Specific Features of Aspergillosis in Paediatrics

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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 Haematol-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

- **ECIL 2011**
  All proven/probable IFD
  9-15% AML
  4-15% allo-HSCT

<table>
<thead>
<tr>
<th>Ref Description</th>
<th>Patients studied</th>
<th>IFD incidence</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobayashi et al. (Japan) 2008.</td>
<td>334 Hem. malignancies, HSCT and others</td>
<td>AML 11.7%; alloHSCT 8.1%; ALL 2.0%; sporadic in solid tumors moulds &gt;&gt; yeast</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Kaya et al. (Turkey) 2009</td>
<td>155 AL during intensive chemotherapy</td>
<td>AML 12.4; ALL 8.4 yeast &gt;&gt; moulds</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Castagnola et al. (Italy) 2010</td>
<td>240 AML</td>
<td>10% of all courses; recurrent AML: 15% moulds &gt;&gt; yeast</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Hale et al. (AUS) 2010</td>
<td>Acute leukemia / HSCT patients</td>
<td>Recurrent leukemia 21%; ALL 18.5%; alloHSCT 15.2%; AML 8.8%; yeast &gt;&gt; moulds</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Mor et al. (Israel) 2011</td>
<td>1047 HSCT and heme/onc patients</td>
<td>AML 13.6%; ALL 5.9%; alloHSCT 3.9%; autoHSCT 3.0%; solid tumors 1.6%; lymphoma 0.8% moulds &gt;&gt; yeast</td>
<td>II retrospective</td>
</tr>
</tbody>
</table>
Risk factors: similar to adults

1) Underlying disease
2) Others:

- Corticosteroid Therapy 69%
- Neutropenia (>3 days) 55%
- Immunosuppressive Therapy 43%
- Malignancy (non BMT) 36%
- Allogeneic BMT 37%
- GVHD 12%
- Cong immunodeficiency 12%
- Solid Organ Transplant 11%

<table>
<thead>
<tr>
<th>Risk stratum</th>
<th>Patient population</th>
</tr>
</thead>
</table>
| 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                                    |

95% of patients had ≥ 1 of these risk factors

Burgos et al, Pediatrics 2007

Bimodal Risk distribution

IFI after hematopoietic stem cell transplantation

ECIL 2011
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
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

- **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)

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 βD-glucan**
  - Cell wall component of a broad range of fungi (not species or genus-specific!)
    - *Aspergillus spp, Fusarium spp, Trichosporium spp, Candida spp, Pneumocystis jiroveci*
  - 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 1,3β-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

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.76 (95%CI 0.62 - 0.87)</td>
<td>0.73 (95%CI 0.46 - 0.61)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.86 (95%CI 0.68 - 0.95)</td>
<td>0.90 (95%CI 0.88 - 0.92)</td>
</tr>
</tbody>
</table>

4th European Conference on Infections in Leukaemia
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

| High rate of colonizing yeasts in the GI tract and in food |

## Table:

<table>
<thead>
<tr>
<th>Medications</th>
<th>(1→3) Beta-D-Glucan Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous amoxicillin-clavulanate or ampicillin-sulbactam</td>
<td>Galactomannan EIA Assays</td>
</tr>
<tr>
<td>Infusions</td>
<td>Intravenous immune globulin</td>
</tr>
<tr>
<td>*Cellulose filters for IV infusion</td>
<td>*Piperacillin-Tazobactam</td>
</tr>
<tr>
<td>*Albumin</td>
<td>*other beta lactam antibiotics</td>
</tr>
<tr>
<td>Medical interventions</td>
<td>*Hemodialysis with cellulose filter</td>
</tr>
<tr>
<td>*Gauze packing on serosal surfaces</td>
<td>*Plasmalyte (electrolyte infusion)</td>
</tr>
<tr>
<td>Other infections</td>
<td>*Pneumocystis jiroveci</td>
</tr>
</tbody>
</table>

- Dietary GM in pasta, cereals, formula milk
- Highly present in the infantile gut microflora

*Histoplasma capsulatum
*Geotrichum
*Neosartoria
*Bifidobacterium
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*
  *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 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
  
  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
    
    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

<table>
<thead>
<tr>
<th>Agent</th>
<th>13–18 Years</th>
<th>2–12 Years</th>
<th>1–24 Months</th>
<th>Neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate, mg/kgΔ</td>
<td>1–1.5</td>
<td>1–1.5</td>
<td>1–1.5</td>
<td>1–1.5</td>
</tr>
<tr>
<td>Liposomal amphotericin B, mg/kg</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Amphotericin B lipid complex, mg/kg</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion, mg/kg</td>
<td>3–4</td>
<td>3–4</td>
<td>3–4</td>
<td>ND</td>
</tr>
<tr>
<td>Voriconazole intravenous solution, mg/kgΔ</td>
<td>8 (12 on day 1; in 2 doses)</td>
<td>14 (in 2 doses)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Voriconazole oral suspension or capsules, mgΔ</td>
<td>400 (in 2 doses)</td>
<td>400 (in 2 doses)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Posaconazole oral suspension, mgΔ</td>
<td>800 (in 2 or 4 doses)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Itraconazole oral suspension or capsules, mg/kgΔ</td>
<td>5 (in 2 doses)</td>
<td>5 (in 2 doses)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Caspofungin, mg/m²</td>
<td>50 (70 on day 1; maximum, 70)</td>
<td>50 (70 on day 1; maximum, 70)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviation: ND, no data or no sufficient data.

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

Δ 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.

Δ Dose recommendations are based on the current European label; dosages used in 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 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.

Δ 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.

Δ 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

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

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

**PID: recently included in the EORTC/MSG revised criteria**

De Pauw et al, Clin Infect Dis 2008

<table>
<thead>
<tr>
<th>Host factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent history of neutropenia (&lt;0.5 × 10³ neutrophils/L [&lt;500 neutrophils/mm³] for &gt;10 days) temporally related to the onset of fungal disease</td>
</tr>
<tr>
<td>Receipt of an allogeneic stem cell transplant</td>
</tr>
<tr>
<td>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 &gt;3 weeks</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

**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 30 years)

- Defective phagocytes killing
  Impairment of the oxidative burst (oxygen radicals production)
  > Dysfunction 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. nidulans (Emericella Nidulans)**
  - Quite exclusively pathogen in CGD
  - More “virulent “
  - higher chest wall invasion/dissemination/mortality rates
  - Segal et al, Medicine 2000
  - higher resistant profiles?
    - Kontoyiannis DP et al, Mycoses 2002
  - 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)
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 βtubulin or calmodulin loci)

### Antifungals susceptibility testing

<table>
<thead>
<tr>
<th>drug</th>
<th><em>E. nidulans</em></th>
<th><em>E. quadrilineata</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.07</td>
<td>0.13</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.26</td>
<td>0.39</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0.25</td>
<td>0.22</td>
</tr>
<tr>
<td>Caspofungin*</td>
<td>0.01</td>
<td>1.83</td>
</tr>
</tbody>
</table>

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**
  
  - Hypothesis: lack of angio-invasion by fungal hyphae
    
  Blumental S et al, Clin Infect Dis 2011
  Walsh TJ et al, IDSA 40th annual meeting; 2002

  - 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

- Benefits
  - Reduction of IFIs incidence
  - Lower fatality rate

- Risks
  - More insidious pattern of infection (older children, longer therapy)
  - Pressure of selection?
  - Drugs interactions (TDM!)
  - Risk of azoles resistance

→ long-term surveillance needed

✔ HSCT

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

✔ Gene 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

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 Th17 differentiation (↓)
- 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 Immunology 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 ≈10 days after birth (3 to 30d)

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!!!

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**
  \[A. \text{fumigatus} > A. \text{flavus} > A. \text{terreus} > A. \text{niger}\]

- **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
IA in Paediatric Haemato-Oncology
Diagnostic Issues: Microbiology

- **IA: almost no detectable fungemia** (≠ Candida spp: 60% cases)
  - Retrospective study over 23 years
  - 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