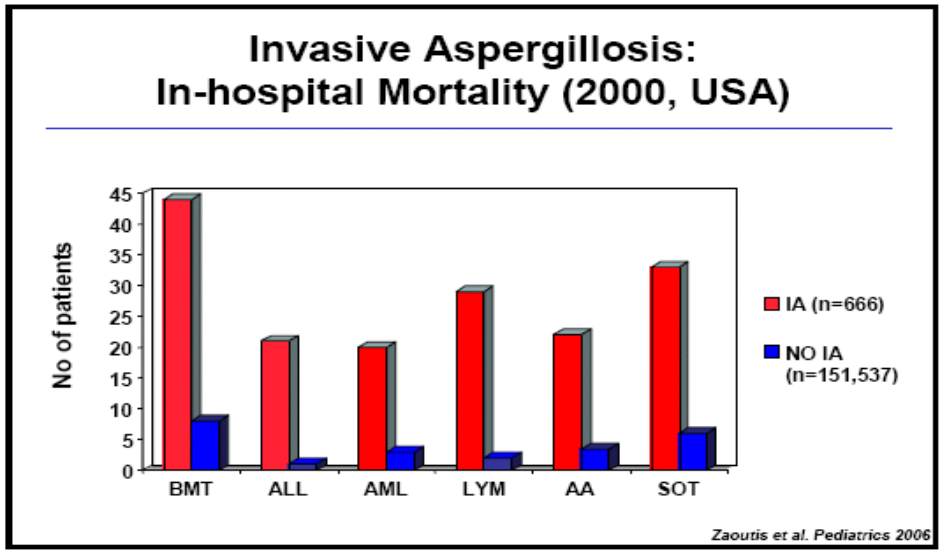
Multivariate analysis for predictors of death:
– Allogenic BMT: OR=6.14 (2.67, 16.21) (fatality 78%)
– Surgery post diagnosis: OR 0.34 (0.06, 0.85)

Burgos et al, Pediatrics 2007
Steinbach et al. Clin Microbiol Infect. 2010

- **US 2000 Kids' Inpatient Study**

Fatality rate among BMT 44%
Overall: risk death X13 if IA

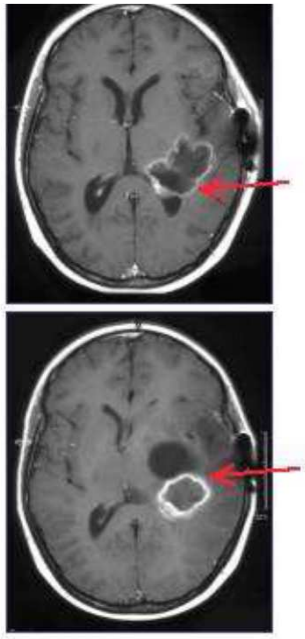
Zaoutis et al, Pediatrics 2006

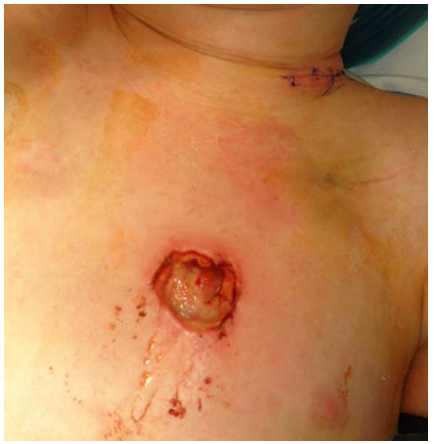


IA in paediatric Haemato-Oncology
Clinical Presentation

✓ **Symptoms/signs: ≈ similar to adults**
(respiratory distress, cough, pleuritic pain, hemoptysis)

……However:
✓ Less primary sinus involvement (10%)





✓ Higher rate of
- CNS dissemination
- Primary skin involvement

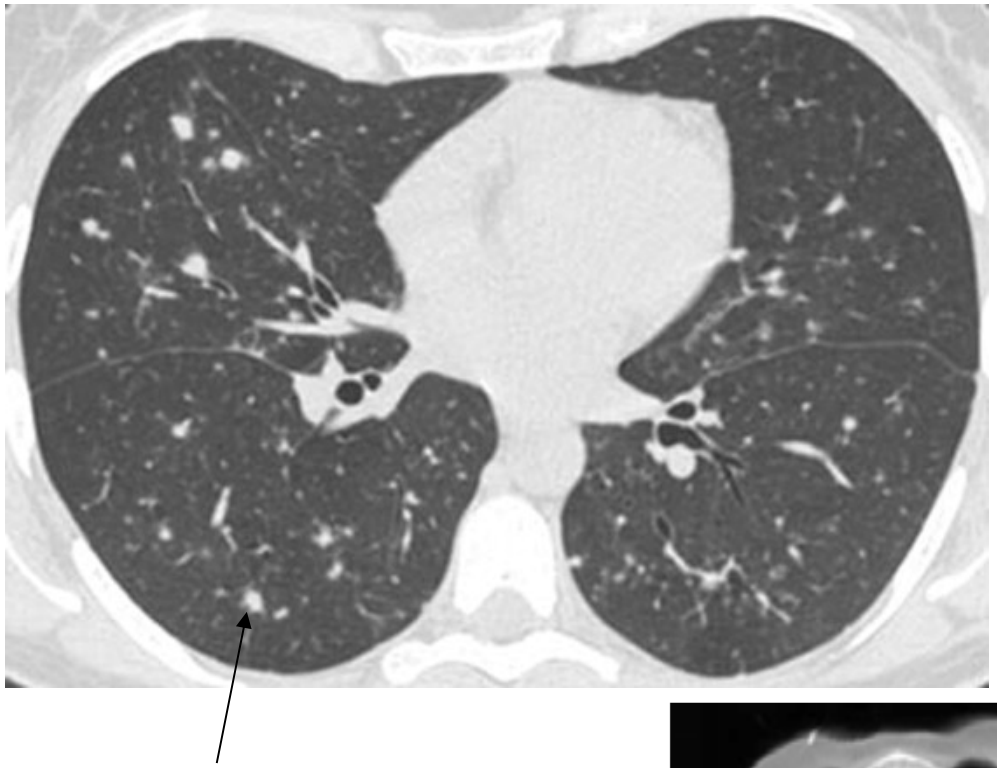
✓ Atypical imaging features (chest CT)

-Mainly nodules (22-35%) or infiltrates (20.7%)
(sometimes central cavitation of small nodules)

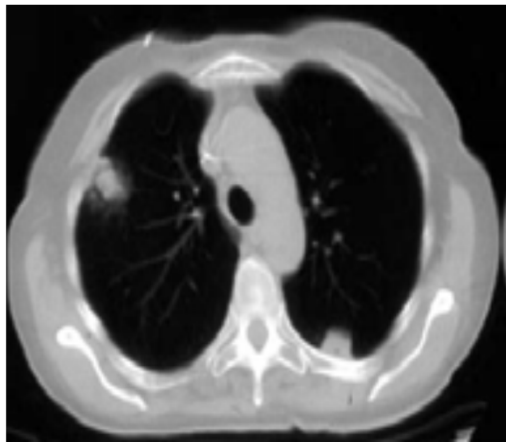
- Rarely halo sign (6%) , air crescent sign (1%) or cavitation (14%)
(of which rates are approximately 40% and 50% in adults series, respectively)

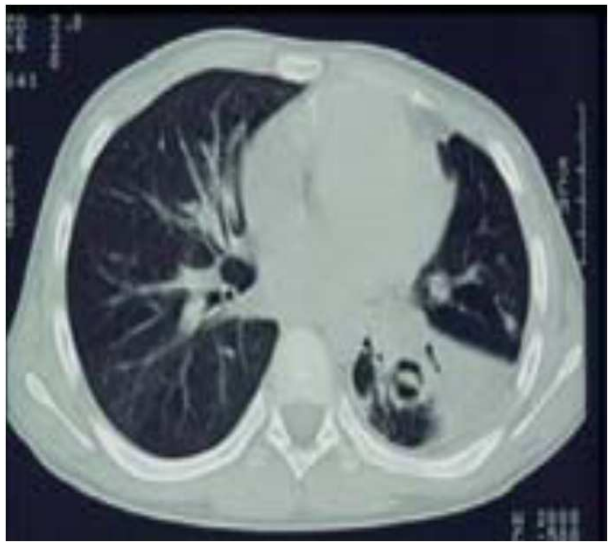
Burgos A, et al. Pediatrics. 2008; Tragiannidis et al, Clin Infect Dis 2012

Chest CT: less “helpful” in paediatrics



- Unspecific findings (reasons?)
- Higher danger due to radiation exposure if serial exams





IA in paediatric Haemato-Oncology
Diagnostic issues: Biomarkers

- **Goals**

✓ Adjunctive argues supporting IA diagnostic in febrile neutropenic children (**empiric approach**)

✓ Early detection of infection and start of therapy (**pre-emptive approach)**

✓ Markers of patient's prognosis (trend under treatment)

- **Galactomannan antigen**

- Heteropolysaccharide component of *Aspergillus spp* cell wall

- Detection by enzyme immuno-assay (Platelia Aspergillus, Biorad, France)

- **1,3 ßD-glucan**

- Cell wall component of a broad range of fungi (not species or genus-specific!)

Aspergillus spp, Fusarium spp, Trichosporium spp, Candida spp, Pneumocystis jirovecci

- Trigger of the coagulation cascade of the horseshoe crab

2 approved assays: Fungitec (Japan) and Fungitell (USA)

IA in paediatric Haemato-Oncology
Diagnostic issues: Biomarkers

- **Biomarkers Galactomannan and 1,3ß-D-glucan**

Inclusion in EORTC criteria based upon performances in adults studies

- **Galactomannan in serum**

Recent paediatric data available (twice weekly screening in HO/HSCT children)

BUT: very heterogeneous studies design, vague endpoint and/or unknown cut-off used

…

"True positive results" from 0 to 100%,

"True negative results" from 22 to 100%

} Cautious interpretation of studies results!

→ **ECIL 2011**

- Comparison of 5 studies which use EORTC/MSG criteria and give adequate information for individual patients with results of a formal meta-analysis of adult data

	Children	Adults
Sensitivity	0.76 (95%CI 0.62 - 0.87)	0.73 (95%CI 0.46 - 0.61)
Specificity	0.86 (95%CI 0.68 - 0.95)	0.90 (95%CI 0.88 - 0.92)

Pfeiffer 2006

ECIL Recommendations

When GM in serum is used for screening for invasive mold infection in children with hematological malignancies/undergoing HSCT, the assay has a sensitivity and specificity profile that is similar to that observed in adults. Despite a number of limitations of the available pediatric data (wide variations amongst the studies regarding cut-off, definition of positivity etc), prospective monitoring of GM in serum every three to four days in children at high risk for IFD is reasonable for early diagnosis of invasive aspergillosis (AII)

GM in BAL/CSF

Very limited data in children

Retrospective analysis on 59 IC children: valuable adjunctive diagnostic tool in BAL (cut off: 1)

Small retrospective case series/reports: support use in CSF (cut off 0.5)

Desai et al, Pediatr infect dis 2009; Roilides et al, 2003

IA in paediatric Haemato-Oncology
Diagnostic issues: Biomarkers

1,3ß-D-glucan

Adults data

Interest for pre-emptive treatment strategies

Se 55-100%, Sp 71-93%, PPV 40-89%, NPV 73-100%

Various cut-off values for positivity! (6 to 120 pg/ml)

Dornbusch HJ, et al, Clin Microb Infect 2010;
Obayashi T et al, Lancet 1995;
Ostrosky-Zeichner Let al, Clin infect Dis 2004

Very limited data in children

Mean BG levels in immuno-competent healthy children higher than adults

→ optimal cut-off in children? (adults ≥ 80pg/ml)

→ Not currently recommended in paediatrics

Smith PB et al, Clin Vaccine Immunol 2007;
Mularoni et al, Clin Vaccine Immunol 2010

High Rate of False Positives in Paediatrics

	(1→3) Beta-D-Glucan Assay	Galactomannan EIA Assays
Medications	Intrvenous amoxicillin-clavulanate or ampicillin-sulbactam	*Piperacillin-Tazobactam *other beta lactam antibiotics
Infusions	*Intravenous immune globulin *Cellulose filters for IV infusion *Albumin	*Plasmalyte (electrolyte infusion) *Intravenous solution with sodium gluconate
Medical interventions	*Hemodialysis with cellulose filter *Gauze packing on serosal surfaces	*Enteral feeding with soybean proteins
Other infections	*Pneumocystis jiroveci*	**Penicillium* spp. **Histoplasma capsulatum* **Geotrichum* **Neosartoria* **Bifidobacterium*

Dietary GM in pasta, cereals, formula milk

\+ High rate of colonizing yeasts in the GI tract and in food

Highly present in the infantile gut microflora

IA in paediatric Haemato-Oncology
Diagnosis issues: *Aspergillus* DNA PCR detection

- Under assessment for inclusion in EORTC criteria

  White PL et al, J Clin Microbiol 2010

- Variable performances (in adults and children)
  Sensibility 63 to 100%, Specificity 87 to 96.7% (blood, CSF,BAL)

- various targets and primers, need for standardization
- role of samples amount and volumes collected

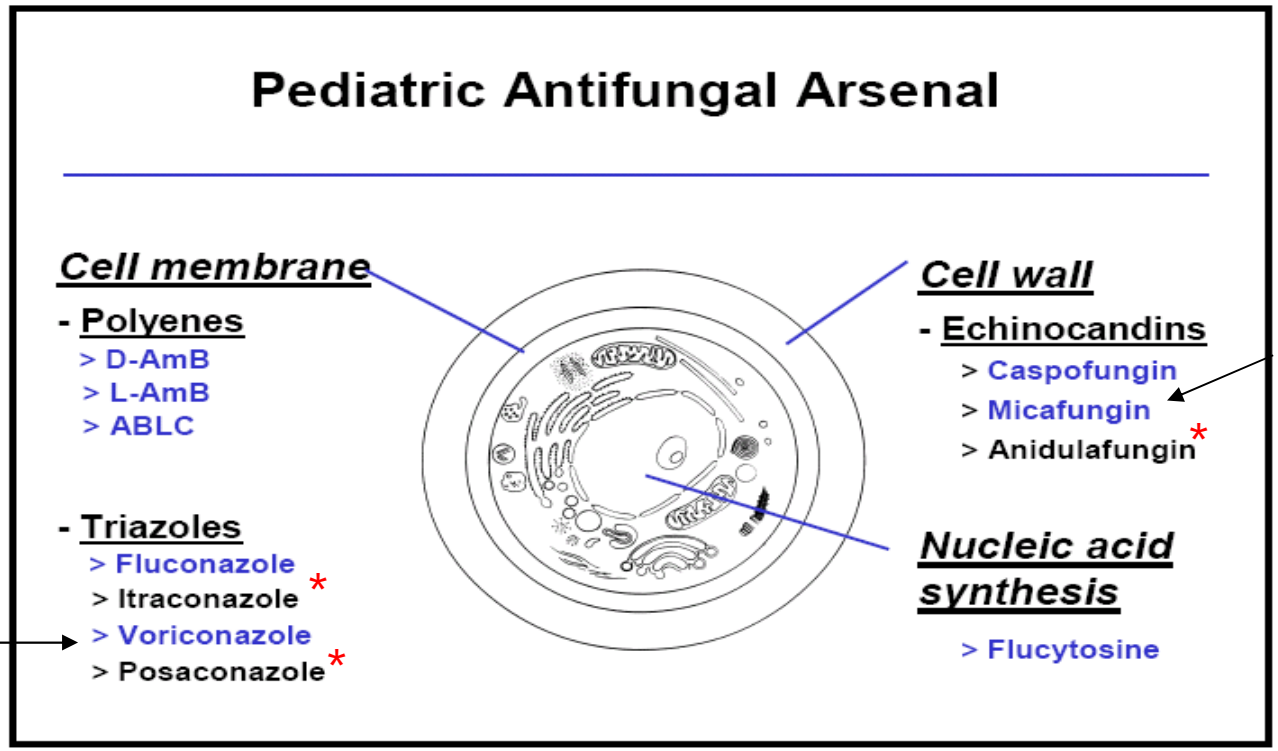
Suarez et al, J Clin Microbiol 2008
Millon L et al, J Clin Microbiol 2011
Mengoli C et al, Lancet Infect Dis 2009
Kourkoumpetis T, et al. Clin Infect Dis 2012
Florent M et al, J Infect Dis 2006
Hummel M et al, J Med Microb 2009
Arvantis M et al, J Clin Microbiol 2014

- High interest for tissues samples (biopsy!)
- Important to exclude IA and early stop of empiric therapy
- New PCR to detect azoles resistance (mutations CYP51A)

→ Need for further multi-centric studies
Role of combined strategy
Interferences from prophylactic regimens

Morrissey CO et al, Lancet infect Dis 2013
Rogers TR et al, Br J Haematol 2013
Duarte RF et al, Clin infect Dis 2014

IA in Paediatric Haemato-Oncology
Therapeutic Features



Not approved < 2y

EMA warning

** not approved in paediatric patients*

Groll & Tragiannidis Clin Microbiol Infect 2010

Restricted options for therapeutic and prophylactic regimens!
(reimbursement issues!)

IA in Paediatric Haemato-Oncology
Therapeutic Features

- Efficacy data: frequent extrapolation from adults clinical trials, few paediatric data

  Walsh TJ et al, Pediatr Infect Dis J 2002; Herbrecht R et al, N Engl J Med 2002
  review in Tragiannidis A et al, Clin Infect Dis 2012

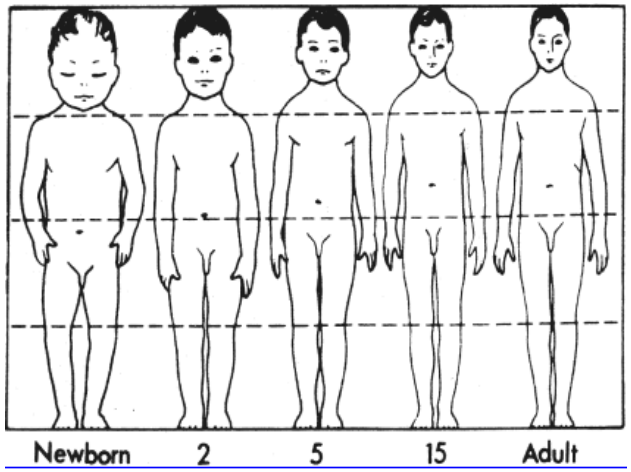
- Safety, tolerability, pharmacokinetics
  - high variation amongst age groups! (not only body weight/surface)
  - crucial paediatric assessment (no extrapolation)

    Walsh TJ et al, Antimicrob Agents Chemother 2004 and 2010;
    Karlsson MO, Antimicrob Agents Chemother 2009
    Hong Y, Antimicrob Agents Chemother 2006

  - accurate dosage challenging, need for TDM

    Steinbach WJ et al, Expert Rev. Anti Infect. Ther 2011
    Groll A et al, Clin Microbiol Infect 2010

- Drugs formulation important



From Groll A, 2011

IA in Paediatrics
Therapeutic Features

Table 3. Pediatric Dosages of Systemic Antifungal Agents Used for Treatment of Invasive Aspergillosis[a]

Agent	Daily Dosage by Age Group			
	13–18 Years	2–12 Years	1–24 Months	Neonates
Amphotericin B deoxycholate, mg/kg[b]	1–1.5	1–1.5	1–1.5	1–1.5
Liposomal amphotericin B, mg/kg	3 (–5)	3 (–5)	3 (–5)	3 (–5)
Amphotericin B lipid complex, mg/kg	5	5	5	5
Amphotericin B colloidal dispersion, mg/kg	3–4	3–4	3–4	ND
Voriconazole intravenous solution, mg/kg[c]	8 (12 on day 1; in 2 doses)	14 (in 2 doses)	ND	ND
Voriconazole oral suspension or capsules, mg[c]	400 (in 2 doses)	400 (in 2 doses)	ND	ND
Posaconazole oral suspension, mg[d]	800 (in 2 or 4 doses)	ND	ND	ND
Itraconazole oral suspension or capsules, mg/kg[e]	5 (in 2 doses)	5 (in 2 doses)	ND	ND
Caspofungin, mg/m^2	50 (70 on day 1; maximum, 70)	50 (70 on day 1; maximum, 70)	50 (70 on day 1)	25

Abbreviation: ND, no data or no sufficient data.

[a] Order is according to drug class and approval status. For detailed indications, please refer to the text. Drugs were given intravenously unless otherwise indicated.

[b] Amphotericin B deoxycholate is a first-line option in countries with limited resources; because of inferior responses and survival in the randomized comparative trial with voriconazole, however, there is little rationale for its use in other settings.

[c] Dose recommendations are based on the current European label; dosages used in current clinical trials for treatment initiated by the manufacturer are 8 mg/kg twice daily (day 1, 9 mg/kg twice daily) for intravenous and 9 mg/kg twice daily for oral administration (maximum, 350 mg twice daily) for patients aged of 2–14 years and the approved adult dose for patients ≥15 years and 12–14-year-olds weighing >50 kg. Therapeutic drug monitoring with dose modification is recommended in these trials to maintain trough concentration of voriconazole of ≥0.2 μg/mL (oral) and ≥0.5 μg/mL (intravenous), respectively.

[d] Not approved in pediatric patients; therapeutic drug monitoring with dose modification is suggested to achieve trough concentration of ≥1.0 μg/mL of posaconazole in the therapeutic setting.

[e] Not approved in pediatric patients; therapeutic drug monitoring with dose modification recommended to maintain trough concentration of itraconazole of ≥0.5 μg/mL.

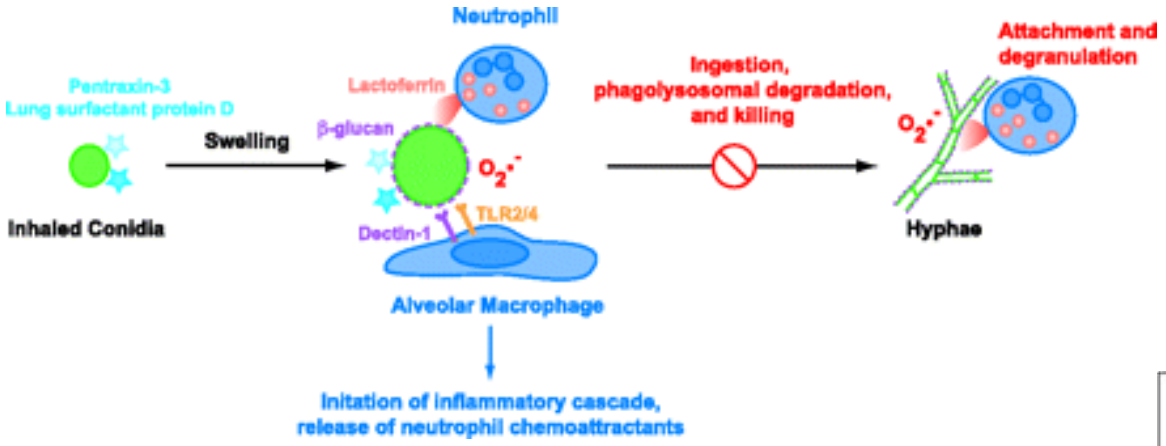
Voriconazole:

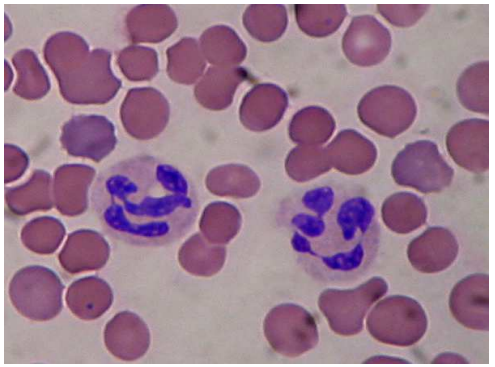
Tragiannidis et al, Clin Infect Dis 2012: 7mg/kg bid

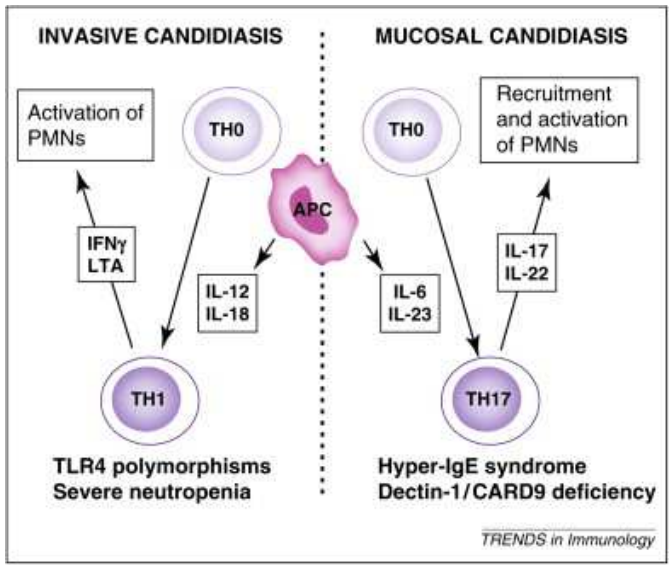
Manufacturers recommendations 2013: 9mg/kg IV bid on day 1 followed by 8mg/kg bid IV or 9mg/kg bid po + TDM!!!

IA and Primary ImmunoDeficiency (PID)
Host defences

❖**Phagocytic cells: cornerstone of defences against moulds invasion**
(intra-and extra-cellular killing, oxydative and non-oxydative mechanisms)







❖Yeast barriers very different:
key role of th1 and th17 lymphocytes

IA and PID

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

Antachopoulos, Eur J Ped 2007

Phagocytic disorders = very high risk condition for IA
In particular Chronic Granulomatous Disease (CGD)

PID: recently included in the EORTC/MSG revised criteria

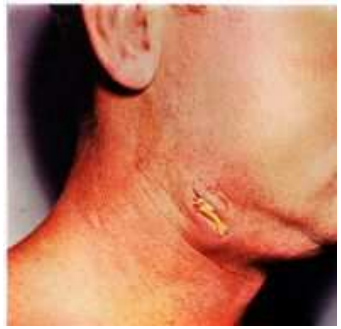
Table 2. Criteria for probable invasive fungal disease except for endemic mycoses.

De Pauw et al, Clin Infect Dis 2008

Host factors[a]

- Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease
- Receipt of an allogeneic stem cell transplant
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
- Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

Chronic Granulomatous Disease

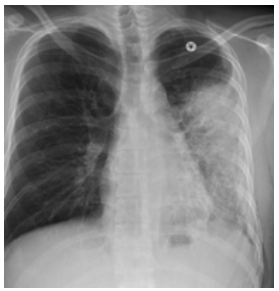


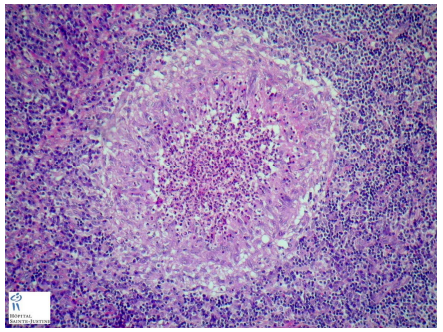
- Prevalence: 1:200.000 to 1:450.000 live births
  Poor prognosis (survival 50% at 30years)
  Winkelstein JA et al, Medicine 2000; Ahlin A et al, Acta Paediatr. 1995; Kobayashi S, Eur J Pediatr 2008

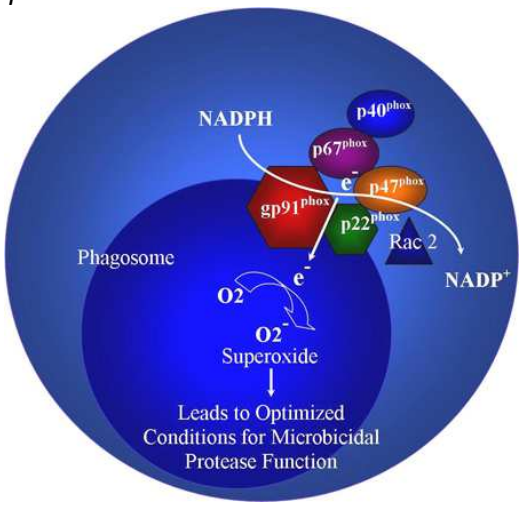
- Defective phagocytes killing
  impairment of the oxidative burst (oxygen radicals production)
  > dysfonction in components of NADPH oxidase complex
  Segal BH et al, Medicine 2000
  Heyworth PG et al, Curr Opin Immunol 2003

- Various forms of disease

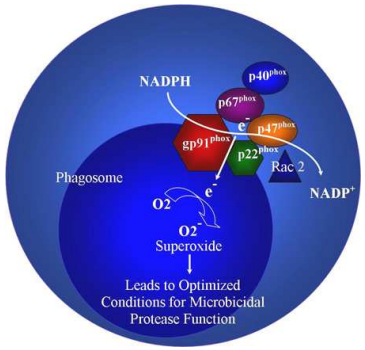
- Mode of inheritance (X-Linked or autosomal recessive inheritance)
- Defective subunit in the NADPH complex





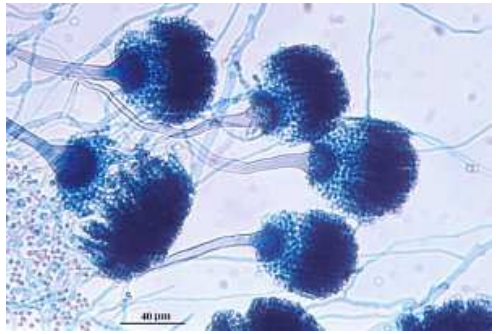


- Recurrent, localized or disseminated life-threatening infections caused by “catalase-positive” bacteria and fungi
- Exuberant inflammatory responses leading to granuloma formation



Chronic Granulomatous Disease and Invasive Aspergillosis

- **High risk** persisting throughout life (lifetime incidence 20-50%!)



- Critical issue : **first cause of death**

  Up to 50% fatality rate

  Responsible of 1/3 of deaths in this population

  Winkelstein JA, Medicine 2000; van den Berg Plos One 2009

- **Specific clinical presentation**

✓ Long insidious stage → severe uncontrolled infection
(median time btw first symptoms and diagnosis: 30d)

✓ Unspecific and heterogeneous symptoms/signs (even asymptomatic)

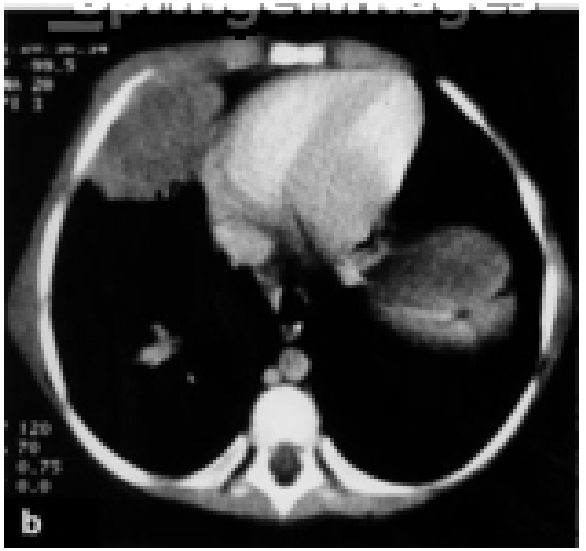
✓ Could be inaugural of the CGD condition
✓ Infected sites:
- pneumonia, brain abscesses, osteomyelitis or disseminated disease
- frequent concurrent thoracic involvement (mass, ribs erosion from pulmonary infiltrate)

Blumental S et al, Clin Infect Dis 2011; Segal BH et al, Medicine 1998

CGD and IA: Clinical Presentation

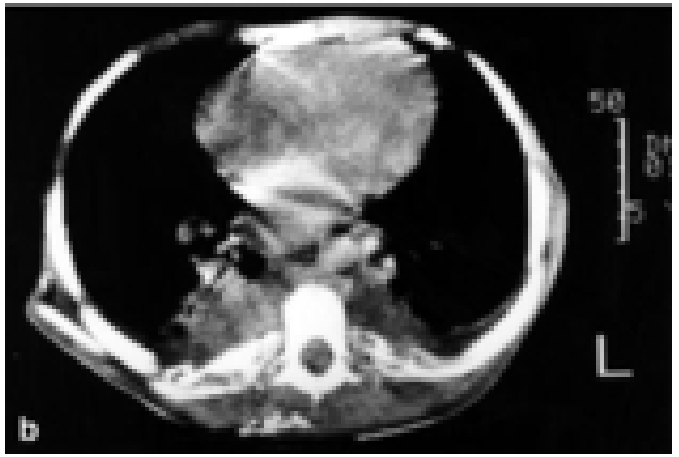
- **Signs and symptoms on admission**

- Failure to thrive	71%
- Respiratory symptoms	55%
- Fever	38%
- Thoracic pain/mass	24%
- Haemoptysis	10%
- Headache	3%
- Seizures	3%



- **Infected sites**

- Lungs	97%
- Pleural effusion	45%
- Thoracic invasion	38%
- Brain	10%
- Vertebrae +/- spine cord	6%
- Femur	3%



Blumental S et al, Clin Infect Dis 2011

CGD and Invasive mold infections: Microbiology

✓ ***A.fumigatus***

A.fumigatus

✓ ***A.nidulans (Emericella Nidulans)***

- Quite exclusively pathogen in CGD
- More "virulent "

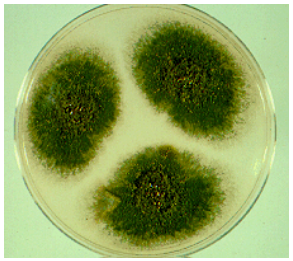
higher chest wall invasion/dissemination/mortality rates

Segal et al, Medicine 2000

Dotis J et al, Int J Infect Dis 2004

higher resistant profiles?

Kontoyiannis DP et al, Mycoses 2002



A.nidulans

- Confusion in some cases with newly discovered cryptic species (*E. quadrilineata*, *E. rugulosa*,…)

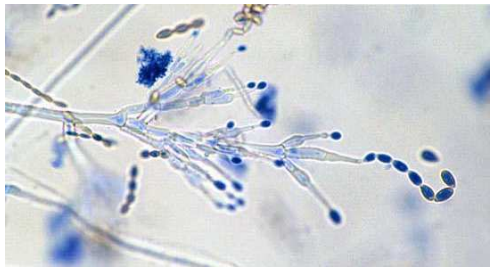
Verweij PE et al,Emerg Infect Dis 2008

✓ New species (*A. tanneri sp*)

Sugui JA et al, J Clin Microbiol 2012

✓ **Other opportunistic filamentous fungi**

- *Fusarium spp*
- *Scedosporium spp*
- *Paecilomyces spp*
- *(Zygomycetes)*

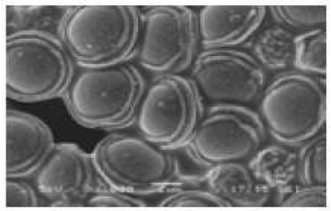


Fusarium spp *Paecilomyces lilacinus*

CGD and Invasive mold infections: Emericella nidulans

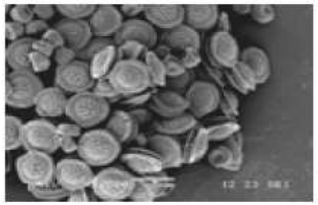
E. nidulans: misidentified in some CGD cases

- confusion with newly discovered cryptic species (*E. quadrilineata*, *E. rugulosa*,…)
- Accurate identification by molecular tools (sequencing of partial ßtubulin or calmodulin loci)



E. quadrilineata

E. rugulosa



E. nidulans var. echinulata

Antifungals susceptibility testing

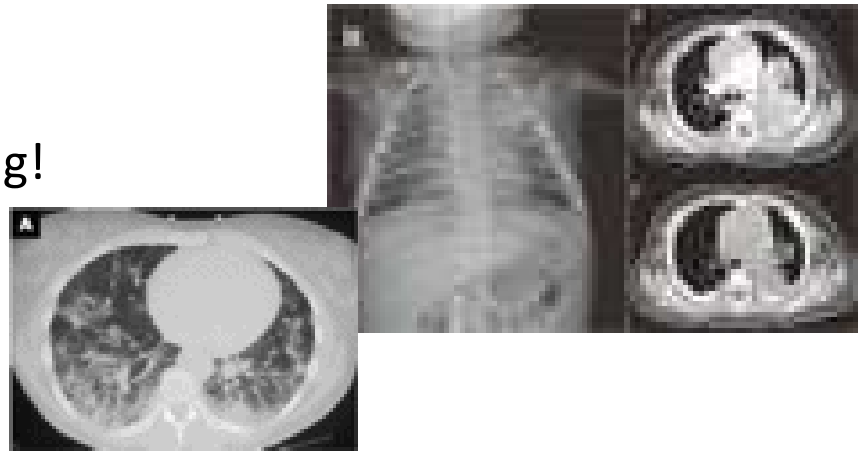
drug	*E.nidulans*	*E.quadrilineata*
Amphotericin B	2.5	0.5
Itraconazole	0.07	0.13
Voriconazole	0.26	0.39
Posaconazole	0.25	0.22
Caspofungin*	0.01	1.83

Verweij PE et al, Emerg Infect Dis 2008
Balajee SA et al, Stud Mycol 2007

CGD and IA: challenges for diagnosis!!

- **Ct-scan**

Very sensitive but not possible as screening!
Infiltrate/lobar consolidation/mass
No halo sign or air-crescent sign



- **Galactomannan antigen**

- Unreliable tool to allow pre-emptive therapeutic approach in this population :
  0% sensitivity

Blumental S et al, Clin Infect Dis 2011
Verweij P et al, J Clin Microbiol 2000
Walsh TJ et al, IDSA 40th annual meeting; 2002

- Hypothesis: lack of angio-invasion by fungal hyphae

Dennis CG et al, Antimicrob Agents Chemother 2006

- No data on others biomarkers (BDG, PCR) as screening tests

- **Invasive procedure often required** (true cut or surgical biopsy) culture and histo-pathologic examination

CGD and IA: specific management

✓ **Frequent careful and aware clinical examinations**

✓ **No screening approach to allow early therapy, crucial role of imaging**

✓ **In case of IA suspected: importance of extensive microbiological work up**

- Diagnosis confirmation of mold infection
- Exact species identification (+/- DNA sequencing)
- Antifungals' resistance profile + MIC

✓ **Long and complex treatment of IA episode**

- up to several years, often use of combined antifungals regimens
- importance of surgery to improve outcome
  (lobectomy, abscess drainage, thoracic mass excision or neurosurgery)
- place for adjunctive immuno-therapies
  (steroids, granulocytes infusions, IFNγ)
- frequent progression under treatment or late recurrence
- long and complicated hospitalizations
- frequent sequelae
- Poor outcome despite significant advances

CGD and IA: Specific Management

✓Primary prophylaxis: itraconazole

Reduction of IFIs incidence

Lower fatality rate

Mouy R et al, J Pediatr 1994
Gallin JI et al, N Engl J Med 2003
Beauté J et al, PIDJ 2011
Blumental et al, Clin Infect Dis 2011

Drugs interactions (TDM!)

Pressure of selection?

Verweij, PE et al, N Engl J Med 2003
Denning DW et al, Antimicrob Agents Chemother 1997

Risk of azoles resistance

Hodiamont CJ et al, Med Mycol 2009

More insidious pattern of infection
(older children, longer therapy)

→ **long-term surveillance needed**

✓ HSCT

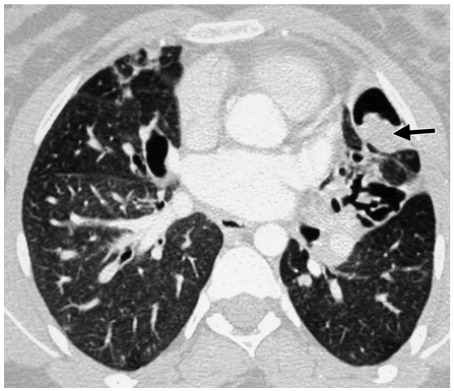
Only curative option
Successful results of geno-identical HSCT (RIC)
Option for salvage therapy

Gungor T et al, Transplantation 2005
Soncini E et al, Br J Haematol 2009
Seger RA et al,Immunol Allergy Clin North Am. 2010

✓ Gene therapy??

Roesler J et al, Blood 2002
Stein et al,Curr Opin Molec Therap 2006

IA and Job Syndrome



➢ Clinical features

- Eczema
- Recurrent skin and pulmonary infections (*S. aureus*!)

(→ abscess and pneumatocele)

- Bone and connective tissues abnormalities (AD form; STAT3 mutation)
- Hyper IgE / hyper eosinophilia
- Normal phagocytic function, impairment of IFNγ production
- Role of STAT3 in lung epithelia homeostasis and Th17differentiation (↓)
- Various clinical phenotypes (diagnostic score)

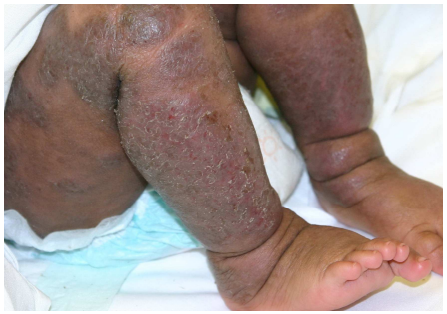
• Increase susceptibility to fungal infections

- Mainly **candidosis** (candidemia, meningitis, disseminated disease)
- **Aspergillosis**: colonization of pre-existing bronchiectasies / pneumatocele

→ Aspergilloma and local invasion of pulmonary parenchyma

Significant risk lifelong (peak: fourth decade)

→ Itraconazole prophylaxis recommended while significant pulmonary lesions during childhood



van der Meer JW et al, Clin infect Dis 1998
Chandesris MO et al, Medicine (Baltimore) 2012
Antachopoulos C et al, Clin Microb infect 2010
Vinh DC et al, J Allergy Clin Immunlogy 2010

Primary Cutaneous Aspergillosis in Neonates (PCA)

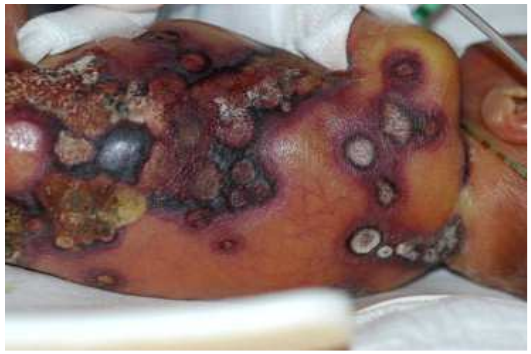
- ✓ New born: highly susceptible to fungal infection (*Candida spp*!)
- Defective keratinisation of the epithelial barrier
- Immaturity of the immune system (phagocytes, T cells)
- Multiple iatrogenic risk factors: corticosteroids, large spectrum antibiotics, central venous Kt..

- ✓ PCA: rare but often fatal condition (70% fatality)

- ✓ Risk population:
  ELBW (<1kg) or/and high prematurity (<28w GA)
  (+ could be inaugural of PID or leukemia)

- ✓ Common nosocomial origin and epidemic risk
  Contamination i.e from non sterile materials (gloves), incubators housing neonates, humidity chambers, ventilator systems

- ✓ Occurrence ≈10days after birth (3 to 30d)

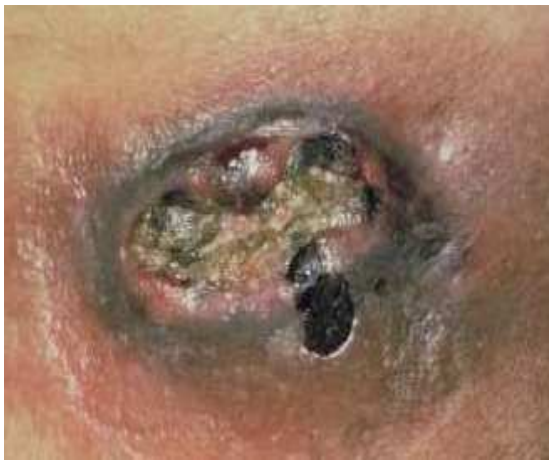


Stock C et al, Arch Pédiatr 2010; Manzoni P et al, Earl Hum Dev 2012
Etienne KA et al, J Hospit Infect 2011; Papouli M et al, Clin infect Dis 1996

Primary Cutaneous Aspergillosis in Neonates

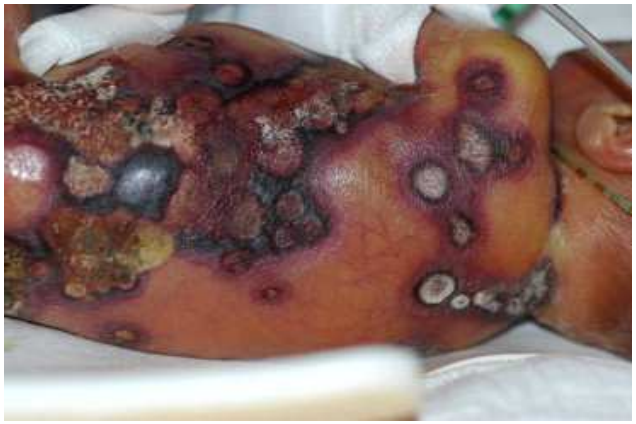
➢Various aspects of skin lesions

- Typically: purplish papule evolving to a necrotic lesion (central ulcer and black eschar in 24h)
- Also pustules, phlyctens, abscess, apparent filaments, bleeding
- Mostly start on abraded surfaces or where maceration (adhesive tape, pulse-oxymeter, KT, plasters)



➢Frequent disseminated infection (lung, CNS)

secondary (angio-invasion) or concurrent to PCA



➢Species: *A. fumigatus* and *A. flavus*

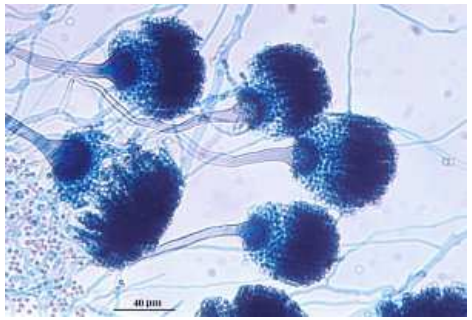
➢Treatment: Amphotericin B

(deoxycholate or liposomal forms)

Duration?

To be started as soon as suspected!!!

Stock C et al, Arch Pédiatr 2010; Manzoni P et al, Earl Hum Dev 2012
Etienne KA et al, J Hospit Infect 2011; Papouli M et al, Clin infect Dis 1996



Conclusions

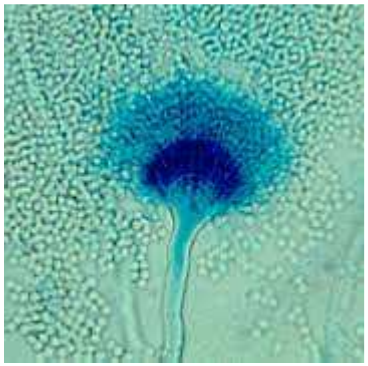
- **Aspergillosis: specific paediatric features!**
- Different clinical and diagnosis pictures in Haemato-Oncology
- Constant therapeutic issues

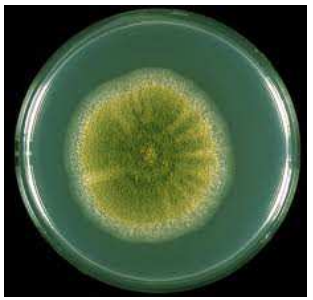
  (less medication available, unknown pharmacokinetics and dosage in some subgroups, inaccurate formulation, no reimbursement…)
- Specific patterns of IA in primary immunodeficiencies
- Life-threatening form (primary cutaneous aspergillosis) in high premature neonates

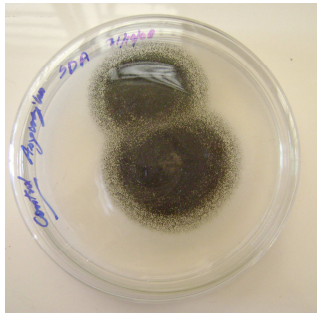
- **Crucial need for specific paediatric multi-centric studies**

- **Careful uses of extrapolated adults data!**

IA in Paediatric Haemato-Oncology
Diagnostic Issues: Microbiology







- Similar distribution of **species**

A. fumigatus > *A. flavus*> *A. terreus* > *A. niger*

- **Microscopy and culture: crucial place**

- Diagnostic confirmation (biomarkers poorly reliable!)
- Identification of the fungus (increasing diversity of fungal pathogens)
- Allow for antifungals resistance profile

Variable spectrum of each antifungal agent

Emergence of azoles resistances (mutation CYP51A)

HOWEVER…LIMITED YIELD

- Appropriate specimen rarely available (BC unreliable, need for tissues samples)
- Extended time for culture results
- Rate of false negative>>>>> (even histology:50%!)

Dornbusch HJ, et al, Clin Microb Infect 2010
Roilides E et al, Med Mycol 2006
Simoneau E et al, Bone Marrow Transplant 2005
Verweij PE et al, N Engl J Med 2007

IA in Paediatric Haemato-Oncology
Diagnostic Issues: Microbiology

➢ IA: almost no detectable fungemia (≠ Candida spp: 60% cases)

- Retrospective study over 23years

- 1453 HSCT recipients- incidence IA ≈4%
- 19 patients with *Aspergillus spp* positive BC
- 1/19: true positive correlating with IA, others false positive (lab contamination)

Simoneau E et al, Bone Marrow Transplant 2005

- Hypothesis? Impaired viability of endocytosed hyphae after angio-invasion???

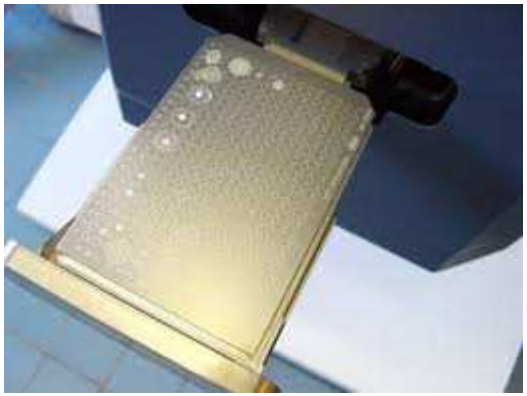
Lopez-Bezerra LM et al, Blood 2004

→ Microbiology requires sterile tissue samples!! (Biopsy, not BAL)

➢ Help from new techniques (MALDITOF)?

- Taxonomy
- High speed and reliable identification (new species!)
- Detection of resistance

But: in daily practice? need for assessable colonies…



Posteraro B et al, Expert Rev Proteomics 2013
Bille E et al, Clin Microb infect 2012
De Carolis E et al, J Clin Microb 2012