risk factors and clinical manifestations of fungal infections in neonates and children

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since this is presentation has educational purposes there are too many slides, but many of them will be commented very rapidly or even left only as “references”. So, do not worry…

potential conflict of interest: none related with this presentation
risk factors for invasive mycoses: an incomplete list of well known factors, some of them peculiar of the pediatric age

<table>
<thead>
<tr>
<th>factor</th>
<th>yeasts</th>
<th>molds</th>
<th>notes/examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>colonization</td>
<td>+++</td>
<td>+++</td>
<td>healthcare workers hands</td>
</tr>
<tr>
<td>mucosal and skin barriers disruption</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>lymphocytes: reduced count or impaired function</td>
<td>+++</td>
<td>++</td>
<td>congenital or iatrogenic (including transplant)</td>
</tr>
<tr>
<td>granulocytes: reduced count or impaired function</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>vascular access devices/total parenteral nutrition</td>
<td>+++</td>
<td></td>
<td>manipulations</td>
</tr>
<tr>
<td>surgery</td>
<td>+++</td>
<td>+</td>
<td>especially abdominal</td>
</tr>
<tr>
<td>dialysis</td>
<td>++</td>
<td></td>
<td>also peritoneal</td>
</tr>
<tr>
<td>mechanical ventilation</td>
<td>+</td>
<td>+ (?)</td>
<td></td>
</tr>
<tr>
<td>malformations</td>
<td>++</td>
<td></td>
<td>mainly urinary tract</td>
</tr>
<tr>
<td>genetic/metabolic disorders</td>
<td>+</td>
<td>+</td>
<td>cystic fibrosis</td>
</tr>
</tbody>
</table>
causes invasive fungal disease in pediatrics by underlying conditions
(Pediatric Fungal network 2012-2014)

do not forget:
P. jirovecii
posibility of mixed infections

sporadic cases:
Cryptococcus, Geotrichum, Histoplasma
Coccidioides, others
candida habitat, and acquisition

colonization is a necessary condition, but is not sufficient
• **Mucosal barrier disruption** by trauma or chemotherapy (mucositis) will contribute to invasion.

• Microbial flora present on the mucosa provides antagonism against Candida. **Broad-spectrum antibiotics** (including anti anaerobes) can disturb the flora and contribute to uncontrolled growth of Candida.

• Loss of the attributable host defense responses of epithelial cells could be an additional factor in the pathogenesis of disseminated candidiasis.

• **Phagocytes** such as macrophages and neutrophils also play an important role in the first line of defense and protection against systemic spread of Candida. Together with monocytes, they have been shown to represent the major producers of pro-inflammatory cytokines (innate immunity)

• The combination of **Candida colonization in the gastrointestinal tract, disruption of the mucosa, neutropenia and/or severe T-cell immune deficiency (congenital or because of medication)** that paves the way for Candida to deeply invade the tissue and cause disseminated disease.

• In some cases C. albicans is **aided by medical procedures** and **bypasses** all the described **host barriers** and directly enters the bloodstream by injection of contaminated fluid or through intravenous catheters. Once Candida has entered the bloodstream and starts invading vital tissues, powerful innate and adaptive host defenses are needed to eliminate the pathogen.
this is a peculiar pediatric condition
localizations of candida infections in neonates

candidemia has been associated with retinopathy of the premature (ROP)
In the neonate: with abdominal disease
Candida: actor or bystander?

Necrotizing enterocolitis

16% Candidemia

focal intestinal perforation, “spontaneous”
(SIP = spontaneous intestinal perforation)

possible localization of candidemia

44% Candida peritonitis
imaging: not pathognomonic, but suggestive of localization in presence of a positive culture
other localizations (courtesy of “Doctor Google”)

- endocarditis
- liver abscess
- osteo arthritis
- endophtalmitis
- disseminated Candida dermatitis
- renal fungus ball in urinary tract malformation
some predisposing conditions must be considered in specific conditions in neonates, also not preterm/LBW

<table>
<thead>
<tr>
<th>cellular immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.jiroveci, Candida, filamentous fungi</td>
</tr>
<tr>
<td>– SCID: superficial candidiasis, meningitis, possible infections due to filamentous fungi</td>
</tr>
<tr>
<td>– DiGeorge syndrome: described invasive mycoses due to Apsergillus</td>
</tr>
<tr>
<td>– X-linked Iper-IgM: Candida, Cryptococcus, Histoplasma</td>
</tr>
<tr>
<td>– Wiskott-Aldrich syndrome: invasive mycoses only in the most severe cases (Wasp-Negative), Candida and Aspergillus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>filamentous fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>skin as site of entry</td>
</tr>
<tr>
<td>check for environmental colonization = hospital infection !</td>
</tr>
</tbody>
</table>
candida infections in non-neutropenic children after the neonatal period (1) (Hacimustafaoglu Expert Rev Anti Infect Ther 2011)

candidemia and disseminated infection (multiorgan candididiasis)
candida infections in non-neutropenic children after the neonatal period (2) (Hacimustafaoglu Expert Rev Anti Infect Ther 2011)

<table>
<thead>
<tr>
<th>Location</th>
<th>Cause</th>
<th>Treatment/Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>oropharyngeal</td>
<td>congenital immunodeficiency/ HIV disease</td>
<td>prolonged antibiotics/inhaled steroids</td>
</tr>
<tr>
<td>esophageal</td>
<td>antineoplastic chemotherapy/ HIV disease</td>
<td>inhaled steroids: rare</td>
</tr>
<tr>
<td>vaginal/vulvovaginal</td>
<td>diapers, antibiotics, immunosuppressive therapy</td>
<td>prepuberal girls</td>
</tr>
<tr>
<td>cutaneous</td>
<td>chronic mucocutaneous candidiasis (APECED)</td>
<td>diapers, thumb sucking, periungueal-finger trauma (persistent: type I diabetes)</td>
</tr>
<tr>
<td>ocular</td>
<td>hematogenous/ trauma</td>
<td>ocular surgery</td>
</tr>
<tr>
<td>(endophthalmitis)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
candida infections in non-neutropenic children after the neonatal period (3)  (Hacimustafaoglu Expert Rev Anti Infect Ther 2011)

<table>
<thead>
<tr>
<th>System</th>
<th>Conditions</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal</td>
<td>Intestinal perforation</td>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td></td>
<td>Abdominal (repeated) surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver transplant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis</td>
<td></td>
</tr>
<tr>
<td>Urinary tract/pielonephritis</td>
<td>Urinary tract malformations</td>
<td>Urinary catheter surgery</td>
</tr>
<tr>
<td></td>
<td>(fungus balls)/prolonged-repeated antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematogenous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac malfunction/surgery</td>
<td>Central venous catheter/</td>
</tr>
<tr>
<td></td>
<td>Prolonged fungemia</td>
<td>Prolonged fungemia</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Hematogenous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthritis/osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Meningitis/encephalitis</td>
<td>Ventricular drainage devices</td>
</tr>
<tr>
<td></td>
<td>(craniotomy/ventriculo-peritoneal/atrial shunts)</td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Hematogenous pneumonia</td>
<td>Primary pneumonia extremely rare</td>
</tr>
<tr>
<td></td>
<td>(histology)</td>
<td></td>
</tr>
</tbody>
</table>
candida infections in neutropenic children

- many clinical pictures similar to those observed in non-neutropenic patients: candidemia, disseminated candidiasis (pneumonia, endophtalmitis)
- specific conditions:
  - hepatosplenic (renal) (chronic) candidiasis: visible with imaging only after bone marrow recovery [=inflammatory immuno-reconstitution syndrome (IRIS)]
  - neutropenic enterocolitis (perforation)
  - Candida-associated vasculitis: pathogenesis is unclear, but immunomediated injury seems more plausible than direct fungal involvement, since no agent is found near vessel walls and vasculitic damage is similar to that found in polyarteritis nodosa. Severity ranges from self-limiting to diffuse life-threatening evolutive process requiring prolonged antifungal treatment, surgery, and quite paradoxically, high dose steroids for its treatment.
observable only after bone marrow recovery
neutropenic

no longer neutropenic
Which is your diagnosis?

• Neutropenic patient

1. Splenic candidiasis

2. Angioma

3. Localization of bacteremia
Which is your diagnosis?

- No longer neutropenic patient
  1. Hepatosplenic candidiasis
  2. I do not know
  3. aspergillosis
anyway beware

- never consider a positive blood culture for Candida (or any other fungi, with the probable exception of Aspergillus) as a contamination

- do not forget congenital immunodeficiency, especially in the youngest

- **primary Candida pneumonia is a very rare condition** that probably occurs in presence of an extensive oropharyngeal and tracheal colonization by Candida, in the setting of other risk factors (e.g. high dose steroids in the neonate), can cause the involvement of lung parenchyma through an alternative mechanism, i.e., colonization and dissemination to the lungs starting from the lower airways following aspiration of Candida oropharyngeal contents (aspiration), so

- recovery of Candida from respiratory tract should usually be considered as colonization **Candida** involvement of the lung is typically secondary to hematogenous dissemination
Aspergillus (molds) habitat, and acquisition

ubiquitous in nature, present in soil as saprophytes which sporulate abundantly and release conidia into the environment

risk of exposure (age related) varies widely depending on the climatic conditions like temperature, humidity, and wind

building renovation/construction works increase the burden of spores

some fungi present in water reservoirs: tap waters and showers

disease is a necessary condition, but not sufficient

food

Disease occurs in presence of weakened immune response or with an overtly exuberant response (allergic brochoalveolar aspergillosis, ABPA, or allergic fungal rhinosinusitis, AFRS) or mycetoma colonizing chronic inflammation or cavitary lesions
invasive aspergillosis (and sometimes other mold diseases)

- infections due to tissue damage, surgery, foreign body; keratitis/endophthalmitis, cutaneous disease in burn patients
- infections in immunocompromised hosts
  - invasive pulmonary: acute (or subacute)-angioinvasive
  - invasive airway disease: tracheo-bronchitis
  - invasive rhinosinusitis: chronic invasive granulomatous, chronic invasive, acute invasive (mainly mucor)
- disseminated disease: ≥2 non contiguous organs, the lung is most frequently involved
- other localization: kidney, liver, gastrointestinal tract, bone, central nervous system, heart, thyroid, peritoneum
acute leukemia

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Which is your hypothesis?

1. Mucormycosis
2. Aspergillosis
3. Bacterial blepharitis
4. Allergic reaction
Tracheal aspergillosis

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pulmonary infections in cancer and HSCT

in spite of the more frequent description of “aspecific” lesions in CT findings and their “temporal” evolution described in adults can be observed also in children

- halo-sign → nodule → cavitation
- increasing numbers of lesions in process of time, associated with bone marrow recovery and in spite of clinical improvement
- reverse halo sign
- inflammatory immuno-reconstitution syndrome (IRIS)
in a neutropenic host
when the patient is no longer neutropenic
angio-CT scan to document pulmonary artery invasion in aspergillosis in adults

at present no data in pediatrics

Figure 1. A, B. Representative high-resolution computed tomographic (HRCT) findings for patients with positive CT pulmonary angiographic (CTPA) findings and proven invasive mold disease. C, False-positive CTPA findings for a patient with Staphylococcus aureus pneumonia with septic emboli. D, Negative CTPA findings for a patient with bacterial pneumonia. Arrows indicate areas of vessel interruption (A–C) or lack of vessel interruption (D).
reversed halo sign in acute leukemia
Disseminated aspergillosis

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skin and bone invasion by Fusarium solani
• all further complications described in adults can be observed also in pediatrics
  
  • pneumothorax
  
  • hemophthisis
  
  • IRIS (also observed in concomitance with other fungal infections e.g. hepatosplenic candidiasis, candidemia, PcP, cryptococcosis)
pneumothorax in aspergillosis in ALL
pneumothorax in neutropenic ALL
Which is your hypothesis?

1. Relapsing aspergillosis
2. Primary aspergillosis
3. Localization of bacteremia
4. Tumerculosi
5. Trauma
pulmonary aspergillosis with hemophthisis
Neutropenic patient with hemoptysis and pulmonary cavitation (arrow) in presence of K.pneumoniae bacteremia

Neutropenic patient with pulmonary avitation (arrows) in presence of methicillin-susceptible S.aureus bacteremia

Your hypothesis
1. Bacterial pneumonia
2. Aspergillosis
3. Tuberculosis
Your hypothesis

1. Bacterial pneumonia
2. Aspergillosis
3. Tuberculosis
4. Different etiologies between a and b
pulmonary aspergillosis in different conditions

Aspergillosis in a patient treated for macrophage activated syndrome

CGD

Tomà Pediatr Radiol 2016

Figure 1
Computed tomography images of invasive pulmonary aspergillosis.

a) Neutropenic patient, early stages: sharply demarcated nodes and dense lesions surrounded by a ground-glass halo.

b) Rheumatology patient on corticosteroid treatment, early stages: centrally cavitating dense lesions.
Cystic fibrosis

Airways of CF patients are frequently colonized with Aspergillus, but the relevance of this colonization remains poorly understood.

In these patients diseases due to Aspergillus have been stratified/classified as

• Serologic ABPA (elevated IgE/IgG)
• Aspergillus bronchitis
• Aspergillus sensitized (elevated IgE, bit IgG)

Patients sensitized for Aspergillus species showed a greater lung function decline and an increase in their need for intravenous antibiotics.

ABPA occurs in children and teenagers with an estimated rate <1 % under 4 years and increasing throughout childhood and adolescence. Its prevalence substantially varies by country, probably due to the current inadequate diagnostic criteria and genetic influences.

It is unknown if these represent a sequential development, e.g. ABPA following Aspergillus sensitization and development of Aspergillus bronchitis following persistent colonization or are separate entities and each entity can progress in terms of severity and lead to progressive lung damage.
Table 1: Stages of allergic bronchopulmonary aspergillosis*

<table>
<thead>
<tr>
<th>Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Acute stage characterized by pulmonary infiltrates, markedly elevated total serum IgE level, and peripheral blood eosinophilia; responds well to steroids, and steroids can be tapered off</td>
</tr>
<tr>
<td>II</td>
<td>A stage of remission in which patients do not have pulmonary infiltrates and do not require steroids</td>
</tr>
<tr>
<td>III</td>
<td>A relapse of the disease (similar to Stage I) that responds well to steroids, leaving little to no radiographic evidence of pulmonary scarring</td>
</tr>
<tr>
<td>IV</td>
<td>A stage of steroid-dependent disease in which the total serum IgE level is variable and radiographic infiltrates may or may not be present; patients require inhaled and systemic steroids for treatment</td>
</tr>
<tr>
<td>V</td>
<td>A stage of &quot;burnt out&quot; disease in which permanent fibrotic damage is evident on radiographic studies with irreversible impairment of pulmonary function; such patients have inadequate response to steroids</td>
</tr>
</tbody>
</table>

*These stages are not sequential phases of the disease

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Table 2: Cystic Fibrosis Foundation – Consensus Conference criteria for diagnosis of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis

<table>
<thead>
<tr>
<th>Classic case</th>
<th>Minimal diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or subacute clinical deterioration that is not attributable to another etiology</td>
<td>Acute or subacute clinical deterioration that is not attributable to another etiology</td>
</tr>
<tr>
<td>A serum total IgE level of &gt;2400 ng/mL unless patient is receiving systemic steroids*</td>
<td>A serum total IgE level of &gt;1200 ng/mL*†</td>
</tr>
<tr>
<td>Presence of IgE antibodies to A. fumigatus in vitro or immediate cutaneous hypersensitivity to Aspergillus†</td>
<td>Immediate cutaneous hypersensitivity to Aspergillus† or presence of IgE antibodies to A. fumigatus</td>
</tr>
<tr>
<td>Precipitating antibodies to A. fumigatus or serum IgG antibody to A. fumigatus by an in vitro test</td>
<td>One of the following</td>
</tr>
<tr>
<td>New or recent infiltrates (or mucus plugging) on chest radiography or computed tomography that do not respond to antibiotics and standard physiotherapy</td>
<td>Precipitins to A. fumigatus or IgG antibody to A. fumigatus in vitro</td>
</tr>
<tr>
<td>New or recent abnormalities on chest radiography or computed tomography that do not respond to antibiotics and standard physiotherapy</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: Stevens et al. If a patient is receiving steroids, check serum total IgE levels when the patient is off steroid treatment. If allergic bronchopulmonary aspergillosis is suspected and serum total IgE level is between 480 ng/mL and 1200 ng/mL, repeat testing in 1-3 months. Cutaneous reactivity to Aspergillus is indicated by a wheal of 3 mm (or more) in diameter with surrounding erythema following a skin prick test in a patient who is currently on systemic antihistamines.

*A. fumigatus = Aspergillus fumigatus
Pneumocystis habitat, and acquisition

Reservoir not defined, but possibly human especially infants and younger children. Proven airborne transmission.

Conditions at highest risk

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Other autoimmune diseases
- Treatment with biologic drugs
- SCID, attack rate > 25%
- Inflammatory diseases
- Hematopoietic stem cell transplant
- Solid tumors
- Hematologic malignancy
- Solid organ transplant
- Very rare in autologous HSCT
- Especially CNS receiving steroids, including HD and NHL
- Mainly ALL

Gigliotti Plos Pathogens 2012
Cryptococcus (neoformans var neoformans/grubii; gattii) habitat, and acquisition

<table>
<thead>
<tr>
<th>Ubiquitous (some differences in species/subspecies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural source: avian guano or trees</td>
</tr>
<tr>
<td>Airborn transmission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions at highest risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>immunodeficiency (including idiopathic T-cell lymphopenia)</td>
</tr>
<tr>
<td>hemopoietic stem cell transplant</td>
</tr>
<tr>
<td>immunosuppressive therapy (including monoclonal antibodies)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (and other autoimmune diseases)</td>
</tr>
<tr>
<td>sarcoidosis</td>
</tr>
<tr>
<td>lymphoproliferative diseases</td>
</tr>
<tr>
<td>kidney transplant (other solid organ)</td>
</tr>
<tr>
<td>steroids</td>
</tr>
</tbody>
</table>
P. jirovecii

Cryptococcus

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many other fungi, some of them with peculiar geographical epidemiology, can cause (much less frequently) invasive diseases and further questions regards diagnosis, prevention and treatment…
when your lecturer asks if you have any questions

Can you repeat the part of the stuff where you said all about the things?