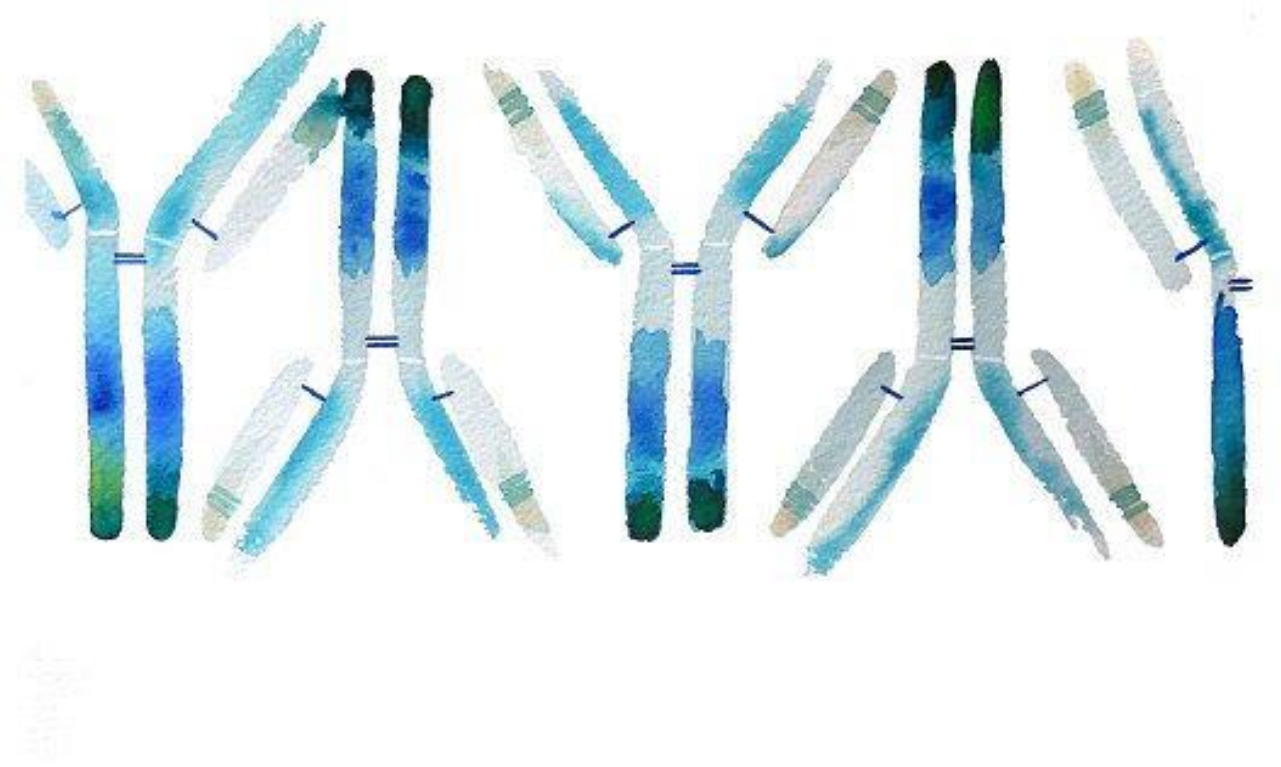


# Medical Immunology

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Anas Abu-Humaidan  
M.D. Ph.D.

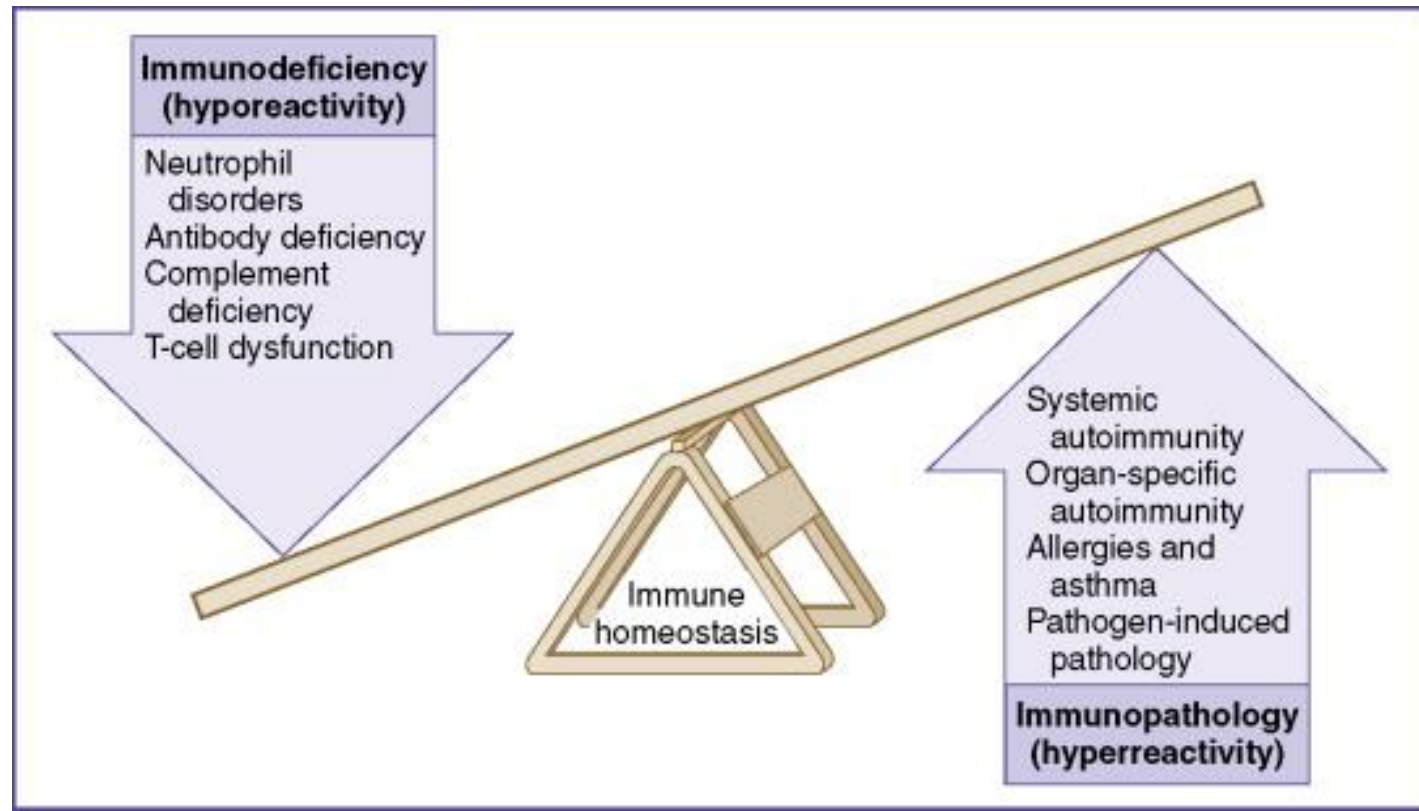
# Secondary immunodeficiencies

In this lecture we will discuss:

- Causes of Secondary immunodeficiencies

# Immune system malfunction

Defects or malfunctions in either the innate or adaptive immune response can provoke illness or disease. Such disorders are generally caused by an overactive immune response (known as **hypersensitivity reactions**), an inappropriate reaction to self (known as **autoimmunity**) or ineffective immune responses (known as **immunodeficiency**).



# Immunodeficiencies

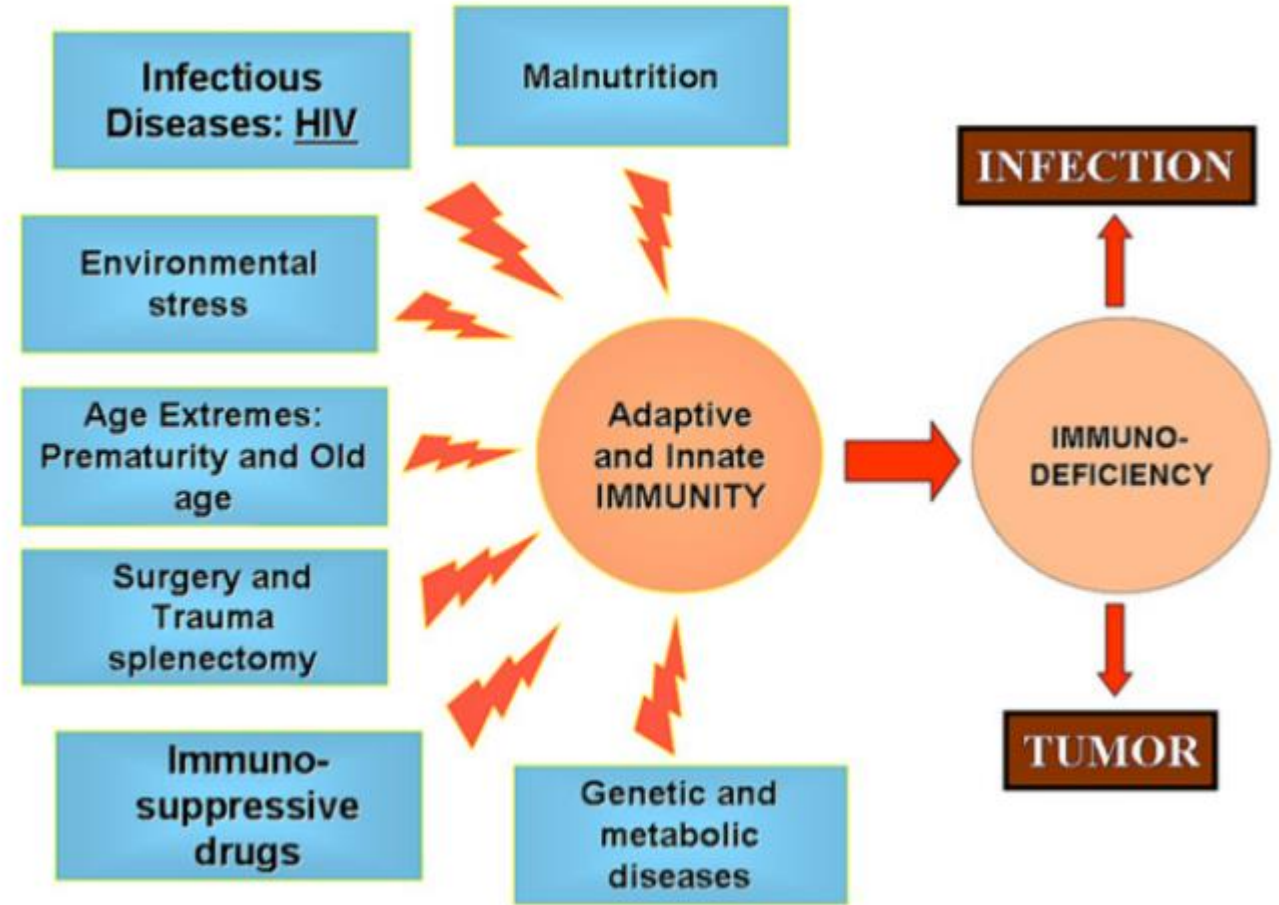
- **Immunodeficiency** results from a failure or absence of elements of the immune system, including lymphocytes, phagocytes, and complement system. These immunodeficiencies can be either primary or secondary.
- In immunodeficiency there is a history of: **Recurrent** infections, infections caused by **rare microorganisms**, and **Opportunistic** infections.

## Secondary immunodeficiencies/ overview

- A secondary immune deficiency disease occurs when the immune system is compromised due to **an environmental factor**.
- **Secondary** immunodeficiencies **are far more common** than **primary** immunodeficiencies, which are, by definition, caused by genetic defects affecting cells of the immune system.
- The immune defects observed in secondary immunodeficiency are usually **heterogeneous in their clinical presentation**, and their prognosis depends on the severity of the immune defect.

# Secondary immunodeficiencies

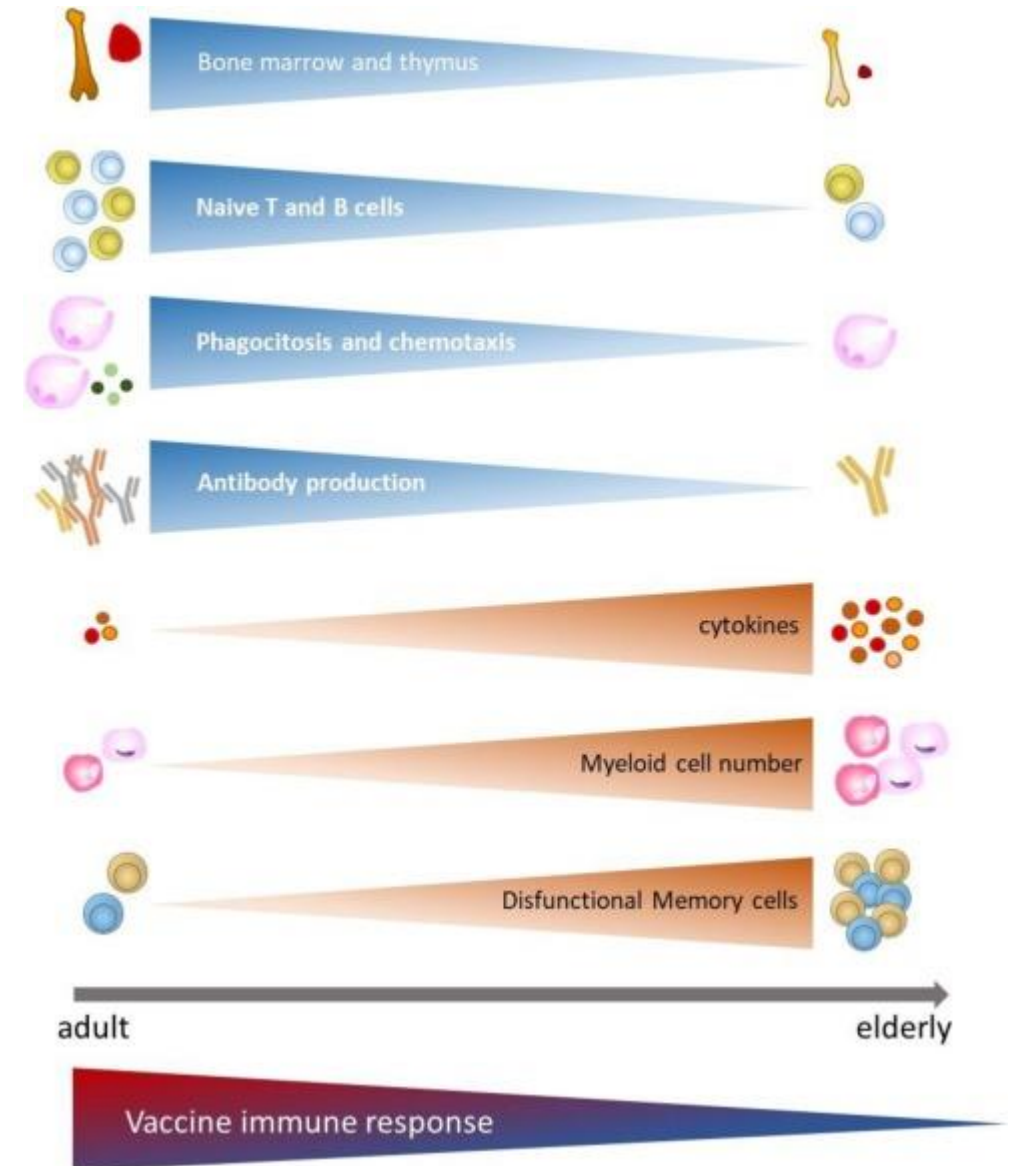
- Secondary immunodeficiencies result from a variety of factors that can affect a host with an intrinsically normal immune system.
- Sometimes more than one factor are present at any one time thereby exacerbating immune defects. ( e.g. Old age and metabolic disorders like diabetes)



**FIG 1.** Extrinsic factors leading to defects of immune function.

# Secondary immunodeficiencies/ Extremes of age

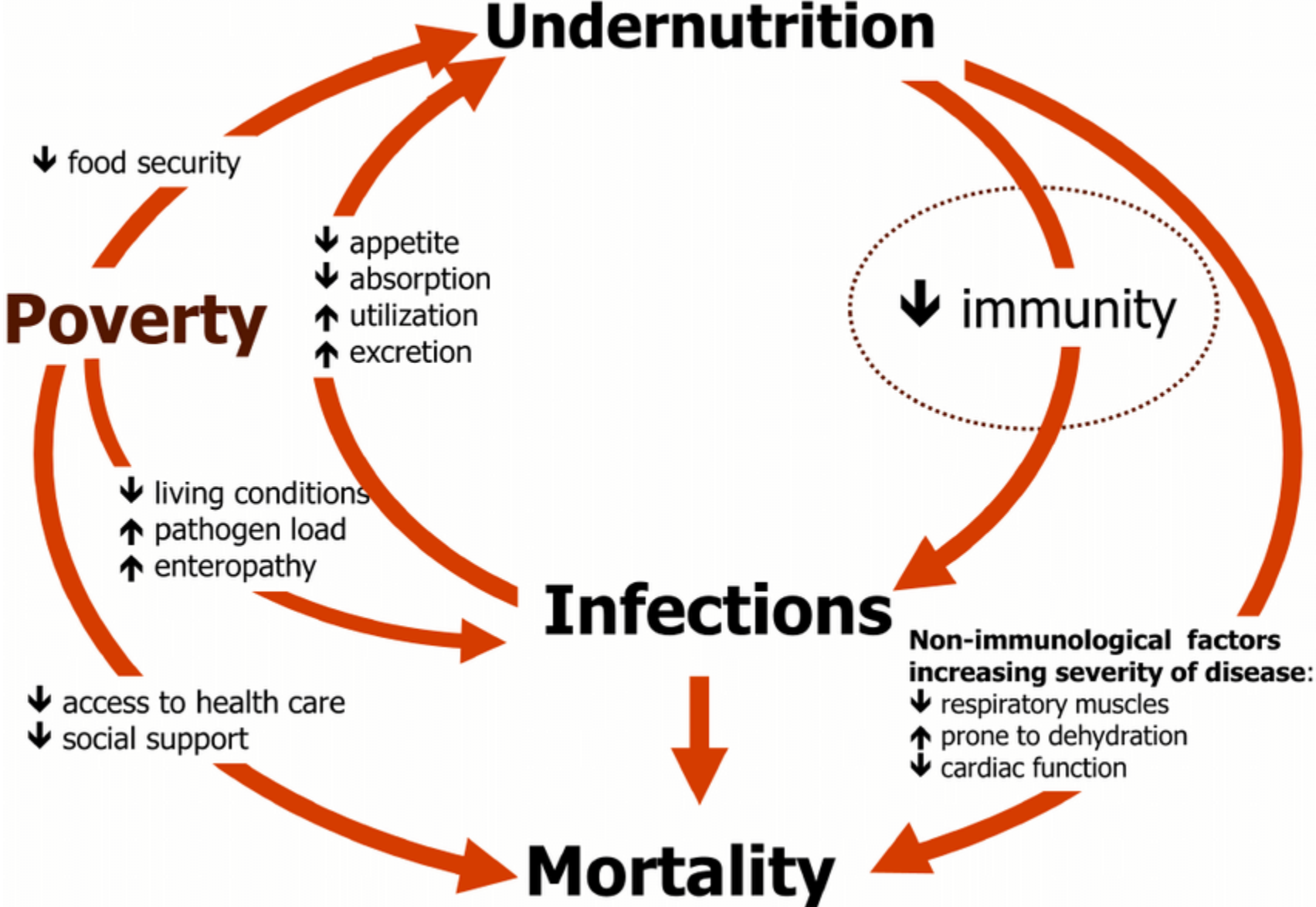
- **Neonates** have an increased susceptibility to common and opportunistic infections and sepsis compared with older children, impaired immunity in newborns can be attributed to the relative **lack of maturity of secondary lymphoid organs**.
- Among the **elderly**, some subjects experience malignancies and an excessive number of infections caused by viruses and bacteria, reflecting a decrease in the immune defenses, particularly in the cellular compartment.



## Secondary immunodeficiencies/ Malnutrition

- Worldwide, **protein-calorie malnutrition** is the most common cause of immunodeficiency
- Malnutrition can result from **limited access to food sources** and **chronic diseases** (e.g. COPD, CHF) that induce cachexia.
- T-cell production and function decrease in proportion to the severity of hypoproteinemia.
- The deficiency of micronutrients (eg, zinc and ascorbic acid) contributes to increased susceptibility to infections through the weakening of barrier mucosa, therefore facilitating a pathogen's invasiveness.

Secondary immunodeficiencies/ Malnutrition



## Secondary immunodeficiencies/ Malnutrition

- **Risk of infection** is several times greater in **malnourished hospital patients** and such patients also suffer more post-operative complications (e.g. pneumonia, renal failure, impaired wound healing)
- **Undernutrition** in critical periods of **gestation** and **neonatal maturation** and during weaning **impairs** the development and differentiation of a **normal immune system**. Infections are both more **frequent** and more often become **chronic** in the malnourished child.
- **Obesity** caused by excess nutrition or excess storage of fats relative to energy expenditure is a form of malnutrition that is increasingly seen in children.
- **Correction** of the nutritional deficiencies often results in the resolution of these immunologic defects.

## Secondary immunodeficiencies/ metabolic disorders

- **Diabetes mellitus** and **uremia** resulting from kidney or liver disease are 2 common metabolic disorders with known deleterious effects on immunity.
- Damage to the **neutrophil function**, depression of the antioxidant system, and humoral immunity.
- Impaired glucose metabolism, insufficient blood supply, and denervation are other factors that contribute to the increased susceptibility to infection in patients with diabetes, who present most commonly with **skin sores, bacterial and fungal respiratory tract infections, and systemic viral diseases.**



Mickaël Tobalem, M.D.  
Ilker Uçkay, M.D.

University Hospitals of Geneva  
Geneva, Switzerland  
mickael Tobalem@gmail.com

**A**N OBESE 50-YEAR-OLD MAN WITH NO KNOWN MEDICAL HISTORY PRESENTED with a necrotizing infection of his right foot that had begun 10 days previously with lesions that he attributed to wearing new shoes. He was found to have diabetes (glycated hemoglobin level, 10.5%) with peripheral neuropathy; he was afebrile, without leukocytosis or radiographic evidence of bone involvement in his right foot. The patient had photographed the lesion twice daily, thinking it would heal spontaneously (Panel A). The preoperative photographs show erythema (day 1), blisters (day 3), a necrotizing abscess (day 6), and wound infection requiring surgery (day 10). The patient underwent operative débridement; tissue cultures grew *Enterobacter cloacae* and *Streptococcus agalactiae*. He was treated with antibiotic agents for 3 weeks. The infection resolved, with no recurrence or sequelae during 3 years of follow-up (Panel B); during this period, the infection-related swelling disappeared and the patient lost a considerable amount of weight. Diabetic foot infection may evolve rapidly, especially in patients with neuropathy.

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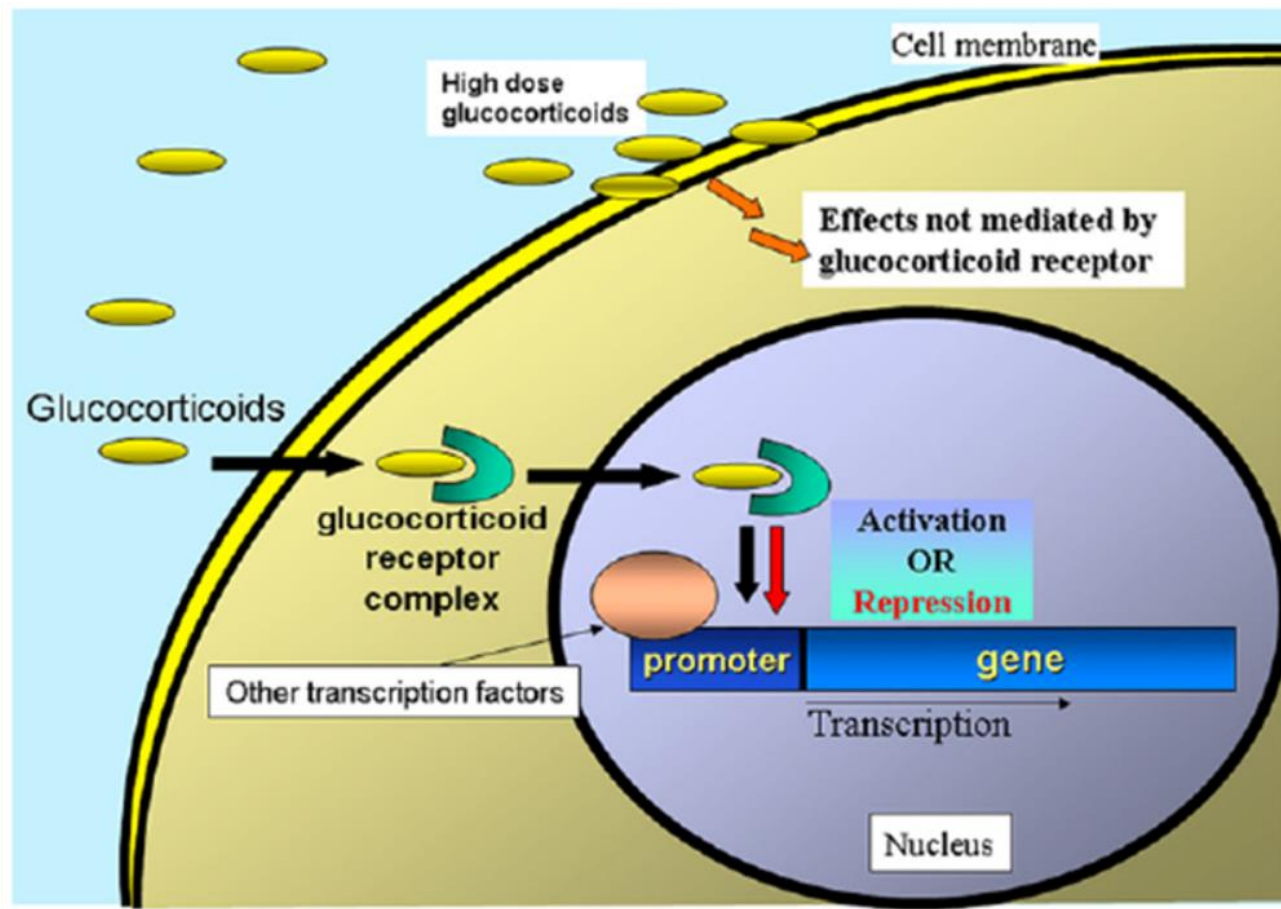
## Secondary immunodeficiencies/ Immunosuppressive drugs

- The use of drugs to ameliorate undesirable immune responses is common in clinical practice as a consequence of the increasing prevalence of inflammatory conditions. These diseases include the categories of autoimmune disorders, allergic disorders, transplant rejection, etc.
- Based on their structure and mechanism of action, most molecules with immunosuppressive activity can be grouped into **corticosteroids**, **calcineurin inhibitors**, and **cytotoxic drugs**. The adverse side effect of these drugs is that they tend to weaken the cellular immune response, rendering patients more susceptible to fungal and viral infections (acute, chronic, and reactivated).
- Physical agents (ie, **ionizing radiation**) can also be used to ablate immune responses. by **depleting the bone marrow** and inducing **cytopenias**, whereas the humoral response and phagocytosis are considered radioresistant.

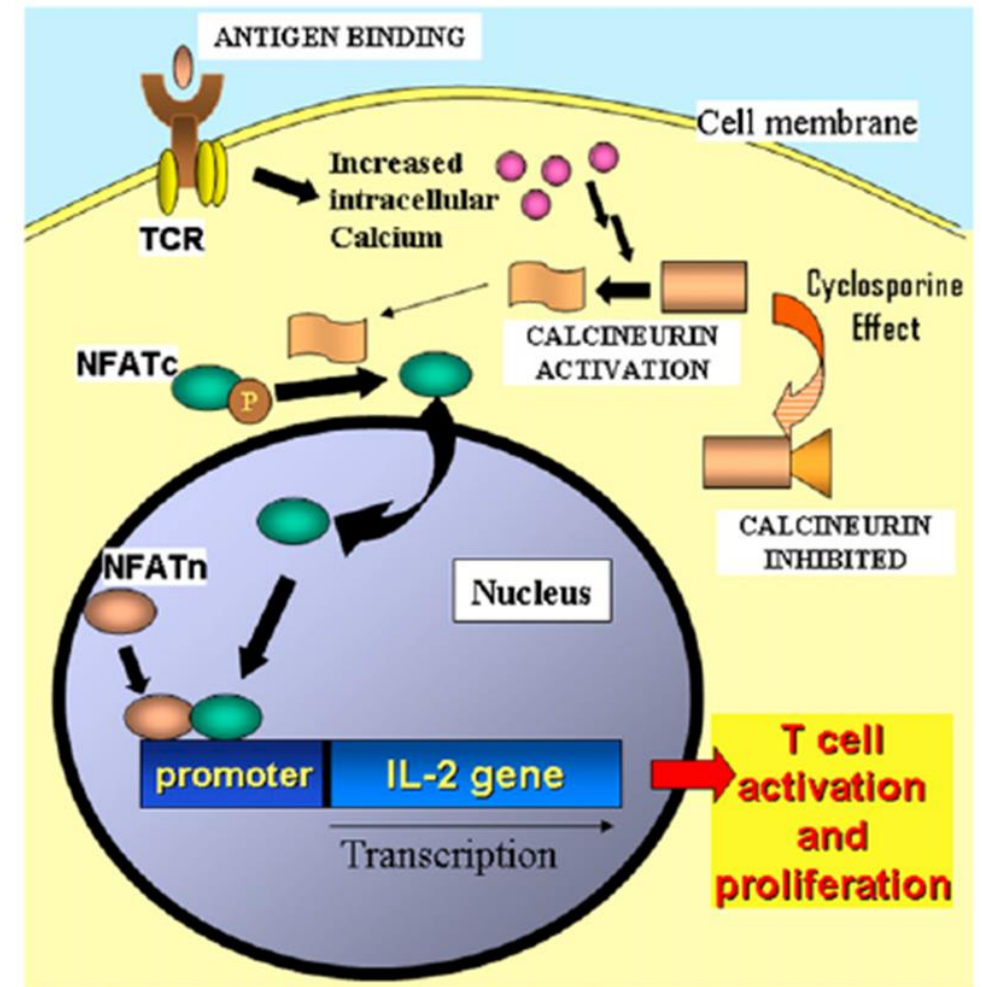
## Secondary immunodeficiencies/ Immunosuppressive drugs

- **Glucocorticoids** bind a cytosolic receptor, which then translocates to the nucleus to act as a transcription factor affecting the expression of a number of genes, resulting in an anti-inflammatory effect. The overall results are decreased cytokine production (IL-1, IL-6, and TNF- $\alpha$ ) and impaired leukocyte chemotaxis, cell adhesion, phagocytosis, and lymphocyte anergy.
- **Calcineurin inhibitors** bind cytoplasmic proteins from the immunophilin family and inhibit their interaction with calcineurin, which is essential for the activation of IL-2 transcription and T-cell function.
- **Cytotoxic agents** were conceived to control neoplastic cell growth and ablate the bone marrow for transplantation, The most common drugs used for these applications are the **alkylating agent** cyclophosphamide and the **antimetabolites** methotrexate.

# Secondary immunodeficiencies/ Immunosuppressive drugs



Molecular mechanism of action of glucocorticoids.



Effect of cyclosporine on T cells. Inhibition of calcineurin activity by cyclosporine results in decreased activation of IL-2 transcription.

## Secondary immunodeficiencies/Surgery and trauma

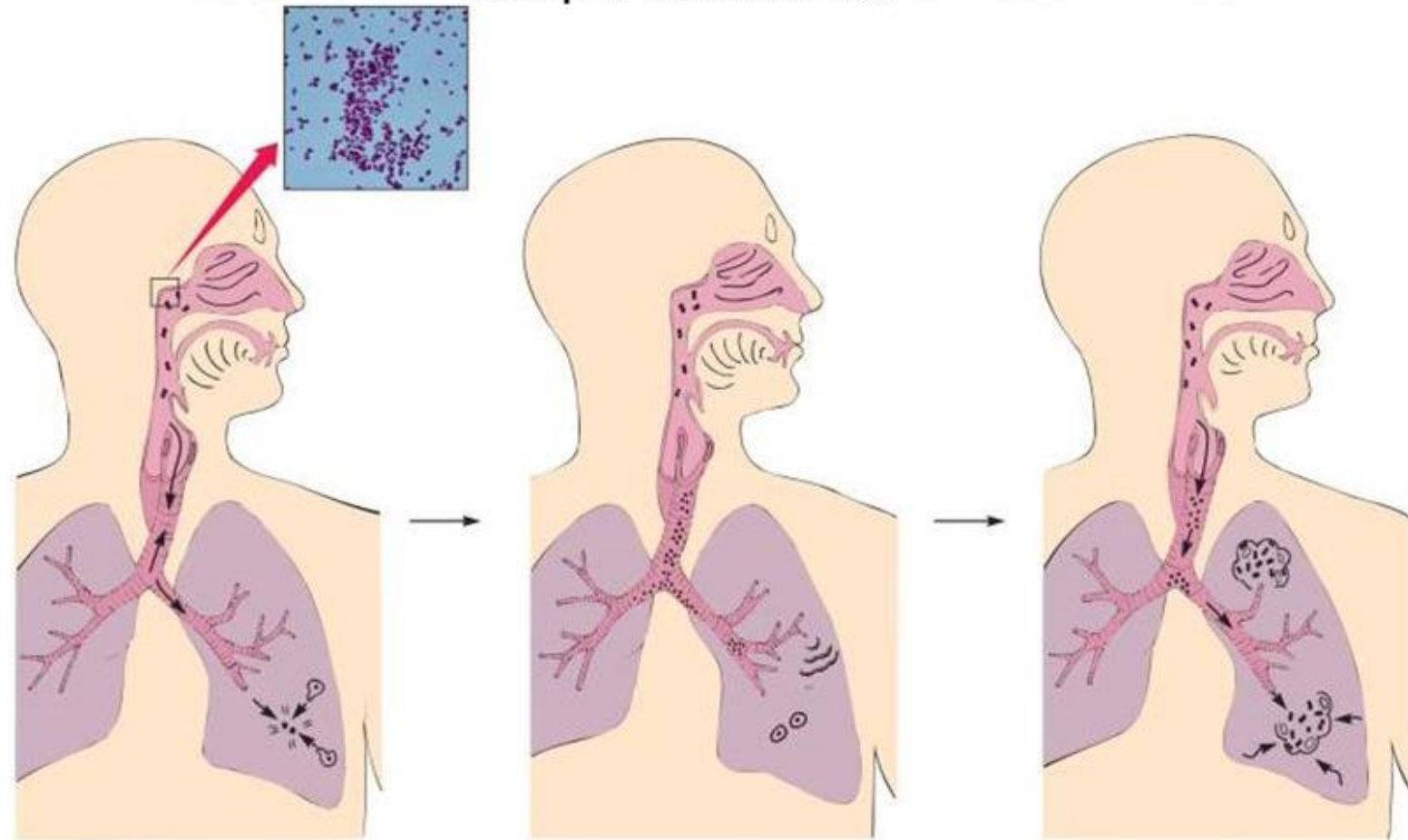
- Surgery and trauma cause **disruption of epithelial barriers** and cell destruction that triggers an inflammatory response to promote healing and local microbicidal activity.
- Release of DAMP and PAMP following massive tissue injury can result in an severe and detrimental inflammatory state.
- Injured patients are relatively immunosuppressed because of **nonspecific cell activation** leading to an anergic immune state and because of increased levels of **cortisol** induced by stress in addition to the loss of containment provided by **epithelial barriers**.
- Patients who have undergone **splenectomy** deserve special consideration because they are particularly susceptible to infections by encapsulated bacteria, such as *Streptococcus pneumoniae*. The mortality for sepsis in splenectomized patients is between 50% and 70%, **emphasizing the need to avoid splenectomy when possible**.

## Secondary immunodeficiencies/INFECTIOUS DISEASES

- Some **infectious agents** or their **toxins** and metabolites might be present in excess amounts to **activate the immune system**, leading to a nonresponsive state, such as the T-cell anergy observed after toxic shock syndrome induced by staphylococcal superantigen.
- **Tissue destruction** caused by microbial-induced damage or **inflammatory reaction to** a particular infection **facilitates access** for other microbes to develop secondary infections. For example, **Bacterial co/secondary infection** further **increases morbidity** and **mortality** of **influenza** infection, with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* reported as the most common causes.

# Secondary immunodeficiencies/INFECTIOUS DISEASES

## Strep Pneumonia



### Normal condition

- 1 Periodic colonization with streptococci
- 2 Some penetration into lower respiratory tract
- 3 Streptococci trapped by mucus and removed by ciliary action
- 4 Phagocytosed by macrophages

### Predisposing factors

- 5 Ciliated epithelium damaged by viruses, toxins, smoking, chemicals
- 6 Fluid accumulation
- 7 Decreased activity of macrophages

### Development of pneumonia

- 8 Growth of streptococci on damaged ciliated epithelium
- 9 Growth in fluids and in alveoli, both of which stimulate increased fluid accumulation

## Secondary immunodeficiencies/ HIV INFECTION: AIDS

- HIV infection begins with the binding of the HIV gp120 protein to the CD4 molecule and the chemokine receptor CCR5 on target cells. Infected cells migrate to the lymph nodes, where initial replication and infection of nearby CD4+ T cells occur.
- HIV induces **T-cell lymphopenia** through several mechanisms: HIV-induced apoptosis, viral cytopathic effect, apoptosis caused by nonspecific immune activation, and cytotoxicity to HIV-infected cells.
- In adults specific anti-HIV therapy is recommended when the patient has an AIDS-defining illness, the CD4+ T-cell count is less than 350 cells/mm<sup>3</sup>, or the HIV viral load is greater than 100,000 copies/mL.
- Highly active antiretroviral therapy (HAART) protocols have been effective in reducing viremia and restoring normal T-cell counts, with drastic reduction of mortality and number of infections.

# Assessment of immunodeficiencies

- The immunological investigation of a patient with immunodeficiency includes the assessment of **immunoglobulins**, B and T-**lymphocyte counts**, lymphocyte stimulation assays, quantification of components of the **complement system** and **phagocytic activity**.
- In addition microbiological studies must be done to aid in the assessment of the patient presenting with recurrent infections.
- The **restoration** of immunity in secondary immunodeficiencies is generally achieved with the **management of the primary condition** or the removal of the offending agent.

<https://www.ouh.nhs.uk/immunology/diagnostic-tests/tests-catalogue/lymphocyte-function-assay.aspx>

## Secondary immunodeficiencies/Conclusion

- When evaluating a patient with increased frequency or severity of infections suggesting immunodeficiency, physicians should consider that secondary immunodeficiencies are far more common than primary immune defects of genetic cause.
- Detailed clinical history might uncover the condition affecting the immune system, such as infection, malnutrition, age extremes, concomitant metabolic or neoplastic diseases, use of immunosuppressive drugs, surgery and trauma, and exposure to harsh environmental conditions. Because of its prevalence and clinical progression, HIV infection should be considered and ruled out.

# Secondary immunodeficiencies

TABLE I. Selected causes of secondary immunodeficiencies

Condition	Effect on immune function
Extremes of age	
Newborn period	Immature lymphoid organs Absent memory immunity Low maternal IgG levels in premature infants Decreased neutrophil storage pool Decreased neutrophil function Decreased natural killer activity
Advanced age	Decreased antigen-specific cellular immunity T-cell oligoclonality Restricted B-cell repertoire
Malnutrition	Decreased cellular immune response Weakened mucosal barriers
Metabolic diseases	
Diabetes mellitus	Decreased mitogen-induced lymphoproliferation Defective phagocytosis Decreased chemotaxis
Chronic uremia	Decreased cellular immune response Decreased generation of memory antibody responses Decreased chemotaxis

# Secondary immunodeficiencies

**TABLE I.** Selected causes of secondary immunodeficiencies

Condition	Effect on immune function
Genetic syndromes: trisomy 21	Defective phagocytosis Defective chemotaxis Variable defects of antigen-specific immune responses
Anti-inflammatory, immunomodulatory, and immunosuppressive drug therapy: corticosteroids, calcineurin inhibitors, cytotoxic agents	Lymphopenia Decreased cellular immune response and anergy Decreased proinflammatory cytokines Decreased phagocytosis Decreased chemotaxis Neutropenia (cytotoxic agents) Weakened mucosal barriers (cytotoxic agents)
Surgery and trauma	Disruption of epithelial and mucosal barriers T-cell anergy caused by nonspecific immune activation
Environmental conditions UV light, radiation, hypoxia, space Flight	Increased lymphocyte apoptosis Increased secretion of tolerogenic cytokines Cytopenias Decreased cellular immunity and anergy Stress-induced nonspecific immune activation
Infectious diseases: HIV infection	T-cell lymphopenia Decreased cellular immune response and anergy Defective antigen-specific antibody responses

## Further reading:

- Chinen J, Shearer WT. Secondary immunodeficiencies, including HIV infection. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S195-S203. doi:10.1016/j.jaci.2009.08.040