Chronic Granulomatous Disease, a Model Phagocytic Disorder

R. Seger
University Children’s Hospital Zürich
Switzerland

Chronic Granulomatous Disease (CGD): Clinical Overview
- Recurrent/severe infections by specific bacteria/fungi
- Recurrent/severe inflammatory conditions
- Incidence: – 1 : 200,000
- Median Survival – 30 years
- Treatment:
  • Continuous prophylaxis/therapy by antibiotics
  • Temporary immunosuppression by steroids
  • Bone marrow transplantation (only with good donor)

CGD: Defect of Bacterial Killing

CGD: Defect of Fungal Killing

Intracellular Microbial Killing by NADPH oxidase

Extracellular Microbial Killing by Neutrophil Extracellular Trap (NET)

Med. n. Brito et al.
Nat Rev Microbiol 2007; 5:577-582
Infectious Agents in CGD: The big 5

1. **Morbidity**: Once every 3-4 years (bacterial or fungal)
2. **Pathogenesis**:
   - Inescapable environmental exposure (excl. Staph. aureus)
   - Intermittent compliance with long-term prophylaxis
3. **Clinical Presentation**:
   - Staph. aureus: Lymphadenitis, Liver abscess
   - Burkholderia complex: Necrotising Pneumonia + Sepsis
   - Serratia marcescens: Sepsis + Osteomyelitis
   - Nocardia: Pneumonia + Dissemination (brain, bone)
   - Aspergillus: Pneumonia + Dissemination (brain, bone)

Pneumonia in CGD: How to Proceed

1. **Onset**:
   - Fulminant: Mulch pneumonitis
   - Acute: Bacterial
   - Subacute: Fungal, Nocardial
2. **Dx Work - Up**:
   - Computed tomography / PET-scan
   - Needle biopsy > BAL
   - Culture susceptibility testing (Fungi: azole resistance?)
3. **Empiric Initial Therapy**:
   - Meropenem
   - Co-trimoxazole (TMP/12 mg/kg)
   - Voriconazole (12 mg/kg/die)
   - ± Steroids (1 mg/kg/die x 3, then taper), (Fungi, Nocardia)

Fulminant Mulch Pneumonitis (Europe, N. America)

- **Ae**: High-level exposure to aerosolized organic matter (mulch, compost, dead leaves)
- **Dx**: ~ 2 days later: Dyspnoea, hypoxia, bilateral infiltrates
  - BAL or lung biopsy: Aspergillus species
- **Th**: 1. Ventilation
  2. Voriconazole + Caspofungin

Severe Chronic Actinomycosis (Europe, N. America)

- **Ae**: Actinomyces species = gram-positive rods
- **Dx**: Fastidious anaerobic growth on sheep blood agar at 37°C
  - 16 S rDNA PCR
- **Th**: Antibiotic therapy and surgery
  (incl. long term Penicillin G and V)
### Chronic Multifocal Necrotizing Lymphadenitis (N. America, Spain)

**Ae:** Granulibacter bethesdensis = gram-negative rod  
**Dx:** Fastidious growth on charcoal yeast extract at 35°C  
16S rDNA PCR: Family Acetobacteraceae  

**Th:** Combined antibiotic therapy and surgery  
(incl. long term ceftriaxone)


### Mycobacterial infections in CGD (China, Iran, Latin America)

**Ae:** M. bovis, M. tuberculosis  
**Dx:** BCG: ulcer, regional adenitis  
TB: pulmonary (not: miliary) infiltrate  
Positive culture (biopsy or gastric aspirate)

**Th:** Antimycobacterial agents


### Infection-associated Haemophagocytic Syndrome (Italy, Spain)

**Ae:** Leishmania donovani; vector: sandflies  
**Dx:** Marrow aspirate: L. amastigotes in mac’s  
Positive L. serology and PCR

**Th:** Liposomal Amphotericin B

(Martin et al: Ped. Infect Dis J 2009)

### CGD: Drugs for Treatment of Granulomatous Colitis

<table>
<thead>
<tr>
<th></th>
<th>Mildly/Moderately active</th>
<th>Severely active</th>
<th>Perianal fistulas <strong>+</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Topical treatments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine oral (40-50 mg/kg/d)</td>
<td>+ (induction)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sulfasalazine oral (1 mg/kg/d, then taper)</td>
<td>–</td>
<td>+ (induction)</td>
<td>maintenance</td>
</tr>
<tr>
<td>Sulfasalazine oral (0.25 mg/kg/d)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>II. Systemic treatments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone oral (1 mg/kg/d, then taper)</td>
<td>–</td>
<td>+ (induction)</td>
<td>–</td>
</tr>
<tr>
<td>Infliximab (5 mg/kg at 0,2,6 wks)</td>
<td>–</td>
<td>+ (induction)</td>
<td>maintenance</td>
</tr>
<tr>
<td>Azathioprine (0.3 mg/kg/d)</td>
<td>–</td>
<td>+ (maintenance)</td>
<td>steroid-dependent or refractory</td>
</tr>
</tbody>
</table>

* In CGD not for maintenance  
** Slow onset of action (3-4 mo)  
*** Add metronidazole/ciprofloxacin

### Exuberant Inflammation in CGD

**IL-1β production†**

(Sample graph showing IL-1β production in CGD patients compared to controls)

(Martin et al: Ped. Infect Dis J 2009)

### CGD Colitis: How to avoid Overtreatment

**Itraconazole increases steroid levels**

|                          | Adjustment of Immunosuppression: 
|--------------------------|Follow up by fecal calprotectin |
| Itraconazole **+**       | History: slight moderate severe |
| Glucocorticosteroids **+**| colitis |

(Vari et al: Pharmacol Toxicol 1999  
Cure of Steroid-dependent Colitis after HSCT

**Growth spurt after HSCT**

Colitis before HSCT

Mount after HSCT

Soncini et al. 2009

---

**MUD-HSCT for CGD: Zürich - RIC Protocol**

- Fludarabine 180 mg/m²
- Campath 0.5 mg/kg
- Busulfan dose adjusted according to kinetics (AUC)
  - Target: 50-60.000 ng*h/µµ µµ

---

**Recent MUD-Transplants for CGD in Europe**

<table>
<thead>
<tr>
<th>CGD- Content</th>
<th>Patient No</th>
<th>gGND (grade)</th>
<th>Graft Failure</th>
<th>Full Engraftment</th>
<th>M.</th>
<th>Conditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Castle</td>
<td>10</td>
<td>3/0 (9)</td>
<td>1/9 (1 retransplant)</td>
<td>7/9 (1 relapse)</td>
<td>5/10</td>
<td>Bu, Cs, Campath 1 H (7/10)</td>
</tr>
<tr>
<td>U.</td>
<td>9</td>
<td>3/0 (9)</td>
<td>2/9 (1 retransplant)</td>
<td>7/9</td>
<td>2/6</td>
<td>Bu-based (5/5)</td>
</tr>
<tr>
<td>Zurich</td>
<td>6</td>
<td>1/6 (2)</td>
<td>0/6</td>
<td>6/6</td>
<td>1/6 * Bu, 10/8 Cs, 10/8 Campath 1 H (1/6)</td>
<td></td>
</tr>
<tr>
<td>Total MUD</td>
<td>25</td>
<td>7/14 (28%)</td>
<td>3/24 (13%)</td>
<td>20/24 (83%)</td>
<td>6/25</td>
<td></td>
</tr>
</tbody>
</table>

| Total MSD    | 16         | 4/16 (25%)   | 8/16          | 15/16 (91%)     | 5/16 |             |

* = Disseminated Aspergillus nidulans  ** = ARDS  ^ = Complication of chronic GvHD  ° = ARDS

---

**HLA-matched-HSCT for CGD: Indications**

- **Standard risk Patient (absence of infection/inflammation)**
  - One life-threatening infection in the past
  - Severe granulomatous disease with progressive organ dysfunction (e.g. lung restriction)
  - Non-availability of specialist care
  - Non-compliance with AB prophylaxis

- **High risk Patient (active infection/inflammation)**
  - Ongoing therapy-refractory infection (e.g. Aspergillosis)
  - Steroid-dependent granulomatous disease (e.g. Colitis)

---

**CGD Research Group**

**Pediatric Patients**

- Div. Immunology/BMT
  - Univ. Children’s Hospital Zürich
    - M. Bianchi
    - T. Güngör (BMT)
    - J. Reichenbach (NETs, GT)
    - U. Siler
    - R. Seger

**NETs**

- MPI Infection Biology Berlin
  - A. Hakim
  - V. Brinkmann
  - A. Zychlinsky

**Gene Therapy**

- Molecular Virology, Frankfurt
  - M. Grez (vector)
  - Eufeta, Idar-Oberstein
  - K. Kühlcke (GMP)
  - NCT Heidelberg
  - M. Schmidt (LAM-PCR)
  - C. von Kalle

---

*Recent MUD-Transplants for CGD in Europe*

*HLA-matched-HSCT for CGD: Indications*

*CGD Research Group*