

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

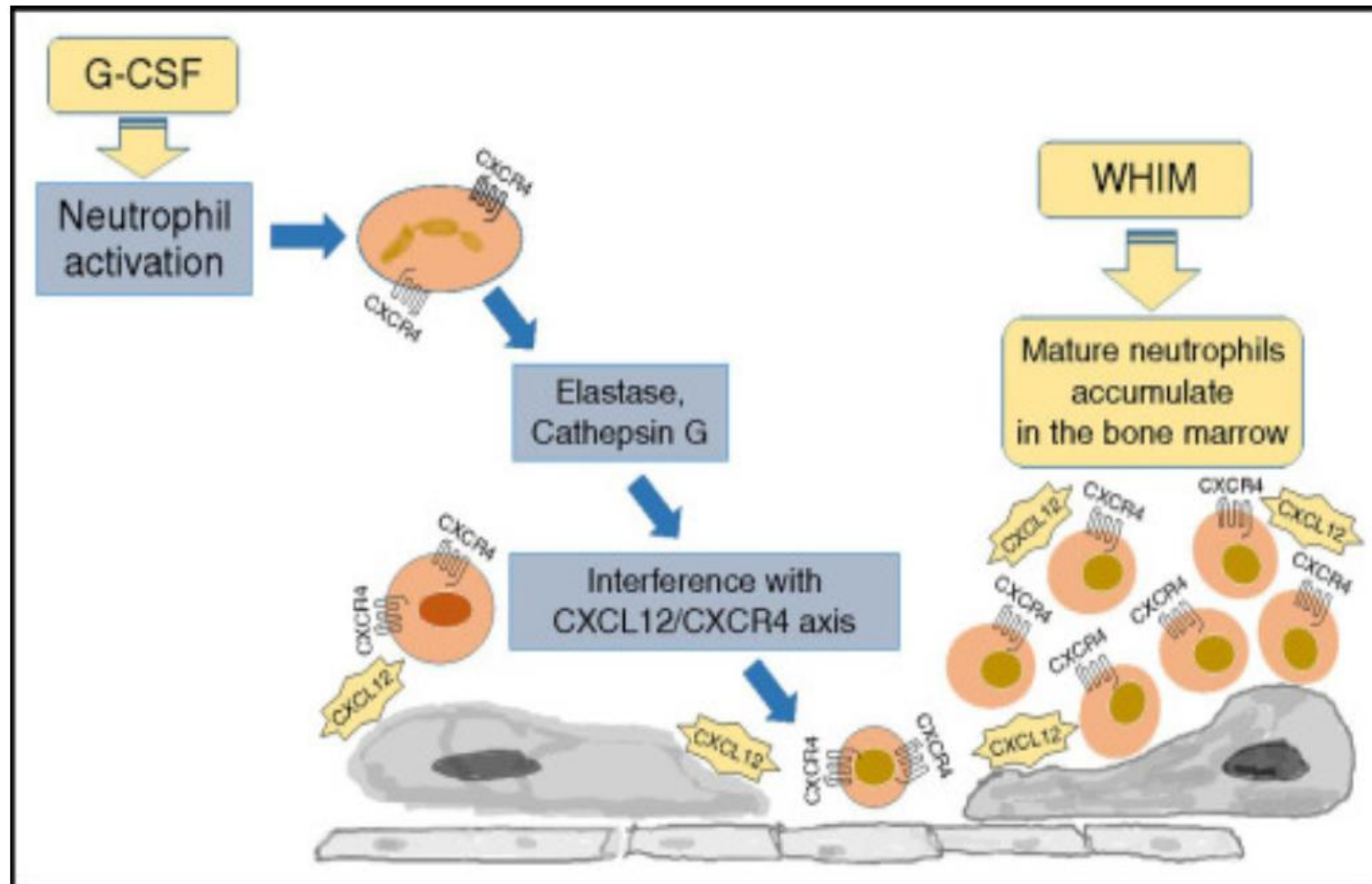
*In the Name of God  
the Compassionate The Merciful*

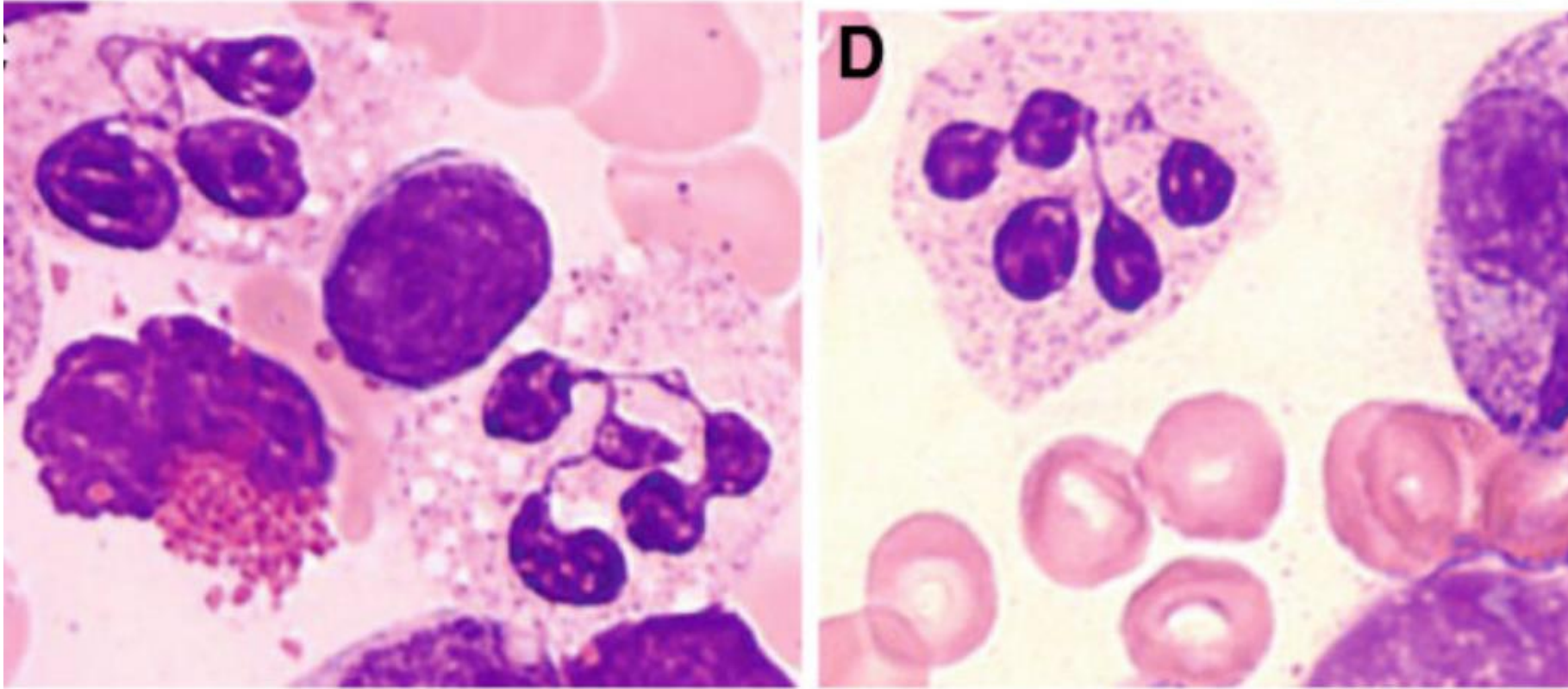
# Primary disorders of neutrophil dysfunction

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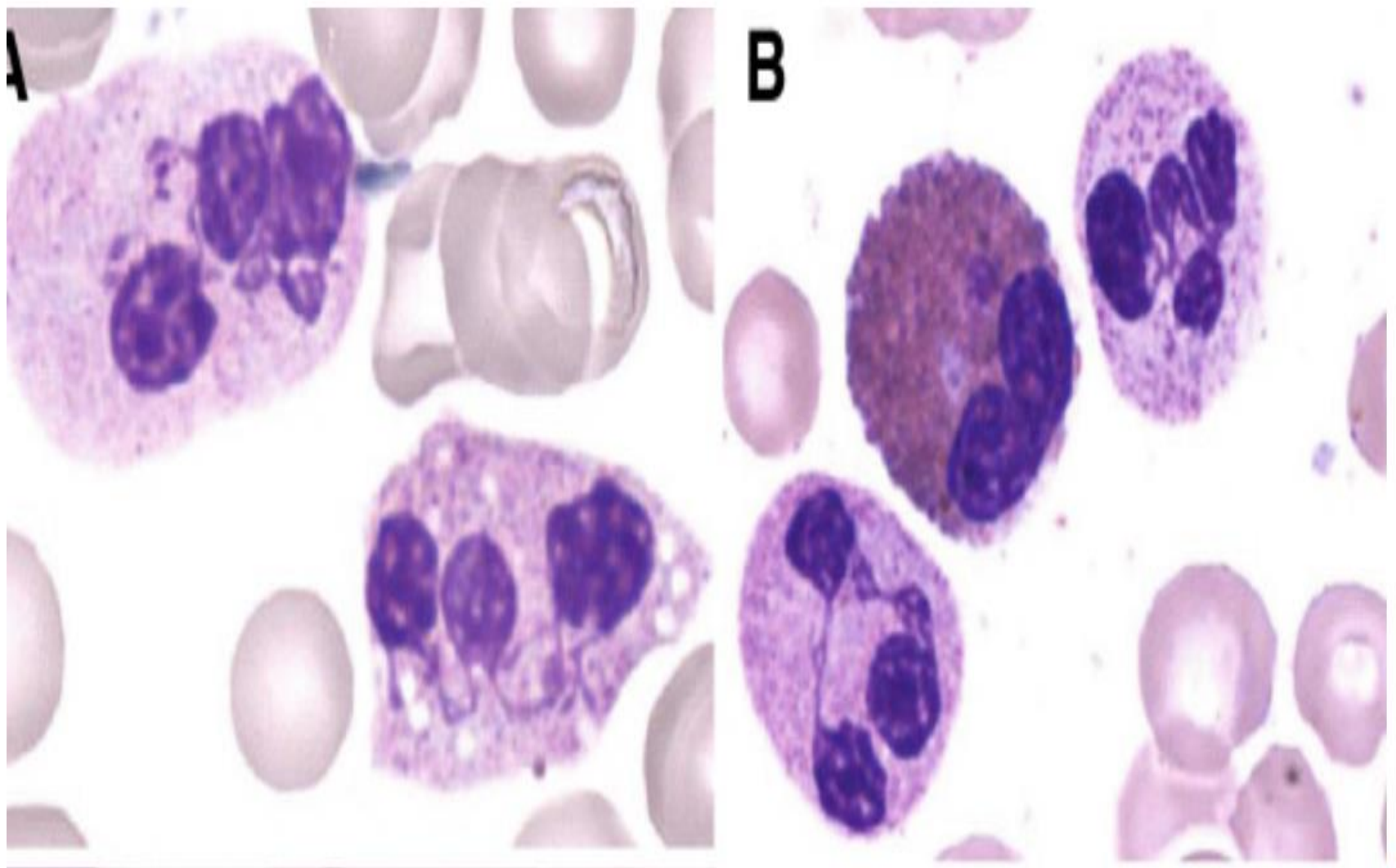
## WHIM (Warts, Hypogammaglobulinemia Infections, Myelokathexis syndrome)

- ▶ - 0.23 cases per million live births
- ▶ - Autosomal dominant
- ▶ - Pathogenic variant in CXCR4





narrow smears from four patients with myelokathexis, revealing over 50% of neutrophils with normal nuclei encompassing 3 to 5 lobes connected by long thin chromatin filaments, less than 10% vacuolated mature neutrophils visible on images A and C. (May-Grunwald-Giemsa stain; original magnification x 1000). A, patient UPN 5780; B, patient UPN 5446; C,



## Clinical Presentation

- ▶ - Severe neutropenia
- ▶ - Recurrent bacterial infections
- ▶ - HPV skin infections (Squamous Cell Cancers)
- ▶ - Tetralogy of Fallot (10%)

## Management and Treatment

- HPV Vaccination
- IV IG
- Prophylactic Clotrimazole or Azithromycin
- Gcsf
- CXCR4 receptor antagonists

## Leukocyte adhesion defect (LAD)

- ▶ - 1 per million live births
- ▶ - Autosomal recessive
- ▶ - Defective CD18

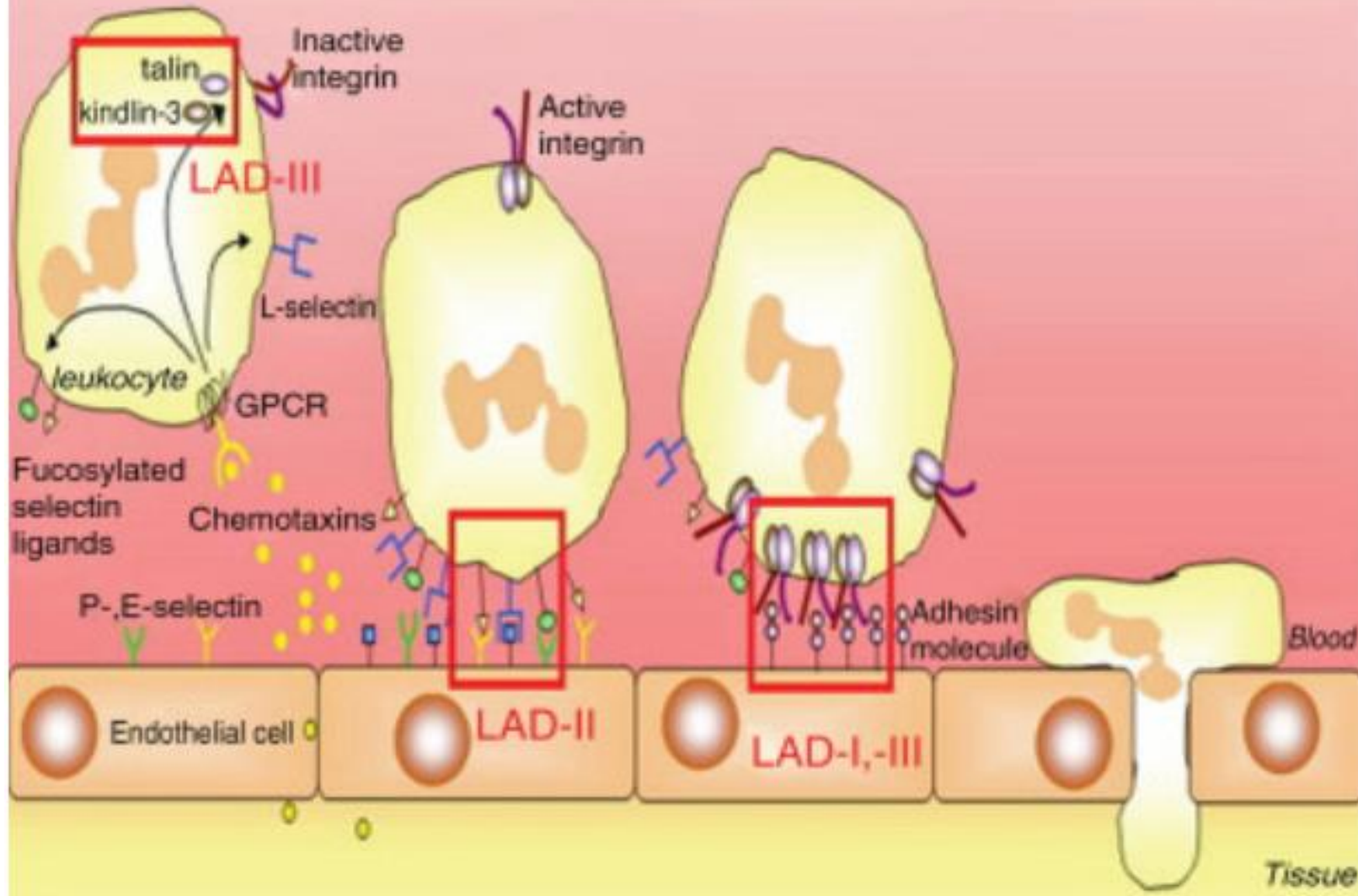
Table 1.

Leukocyte Adhesion Deficiencies Syndrome

	Discovered	Frequency	Mutated Molecules	Molecular Defect	Major Defect in
LAD-I (3)	1980	Rare (~300 cases)	CD18 (integrin $\beta_2$ )	Reduced or altered expression of CD18	Neutrophils
LAD-II (6)	1992	Very rare (11 cases)	GFTP	No functional selectin ligands	Neutrophils
LAD-III (8)	1997	Rare (27 cases)	Kindlin-3	Impaired $\beta_2$ and $\beta_3$ integrin activation	Neutrophils, platelets
LAD-IV	2015	Common (~70,000 cases; ~1,000 cases/yr)	CFTR	Impaired $\alpha_4$ and $\beta_2$ integrin activation	Monocytes

Definition of abbreviations: CFTR = cystic fibrosis transmembrane conductance regulator; GFTP = GDP-fucose transporter 1; LAD = leukocyte adhesion deficiencies.

Recruitment → rolling → firm adhesion → extravasation



## Clinical Presentation

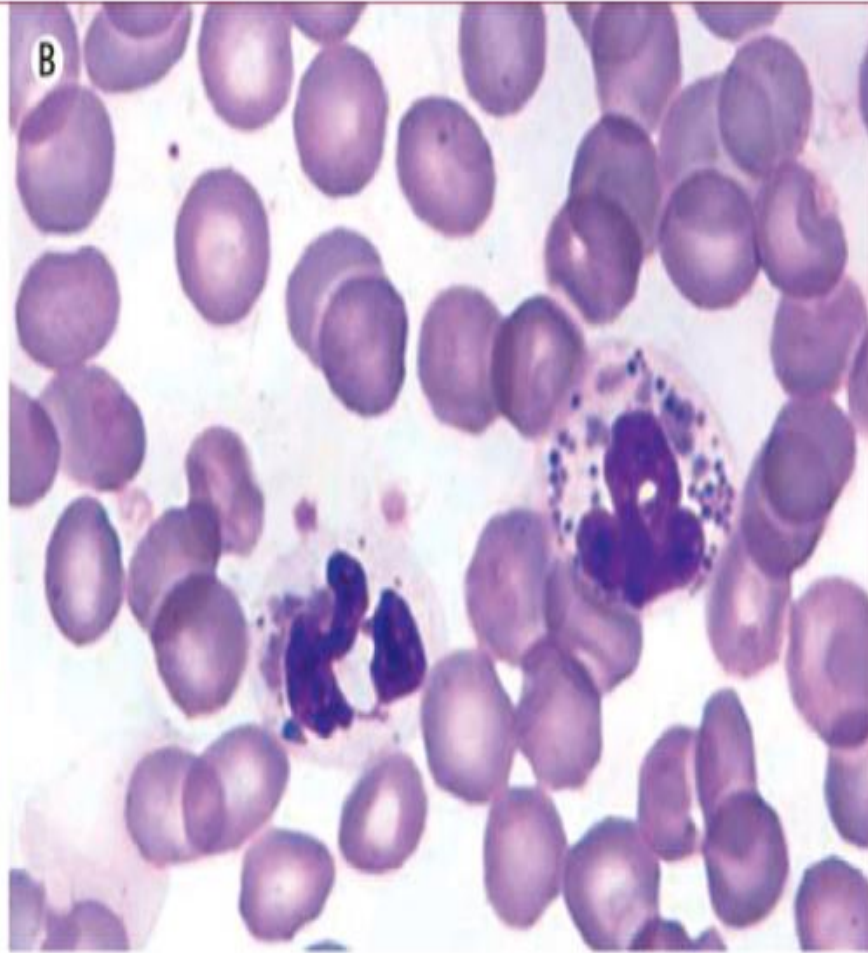
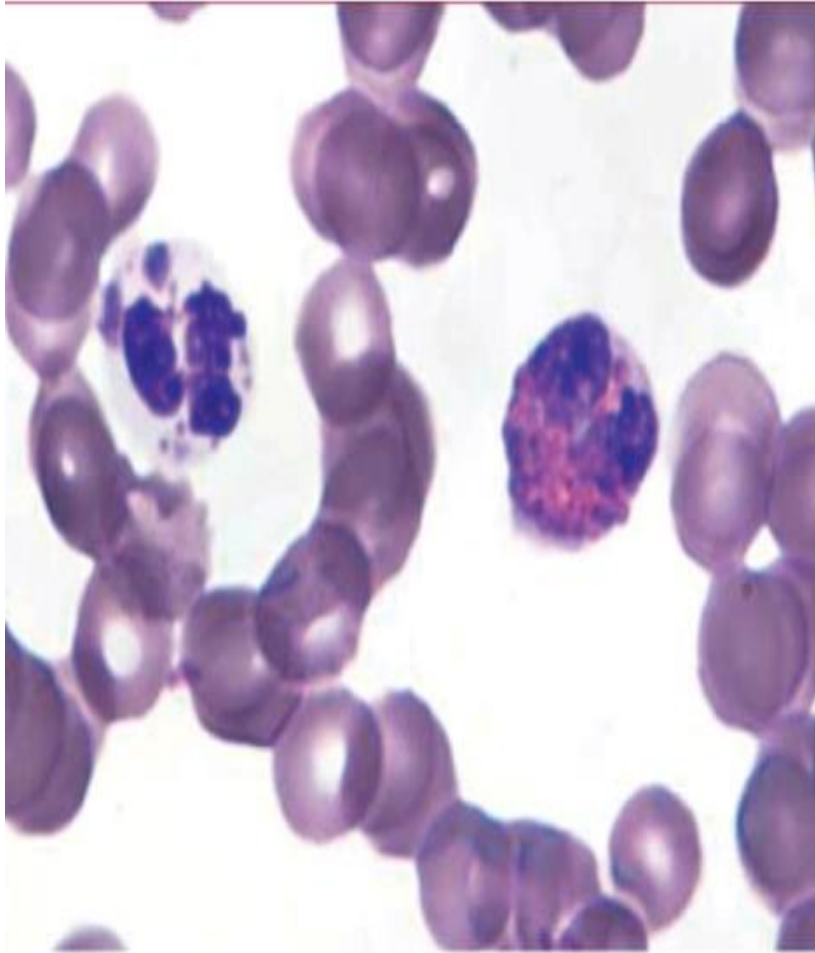
- ▶ - Omphalitis and / or delayed umbilical cord detachment
- ▶ - Gingivitis and periodontal disease
- ▶ - Nonhealing ulcers
- ▶ - Basal neutrophilia with absence of pus
- ▶ - Leukocytosis  $> 100000 / \mu\text{l}$  with infections

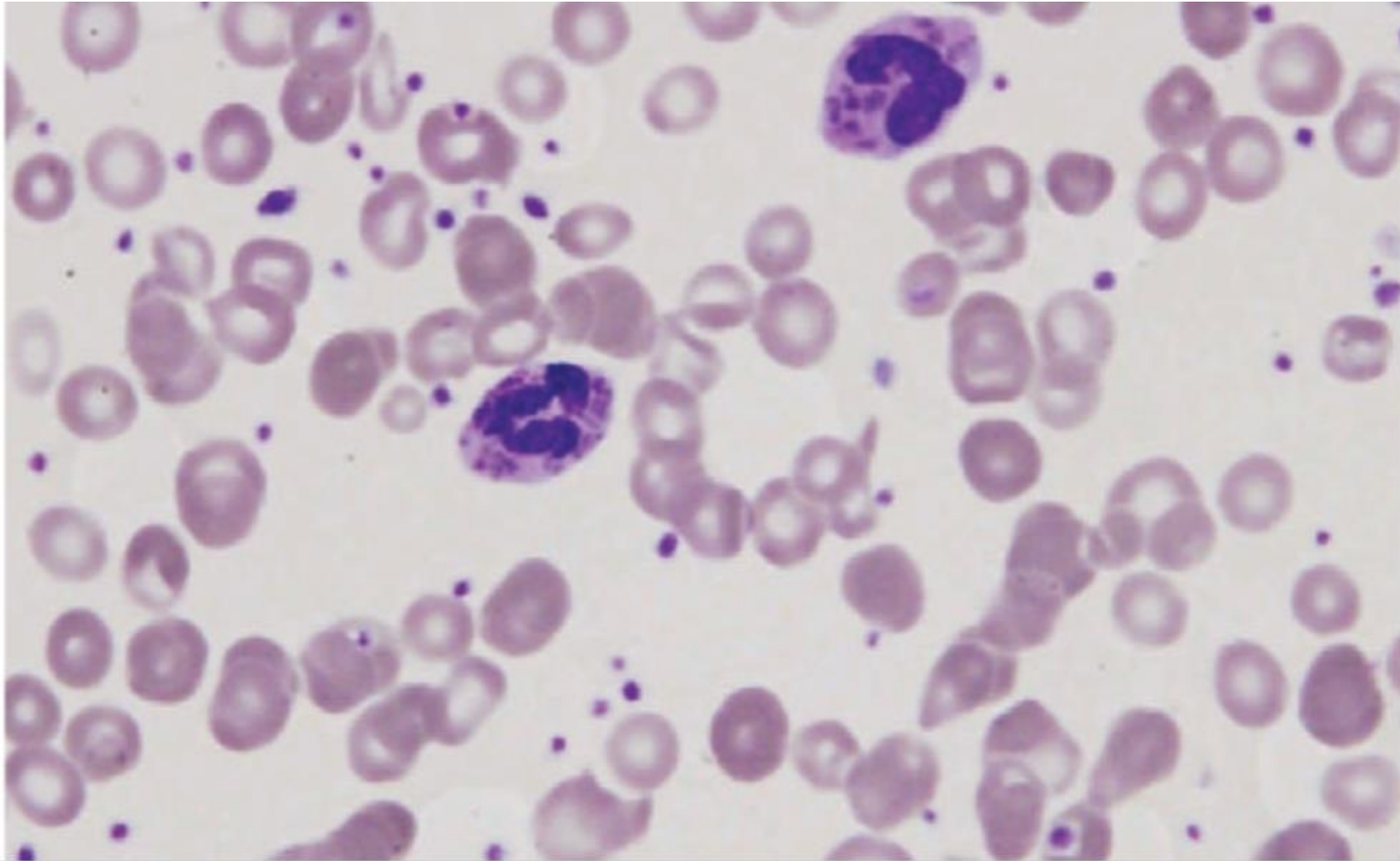
## Management and Treatment

- ▶ - Early vaccination against HPV
- ▶ - Encourage oral hygiene
- ▶ - Ustekinumab (monoclonal Ab) for periodontitis
- ▶ - Prophylactic antimicrobials
- ▶ - HSCT for severe disease

## (CHS) chediak - Higashi Syndrome

- ▶ - Fewer than 500 cases worldwide
- ▶ - Autosomal recessive
- ▶ - Abnormal organelle protein trafficking
- ▶ - Neutropenia and impaired bactericidal activity
- ▶ - Giant Azurophilic granules in neutrophils
- ▶ - Abnormal plt aggregation





## Clinical Presentation

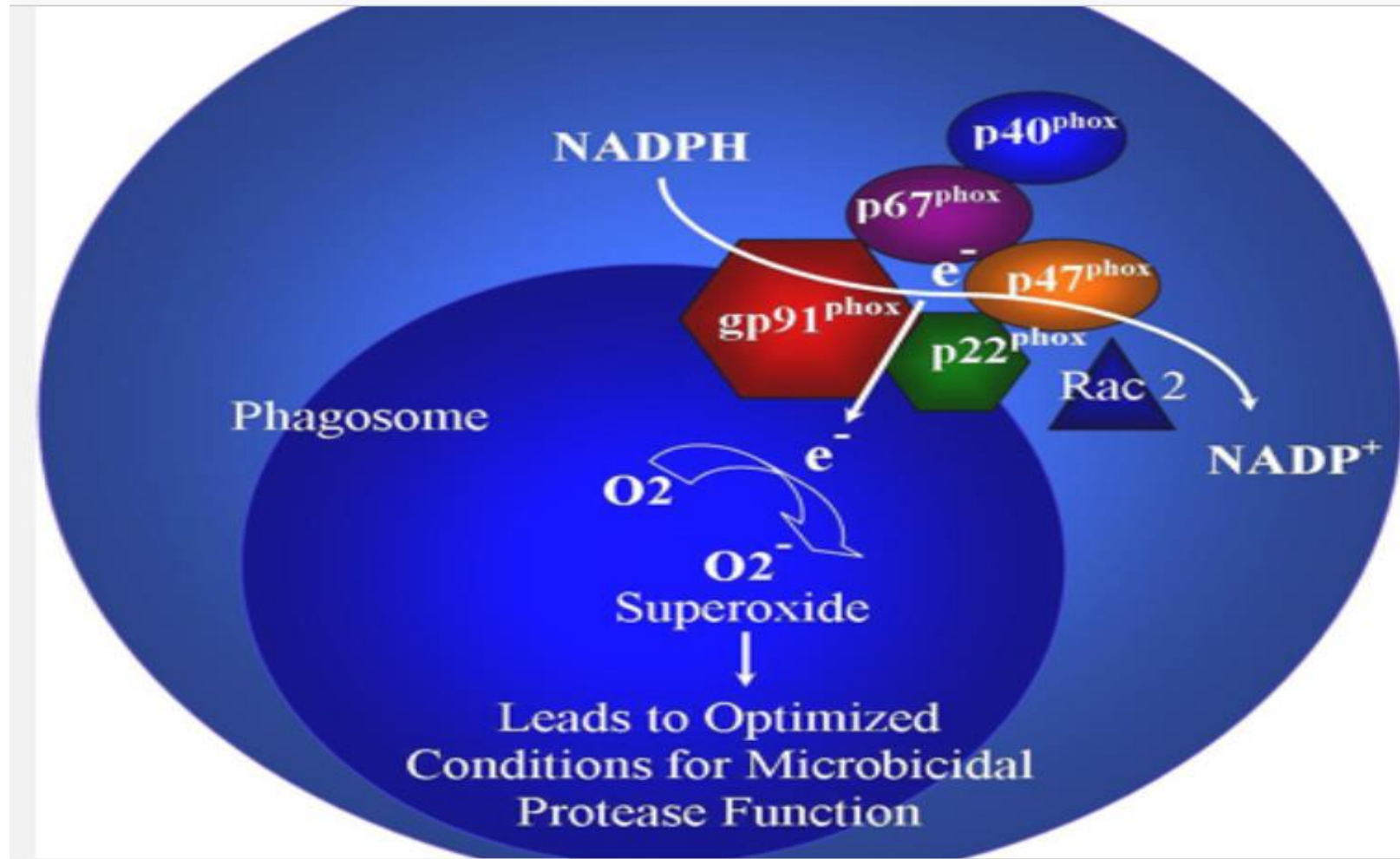
- ▶ - Variable oculocutaneous albinism
- ▶ - Progressive neurologic deterioration

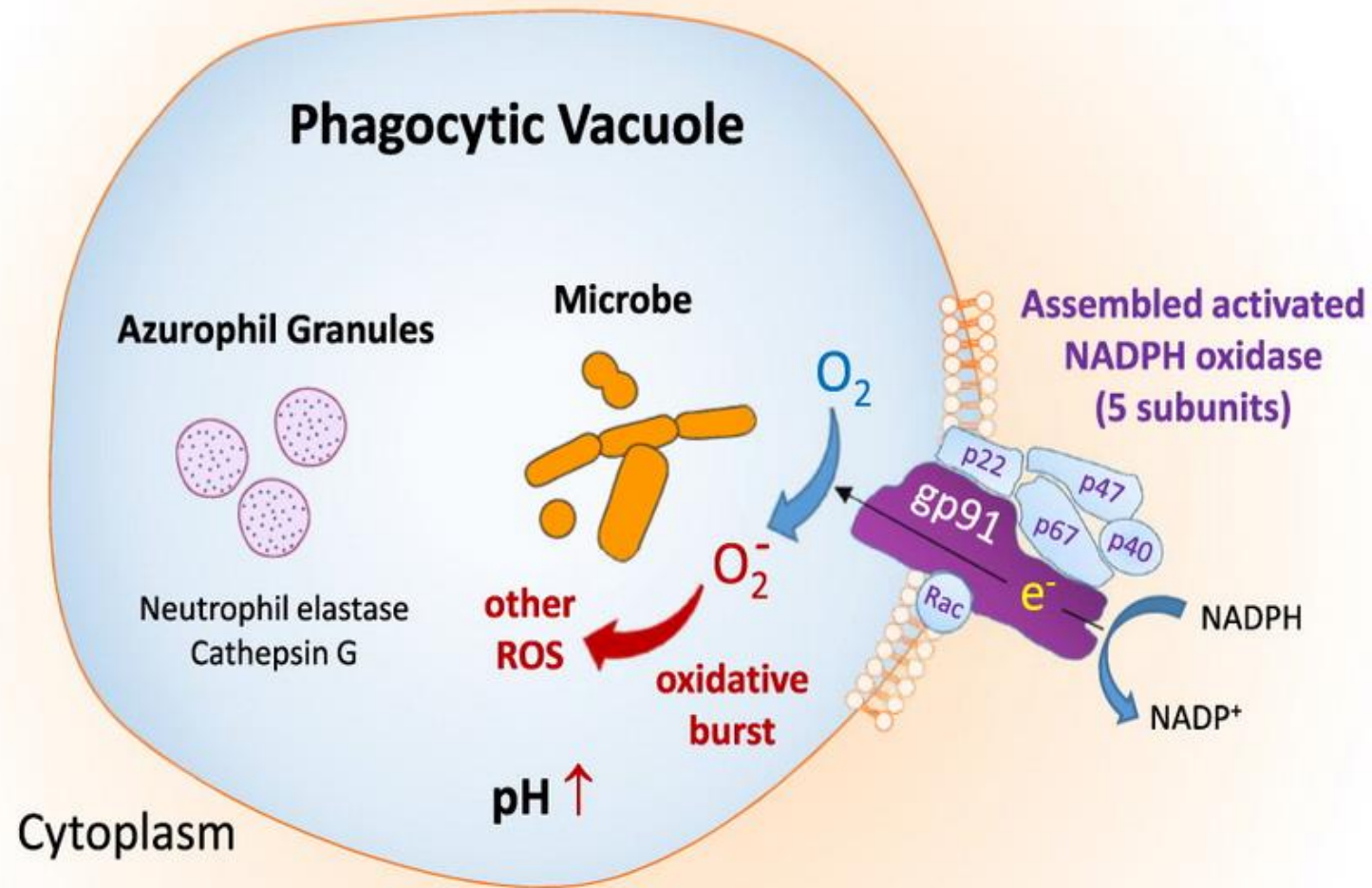
## Management and Treatment

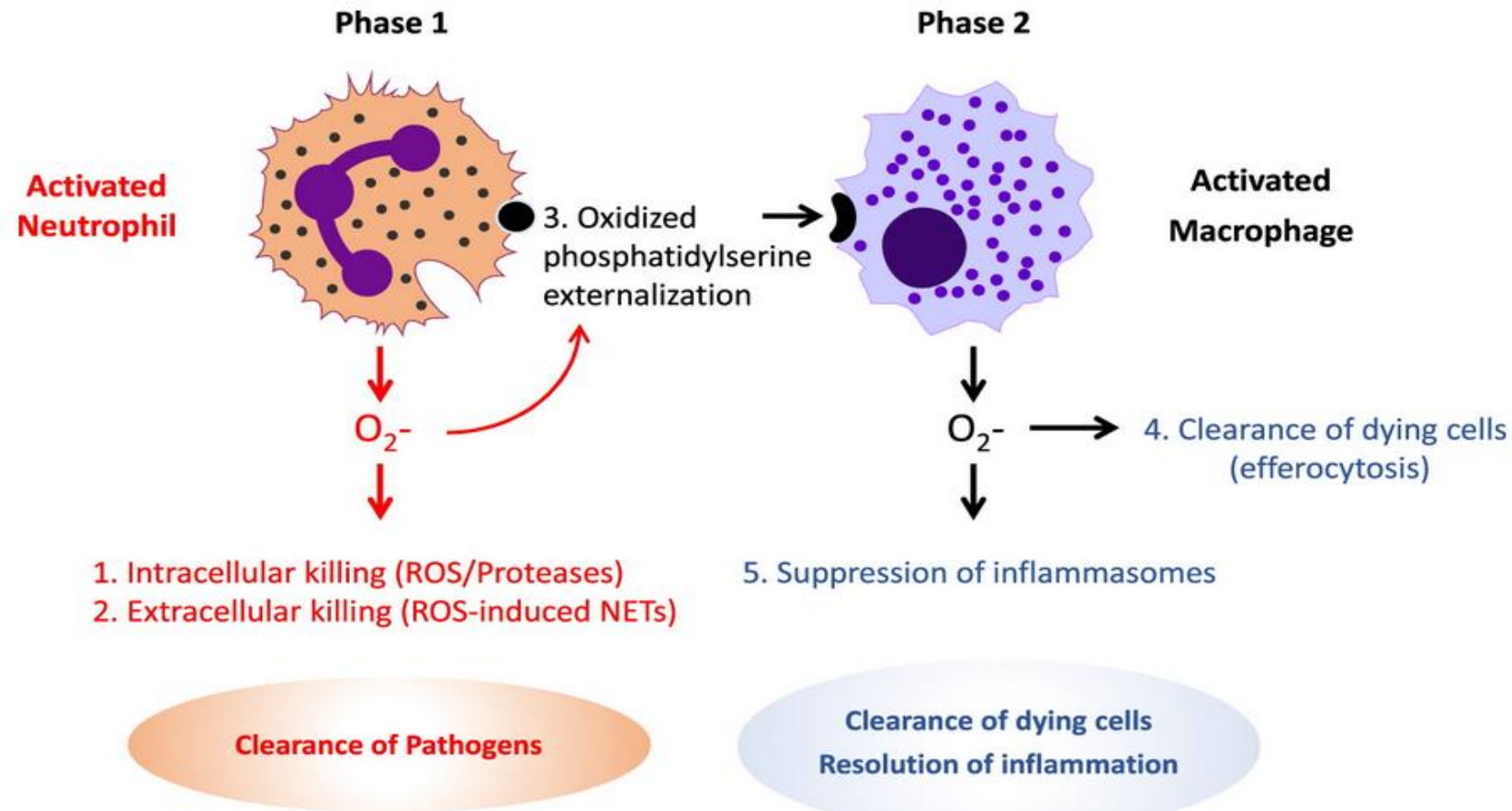
- ▶ - HSCT
- ▶ - Supportive care (antimicrobials - Gcsf)
- ▶ - Standard HLH therapy (accelerated phase)

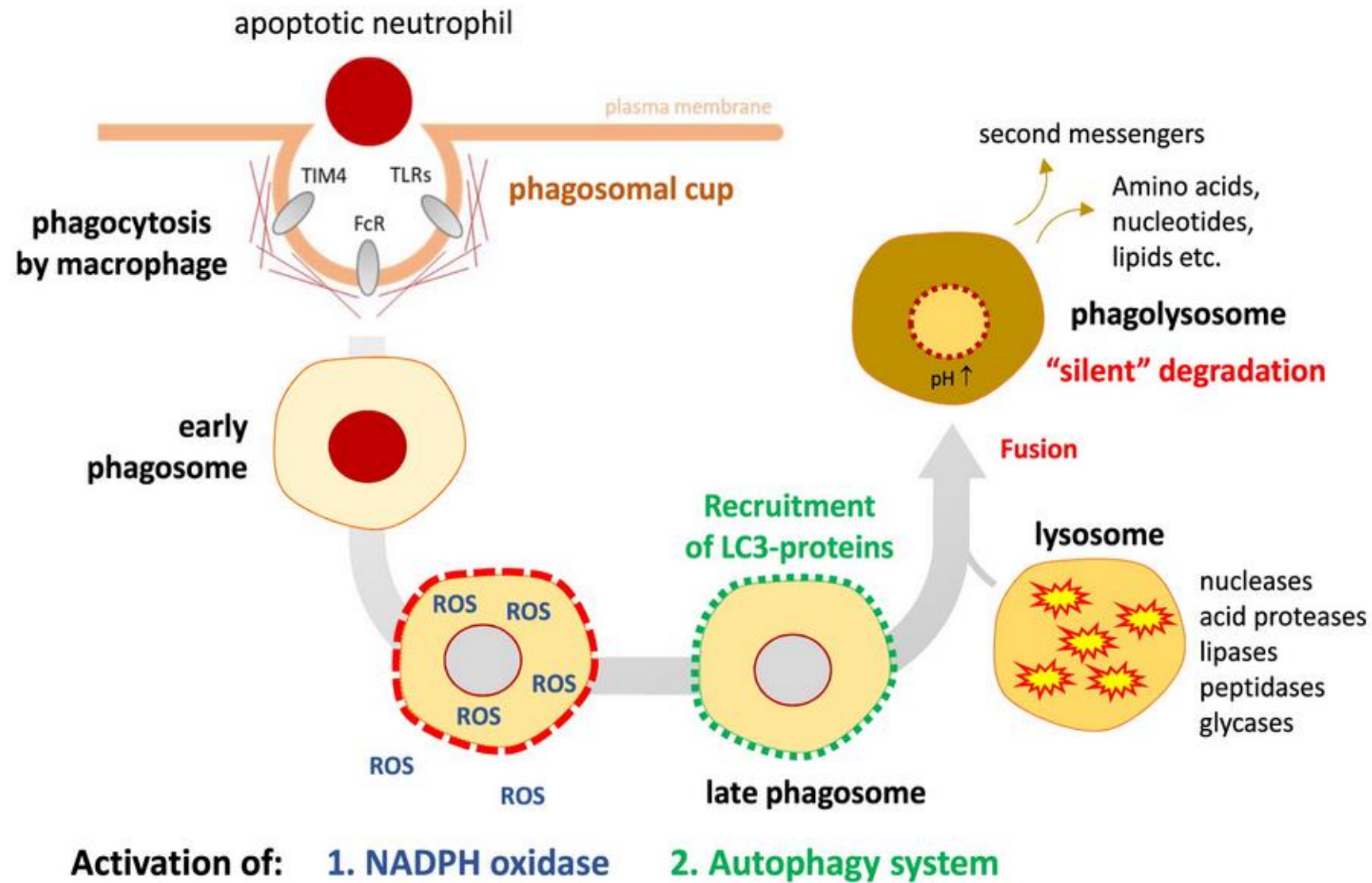
## CGD (chronic granulomatous disease)

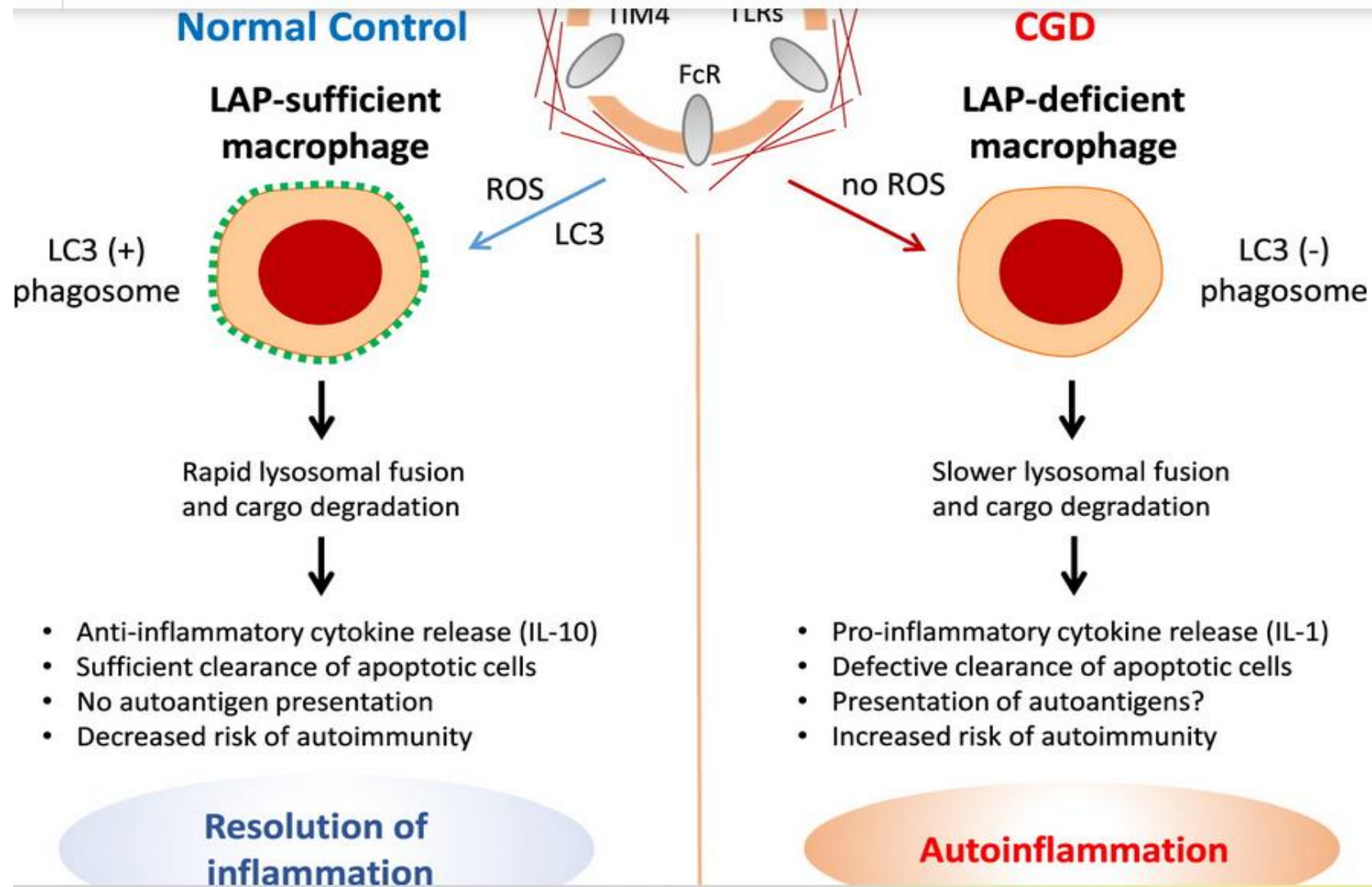
- ▶ - 1 in 200/000 live births
- ▶ - Genetically heterogeneous disorder
- ▶ - Defects in the phagocyte NADPH oxidase











## Clinical Presentation

- ▶ - Recurrent, serious infection with catalase-pos bacteria (Staph aureus), Fungi (Aspergillus)
- ▶ - Inflammatory bowel disease and SLE
- ▶ - Skin, lungs, liver, GI, lymph node involved from both infectious and inflammatory pathology

## Management and Treatment

- ▶ - Avoiding from BCG, and live bacterial vaccines
- ▶ - Life time prophylactic antibiotics (Co-trimoxasol) and antifungals (Itraconazole)
- ▶ - Interferon - gamma therapy - HSCT and Gene therapy



