Role of immunomodulation in treatment of severe fungal infections in patients with chronic granulomatous disease

Mario Abinun

Department of Paediatric Immunology,
Great North Children's Hospital, and

Primary Immunodeficiency Group,
Institute of Cellura Medicine, Newcastle University,

Newcastle upon Tyne, U.K.

mario.abinun@ncl.ac.uk

Uloga imunomodulacije u lecenju gljivicnih infekcija u bolesnika obolelih od hronicne granulomatozne bolesti

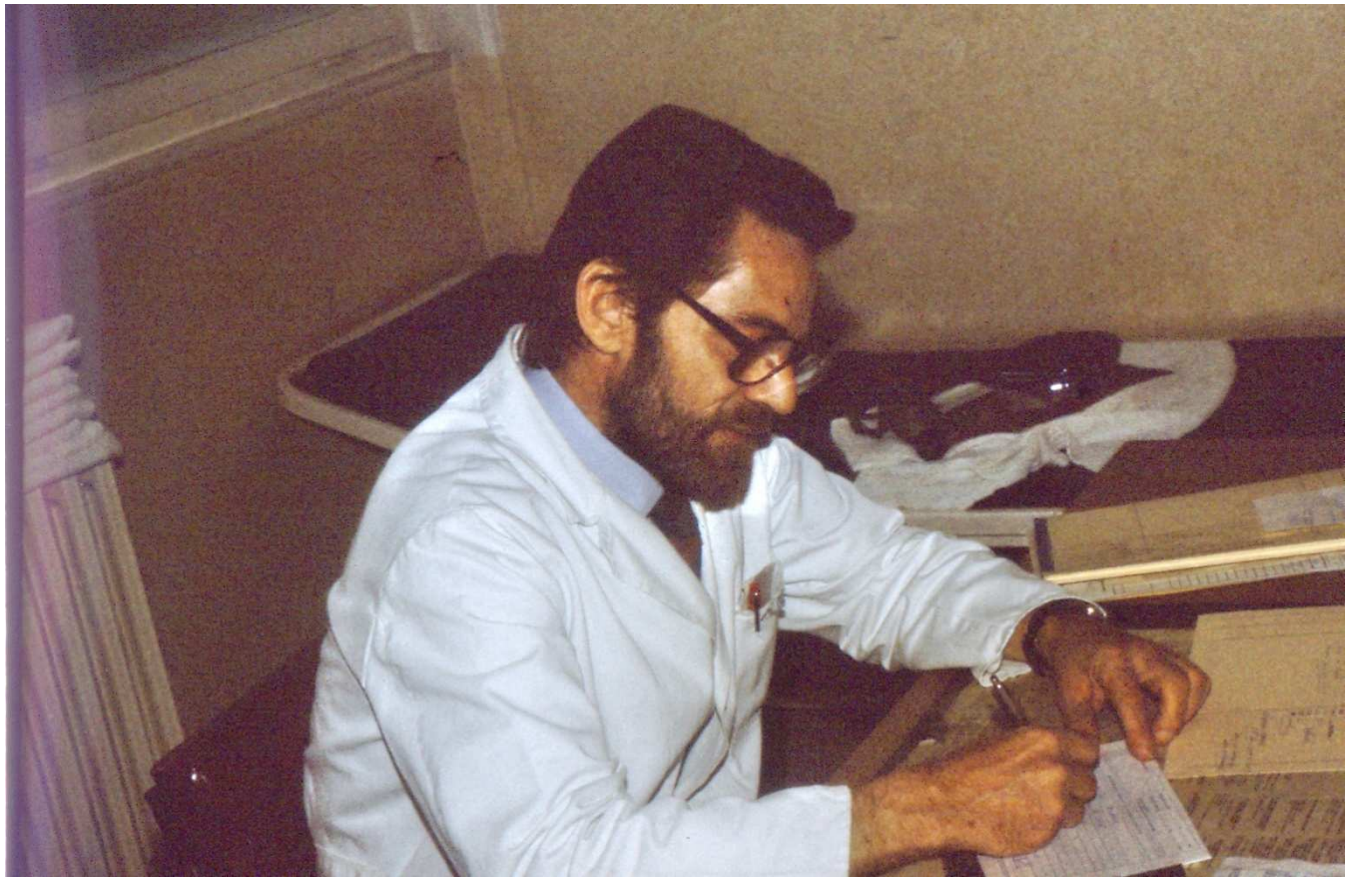
Mario Abinun

Department of Paediatric Immunology,
Great North Children's Hospital, and

Primary Immunodeficiency Group,
Institute of Cellura Medicine, Newcastle University,

Newcastle upon Tyne, U.K.

mario.abinun@ncl.ac.uk

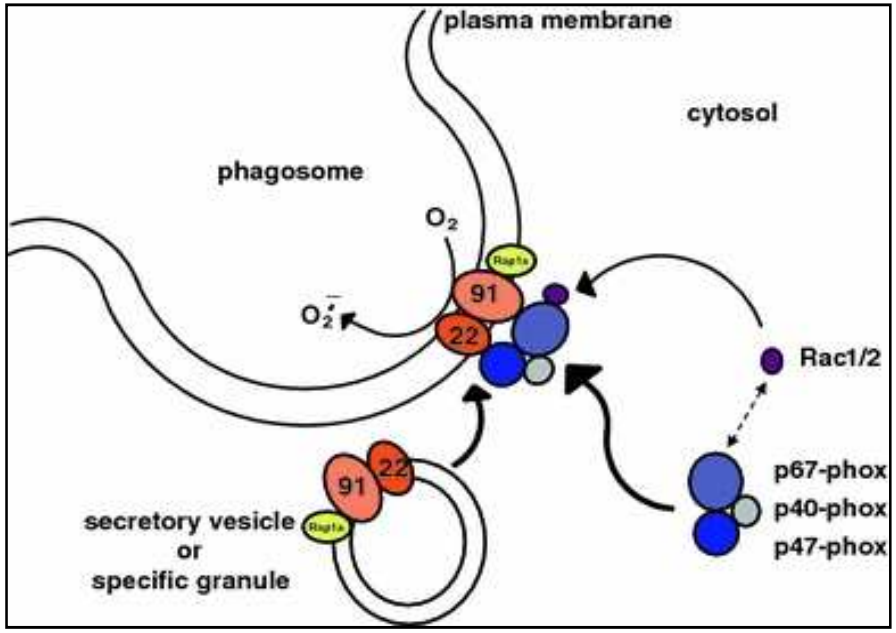


Mirko Mikuska

Hronicna granulomatozna bolest

- **Retka bolest (~ 1/200 000)**
- **1957 - primarni poremecaj u funkciji fagocita**

enzimski kompleks NADPH oksidaze u neutrofilima



Cell Mol Life Sci. 2012 January; 69(1): 7–15.

5 gena – komponente nikotinamid adenin dinukleotid fosfat (NADPH) oksidaze

gp91^{phox}	*CYBB*	65%	XL
	[cytochrome b-245, beta polypeptide]		
p22^{phox}	*CYBA*	<5%	AR
p47^{phox}	*NCF1*	30%	AR
	[neutrophil cytosolic factor 1]		
p67^{phox}	*NCF2*	<5%	AR
p40^{phox}	*NCF4*	1 bolesnik	AR

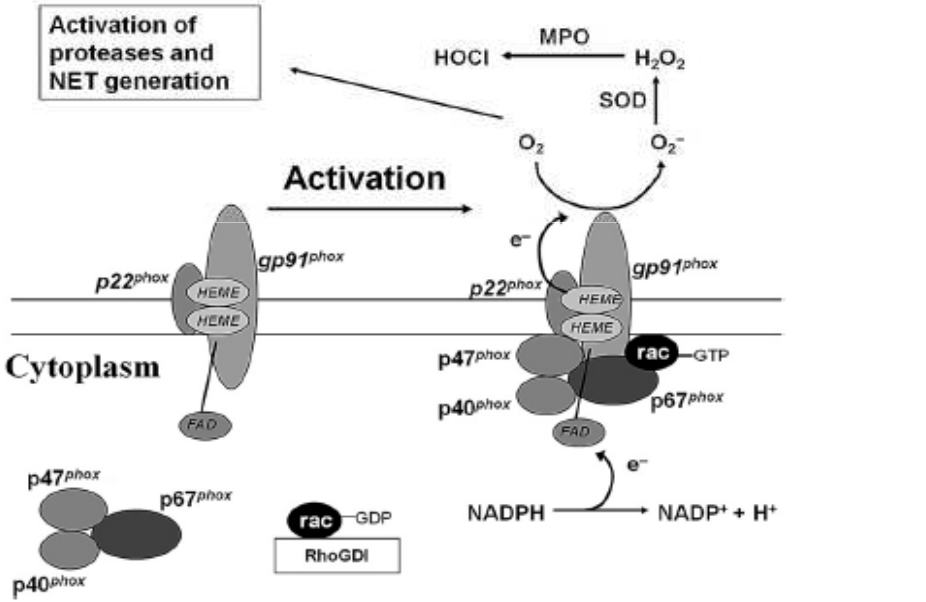
<u>Fagocitne celije</u> - neutrofili, monociti, makrofagi, eozinofili:

- **<u>Smanjena</u> produkcija superoksida i kiseonickih radikala (hidrogen peroksid, hipohlorna kiselina) ("reactive oxygen intermediates – ROIs; reactive oxygen species – ROS")**
  - **Ostecena funkcija intracelijskog ubijanja mikro-organizama**
  - **Ostecena funkcija formiranja 'Ne extracellular traps' (NET)**

- **Ogranicen spektar bakterijskih i gljivicnih infekcija**
  - ***Staphylococcus aureus***
  - ***Serratia marcescens***
  - ***Burkholderia cepacia complex***
  - ***Nocardia species***
  - ***<u>Aspergillus species</u>***
  - ***<u>Candida species</u>***

- **Pluca**
- **Koza i limfni cvorovi**
- **Gastrointestinalni sistem i jetra**

- **Deregulacija zapaljenske reakcije**
  - **Formiranje granuloma**



Bolest I Prognoza

Journal of Clinical Immunology, Vol. 23, No. 1, January 2003 (© 2003)

Long-Term Follow-Up and Prognosis of Chronic Granulomatous Disease in Yugoslavia: Is There a Role for Early Bone Marrow Transplantation?

SRDJAN PASIC,[1,5] ALEKSANDRA MINIC,[1] PREDRAG MINIC,[1] DOBRILA VELJKOVIC,[1] DESA LILIC,[2] BOJANA SLAVKOVIC,[1] NADA PEJNOVIC,[3] and MARIO ABINUN[4]

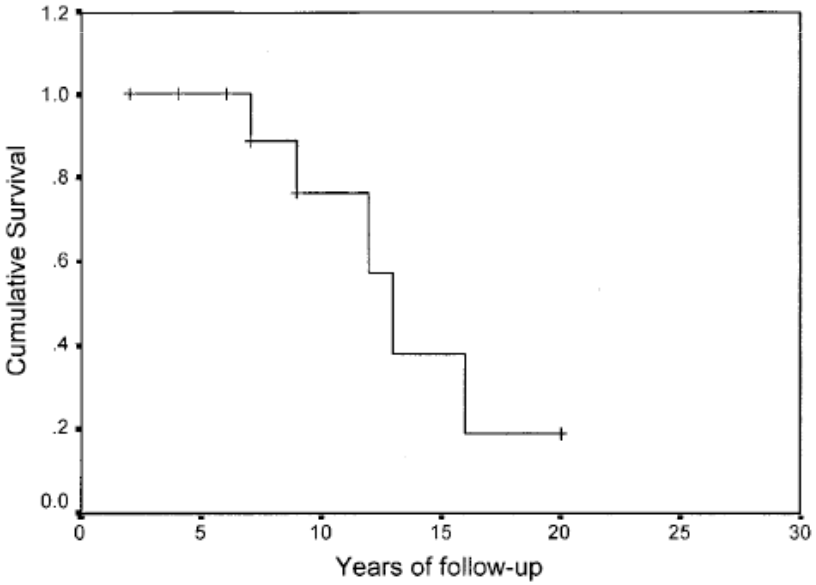


Fig. 1. Probability of long-term survival for 12 patients with chronic granulomatous disease.

Table II. Localization and Frequency of Infections in 12 Patients with CGD

	No. of episodes	% of pts	Episodes per patient year
Pneumonitis	31	91	0.21
Ear, nose and throat infections	20	68	0.13
Suppurative lymphadenitis	16	83	0.11
Skin infections	16	83	0.11
Subcutaneous abscesses	11	25	0.07
Liver abscesses	5	25	0.03
Sepsis	4		
Osteomyelitis	2	12	0.008
Meningitis	1	8	0.006
Splenic abscess	1	8	0.006
UTI/ Obstructive uropathy	1	8	0.006

Table III. Microbiological Isolates in 12 Patients with CGD

Infection	Infective agent	No. of isolates
Lymphadenitis	*Staphylococcus aureus*	11
	Serratia spp.	4
	Bacille Calmette–Guérin	5
Pneumonitis	*Aspergillus* spp.	1 (2[a])
	Staphylococcus aureus	1
	Serratia spp.	3
	Burkholderia cepacia	1
	Propionibacterium propionicum	1
Sepsis	*Salmonella* spp.	2
	Pseudomonas aeruginosa	1
	Staphylococcus aureus	1
Liver abscesses	*Staphylococcus aureus*	5
Osteomyelitis	*Aspergillus fumigatus*	1
	Serratia spp.	1
Meningitis	*Serratia marcescens*	1

[a] Invasive lung aspergillosis was proven in two patients on autopsy.

Prevencija I Terapija

- Antibiotici
- Antiglivicni lekovi
- Interferon Gamma
- Hirurgija

- Imunosupresivni i anti-inflamatorni lekovi

- Presadjivanje maticnih celija kostne srzi
- Genska terapija
- Indukovane pluripotentne maticne celije (iPSC)

Unrelated donor and HLA-identical sibling haematopoeitic stem cell transplantation cure chronic granulomatous disease with good long-term outcome and growth

 British Journal of Haematology

Elena Soncini,[1,*] Mary A. Slatter,[1,*] Laura B. K. R. Jones,[1] Stephen Hughes,[1] Stephen Hodges,[2] Terence J. Flood,[1] Dawn Barge,[3] Gavin P. Spickett,[3] Graham H. Jackson,[4] Matthew P. Collin,[4] Mario Abinun,[1,5] Andrew J. Cant[1,5] and Andrew R. Gennery[1,5]

Departments of [1]Paediatric Immunology, [2]Paediatric Gastroenterology, Newcastle upon Tyne Hospitals Foundation Trust, [3]Regional Immunology laboratory, Newcastle upon Tyne Hospitals Foundation Trust, [4]Department of Haematology, Newcastle upon Tyne Hospitals Foundation Trust, and [5]Institute of Cellular Medicine, Child Health, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Received 29 September 2008; accepted for publication 12 November 2008

Correspondence: A. R. Gennery, Ward 23, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK.
E-mail: a.r.gennery@ncl.ac.uk
*E. Soncini and M.A. Slatter contributed equally to the manuscript.

Summary

Chronic granulomatous disease (CGD) causes recurrent infection and inflammatory disease. Despite antimicrobial prophylaxis, patients experience frequent hospitalisations and 50% mortality by 30 years. Haematopoietic stem cell transplantation (HSCT) can cure CGD with resolution of infection and colitis. This study reports the survival and long-term outcome in 20 conditioned patients treated between 1998 and 2007, using 10 matched sibling (MSD) and 10 unrelated donors (URD). Age at HSCT, graft-*versus*-host disease (GvHD), growth, and outcome were analysed. Fourteen had ≥1 invasive infection, 10 had colitis and seven had growth failure before HSCT. Median age at transplantation was 75 months (range 15 months–21 years). Eighteen (90%) were alive 4–117 months (median 61) after HSCT with normal neutrophil function. Two died from disseminated fungal infection. Two experienced significant chronic GvHD, with continuing sequelae in 1. Colitis resolved within 8 weeks of HSCT. Mean weight and height for age *Z* scores on recovery from HSCT rose significantly ($P < 0{\cdot}001$). HSCT with MSD or URD gave excellent engraftment and survival, remission of colitis and catch-up growth, with low incidence of significant GvHD. Transplant-associated complications were restricted to those with pre-existing infection or inflammation, supporting the argument for early HSCT for more CGD patients with a well matched donor.

Keywords: chronic granulomatous disease, graft-*versus*-host disease, haematopoietic stem cell transplantation.

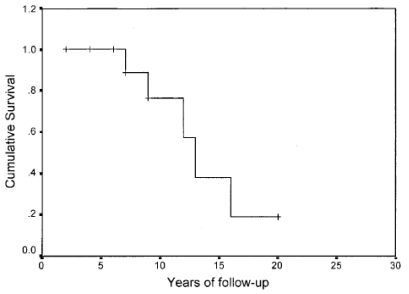


Fig. 1. Probability of long-term survival for 12 patients with chronic granulomatous disease.

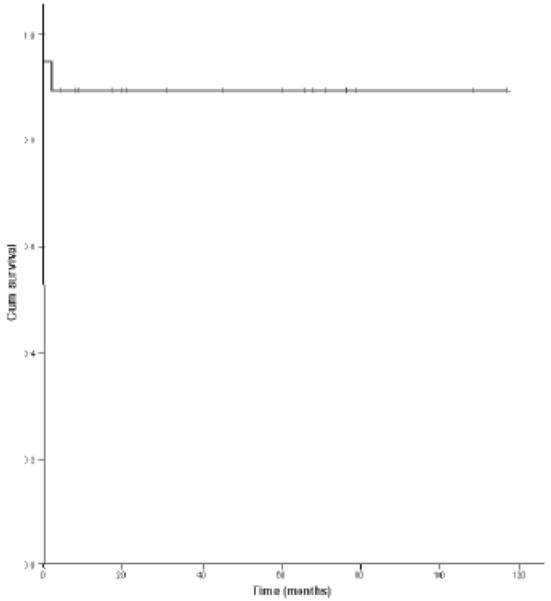


Fig 1. Kaplan–Meier survival estimates.

2009

- 20 bolesnika (2 U)

Feb 2012

- 40 bolesnika (5 U)

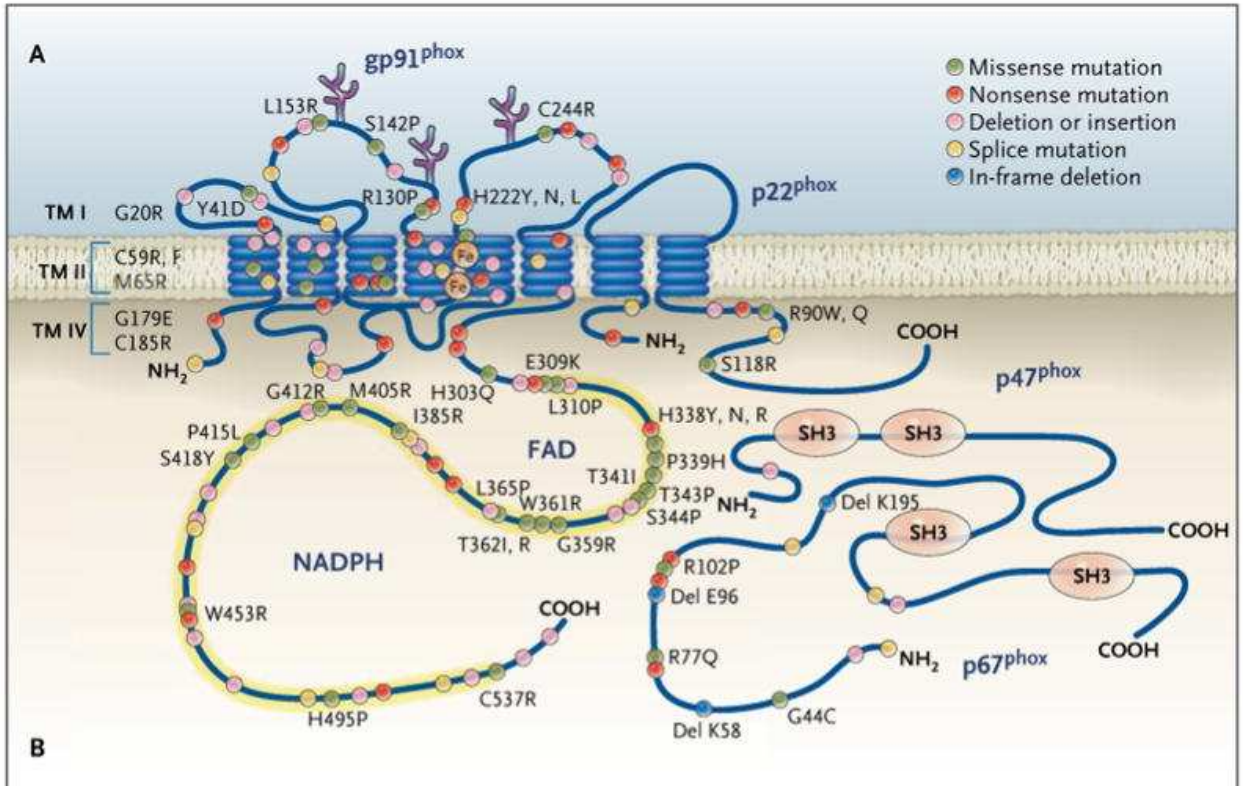
Da li su svi bolesnici kandidati za HSCT ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Residual NADPH Oxidase and Survival in Chronic Granulomatous Disease

Douglas B. Kuhns, Ph.D., W. Gregory Alvord, Ph.D., Theo Heller, M.B., Ch.B., Jordan J. Feld, M.D., M.P.H., Kristen M. Pike, M.S., Beatriz E. Marciano, M.D., Gulbu Uzel, M.D., Suk See DeRavin, M.D., Ph.D., Debra A. Long Priel, M.S., Benjamin P. Soule, M.D., Kol A. Zarember, Ph.D., Harry L. Malech, M.D., Steven M. Holland, M.D., and John I. Gallin, M.D.



N Engl J Med. 2010 December 30

NATURE MEDICINE VOLUME 12 | NUMBER 4 | APRIL 2006

Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of *MDS1-EVI1*, *PRDM16* or *SETBP1*

Marion G Ott[1,16], Manfred Schmidt[2–4,16], Kerstin Schwarzwaelder[3–5,16], Stefan Stein[6,16], Ulrich Siler[7,16], Ulrike Koehl[8], Hanno Glimm[2,3], Klaus Kühlcke[9], Andrea Schilz[9], Hana Kunkel[6], Sonja Naundorf[9], Andrea Brinkmann[8], Annette Deichmann[3,4], Marlene Fischer[2,3,5], Claudia Ball[3–5], Ingo Pilz[3,5], Cynthia Dunbar[10], Yang Du[11], Nancy A Jenkins[11], Neal G Copeland[11], Ursula Lüthi[12], Moustapha Hassan[13], Adrian J Thrasher[14], Dieter Hoelzer[1], Christof von Kalle[2–4,15,16], Reinhard Seger[7,16] & Manuel Grez[6,16]

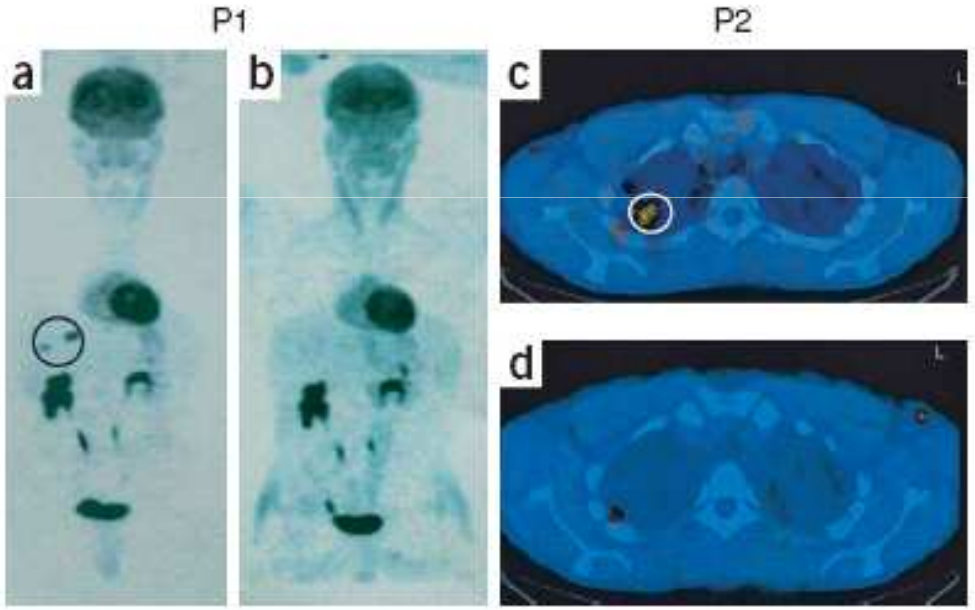
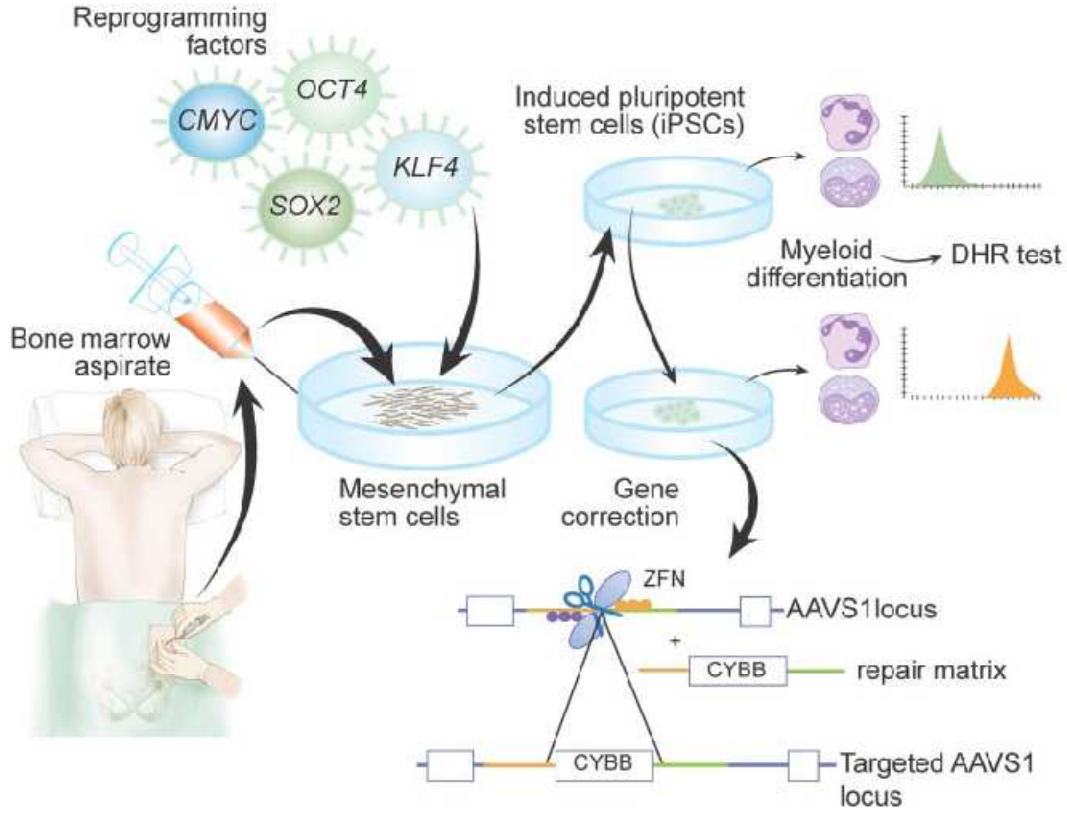


Figure 6 Fused PET scans of P1 (**a**,**b**) and fused PET-CT scans of P2 (**c**,**d**) before (**a**,**c**) and 50 (**b**) or 53 d (**d**) after gene therapy. Circle in **a** denotes two active abscesses due to *Staphylococcus aureus* infection in the liver of P1, and the circle in **c** shows ^{18}F-FDG uptake in the wall of a lung cavity of P2 due to *A. fumigatus* infection.

Stein S et al.

Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease.

Nat Med. 2010 Feb;16(2):198-204

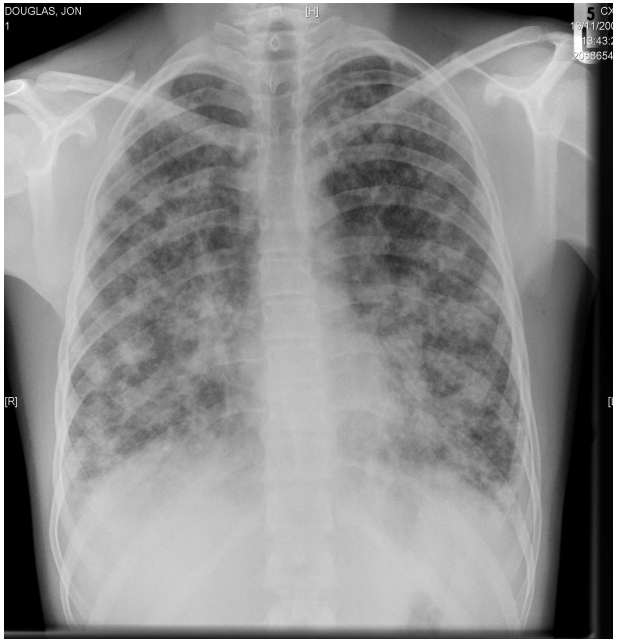


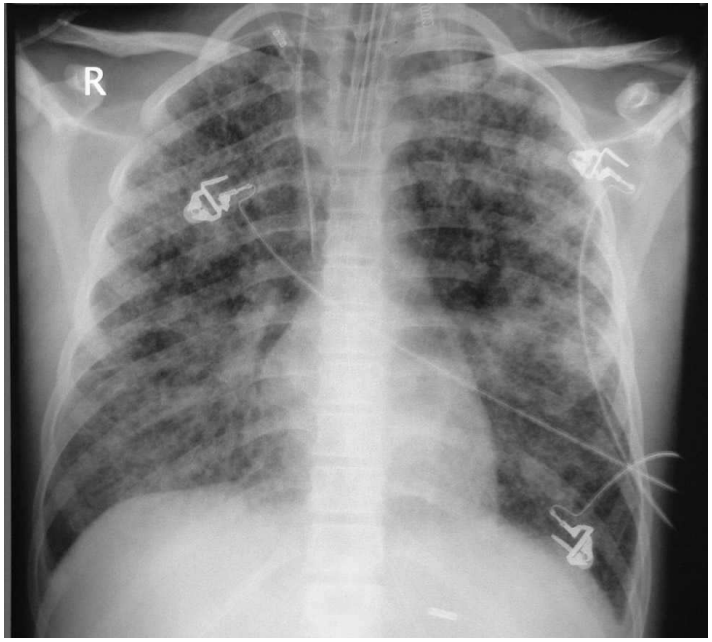
Luigi D. Notarangelo CHILDRENS HOSPITAL, HARVARD MEDICAL SCHOOL

Patient-derived induced pluripotent stem cells (iPSCs) represent a novel and powerful tool for in vitro modeling and correction of human diseases.

In this issue of ***Blood*****,** Zou et al report on the generation and correction of iPSCs from a patient with X-linked chronic granulomatous disease (X-CGD), a severe primary immunodeficiency (PID) because of defects of the NADPH oxidase.

Problemi sa gljivama

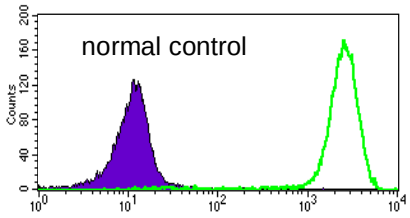


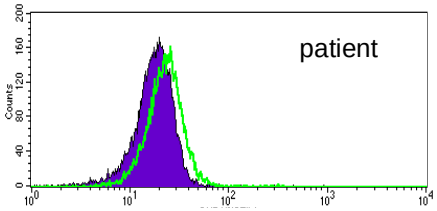


- Antibiotici ‘sirokog spektra’
- Respiratorni distres
- Metilprednizolon ‘puls’ 1g/d x 3 dana
    - sumnja na ‘vaskulitis/ARDS’
- ECMO – ekstra-korporalna membranozna oksigenacija

***Aspergillus* u BAL**

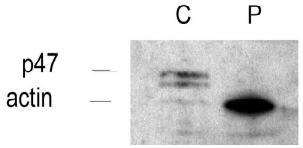
Absent neutrophil oxidative burst (dihydrorodamine DHR)

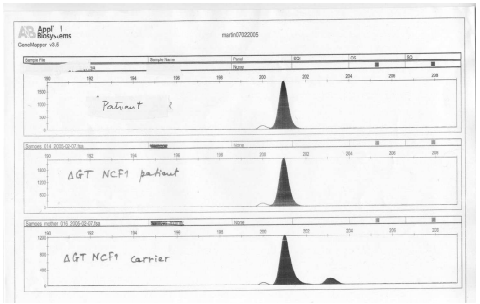




Absent protein (p47-phox) expression

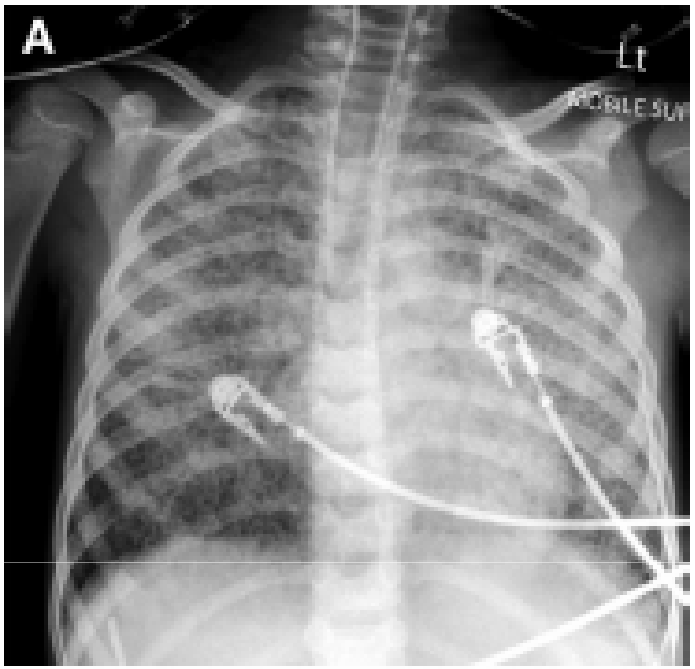
Gene scan (*NFC1*):
only pseudogenes present, indicating autosomal recessive
(p47-phox – negative) CGD

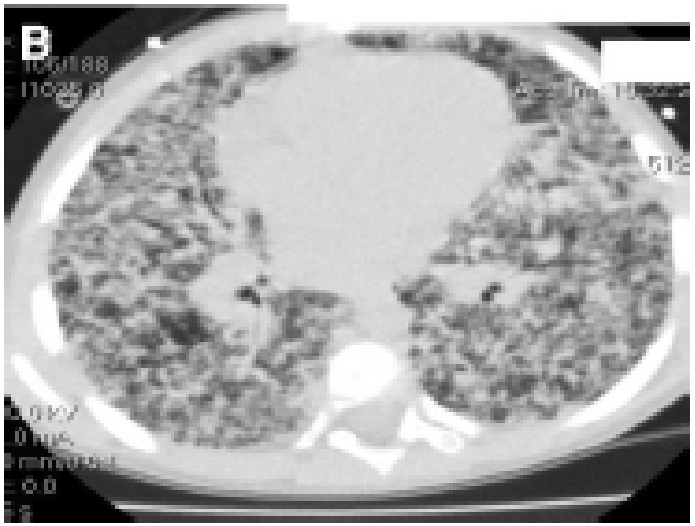


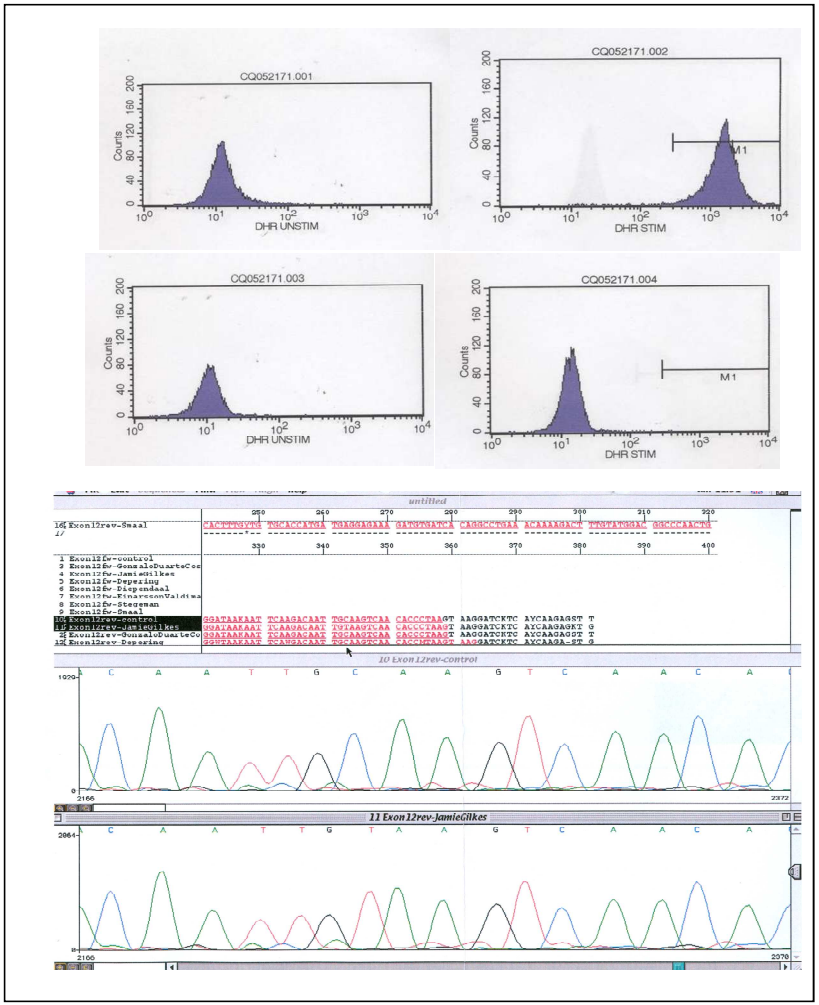


Antibiotici ‘sirokog spektra’

Metilprednizolon ‘puls’ 300 mg/d x 3 dana - ‘ARDS’







***CYBB* (C1571>T subst., exon 9)**

• No 1

- Vorikonazol + Kaspofungin
- IFN-G
- Transfuzije leukocita

- MP 1 mg/kg/d

- ECMO (2 nedelje) => MOF
- Aspergillus fumigatus (PM)

• No 2

- Vorikonazol + Kaspofungin + Ambizom

- MP 1 mg/kg/d

- ECMO
  7 dana => MOF
  Aspergillus fumigatus destruktivna pneumonia (PM)

Chronic granulomatous disease presenting as fulminant *Aspergillus* pneumonitis: A lethal combination?

Atul Gupta, MD, DNB, MRCPCH; Michael McKean, MD; Simon Haynes, MBChB; Chris Wright, FRCPath; Dawn Barge, PhD; Terrence J. Flood, MA, MRCPI; Kate Gould, FRCPath; Jon Smith, MRCP(UK), FRCA; Fraser G. Charlton, FRCPath, PhD; Sachin Mannikar, MD, MRCPCH; Mario Abinun, MD, PhD; Jane Cassidy, MRCP

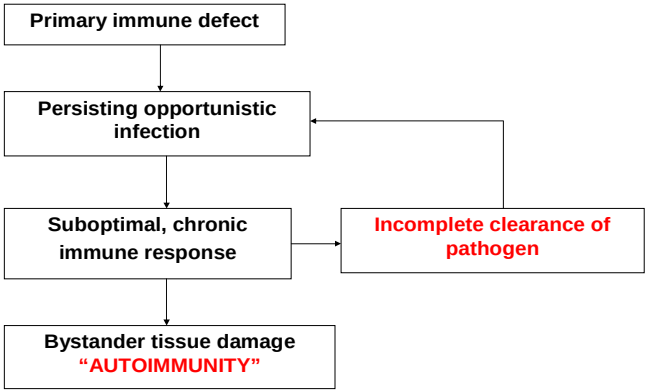
Pediatr Crit Care Med 2009

‘Hiperinflamacija’ i CGD - I

Smanjen oksidativni metabolizam

- glavni uzrok ponavljanih infekcija, granulomatoznih komplikacija i prerane smtrtnosti

Reeves et al. Nature 2002



Arkwright, Abinun, Cant. Blood 2002

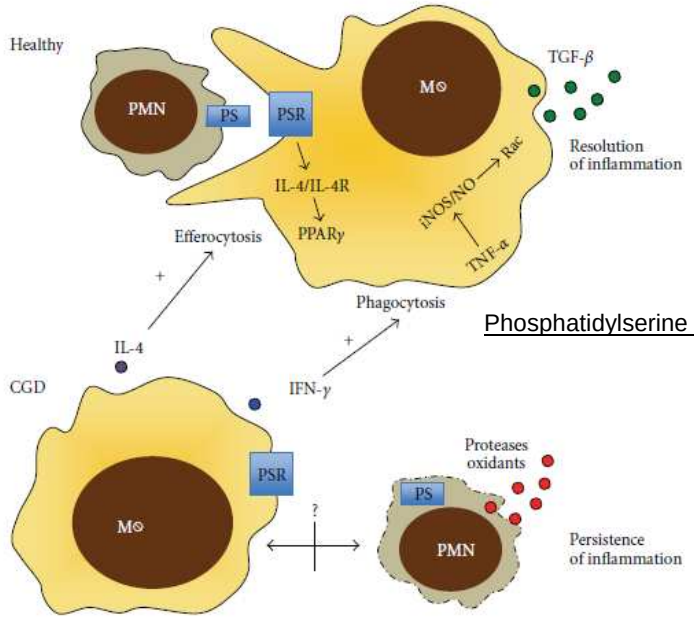
Hronicna granulomatozna bolest i ‘autoimunost’

- ostecen postupak ‘ciscenja’ apoptoticnih celija
- genski polimorfizmi (FcγR; MBL) (‘background genes’)

=> SEL

Foster et al. *JCI* 1998

Clinical and Developmental Immunology 2012



Phosphatidylserine

Kortikosteroidi u CGD

- Kortikosteroidi smanjuju aktivaciju, proliferaciju i diferencijaciju makrofaga i limfocita, celija koje imaju znacajnu ulogu u zapaljenskom procesu i stvaranju granuloma
- Istorijski, efekat kod opstruktivnih i zapaljenskih komplikacija

- 'Mulch' pneumonitis

Fulminant Mulch Pneumonitis: An Emergency Presentation of Chronic Granulomatous Disease

Sophia Siddiqui,[1] Victoria L. Anderson,[3] Diane M. Hilligoss,[2] Mario Abinun,[6] Taco W. Kuijpers,[7] Henry Masur,[4] Frank G. Witebsky,[5] Yvonne R. Shea,[5] John I. Gallin,[2] Henry L. Malech,[2] and Steven M. Holland[3]

Clinical Infectious Diseases 2007;

- Apsces jetre

Corticosteroid Therapy for Liver Abscess in Chronic Granulomatous Disease

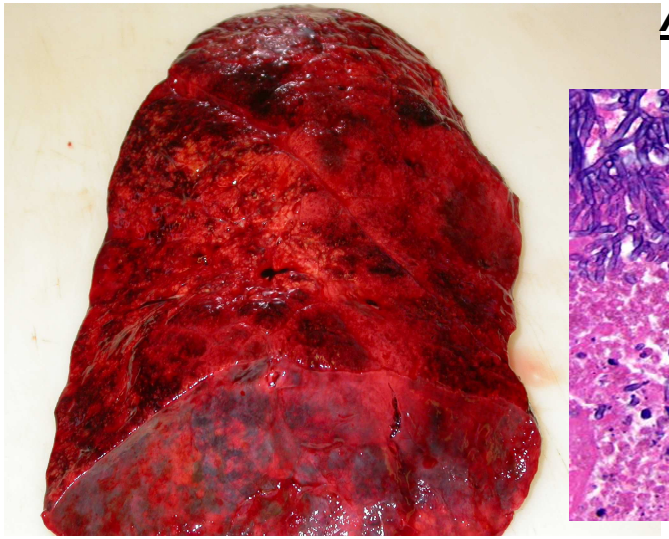
Jennifer W. Leiding,[1] Alexandra F. Freeman,[1] Beatriz E. Marciano,[1] Victoria L. Anderson,[1] Gulbu Uzel,[1] Harry L. Malech,[2] SukSee DeRavin,[2] David Wilks,[3] Aradhana M. Venkatesan,[4] Christa S. Zerbe,[1] Theo Heller,[5] and Steven M. Holland[1]

Clinical Infectious Diseases 2012;

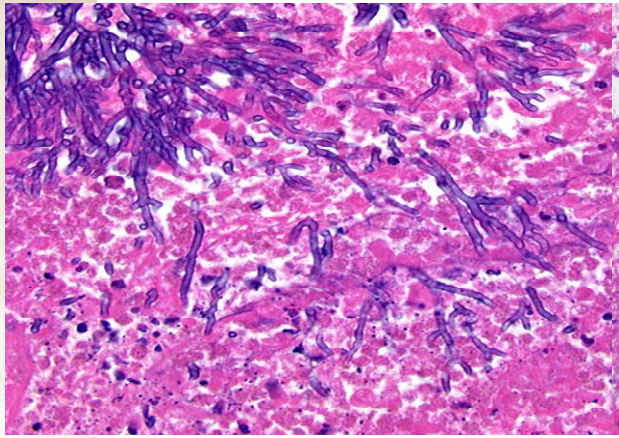
- 1 mg/kg/d 2-3 nedelje
- Postepeno smanjenje doze
  (nedelje - meseci)
- Istovremeno sa antimikrobijalnom terapijom

No 1

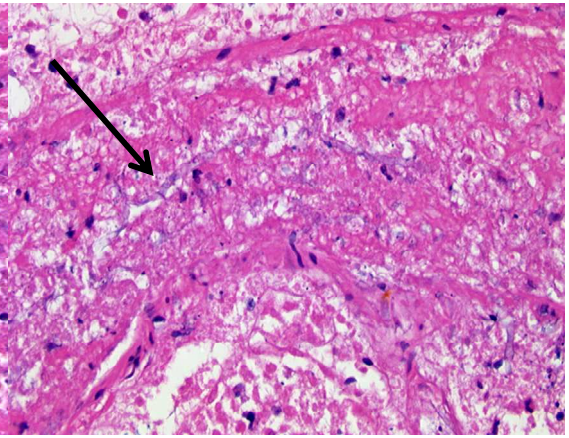
Post mortem



Aspergillus fumigatus



Absidia corymbifera



Abinun M et al.
Absidia corymbifera in a Patient With Chronic Granulomatous Disease.
Ped Inf Dis J 2007

Kortikosteroidi u CGD

- Kortikosteroidi smanjuju aktivaciju, proliferaciju i diferencijaciju makrofaga i limfocita, celija koje imaju znacajnu ulogu u zapaljenskom procesu i stvaranju granuloma
- Istorijski, efekat kod opstruktivnih i zapaljenskih komplikacija

- 'Mulch' pneumonitis
- Apsces jetre

- 1 mg/kg/d 2-3 nedelje
- Postepeno smanjenje doze
  (nedelje - meseci)
- Istovremeno sa antimikrobijalnom terapijom

- **Cave!**
  - **Jatrogena imunosupresija**
  - **Infekcije**

J Allergy Clin Immunol. 2009

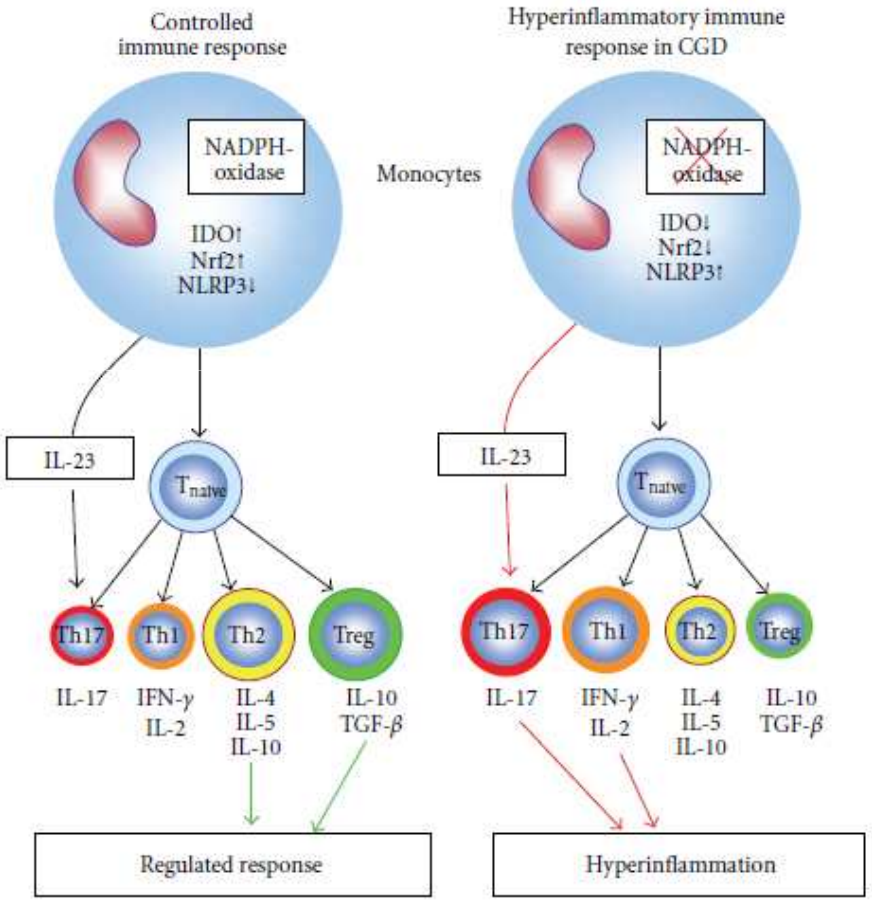
Mucormycosis in chronic granulomatous disease: association with iatrogenic immunosuppression.

Vinh DC, Freeman AF, Shea YR, Malech HL, Abinun M, Weinberg GA, Holland SM

‘Hiperinflamacija’ i CGD - II

Moguci poremecaji:

- Apoptoza Ne
- Mehanizmi urodjene imunosti
  - NfKB-signalni mehanizmi
  - Regulacija TNF-a, IL-17, IL-6, GCSF
  - Razgradnja leukotriena B4 i C5a
  - Produzena aktivacija IL-8 m-RNA
- Regulacija zapaljenske reakcije
  - Aktivacija Nrf2 (anti-iflamatorni regulator)
  - Aktivacija peroxisome proliferator activated receptor c (PPARC)
  - Katabolizam triptofana (misevi, ne i ljudi)
    - Romani et al. Nature 2008
    - Segal BH et al. PLoS One 2010
  - Aktivacija inflamazoma



Clinical and Developmental Immunology 2012

Blokada TNF-alfa

Deffert C et al.

TNF-α blockade in chronic granulomatous disease-induced hyperinflammation: patient analysis and murine model.

J Allergy Clin Immunol. 2011 Sep

T McG m (Jun 2011)

XL CGD

Varicella; *S Aureus* lymphadenitis (LC vrata); Kolitis (‘akutni abdomen’); Apsces jetre

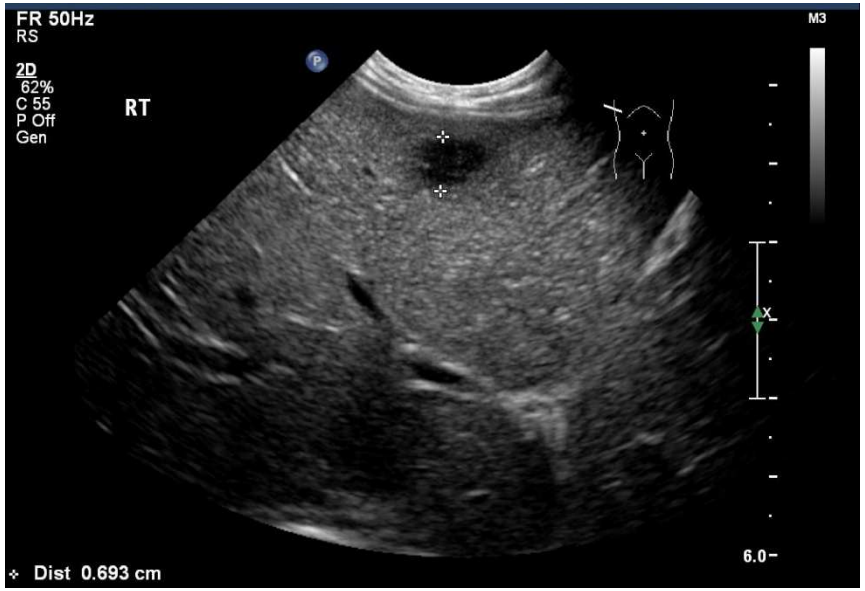
Antibiotici (meropenem/teikoplanin/amikacin)

- ciprofloksacin, klindamicin, septrin

Ambizom, Vorikonazol

M-Prednizolon 1 mg/kg/d 7 dana – Pronizon, postepeno smanjena doza (2 nedelje)

Infliximab 10 mg/kg x1



Dec 2011

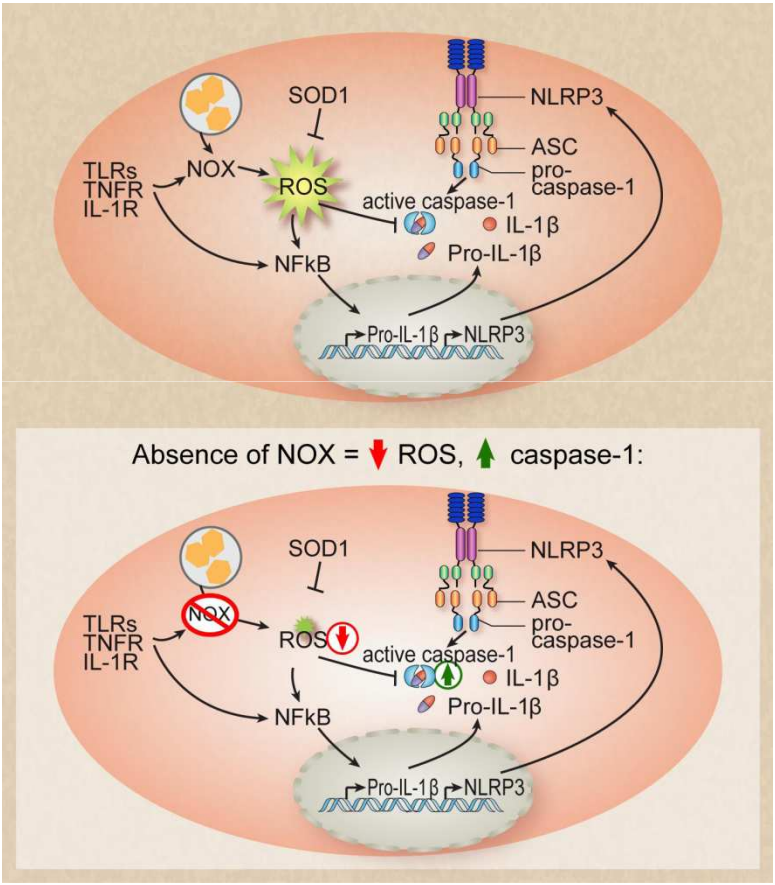
Jan 2012

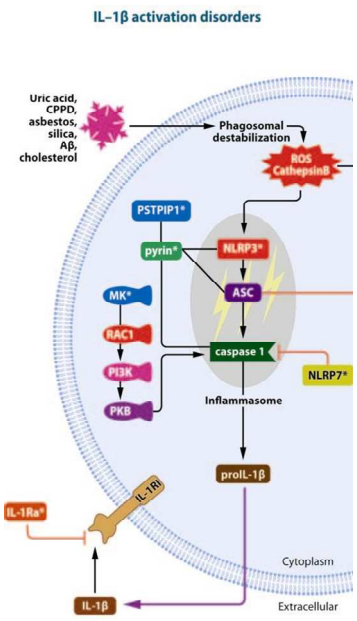
Blokada IL-1

Meissner F et al.
Inflammasome activation in NADPH oxidase defective mononuclear phagocytes from patients with chronic granulomatous disease.
Blood. 2010; 116(9):1570-1573.

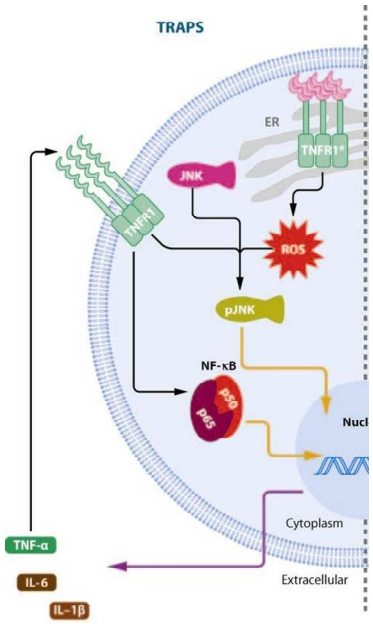
Latz E. Blood 116(9), 2 SEPTEMBER 2010

van de Veerdonk FL et al.
Reactive oxygen species-independent activation of the IL-1beta inflammasome in cells from patients with chronic granulomatous disease.
Proc Natl Acad SciUS A. 2010(7); 107:3030-3033.





Masters SL, et al. 2009.
Annu. Rev. Immunol. 27:621–68



Masters SL, et al. 2009.
Annu. Rev. Immunol. 27:621–68

AI m (Sept 2002)
upucen za HSCT Januar 2010

- X Linked Chronic Granulomatous Disease (1 yr)
  - negative neutrophil oxidative burst
  - hemizygous for *CYBB* mutation (exon 11: c.1375C>T, p.G1n459X)

- T cell lymphopaenia with absent naïve cells post thymectomy (for thymic abscess) aged 7 months
  - Severe varicella (March 2008)

- Chronic inflammatory colitis with focal lymphangectasia and poor weight gain (aged 6 mo-1 yr)
- Non specific hepatitis (Jan 2007)

- Frontal skin/bone abscess (*Klebsiella pneumonaie*) (2003)
- Right parietal Cerebral abscess – presumed fungal (Oct 2009)
  - Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH), July 2009

- *Aspergillus nidulans* pneumonia with rib invasion (Feb 2007)
- *Scopulariopsis* pneumonia (Right Middle Lobe) (July 2009) with persistent consolidation on CT
- Interstitial lung disease with areas of destruction on CT (Jan 10)

- *Mb Avium Complex (MAC)* osteomyelitis of left cuboid bone (May 2009)
  - Hearing impairment post Amikacin (Aug-Dec 2009) requiring hearing aids

- Biochemical rickets (fractures after minimal trauma; left tibia, fibula and humerus) (Nov 2009)

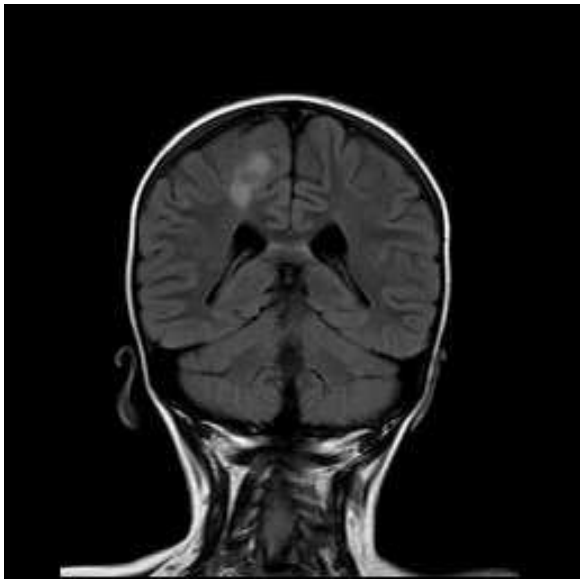
Feb 07: *Aspergillus nidulans* (BAL)

		MIC (mg/l)
Amphotericin	Sensitive	1
Caspofungin	Sensitive	0.25
Itraconazole	Sensitive	0.125
Posaconazole	Sensitive	0.125
Voriconazole	Sensitive	0.06

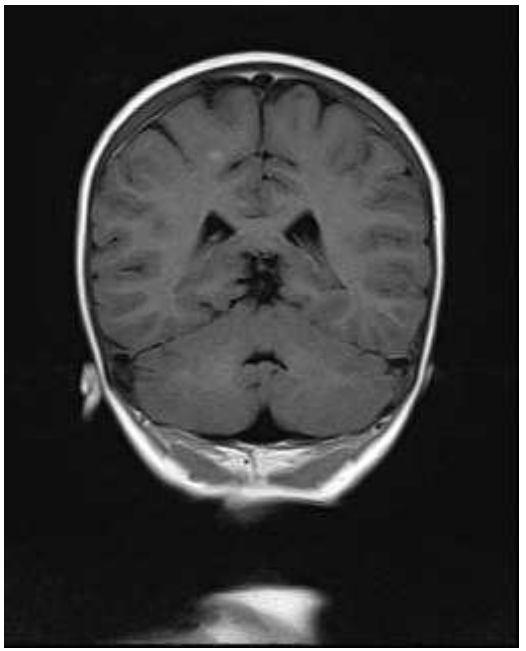
Aug 09: *Scopulariopsis (*Microascus cinereus) filamentus fungus (BAL)

		MIC (mg/l)
Amphotericin	Sensitive	1
Caspofungin	Intermediate	4
Itraconazole	Resistant	>16
Posaconazole	Intermediate	2
Voriconazole	Intermediate	4
Micafungin	Sensitive	0.25
Terbinafine	U	2

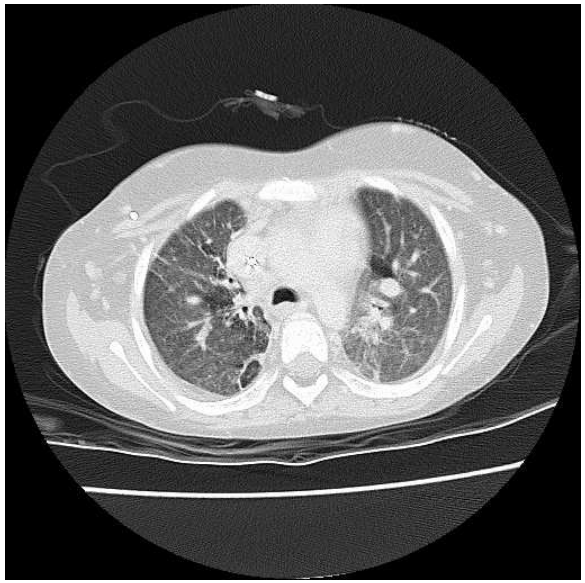
July 09: Mycobacterium avium Complex isolated from left cuboid bone.
Sensitive to: Amikacin, Streptomycin, Clarithromycin, Ethambutol, Prothionamide, Clofazimine, Capreomycin.
Resistant to: Ciprofloxacin, Rifampicin, Rifambutin.



- Interferon gamma
- Ambisome (Vori+/-Caspo)
- Micafungin
- (Amikacin)
- Ethambutol
- Clarithromycin
- Ergocalciferol
- Posaconazole



- Steroidi
  (1 mg/kg/d – 0.5 mg/kg/alt d)
- Infliximab
  (10 mg/kg) mesecno
- Anakinra
  (1-3 mg/kg/d) u OIN



Matched sibling donor bone marrow + cord transplant (Treo/Flu) Nov 2011

- Chronic inflammatory colitis

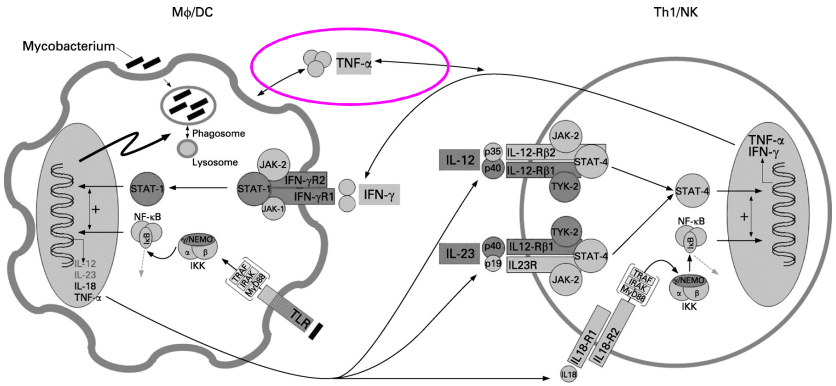
- Slow healing of grafted laparotomy wound - post-splenectomy / complications

- Chronic lung infections (*Aspergillus nidulans* and *Scopulariopsis spp.)*
  Persistent right middle lobe (CT / MRI) bronchiectasis / interstitial lung disease

- Right parietal cerebral abscess
- Avium Complex (MAC) osteomyelitis of left cuboid bone
- Fluid retention and generalised pitting oedema
  Haematuria / Friable bladder epithelium / Calyceal papillary necrosis / Calciuria
- Hearing impairment

- MOF

Major pathways in the control of intracellular infections with Mycobacterium and Salmonella.



Patel S Y et al. J Clin Pathol 2008;61:1006-1012

JCP

The New England Journal of Medicine

TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

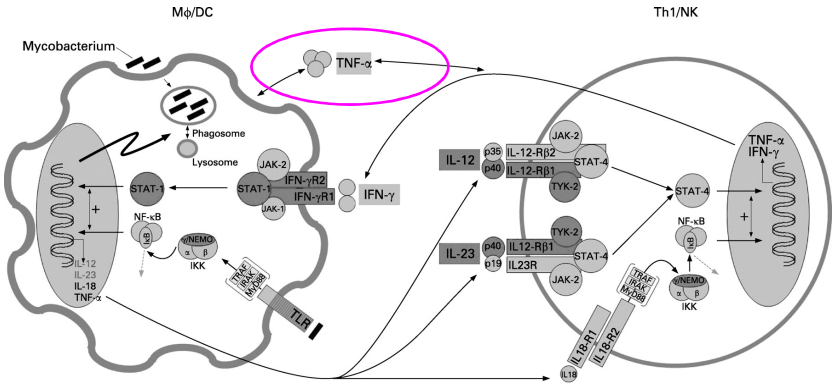
Pediatric Health (2010) **4**(5), 509–517 REVIEW

An overview of infectious complications in children on new biologic response-modifying agents

Mario Abinun[1]

Moshous D et al.
Granulomatous inflammation in cartilage-hair hypoplasia: risks and benefits of anti-TNF-α mAbs.
J Allergy Clin Immunol. 2011 Oct

Major pathways in the control of intracellular infections with Mycobacterium and Salmonella.



Patel S Y et al. J Clin Pathol 2008;61:1006-1012

JCP

The New England Journal of Medicine

TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

Pediatric Health (2010) **4**(5), 509–517 REVIEW

An overview of infectious complications in children on new biologic response-modifying agents

Mario Abinun[1]

Moshous D et al.
Granulomatous inflammation in cartilage-hair hypoplasia: risks and benefits of anti-TNF-α mAbs.
J Allergy Clin Immunol. 2011 Oct

Complications of Tumor Necrosis Factor–α Blockade in Chronic Granulomatous Disease–Related Colitis

Gulbu Uzel,[1] Jordan S. Orange,[2] Nira Pollak,[3] Beatriz E Marciano,[1] Theo Heller,[4] and Steven M. Holland[1]

CID 2010:51 (15 December)(

Primary immunodeficiencies may reveal potential infectious diseases associated with immune-targeting mAb treatments

László Maródi, MD, PhD,[a] and Jean-Laurent Casanova, MD, PhD[b,c] *Debrecen, Hungary, New York, NY, and Paris, France*

J ALLERGY CLIN IMMUNOL
2010