Severe neutropenia management

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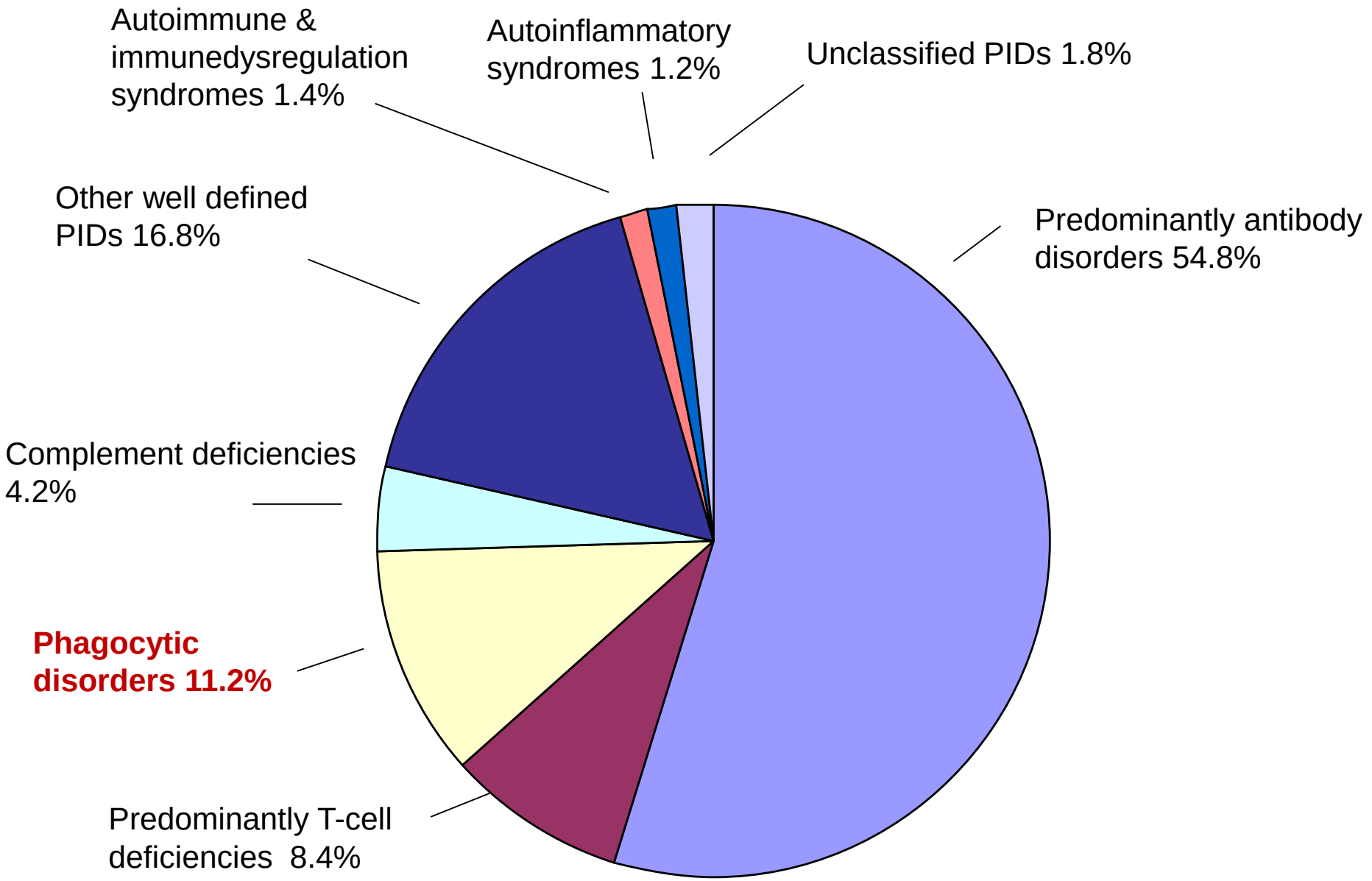
Ho Chi Min, November th, 2019

Distribution per PID category in Europe (n=10,003)*



* Based on the ESID registration, www.esid.org

Severe neutropenia management

- What is neutropenia?
- Who are you treating?
- Management ?

Severe neutropenia management

The definition of neutropenia may vary from institution to institution

- **Mild neutropenia; (1.0 ≤ ANC < 1.5) 10^9/l — minimal risk of infection**
- **Moderate neutropenia; (0.50 ≤ ANC < 1.0) 10^9/l — moderate risk of infection**
- **Severe neutropenia; (ANC < 0.5) 10^9/l or expected to develop over next 48 hours— severe risk of infection**
- **Profound neutropenia as an ANC < 0.1 10^9/l**

$T_{1/2}$ = 6-7 hours in Peripheral blood and 1-2 days in tissues

Freifeld AG et al., Infectious Diseases Society of America, Clin Infect Dis. 2011
Bow and Wingard., UptoDate, Oct 2019

Severe neutropenia management

- What kind of neutropenia?
  - Persistent
    - Differentiation defect like in certain PID
  - Temporary
    - Chemotherapy/toxicity induced?

Prolonged neutropenia; >7 days

Causes of neutropenia

Classification	Etiology
Hematological	Congenital neutropenia
	Myelodysplastic syndrome
	Aplastic anemia
	Leukemia
Immunological/inflammatory disorders	Autoimmune neutropenia
	Cyclic neutropenia
Infections	Malaria
	Cytomegalovirus
	sepsis
Drugs/toxins	

Drug Induced Neutropenia

Antibiotics

Bactrim
Ciprofloxacin
Clindamycin
Vancomycin
Metronidazole
Doxycycline

Analgesics

NSAIDS
Aspirin

Chemotherapy

Antihypertensives & Antiarrythmics

Neuropsychotropics

Respiridone
Valproic acid
Phenytoin
Carbamazepine
Barbiturates

Treatment?

Severe neutropenia management

- Data concerning PID, relatively limited and diverse
- Why?

World Health Organization (WHO) and International Union of Immunological Societies (IUIS) classification of PID

- 1. Combined T- en B- lymphocyte immunodeficiencies
  - *Severe Combined Immunodeficiency*
- 2. Predominantly antibody deficiency
  - *X-Linked Agammaglobulinemia*
  - *Common Variable Immunodeficiency (CVID)*
  - *IgG Subclass Deficiency*
  - *Selective IgA Deficiency*
- **3. Phagocyte defects**
  - ***Cyclic neutropenia***
  - ***Chronic Granulomatous Disease (CGD)***
  - ***Leukocyte Adhesion Deficiency (LAD)***
- 4. Genetic disorders with immunodysregulation
  - *X-linked lymphoproliferative syndrome (XLP)*
  - *APECED*
- 5. Defects in congenital immunity; receptors and signal components
  - *Impaired Toll-like receptor signaling*
- 6. Autoinflammatory disorders
- 7 Complement *Deficiency*
  - *Mannan binding lectin Deficiency*
- 8. Other well-defined immunodeficiencies
  - *Wiskott-Aldrich Syndrome*
  - *Ataxia-Telangiectasia*
  - *DiGeorge Syndrome*

V. Congenital defects of phagocyte number, function, or both. a : Neutropenia (without anti-PMN)

Syndrome associated

Shwachman-Diamond syndrome. *SBDS.* *AR.* ***DNAJC21.*** *AR.*
Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia

G6PC3 deficiency (SCN4). *G6PC3.* *AR.* Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected functions: Myeloid differentiation, chemotaxis, O_2^- production.

Glycogen storage disease type 1b. *G6PT1.* *AR.*
Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly.

Cohen syndrome. *COH1.* *AR.* Dysmorphism, mental retardation, obesity, deafness.

Barth Syndrome (3-Methylglutaconic aciduria type II). *TAZ.* *XL.*
Cardiomyopathy, myopathy, growth retardation.

Clericuzio syndrome (Poikiloderma with neutropenia). *C16ORF57* *(USB1). AR.*
Retinopathy, developmental delay, facial dysmorphism, poikiloderma.

VPS45 deficiency (SCN5). *VPS45.* AR.
Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.

P14/LAMTOR2 deficiency. *LAMTOR2.* *AR.*
Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.

JAGN1 deficiency. *JAGN1.* *AR.* Osteopenia. Myeloid maturation arrest.

3-Methylglutaconic aciduria. *CLPB.* *AR.* Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR.

SMARCD2 deficiency. *SMARCD2.* *AR.*
Developmental aberrations, bones defect, myelodysplasia

WDR1 deficiency. *WDR1.* *AR.*
Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia.

HYOU1 deficiency. *HYOU1.* *AR.* Hypoglycemia, inflammatory complications.

No syndrome associated

Elastase deficiency (SCN1). *ELANE.* *AD.*
Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks).

HAX1 deficiency (Kostmann Disease) (SCN3). HAX1. AR. Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia

GFI 1 deficiency (SCN2). *GFI1.* *AD.*
B/T lymphopenia

X-linked neutropenia/ myelodysplasia WAS GOF. *WAS.* Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies .

G-CSF receptor deficiency. *CSF3R.* *AR.*
Stress granulopoiesis disturbed

Neutropenia with combined immune deficiency. *MKL1.* *AR.*
Mild thrombocytopenia. Lymphopenia.

International Union of Immunological Societies (IUIS) classification of PID 2017

V. Congenital defects of phagocyte. b : Functional defects

Syndrome associated

Cystic fibrosis. ***CFTR.*** *AR.*
Pancreatic insufficiency, Respiratory infections, elevated sweat chloride

Papillon-Lefèvre . ***CTSC.***
Periodontitis, palmoplantar hyperkeratosis

Localized juvenile periodontitis . ***FPR1.***
Periodontitis only

β-Actin . ***ACTB***
Mental retardation.

Leukocyte adhesion deficiency.
Skin infections evolve to large ulcers. Leukocytosis with neutrophilia (WBC > 25000)

LAD I . ***ITGB2***
Delayed cord separation with omphalitis+++, no pus formation, lack of inflammation is observed in infection area. Periodontitis leads to early loss of teeth. , CD18 def (CMF) severity of the disease correlates with the degree of deficiency in CD18. (WBC 20,000–150,000 with 60–85 % neutrophils)

LAD II. ***SLC35C1***
Extremely rare. Recurrent infections. Severe growth delay and severe intellectual deficit. Facial dysmorphism (depressed nasal bridge). Severe periodontitis later in life. Bombay blood group. Infections: rarely life threatening. Patients may live to adulthood.

LAD III. ***FERMT3***
Severe bacterial infections and severe bleeding disorder; osteopetrosis (severe cases). Platelet aggregation assay.

No Syndrome associated: DHR assay (or NBT test)?

Normal

GATA2 def (MonoMac sd) .
GATA2, AD.
Susceptibility to Mycocbacteria, Papilloma Viruses, Histoplasmosis, Lymphedema. Pulmonary alveolar proteinosis, myelodysplasia/AML/ CMML . Monocytopenia. Low NK.

Specific granule deficiency.
C/EBPE.
Bilobed nuclei

Pulmonary alveolar proteinosis. ***CSF2RA,*** *AR.*
CSF2RB*, XL.*
Affected cells: Alveolar macrophages. Affected fonction: GM-CSF signaling

Abnormal

CGD.
Early onset of severe and recurrent infections affecting initially the natural barriers of the organism (lungs, lymph nodes, skin), and eventually inner structures (liver, spleen, bones, brain, and +++ hepatic abscess). Autoinflammatory phenotype, IBD

Granulomas obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn's like disease) and perianal disease : up to 30 %

Pathogens : typically catalase positive bacteria (*S. aureus* and gram-negative bacilli, *Aspergillus*, *Candida*); other: *Burkholderia cepacia, Chromobacterium violaceum, Nocardia*, and invasive *Serratia marcescens.* In developing countries, BCG : adverse effects in up to 20 %. Microscopic granulomas.

XL CGD: ***CYBB*** ($gp91^{phox}$)
NCF1 ($p47^{phox}$) , AR
CYBA ($p22^{phox}$), AR
NCF4 ($p40^{phox}$), AR
NCF2 ($p67^{phox}$), AR

Rac 2 def . ***RAC2.***
Poor wound healing. LAD phenotype.

G6PD def Class I. ***G6PD.***
Reduced DHR. Infections.

International Union of Immunological Societies (IUIS) classification of PID 2017

Examples of Immunodeficiency diseases caused by defects in/around phagocytes

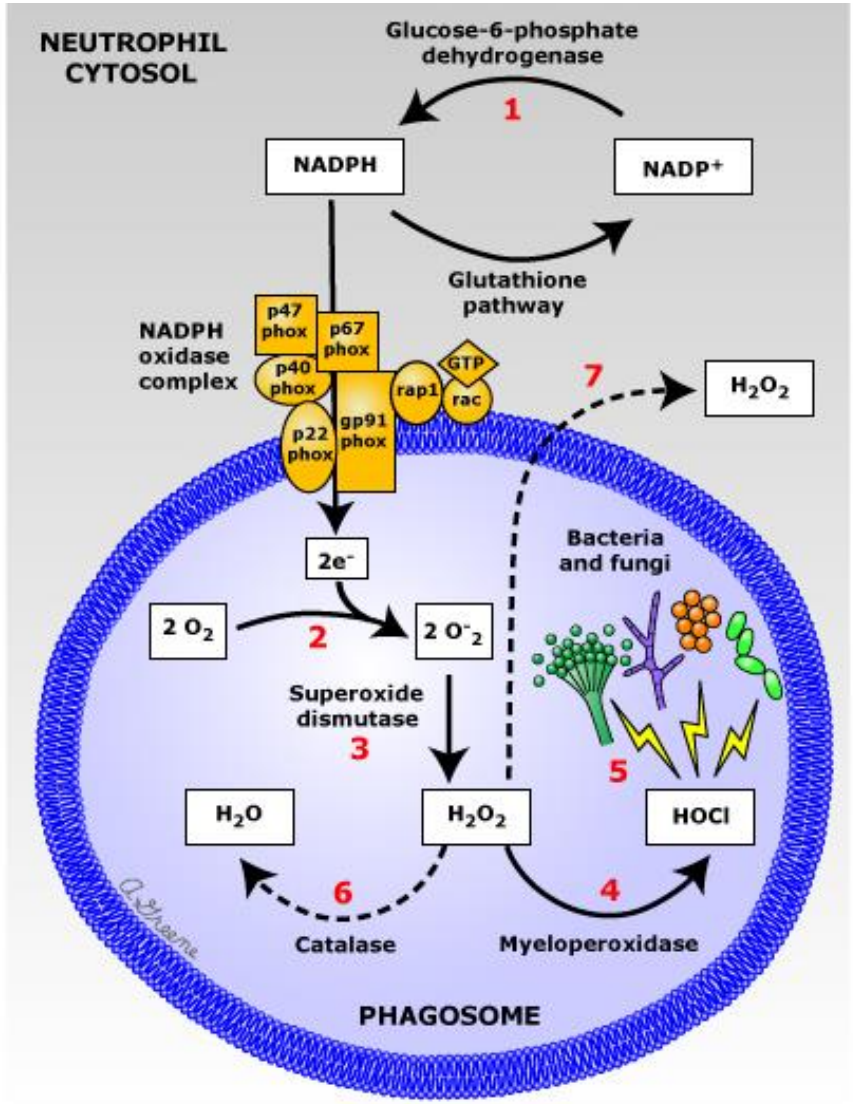
Disease	Molecular on genetic defect	Pathogenic organisms/clinic	Management (apart from ab)
Cyclic neutropenia	Mutation in ELA2, encoding neutrophil elastase	eposidic bacterial infections	G-CSF
Severe congenital neutropenia	Unknown	cellulitis etc ao staphylococcus	G-CSF, BMT
GATA-2	GATA-2 defect	Fungal, bacterial	BMT?
Leukocyte adhesion	CD18…..	G- enteric bacteria/ fungal deficiency	BMT?
Interferon-γ and interleukin-12 defects	Interferon-γ-receptor ligand-binding chain, interferon-γ-receptor signaling chain, interleukin-12-receptor β1	mycobacteria	anti-mycobacterial/iNF-γ?
Hyper IgE syndrome	STAT 3 LOF	staphylococ/ aspergillus/Candida	
CGD	$gp91^{phox}$ (in X-linked) $p47^{phox}$ $p67^{phox}$ $p22^{phox}$	recur. infections, abcesses, granuloma formation	IFN-γ, BMT, gene therapy?
Myeloperoxidase def	Defects in MPO at chromosome 17, q11-21, q22-24, q21.2-23	usually no clinical disease	none

For example; CGD characterized by:

1. **Decreased production of reactive oxygen species**
2. **Disturbed formation of NETs**

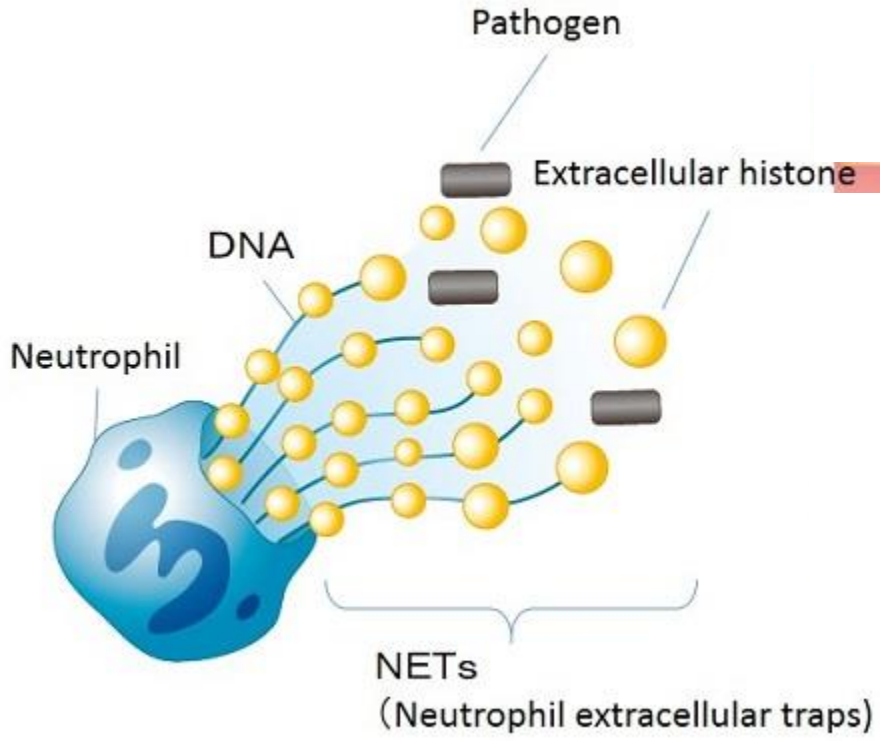
Resulting in decreased microbial killing

Normal NADPH oxidase activation



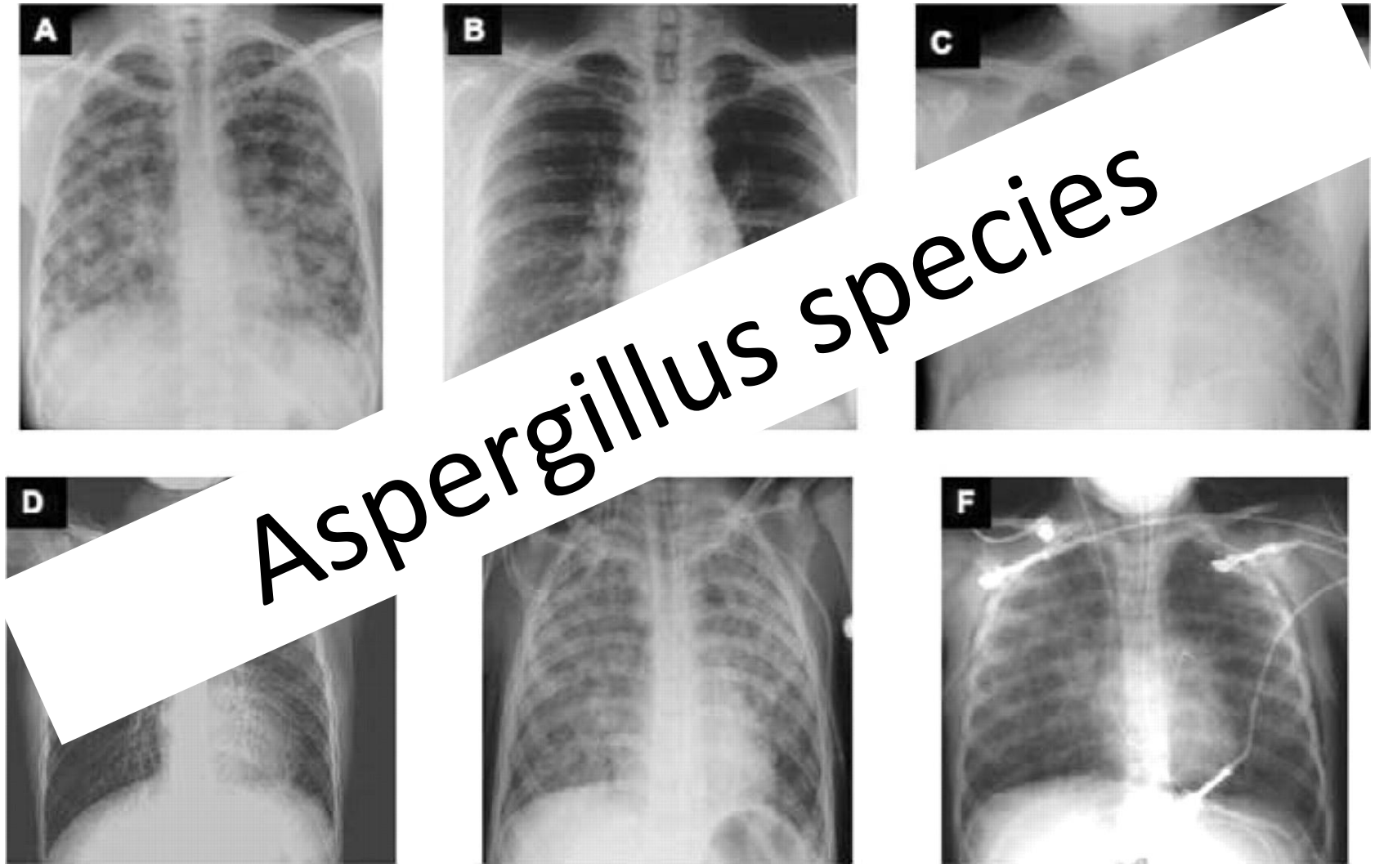
Also disturbed NET formation in CGD

NET formation is NADPH dependent



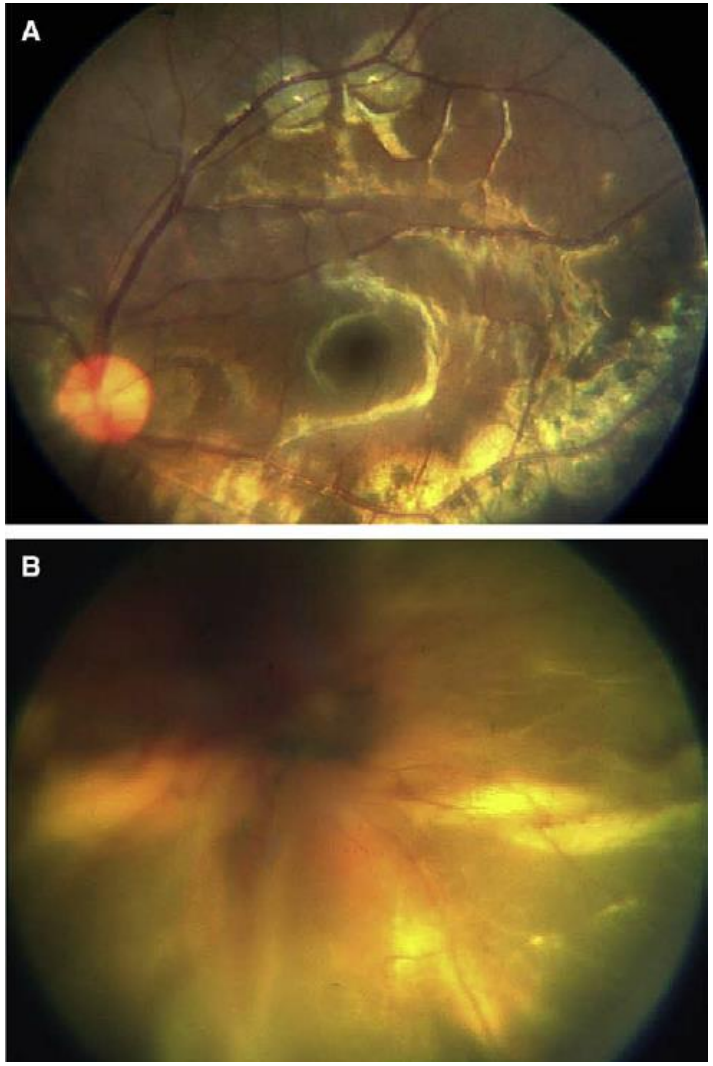
Bianchi M et al. 2011 J Allergy Clin Immunol

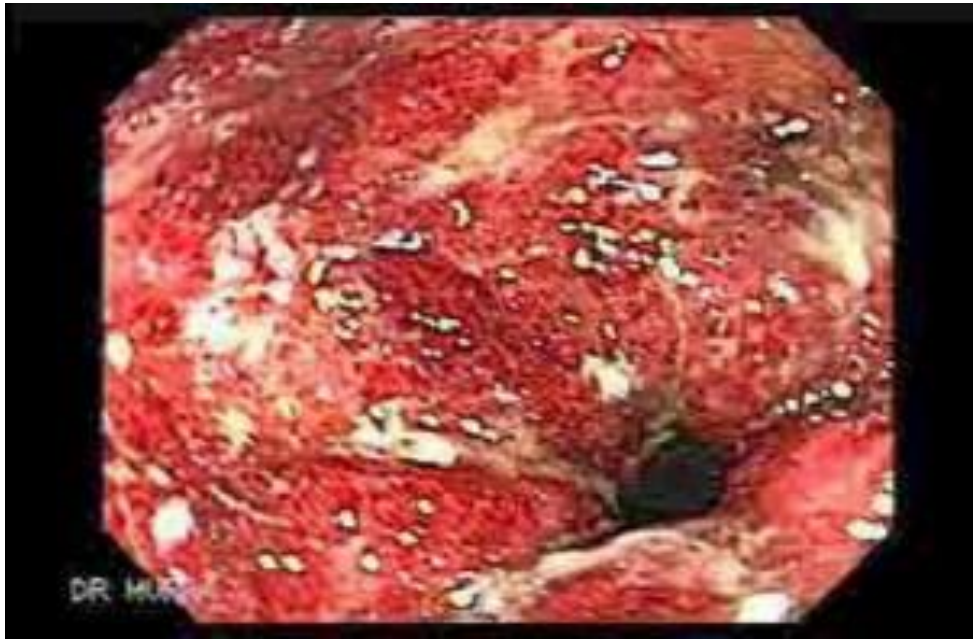
Clinical picture of CGD



Siddiqui S et al. 2007 Clin Infect Dis

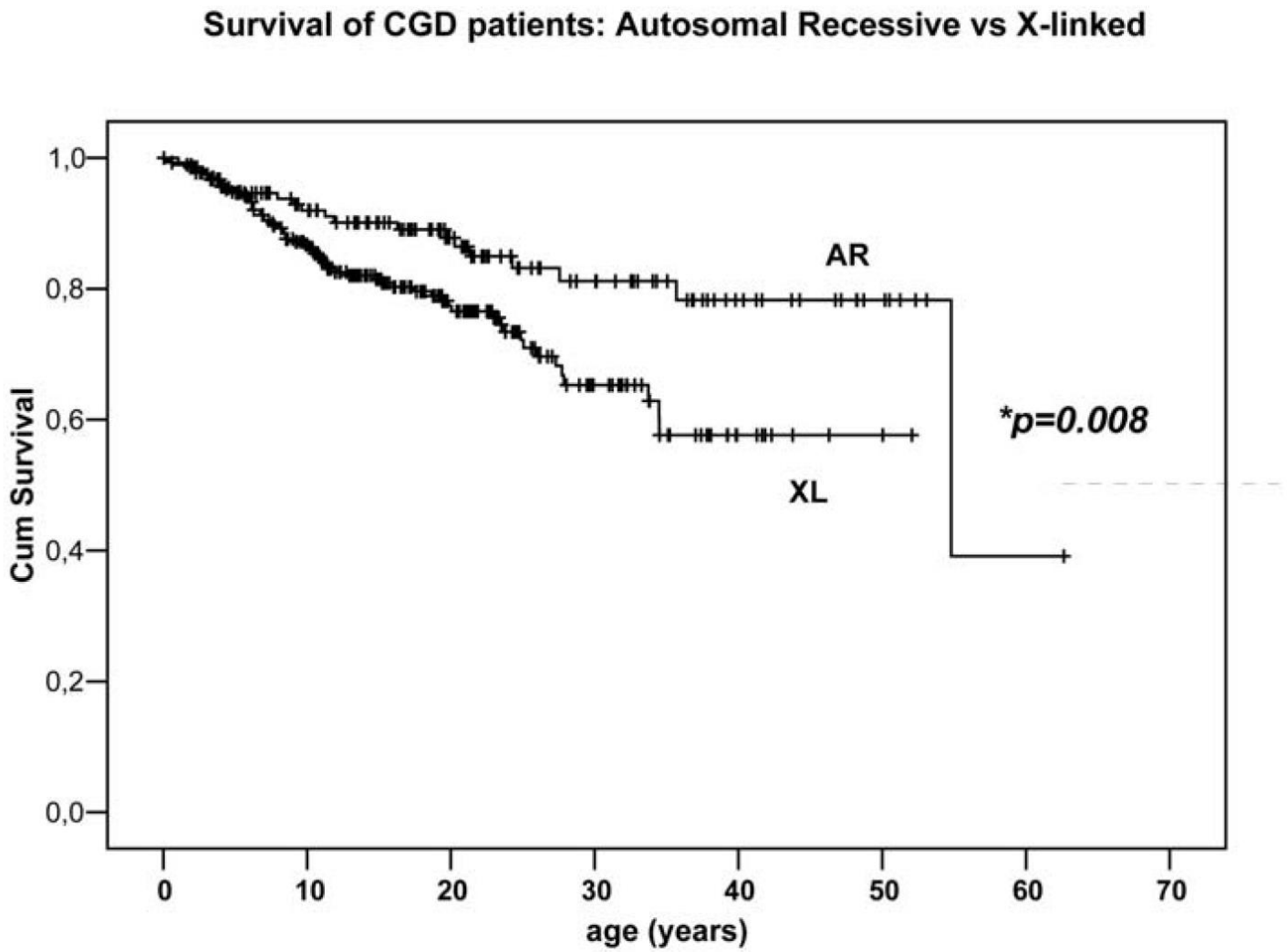
Uncontrolled inflammation





Al-Muhsen S et al. 2009 Journal of AAPOS

Survival in CGD



Van de Berg J et al. 2009 PLoS One

Treatment of CGD

Prophylactic antibiotics and anti-fungal therapy

Treatment of hyperinflammation

Immunosuppressants

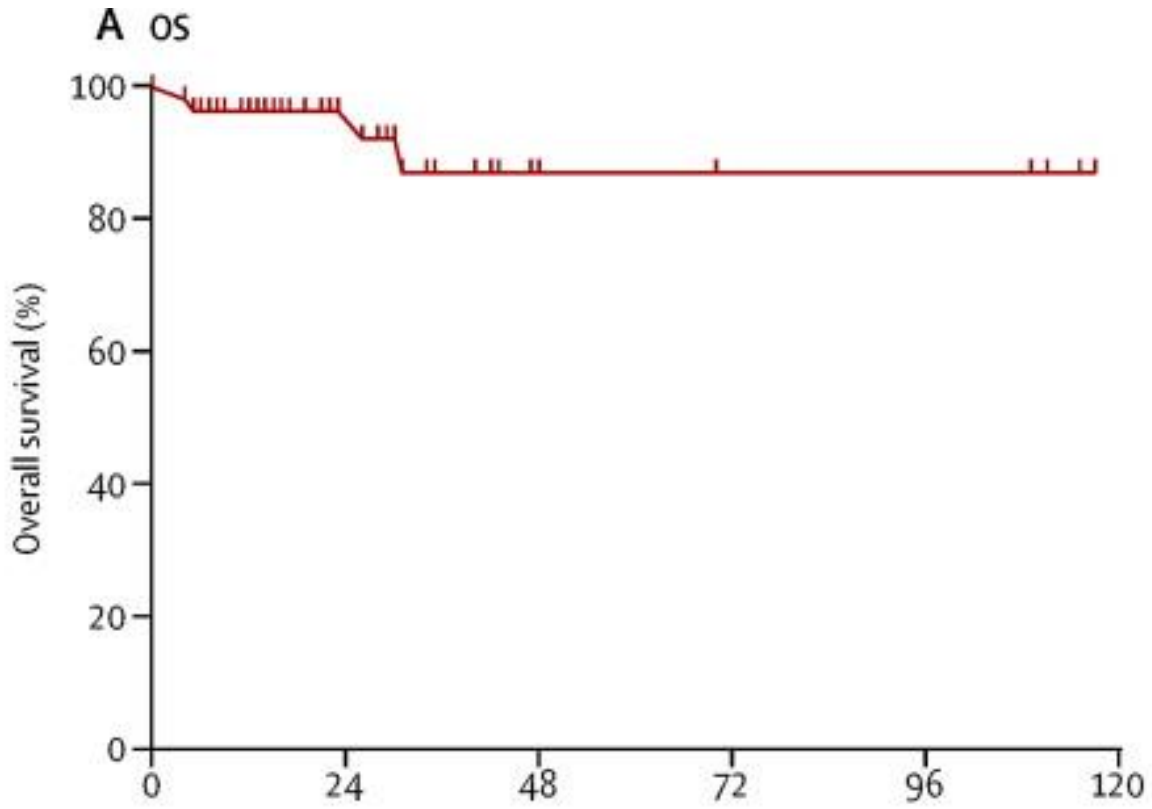
Steroids

Anti-TNF-alpha in IBD-like colitis

Magnani A et al. 2014 JACI

Treatment of CGD : HSCT

Reduced intensity : fludarabine, ATG, busalfan



Gungor T et al. 2014 Lancet

Treatment of CGD : gene therapy

Only short term recovery of NADPH-oxidase activity

Absence of long term engraftment

Development of myeloid dysplasia

Introduction of a lentiviral vector

Kang HJ et al. 2011 Moll Ther
Stein S et al. 2010 Nat Med

Congenital Neutropenia

Defined by the number of neutrophils in blood

Mild	**1.0 – 1.5 x 10^9 / l**
Moderate	**0.5 – 1.0 x 10^9 / l**
Severe	**< 0.5 x 10^9 / l**

Relative monocytosis

Congenital neutropenia

- **Several genetic defects cause neutropenia**

ELANE	**(AD, 50-60% of patients)**
HAX1	**(AR)**
G6PC3	
GFI1	
SBDS	
JAGN1	
Unknown in 30-50% of patients	

- **Increased apoptosis of myeloid cells**

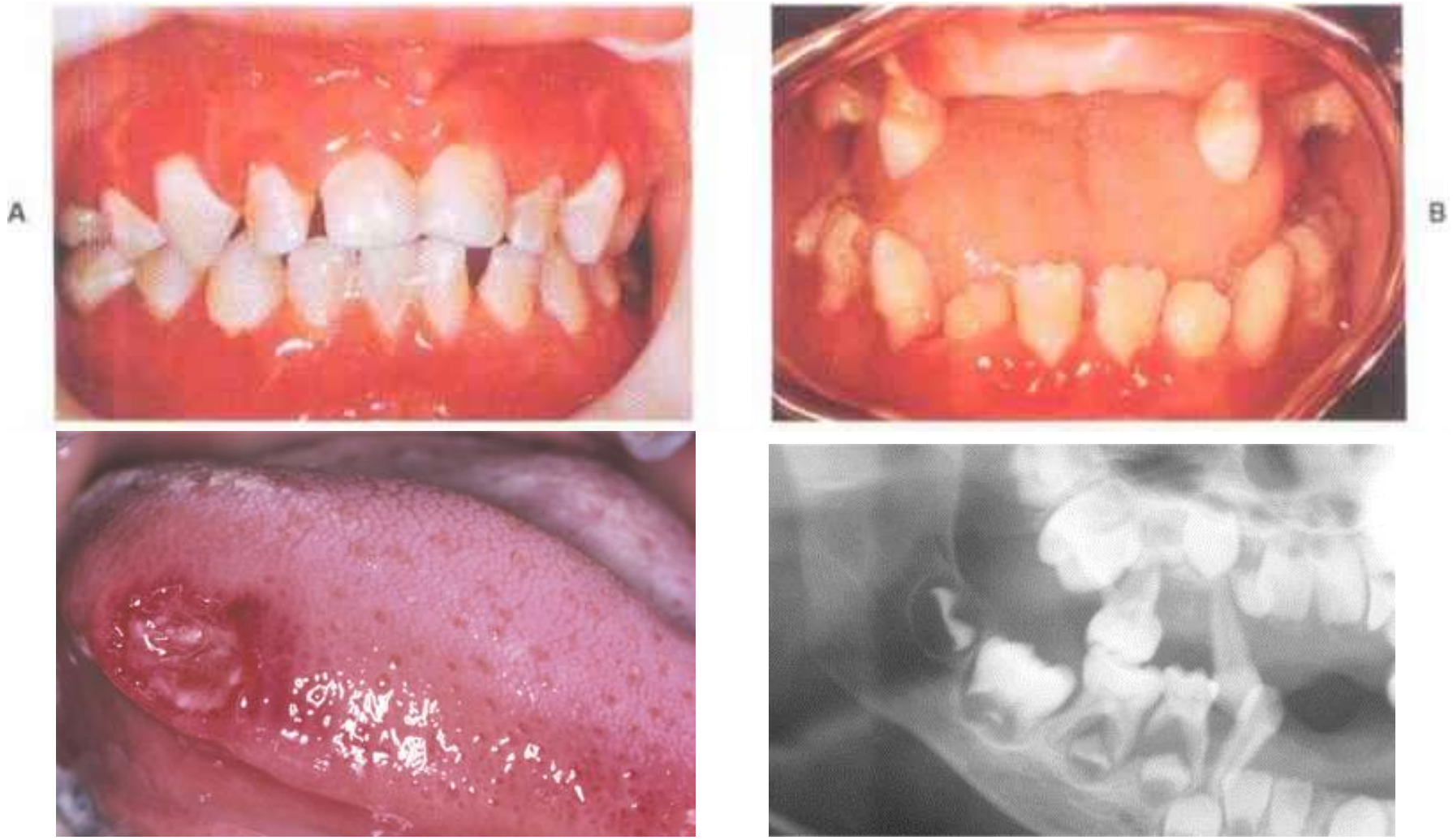
Congenital neutropenia

Clinical features include:

- **Oropharyngeal problems**
- **Otitis media**
- **Respiratory tract infections**
- **Skin infections**

Donadieu J et al. 2013 Hematol Oncol Clin North Am

Gingivitis, ulcers and premature bone loss



Congenital neutropenia

Acute and life-threatening invasive bacterial and fungal infections

Staph. Aureus

Streptococcal infections

ELANE mutations

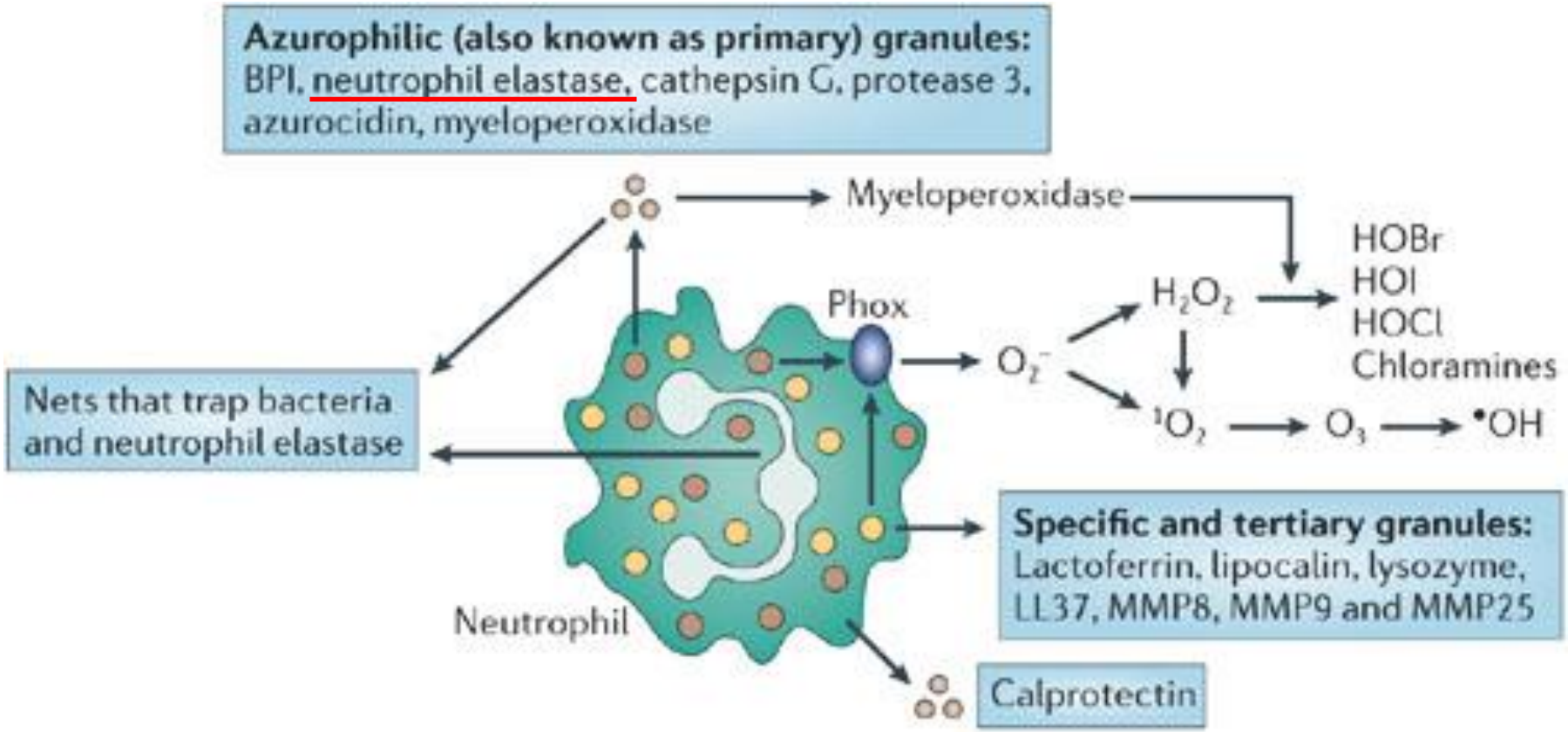
Most common

Gives rise to both:

severe congenital neutropenia

cyclic neutropenia

ELANE mutations



Nature Reviews | Immunology

Neutrophil elastase

Major component of neutrophil granules

Targets bacterial virulence factors

Processes cytokines; chemokines, G-CSF, G-CSFR

Involved in bacterial killing, signalling and homeostatic circuits

Hauck F et al. 2013 Curr Opin Allergy Clin Immunol

ELANE mutations

Molecular Pathogenesis of SCN associated with ELANE mutations

Working hypothesis:

ELANE mutations lead to the production of misfolded neutrophil elastase, induction of the unfolded protein response, and the subsequent apoptosis of granulocytic precursors resulting in neutropenia

ELANE mutations

p.G815R mutation – G-CSF refractory neutropenia

Frequent progression to hematological malignancy

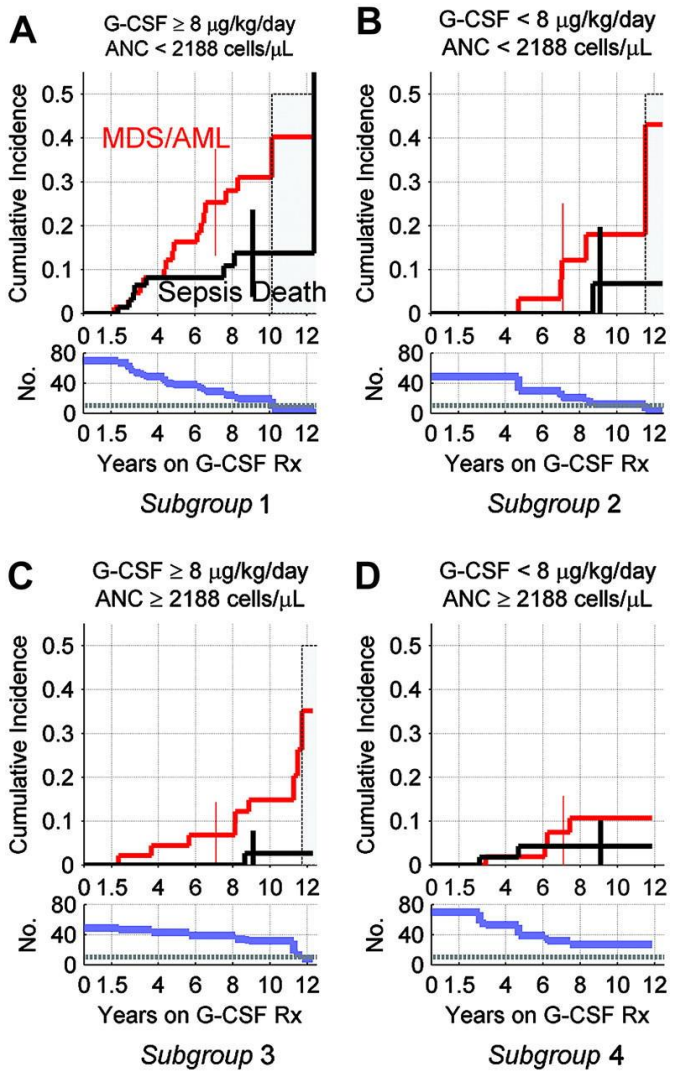
Hporwitz MS et al. 2013 Hematol Oncol Clin North Am

Treatment

G-CSF

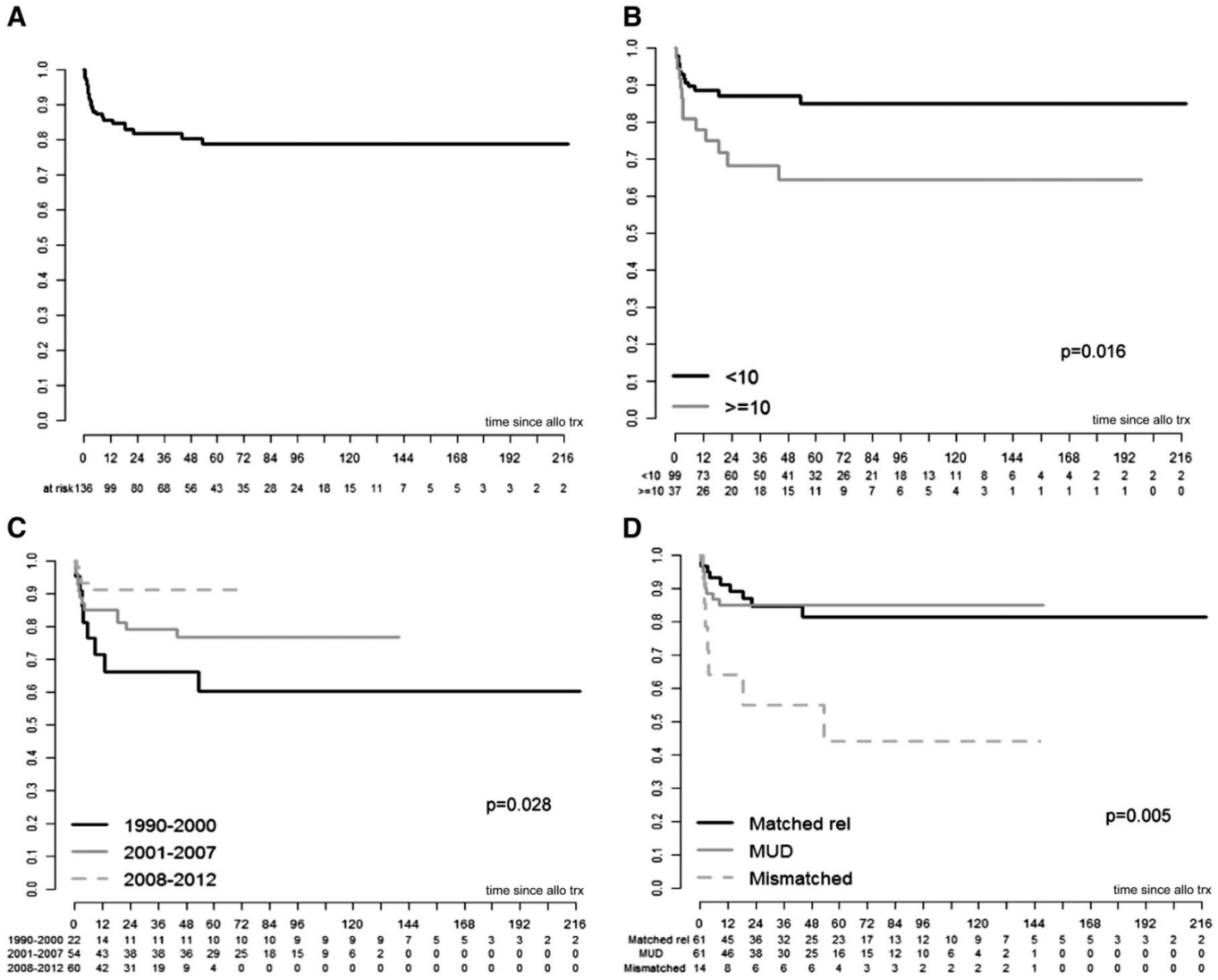
Increased risk of hematological malignancies

Risk of malignant evolution



Rosenberg PS et al. 2006 Blood

Treatment : HSCT



Fioredda F et al. 2015 Blood

Benign Ethnic Neutropenia

- Overall WBC and ANC vary by ethnic group
  - African Americans tend to run lower compared to causcasians
  - ANC of 1100 may not be abnormal for some patients

- Slightly low ANC without any signficant infectious history may not require any further work up!

Infection risk by type of neutropenia

Relation of non-chemotherapy-related neutropenia and infection risk

Inadequate bone marrow reserve; G-CSF

- G-CSF; recurrent infections or oral ulcers related to the neutropenie
- Acute administration of G-CSF is indicated;
- Severe congenital neutropenia
  - Cyclic neutropenia
  - Neutropenia associated with early myeloid arrest
  - Acquired immune deficiency syndrome (AIDS)
  - Acquired bone marrow defects with severe neutropenia (ie, ANC <500 cells/microL)
  - Chronic idiopathic neutropenia with severe neutropenia
  - Drug-induced neutropenia/agranulocytosis with severe neutropenia

UptoDate 2019

Quality versus quantity

- Neutrophil dysfunction results in life-threatening infections, early in life
- Specific pathogens
- Sites of infection
- Functional or quantative assays
- Genetic screening for confirmation of diagnosis
- HSCT therapy of choice when available and early

Severe neutropenia management

- Neutropenic patients are unable to mount robust inflammatory responses, serious infection can occur with minimal symptoms and signs

- In such patients, fever is often the only sign of infection

Antibiotics

- Immunocompromised individuals do not clear infections or respond to anti-infective therapy as well as immunocompetent individuals
- Optimal duration of antimicrobial treatment of immunodeficient patients has not been defined
- Experienced clinical immunologists often prescribe courses of antimicrobials that are two to three times longer than standard recommendations

The choice and dose of prophylactic antibiotic in PID

Depends on the type of PID

- the presence of complications such as lung, sinus or ear disease
- information from previous laboratory tests
- local guidelines on antibiotic use
- Patient-specific concerns, such as dosing intervals and previous side effects

Antibiotics in PID

• There is no standardized approach to the use of prophylactic antimicrobials in patients with an immunodeficiency!!

•Studies of the efficacy of prophylaxis in specific immune disorders are lacking, with a few notable exceptions (eg, chronic granulomatous disease)

•Approximately 75 percent of practitioners administered prophylactic antibiotics to at least some of their immunodeficiency patients

•Antibiotic prophylaxis is most consistently offered to patients with mild hypogammaglobulinemia, IgA deficiency, or IgG subclass deficiency, who are not receiving immunoglobulin

UptoDate 2016

Side effects of antimicrobial therapie

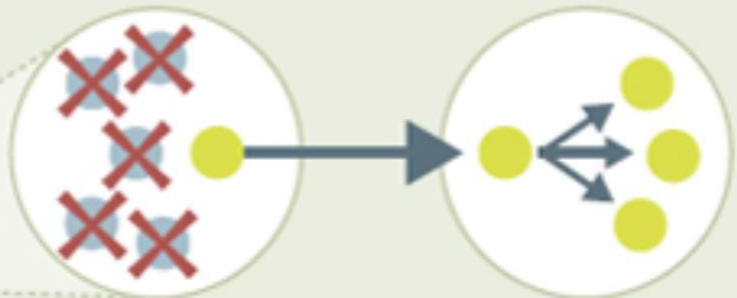
- Skin: allergy
- Central nervous system: insults
- Blood: leuco- en thromcytobopenia
- Gastro-intestinal toxicity: diarhroea
  direct: clavulanic acid, indirect: change gut flora
- Renal toxicity: renal failure
- Ototoxicity (nervus VIII): hearing loss, also vertigo
- Liver toxicity: icterus and liver failure

ANTIBIOTIC RESISTANCE

from the farm to the table

RESISTANCE All animals carry **bacteria** in their intestines

Antibiotics are given to animals



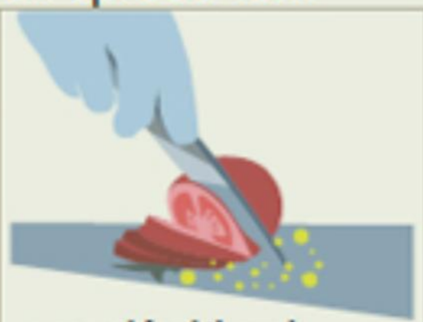
Antibiotics kill most bacteria

But resistant bacteria survive and multiply

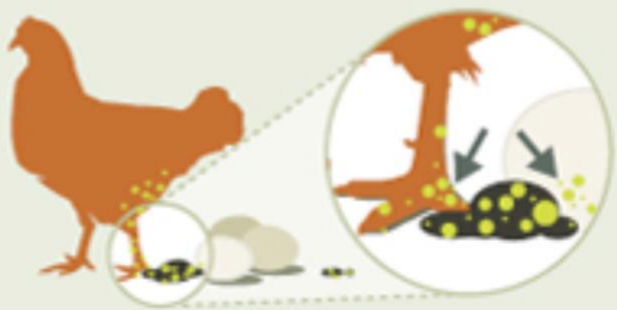
SPREAD Resistant bacteria can spread to...

animal products

produce through contaminated water or soil



prepared food through contaminated surfaces



the environment when animals poop

Conclusions

non-chemotherapy neutropenia

- Rx of neutropenia or neutrophil dysfunction depends on the underlying cause
- Neutropenia has a broad etiology, which needs to be diagnosed
- Because of the heterogenity there is no general approach
- All patients should be counseled regarding to their infectious risk
- Bone marrow neutrophil reserve; examination of a bone marrow aspirate and biopsy, inadequate bone marrow reserve may benefit from G-CSF therapy
- Patients with non-chemotherapy-induced neutropenia have variable risk of infection, ranging from life-threatening sepsis to chronic or no infections

Immunodeficiency Centre Rotterdam

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