

Clinical Immunology

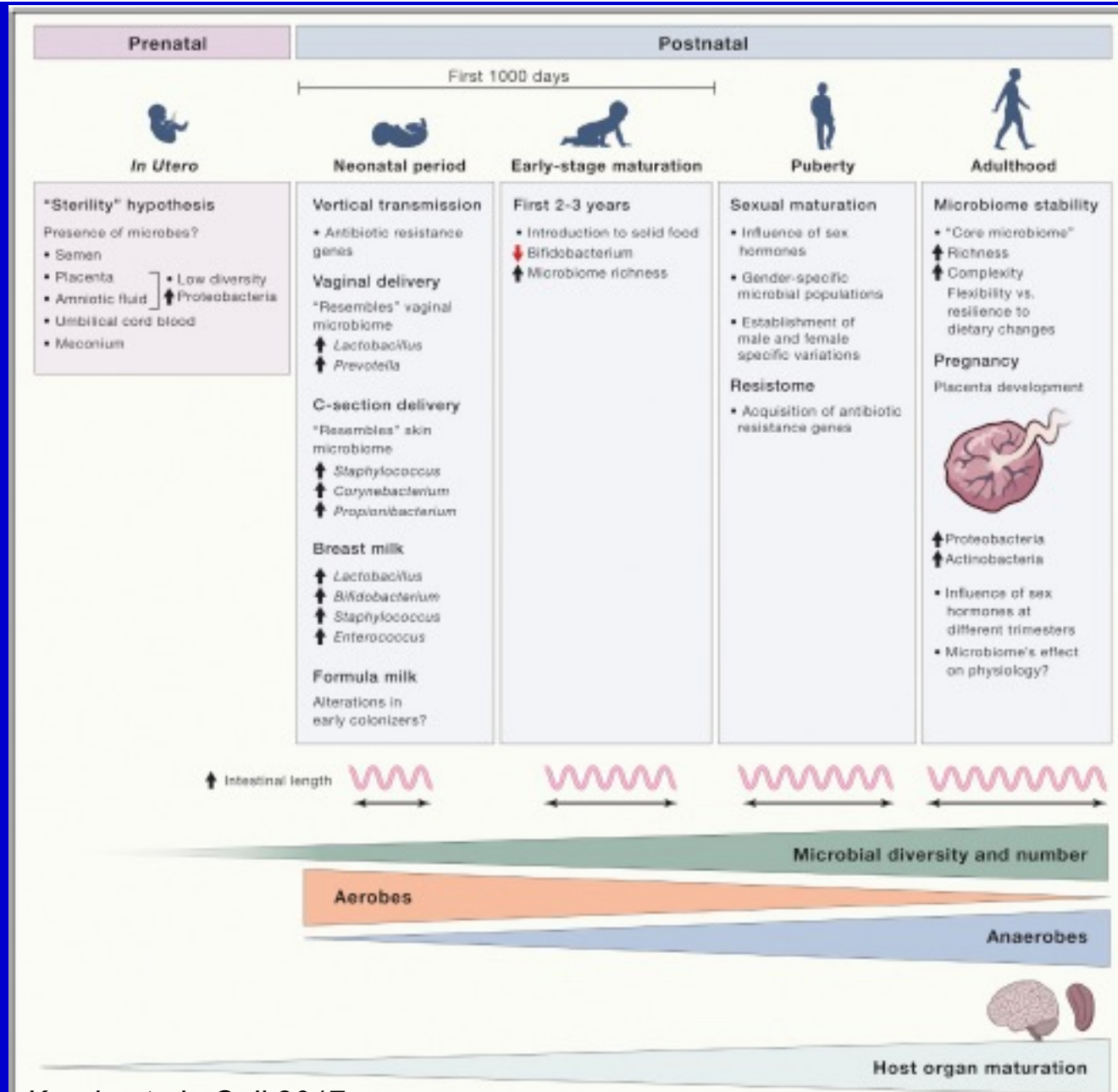
Part I: Immune Deficiency & Reconstitution

Harry Fuchssteiner 01/06/2023

Innere Medizin 4

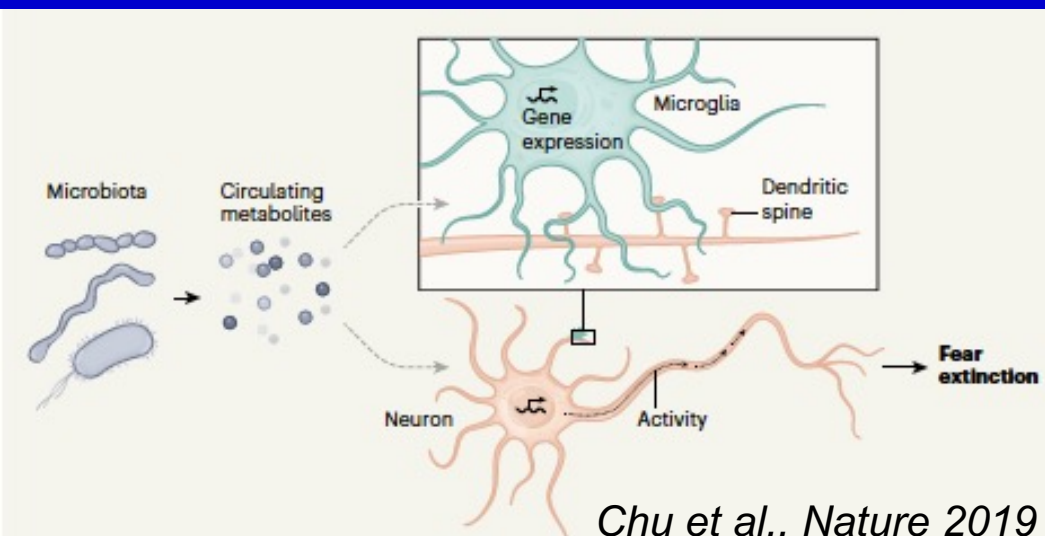
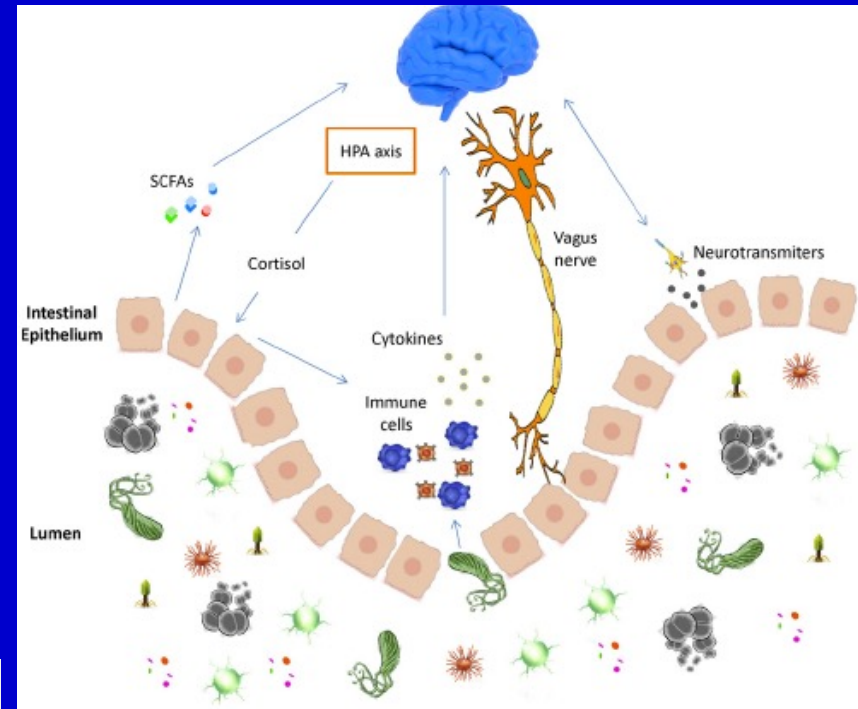
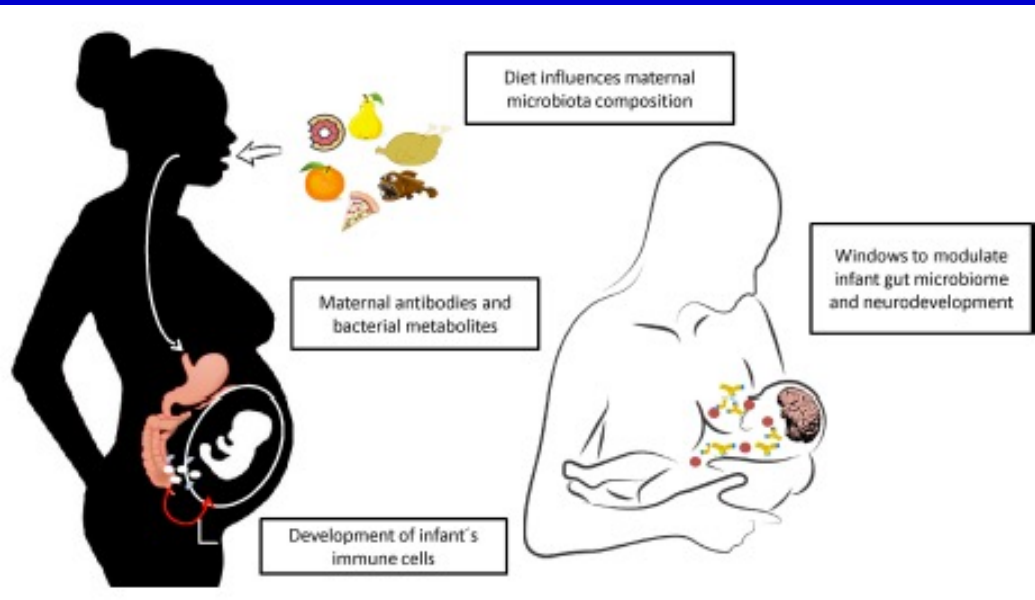
Ordensklinikum Linz – **Barmherzige Schwestern**

Our Gut Microbiome: The Evolving Inner Self



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

Cerdo et al., Am J Physiol Endocrinol Metabol 2019

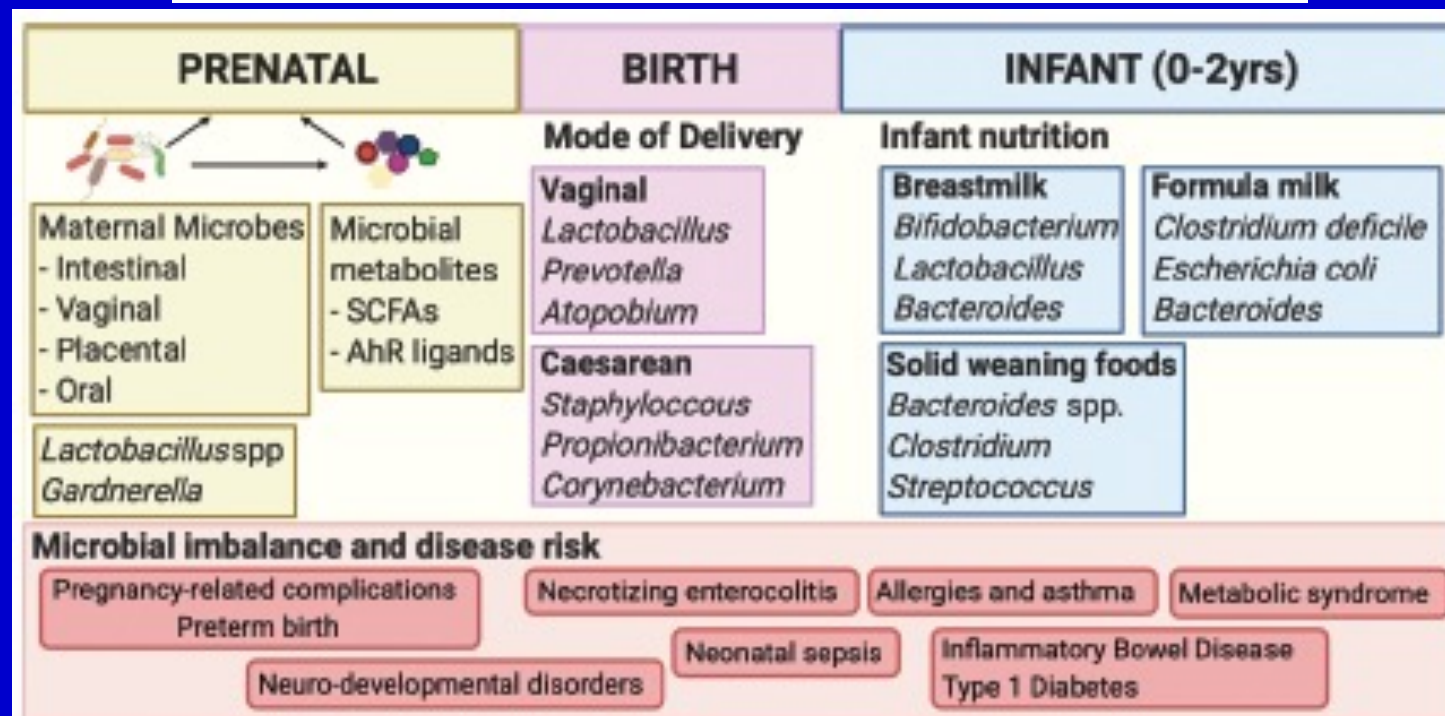
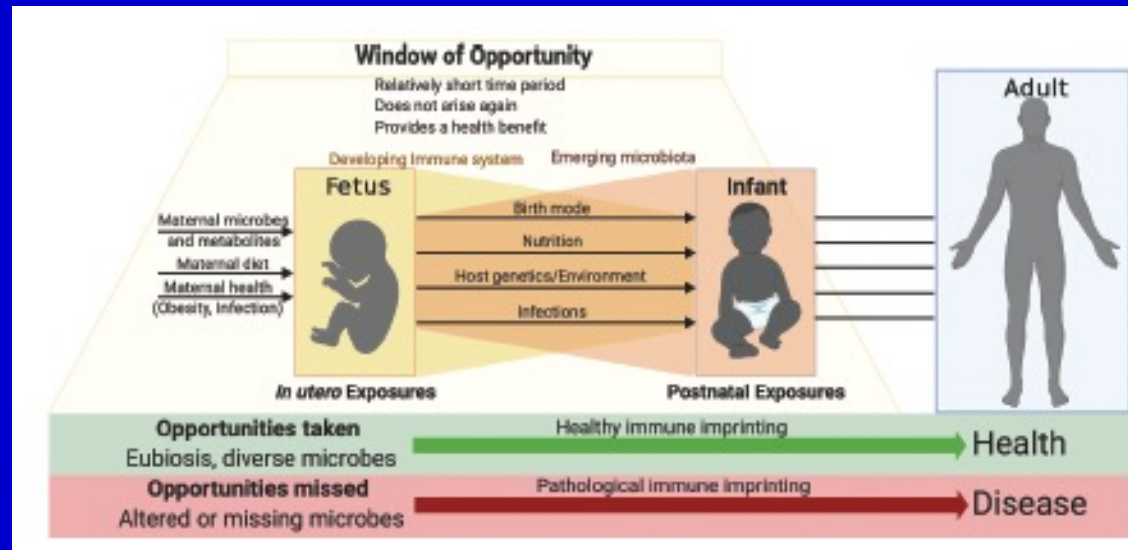


Chu et al., Nature 2019

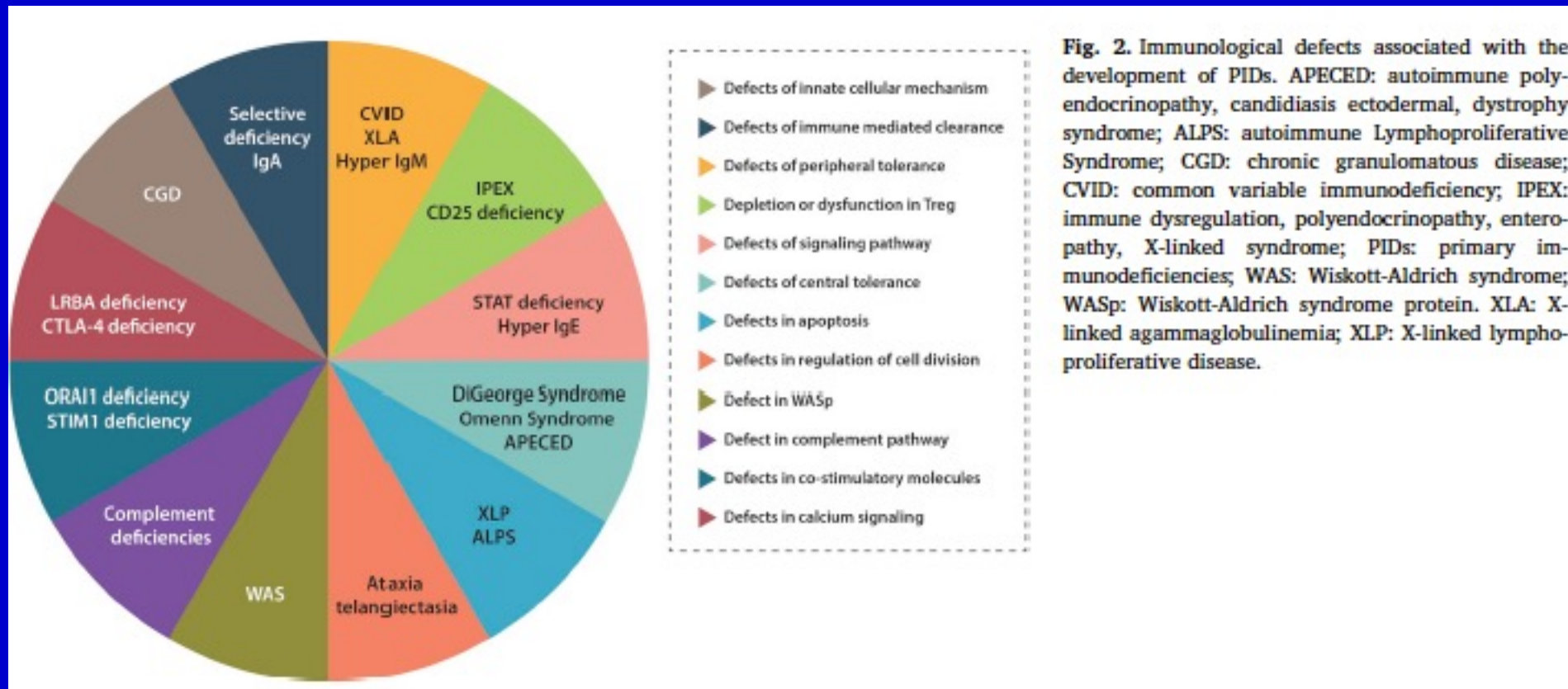
The microbiota regulate neuronal function and fear extinction learning

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

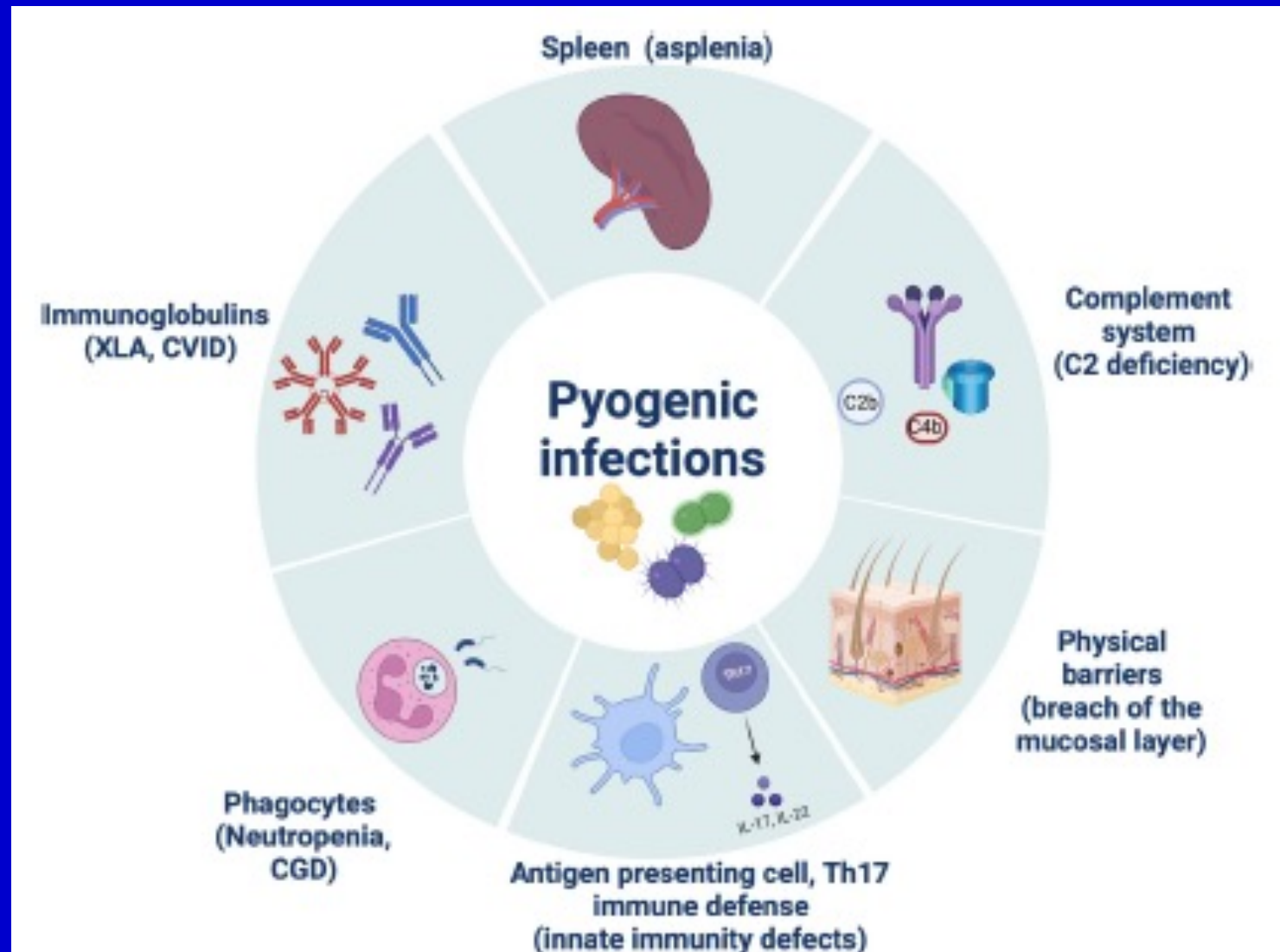
Jain, Gut Microbes 2020



Primary immunodeficiency and autoimmunity: A comprehensive review



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



Primary immunodeficiency and autoimmunity: A comprehensive review

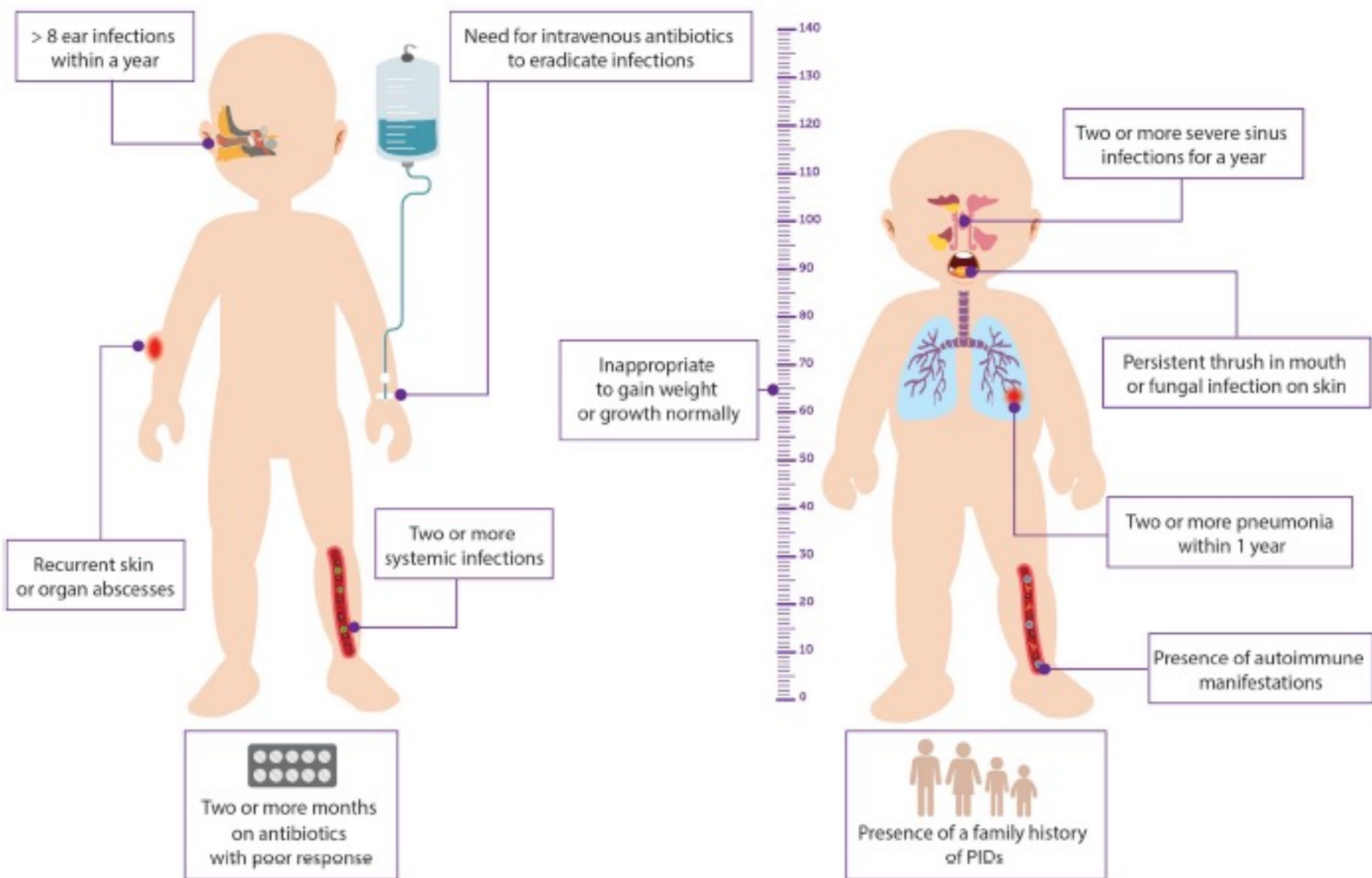
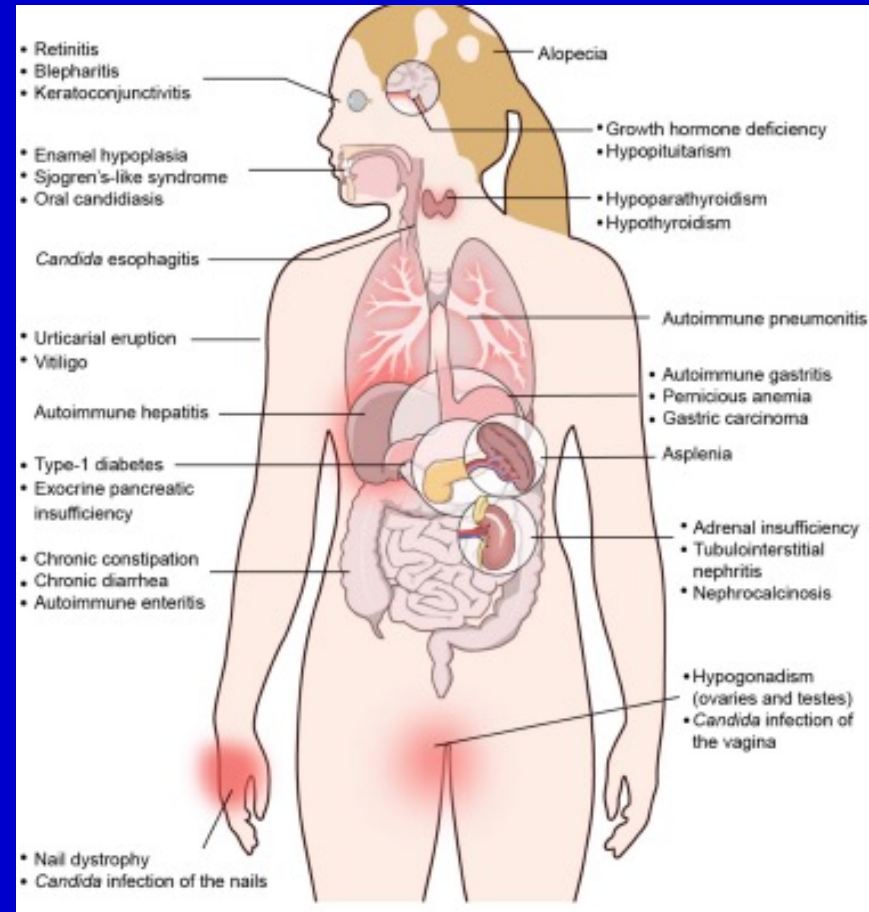
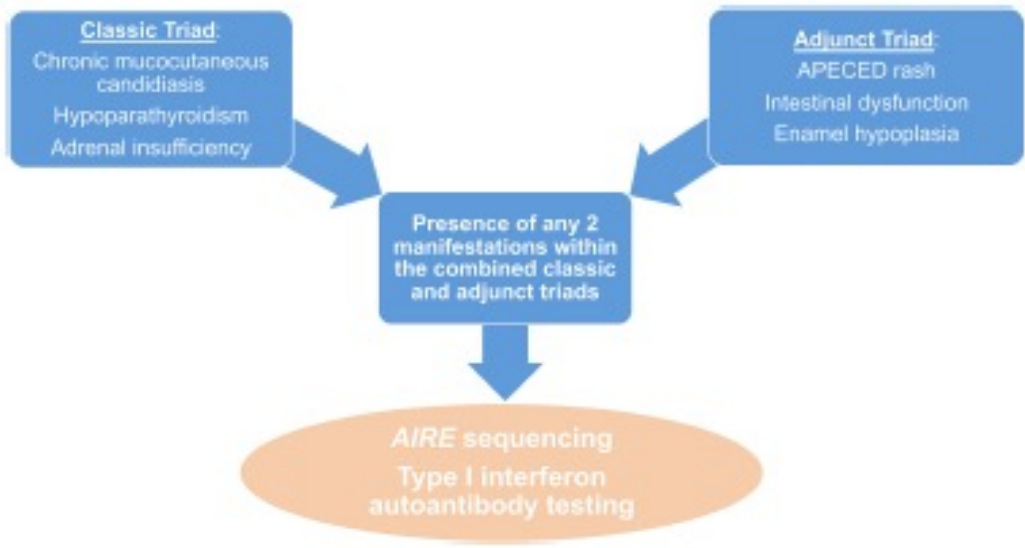
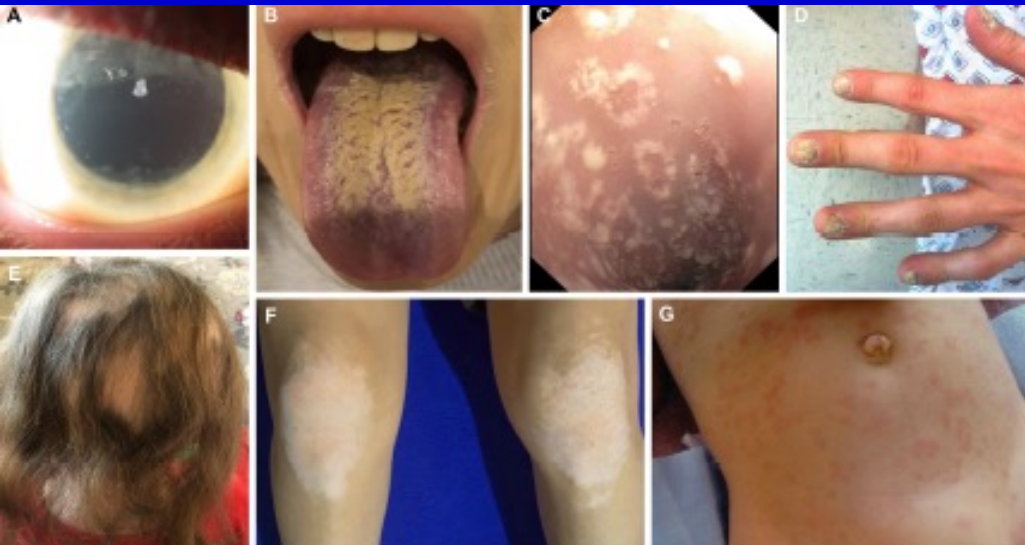


Fig. 3. The Jeffrey Modell Foundation warning signs for primary immunodeficiencies. The inclusion of autoimmunity as an additional criterion may help to improve diagnosis and follow up of comorbidities associated with these diseases.

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy



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

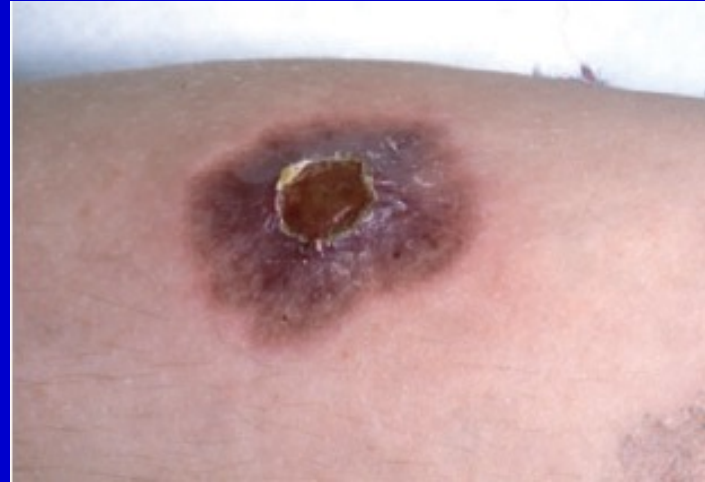
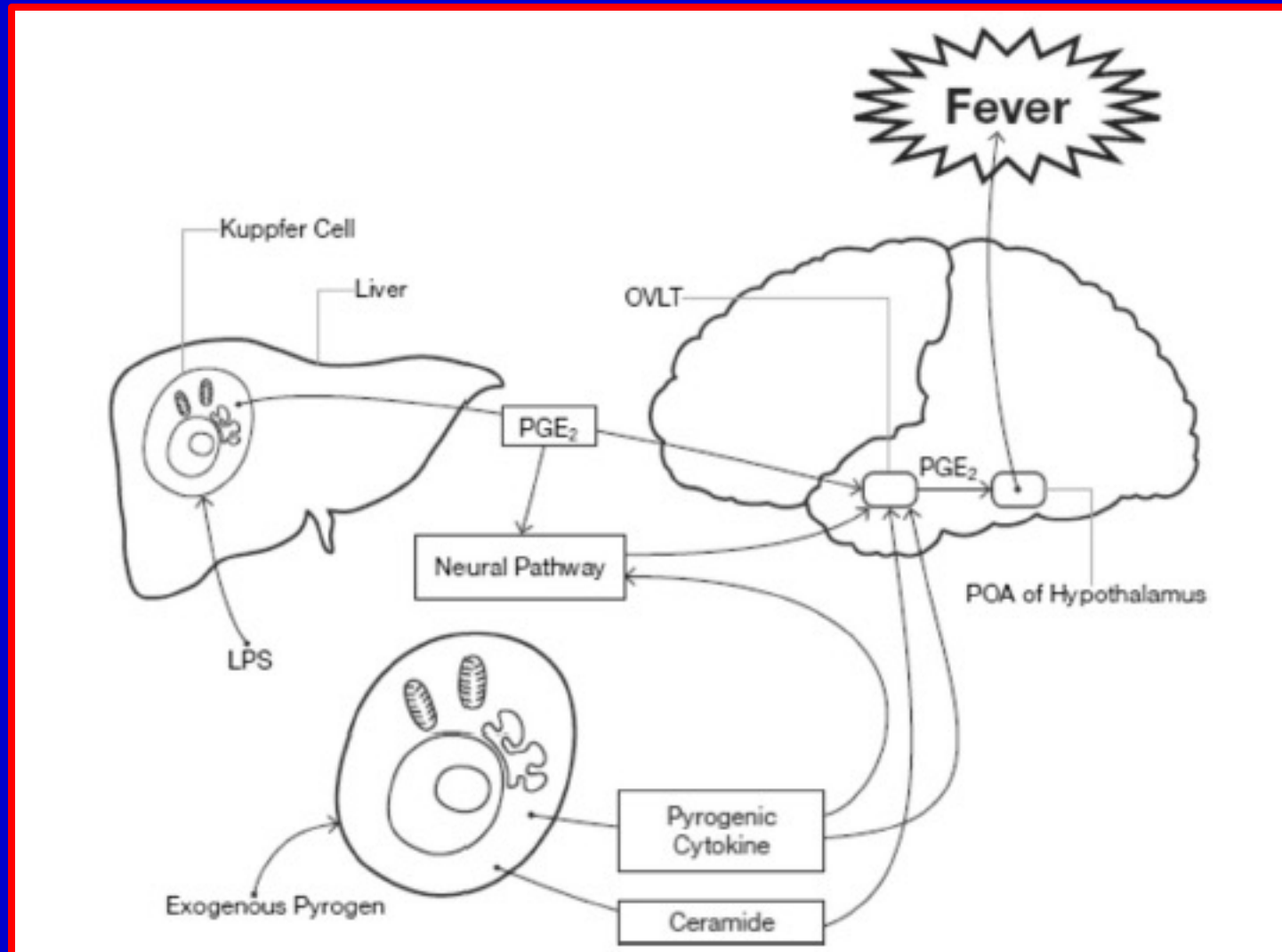


Table 3. Specific warning signs of primary immunodeficiency.

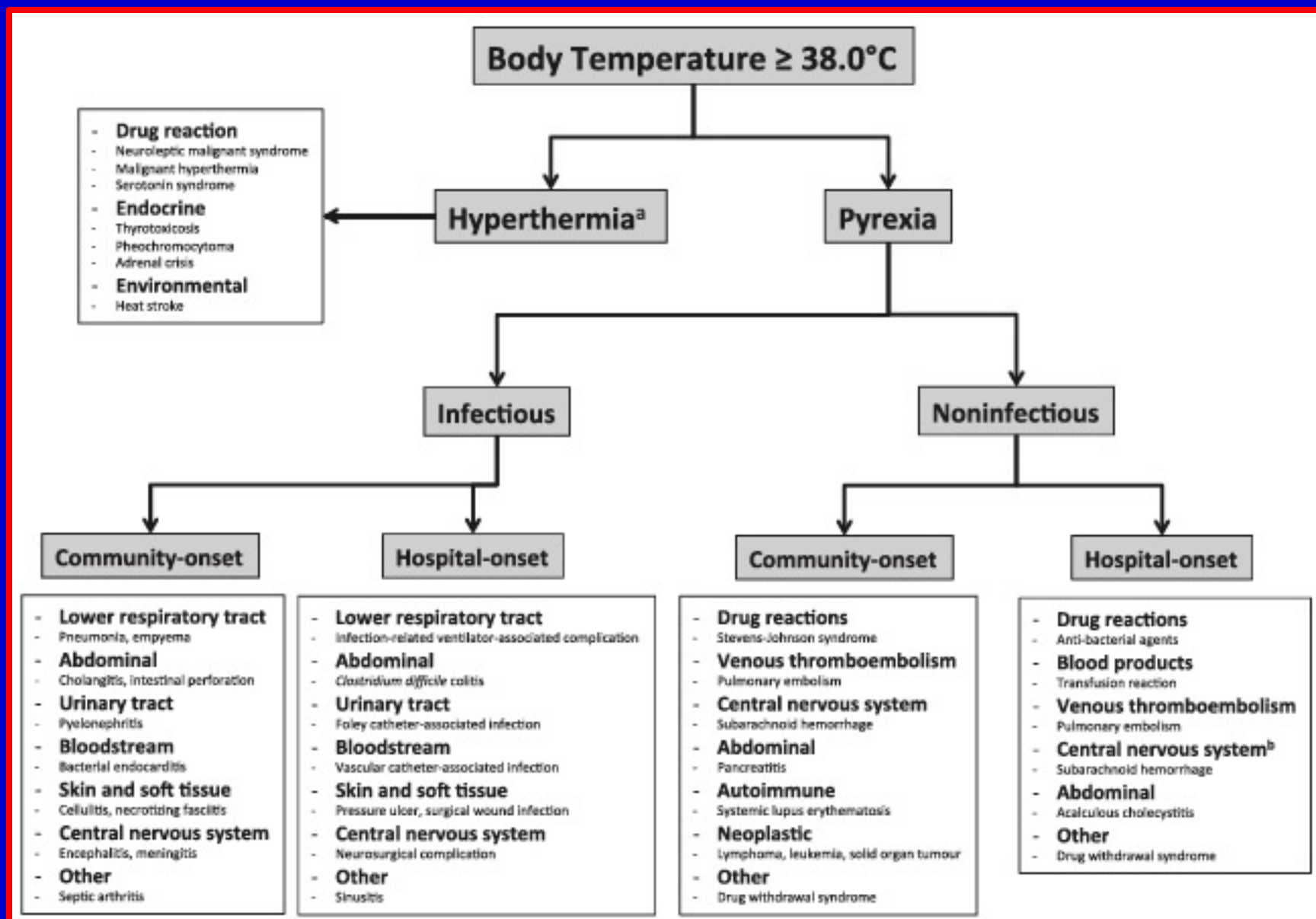
- Eight or more new infections within 12 months
- Two or more serious sinus infections or episodes of pneumonia within 1 year
- Two or more months on antibiotics with little effect
- Failure of an infant to gain weight or grow normally
- Recurrent deep skin or organ abscesses
- Persistent superficial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



The pathophysiological basis and consequences of fever



Pyrexia: aetiology in the ICU



„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

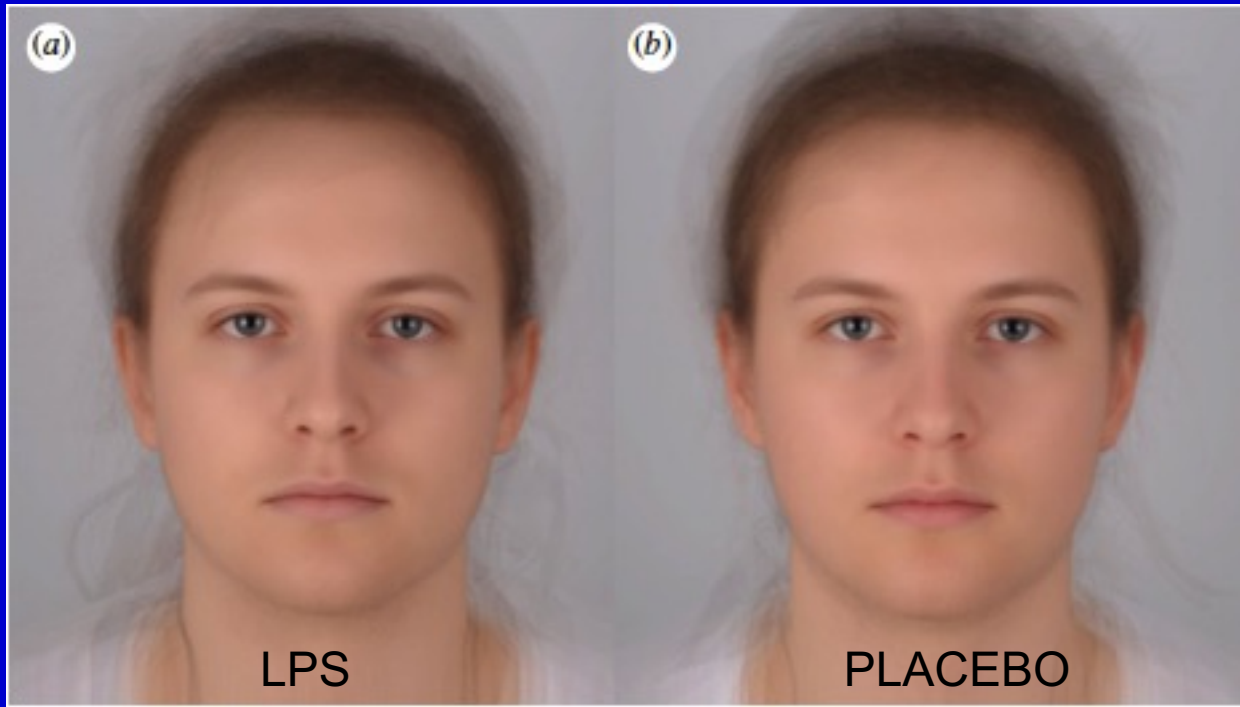
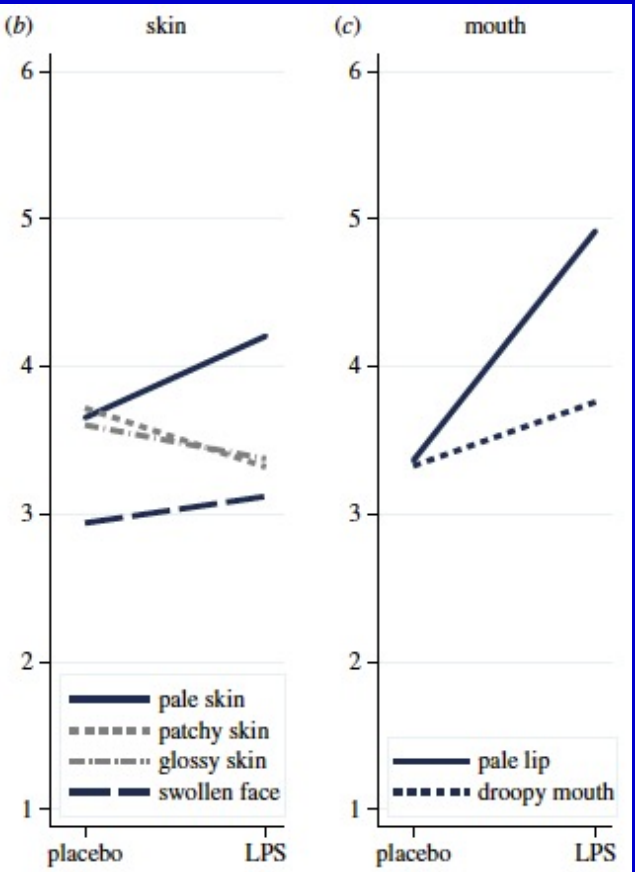
Adler, Hemmeler: *Praxis und Theorie der Anamnese*, G. Fischer 1989

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



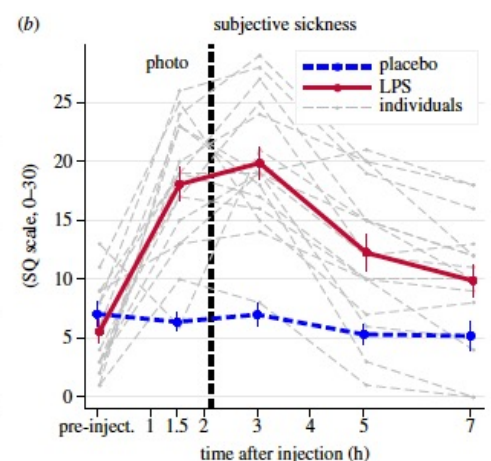
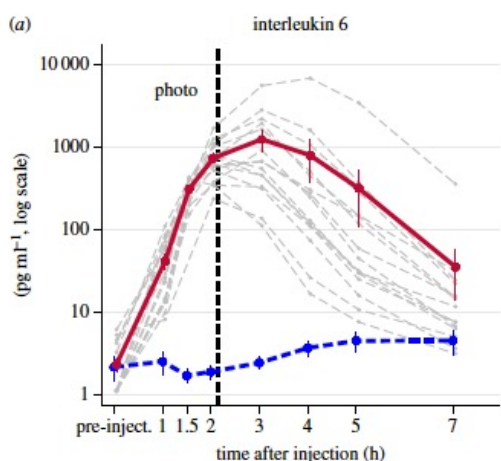
Singer et al., JAMA 2016;

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₋>+

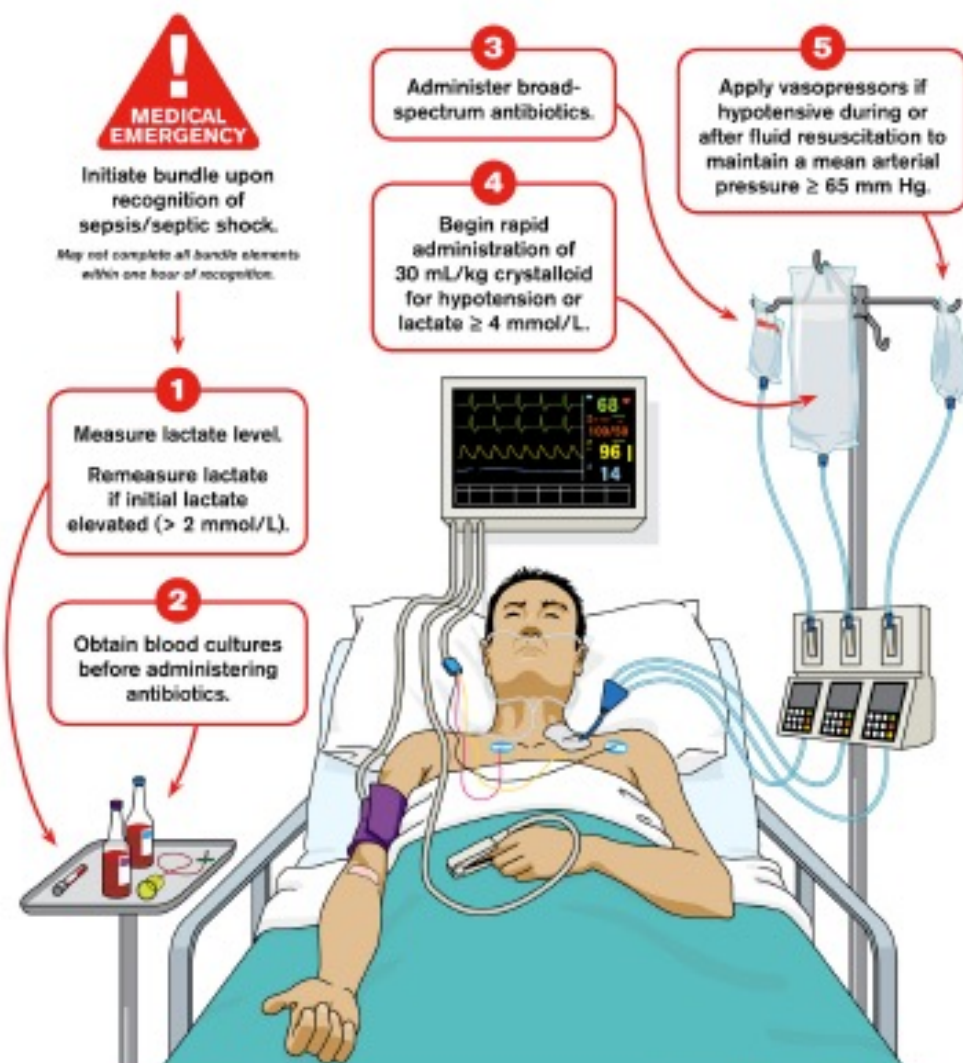


European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstances

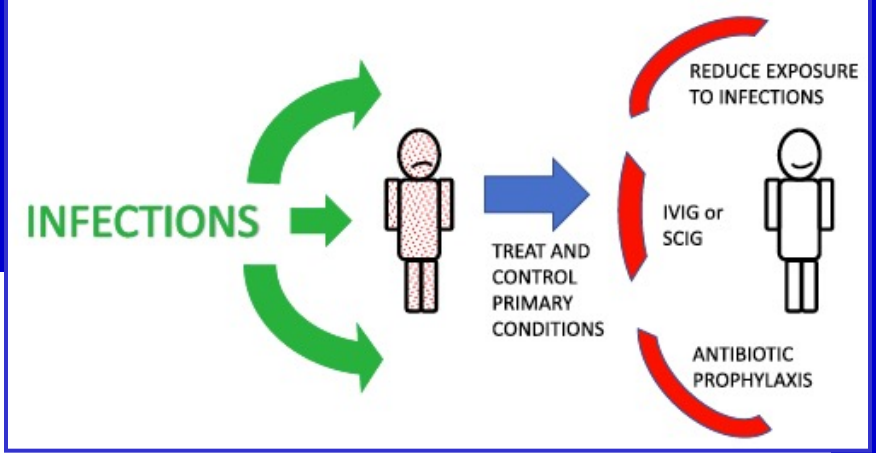
Hour-1 Bundle

Initial Resuscitation for Sepsis and Septic Shock

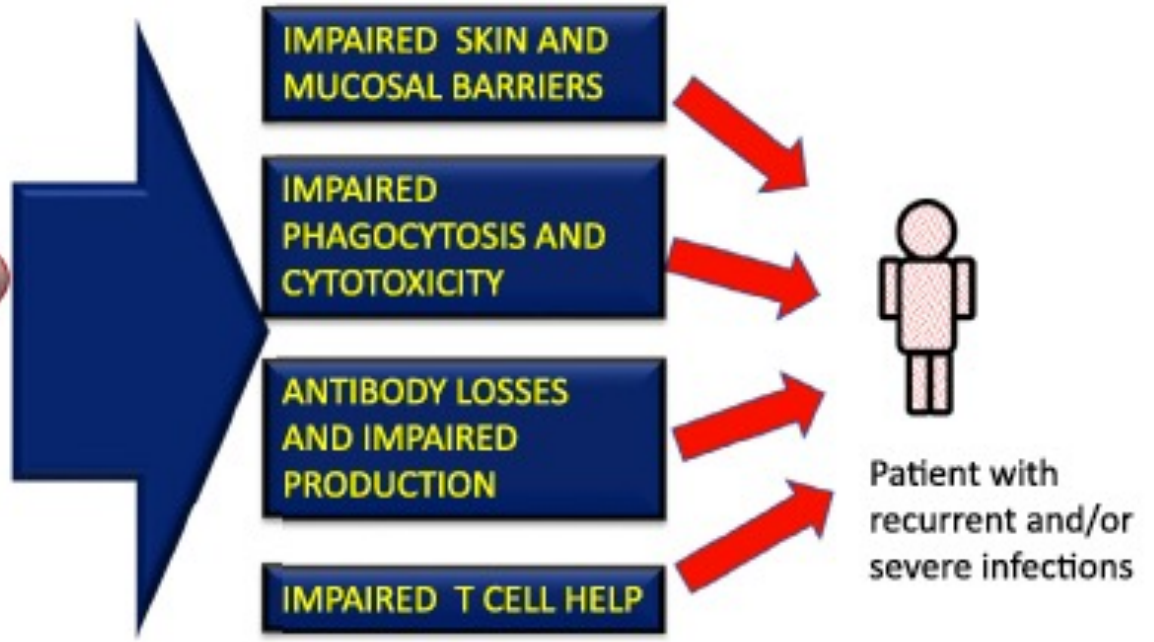
Surviving Sepsis
Campaign



Secondary immunodeficiencies

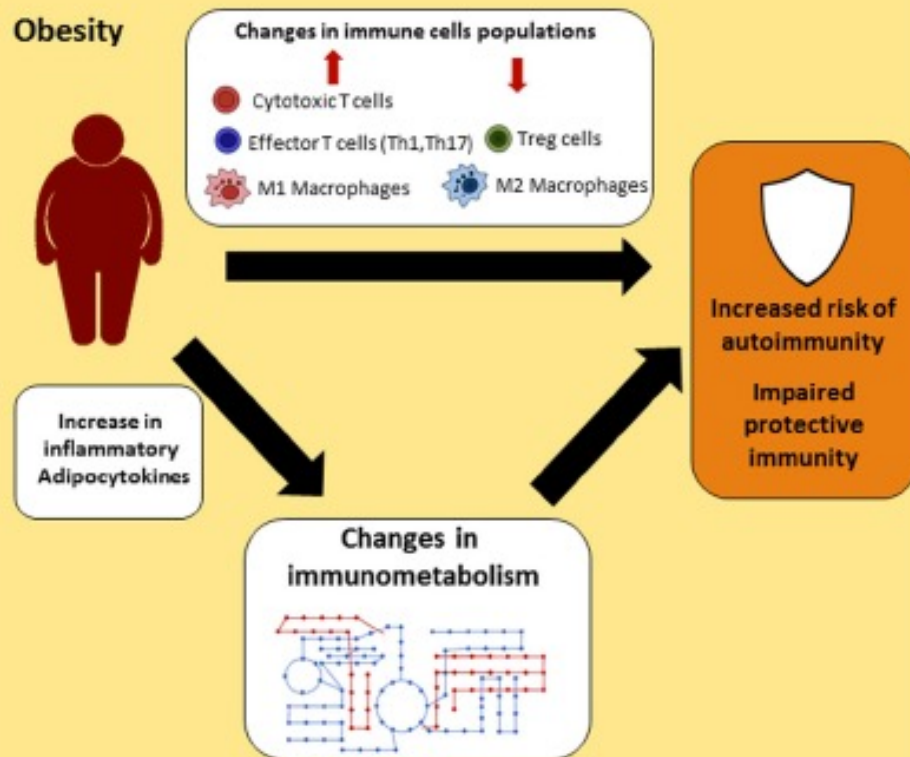


- PREMATURITY AND AGING
- NON-PID GENETIC SYNDROMES
- INFECTIONS: HIV
- CORTICOSTEROIDS
CHEMOTHERAPY
IMMUNOSUPPRESSION
RADIOTHERAPY
- LYMPHOMA
LEUKEMIA
MYELOMA
- MALNUTRITION
- PROTEIN-LOSING ENTEROPATHY
NEPHROPATHY
- UV LIGHT
HYPOXIA
STRESS

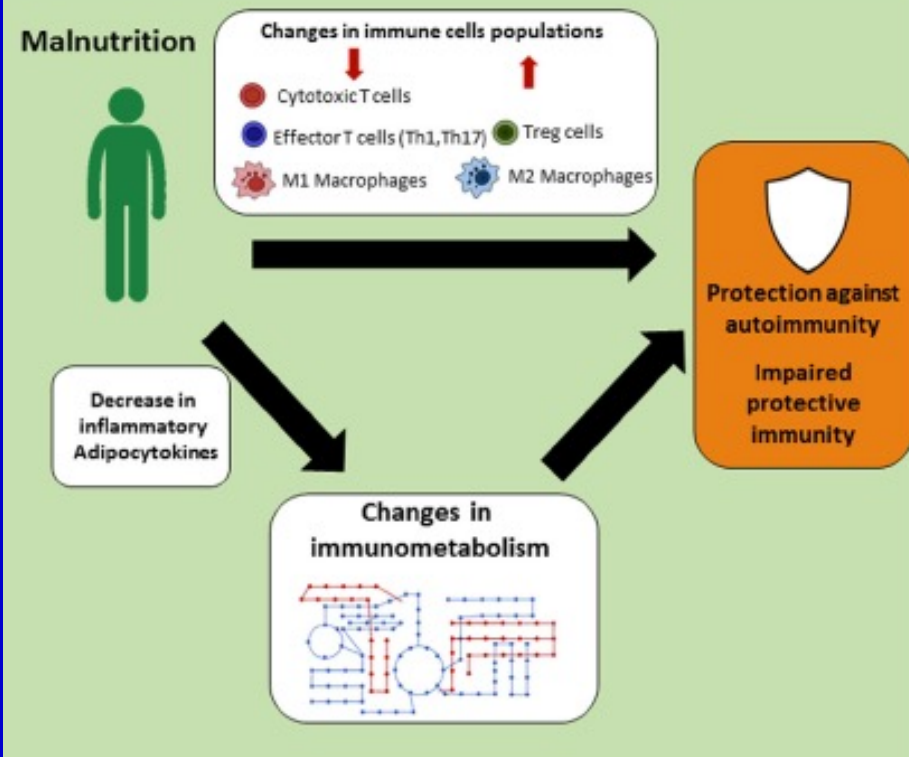


Changes in Nutritional Status Impact Immune Cell Metabolism and Function

Obesity

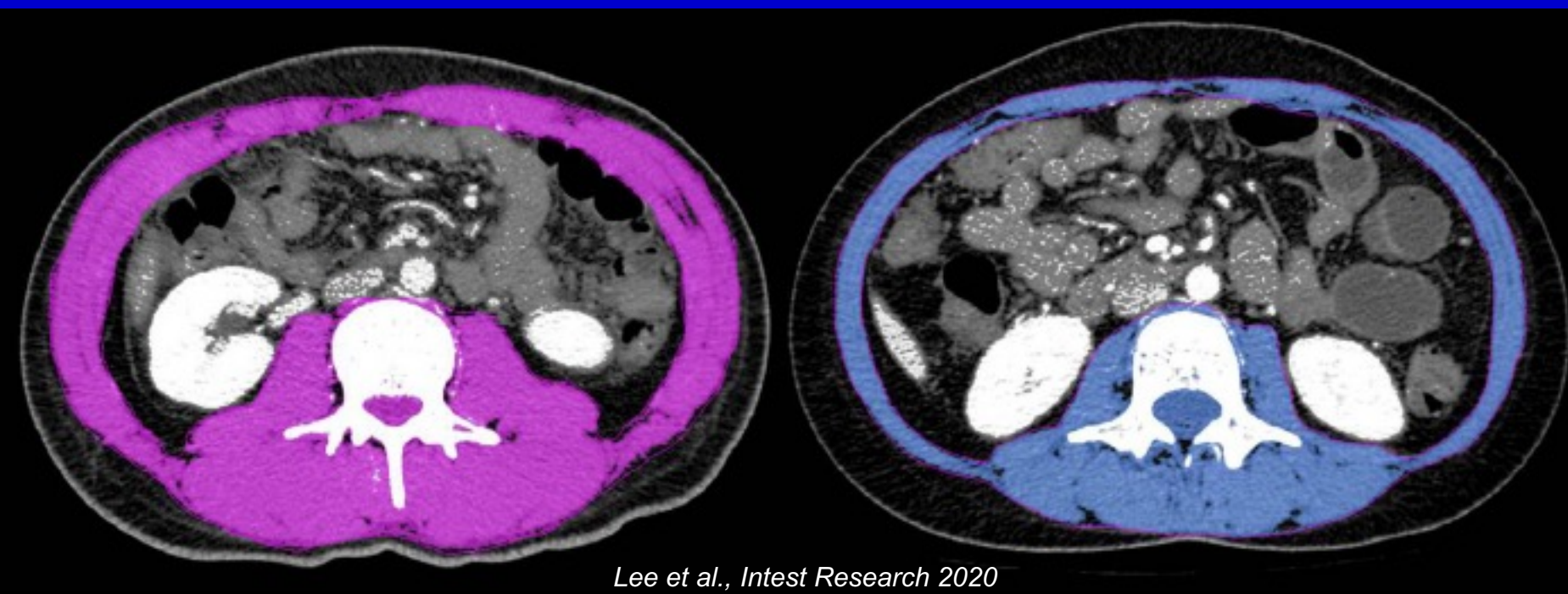


Malnutrition



Sarcopenia and Inflammatory Bowel Disease: A Systematic Review

Sarcopenia Prevalence IBD: 42% (70% CD)



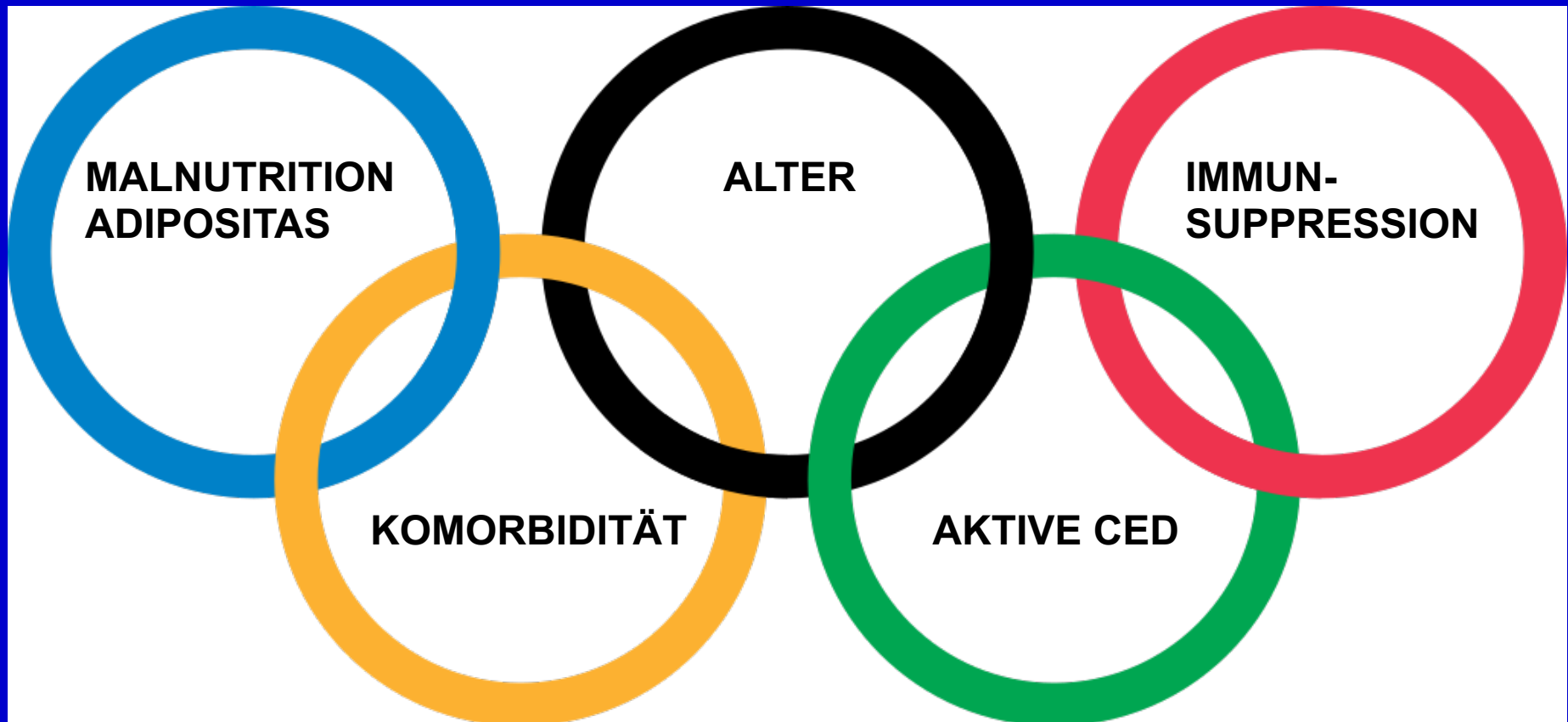
Lee et al., Intest Research 2020

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



HIV and AIDS are still present

(aus Janeway Immunobiology 6th edition)

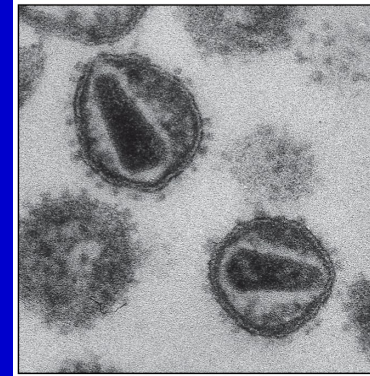


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

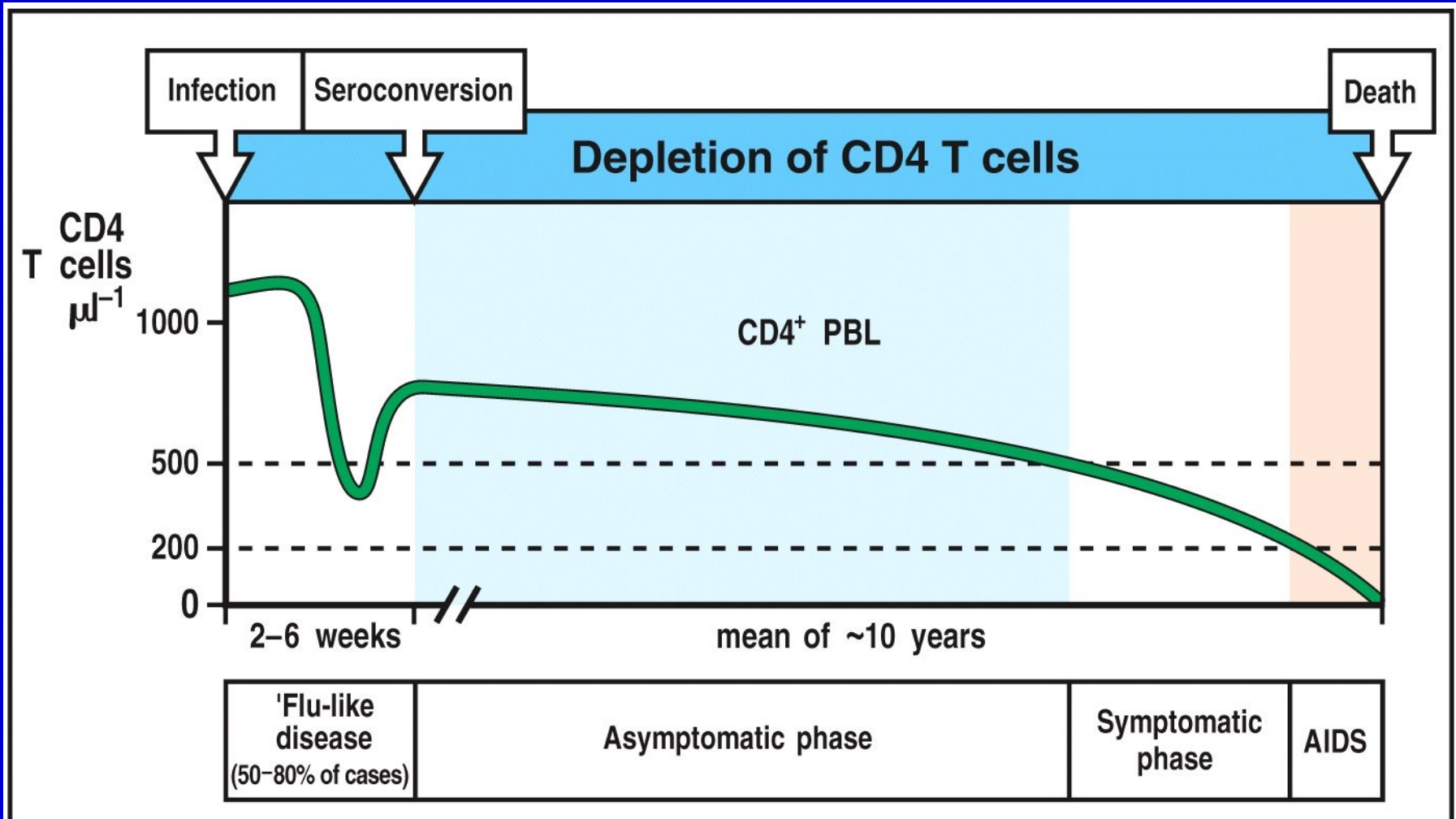
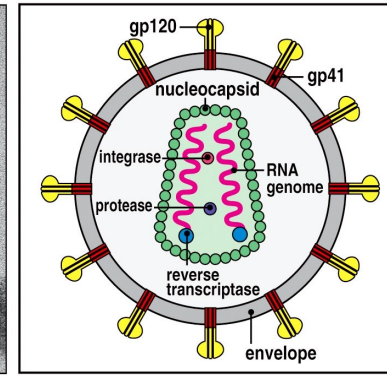
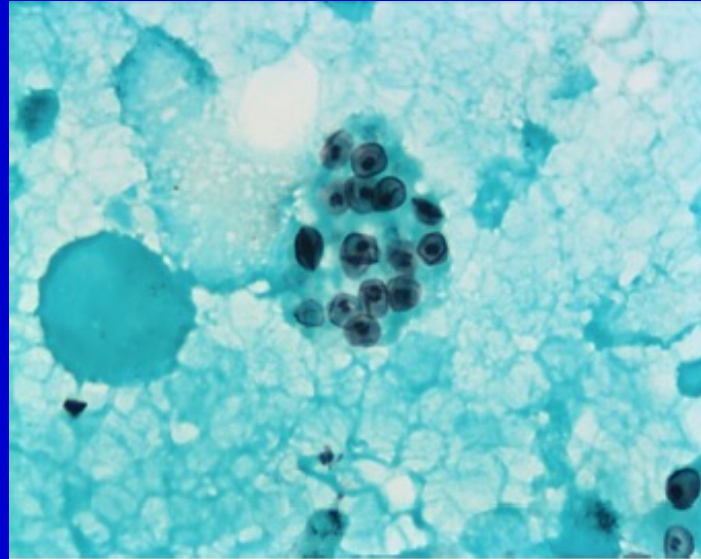
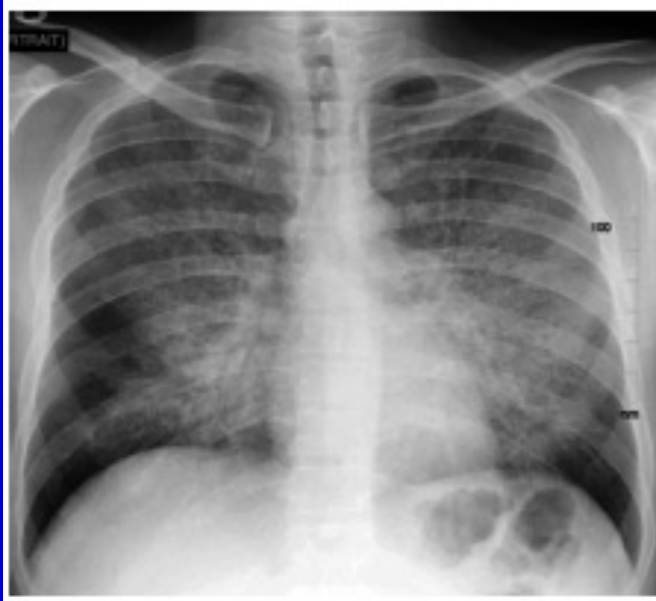


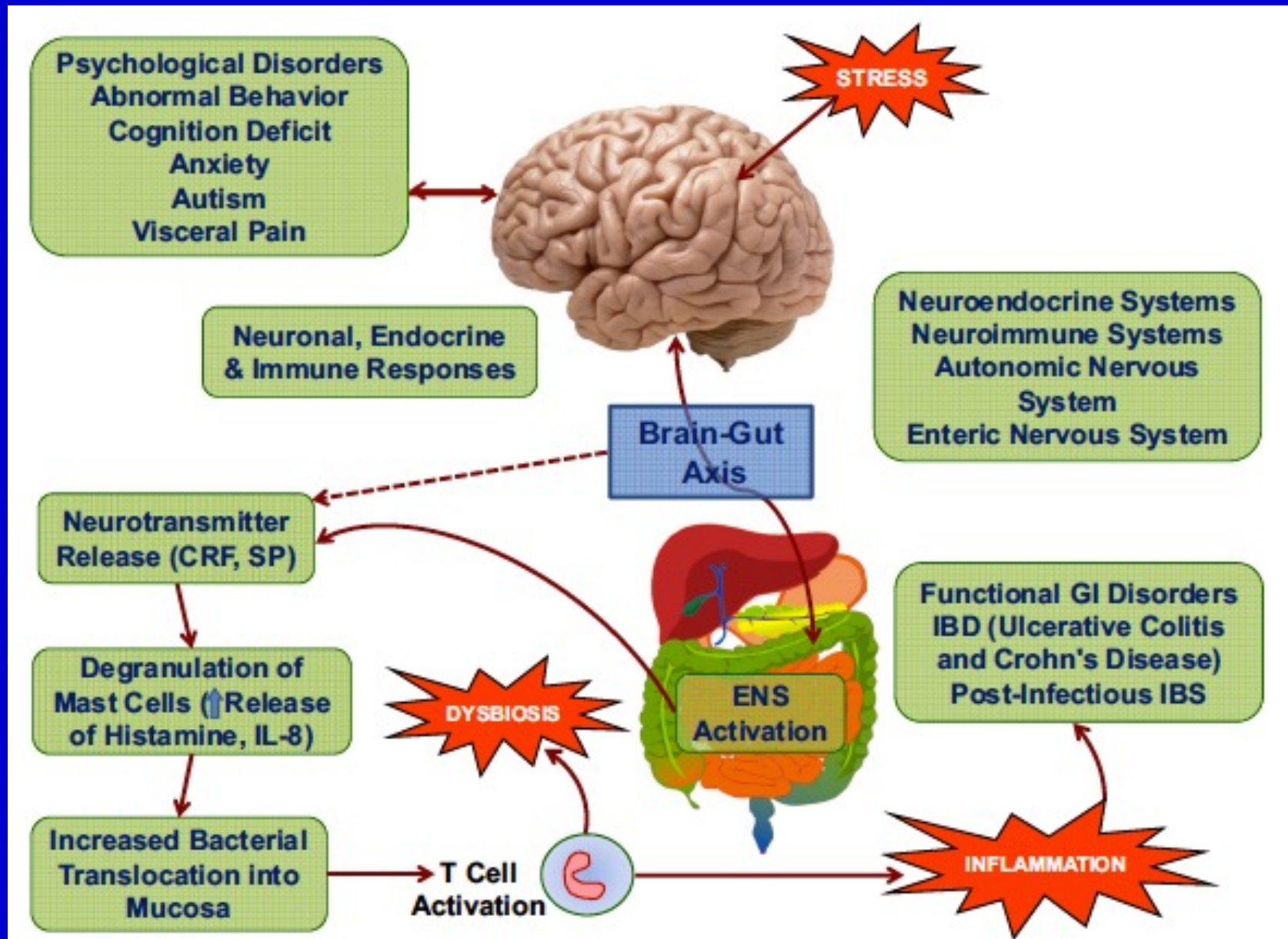
Figure 11-20 Immunobiology, 6/e. (© Garland Science 2005)

AIDS Clinical Images

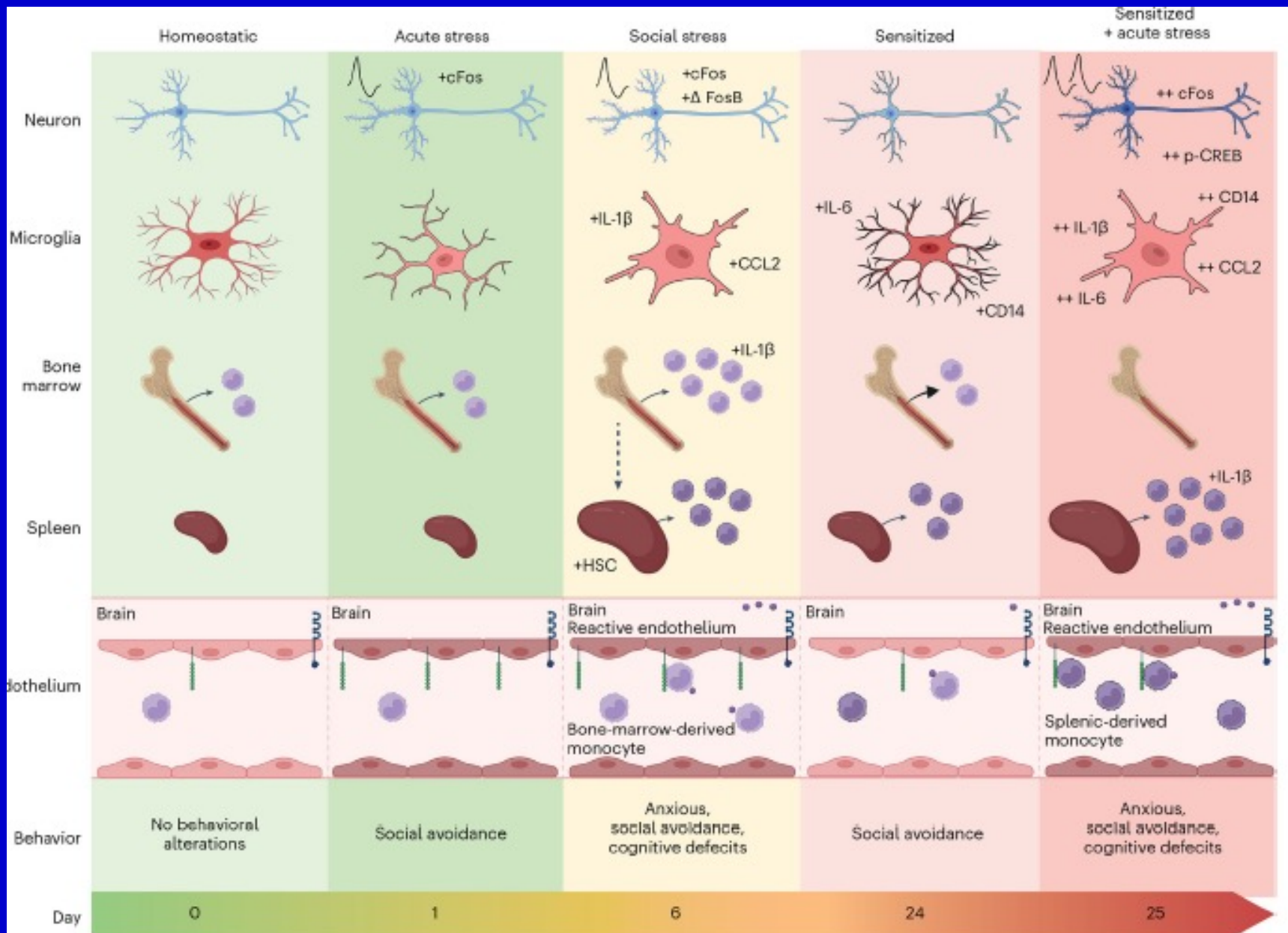
Salzer et al., *Respiration* 2018; Kenner et al., *NEJM*; Cotelli et al., *NEJM* 1998



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

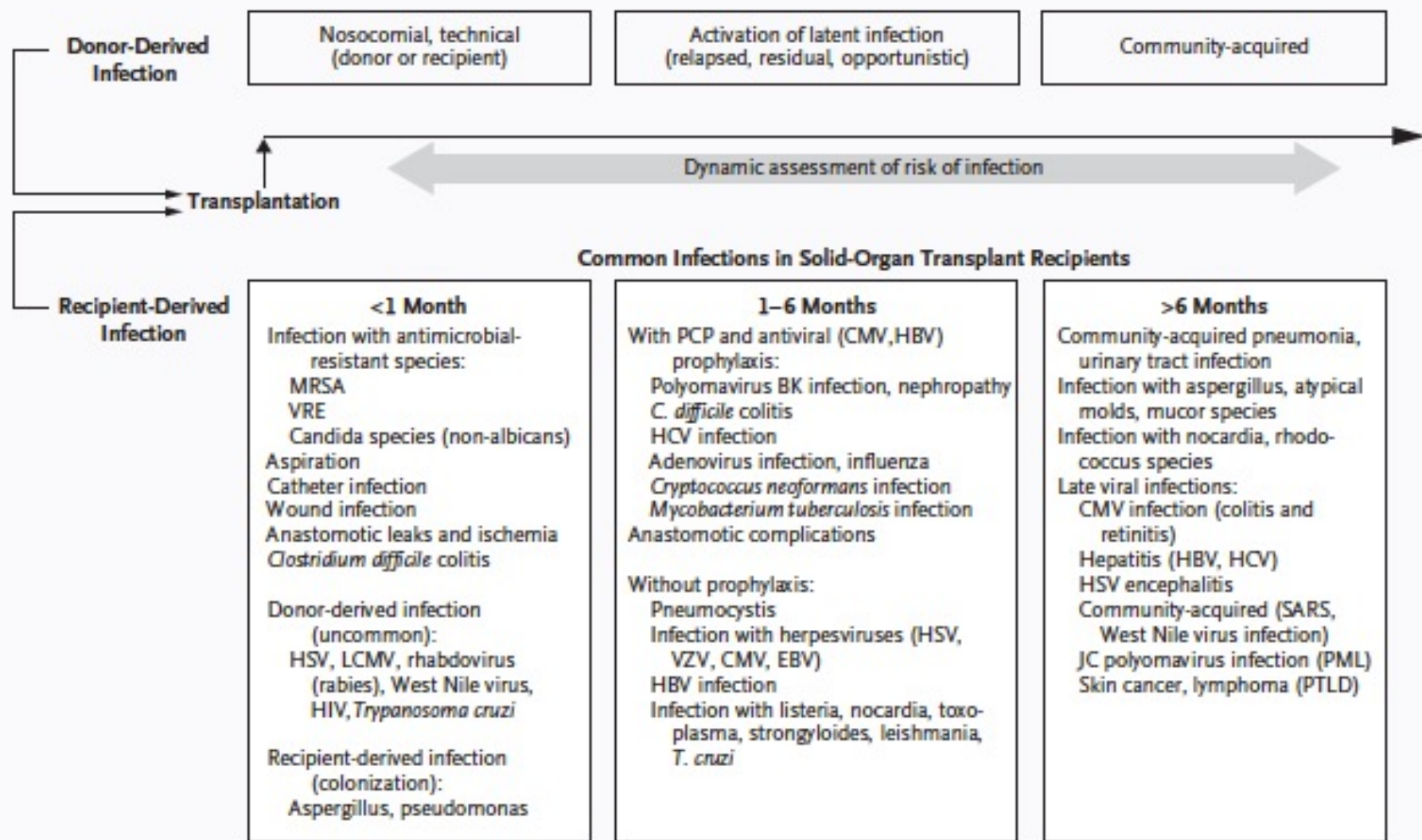
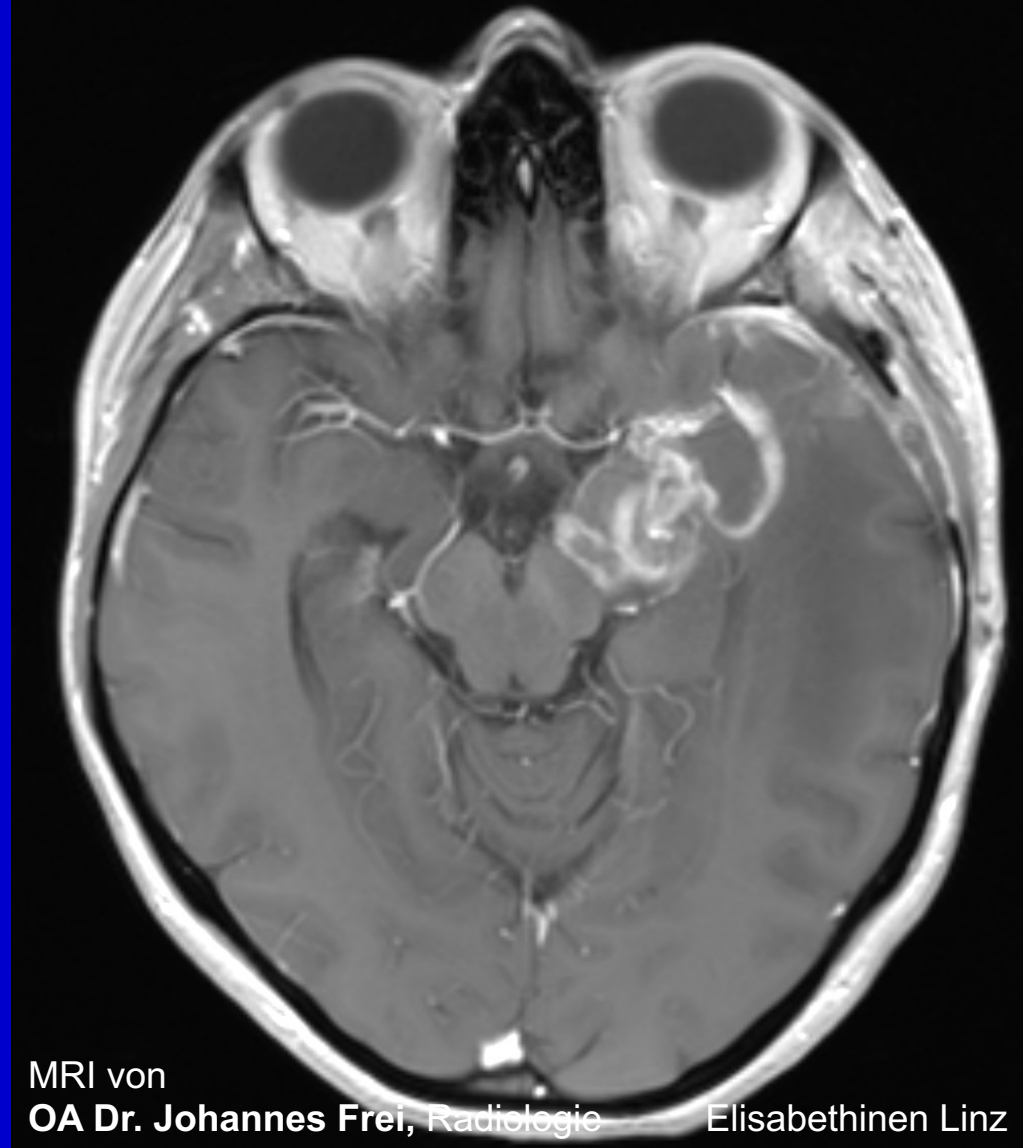


Figure 4. Changing Timeline of Infection after Organ Transplantation.

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;**
- Spontanremission;
- 03/2017 **ZNS Rezidiv** der **EBV assoziierten Lymphoproliferation**

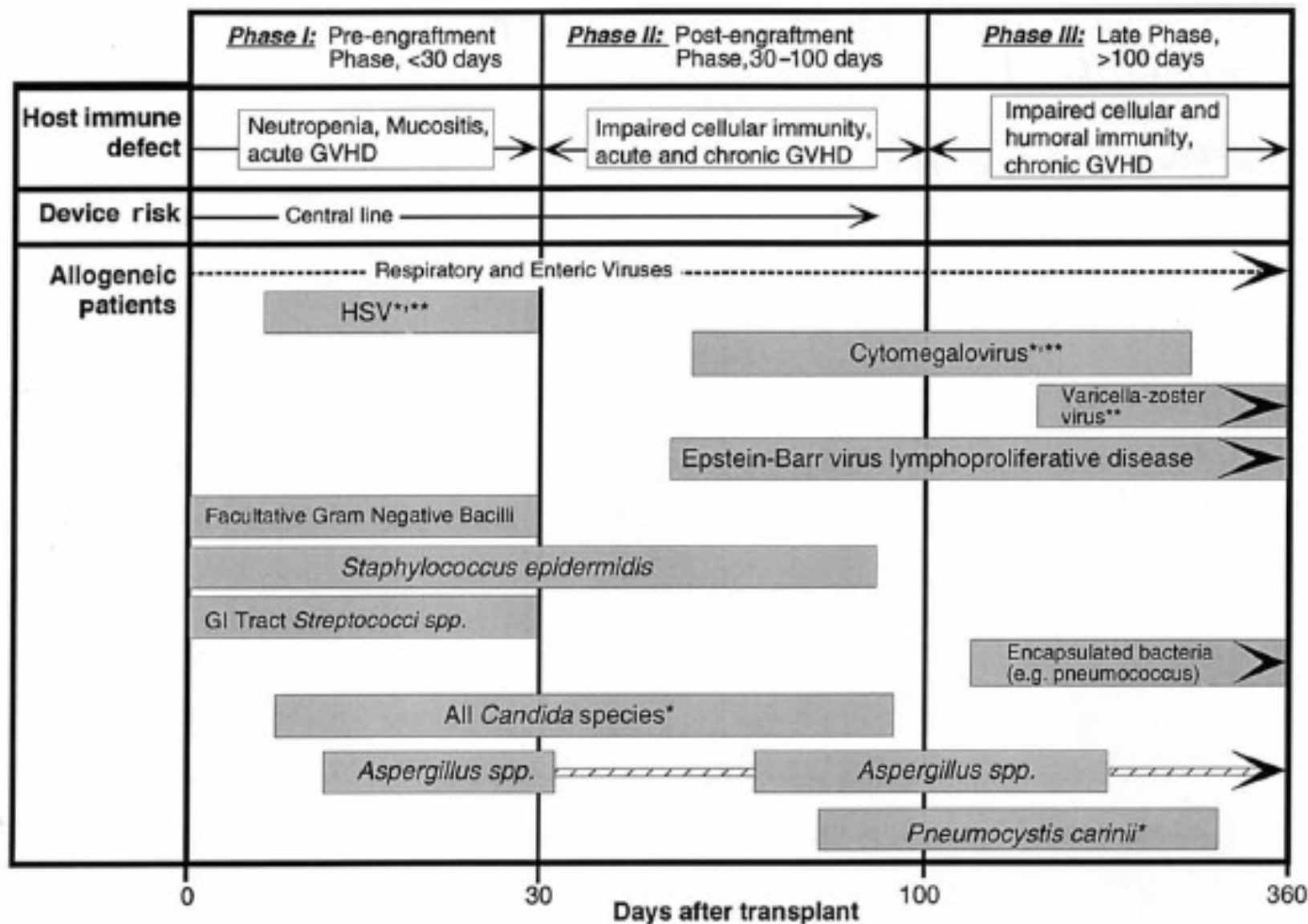


MRI von
OA Dr. Johannes Frei, Radiologie Elisabethinen Linz

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



Optimal Management of Neutropenic Fever in Patients With Cancer

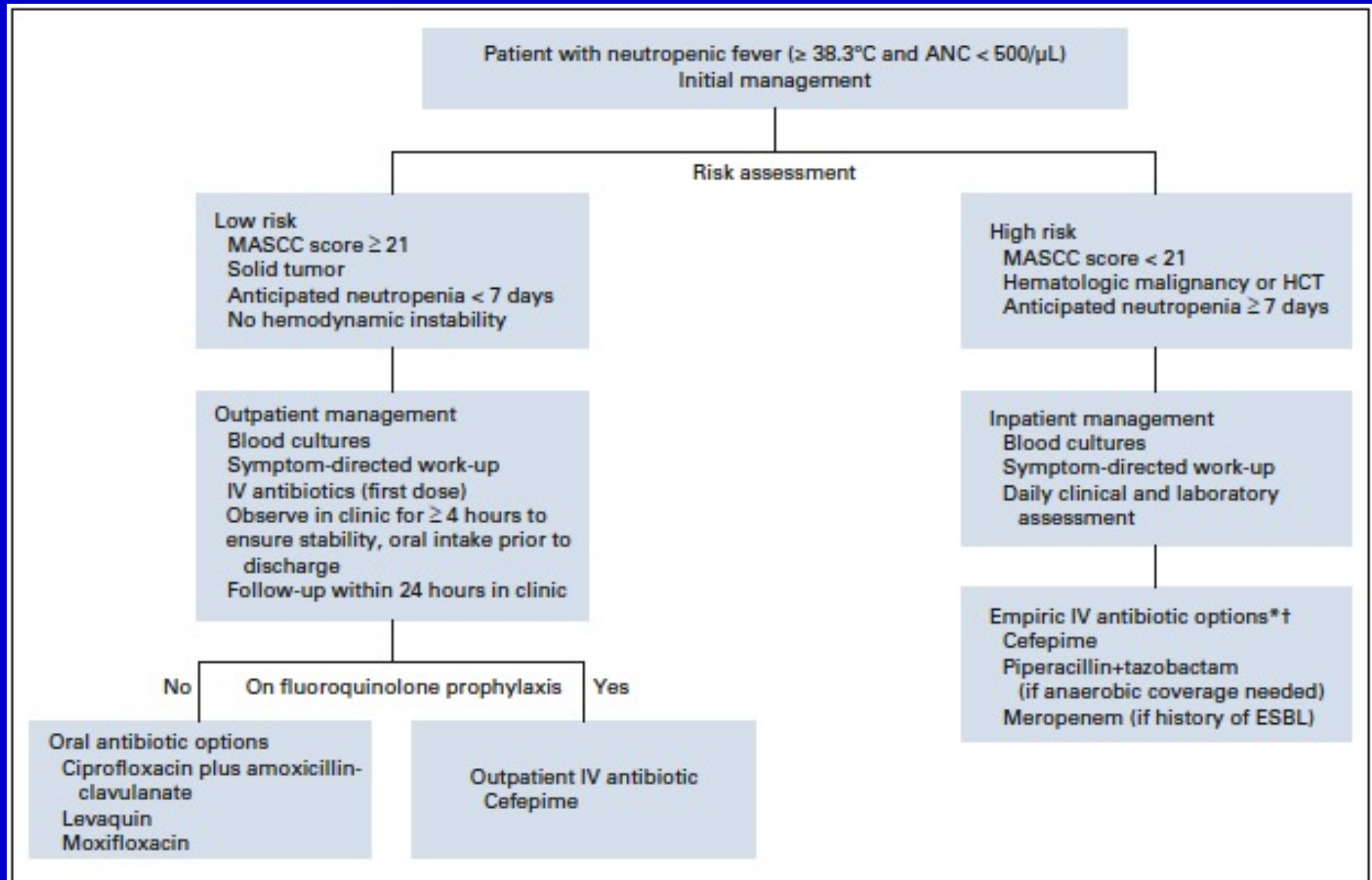
Zimmer et al., JCO 2019

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

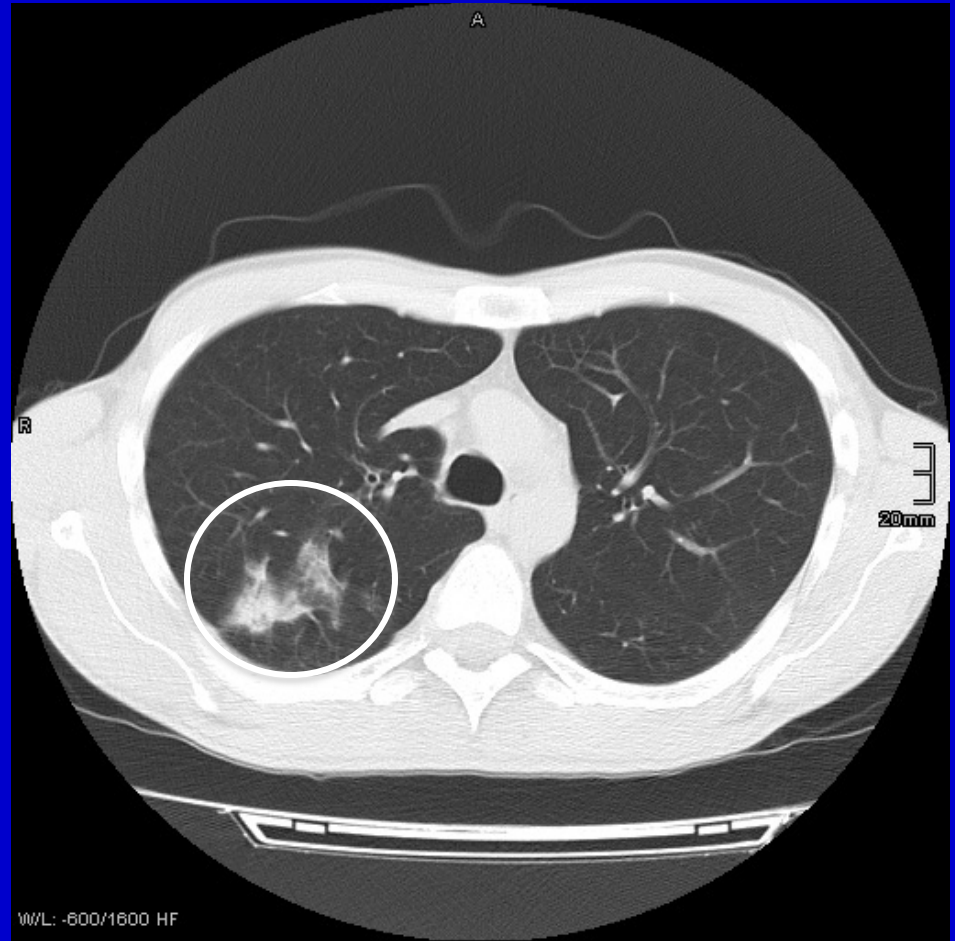
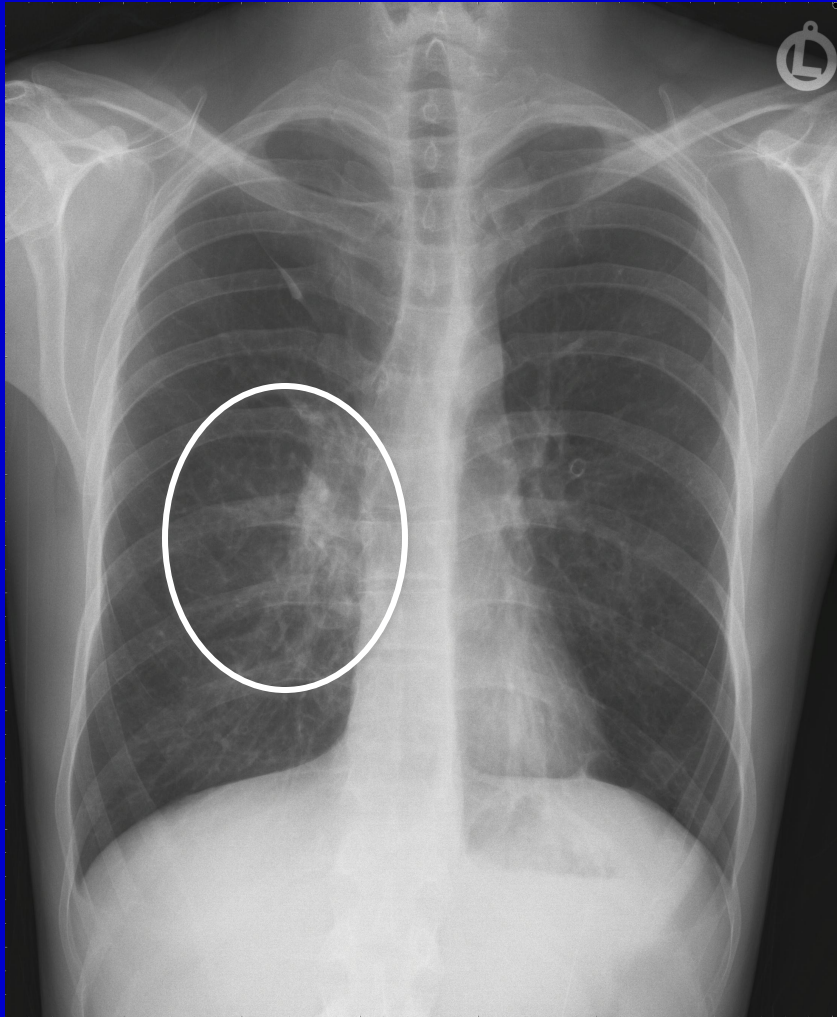


Fallbericht: Patient KG, m, 41a

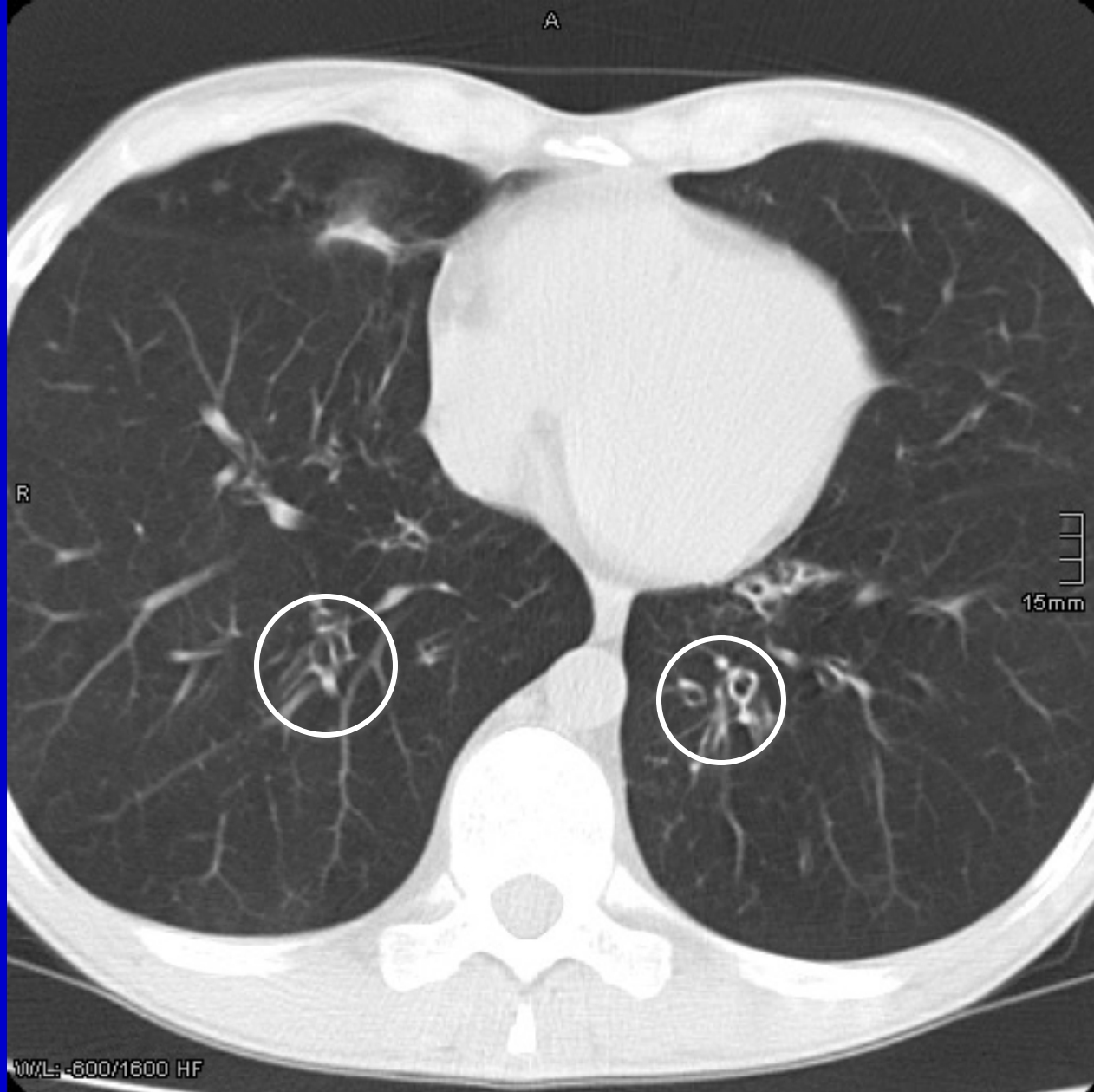
- FA: keine Auffälligkeiten
- FK: in der Jugend wiederholte Sinusitiden, Bronchitiden und Durchfallsepisoden
- seit 2001 (29a): wiederholte Pneumonien (CAP) die ambulant mit Clavamox behandelt wurden
- seit 2001 Gewichtsverlust – Untergewicht
- Biometrie: KG 59kg, KL 179cm, **BMI 18 - Leichtgewicht**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

Anamnese 2

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

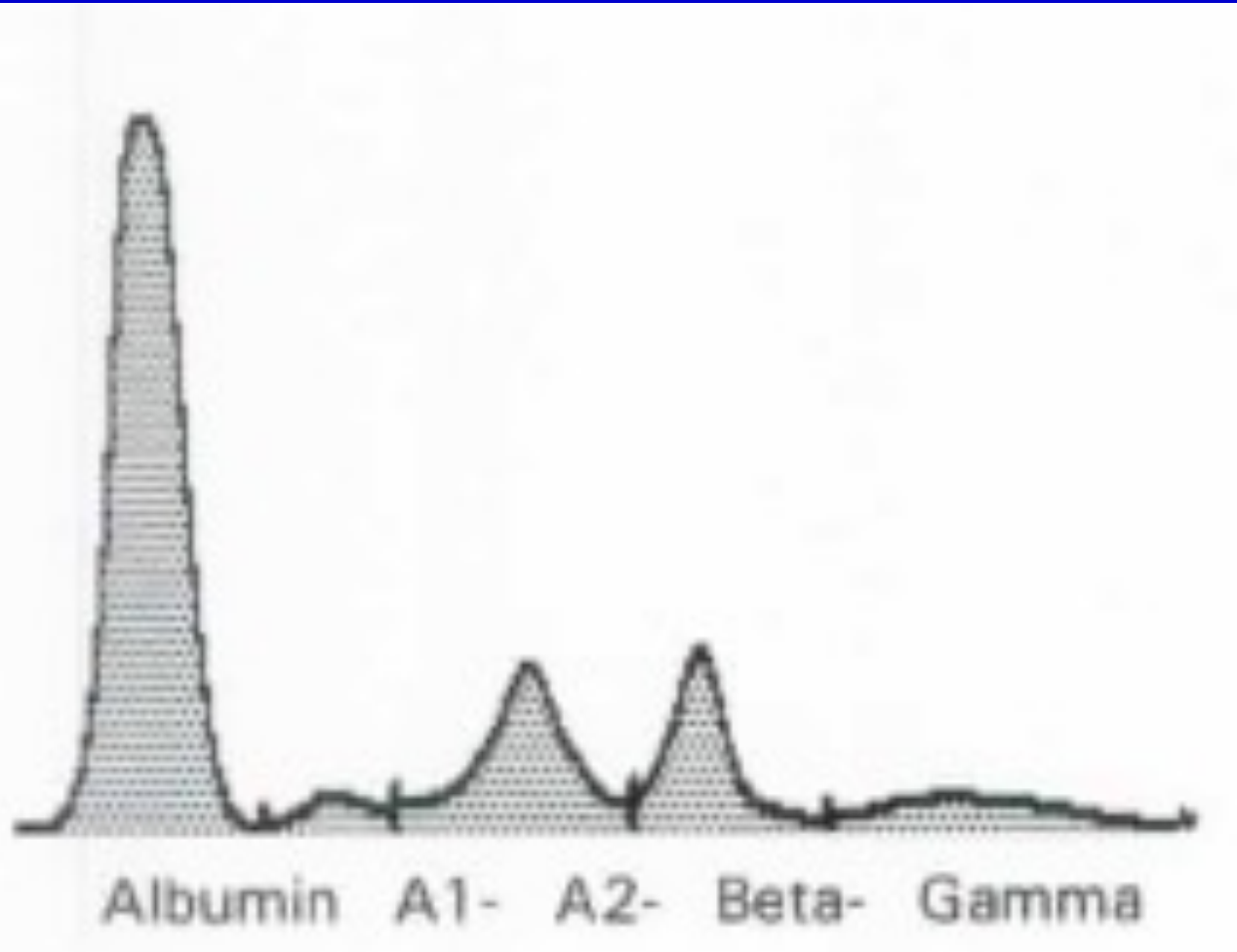
1. Complement
2. Phagozyten
3. T – Zellen
4. B – Zellen/Antikörper
5. T + B-Zellen
6. Innate Immunity

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, <i>Haemophilus influenzae</i> Enteroviruses: ECHO, polio <i>Mycoplasma</i> species
T cells	Sepsis, lung, GI tract, skin	Viruses: CMV, adenovirus, measles, molluscum Fungi: <i>Candida</i> and <i>Aspergillus</i> species, <i>Pneumocystis jiroveci</i> Pyogenic bacteria Protozoa: <i>Cryptosporidium</i> species
Phagocytes	Skin infections, lymphadenitis, liver, lung, bone, GI tract, gingivitis/periodontitis	Bacteria: staphylococci, <i>Serratia marcescens</i> , <i>Burkholderia cepacia</i> , <i>Klebsiella</i> species, <i>Escherichia coli</i> , <i>Salmonella</i> species, <i>Proteus</i> species Fungi: <i>Candida</i> , <i>Aspergillus</i> , and <i>Nocardia</i> species
Complement	Systemic infections, meningitis	Pyogenic bacteria: streptococci, <i>Haemophilus influenzae</i> , <i>Neisseria</i> species

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



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

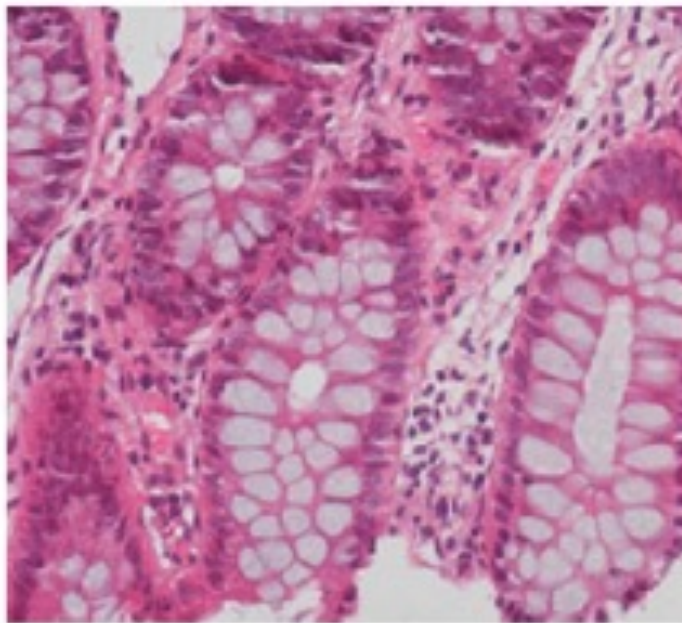
GI Leichtgewichtabklärung

- 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**

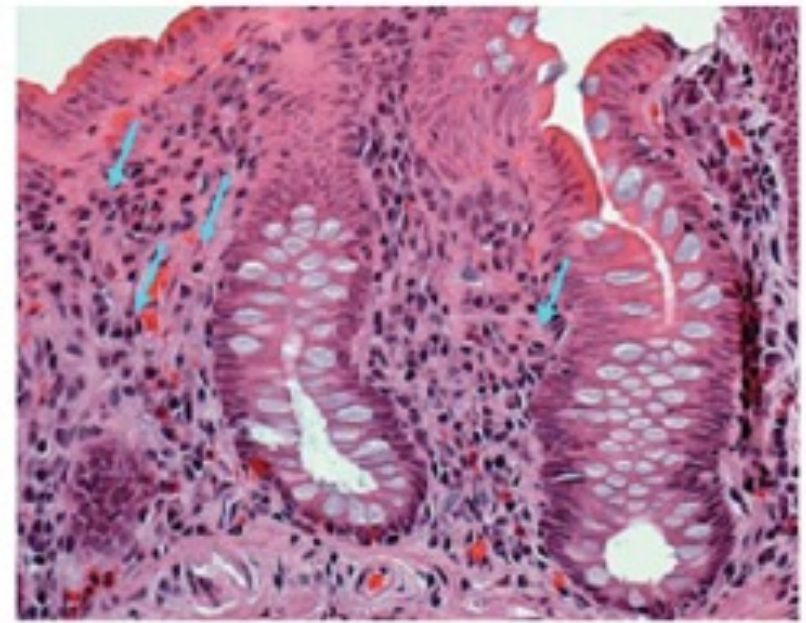
Characterization of Immunologic Defects in Patients with Common Variable Immunodeficiency (CVID) with Intestinal Disease



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



CVID



IBD

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'*)

Common Variable Immunodeficiency

CVID Prävalenz 1 : 10 000 – 1 : 50 000

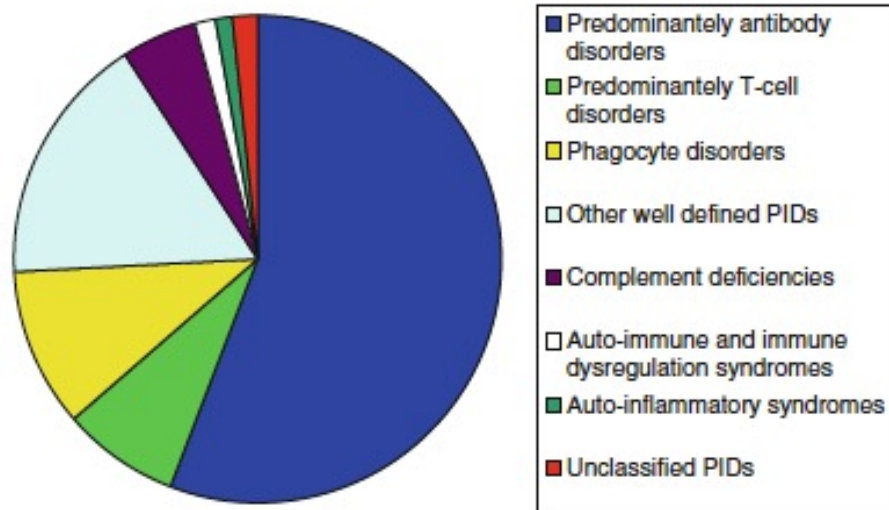


Fig. 1 Distribution of PID in Europe according to the ESID patient registry 2010 (<http://www.esid.org/statistics.php?sub=2>), $n=10,747$. PIDs primary immunodeficiencies, ESID European Society for Immunodeficiencies

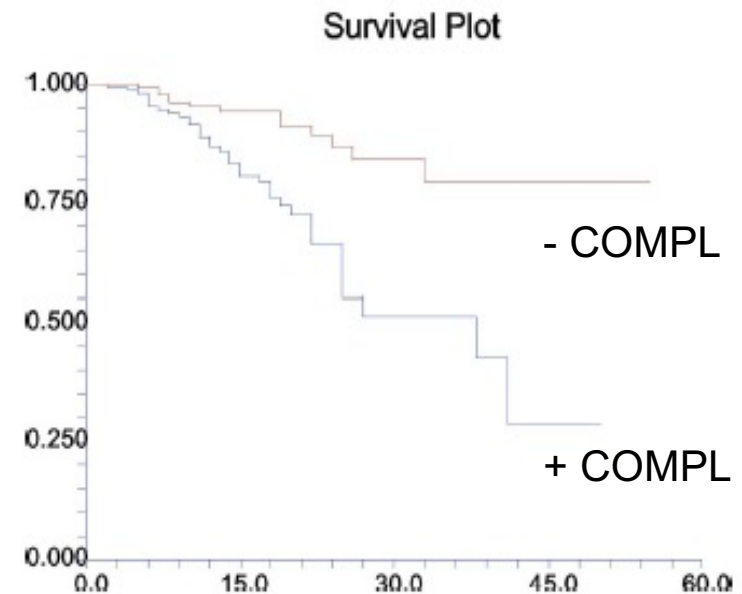


Figure 4. Mortality by years since diagnosis and by clinical phenotype. Red line represents those without complications; blue line, those with at least one disease-related complication. Kaplan-Meier plot of survival.



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



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.

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

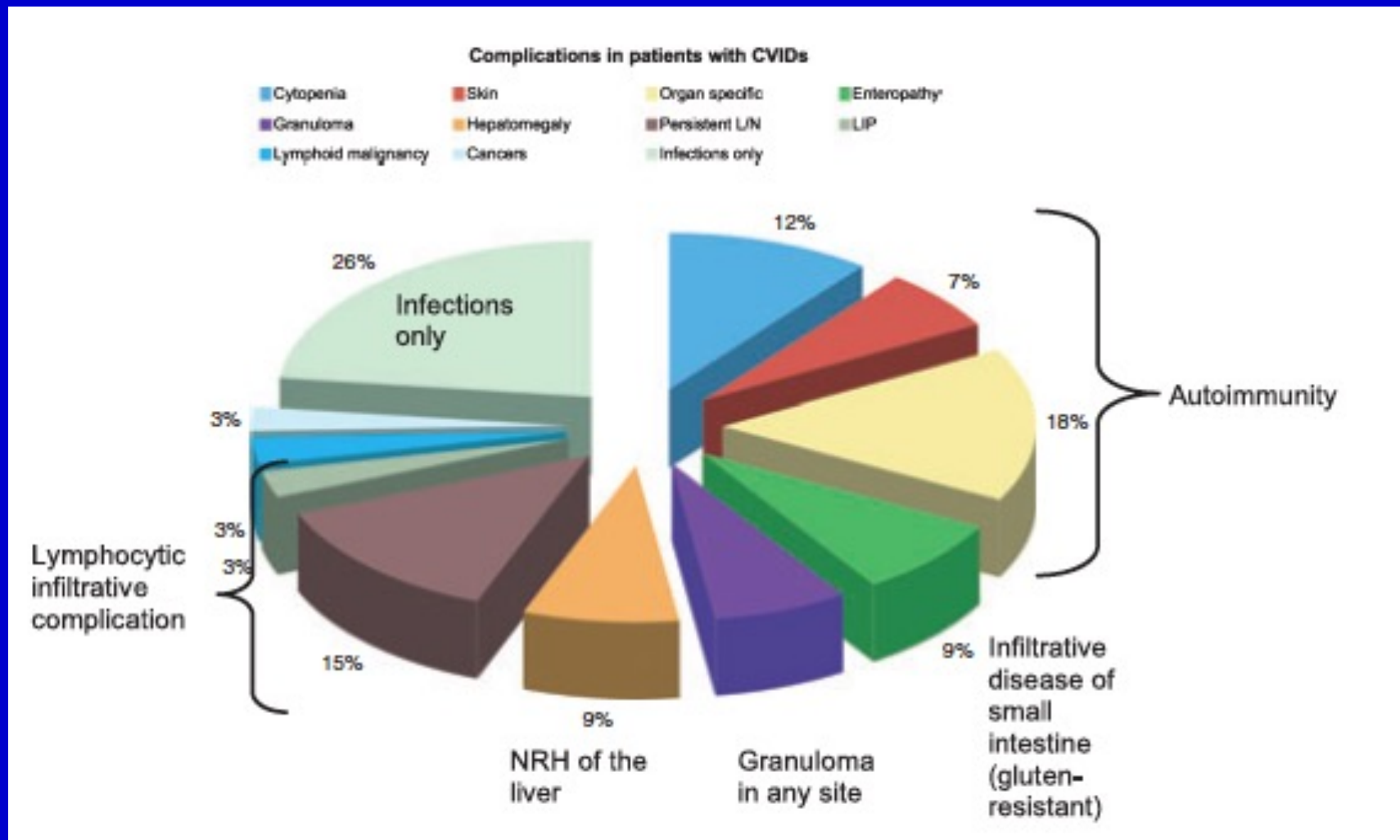
(Tabelle vereinfacht)

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

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 Immunity	Exposition Anatom. Disposit. Inad. Therapie
Autoimmunität Chron. Inflammat. Lymphoprolif.		Kombinierte T+B Zelldefekte Immunsregul.	
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



The EUROclass trial: defining subgroups in common variable immunodeficiency

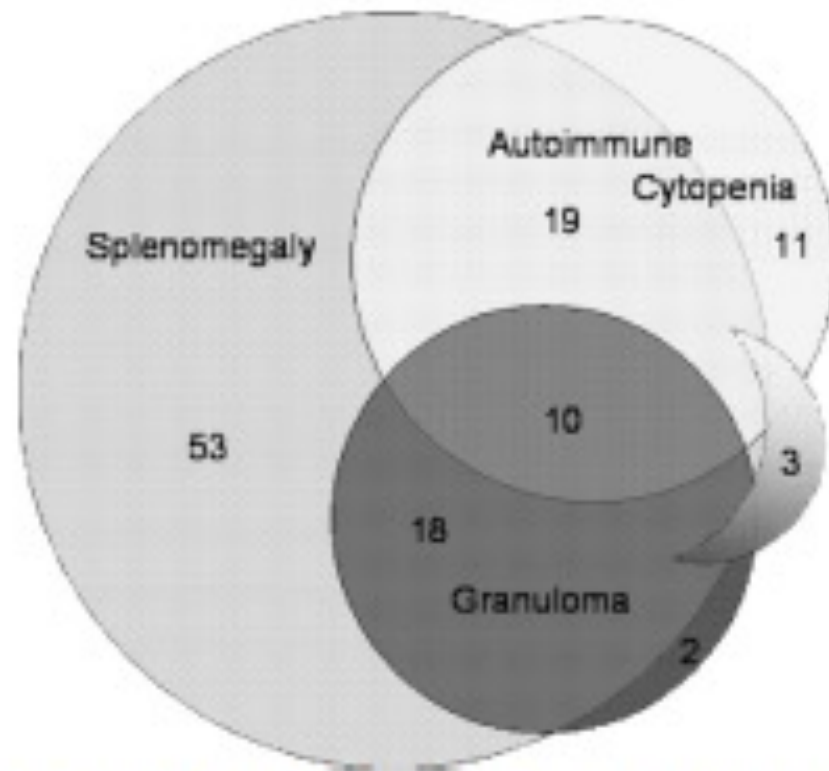


Figure 1. Coincidence of granulomatous disease and autoimmune cytopenia with splenomegaly in patients with CVID. The diagram indicates the coincidence of splenomegaly, granulomatous disease, and autoimmune cytopenia in the European cohort of CVID patients. In 3 patients, granulomatous disease and autoimmune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

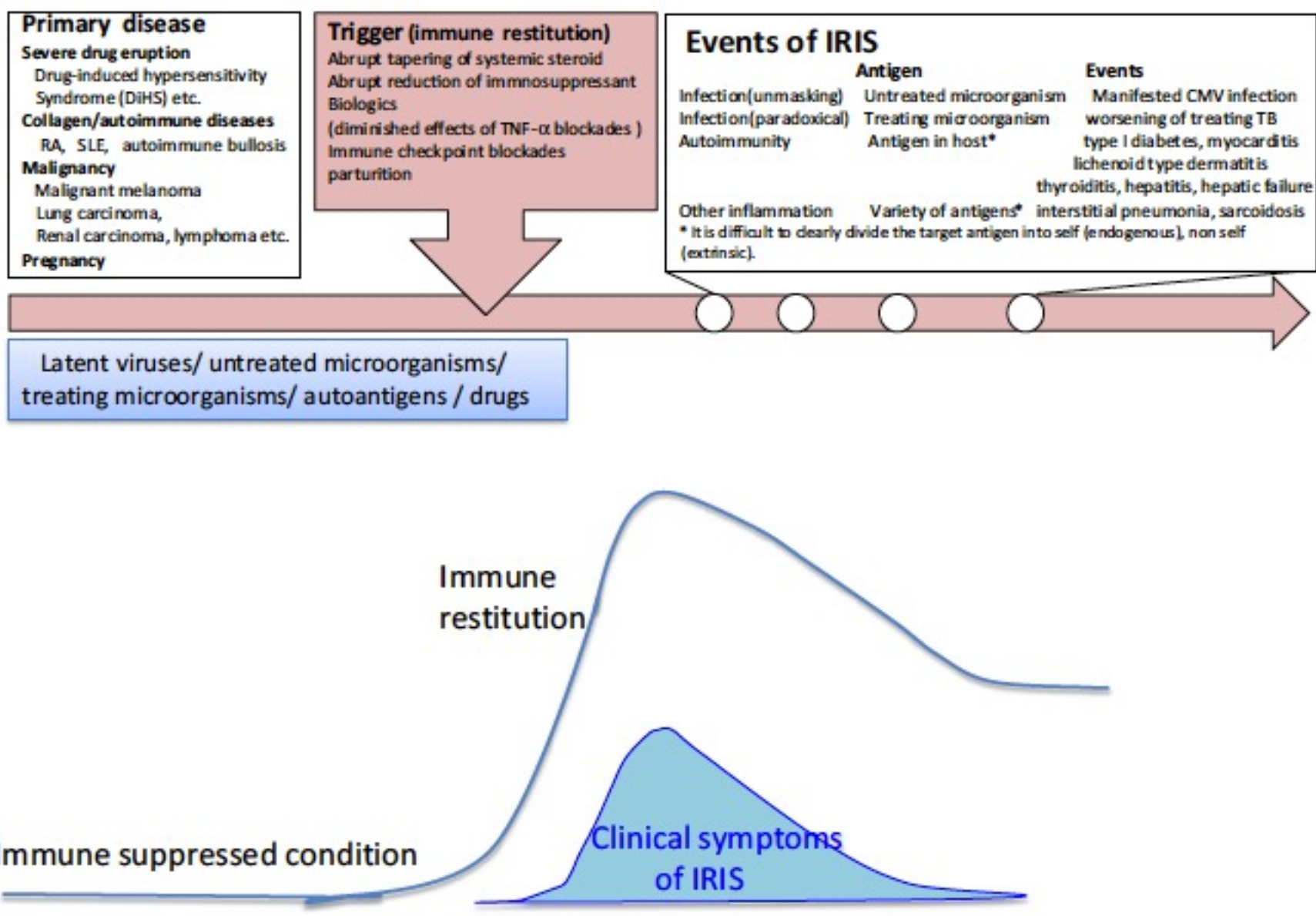
Table 1. Abstracted guideline for management of common variable immunodeficiency complications.

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	<i>Helicobacter pylori</i> 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



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Table 2. Comparison of irAE and events following DIHS

irAE due to immune checkpoint blockades	Events following the DIHS
Diarrhea, enterocolitis	<u>Gastrointestinal bleeding</u>
<u>Gastrointestinal bleeding</u>	<u>Hepatitis, hepatic dysfunction</u>
<u>Hepatitis, fulminant hepatitis</u>	Alopecia
Pancreatitis	<u>Nephritis, renal dysfunction</u>
<u>Nephritis</u>	<u>Interstitial pneumonia/pneumonia</u>
<u>Interstitial pneumonia</u>	<u>Dermatitis, drug rash</u>
<u>Dermatitis, drug rash</u>	Herpes zoster, herpes simplex
Rheumatoid arthritis	Cryptococcus pneumonia
<u>Thyroid dysfunction</u>	Pneumocystis carinii pneumonia
Hypophysitis	<u>Thyroid dysfunction/thyroiditis</u>
<u>Encephalitis</u>	<u>Encephalitis/limbic encephalitis</u>
<u>Myocarditis</u>	<u>Myocarditis</u>
<u>Type 1 diabetes mellitus</u>	<u>Type 1 diabetes mellitus</u>
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)