Infections in the Immunocompromised Child

Christoph Berger
Infectious Diseases and Hospital Epidemiology
University Children’s Hospital
8032 Zürich

The immunodeficient child

<table>
<thead>
<tr>
<th>Immunodeficiency</th>
<th>Unknown</th>
<th>Primary (inborn)</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertically acquired (HIV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iatrogenic Immuno-suppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cancer chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Solid organ transplant (SOT) recipient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Autoimmune disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Infections in the immunodeficient child

- Severe infection with common pathogens:
  - unusually severe manifestation / complicated disease
  - insufficient treatment success to appropriate antimicrobial treatment
  - higher relapse rate (Ø eradication / Ø protection against reinfection)

- Infection by unusual pathogens or usually less pathogenic microbes
  = opportunistic infections

- High number of infections or simultaneously different infections

- Delay of growth and development

Innate and adaptive immunity

1. Neutrophils
2. Dendritic cells
3. Innate immunity
4. Adaptive immunity
5. Specific immunologic memory
6. T and B cell memory

T and B lymphocytes
Immunoglobulins
Susceptibility to infection

Extracellular Pathogens
- Pneumococci
- Staphylococci
- Streptococci
- Enterobacteriaceae

Intracellular Pathogens
- Entero-Myobacteria
- Candida
- Aspergillus
- Pneumocystis

Viruses

Cytotoxic Chemotherapy in Cancer Patients

Exterior defenses
- Mucositis
  - destroyed exterior defense
  - commensal flora
  - change in commensal flora (chemotherapy, antimicrobial treatment)
- Indwelling CVC: portal of entry?
- Bone marrow suppression
- Suppression of cell proliferation in the immune response

Cancer Chemotherapy

Fever and neutropenia in children treated for Cancer

Immediate examination
- Vital signs: admission to hospital or PICU
- Clinical focus
- Microbiological work up (blood cultures, urine, swabs...)

and empiric treatment with iv broad spectrum antibiotics
- Carabapenem, Ceftazidime +/- aminoglycoside
- Persitisting fever and neutropenia 48h, aetiology unknown
  - add glycopeptide (vancomycin, teicoplanin)
- Persitisting fever and neutropenia 72h
  - add antifungal (amphotericin B)

Treatment re-evaluation
- if causative agent identified
- consider stop of treatment if - cultures negative and resolution of fever and / or neutropenia for 3-5 days

Incidence of Infections in Relation to the Granulocyte Count

Fever (> 38.3°C) and neutropenia (> 500 cells/mm3)

- Addition of antibiotics based on fever persistence and neutropenia duration.
Fever and neutropenia in children treated for cancer

Aetiology
- Gram positive sepsis
- Gram negative sepsis
- Port a cath infections
- Fungal infections: mucosal and invasive
- Pneumocystis pneumonia
- Viral infections
  - RSV, influenza…
  - cave varicella, EBV

2000: 2/3 infections: Gram positive

Port a cath-associated infections in children

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>N</th>
<th>BSI rate /10^3 CVC days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteraemia</td>
<td>48</td>
<td>0.36</td>
</tr>
<tr>
<td>PAC-associated infections</td>
<td>15</td>
<td>0.11</td>
</tr>
<tr>
<td>155 patients, 134733 PAC days (median 738 days/patient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 explantations (10%) due to PAC-associated infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hung et al (Immunology Infection 2009; 42:166)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>138000 PAC days (median, 660 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/17 PACs were removed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adler et al (J Hosp Infect 2006; 62:358)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>243 PACs (median 227 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57 removed due to infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Strict instructions and SOP for insertion and handling!

Port a cath-associated bacteraemia: management: explantation

i.e. >1 positive blood culture; clinical signs of infection, no focus but PAC

Complication?
- No
- Agent
- S. aureus
- Gram neg.
- Candida spp.

If causative agent?
- coagulase negative staphylococci

Port a Cath explantation
- to be planned, if stable with antimicrobial treatment
- immediately if deterioration or persisting bacteraemia
- antimicrobial treatment 10-14 days
- microbiol. cultures of chamber and catheter tip

If clinically stable:
- 7-10 days systemic antibiotic treatment
- +/- lock (???)

If again:
- positive blood culture
- clinical signs

* Treatment may be longer depending on diagnosis

15 year old boy, AML

PCR: Rhizopus spp.
Invasive fungal infections in children: treatment

**Zygomycosis**
- Life-threatening infection in children
- Predisposing factors: neutropenia, diabetes mellitus, and prematurity
- High mortality in untreated disease, disseminated infection, age <1 year.

Amphotericin B and surgery significantly improve outcome.

**Candidemia**
- Mortality rate: 19-31%

**Invasive aspergillosis**

**Empirical treatment of children with prolonged fever and neutropenia**
- Amphotericin B or liposomal amphotericin B are equally effective.
- Less data but also effective are caspofungin, voriconazole (and fluconazole in azole-naïve patients).

**Antifungal therapy in proven candidaemia or invasive candidiasis**
- No good comparative data.
- Amphotericin B (echinocandins and azoles seem equally effective).
- Cave: consider previous antifungal therapy for empiric treatment.

**Antifungal therapy in proven or suspected aspergillosis**
- Not sufficient pediatric data, data from adults:
- Voriconazole superior to amphotericin B (caspofungin also effective).

**Combination therapy**: insufficient data: for salvage only.

---

3 month old boy

**Dry cough, fever**
- Does not drink

**Tachypnea (60/min)**
- O2 saturation 75%
- Hepatomegaly
**Pneumocystis Pneumonia**

*Pneumocystis jirovecii*

**Patients at risk:** severe T cell deficiency
- low CD4+ T cell number
- HIV+ Infants (AIDS)
  - especially < 6 months of age
  - (Botswana 48% of deaths in infants)
- Immunosuppressive treatment
  - (cancer, organ transplant, anti TNFα, prednisone > 0.4mg/kg/day for weeks)

**Diagnosis:** Pneumonia
- shortness of breath, fever, cough
- tachypnea, hypoxaemia (O2 sat < 90%)
- rx: diffuse bilateral interstitial infiltrates
- BAL: immunofluorescence, PCR

**Mortality:** without HAART ≥40%

---

**Preferred Prophylaxis**

**Pneumocystis Pneumonia**

*Pneumocystis jirovecii*

- **TMP-SMX**: Preferred therapy for all cases
- **Pentamidine**: Alternative, if not responding to or intolerant of TMP–SMX

<table>
<thead>
<tr>
<th>Compound(s)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP–SMX, Pentamidine</td>
<td>TMP: 15–20 mg/kg/day + SMX: 75–100 mg/kg/day + 4 mg/kg/day intravenously</td>
</tr>
</tbody>
</table>

**Alternative therapy for mild to moderate disease**

- Azithromycin (500 mg/day)
- Clarithromycin (500 mg/day + 300 mg/day for weeks)
- Dapsone (100 mg/day)

**Indication:**
- vertically HIV-infected children >6 weeks -1 year (all)
  - 1-5 years if CD4 < 500 cells/ul
  - severe iatrogenic immunosuppression (chemotherapy, ALL !)
  - secondary prophylaxis after PJP to prevent recurrences

---

**CD4+ T cell number in relation to age and HIV infection**

- Not infected
- HIV infected

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>CD4+ T cell number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>1000</td>
</tr>
<tr>
<td>1-2</td>
<td>2000</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>≥2000</td>
</tr>
</tbody>
</table>

*Limited pediatric data

IDSA Guideline; IDSA Guideline; IDSA Guideline; IDSA Guideline;
**HIV classification in children**

<table>
<thead>
<tr>
<th>Age: CD4 cells*</th>
<th>Symptom classification</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>1-5</td>
<td>mild</td>
<td>moderate</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>severe</td>
<td>severe</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>&lt;1000</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>&gt;25%</td>
<td>&gt;25%</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>750 - 1499</td>
<td>500 - 999</td>
<td>15-24%</td>
</tr>
<tr>
<td>15-24%</td>
<td>15-24%</td>
<td>15-24%</td>
</tr>
<tr>
<td>&lt;750</td>
<td>&lt;500</td>
<td>&lt;15%</td>
</tr>
<tr>
<td>&lt;15%</td>
<td>&lt;15%</td>
<td>&lt;15%</td>
</tr>
</tbody>
</table>

* cells/μl and in percent

**Opportunistic infections among HIV- (exposed and) infected children**

Note in children:
1. Vertical co-infection (HIV, CMV, Toxo, HBV, HCV..)
2. Diagnosis of HIV infection
3. HAART

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>11.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>3.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>2.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>1.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>1.3</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Tuberculosis in immunocompromised children**

- Primary TB more disseminated: miliary and extrapulmonary TB
- Reactivation
- Cave: IRIS

**3 month old boy**

Cumulative morbidity and mortality rate due to AIDS in HIV-1 infected children according to CMV status at 18 months of age

Kovacs et al NEJM 1999;341:77-84.
Cytomegalovirus Infection

Severe disease in the immunocompromised host: HIV / AIDS; solid organ and stem cell transplantation and intrauterine!

Herpesviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Tropism</th>
<th>Insufficient, impaired absent immune control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHV1 (HSV1)</td>
<td>neurons</td>
<td>encephalitis ? severe, disseminated, not healing Infections</td>
</tr>
<tr>
<td>HHV2 (HSV2)</td>
<td>sensor. ganglia</td>
<td></td>
</tr>
<tr>
<td>HHV3 (VZV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHV4 (EBV)</td>
<td>lymphocytes</td>
<td>lymphoproliferation, lymphoma</td>
</tr>
<tr>
<td>HHV5 (CMV)</td>
<td>lympho- reticular</td>
<td>CMV disease, plus encephalitis, suppression of bone marrow + immune response</td>
</tr>
<tr>
<td>HHV6</td>
<td>cells</td>
<td></td>
</tr>
<tr>
<td>HHV7</td>
<td>lymphocytes</td>
<td></td>
</tr>
<tr>
<td>HHV8 (KSHV)</td>
<td>lymphocytes</td>
<td>Kaposi sarcoma, lymphoma</td>
</tr>
</tbody>
</table>

Risk factors
- Primary infection (D+, R-)
- Intensity of T cell suppression (OKT3, ALG)

CMV in solid organ transplant recipients

Management of Transplant Recipient: Cytomegalovirus Infection

Determination of CMV DNA copy levels in the blood

Risk factors
- Primary infection (D+, R-)
- Intensity of T cell suppression (OKT3, ALG)

CMV DNA copies / ml blood

Preemptive Therapy
Symptomatic Therapy
Asymptomatic Therapy

Risk for disease
Pediatric solid organ transplant recipients

Infections following SOT

- Early (postop)
- Middle (opportunistic, reactivation)
- Late (community-acquired, graft day function associated)

Pediatric solid organ transplant recipients

Infections in SOT: not just small adults

- Invasive bacterial infections
- RSV, parainfluenza, Rotavirus
- Measles, Varicella

Risk for SOT recipients (immunosuppressed) in relation to age

- High incidence for invasive infections and viral infections
- Naive to childhood infections (no previous exposure) and CMV and EBV
- Delay in vaccination due to chronic disease
- Colonised with multiresistant bacteria due repeated treatment of infections due to chronic underlying disease

Pediatric solid organ transplant recipients

Infection prevention

1. Vaccine preventable diseases:
   - High risk for severe / complicated disease
2. Herpesvirus infections:
   - High risk for severe primary infection (cf D+/R-)
3. After tx:
   - live vaccines contraindicated
   - inactivated vaccines: (in)sufficient response?

Thus:
- Evaluate immunity to HIV, Hepatitis B, EBV, CMV, VZV
- Know the carrier status of the donor (EBV, CMV, Hepatitis)
- Check and update vaccination status before transplantation

Standard recommendation: DTPa IPV, Hib, PCV, MenC, MMR

Indication for vaccines as: Influenza, VZV, Hepatitis B (and A)

→ Accelerated catch-up for missing vaccinations before tx.

Pediatric solid organ transplant recipients

Epstein-Barr Virus: posttransplant lymphoproliferative disease (PTLD)

- Primary EBV infection (↑10-75x):
  - D+/R- (children) > D-/R- > R+
- Mode and intensity of T cell suppression (OKT3, ALG)
- Transplant: solid organ (R) vs. stem cells (D)
- CMV disease / CMV mismatch

Risk factors

Cockfield, Transpl Infect Dis 2001;3:70
PTLD: transplant-related incidence

- Kidney: 1%
- Liver: 2.2%
- Heart: 3.4%
- Lung: 1.8 - 7.9%
- Heart-Lung: 9.4%
- Small bowel: 7-11%
- Multi-organ: 13-33%
- Stem cells (allogeneic): <1%
  - depending on depletion of donor T and B lymphocytes

Cockfield, Transpl Infect Dis 2001;3:70

Immune reconstitution after hematopoietic stem cell transplantation

Time pattern of infectious disease after HSCT

Infections in the immunocompromised host

- Susceptibility and manifestation of the infection depending on the kind and degree of impaired defence.
- Secondary (acquired) vs. primary immunodeficiency, the latter often detected by „atypical”/severe infection
- The spectrum of infectious diseases is determined by the nature of the immunodeficiency
- Immunocompromised children are especially naïve to
  - ubiquitous pathogens (opportunistic infections)
  - common pathogens (vaccine preventable diseases)
  - pathogens establishing latent infection (uncontrolled reactivation)