KINDERSPITAL ZÜRICH

Chronic Granulomatous Disease, a Model Phagocytic Disorder

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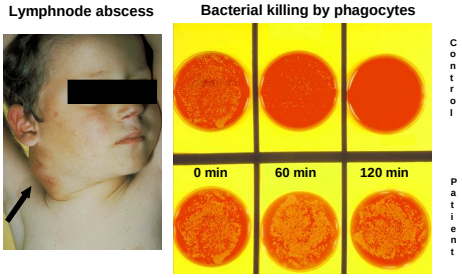
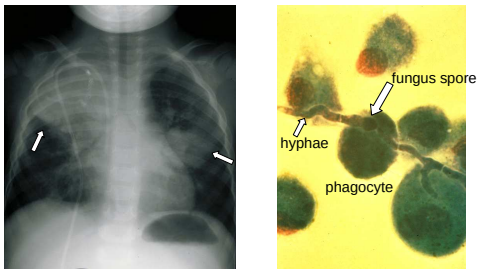
Chronic Granulomatous Disease (CGD): Clinical Overview

- 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 immunsuppression by steroids
  - Bone marrow transplantation (only with good donor)

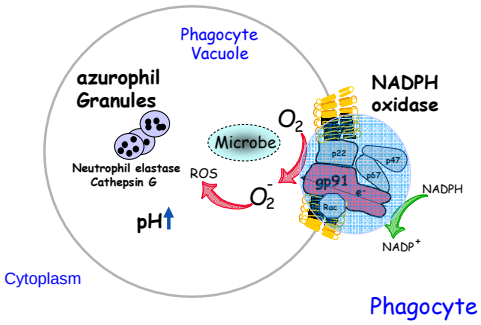
CGD: Defect of Bacterial Killing



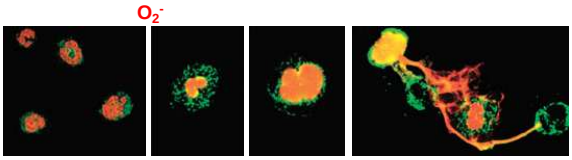
CGD: Defect of Fungal Killing



Intracellular Microbial Killing by NADPH oxidase



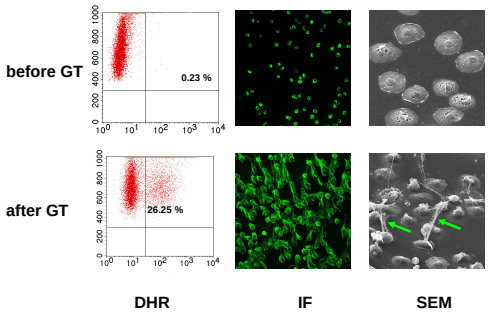
Extracellular Microbial Killing by Neutrophil Extracellular Trap (NET)



1	2	3	4
Neutrophils intact	Rounding of Nucleus	Contraction	NET Liberation

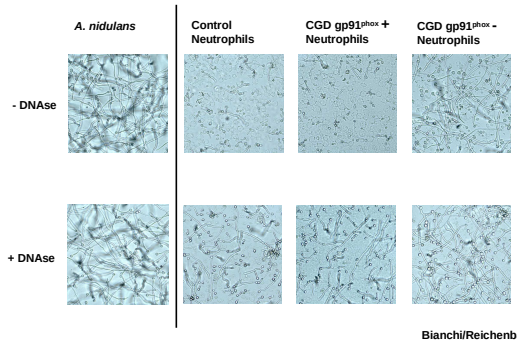
Mod. n. Brinkmann *et al*: *Nat Rev Microbiol* 2007; 5:577-582

Reconstitution of NET Formation after GT



Bianchi/Reichenbach et al
Blood, 2009;114:2619-22

Reconstitution of Aspergillus Killing by NETs



Bianchi/Reichenbach et al
Blood, 2009;114:2619-22

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 absess
   - Burkholderia complex: Necrotising Pneumonia ± Sepsis
   - Serratia marcescens: Sepsis ± Osteomyelitis
   - Nocardia: Pneumonia ± Dissemination (brain, bone)
   - Aspergillus: Pneumonia ± Dissemination (brain, bon

Pneumonia in CGD: How to Procede

1. **Onset**: Fulminant: Mulch pneumonitis
   Acute: Bacterial
   Subacute: Fungal, Nocardial

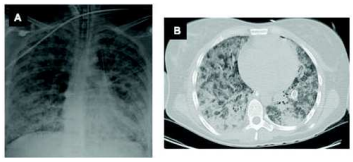
2. **Dx Work - Up**
   - Computed tomography / PET-scan
   - Needle biopsy > BAL
   - Culture susceptibility testing (Fungi: azole resistance?)

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



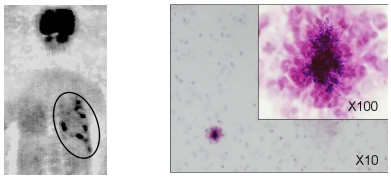
Th: **1. Ventilation**
2. Voriconazole + Caspofungin
3. Methylprednisolone iv.

Siddiqui et al: CID 2007

Severe Chronic Actinomycosis (Europe, N. America)

Ae: **Actinomyces species = gram-positive rods**

Dx: **Fastidious anaerobic growth on sheep blood agar at 37℃**
16 S rDNA PCR



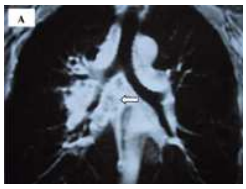
Th: **Antibiotic therapy and surgery**
(incl. long term Penicillin G and V)

Reichenbach et al: CID 2009

Chronic Multifocal Necrotizing Lymphadenitis (N. America, Spain)

Ae: **Granulibacter bethesdensis = gram-negative rod**

Dx: **Fastidious growth on charcoal yeast extract at 35℃**
16 S rDNA PCR: Family Acetobacteraceae



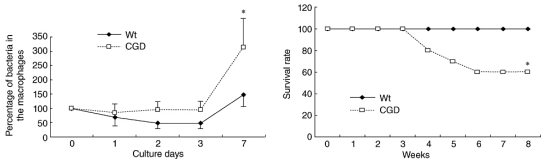
Th: **Combined antibiotic therapy and surgery (incl. long term ceftriaxone)**

Greenberg et al: PLoS Pathogens 2006

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)



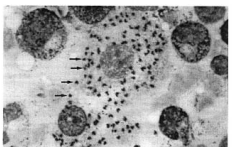
Th: **Antimycobacterial agents**

Lee et al: Ped. Infect Dis J 2008
Fujita et al: Clin Exp Immunol 2010

Infection-associated Haemophagocytic Syndrome (Italy, Spain)

Ae: **Leishmania donovani; vector: sandflies**

Dx: **Marrow aspirate: L. amastigotes in mac's**
Positive L. serology and PCR

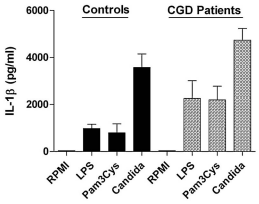


Th: **Liposomal Amphotericin B**

Martin et al: Ped. Infect Dis J 2009

Exuberant Inflammation in CGD

IL-1β production↑



van de Veerdonk et al. PNAS 2010

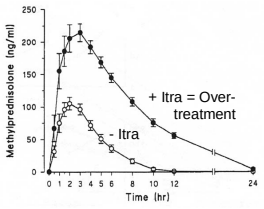
CGD: Drugs for Treatment of Granulomatous Colitis

	Mildly/ Moderately active	Severely active	Perianal fistulas ***
I. **Topical treatments**			
Sulfasalazine oral (40-50 mg/kg/d)	+ (induction ± aintenance)	–	–
II. **Systemic treatments**			
Prednisone oral (1 mg/kg/d, then taper)	+ (induction)	+ (induction ± maintenance)	–
iv. (1 mg/kg/d, then slow taper)	–		
Infliximab (5 mg/kg at 0,2,6 wks) *	–	+ (induction, if steroid refractory)	+ (induction)
Azathioprine (2-3 mg/kg/d) **	–	+ (maintenance, if steroid dependent or refractory	+ (maintenance)

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

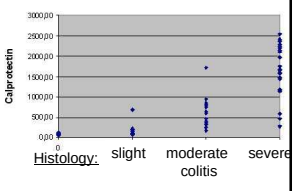
CGD Colitis: How to avoid Overtreatment

Itraconazole increases steroid levels



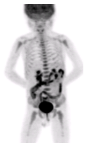
Varis et al. Pharmacol Toxicol 1999

Adjustment of Immunosuppression:
Follow up by fecal calprotectin



Vieira et al. BMC Res Notes 2009

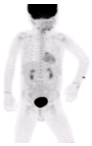
Cure of Steroid-dependent Colitis after HSCT



before

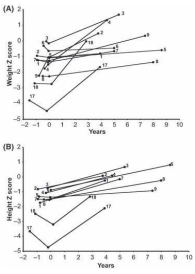
Colitis

HSCT



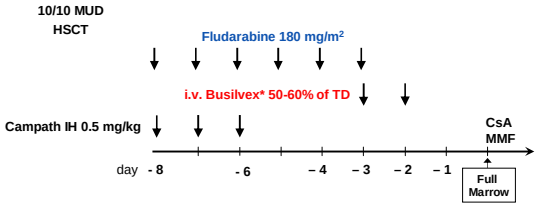
after

Growth spurt after HSCT



Soncini et al. 2009

MUD-HSCT for CGD: Zürich - RIC Protocol



Busulfan dose adjusted according to kinetics (AUC)
Target: 50-60.000 ng*h/µL

Recent MUD-Transplants for CGD in Europe

CGD-Cohort	Patient No	aGvHD (grade)	Graft Failure	Full Engraftment	Mortality	Conditioning
1. New Castle	10	3/9 (II)	1/9 (1 retransplant)	7/9 (1/9 partial)	1/10 *	Bu, Cy, Campath 1 H (7/10)
2. Ulm	9	3/9 (II)	2/9 (1 retransplant)	7/9	2/9 □ ◆	Bu based (6/9)
3. Zürich	6	1/6 (II)	0/6	6/6	1/6 °	Bu 50-60% Flu 180 Campath 0.5 (5/6)
Total MUD	**25**	**7/24 (II) (= 29%)**	**3/24 (= 12%)**	**20/24 (= 83%)**	**4/25 (= 16%)**	
Total MSD	**16**	**4/16 (II) (= 25%)**	**0/16**	**13/16 (= 81%)**	**1/16 (= 6%)**	

* = 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)

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