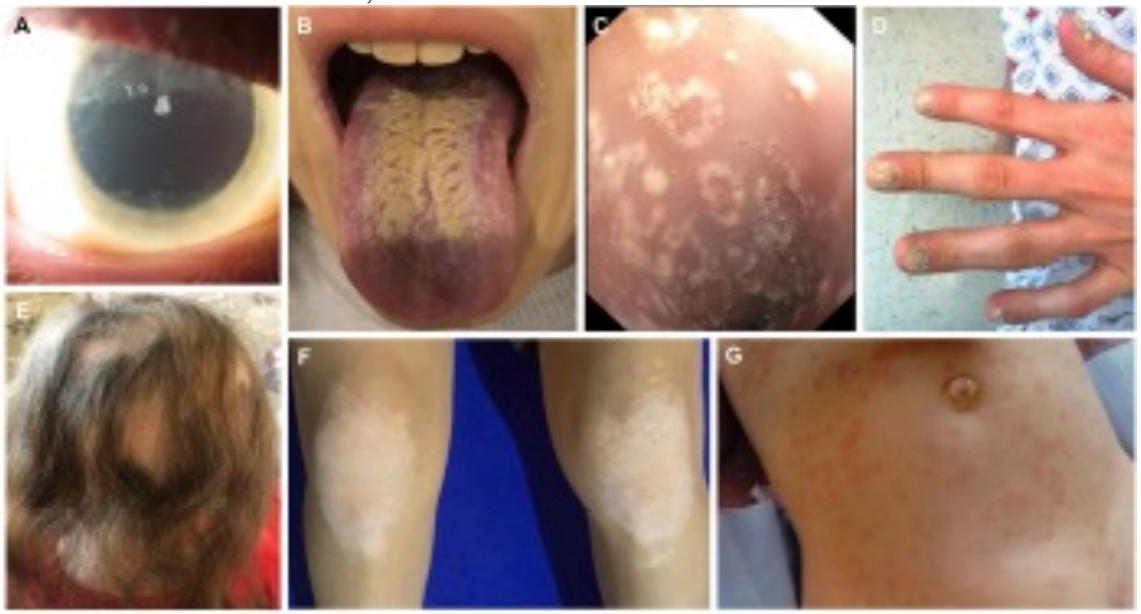
*Ferre et al., Frontiers in Pediatrics 2021*



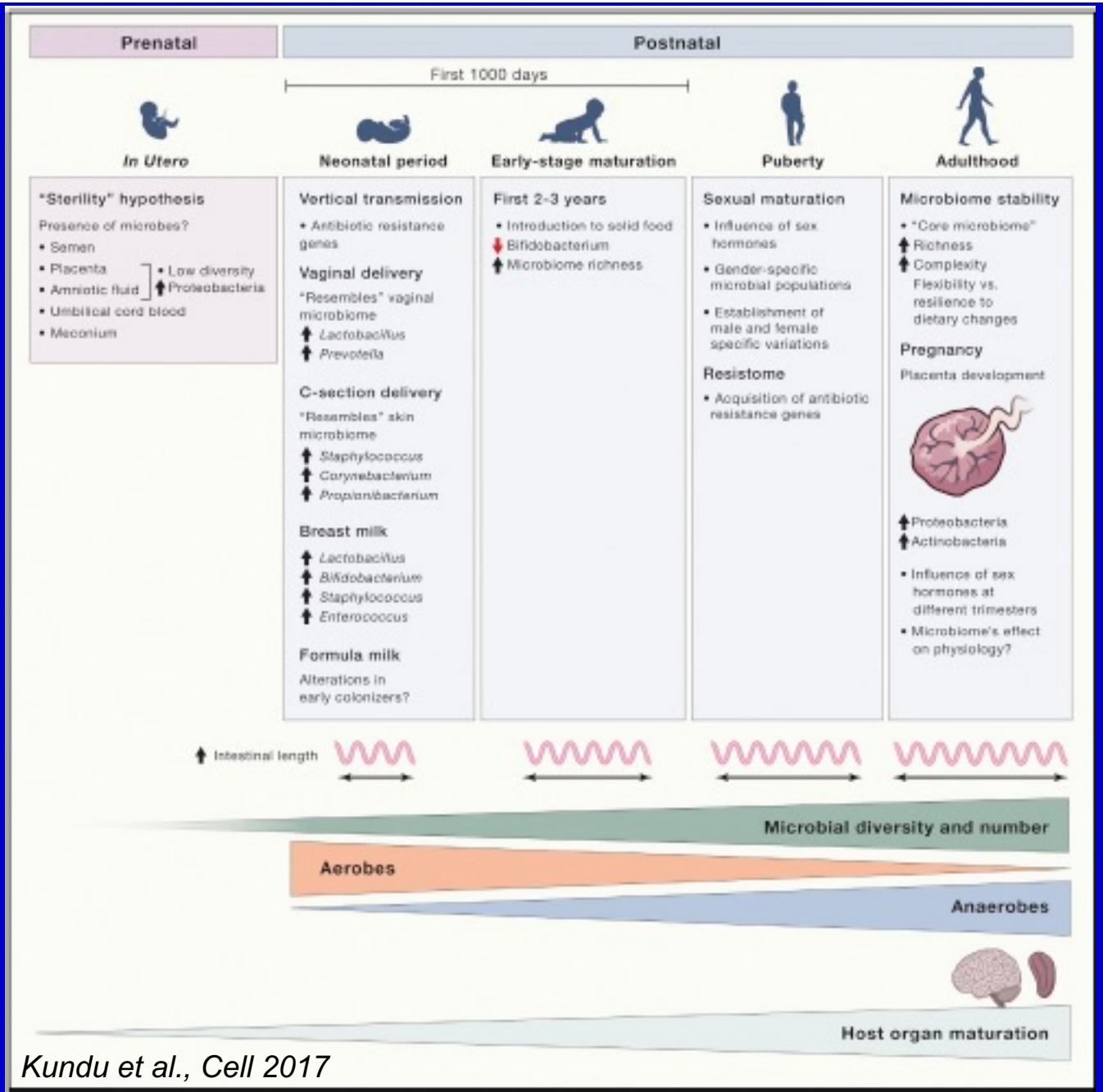

Ordensklinikum Linz
Barmherzige Schwestern Elisabethinen

# Clinical Immunology

## Part I: Immune Deficiency & Reconstituition

Harry Fuchssteiner 01/06/2023
Innere Medizin 4
Ordensklinikum Linz – **Barmherzige Schwestern**

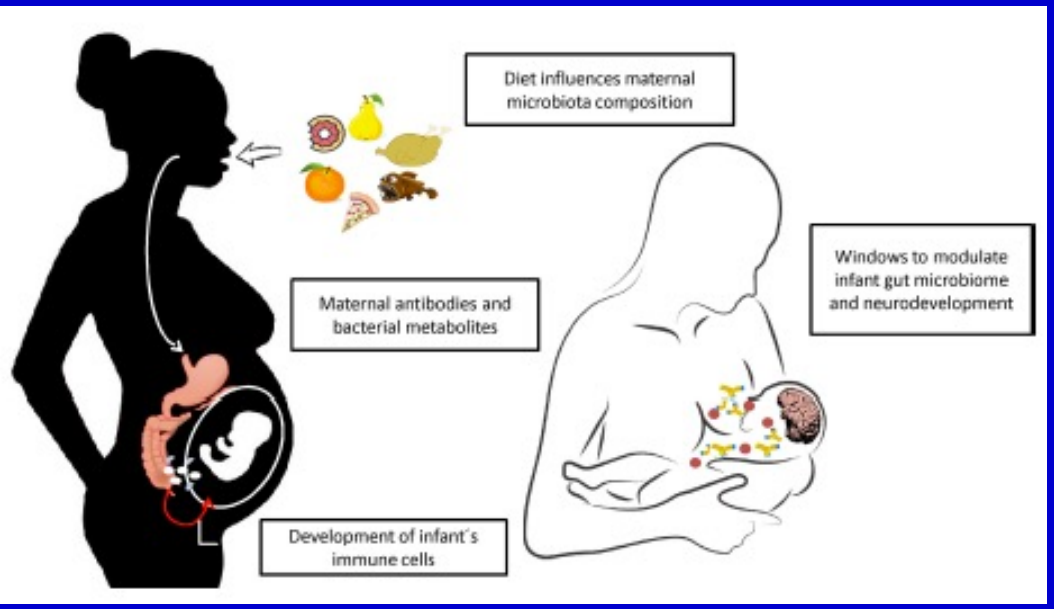
# Our Gut Microbiome: The Evolving Inner Self

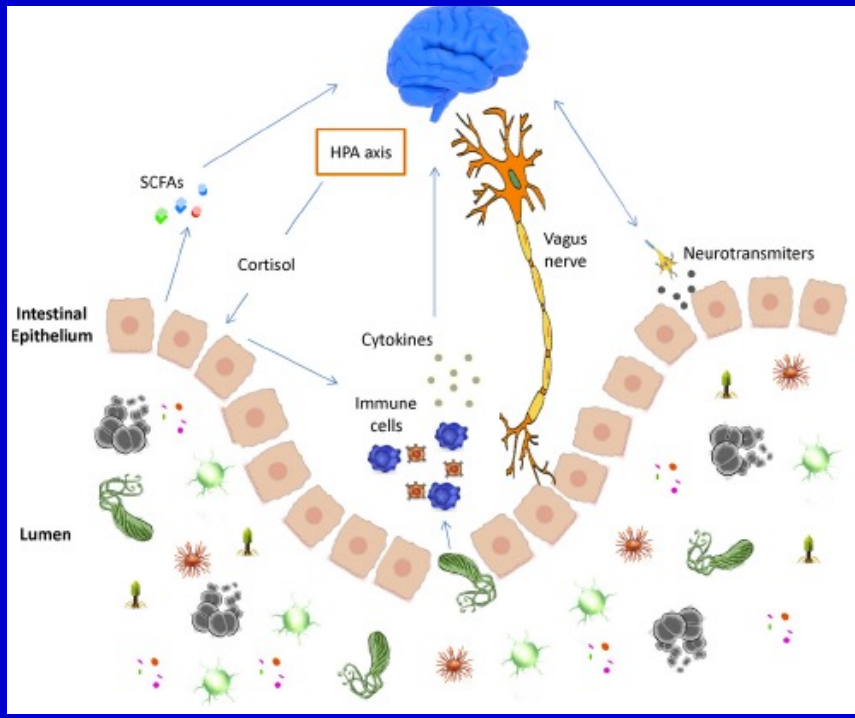


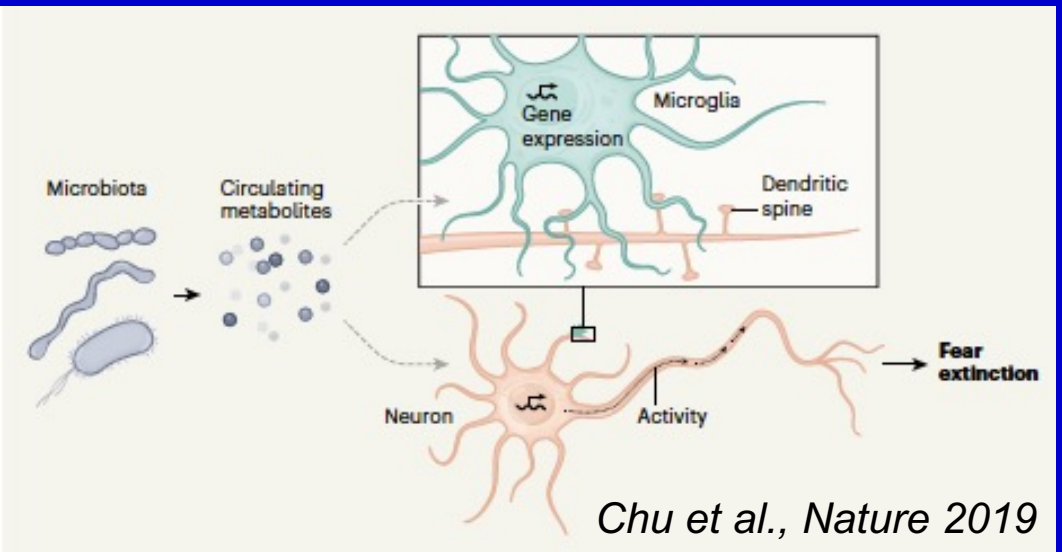

*Kundu et al., Cell 2017*

# Early nutrition and gut microbiome: interrelationship between bacterial metabolism, immune system, brain structure, and neurodevelopment

*Cerdo et al., Am J Physiol Endocrinol Metabol 2019*



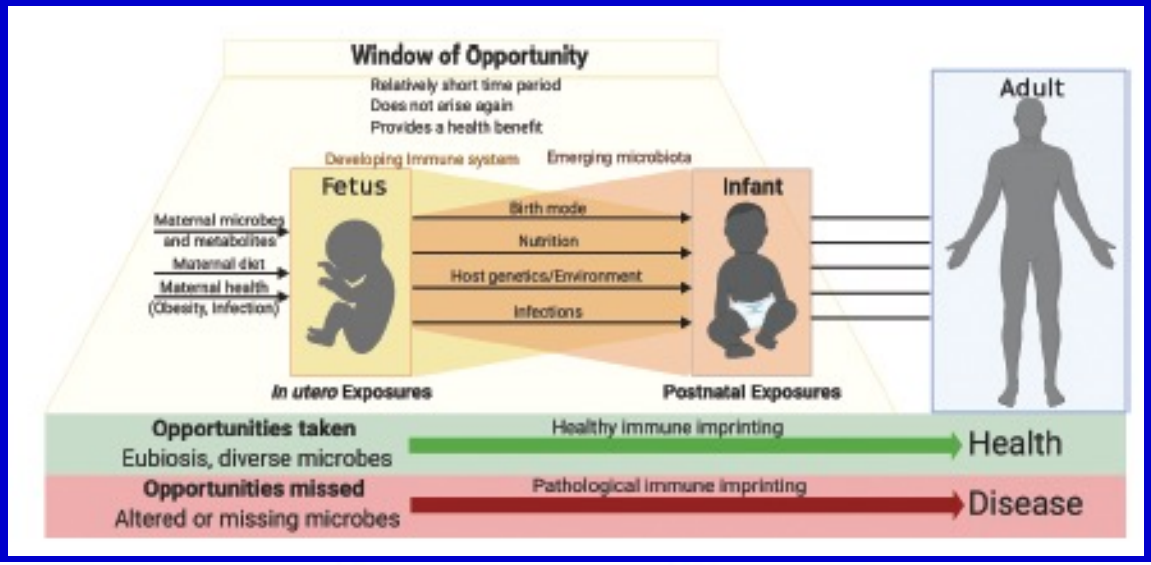



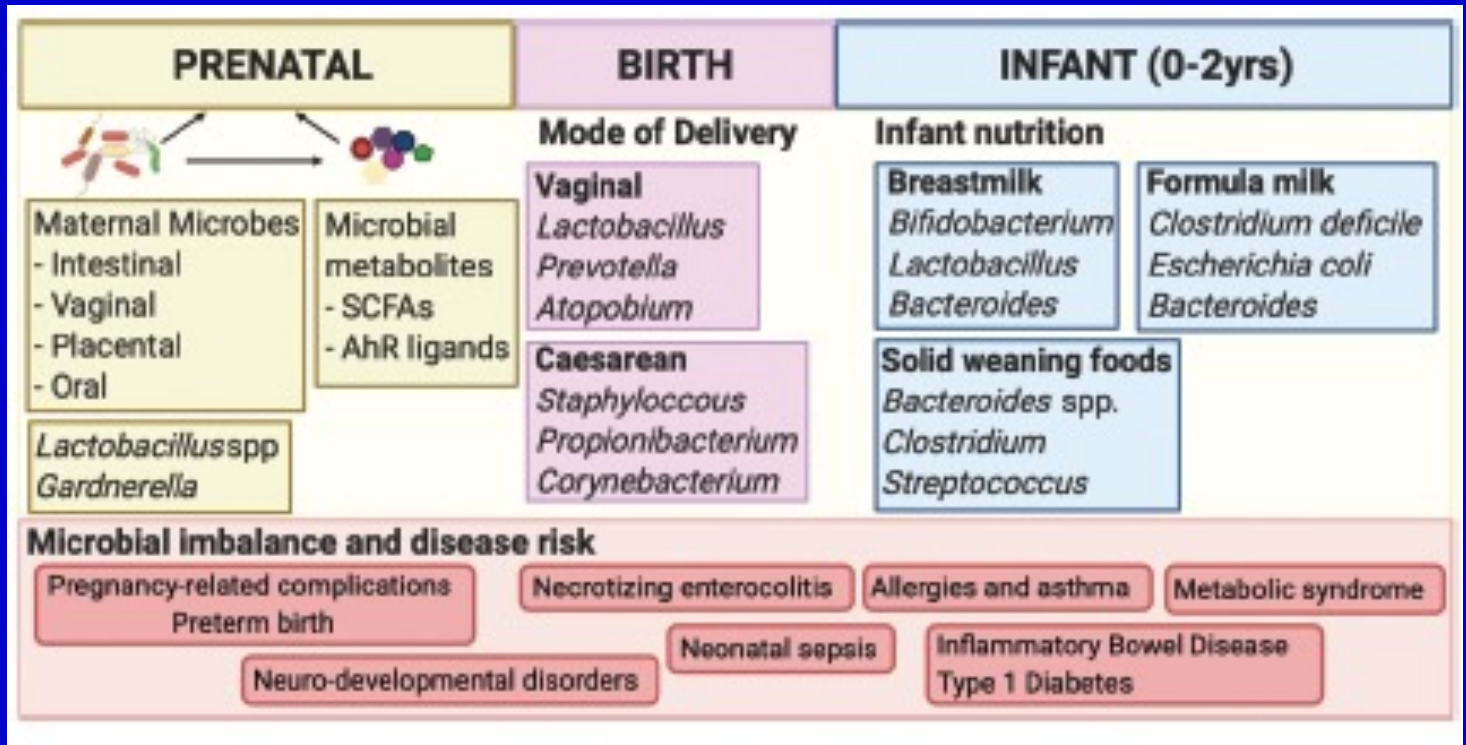

*Chu et al., Nature 2019*

**The microbiota regulate neuronal function and fear extinction learning**

# The early life education of the immune system: Moms, microbes and (missed) opportunities

*Jain, Gut Microbes 2020*



# Primary immunodeficiency and autoimmunity: A comprehensive review

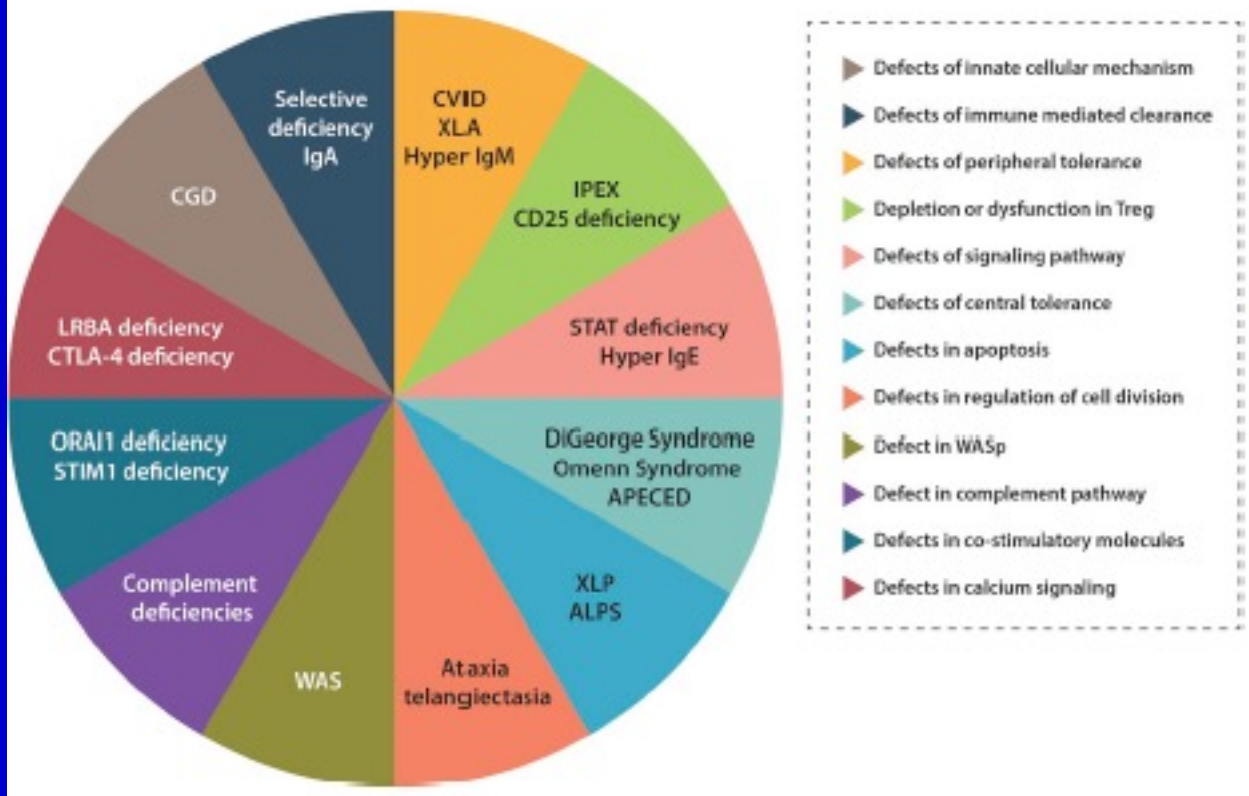
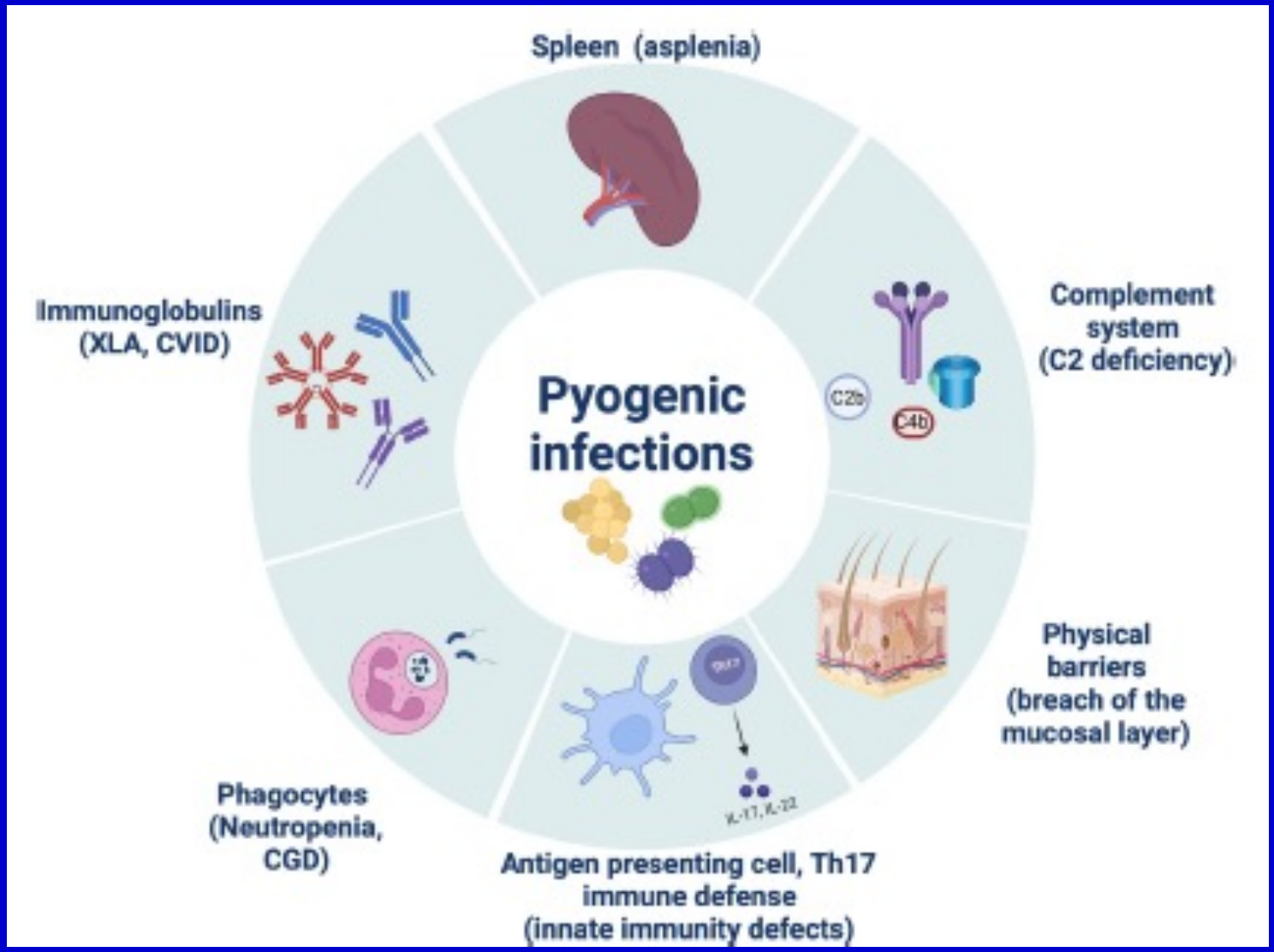



**Fig. 2.** Immunological defects associated with the development of PIDs. APECED: autoimmune polyendocrinopathy, candidiasis ectodermal, dystrophy syndrome; ALPS: autoimmune Lymphoproliferative Syndrome; CGD: chronic granulomatous disease; CVID: common variable immunodeficiency; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PIDs: primary immunodeficiencies; WAS: Wiskott-Aldrich syndrome; WASp: Wiskott-Aldrich syndrome protein. XLA: X-linked agammaglobulinemia; XLP: X-linked lymphoproliferative disease.

# Inborn errors of immunity underlying a susceptibility to pyogenic infections: from innate immune system deficiency to complex phenotypes




F. Conti et al. / Clinical Microbiology and Infection 28 (2022) 1422–1428

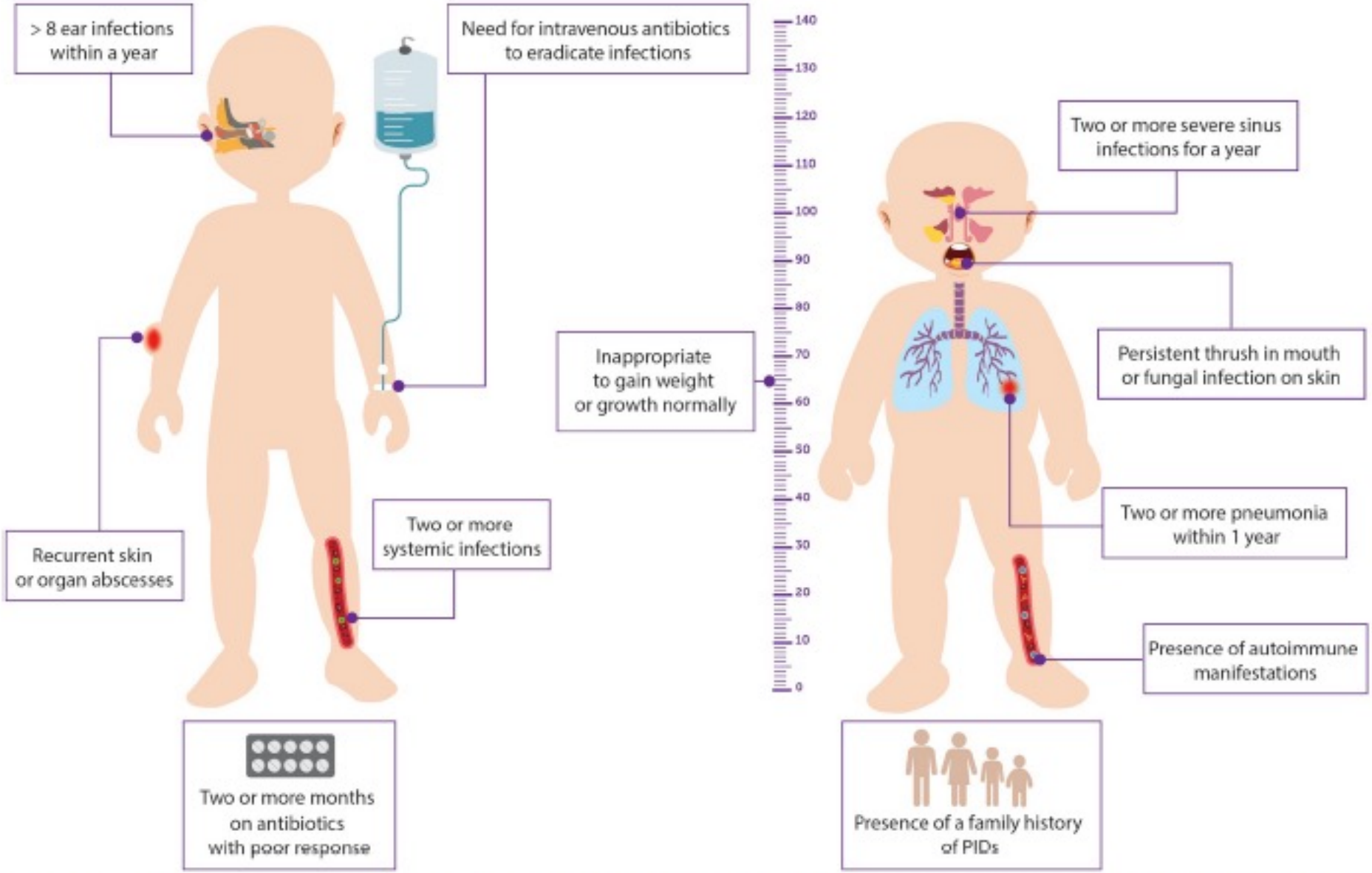
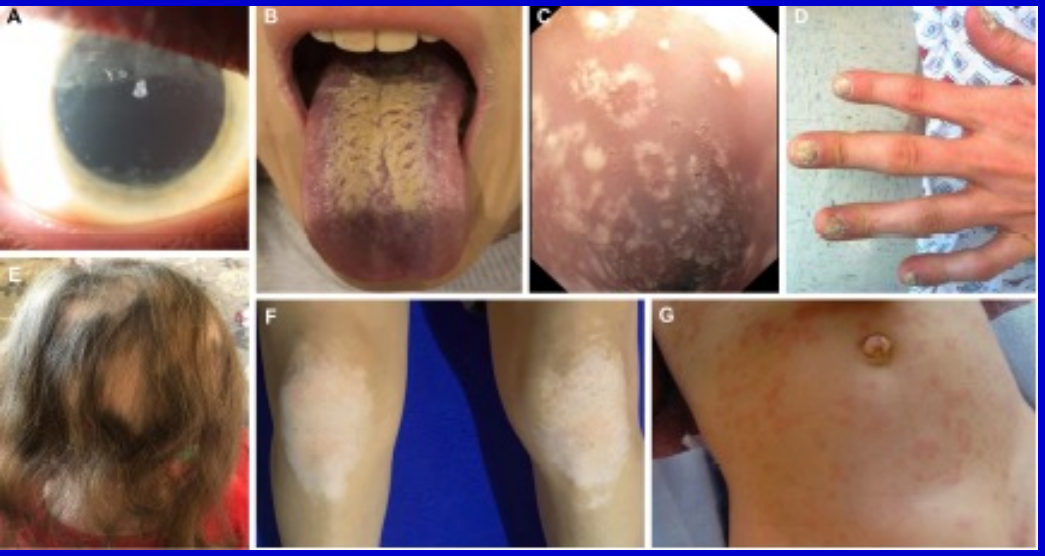
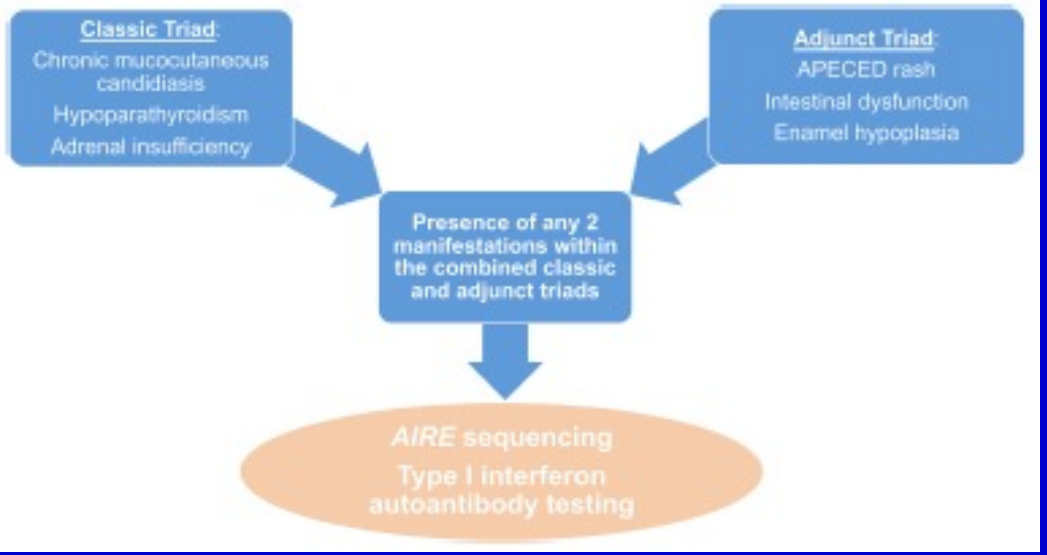
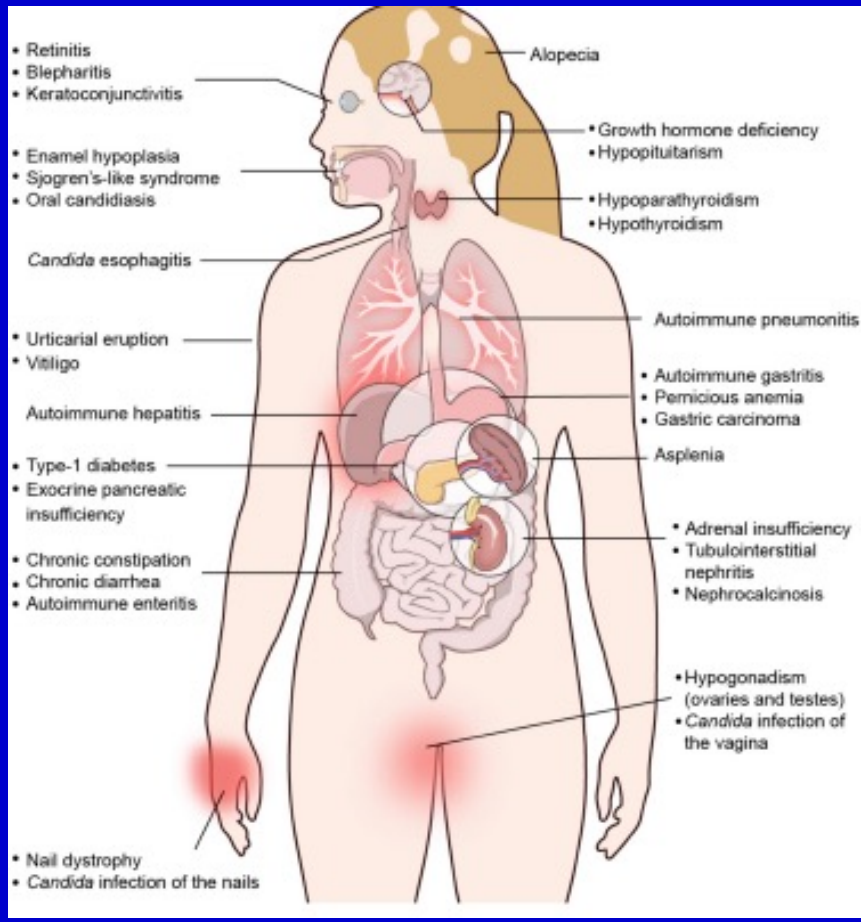



**Fig. 3.** The Jeffrey Modell Foundation warning signs for primary immunodeficiencies. The inclusion of autoimmunity as an additional criterion may help to improve diagnosis and follow up of comorbidities associated with these diseases.

# Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

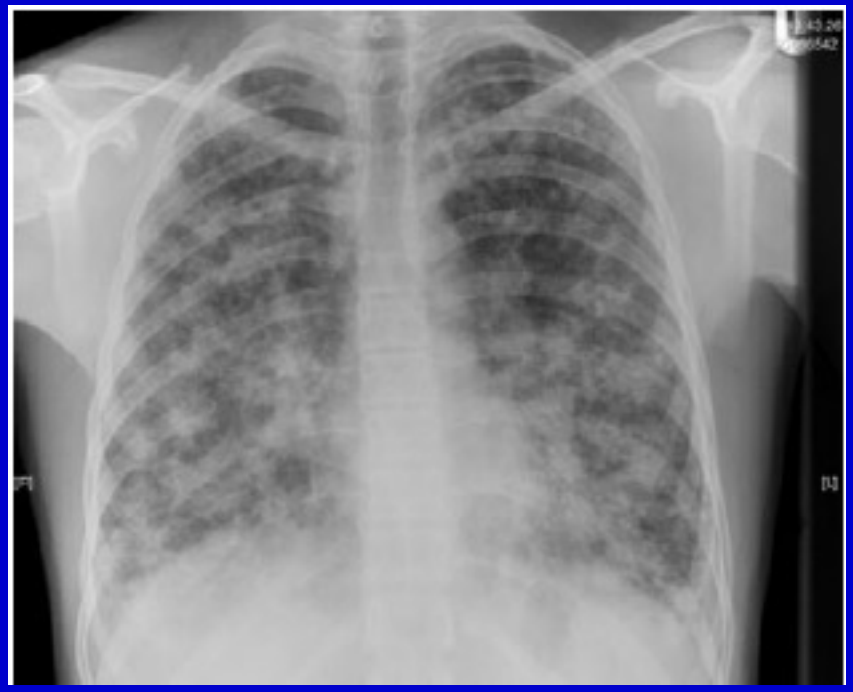



*Ferre et al., Frontiers in Pediatrics 2021*

# Clinical Immunology Review Series: An approach to the patient with recurrent infections in childhood



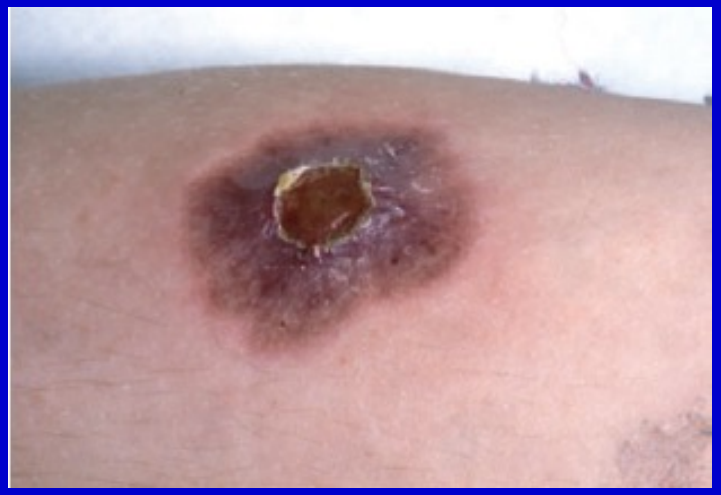
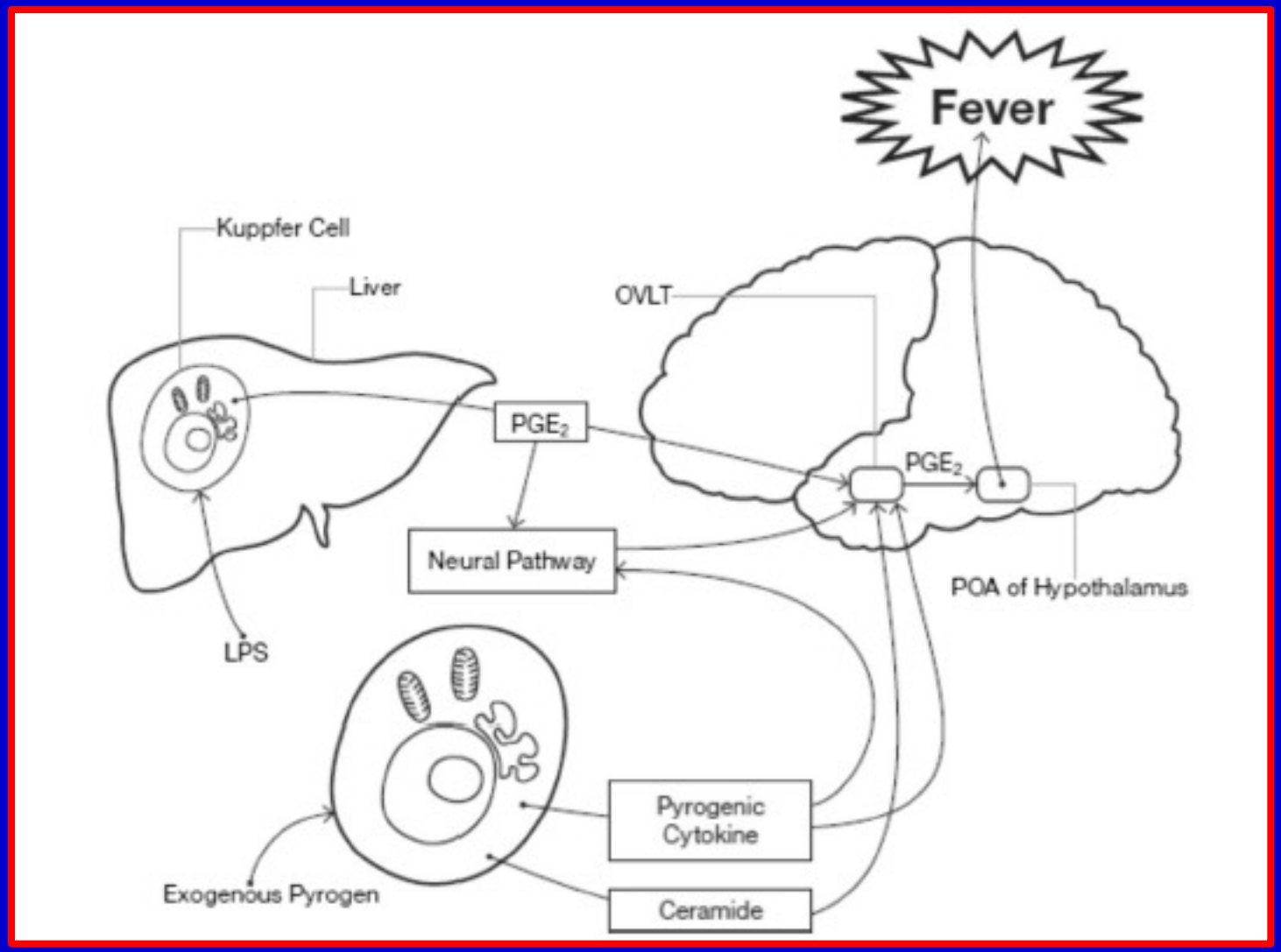


**Table 3.** Specific warning signs of primary immunodeficiency.

- Eight or more new infections within 12 months
- Two or more serious sinus infections or episodes of pneumonia within 1 year
- Two or more months on antibiotics with little effect
- Failure of an infant to gain weight or grow normally
- Recurrent deep skin or organ abscesses
- Persistent superficial candidiasis after age 1 year
  - Episode of opportunistic infection
  - Complication associated with live vacination
- Need for intravenous antibiotics to clear infections
- Two or more invasive infections
- A family history of primary immune deficiency
- Unexplained autoimmune disease

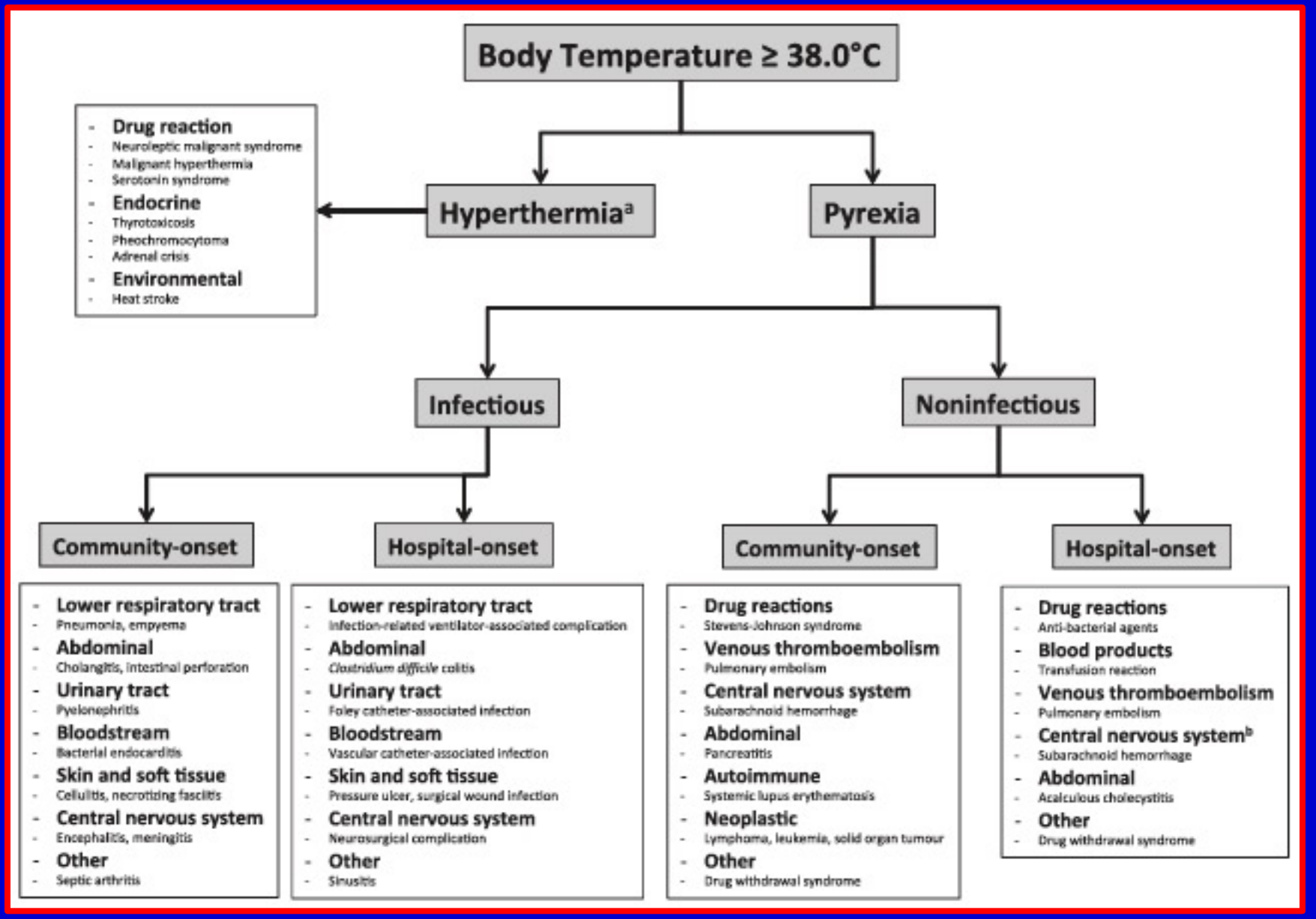
*Slatter et al., Clinical and Experimental Immunology 2008*

# The pathophysiological basis and consequences of fever




Walter *et al. Critical Care* (2016) 20:200

# Pyrexia: aetiology in the ICU




Niven and Laupland *Critical Care* (2016) 20:247

*„Der Stein der Weisen in der Inneren Medizin“...:*

# *DIE ANAMNESE*

*Zeichnung von **George L. Engel**,*
*(Professor of Psychiatry and Medicine emeritus, University of Rochester, New York*
*aus Adler, Hemmeler: Praxis und Theorie der Anamnese, G. Fischer 1989)*

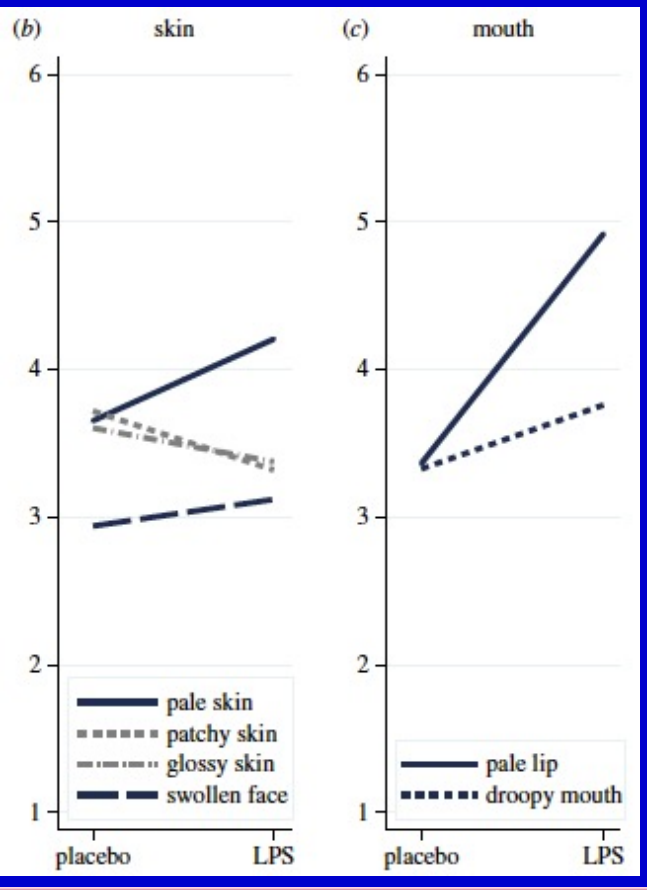
**Zielsetzungen eines Anamnesegespräches:**

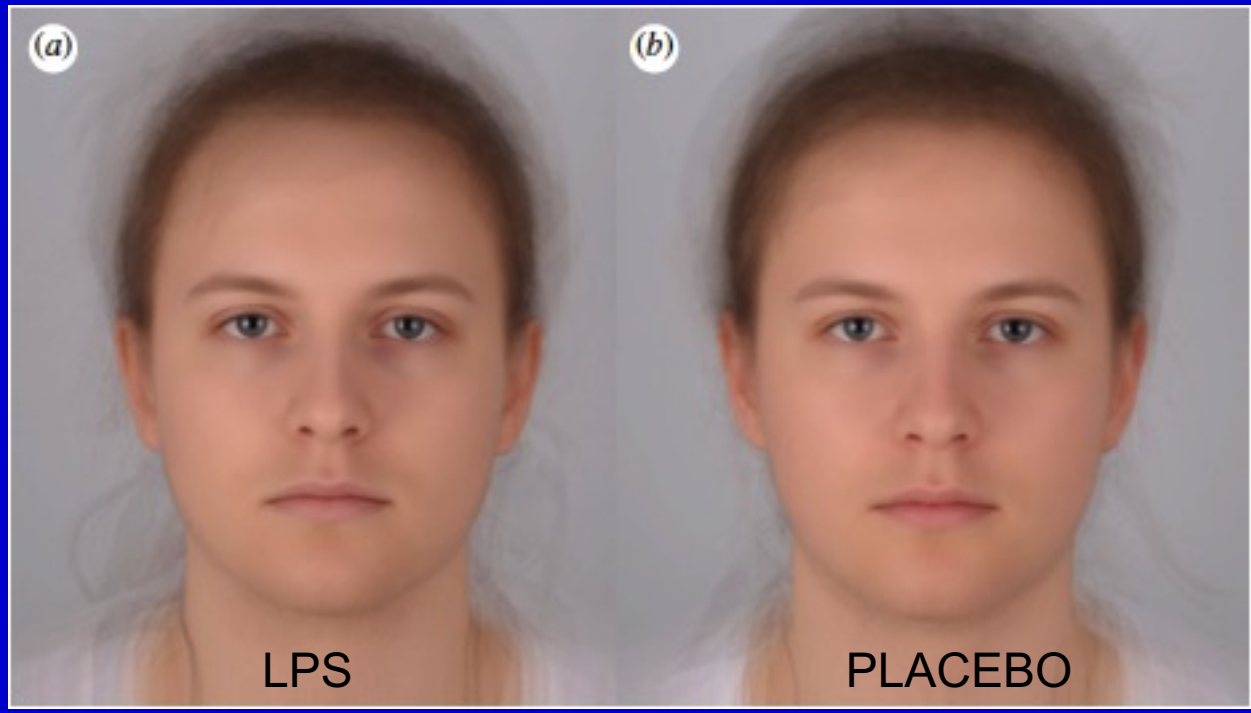
- Herstellung einer **Beziehung** zum Patienten
- Erheben einer **biopsychosozialen** Anamnese
- **erste Beurteilung** der relevanten Mitteilungen
- Formulierung einer **vorläufigen Diagnose**
- **Festlegen des weiteren diagnostischen und therapeutischen Vorgehens**
- **Motivieren des Patienten** („motivational interview“)

Buddeberg: Psychosoziale Medizin, Springer 2004
Adler, Hemmeler: Praxis und Theorie der Anamnese, G. Fischer 1989
Dahmer: Anamnese und Befund, Thieme 2006
Watzlawick: Menschliche Kommunikation, hogrefe 2017

# LOOK TWICE AND USE qSOFA

Identification of acutely sick people and facial cues of sickness




*Singer et al., JAMA 2016;* *Axelsson et al., Royal Society 2018*

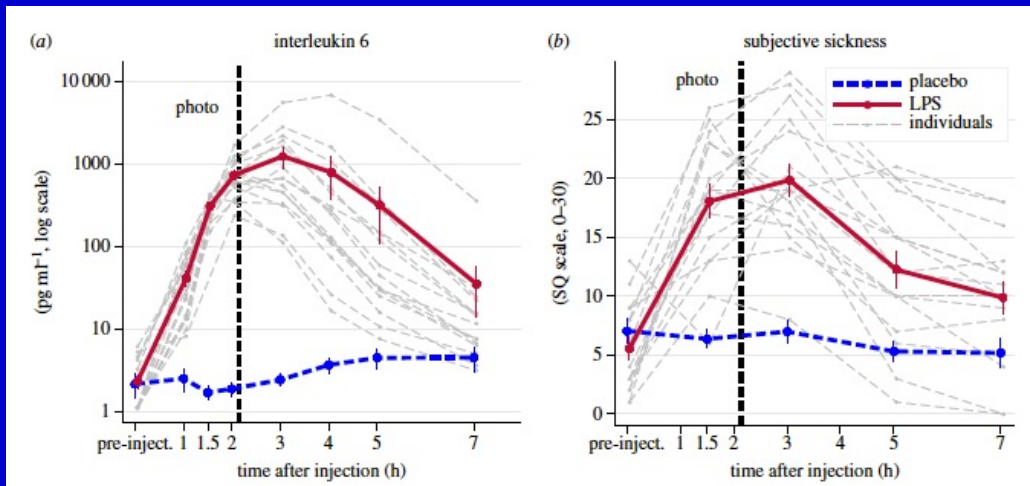
**Box 4. qSOFA (Quick SOFA) Criteria**

Respiratory rate ≥22/min

Altered mentation

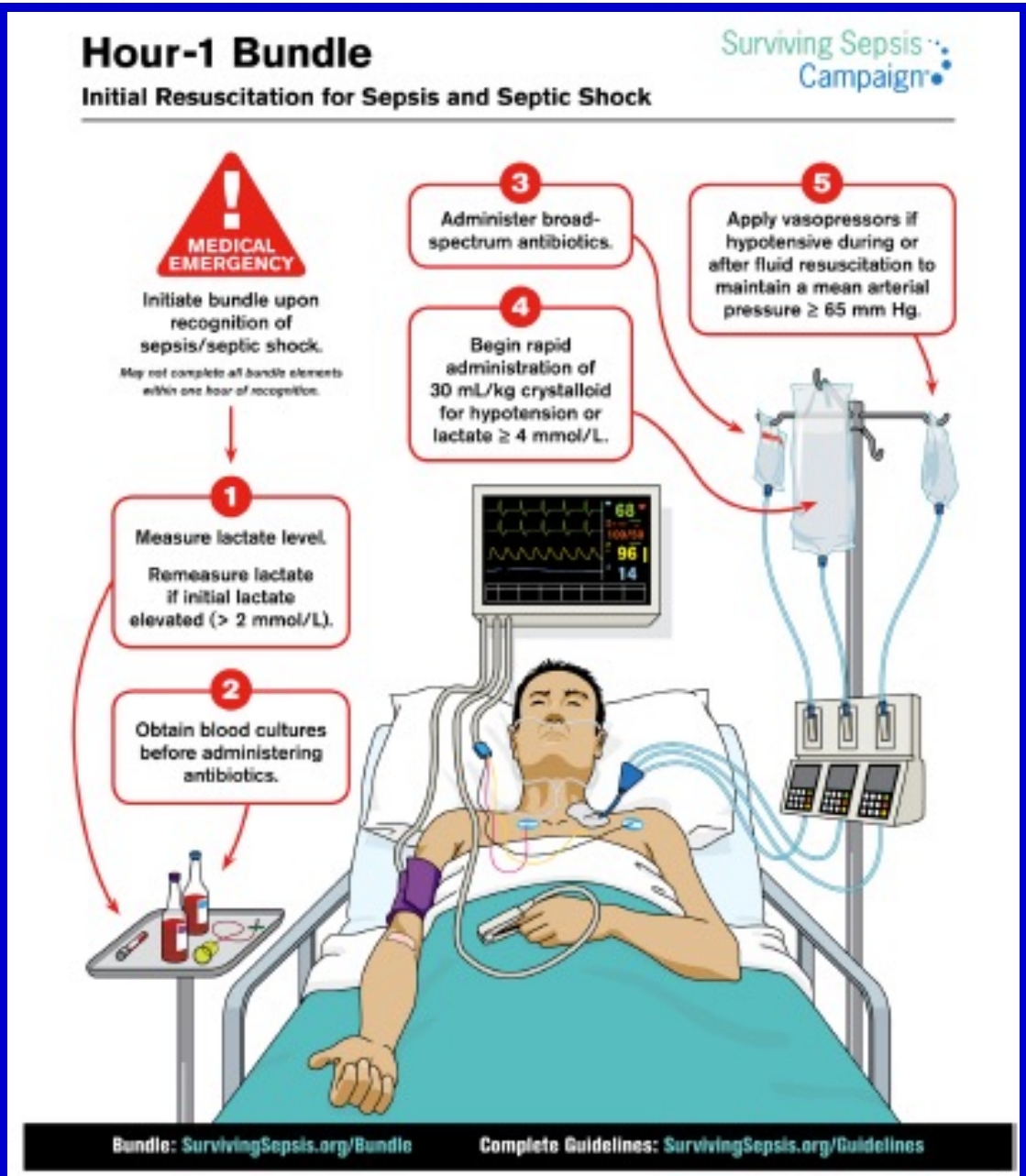
Systolic blood pressure ≤100 mm Hg

**2≥+**

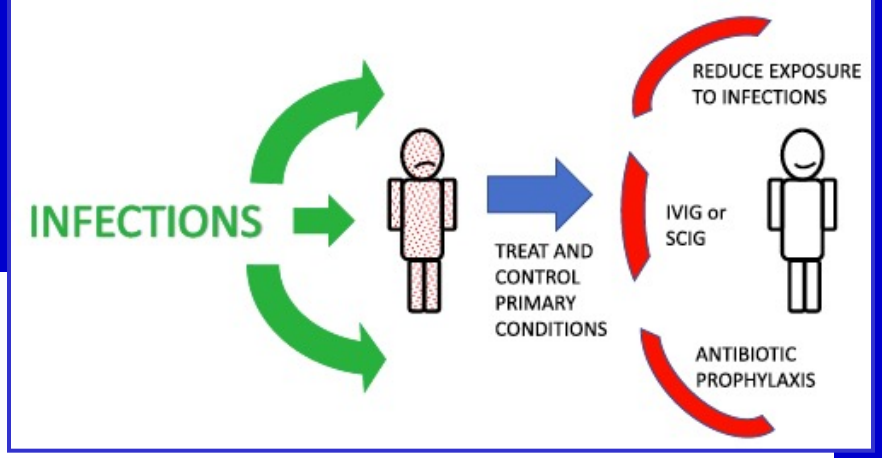


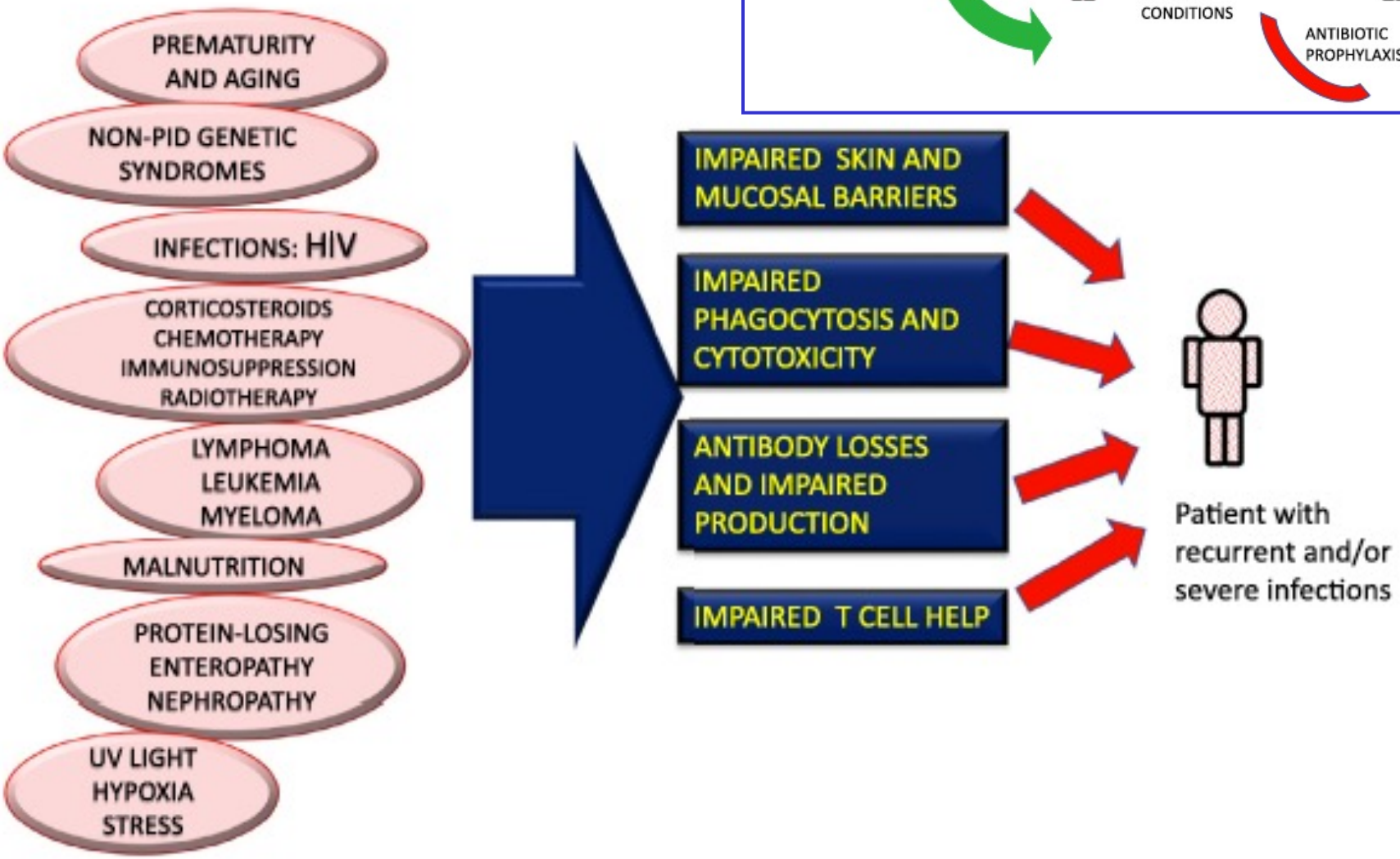
# European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstances

EUROPEAN RESUSCITATION COUNCIL



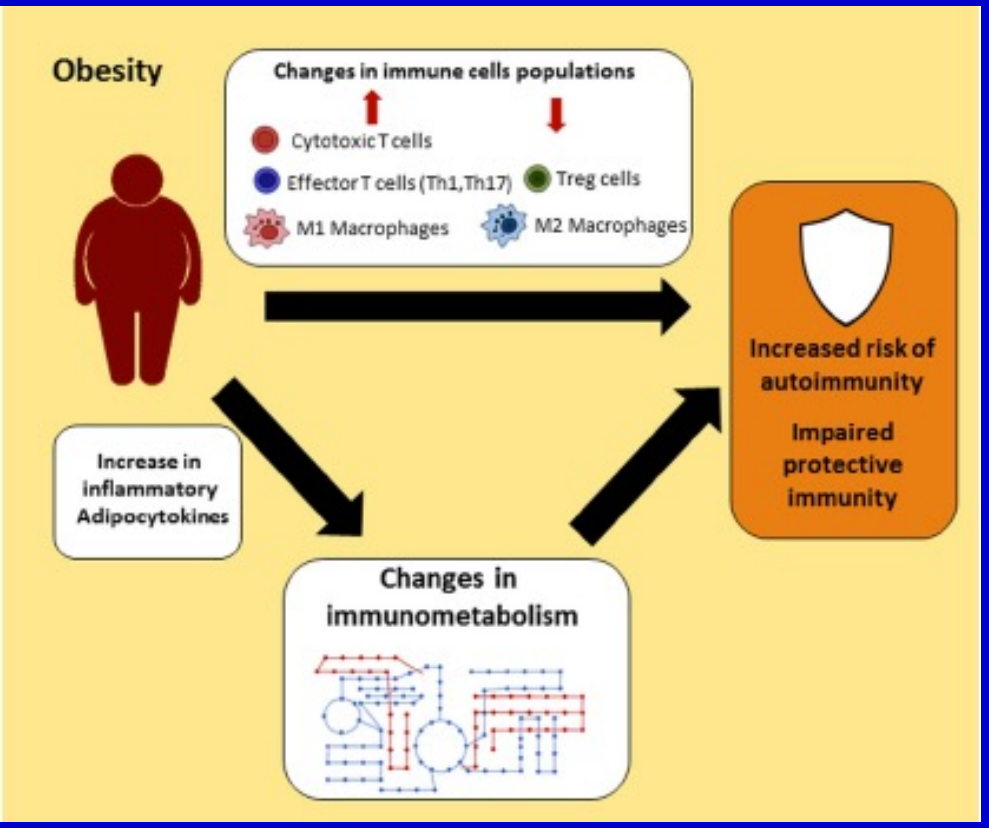
# Secondary immunodeficiencies

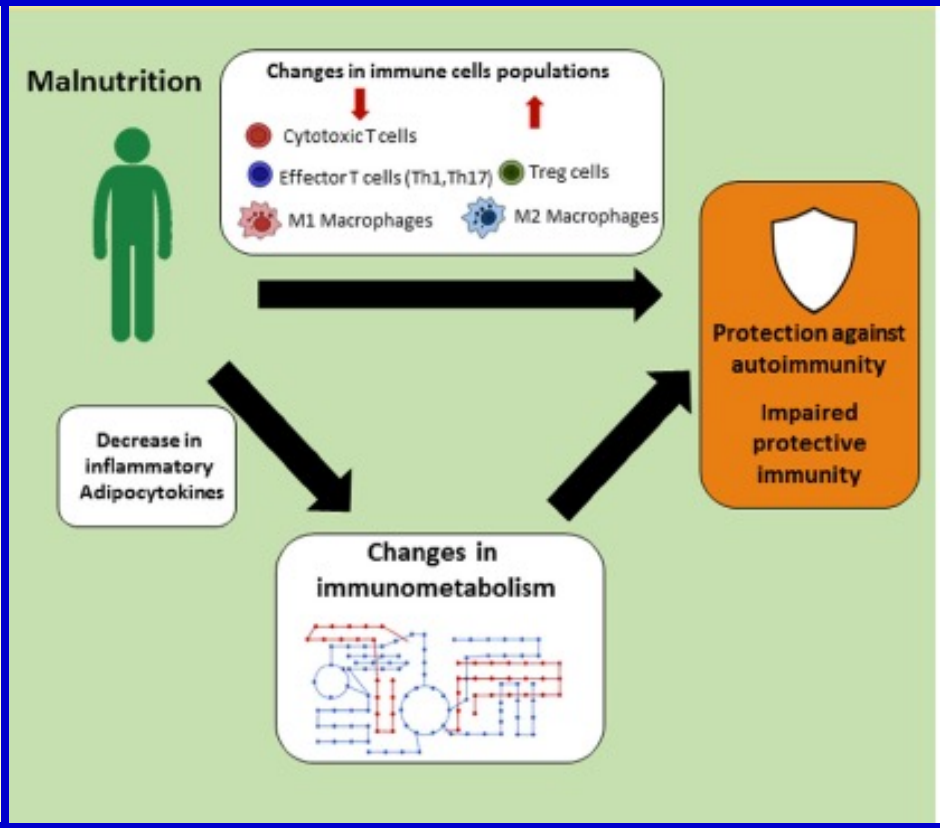



K.S. Tuano et al. / Ann Allergy Asthma Immunol 127 (2021) 617–626

# Changes in Nutritional Status Impact Immune Cell Metabolism and Function

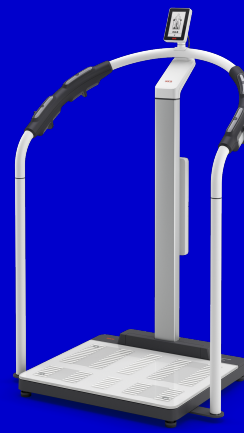


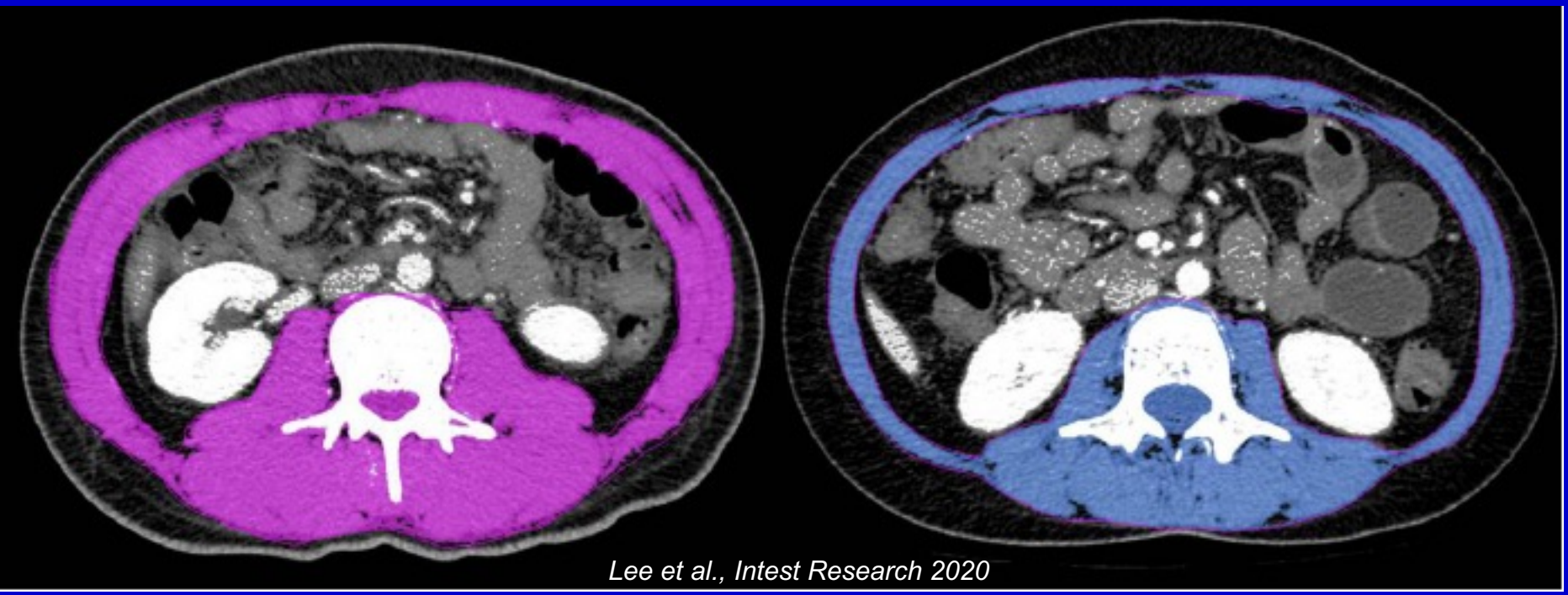

Alwarawrah et al.

May 2018 | Volume 9
frontiers in Immunology

# Sarcopenia and Inflammatory Bowel Disease: A Systematic Review



## Sarcopenia Prevalence IBD: 42% (70% CD)



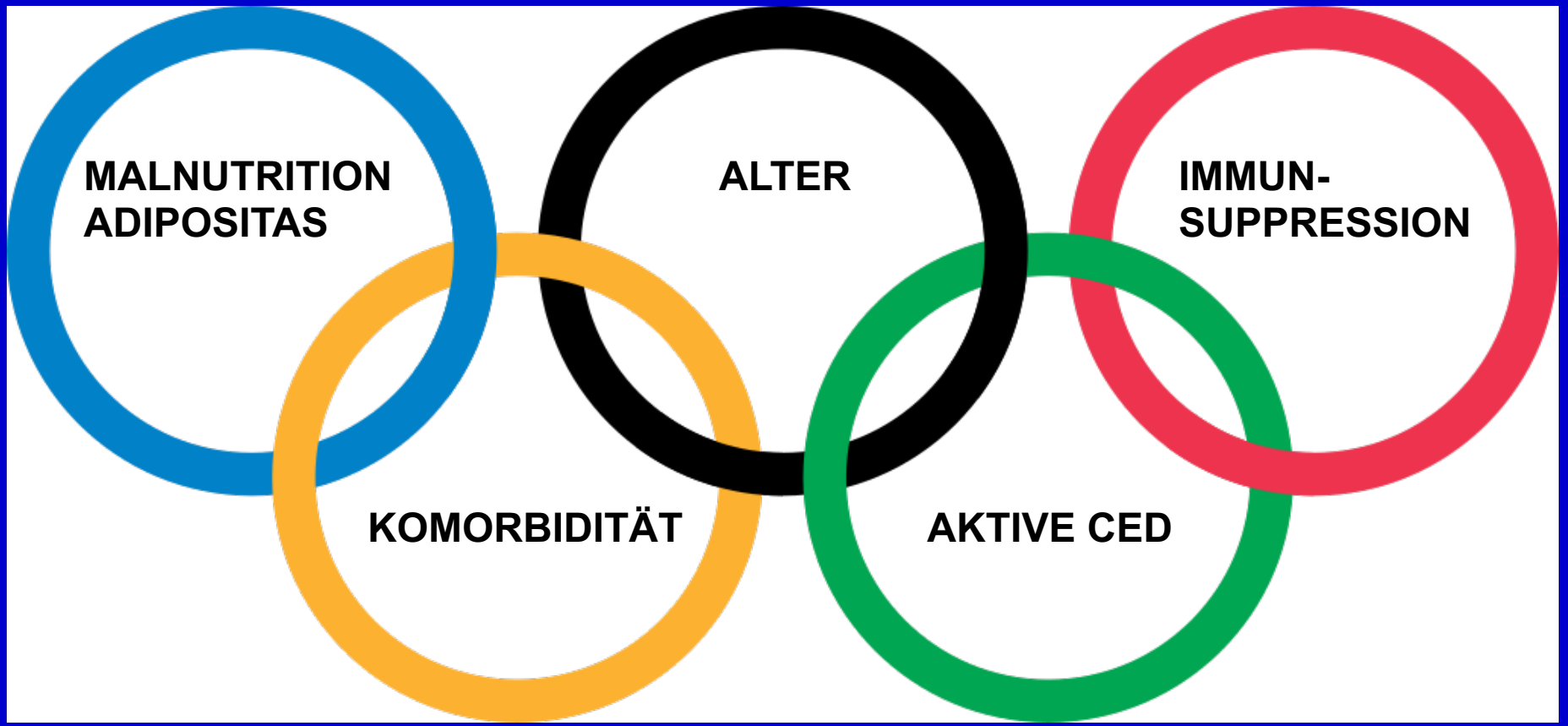
*Lee et al., Intest Research 2020*

**Conclusion:** Many IBD patients are young, may be malnourished, and commonly require emergent surgery. There is considerable heterogeneity in the assessment of sarcopenia. Sarcopenia is common in the IBD population and can predict the need for surgical intervention. Sarcopenia correlates with an increased rate of major postoperative complications. Improved perioperative intervention may diminish this risk. A formal assessment, screening by a dedicated IBD dietician, and preoperative physical therapy may facilitate early intervention.

*Ryan et al., IBD 2019*

# RISIKO FÜR OPPORTUNISTISCHE INFEKTIONEN

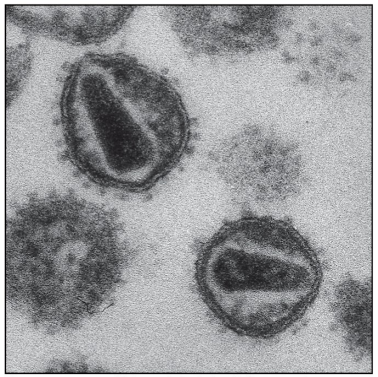
**ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease** *ECCO 2021*




*Kucharzik et al., JCC 2021*

# HIV and AIDS are still present

*(aus Janeway Immunobiology 6th edition)*



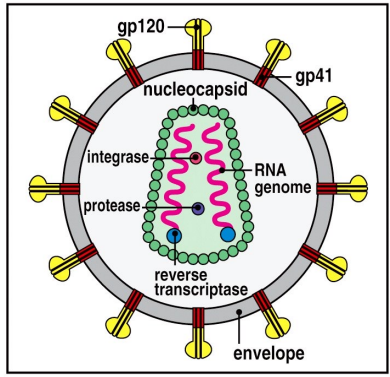



Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

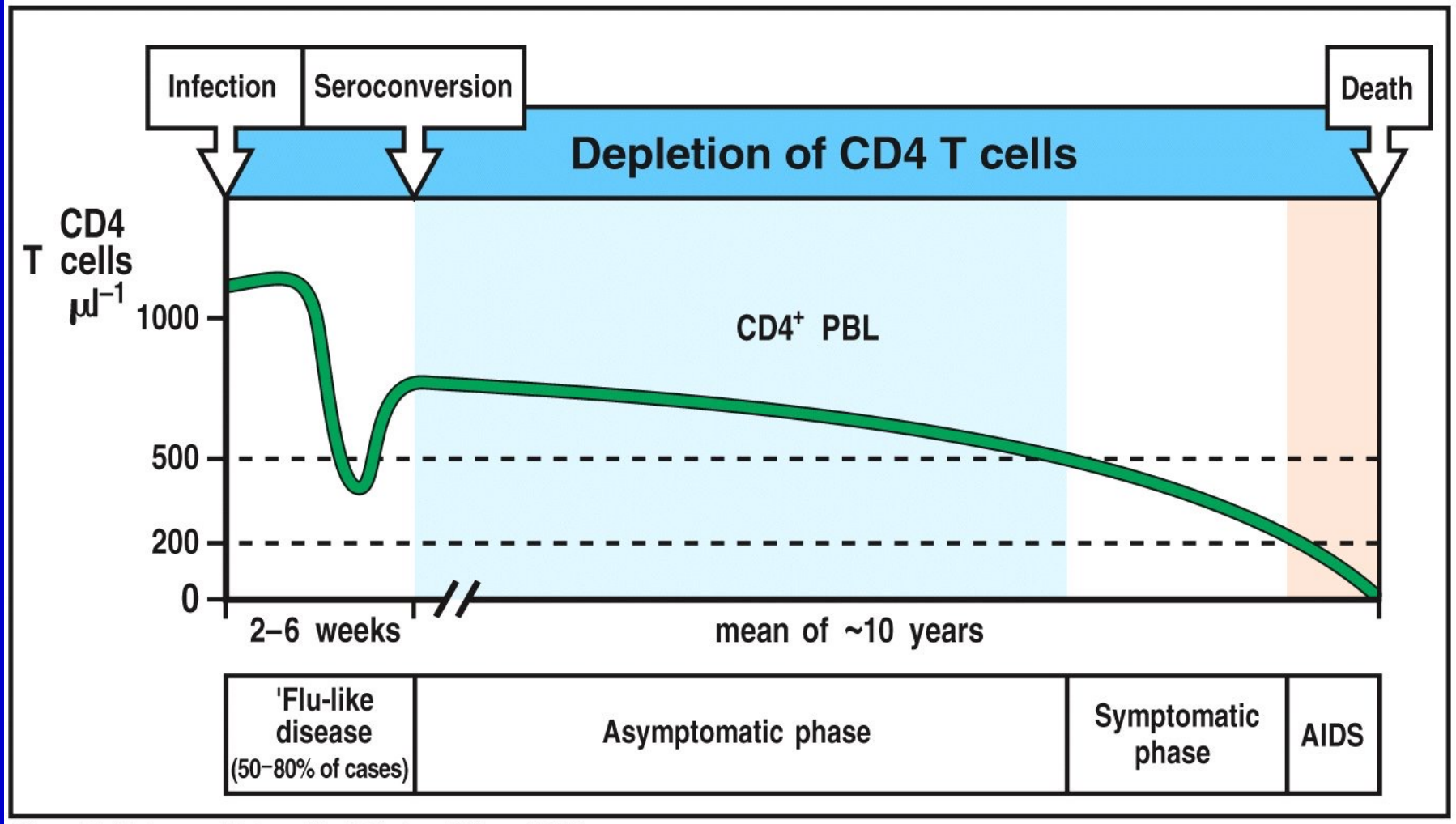
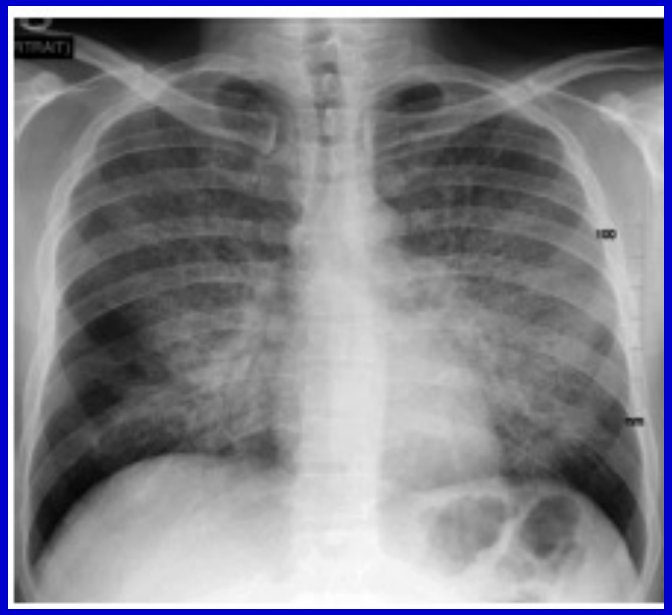
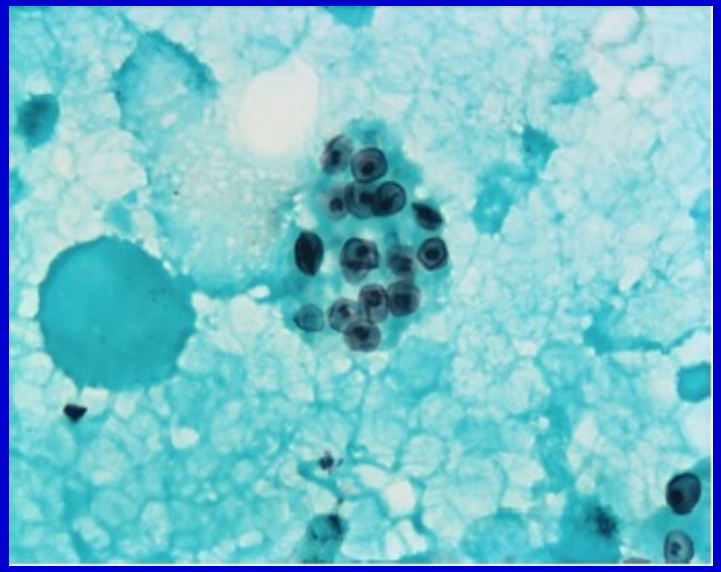


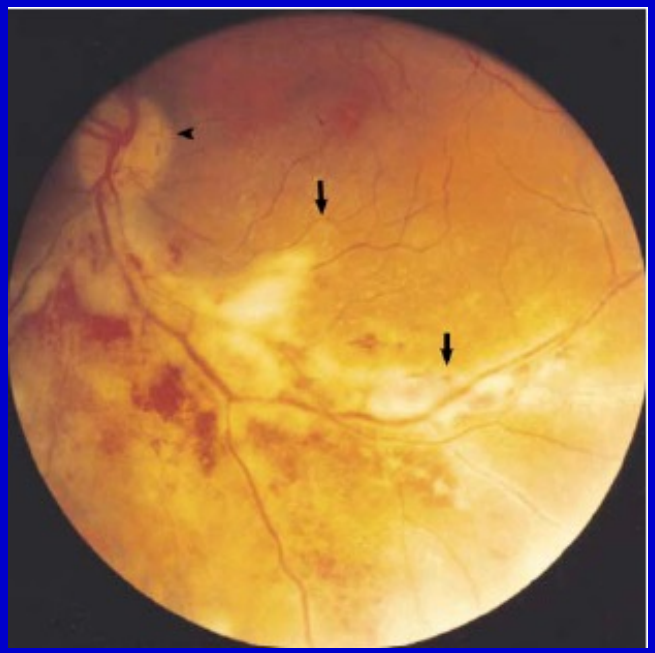

Figure 11-20 Immunobiology, 6/e. (© Garland Science 2005)

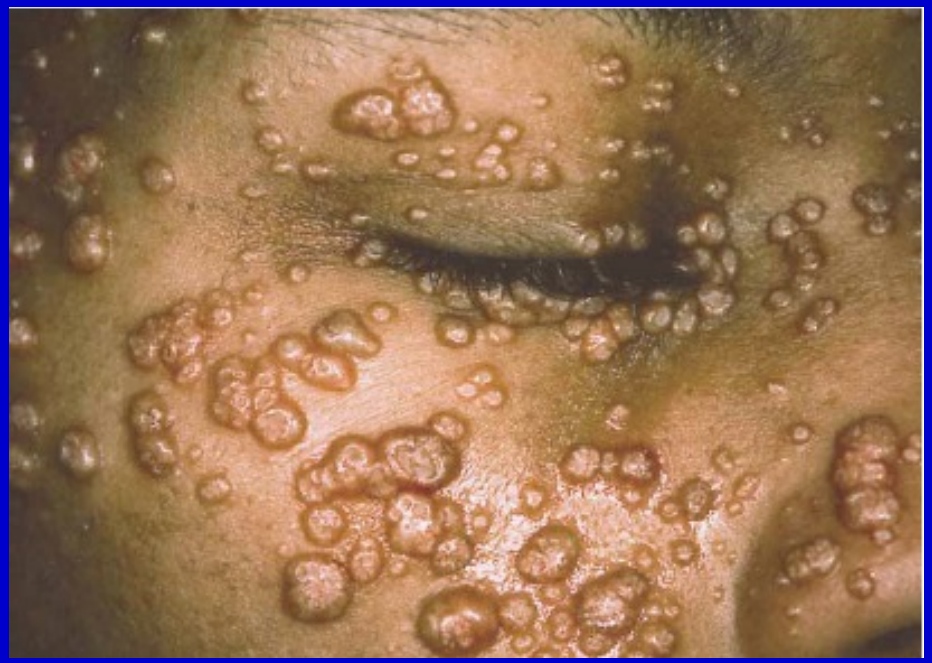
# AIDS Clinical Images

*Salzer et al., Respiration 2018; Kenner et al., NEJM; Cotelli et al., NEJM 1998*

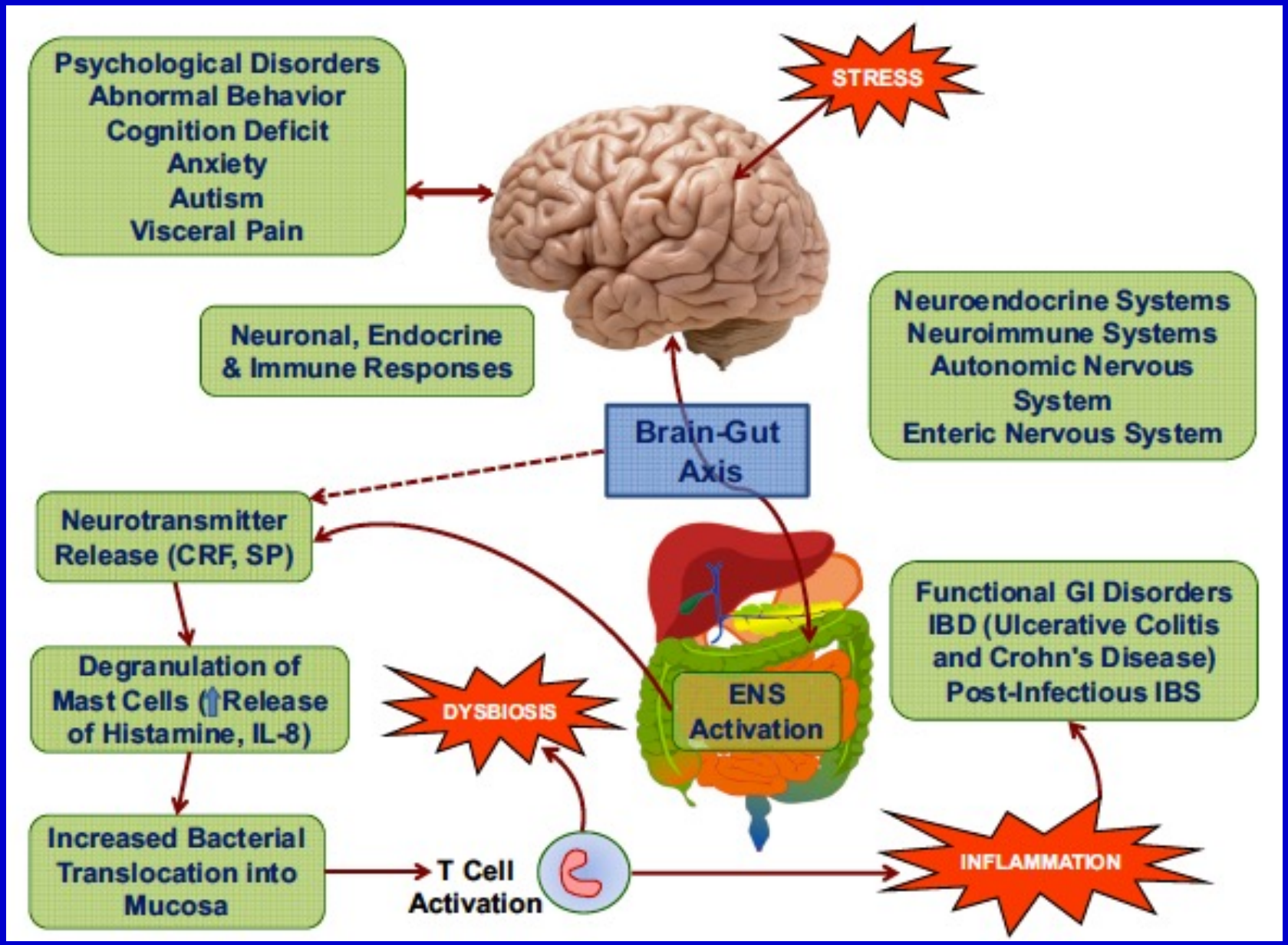




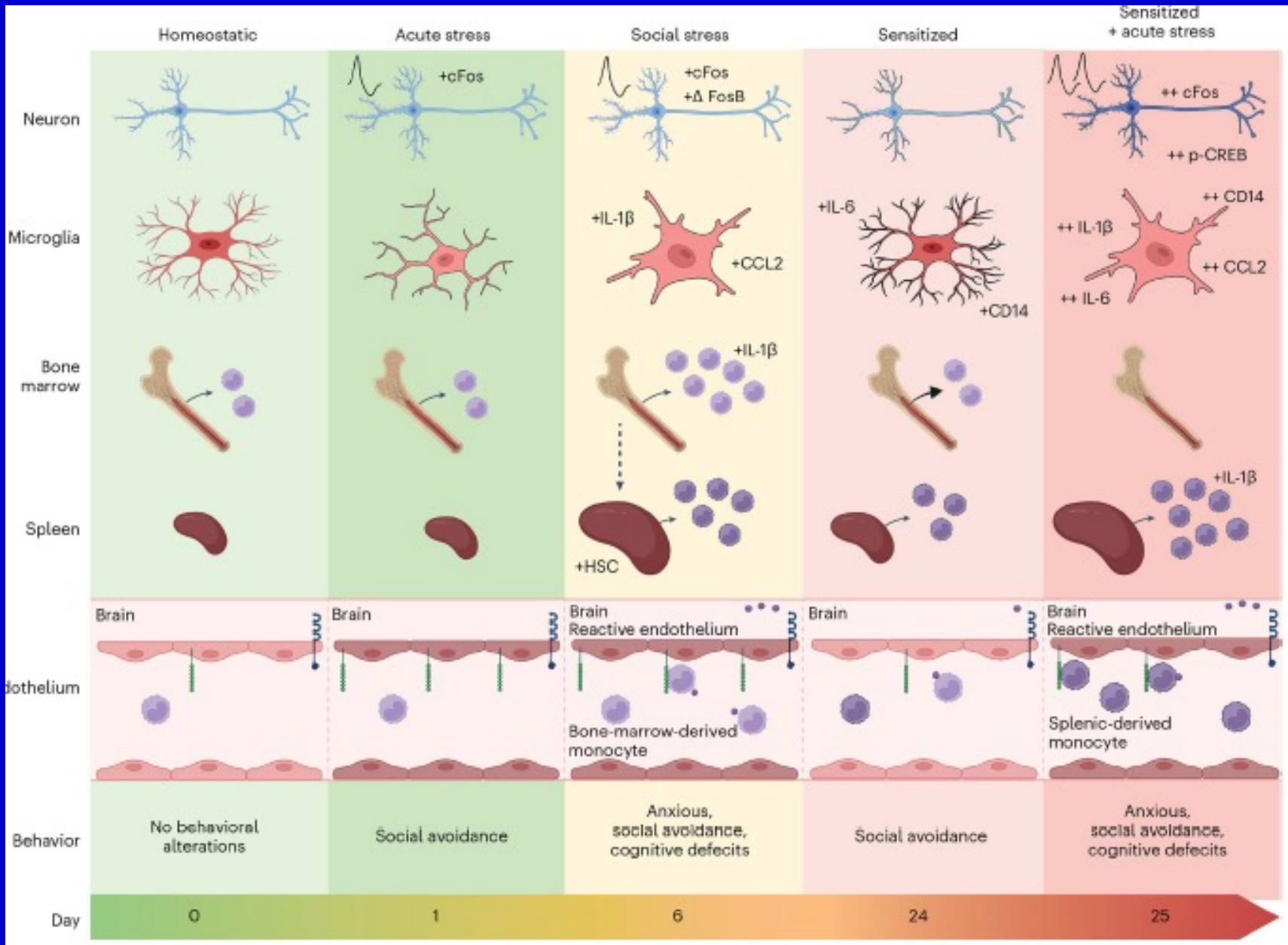




**Mechanisms by which Stress Affects the Experimental and Clinical Inflammatory Bowel Disease (IBD): Role of Brain-Gut Axis**



# The neuroimmunology of social-stress-induced sensitization




*Blitz et al., Nat Immunol 2022*

**Fig. 3 | Overview of repeated social defeat and stress sensitization of central and peripheral immune compartments.**

# Infection in Solid-Organ Transplant Recipients

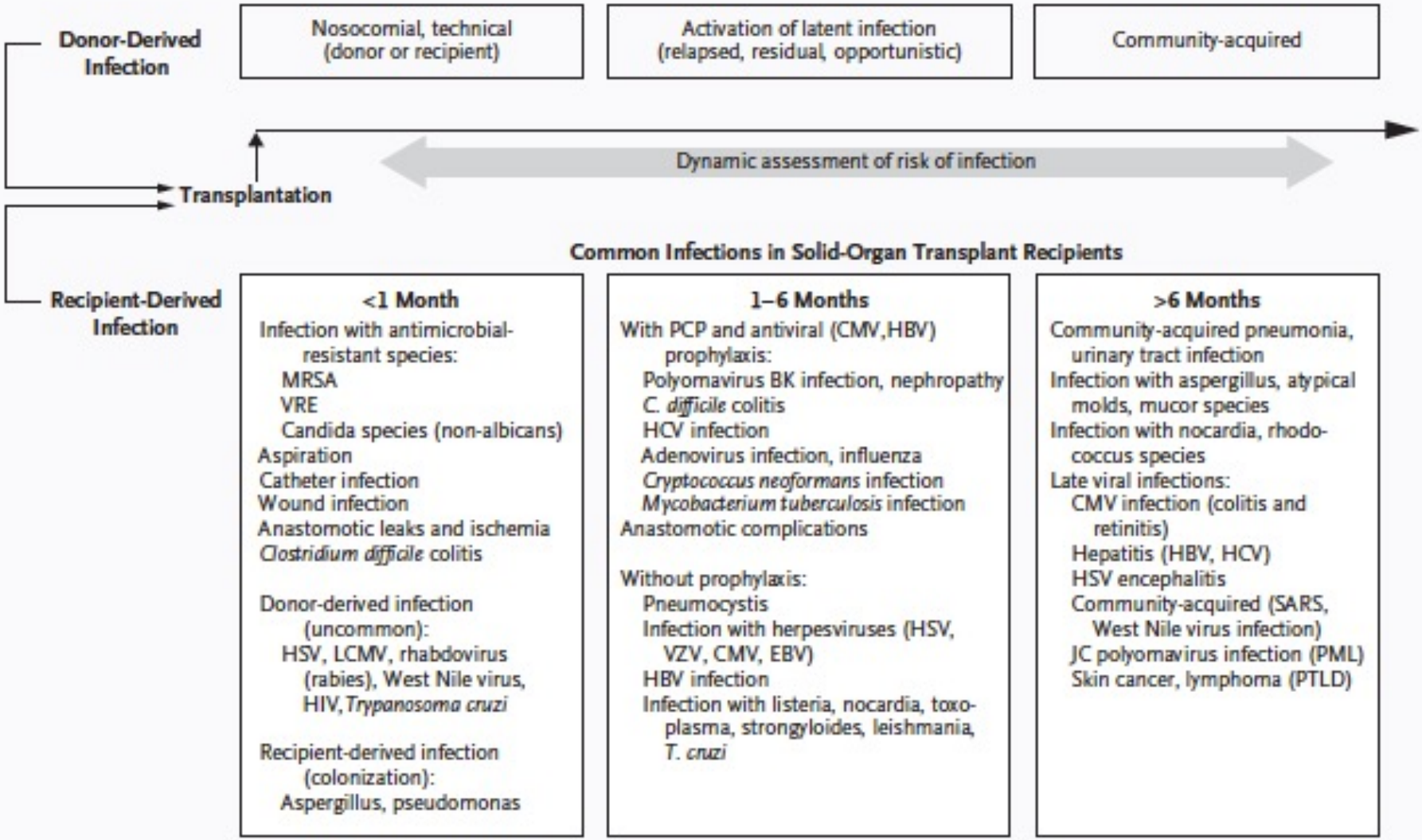


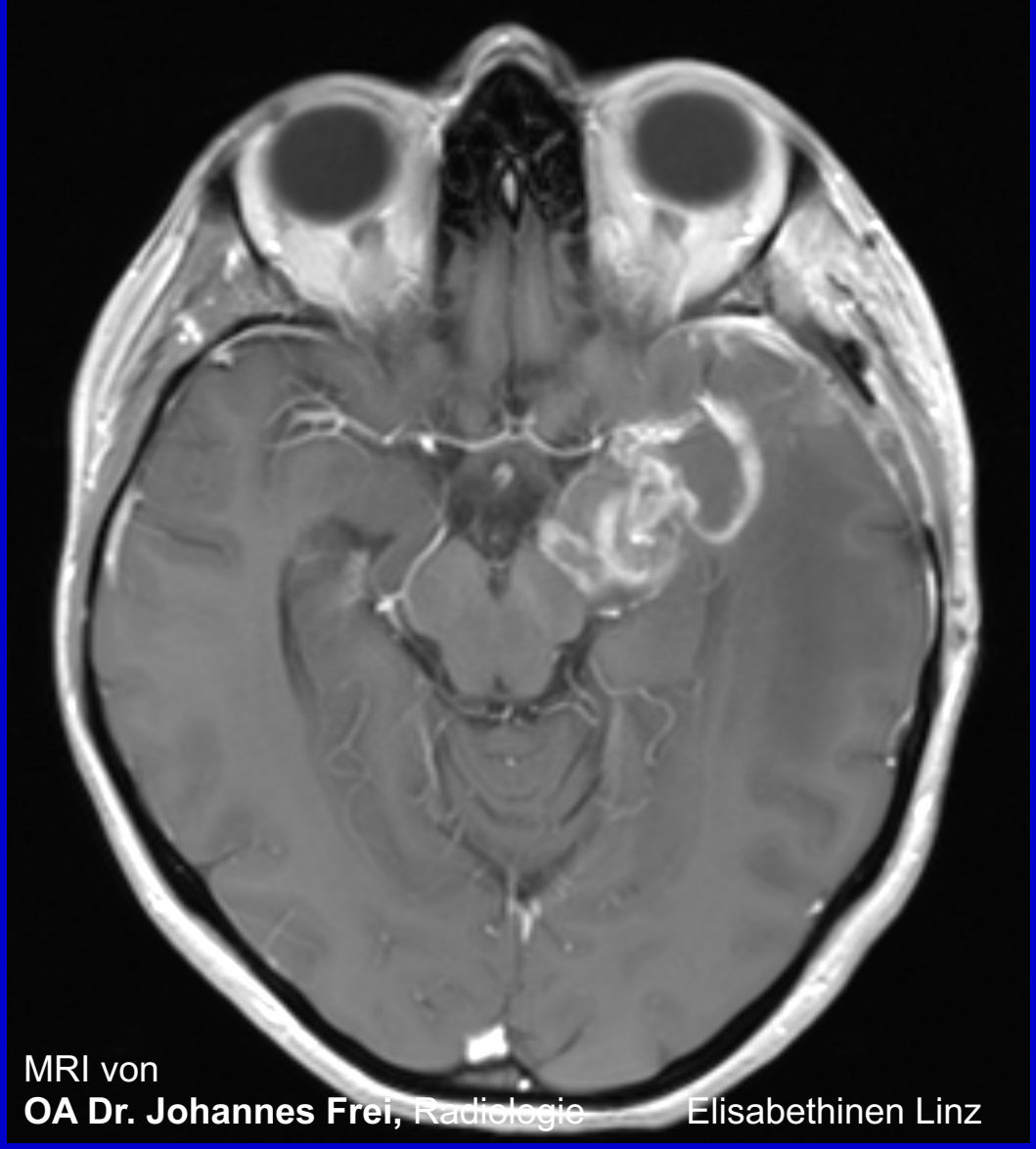

**Figure 4. Changing Timeline of Infection after Organ Transplantation.**



N Engl J Med 2007;357:2601-14.

# CASE

- **33 jährige Patientin mit ilekolonischem Morbus Crohn** (luminal, ED 07/2015; A2 L3+L4 B1);
- **EBV IgG +; EBV IgM** -;
- Nach Therapie mit AZA für 1 Jahr in klinischer Remission mit normalem Calprotectin;
- 2 wöchiges Fieber im August 2016 mit cervikaler Lymphadenopathie, Splenomegalie mit Milz und Leberherden und Panzytopenie;
- LK Histologie: **EBV ass. Lymphoproliferative Erkrankung**;
- Spontanremmission;
- 03/2017 **ZNS Rezidiv** der **EBV assoziierten Lymphoproliferation**

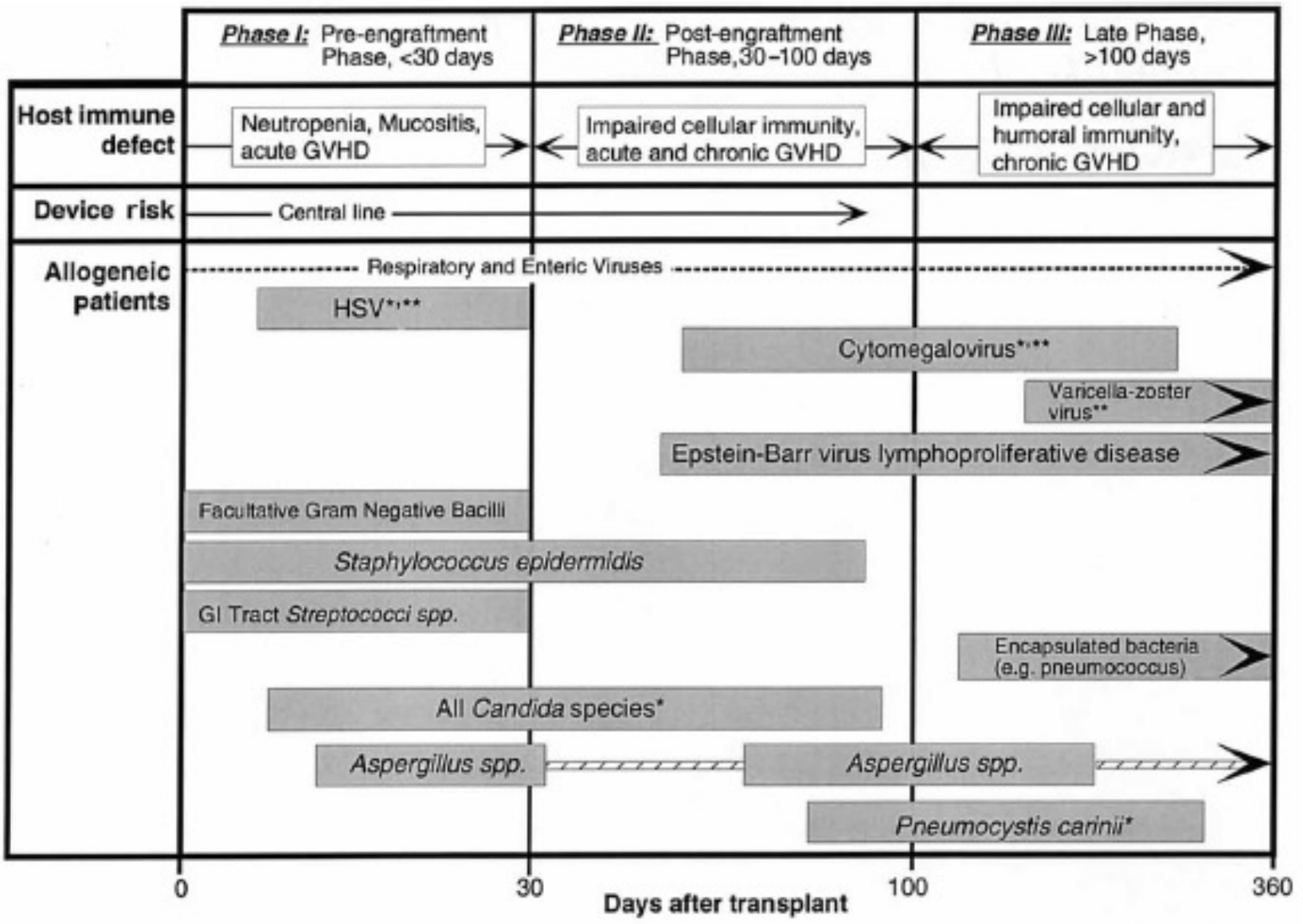


MRI von
**OA Dr. Johannes Frei,** Radiologie Elisabethinen Linz

Therapie: 8x Rituximab + 4x HD-MTX > Partieller guter Response > seither in **stable disease** (Stand 9/2022)

# Preventing opportunistic infections in bone marrow transplant recipients

C.A. Dykewicz




Transplant Infectious Disease 1999: 1: 40–49

# Optimal Management of Neutropenic Fever in Patients With Cancer

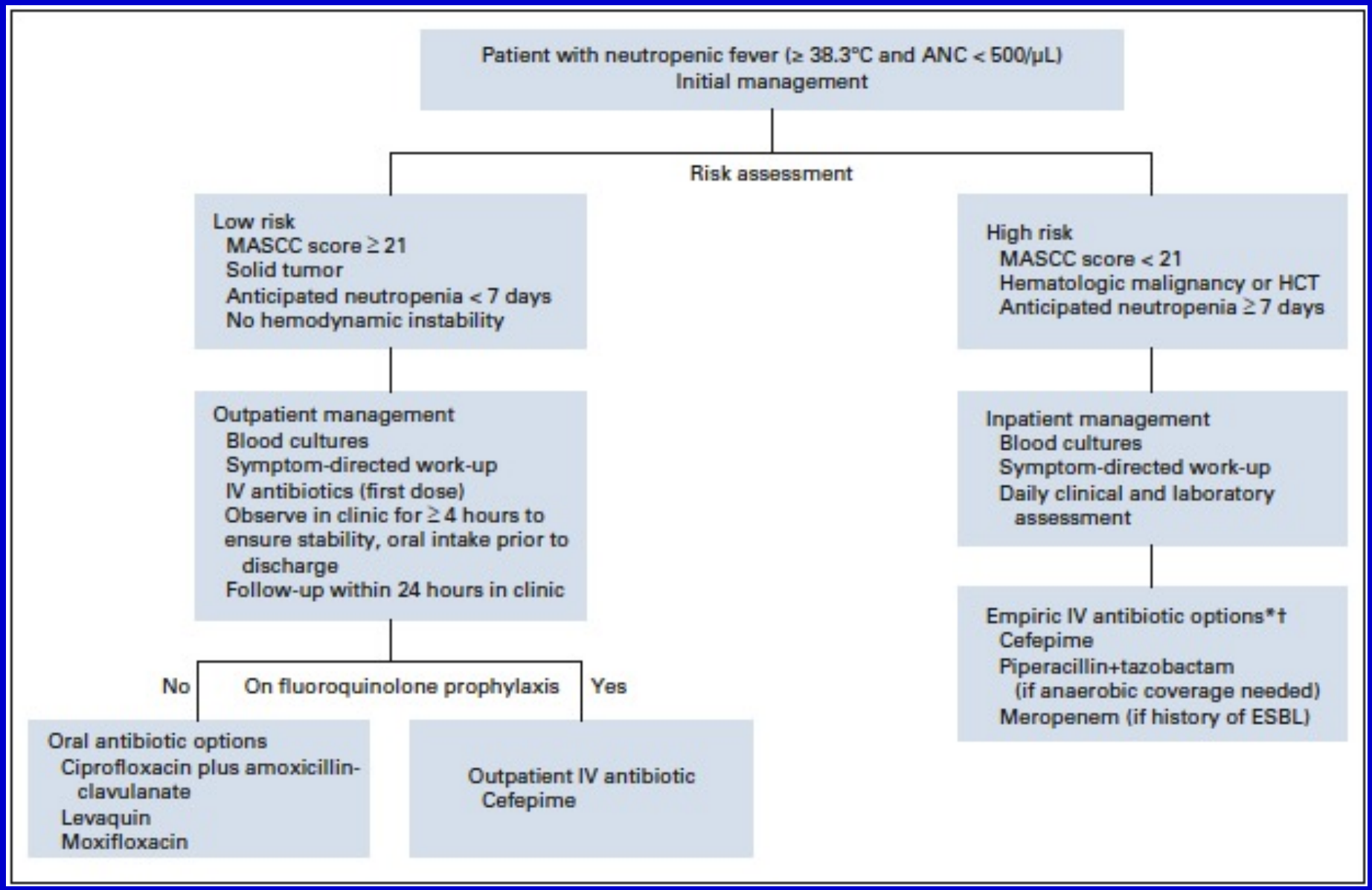
*Zimmer et al., JCO 2019*

**TABLE 1.** The Multinational Association for Supportive Care in Cancer (MASCC) Score

| Characteristic | Weight |
|---|---|
| Burden of febrile neutropenia | |
| No or mild symptoms | 5 |
| Moderate symptoms | 3 |
| No hypotension (SBP > 90 mm Hg) | 5 |
| No active COPD | 4 |
| Solid tumor or no previous fungal infection | 4 |
| No dehydration requiring parenteral fluids | 3 |
| Outpatient status | 3 |
| Age < 60 years | 2 |

# Optimal Management of Neutropenic Fever in Patients With Cancer

*Zimmer et al., JCO 2019*



# Fallbericht: Patient KG, m, 41a

- FA: keine Auffälligkeiten
- FK: in der Jugend wiederholte Sinusitiden, Bronchitiden und Durchfallsepisoden
- seit 2001 (29a): wiederholte Pneumonien (CAP) die ambulant mit Clavamox behandelt wurden
- seit 2001 Gewichtsverlust – Untergewicht
- Biometrie: KG 59kg, KL 179cm, **BMI 18 - Leichtgewicht**
- PKU: Sarkopenie, Pulmo: re basal leises Giemen, sonst keine Auffälligkeiten

# Anamnese 2

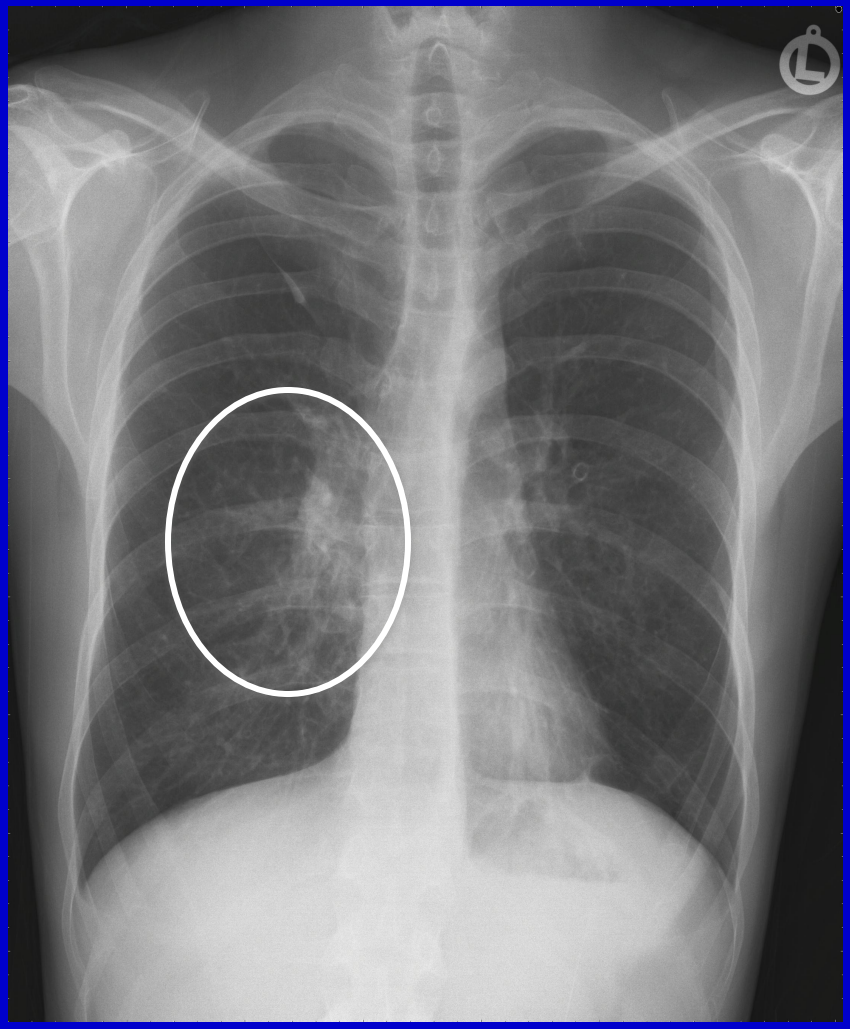
- 2006 ( 34a) Pulmologische Aufnahme wegen therapierefraktärem Husten und Dyspnoe, morgendlich putride Expektoration

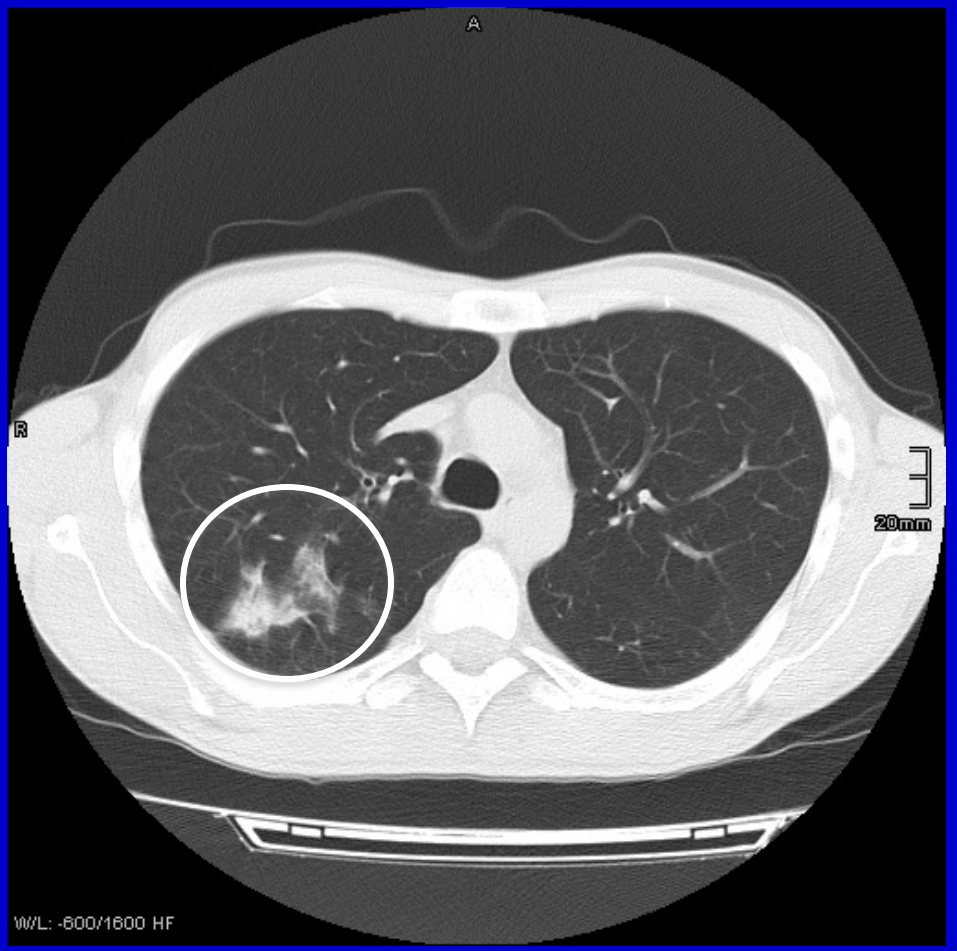
- 2006 Diagnosen: Bronchiektasien, Pansinusitis

- 2006 Therapie: Klacid, Symbicort, Vibrocil

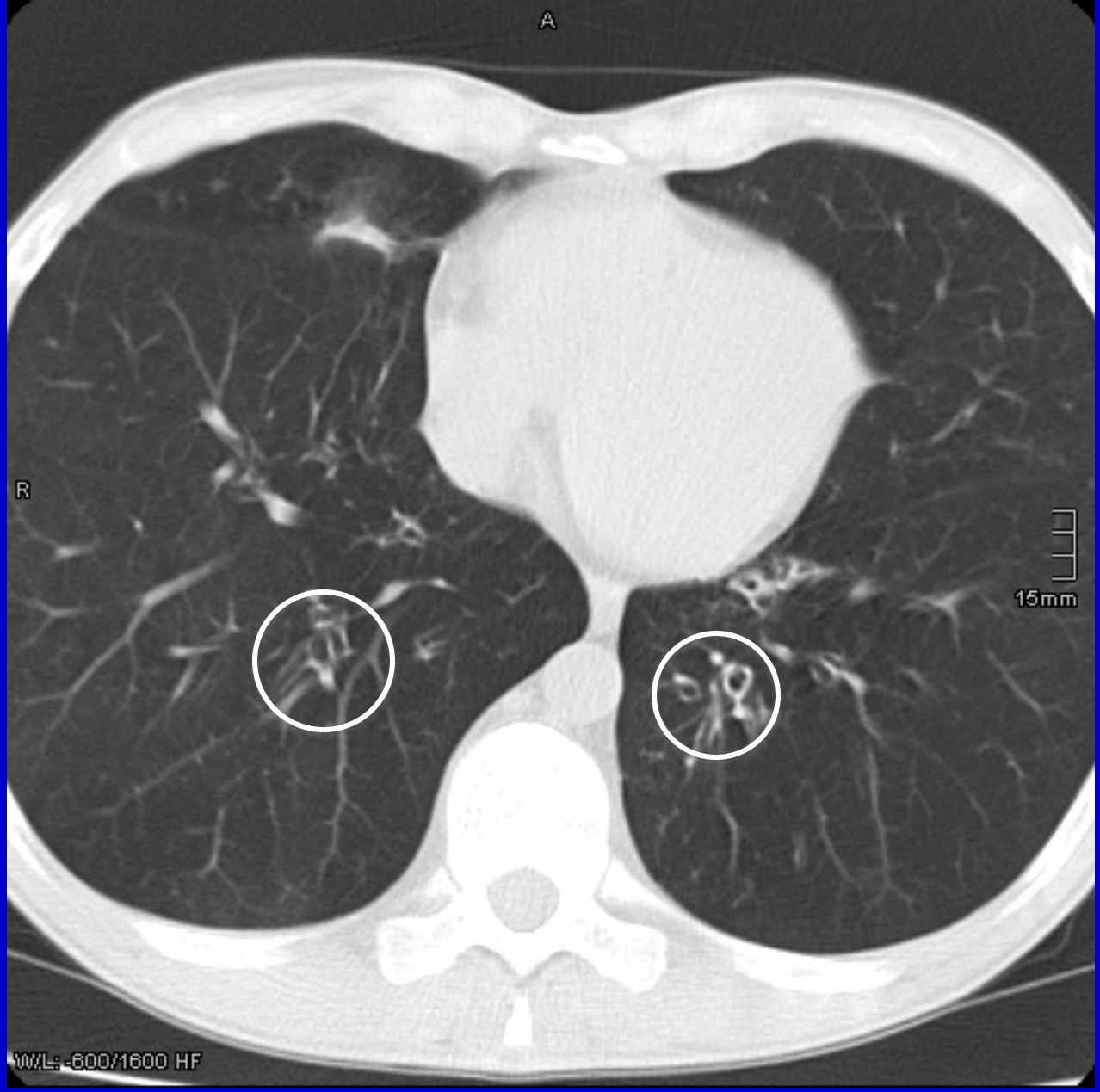
- 2006 NNH OP (FESS)

- 2007 (35a) neuerliche pneumologische Aufnahme wegen bilat. Pneumonie






Pneumonische Infiltrate




Bronchiektasien

# Differentialdiagnosen

1. Ciliendysfunktion?
2. Zystische Fibrose?
3. AIDS?
4. Malabsorptionserkrankung mit sekundärem Immunglobulinmangel?
5. CLL?
6. Common Variable Immundeficiency?
7. Sinubronchiales Syndrom - Allergie?

# Wenn Immundefekt – welches System?

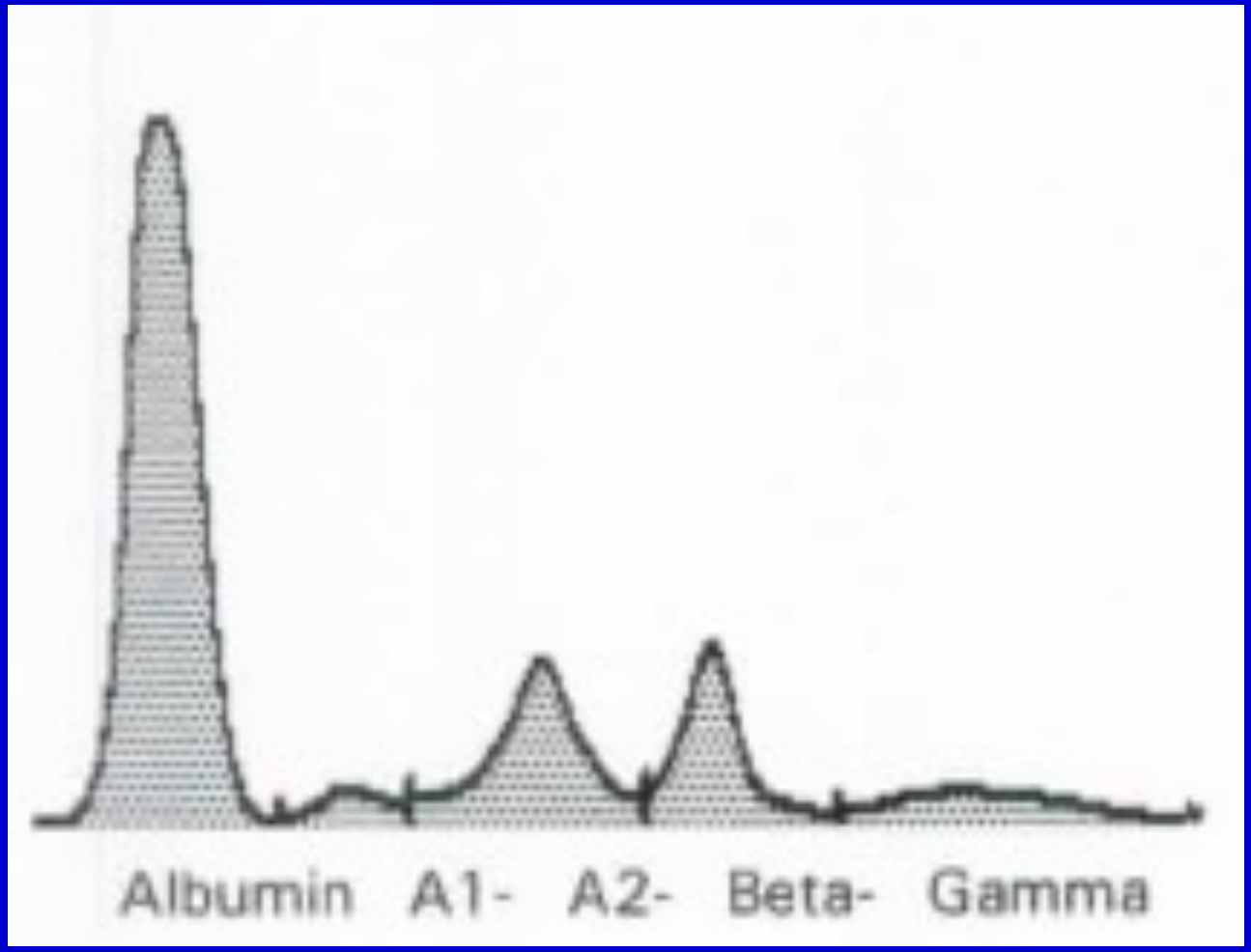
1. Complement
2. Phagozyten
3. T – Zellen
4. B – Zellen/Antikörper
5. T + B-Zellen
6. Innate Immunity

# Laboratory evaluation of primary immunodeficiencies

**TABLE I.** Common pathogens and infection sites according to the underlying immune defect

| Affected immunity arm | Typical site of infection | Common pathogens |
|---|---|---|
| B cells | Sinopulmonary tract, GI tract, joints, CNS | Pyogenic bacteria: streptococci, staphylococci, *Haemophilus influenzae*<br>Enteroviruses: ECHO, polio<br>*Mycoplasma* species |
| T cells | Sepsis, lung, GI tract, skin | Viruses: CMV,<br>adenovirus, measles, molluscum<br>Fungi: *Candida* and *Aspergillus* species, *Pneumocystis jiroveci*<br>Pyogenic bacteria<br>Protozoa: *Cryptosporidium* species |
| Phagocytes | Skin infections, lymphadenitis, liver, lung, bone, GI tract, gingivitis/periodontitis | Bacteria: staphylococci, *Serratia marcescens*, *Burkholderia cepacia*, *Klebsiella* species, *Escherichia coli*, *Salmonella* species, *Proteus* species<br>Fungi: *Candida*, *Aspergillus*, and *Nocardia* species |
| Complement | Systemic infections, meningitis | Pyogenic bacteria: streptococci, *Haemophilus influenzae*, *Neisseria* species |

*GI*, gastrointestinal; *CNS*, central nervous system; *ECHO*, echovirus; *CMV*, cytomegalovirus.


Albumin
A1-
A2-
Beta-
Gamma

# Labor

- L 7,2 G/l
- Hb 16 g/dl
- MCV 85 fl
- Thr 211 G/l

- Seg 65%
- Ly 20%
- Eos 0,2
- Baso 0,5%
- Mono 5,9%

- Albumin 5,1g/dl

- CD4 860 (44%)
- CD8 627 (32%)
- CD 16/56 NK 189 (10%)
- T4/T8 Ratio 1,38

- IgG 21 mg/dl
- IgA <5 mg/dl
- IgM <5 mg/dl

- HIV Serologie negativ

# GI Leichtgewichtabklärung

- Gastroskopie: Refluxösophagitis I, sonst makrosko. Unauffällig
- Duodenalhistologie: gering chronische Entzündung, keine Zottenatrophie

- Videokapselendoskopie: normal

- Ilekoloskopie: makroskopisch unauffällig
- **Ileumhistologie: lymphatische Hyperplasie, Zotten unauffällig**
- **Colonhistologie: gering lymphoplasmazellulär infiltriert, angedeutete Eitheloidzellhaufen**

- EMA: negativ
- Fäkales Calprotectin: normal
- Pankreaslastase im Stuhl: normal
- Lambliennachweis: negativ

- **Fosläuremangel, Vitamin D Mangel**
- **Osteopenie**

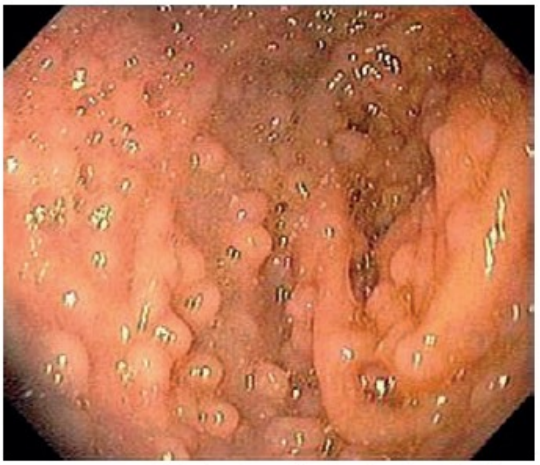
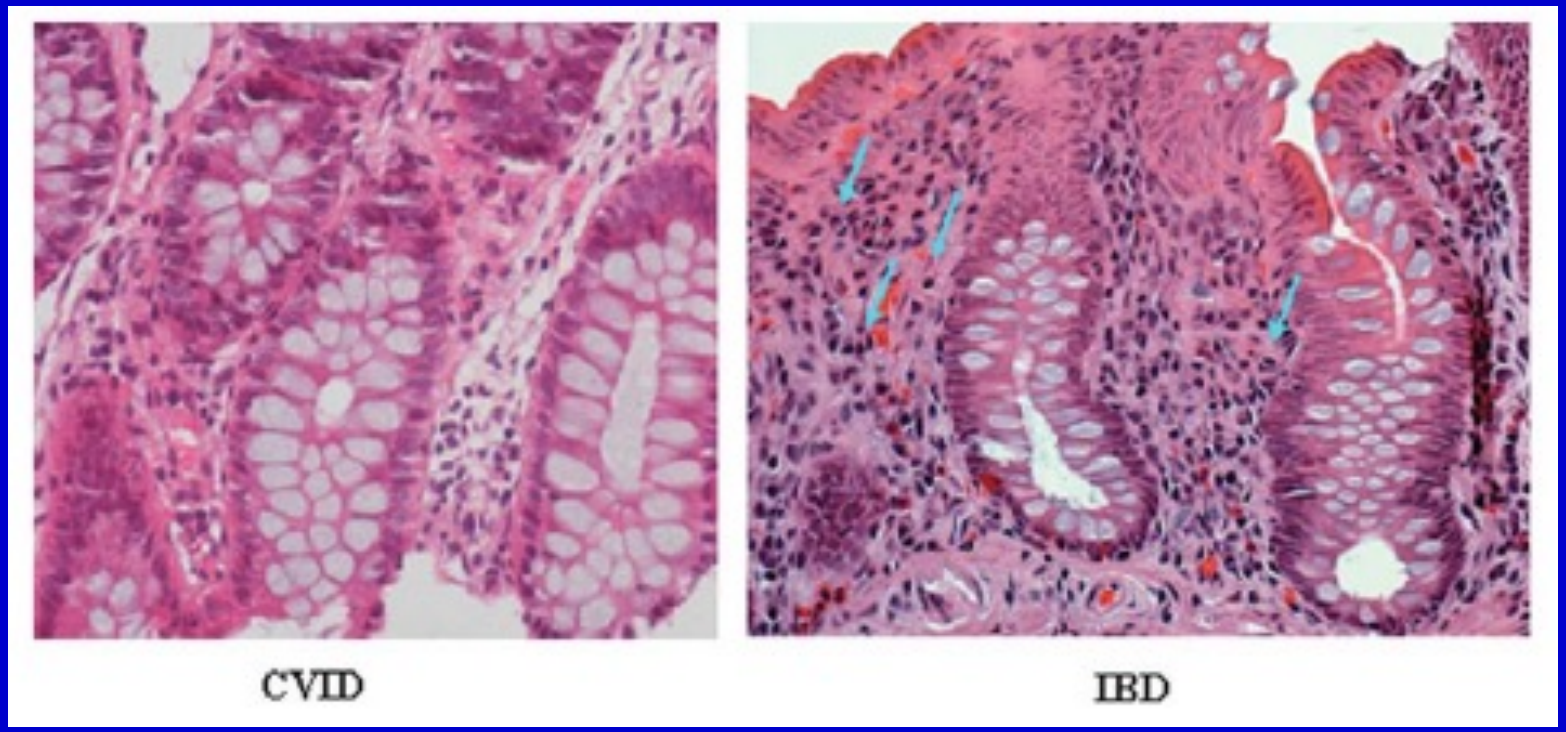


**Fig 1.** Gross nodularity found in the duodenal bulb on EGD.

# Characterization of Immunologic Defects in Patients with Common Variable Immunodeficiency (CVID) with Intestinal Disease




*Agarwal et al. IBD 2011*

# Diagnostic criteria: **CVID** (www.esid.org)

**Probable**

Male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria:

1) Onset of immunodeficiency at greater than 2 years of age
2) Absent isohemagglutinins and/or poor response to vaccines
3) Defined causes of hypogammaglobulinemia have been excluded *(see 'Differential Diagnosis of Hypogammaglobulinemia')*

**C**ommon **V**ariable **I**mmuno**d**eficiency

# CVID Prävalenz 1 : 10 000 – 1 : 50 000

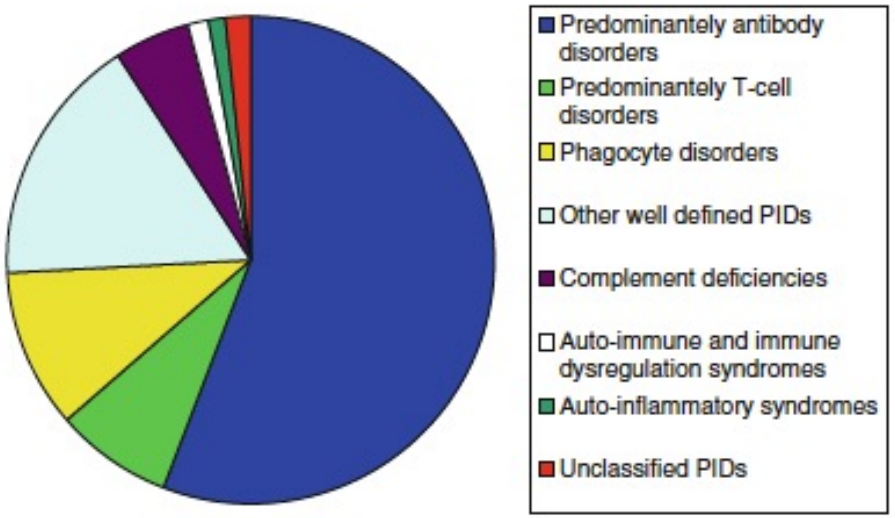



**Fig. 1** Distribution of PID in Europe according to the ESID patient registry 2010 (http://www.esid.org/statistics.php?sub=2), $n$=10,747. *PIDs* primary immunodeficiencies, *ESID* European Society for Immunodeficiencies

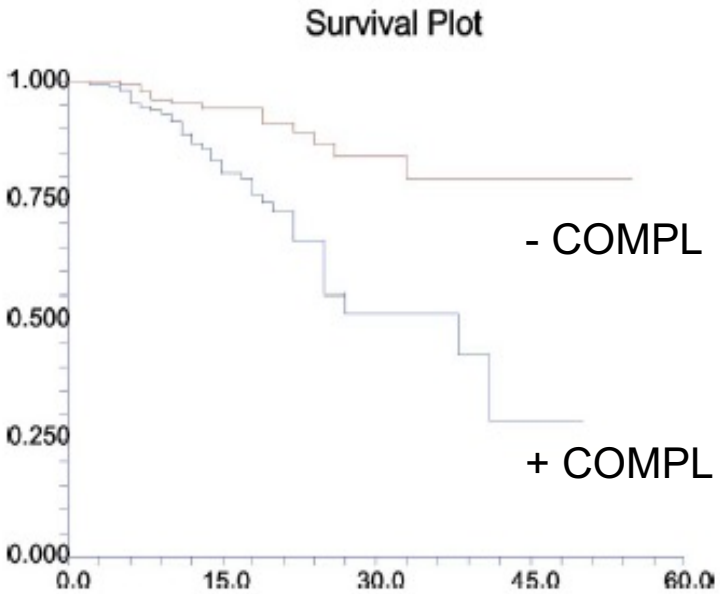



**Figure 4. Mortality by years since diagnosis and by clinical phenotype.** Red line represents those without complications; blue line, those with at least one disease-related complication. Kaplan-Meier plot of survival.

*de Vries et al., Eur J Pediatr 2011*

*Chapel et al., blood 2008*


# Therapie

A: 20g IVIG / alle 4 Wochen

B: 6g SCIG / wöchentlich Selbstapplikation

- IVIG 400 – 600mg/kg//q3-4 Wochen

- SCIG Start: 100-200mg/kg

- SCIG Erhaltung 160mg/kg//wöchentlich

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/j.1365-2249.2011.04461.x

# Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update

## Take-home messages

- The key to detect a PID is to consider the possibility.
- PIDs almost always present with one or more of eight clinical presentations; these can be used as the starting-point to enter the appropriate diagnostic protocol.
- SCID is an emergency.
- Timely recognition of antibody deficiency prevents future organ damage.
- If PID is suspected or runs in the family, delay live-attenuated vaccinations and do not postpone immunological investigations.
- Use age-matched reference values to avoid misinterpretation of immunological test results.

*de Vries in Collaboration with ESID*

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/j.1365-2249.2011.04461.x

# Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update

(Tabelle vereinfacht)

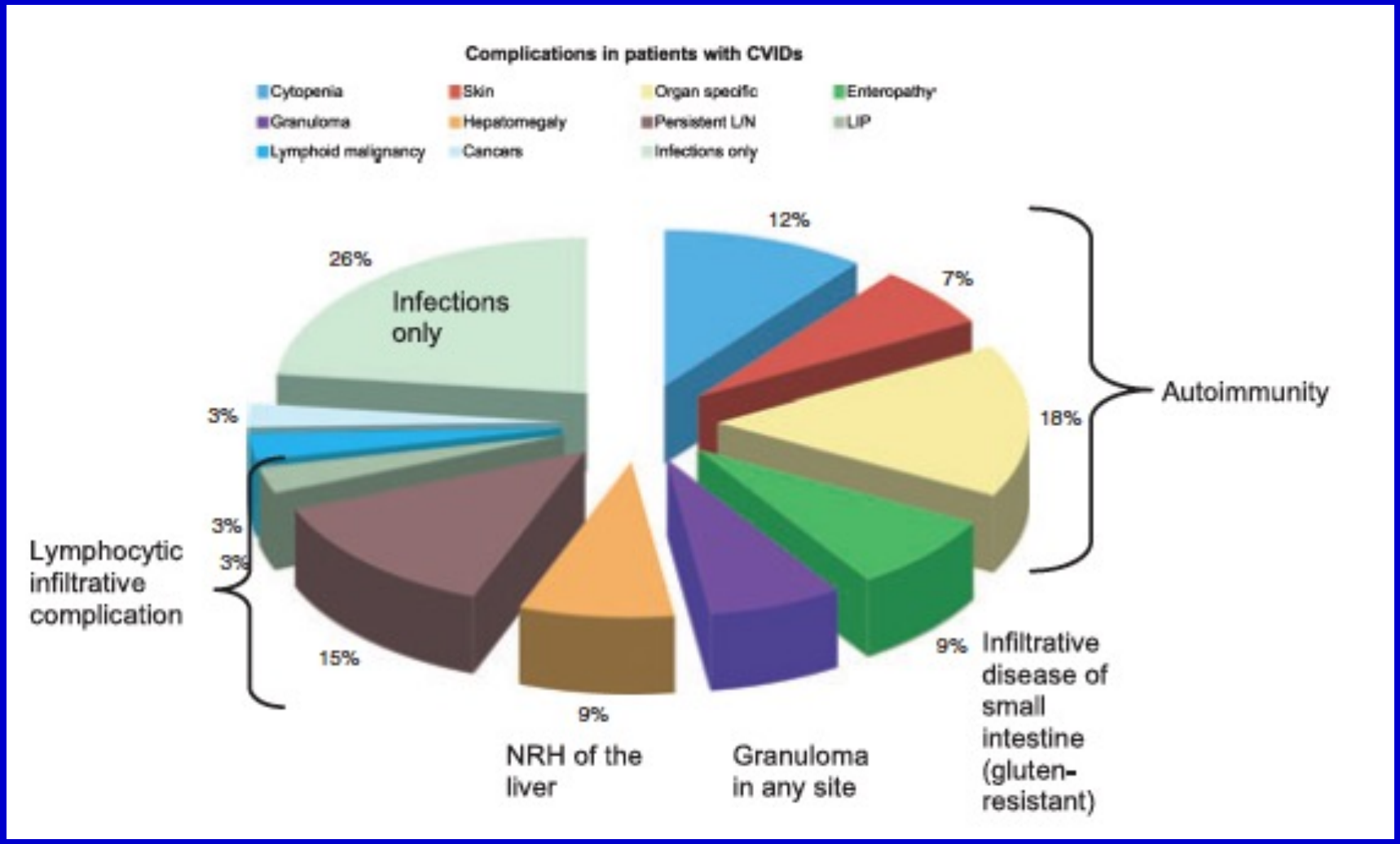
| Präsentation | Pathogen | PID | DD |
|---|---|---|---|
| **HNO<br>Atemwege<br>Bronchiektasien** | Bakterien<br>meist extrazellulär | **Antikörpermangel** | CF<br>Allergie<br>COPD |
| **Wachtumsdefekt** | Viren, Pilze<br>Parasiten<br>Intrazellul. Bakter. | **Kombinierte<br>T+B Zelldefekte** | GI, cardiopulm<br>Renal,metabol<br>Neurol., endokrin. |
| **Rekurrente<br>Pyogene Infekte** | Staphylokokken<br>Invasive Pilze | **Phagozytenzahl↓<br>oder Funktion ↓** | Med. Neutropenie<br>Autoimmun<br>Hautbarriere |
| **Ungewöhnliche<br>oder ungew.<br>Schwere Infekte** | Meist intrazelluläre<br>Errger | **T+B Zellen<br>Innate Immunity** | Virulenz<br>Malnutrition<br>Sek. Immunsuppr. |

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/j.1365-2249.2011.04461.x

# Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update

| Präsentation | Pathogen | PID | DD |
|---|---|---|---|
| **Rekurrente Infekte identer Erreger** | Intrazelluläre Erreger | **Phagozyten Complement Innate Immunitiy** | Exposition Anatom. Disposit. Inad. Therapie |
| **Autoimmunität Chron. Inflammat. Lymphoprolif.** | | **Kombinierte T+B Zelldefekte Immundysregul.** | |
| **Syndrome** | Differente Immundefekte | **T+B Zellen Phagozyten Innate Immunity** | |
| **Angioödem** | | **Complement Defekte** | Allergie ACE Inhibitor |

# Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions




*Chapel et al. BJH 2009*

# The EUROclass trial: defining subgroups in common variable immunodeficiency

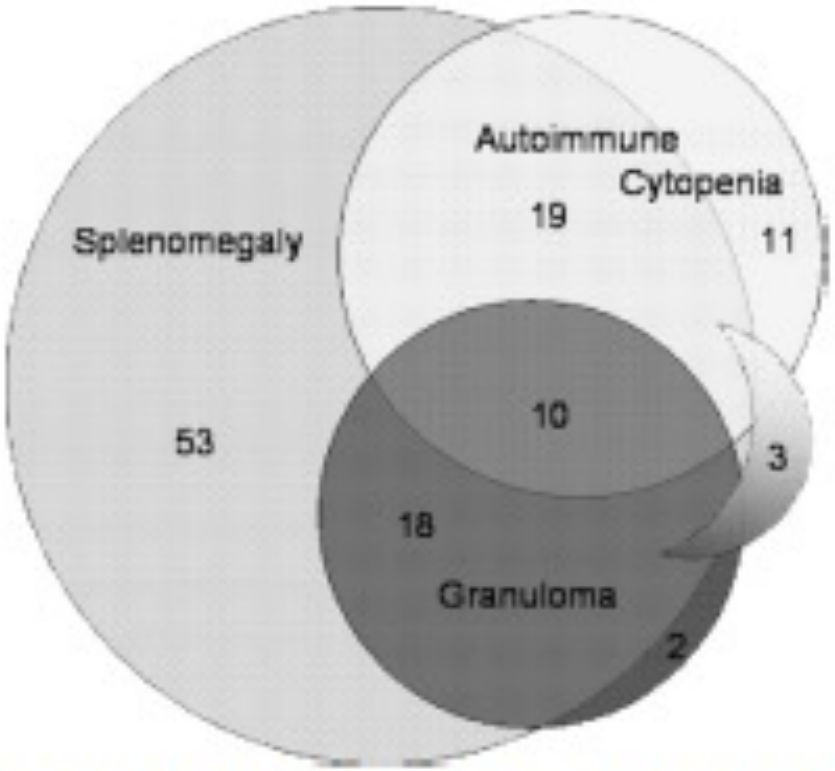



**Figure 1. Coincidence of granulomatous disease and autoimmune cytopenia with splenomegaly in patients with CVID.** The diagram indicates the coincidence of splenomegaly, granulomatous disease, and autoimmune cytopenia in the European cohort of CVID patients. In 3 patients, granulomatous disease and autoimmune cytopenia were detectable in the absence of splenomegaly (sickle shape).

*Wehr et al., blood 2008*

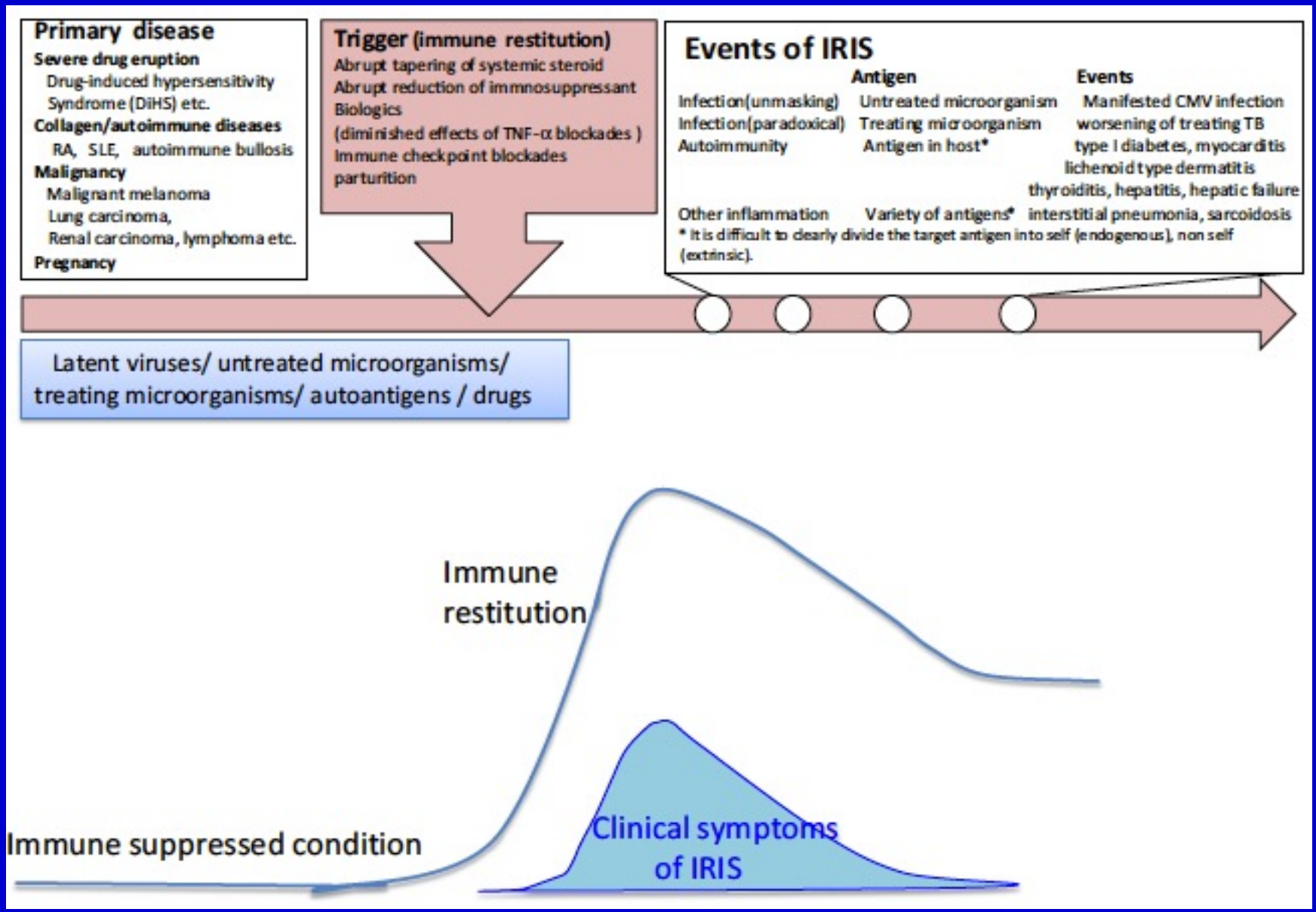
**Table 1. Abstracted guideline for management of common variable immunodeficiency complications.**

| Type of clinical complication | Prevention | Screening | Treatment |
|---|---|---|---|
| Infectious | Ig replacment; prophylactic antibiotics; vaccination | Patients' awareness; sputum monitoring; routine visits | High dose Ig; threaputic antibiotics |
| Pulmonary | Control of infection; high dose Ig | Spirometry; HRCT; routine visits | Endoscopic sinus surgery; inhaled corticosteroids; anti-inflammatory antibiotics; IL-2 therapy; $B_2$ agonists; leukotriene receptor antagonists; lung transplantation |
| Lymphoproliferative | | Lymph nodes biopsy; spirometry; imaging; routine visits | Systemic corticosteroids; hydroxychloroquine; immunosuppressive agents |
| Autoimmunity | Ig replacment? | CBC, diff, PBS; thyroid examination and thyroid function; routine visits | Corticosteroids; anti-CD20 monoclonal antibodies; TNF-α inhibitors |
| Gastrointestinal | Control of infection, autoimmunity and lymphoproliferative complications | Upper and/or lower endoscopy and yearly ultrasonography; routine visits | Immunomodulators; TNF-α inhibitors |
| Neopelasis | *Helicobacter pylori* eradication; decreasing unnecessary irradiation | Routine cancer screening; screening by endoscopy; bone marrow examinations | Routine chemotherapy; rituximab protocols; surgical modalities; allogeneic stem cell transplantation |

CBC: Complete blood count; diff: Differentiation of cell blood count; HRCT: High-resolution computed tomography; Ig: Immunoglobulin; PBS: Peripheral blood smear.

# Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients

*Sueki et al., Journal of dermatology 2018*



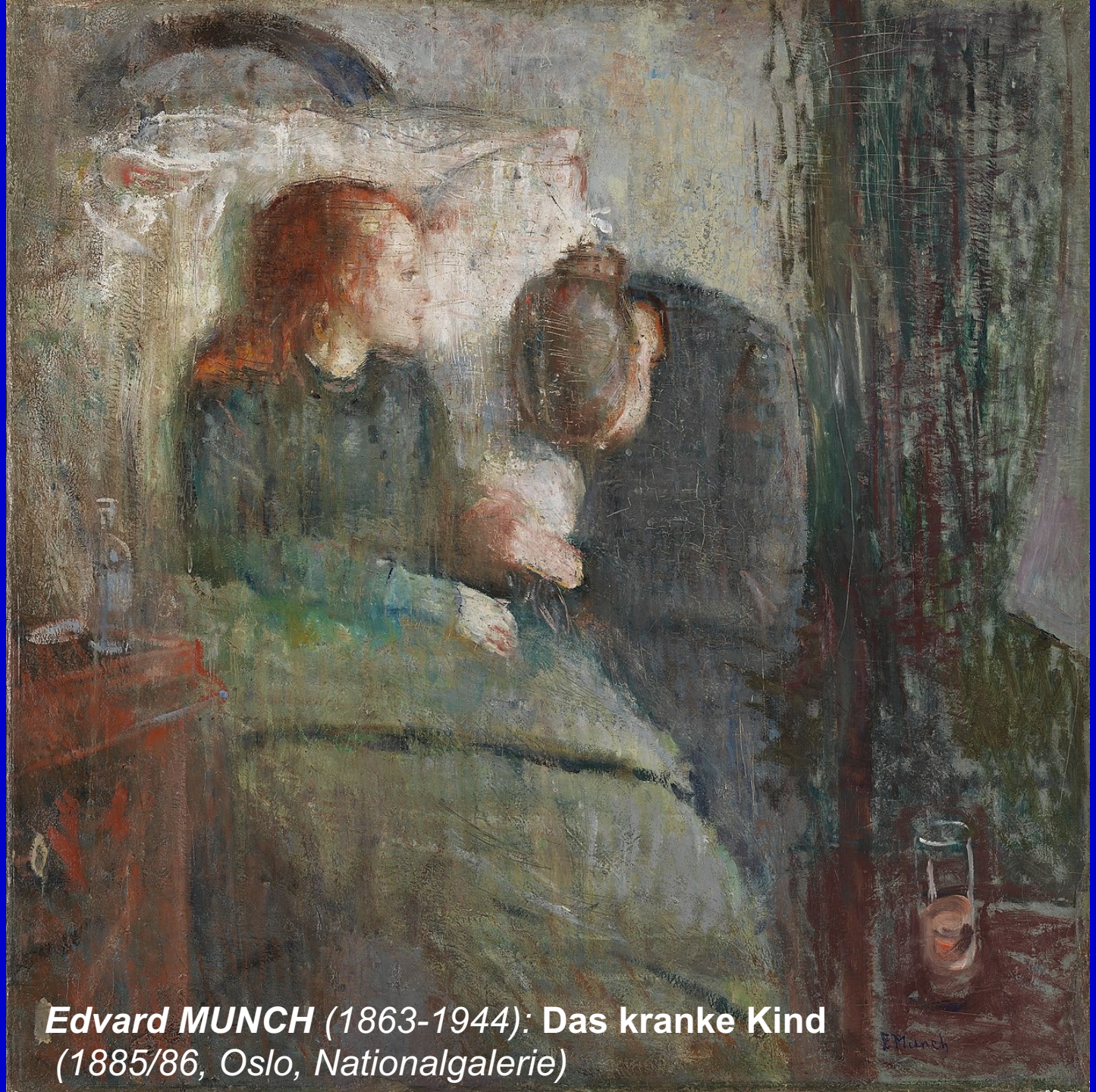
# Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients

*Sueki et al., Journal of dermatology 2018*

**Table 2.** Comparison of irAE and events following DIHS

| irAE due to immune checkpoint blockades | Events following the DIHS |
|---|---|
| Diarrhea, enterocolitis | Gastrointestinal bleeding |
| Gastrointestinal bleeding | Hepatitis, hepatic dysfunction |
| Hepatitis, fulminant hepatitis | Alopecia |
| Pancreatitis | Nephritis, renal dysfunction |
| Nephritis | Interstitial pneumonia/pneumonia |
| Interstitial pneumonia | Dermatitis, drug rash |
| Dermatitis, drug rash | Herpes zoster, herpes simplex |
| Rheumatoid arthritis | Cryptococcus pneumonia |
| Thyroid dysfunction | Pneumocystis carinii pneumonia |
| Hypophysitis | Thyroid dysfunction/thyroiditis |
| Encephalitis | Encephalitis/limbic encephalitis |
| Myocarditis | Myocarditis |
| Type 1 diabetes mellitus | Type 1 diabetes mellitus |
| Adrenal failure | |
| Vasculitis | |
| Sarcoidosis | |
| Myasthenia gravis | |
| Vitiligo | |

Underlined events are common in both independent diseases. DIHS, drug-induced hypersensitivity syndrome; irAE, immune-related adverse events.




***Edvard MUNCH*** *(1863-1944):* **Das kranke Kind**
*(1885/86, Oslo, Nationalgalerie)*