Figure 2 Transfusion of a patient with animal blood (from Scultatus, courtesy of the National Library of Medicine)

Immunology in Pulmonology

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Outline

- Primary Immunodeficiency Diseases/ Inborn errors of Immunity
  - Respiratory manifestations
  - Red flags
  - Workup
- Asthma
  - Immunology
  - Therapies

Primary immunodeficiency
→ Inborn Errors of Immunity

"When you hear hoof beats, think of horses not zebras"

~Dr. Thomas Woodward
Professor, University of Maryland
School of Medicine

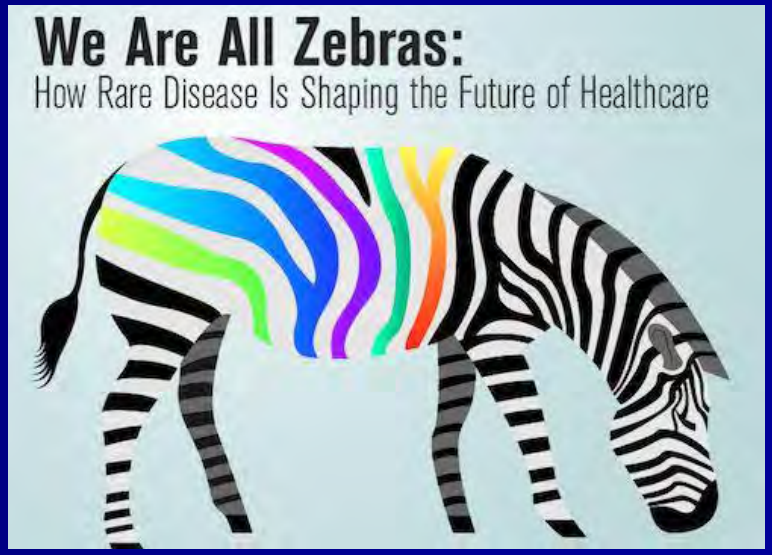
According to John Sotos' book Zebra Cards: An Aid to Obscure Diagnoses, the term was first coined in the 1940s.

What does the phrase mean? While in training, doctors are taught to look for the most common causes of illness – the horses. Those with primary immune deficiencies and other rare diseases are the zebras.

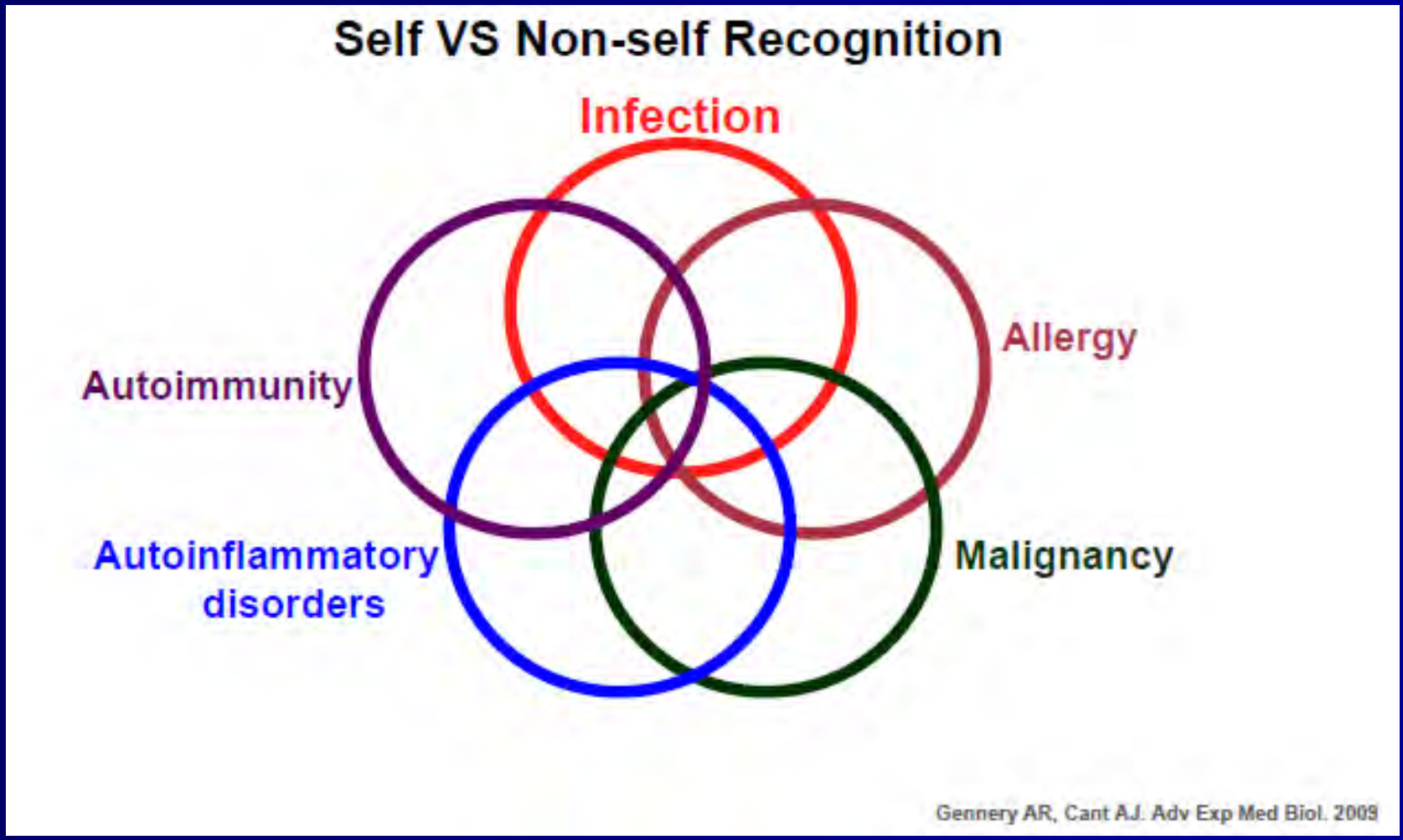
www.immunecompetence.org

We say embrace being a Zebra!

- Primary immunodeficiency diseases is a window to the immune system
- Inborn Errors of Immunity
- ~350 single gene defect described



PID - Immune system failure



Respiratory manifestations of PID

- Infections
  - Bacteria
    - Pneumonia/Empyema/ Bronchiectasis
    - Lung abscess
  - Viral
    - Pneumonitis/ ARDS
  - Fungal/PCP
  - Mycobacterium
- Allergy
  - Asthma, ABPA
- Interstitial lung disease
  - Granulomatous inflammation
- Malignancy
  - Mediastinum Lymphoma

PIDs

Agammaglobulinaemia/CVID/CID

Hypogamm/Complement deficiency

CGD, AD-HIES

SCID/ CID

SCID/ CID/ XHIGM

SCID/CGD/MSMD

IgAD, CVID, CID

CVID/CGD

CID (NBS), WAS, Artemesis

"Reg Flags" for Primary Immunodeficiency

Adapted from Jeffery Modell Foundation poster: 10 Warning signs of PID

1	Family history	Positive for early unexplained death, sepsis, recurrent infections, or specific immunodeficiency diagnoses
2	Frequent infections	Elevated frequency of documented infections including: • Pneumonia ≥ 2 per year • Sinus infection ≥ 2 per year • Ear infections ≥ 4 per year
3	Chronic/ Unusual sites/ Complications of infection	Bronchiectasis Recurrent deep skin or organ abscesses (e.g., liver or brain abscess) Two or more deep seated infections ARDS from common respiratory infections
4	Infecting organism	Opportunistic, recurrent, or unusual pathogens (e.g. *Pneumocystis Carinii*, *Mycobacterium bovis*, *Aspergillus, Serratia, Nocardia, Burkholderia cepacia*) Persistent thrush in mouth or elsewhere on skin after 1 year old
5	Response to therapy	Poor response or recurring infection after antimicrobial discontinuation; Need for IV antibiotics to clear infections
6	Other signs	Failure to thrive, dermatitis, recurrent diarrhoea, history of autoimmune disease, malignancy

Pattern of illness associated with PID

Disorder	Illness	
	Infection	Others
Antibody	Sinopulmonary infection (pyogenic, encapsulated bacteria) Gastrointestinal (enteroviruses, *Giardia lamblia*)	Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, *Pneumocystits carinii*, viruses) Gastrointestinal (viruses) Skin, mucus membrane (fungi - *Candida*)	Graft vs host disease in SCID
Complement	Sepsis and other blood-borne encapsulated bacteria (*Streptococcus*, *Pneumococcus*, *Neisseria*)	Autoimmune disease (SLE, GN)
Phagocytes	Skin, reticulendothelial system, abscesses (Catalase positive organism: *Staph aureus*, *Burkholderia cepacia*, *Aspergillus* sp, Nocardia sp, and *Serratia marcescens*.	

Host Defense Mechanisms

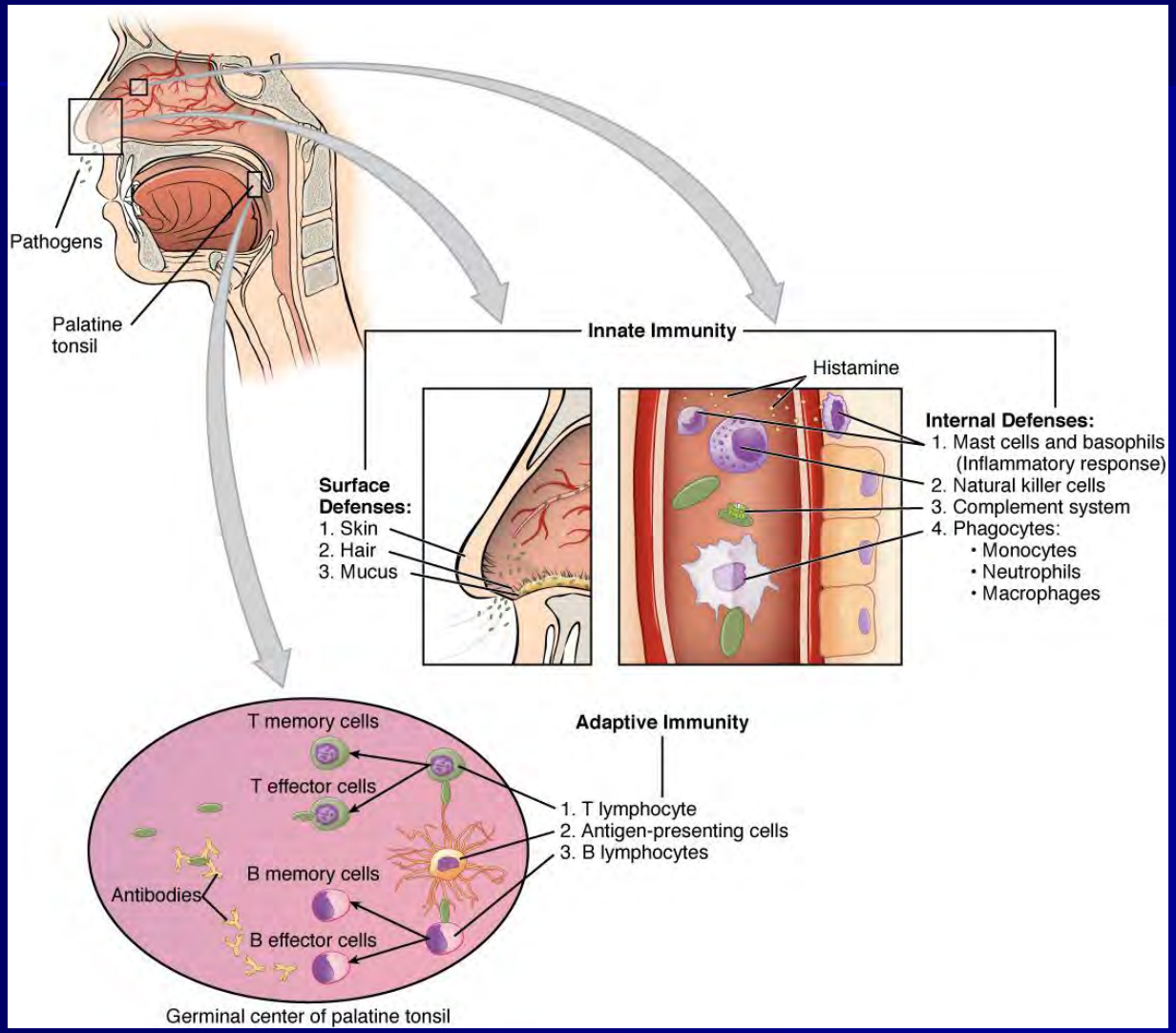
- breakdown results in recurrent infections

- INNATE IMMUNITY
  - Skin and Mucosal Barriers
  - Pattern recognition molecules/Toll-Like Receptors/ Dendritic cells/ HLA – self vs microbial recognition
  - Interferons/ Cytokines
  - Complement
  - Macrophages/ NK cells/ Phagocytes

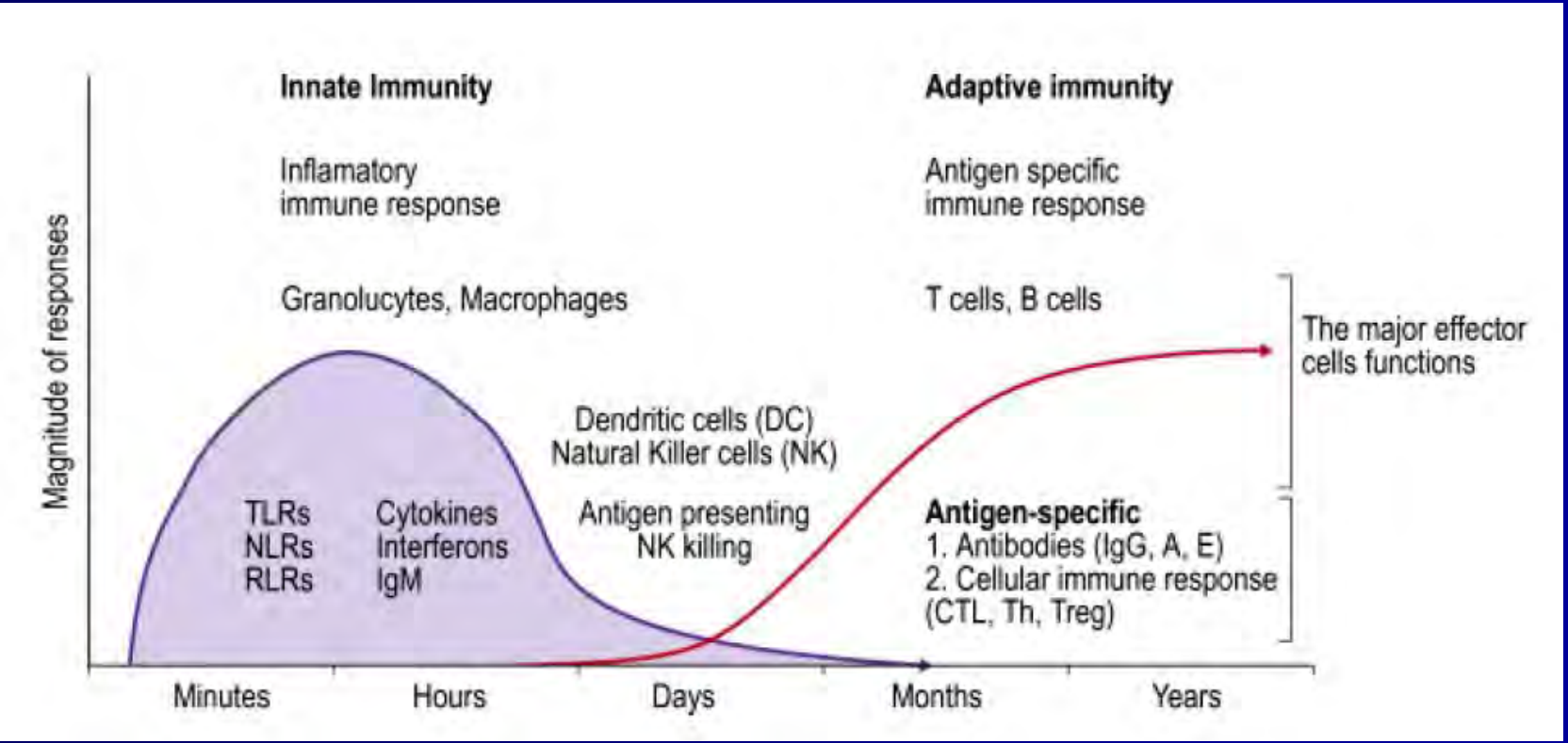
- ADAPTIVE IMMUNITY
  - B cells – humoral (antibody) arm
  - T cells – cellular arm

Classical PID

Innate and Adaptive Immunity



Innate and Adaptive Immunity



Barriers of the Lungs

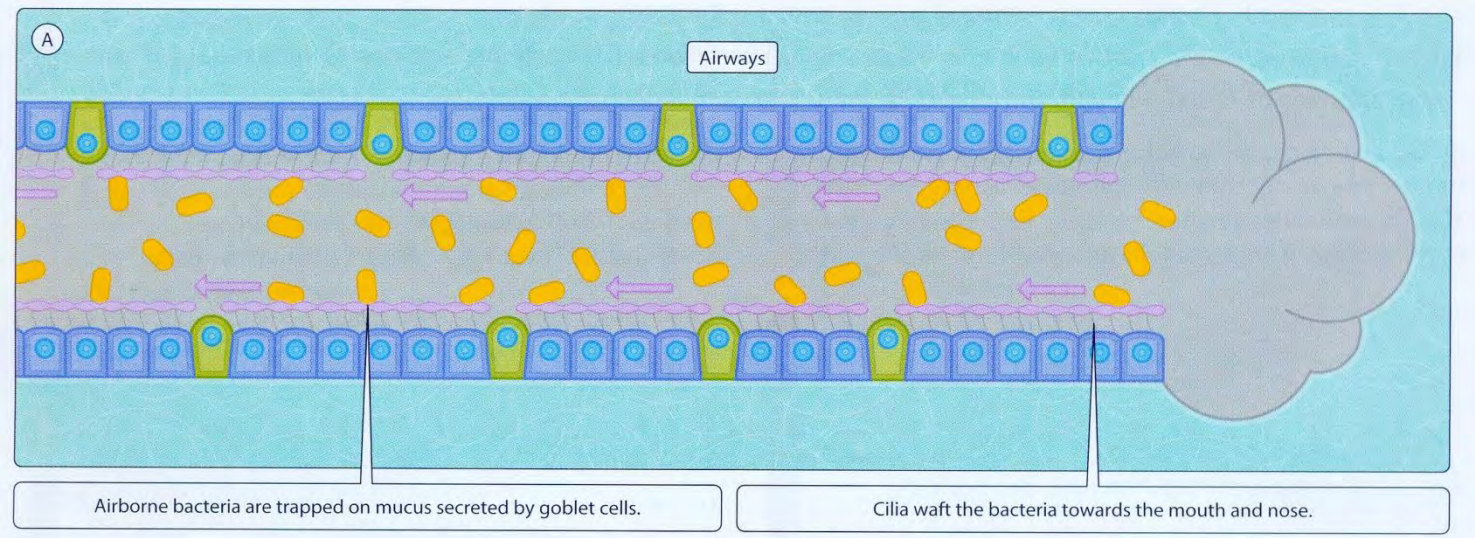
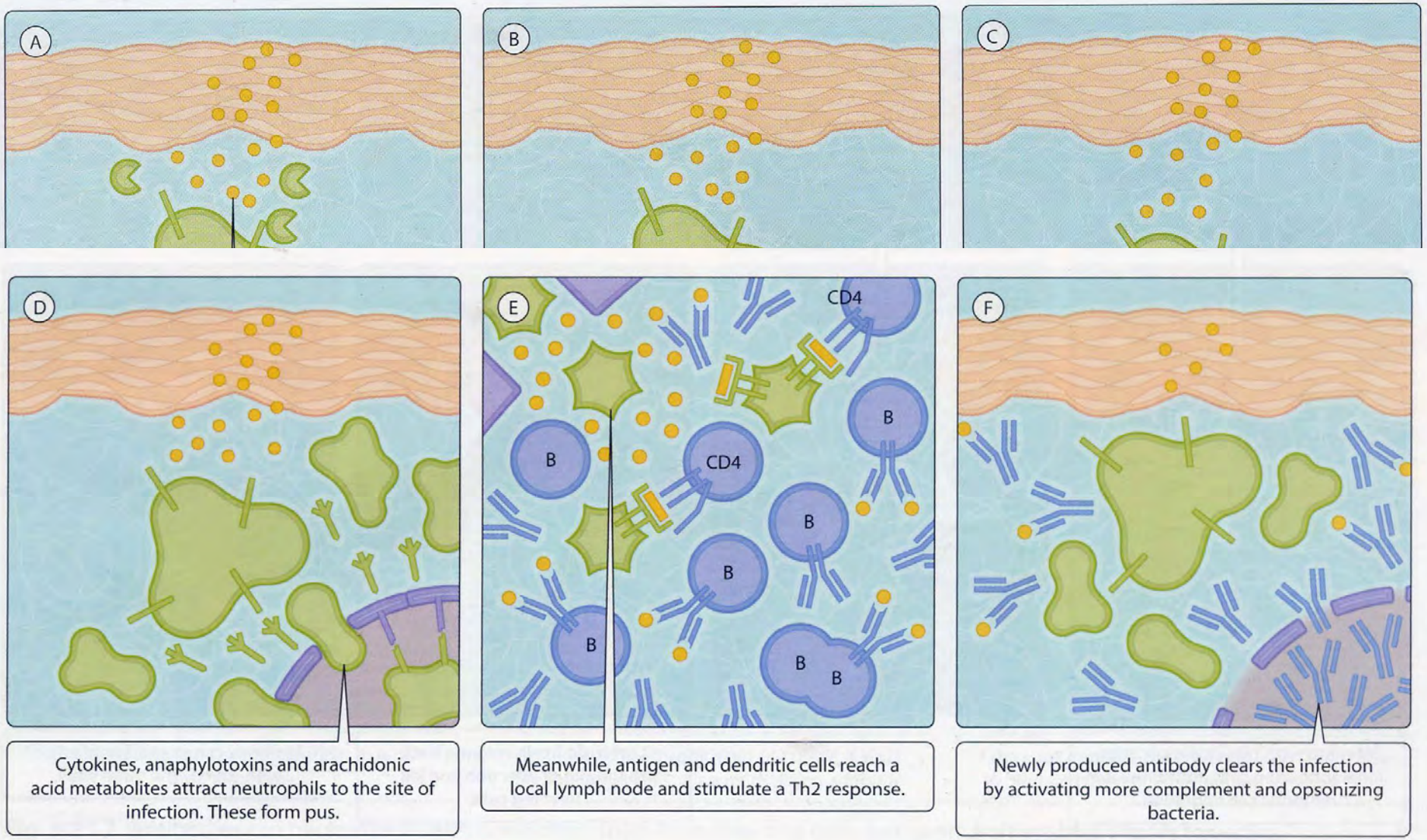


Fig. 3.1.1 Barriers to infection: in airways **(A)** and gastrointestinal tract **(B**, facing page**)**.

- Lung anatomical defects predispose to recurrent infections
  - CCAM, TOF
  - PCD, Cystic fibrosis

Acute bacteria infections are mainly cleared by the innate immune system



Response to encapsulated bacteria

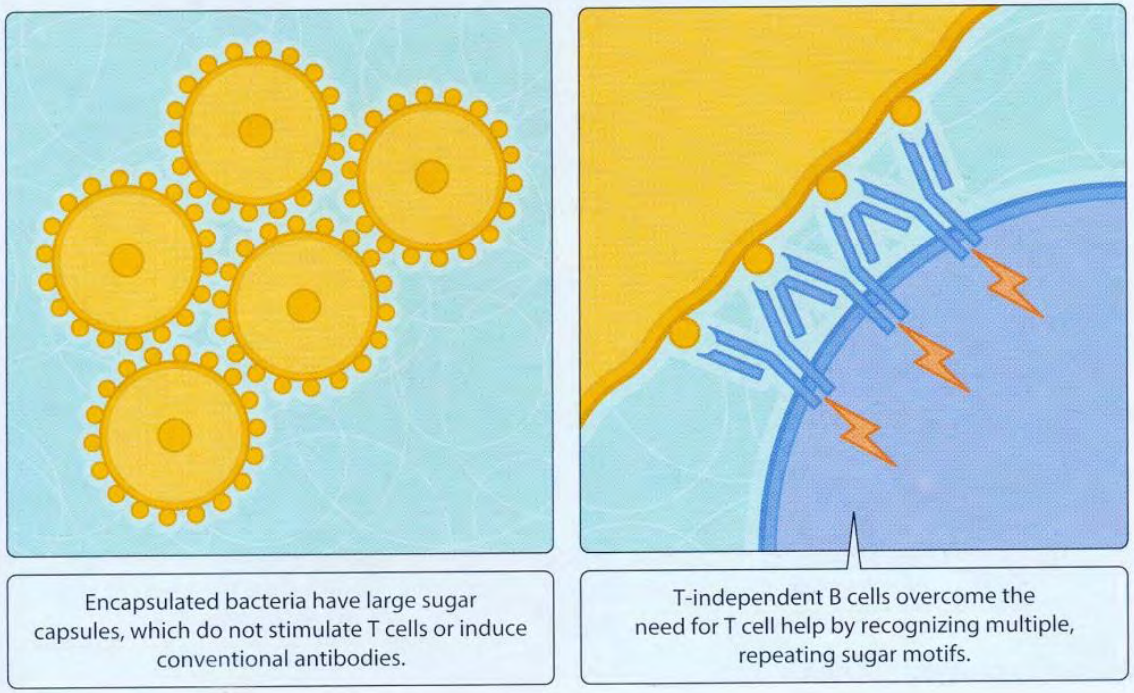
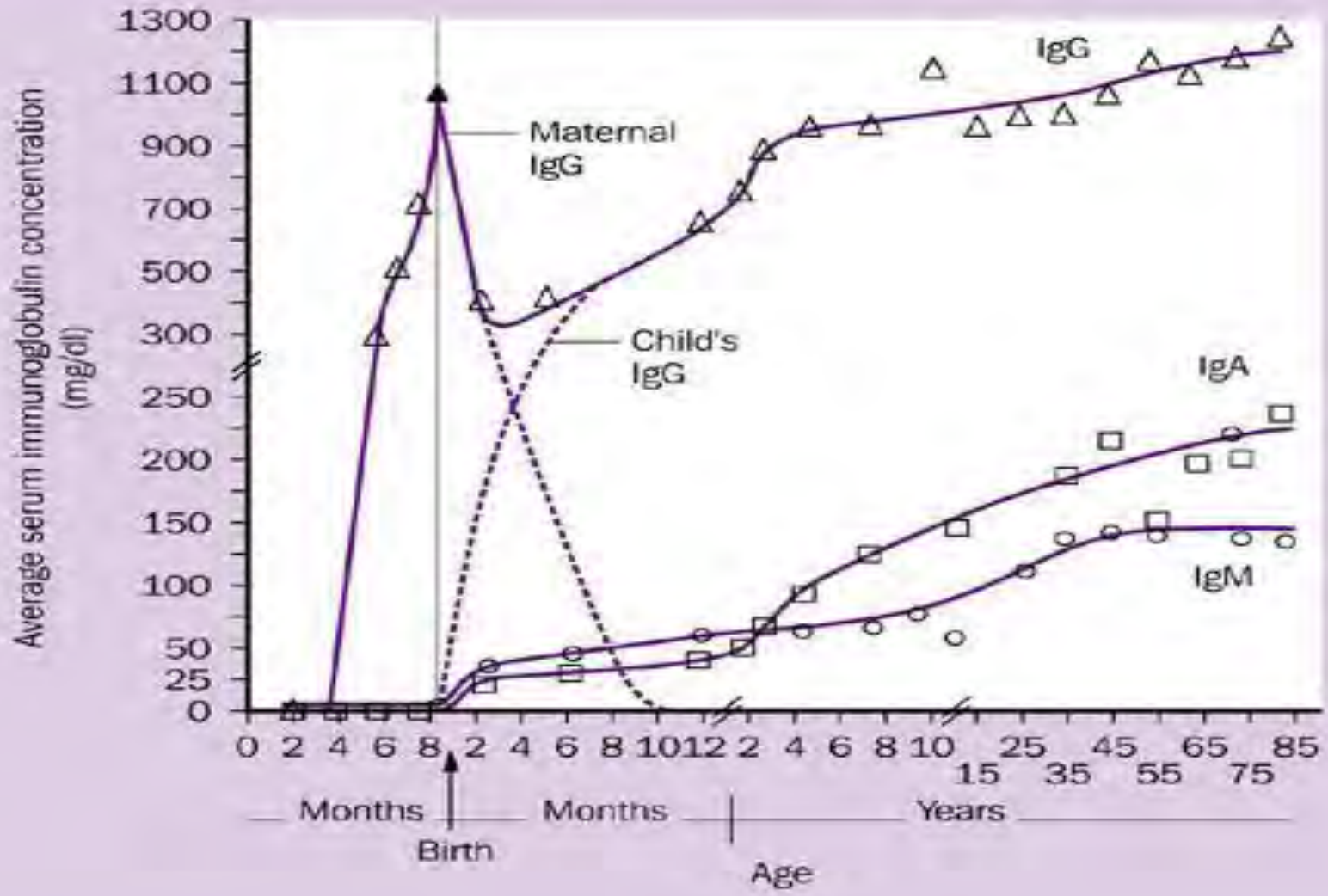
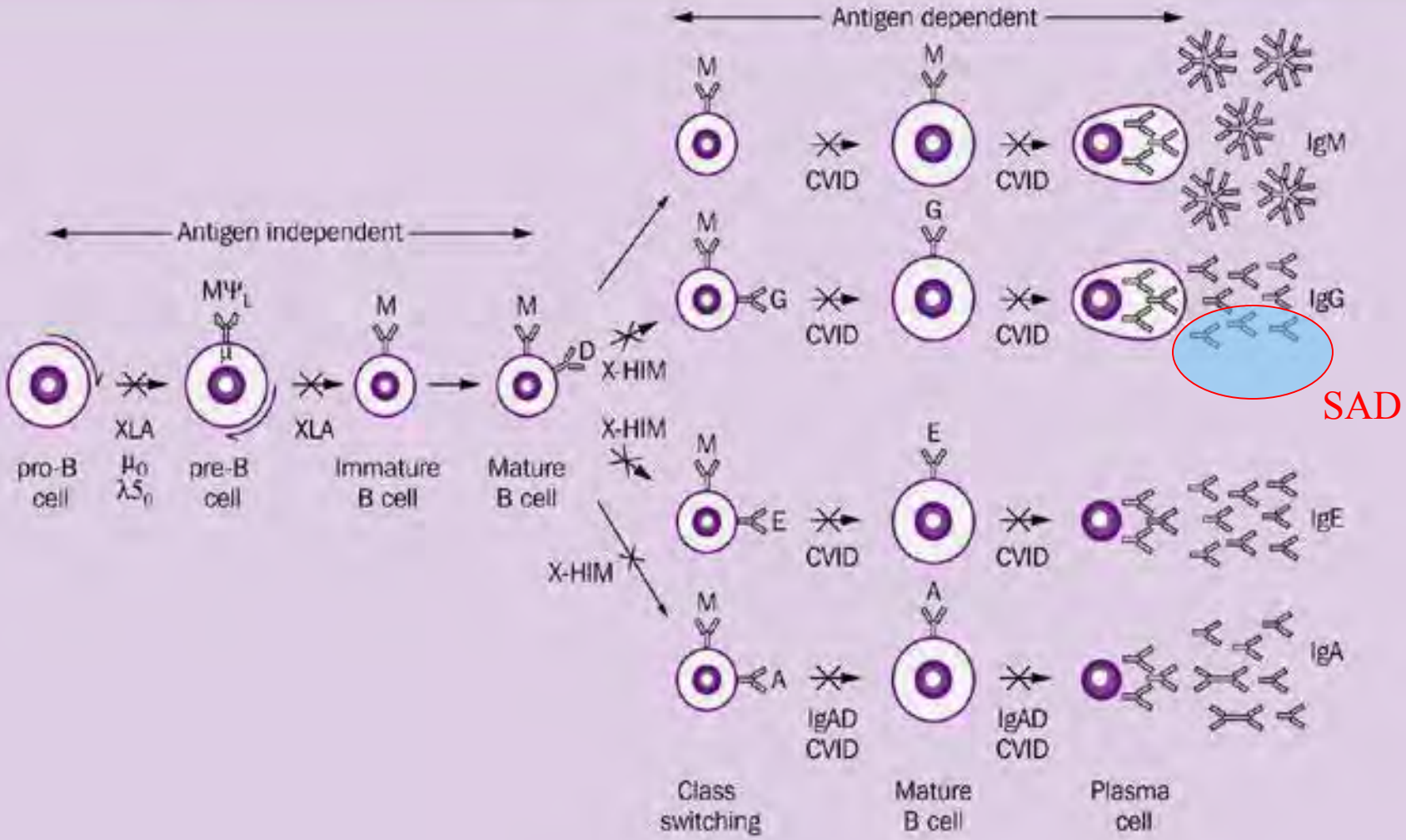


Fig. 3.20.3 T-independent B cells are activated by sugar antigens on bacterial capsules.

Age-related changes in the serum concentration of immunoglobulins



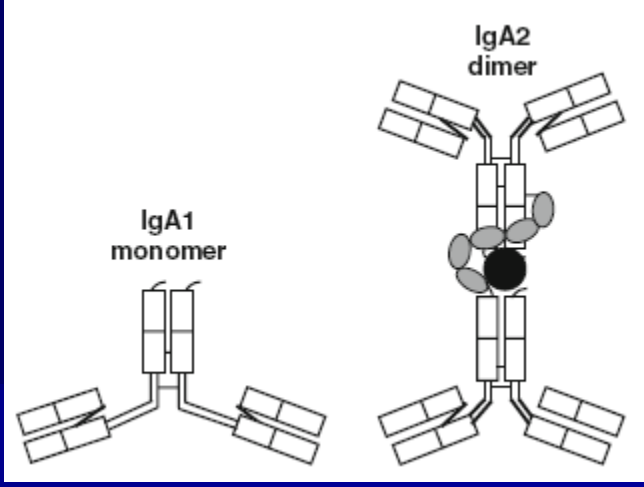
Defects in B-cell development can lead to humoral immune deficiency



PIDs with Bacteria infections

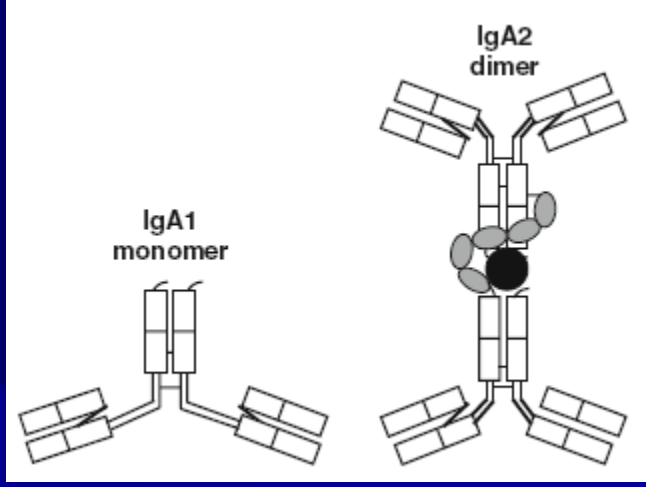
- IgA Deficiency (IgAD)
- X-linked agammaglobulinemia (XLA)
- Common Variable Immunodeficiency (CVID)
- AD Hyper-IgE syndromes (AD HIES)
- Chronic granulomatous disease (CGD)
- X-linked hyper-IgM syndrome (XHIGM)

IgA Deficiency



- Most common ID, 1:700 Caucasians
- Uncommon in Asians, 1:2600-5300 China, 1:15000-18500 Japan
- Autosomal recessive / dominant
- Males = Females
- B cell maturation defect in IgA production
- IgA < 0.07g/L with normal IgM and IgG, > 4yrs old
- Small proportion with IgG subclass (IgG2) defect
- Normal IgG response to most vaccines, variable response to polysaccharide vaccines (depending on IgG2 levels)
- May progress into CVID

IgA Deficiency



- Presentation:
  - 85-90% asymptomatic
  - Recurrent sinopulmonary infections (esp. those with IgG2 subclass def)
  - Gastrointestinal infections/ Disorders
  - Autoimmunity
  - Allergic disorders
  - Malignancy

Clinical associations of referred IgA-deficient subjects[a]

Condition	Number of patients	Patients (%)	Median age	IQR[b] years
Recurrent Infections	63	50	12.5	26.0
Autoimmunity	34	28	29.0	27.5
Allergy/Asthma	16	13	10.5	36.5
Cancer	9	7	59.0	15.0
Healthy	7	6	25.0	22.5
Gastrointestinal disorders	4	3	24.5	24.0

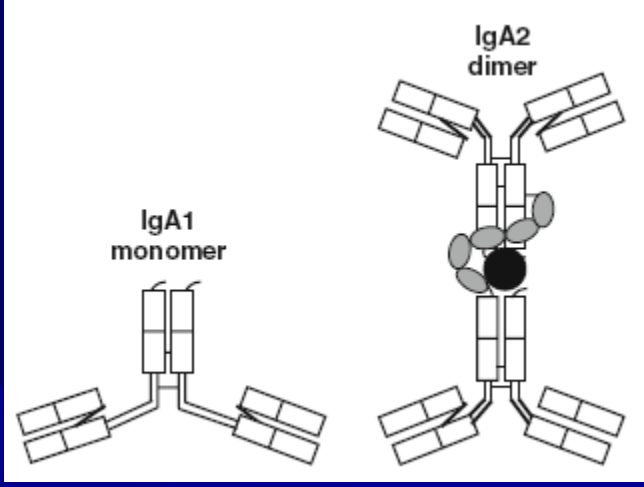
$N = 127$.

[a] Twenty-nine patients (23%) had more than one of these conditions.

[b] Interquartile range (age).

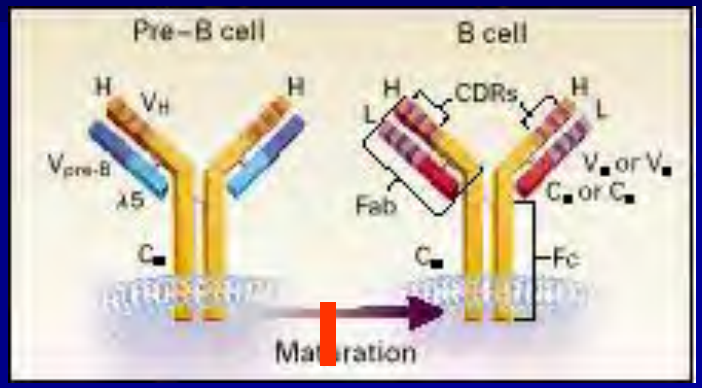
IgA deficiencies: Correlation between clinical and immunological phenotypes, J Clin Immunol 2009

IgA Deficiency



- Allergic disorders
  - Atopy in IgA deficiency range from 13-84%
  - Dermatitis resembling AD present
  - Increased incidence of asthma, AR/AC and food allergies
  - Total IgE raised or normal
  - Secretory IgA protective of allergy development?
- Treatment
  - Nil for asymptomatic group
  - Clinical importance of screening for anti-IgA antibodies as at risk of blood transfusion anaphylactic reaction
  - Range from prophylactic antibiotics to IVIG in those with IgG subclass deficiency

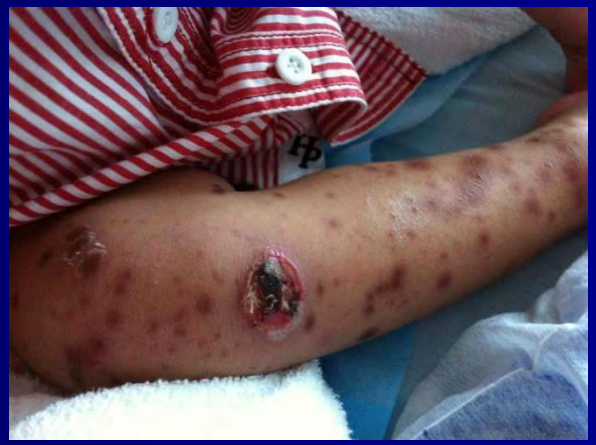
X-linked (Bruton's) Agammaglobulinaemia

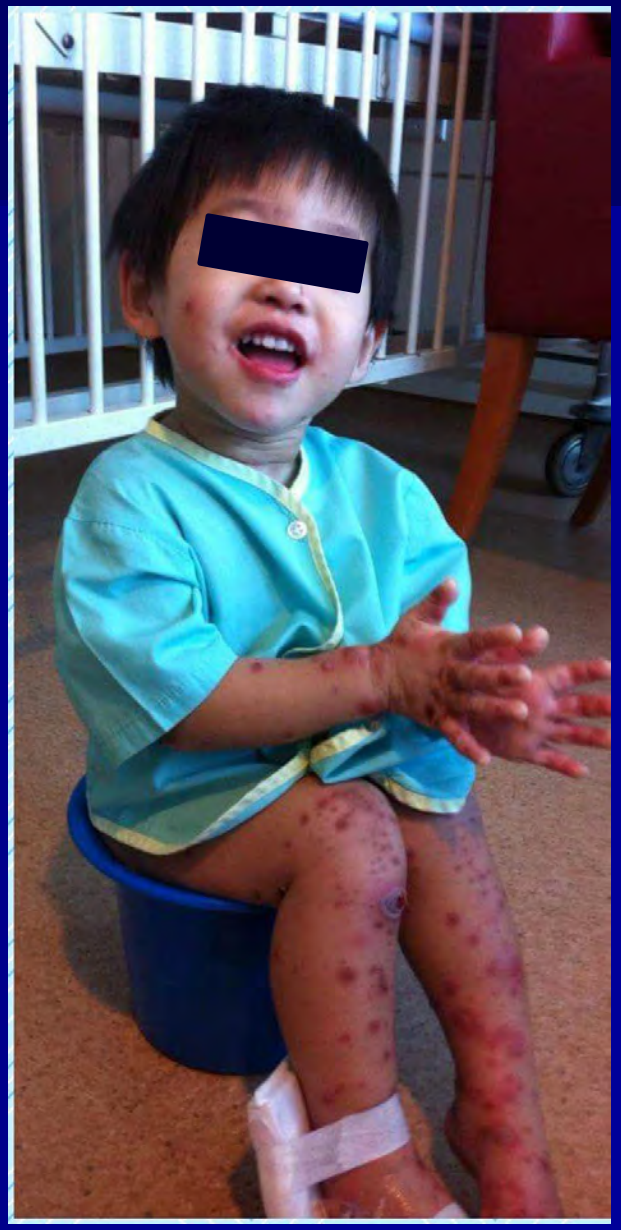


- Males, Xq21.3-22, familial
- Recurrent pyogenic infections
- All Ig classes < 2SD's for age
- < 2% CD19+ B cells
- Absent isohemagglutinins, poor response to vaccines
- No palp. lymph nodes, no germinal centers
- Cell mediated immunity intact
- BM - normal B cell precursors (pre-B)
- Mutations in Btk tyrosine kinase, 1:200,000
- Lifelong IVIG replacement
  - reduced lifespan Cx by bronchiectasis and sclerosing cholangitis
- AD-like eruptions occur (but IgE low), superimposed with infections

X-linked (Bruton's) Agammaglobulinaemia

- Recurrent pyogenic infections in skin and sinopulmonary tract
  - Encapsulated bacteria eg. *Streptococcus Pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa*
- Prone to bronchiectasis
- Severe enterovirus/HFM





Common Variable Immunodeficiency

- Most common symptomatic primary antibody ID in adults and children, ~ 1:10,000-50,000 Caucasian
- Onset after 4 years of age (usually in second decade)
- Decreased levels in 2 IgG, IgA, and/or IgM
- Absent isohemagglutinins, Poor response to vaccines
- Usually normal peripheral B cell numbers, classification based on B-cell subsets;
  - naïve B cells (IgM+IgD+CD27-);
  - IgM memory B cells (IgM+IgD+CD27+);
  - isotype-switched memory B cells (IgM-IgD-CD27+)
- Abnormal T cell number or function - common
- Several rare recessive genes found: routine genetic testing not recommended
  - ICOS, CD19, BAFF receptor, TNFRSF13B, TNFRSF13C, MSH5, TACI, APRIL

Common Variable Immunodeficiency

- Presentation
  - Predominantly recurrent bacterial infections of the respiratory and gastrointestinal tract
  - Also viral, fungal and parasitic infections if T cell involved
  - Autoimmune manifestations and malignancies
  - AD-like eruptions (IgE elevated or normal), superimposed with viral/bacterial/fungal infections

Table 2. Summary of complications and incidence*

	Numbers	Percentage
Infections	428	90
Autoimmunity	97	25
Lung impairment	88	24
Gastrointestinal disease	51	14
Malabsorption	31	5
Lymphoid malignancy	36	10
Previous splenectomy	31	8
Granulomatous disease	31	8
Other cancers	21	6

*On the basis of on a cohort of 476 subjects.

C Cunningham-Rundles, How I treat CVID, Blood Jul 10

Common Variable Immunodeficiency

- Treatment: Lifelong IVIG replacement
  - aim to reduce breatkthrough infections rather than to achieve particular IgG trough level

Infection outcomes in patients with CVID, JACI June 10

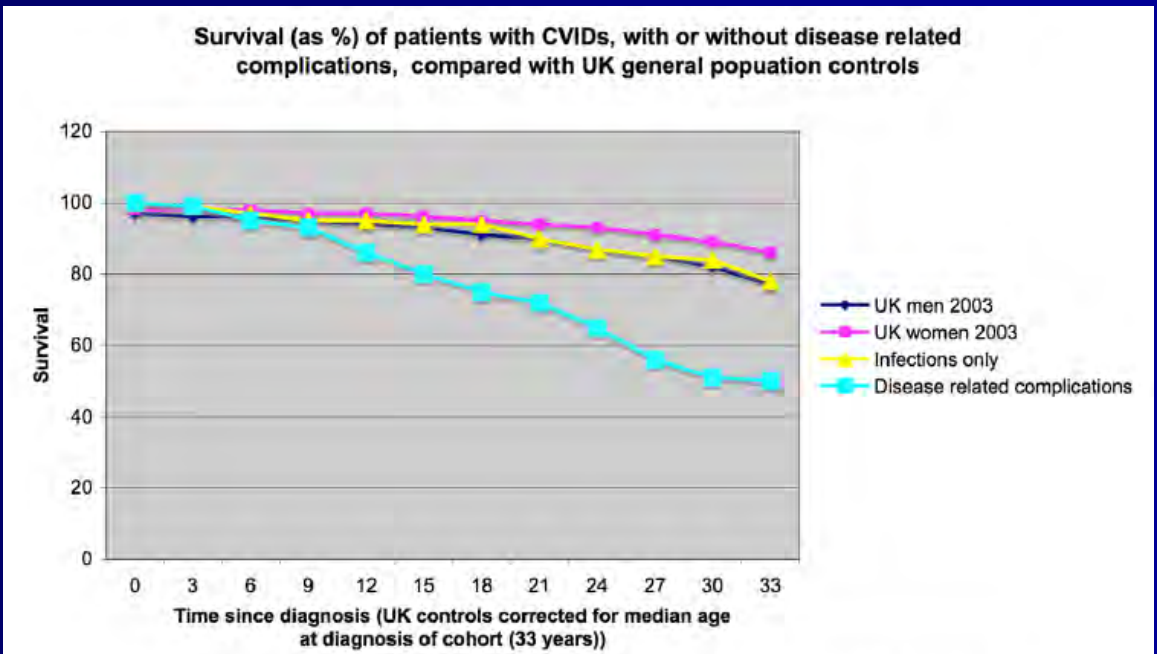
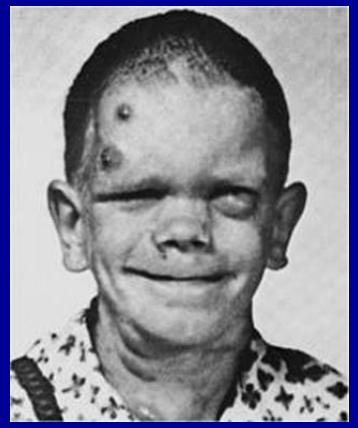


Figure 4. Survival of patients with CVIDs, by years since diagnosis and by clinical phenotype
(a) Yellow line represents those patients without complications. (b) Turquoise line represents those patients with at least one disease related complication. Kaplan-Meier plot of survival.
(Data from Chapel et al 2008)

HyperIgE syndromes

- AD HIES - Coarse facies, severe eczema, and recurrent cold skin abscesses
- AR HIES (DOCK8 and TYK2) – bacteria cold skin abscess and severe viral infections



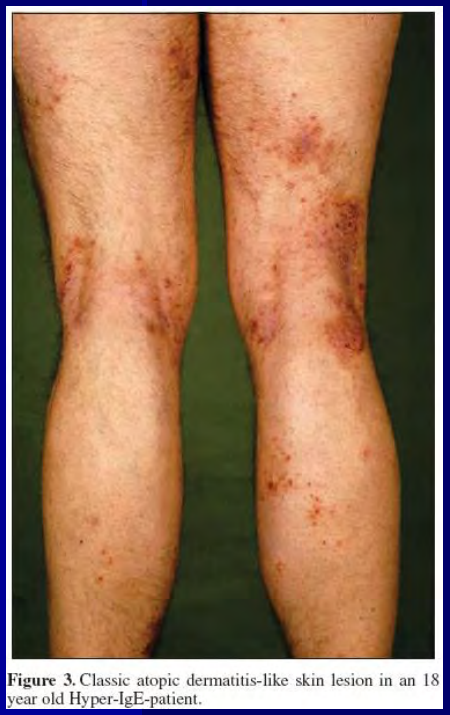
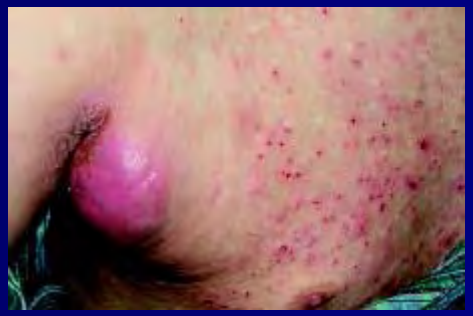
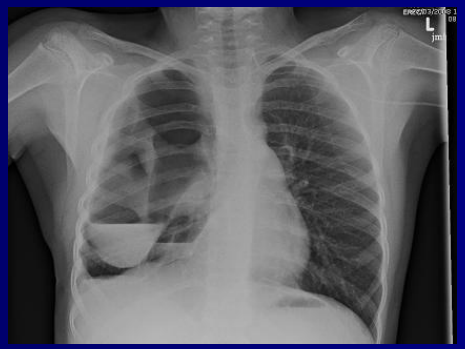
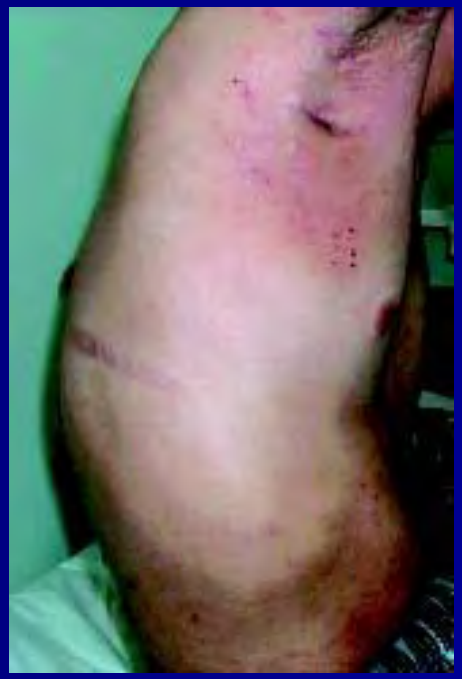
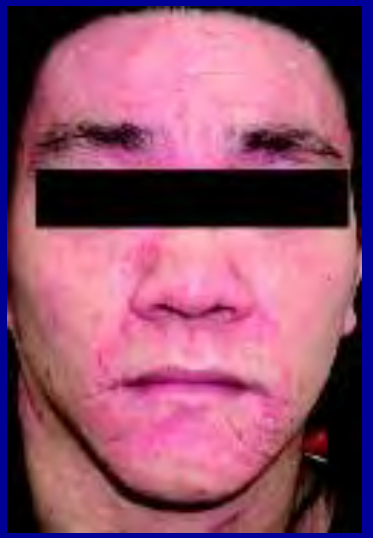


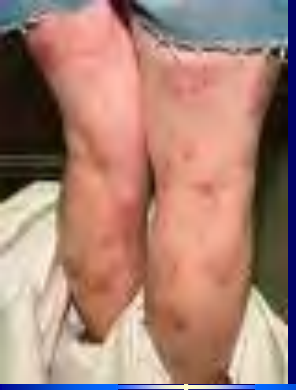
Figure 3. Classic atopic dermatitis-like skin lesion in an 18 year old Hyper-IgE-patient.











AD HyperIgE Syndrome

Table 1 | Summary of patient characteristics

Patient ID	Age (yr)	Sex	*stat3* mutation	HIES clinical score	Serum IgE* (IU ml^{-1})	Skeletal abnormalities	Recurrent candidiasis/staphylococcal abscess or lung infection	Atopic dermatitis
1† (J112)	6	M	1970 A→G (SH2)	31	4,190	+	+	+
2 (J088)	7	M	1145 G→T (DNA)	70	18,000	+	+	+
3 (J083)	10	F	1909 G→A (SH2)	78	5,070	+	+	+
4 (J005)	13	F	1144 C→T (DNA)	60	18,600	+	+	+
5 (J100)	22	F	1909 G→A (SH2)	76	1,020	+	+	+
6 (J017)	23	M	1145 G→A (DNA)	82	20,500	+	+	+
7‡ (J002)	24	F	1865 C→T (SH2)	85	8,550	+	+	+
8† (J112)	51	M	1970 A→G (SH2)	79	6,380	+	+	+
9 (J054)	40	F	1393 T→G (DNA)	78	239 (47,338)	+	+	+
10‡ (J002)	56	M	1865 C→T (SH2)	90	26 (2,392)	+	+	+
11	48	M	1268 G→A (DNA)	65	1,340 (20,700)	+	+	+
12	37	F	1909 G→A	94	495 (25,058)	+	+	+
13 (J015)	36	F	1861 T→G	96		+	+	+
14§	16	M	None	27	11,100	−	− (other recurrent infections)	−
15§	13	F	None	30	14,000	−	− (other recurrent infections)	−
16§	18	F	None	n.a.	136	−	− (other recurrent infections)	−
17	15	M	None	49	6,880	+	−	+
18	15	M	None	55	160 (69,280)	+	−	+
19	4	F	None	n.d.	>30,000	+	−	+

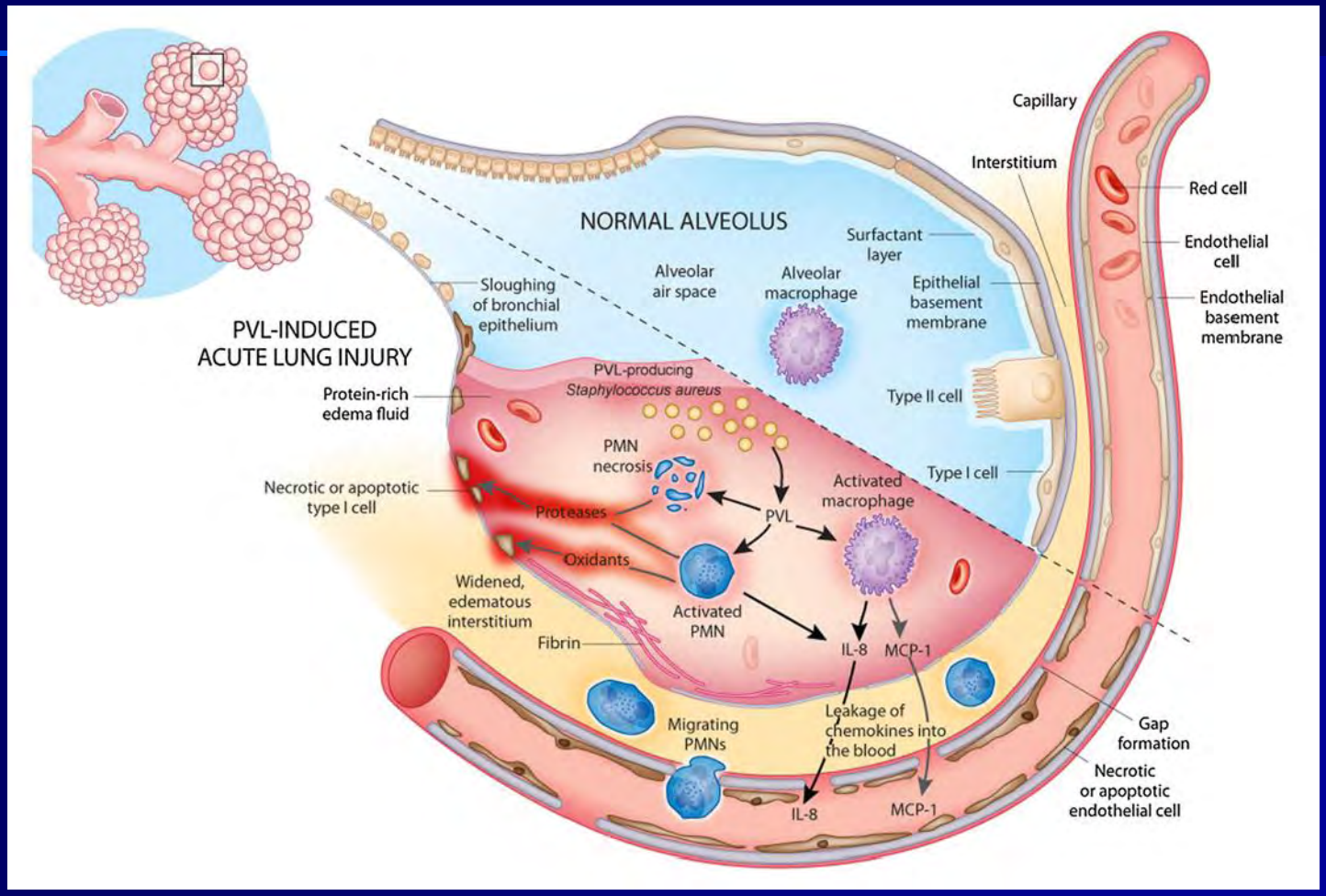
n.a., not available; n.d., not determined. *Peak values in parentheses. †‡Parent–child pairs. §Siblings with similar phenotypes.

STAT 3 gene mutation with impaired TH17 cell differentiation discovered in subjects with AD HIES

Nature Apr 08

Panton-Valentine leukocidin (PVL)

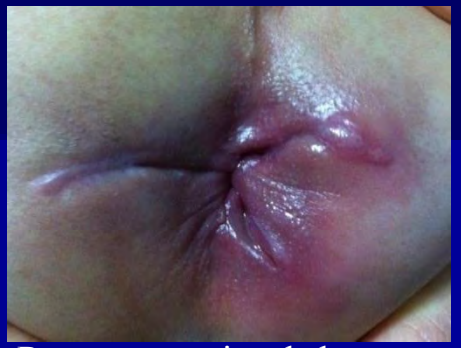
- pore-forming toxin that targets polymorphonuclear leukocytes
- key role in the pathogenesis of necrotizing pneumonia



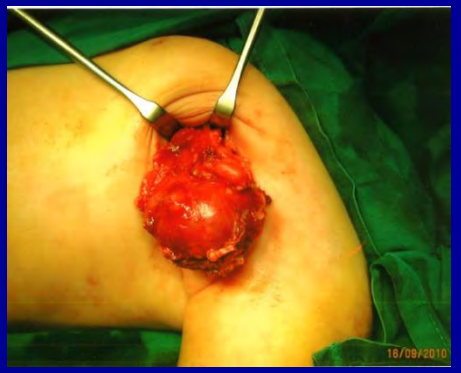
Polymorphonuclear leukocytes mediate Staphylococcus aureus Panton-Valentine leukocidin induced lung inflammation and injury, PNAS Mar 2010

Chronic Granulomatous Disease (CGD)

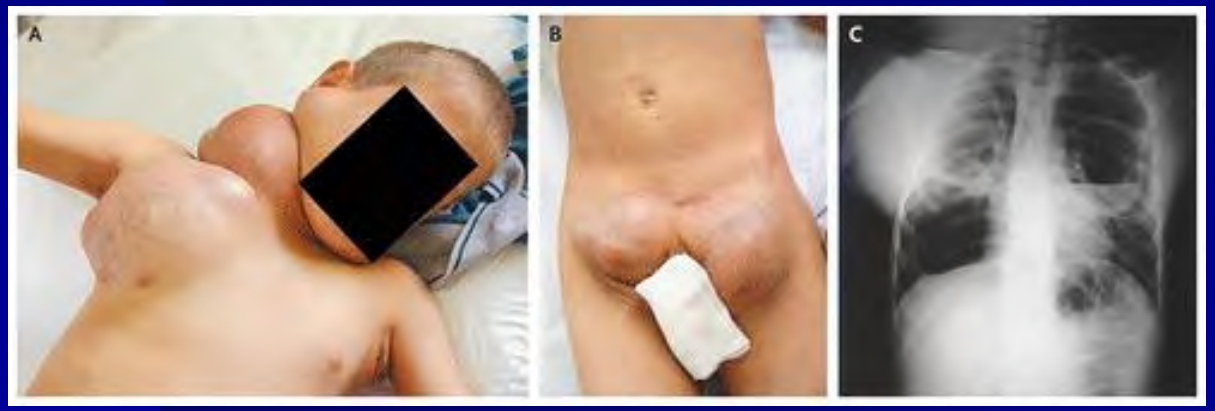
- Infections
  - Bacteria – Staph Aureus, Serratia
  - Mycobacterium – BCGitis
  - Fungus – Nocardia, Aspergillus
- Granuloma



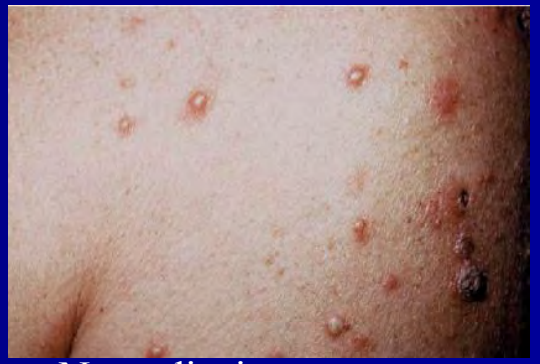
Recurrent perianal abscesses



BCGitis

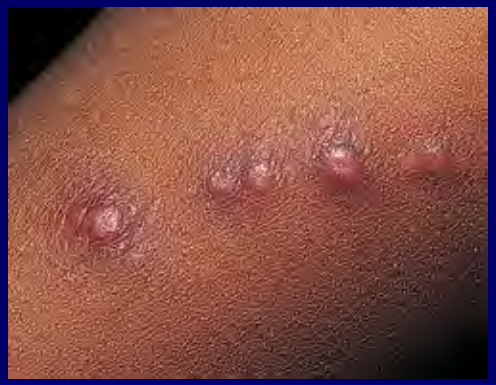


Staph aureus bacteraemia, lymphadenitis and pneumatocoele



Nocardiosis

CGD clinical



- Hallmark of CGD is early onset of severe recurrent bacterial and fungal infections
  - Catalase positive organism: *Staph aureus*, *Burkholderia cepacia*,*Aspergillus* sp, Nocardia sp, and *Serratia marcescens*
- Most present during the first 5 years of life.
- Common presentations include the following infections:
  - Skin infections; Pneumonia/ Lung abscesses; Suppurative lymphadenitis; Diarrhea secondary to enteritis; Perianal or perirectal abscesses; Hepatic or splenic abscesses; Osteomyelitis, septicaemia
- Second most common manifestation include development of granulomas in the skin, GI tract, and genitourinary tract

Chronic Granulomatous Disease

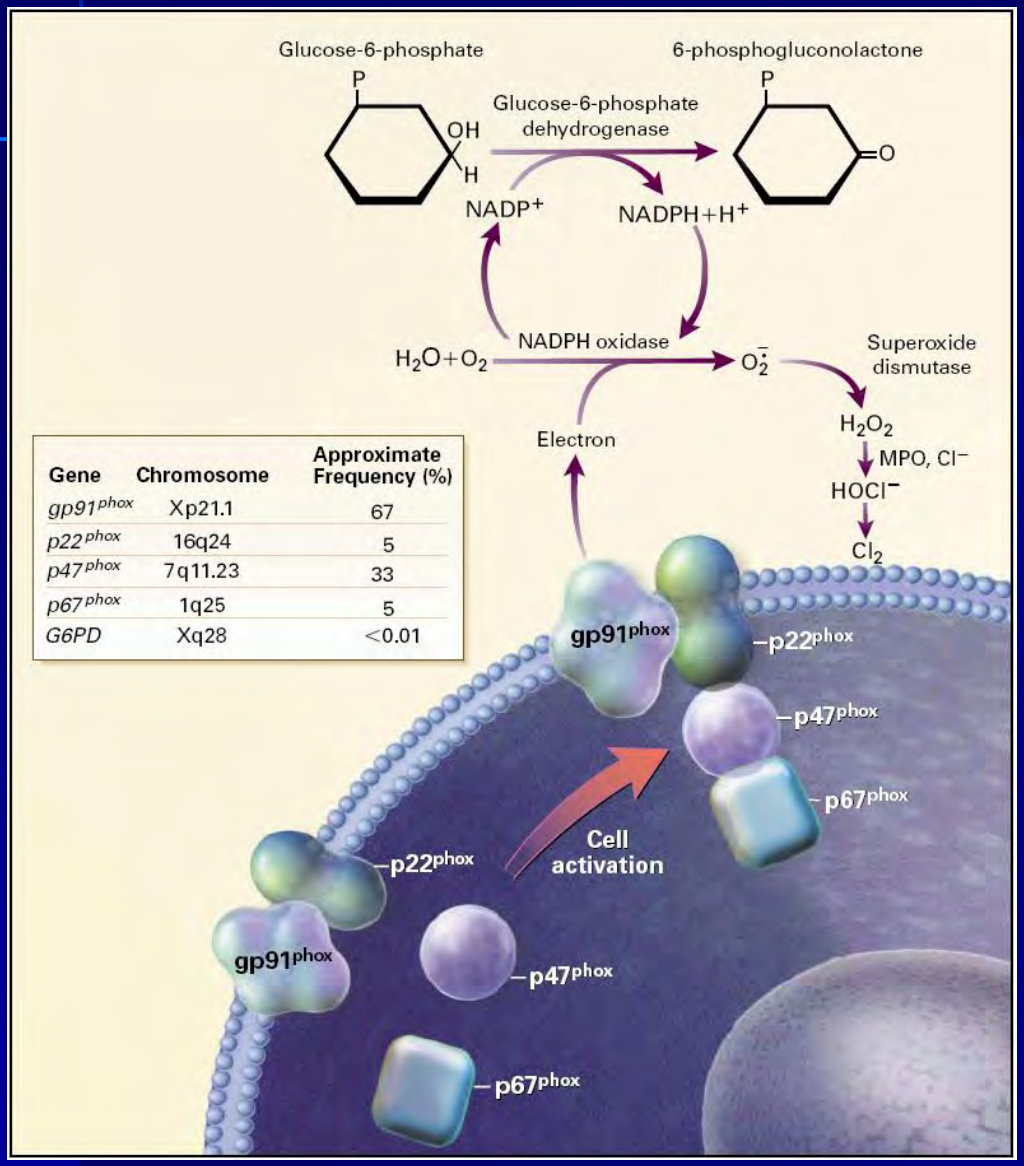
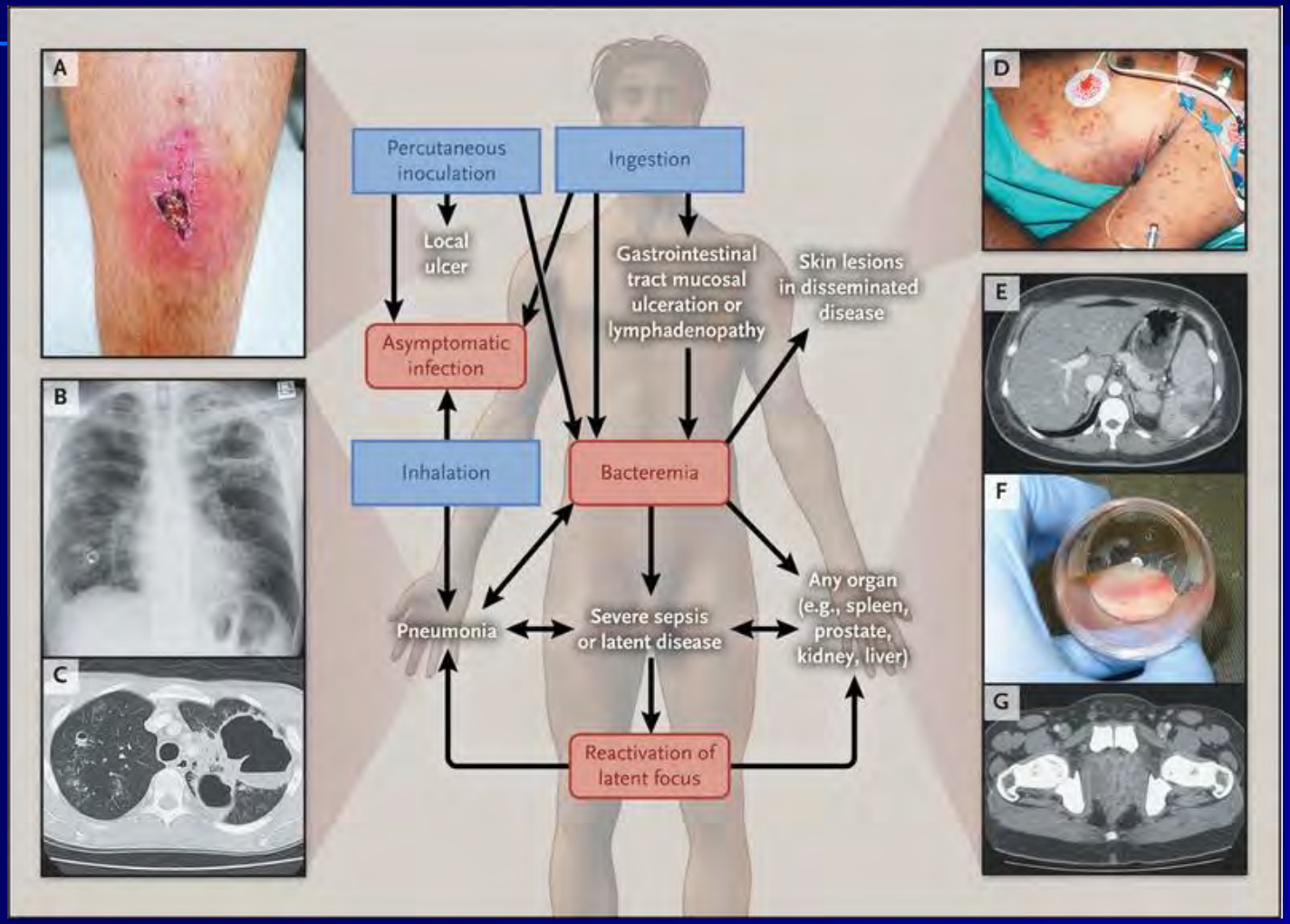


Figure 3. Relation among the Components of NADPH Oxidase That Are Affected in Patients with Chronic Granulomatous Disease.

The membrane-bound phagocyte oxidase components, the 91-kd glycoprotein (gp91^{phox}) and the 22-kd protein (p22^{phox}), interact with the cytoplasmic components, the 47-kd protein (p47^{phox}) and the 67-kd protein (p67^{phox}). Glucose-6-phosphate dehydrogenase (G6PD) converts glucose-6-phosphate to 6-phosphogluconolactone, generating NADPH and a hydrogen ion from $NADP^+$. NADPH oxidase catalyzes the monovalent reduction of O_2 to superoxide anion (O_2^-), with the subsequent conversion to hydrogen peroxide (H_2O_2) by superoxide dismutase. Neutrophil-derived myeloperoxidase (MPO) converts hydrogen peroxide to hypochlorous acid (HOCl- [bleach]), which is then converted to chlorine (Cl_2). The genes for the components of NADPH oxidase, their chromosomal locations, and the frequency of mutations as a cause of chronic granulomatous disease are indicated in the box.

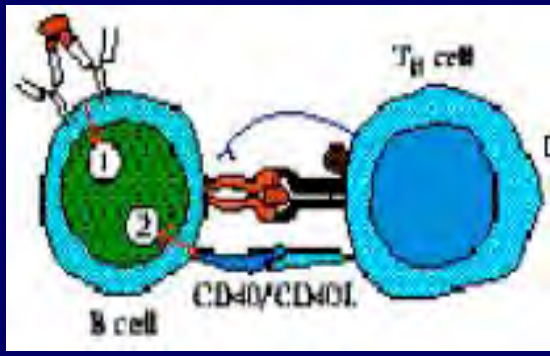
Immunodeficiency diseases caused by defects in phagocytes, NEJM Dec 2000

CGD prone to Melioidosis



Melioidosis, N Engl J Med Sep 2012

Hyper IgM Syndrome



- 70% X linked, Xq26, CD40 ligand glycoprotein
- Early sinopulmonary infections
  - Encapsulated bacteria, PCP, Cryptococcus, Parvovirus
- Intact IgM antibody response
- IgG and IgA < 2SD for age
- Absent antigen specific IgG
- Circulating B lymphocytes bear only IgD/IgM
- Cell mediated immunity may be impaired
- Subtype with recurrent/persistent neutropenia and thrombocytopenia

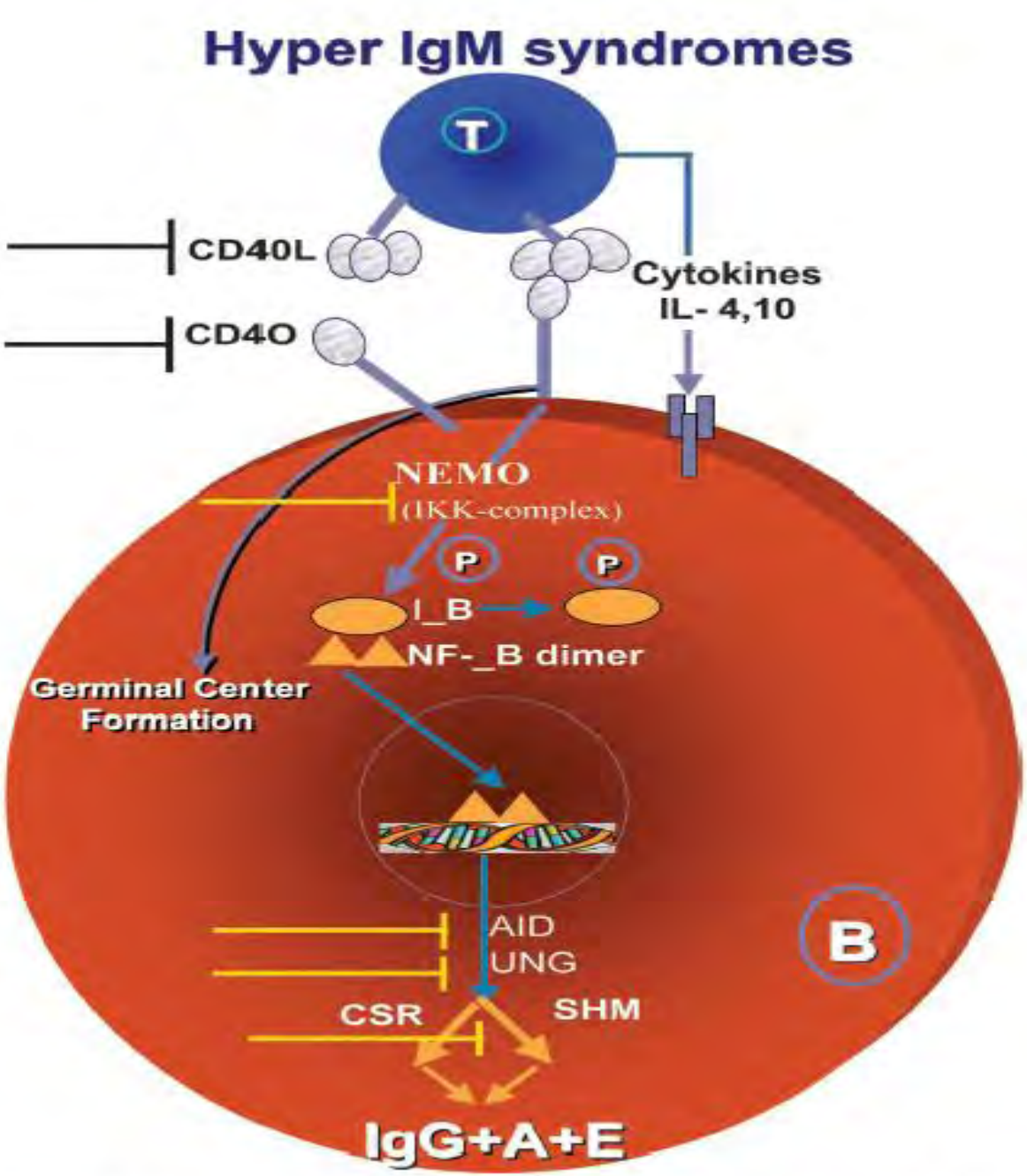
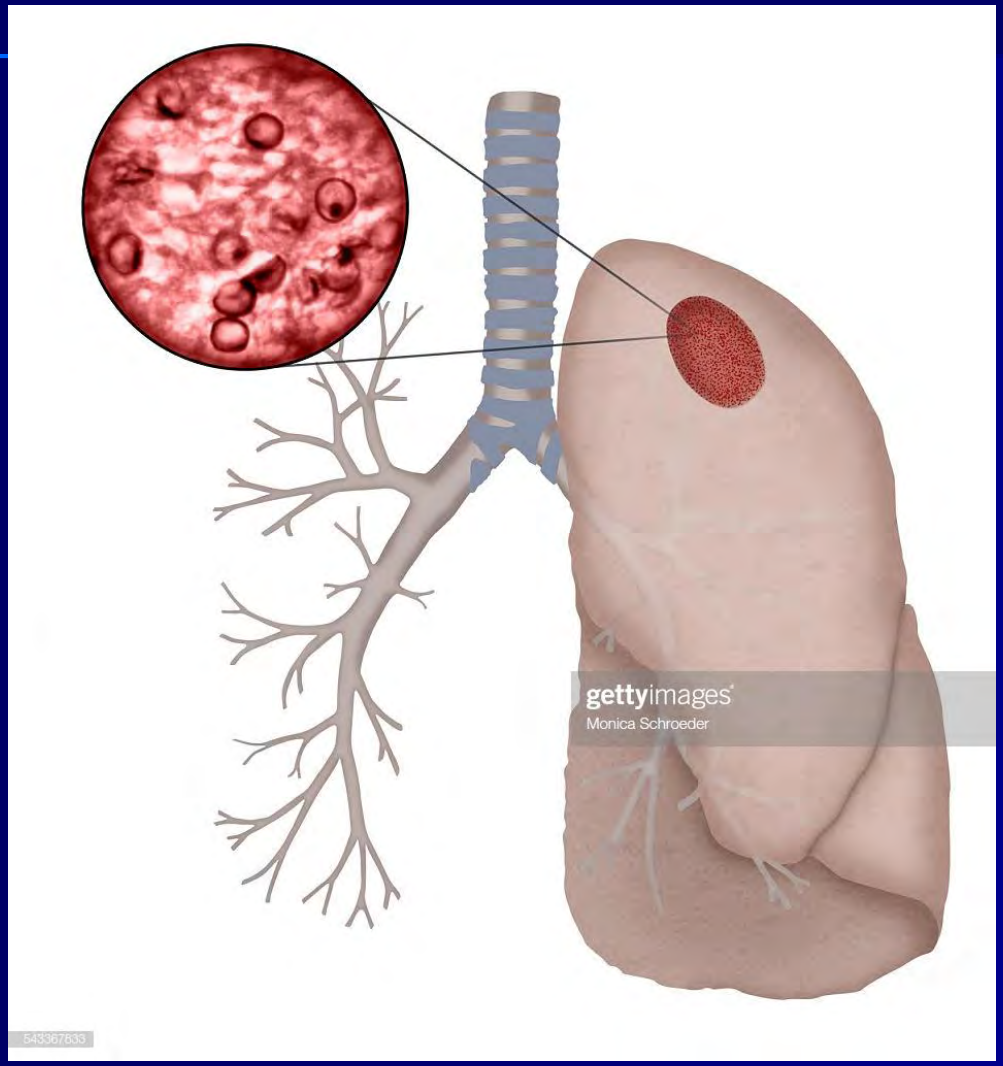


Figure 1. Schematic representation of the various known molecular defects leading to hyper IgM syndromes.

XHIGM has T cell defect and prone to Pneumocystis jirovecii



Response to an acute viral illness

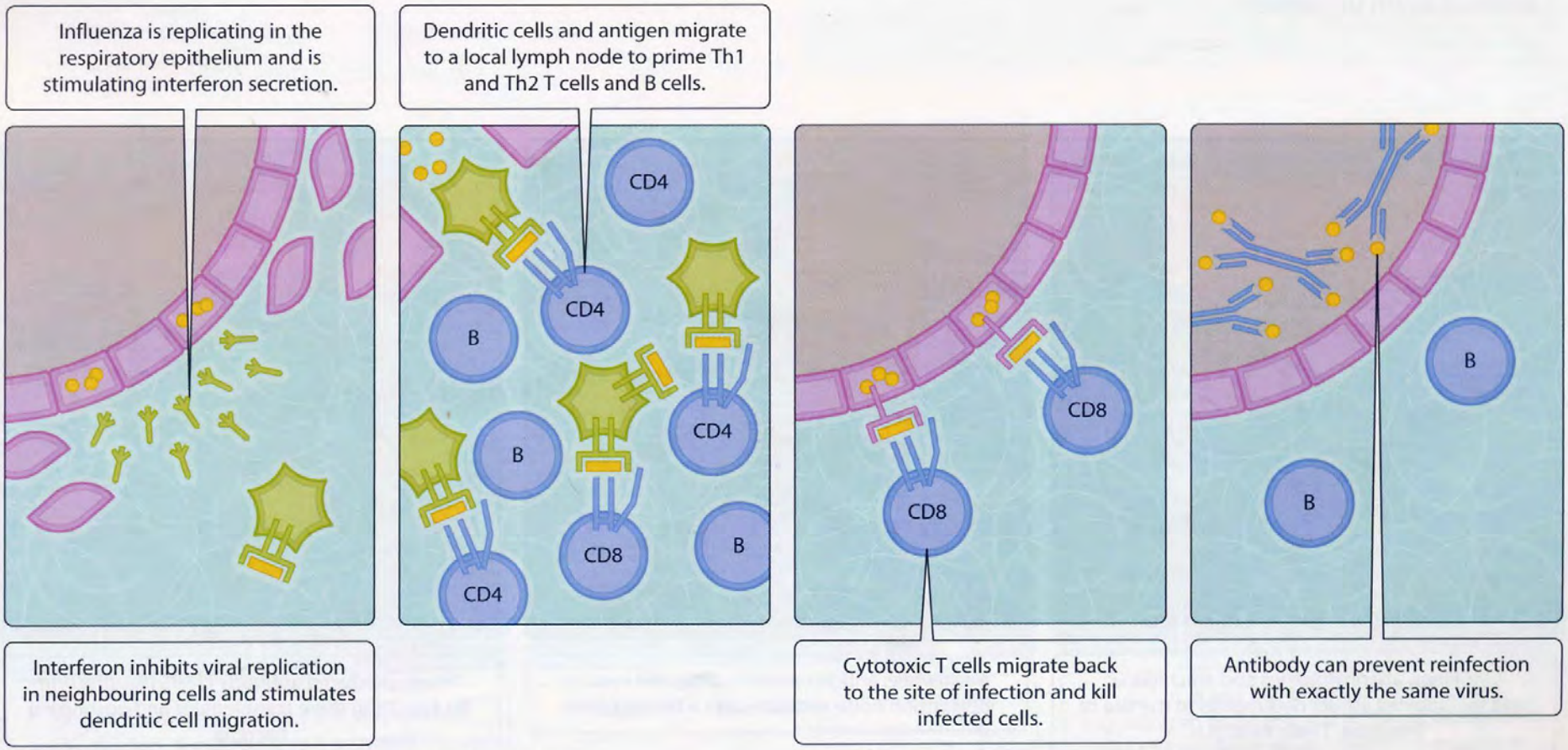
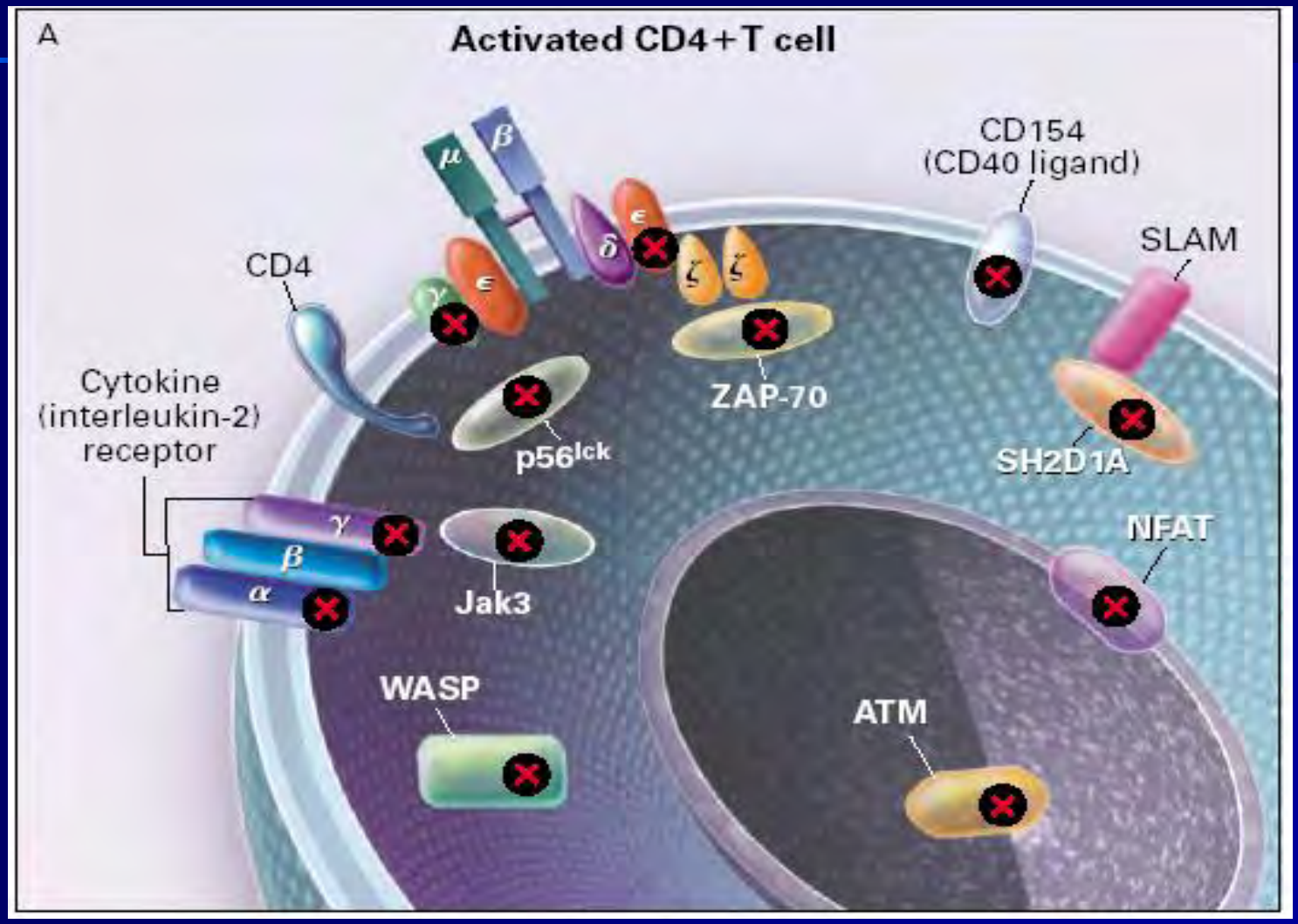


Fig. 3.25.1 Response to an acute viral infection.

PIDs with Viral infections

- SCID
  - Common respiratory virus -> ARDS
- STAT1 GOF
  - Herpes virus eg. CMV, EBV

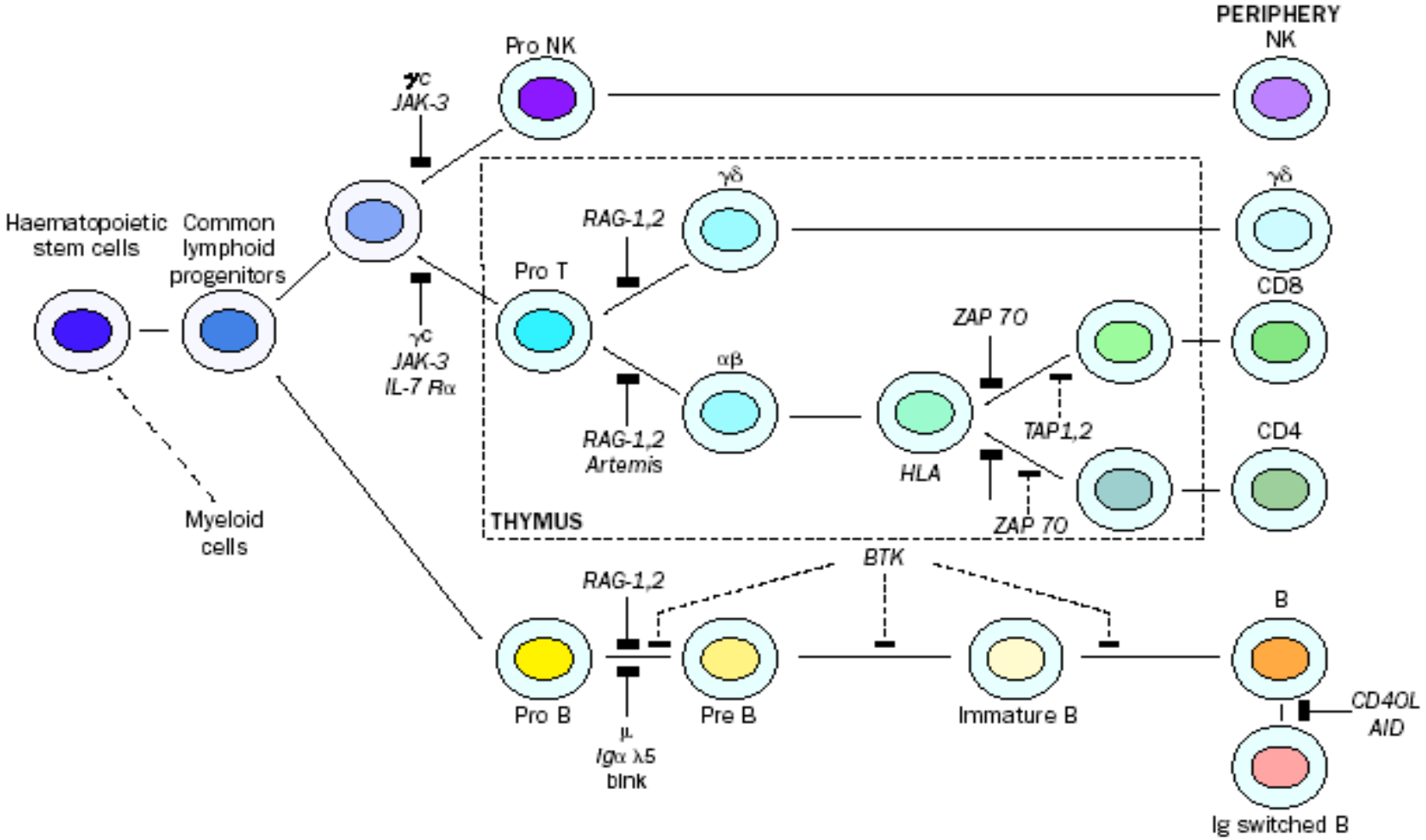
Primary Immunodeficiency due to Defects in Lymphocytes



Buckley RH et al, NEJM Nov 2, 2000

Severe Combined Immunodeficiency

Lymphocyte Maturation and Development - SCID



Immunology, THE LANCET • Vol 357 • June 2, 2001

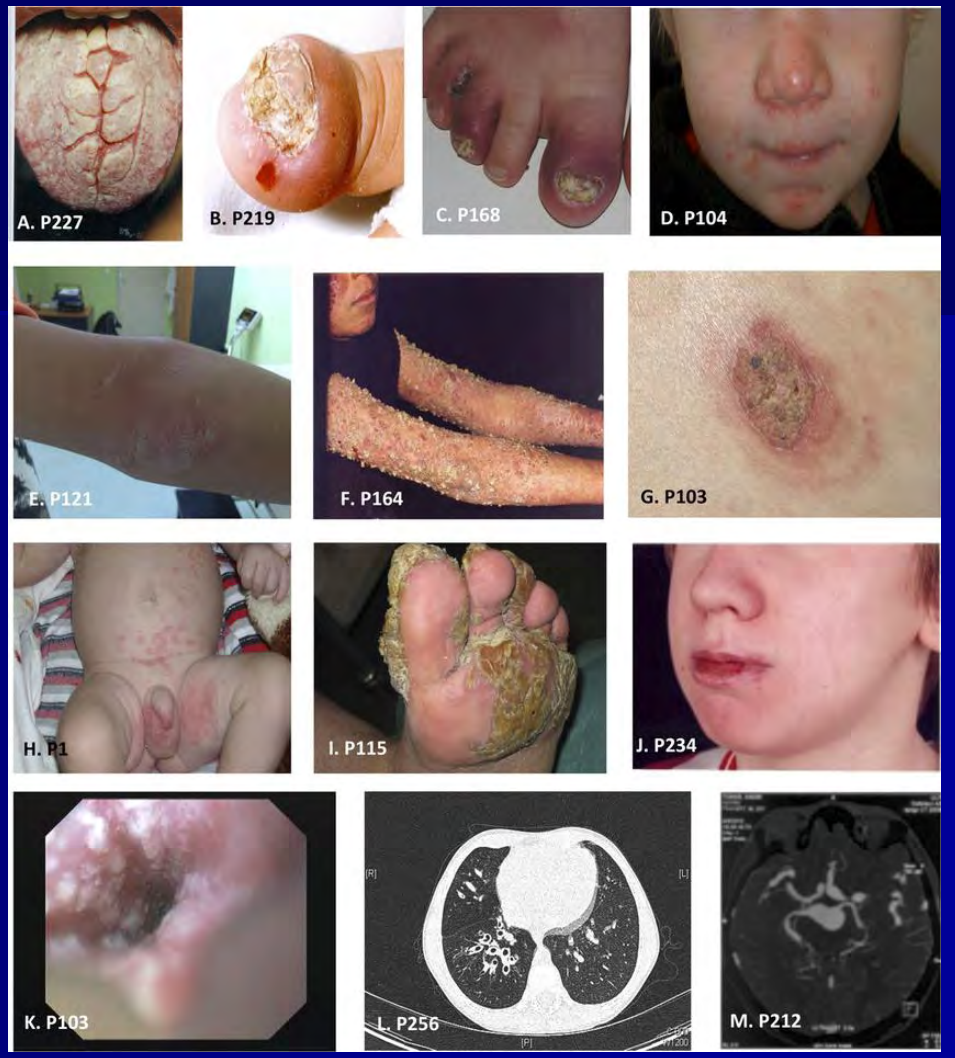
SCID Clinical Presentation

- A Pediatric Emergency!!!
- Early presentation - Average age at diagnosis < 6mo
- Family history of early infant death from infections or recurrent infections
- Most frequent manifestations:
  - Oral candidiasis
  - Persistent diarrhea
  - Failure to thrive
  - Interstitial pneumonitis – viral/ PCP
  - Disseminated BCGitis

STAT1 GOF

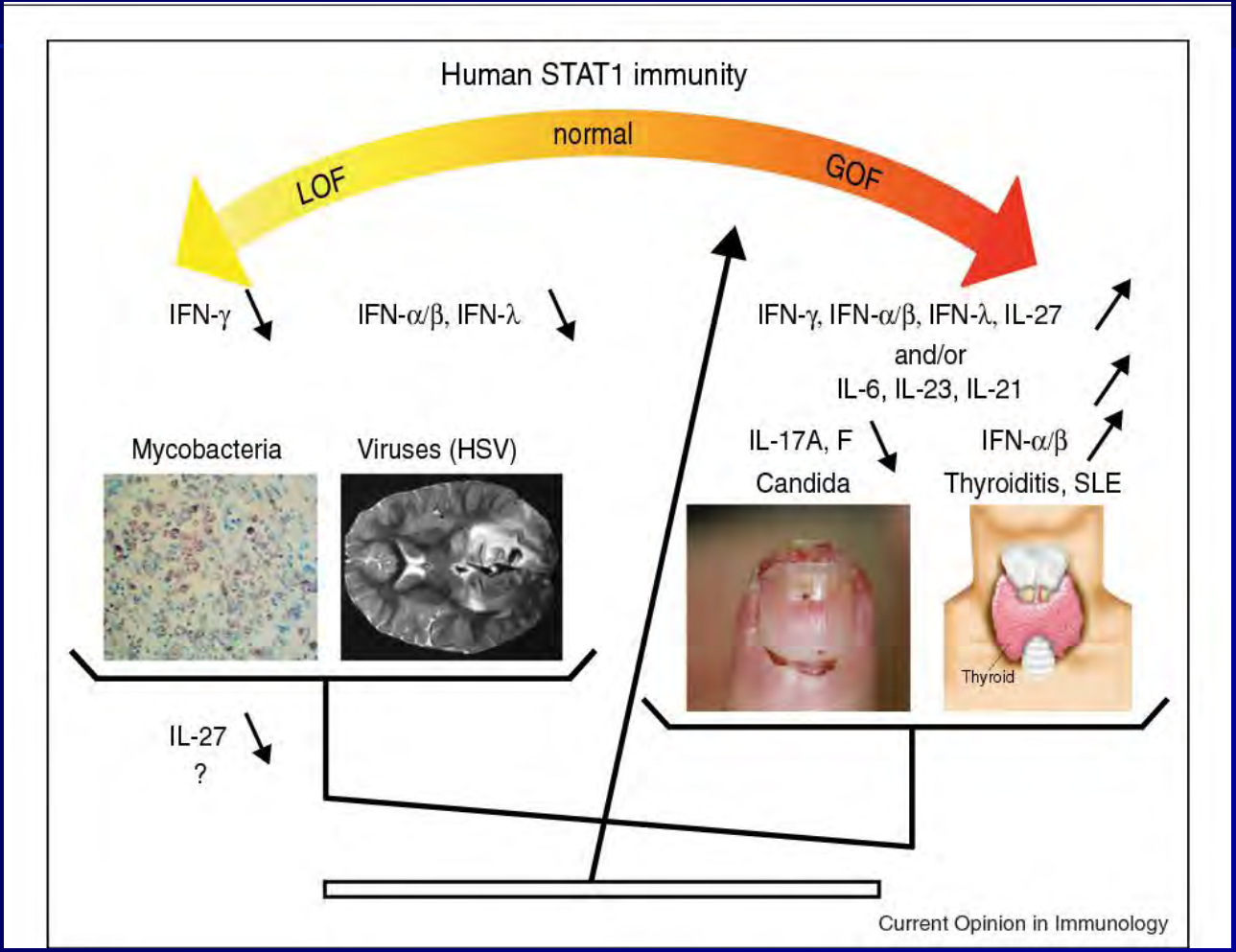
Type of infections	Patients (%) n = 274
Mucocutaneous fungal infections	268 (98)
Oropharyngeal mycosis	254 (93)
Cutaneous mycosis	155 (57)
Esophageal/genital mycosis	153 (56)
Onychomycosis	153 (56)
Aphtous stomatitis	125 (46)
Scalp mycosis	55 (20)
Invasive fungal infections	28 (10)
Invasive candidiasis	10 (4)
Other invasive infections	20 (7)
Bacterial infections*	202 (74)
LRI	129 (47)
ENT	121 (44)
Skin	77 (28)
Others†	24 (9)
Mycobacterial infections	17 (6)
Lung disease	6 (2)
Adenitis/skin disease	5 (2)
Disseminated disease	6 (2)
Viral infections*	103 (38)
Cutaneous	88 (32)
Systemic	23 (8)

ENT: ear, nose, and throat.
*Probable or proven bacterial/viral infection.
†Severe acute gastroenteritis, septicemia, bone and joint infections, recurrent urinary tract infections.



Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype: an international survey of 274 patients from 167 kindreds, Blood Apr 2016

STAT1 GOF



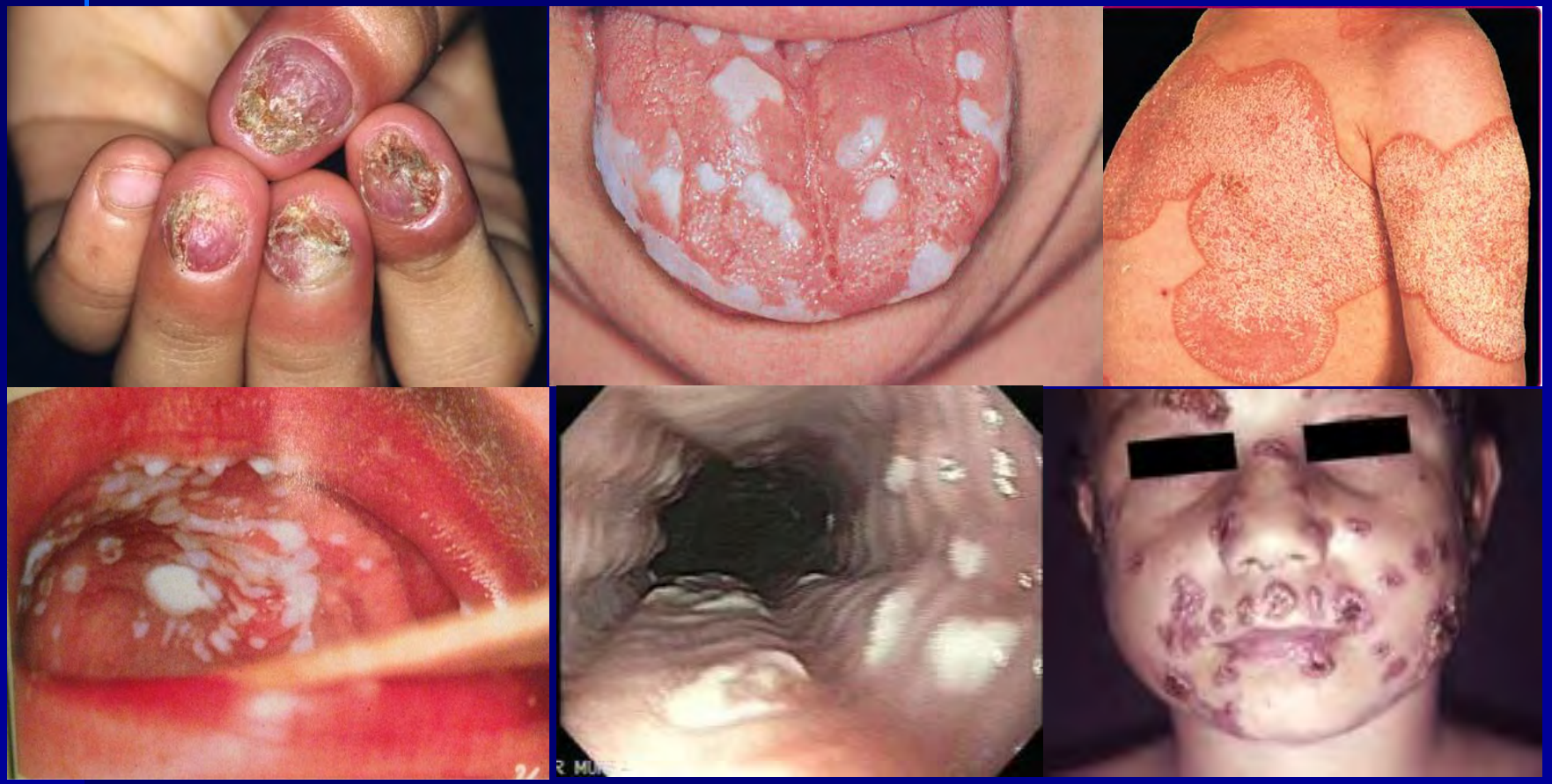
Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes, Current opinion in immunology 2012

PIDs with chronic mucocutaneous candidiasis

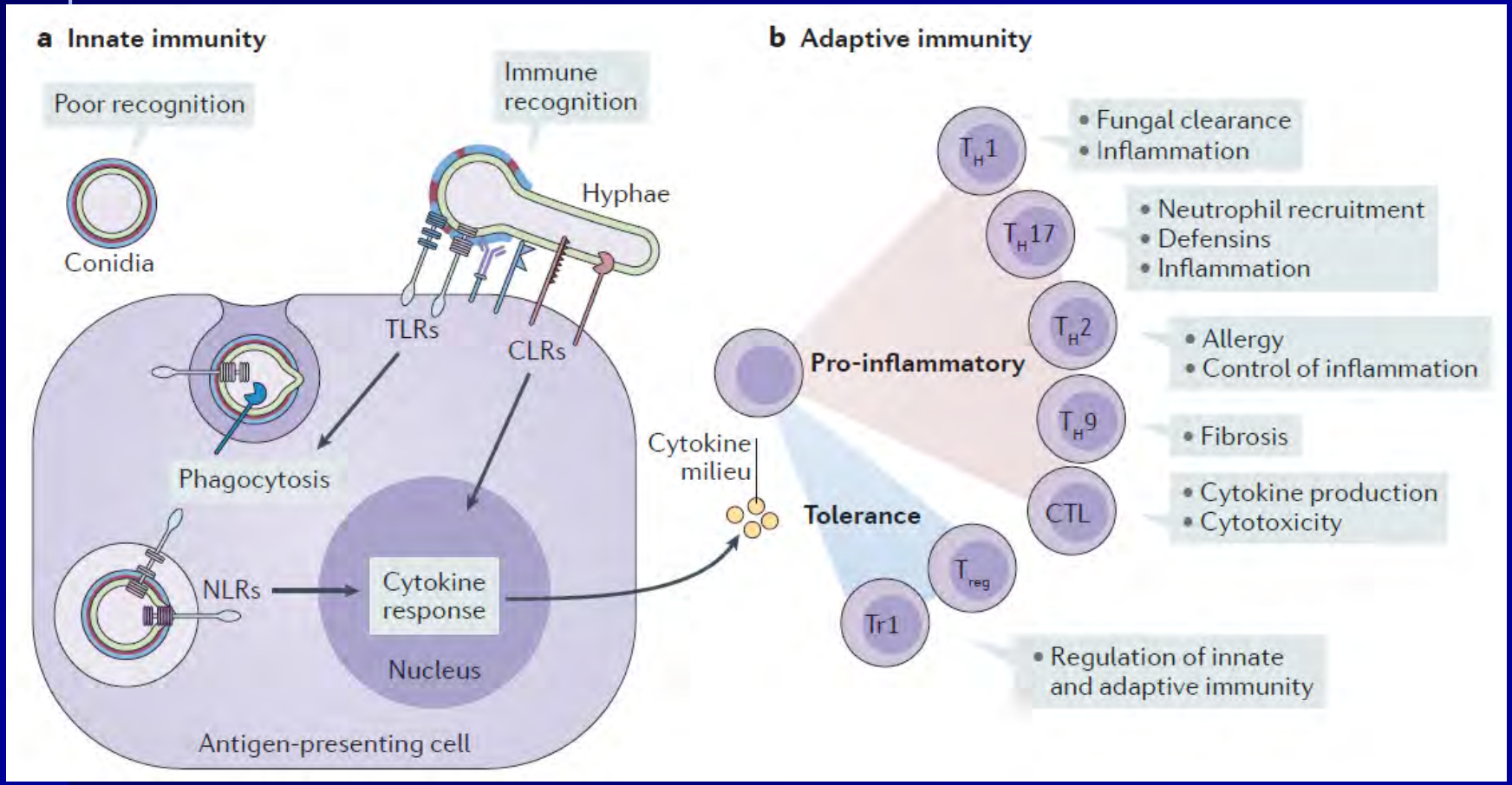
Disease	Molecular defect	Associated gene/transmission	Clinical picture
AD-HIES	Dominant-negative effect on multiple intracellular signaling pathways, including impaired generation of TH17 cells, and impaired intracellular signaling by receptors of IL-17 and 22.	STAT3, AD	Serious CMC, in particular fingernail, vaginal, and oral disease
APECED	Loss of tolerance, with persistence of autoreactive T cells, including the production of autoantibodies to cytokines (e.g., IL-17 and 22).	AIRE, AR	Serious CMC, usually arising within the first decade of life
SCID	Impaired generation of T cells, with or without accompanying B and NK lymphocytopenia.	IL2RG, X-linked; JAK3, AR; IL7Rα, AR; CD3δ, AR; CD3ε, AR; RAG1, AR; RAG2, AR; ARTEMIS, AR; CD45, AR	CMC possible, perianal rash and thrush arise in the first few months of life
AR-HIES	Impaired T-cell activation, possibly impaired maintenance of memory Th17 cells or impaired formation of immunological synapse.	DOCK8, AR	Serious CMC
IL-12 and IL-23 deficiency	Impaired development of Th17 cells.	IL12B, AR; IL12RB1, AR	CMC but milder than in STAT3 deficiency
IL-17 deficiency	Impaired or abolished cellular responses to IL-17, due to either impaired production of or abolished response capacity to IL-17.	IL17F, AD; IL17RA, AR	Neonatal candidiasis, serious CMC
Dectin 1 deficiency [13]	Cell surface expression of the (mutated) receptor is lost, leading to impaired IL-6, IL-17 and TNFα on stimulation *in vitro*.	Dectin-1, AR	Increased susceptibility to vulvovaginal candidiasis and onychomycosis
CARD9 deficiency	Impaired function of signalosomes for dectin (dectin 1 and dectin 2) and other recognition molecules.	CARD9, AR	Severe or recurrent oral, vaginal candidiasis, dermatophytosis, invasive candidiasis (meningitis)
TYK2 deficiency	Adaptor molecule for several receptor complexes, including IL23 receptor.	TYK2, AR	Oral candidiasis
STAT1 mutations	The mutations in the coiled-coil domain of STAT1.	STAT1, AD	Severe CMC and dermatophytosis

Sillevis Smitt and Kuijpers, Curr Opin Paediatri Aug 2013

Chronic Mucocutaneous Candidiasis

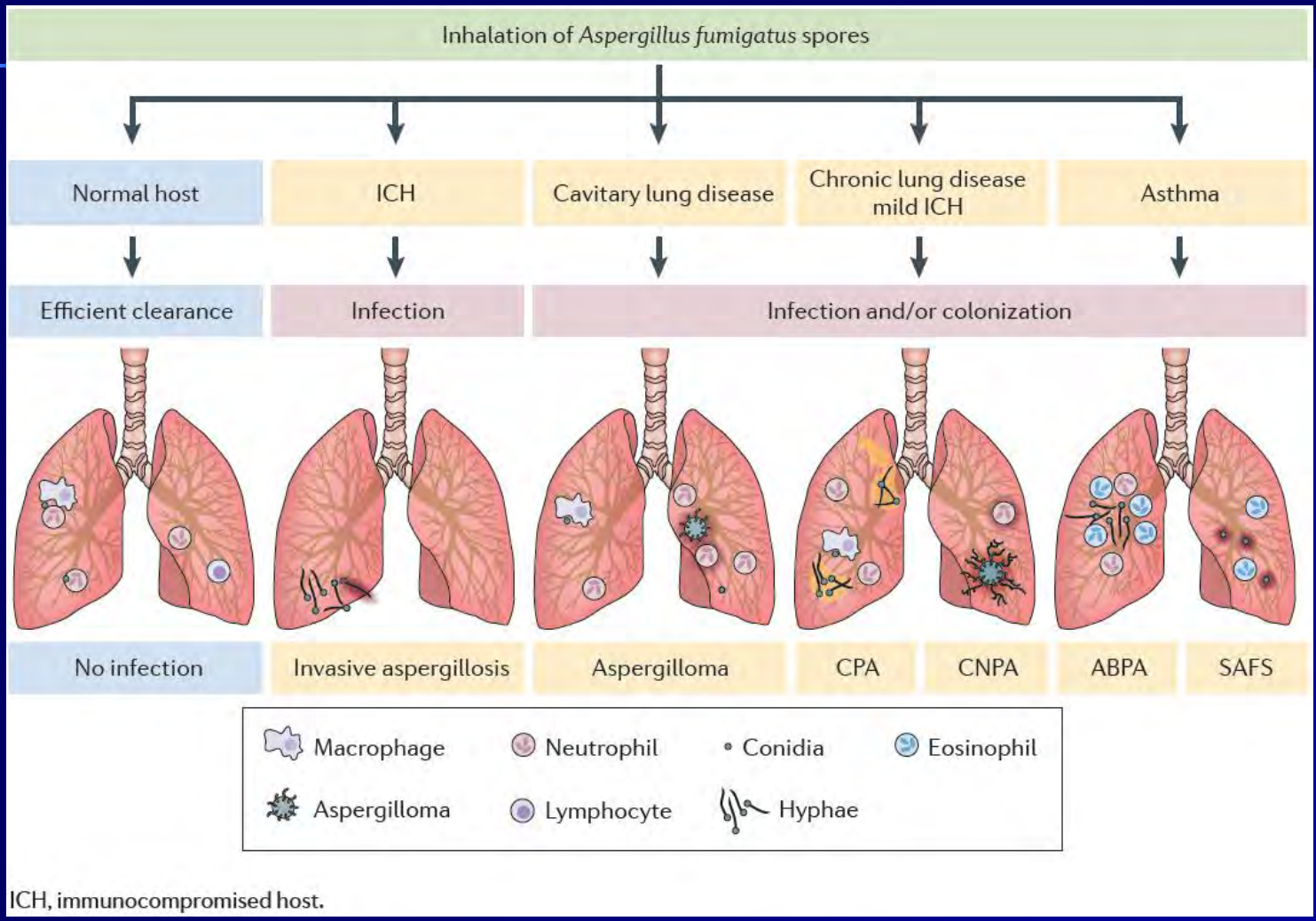


Innate host defence and T cell responses to Aspergillus fumigatus infection



Aspergillus fumigatus morphology and dynamic host interactions, Nat Rev Microbiol 2017

Clinical spectrum of Aspergillosis



Aspergillus fumigatus morphology and dynamic host interactions, Nat Rev Microbiol 2017

Response to chronic/TB infection

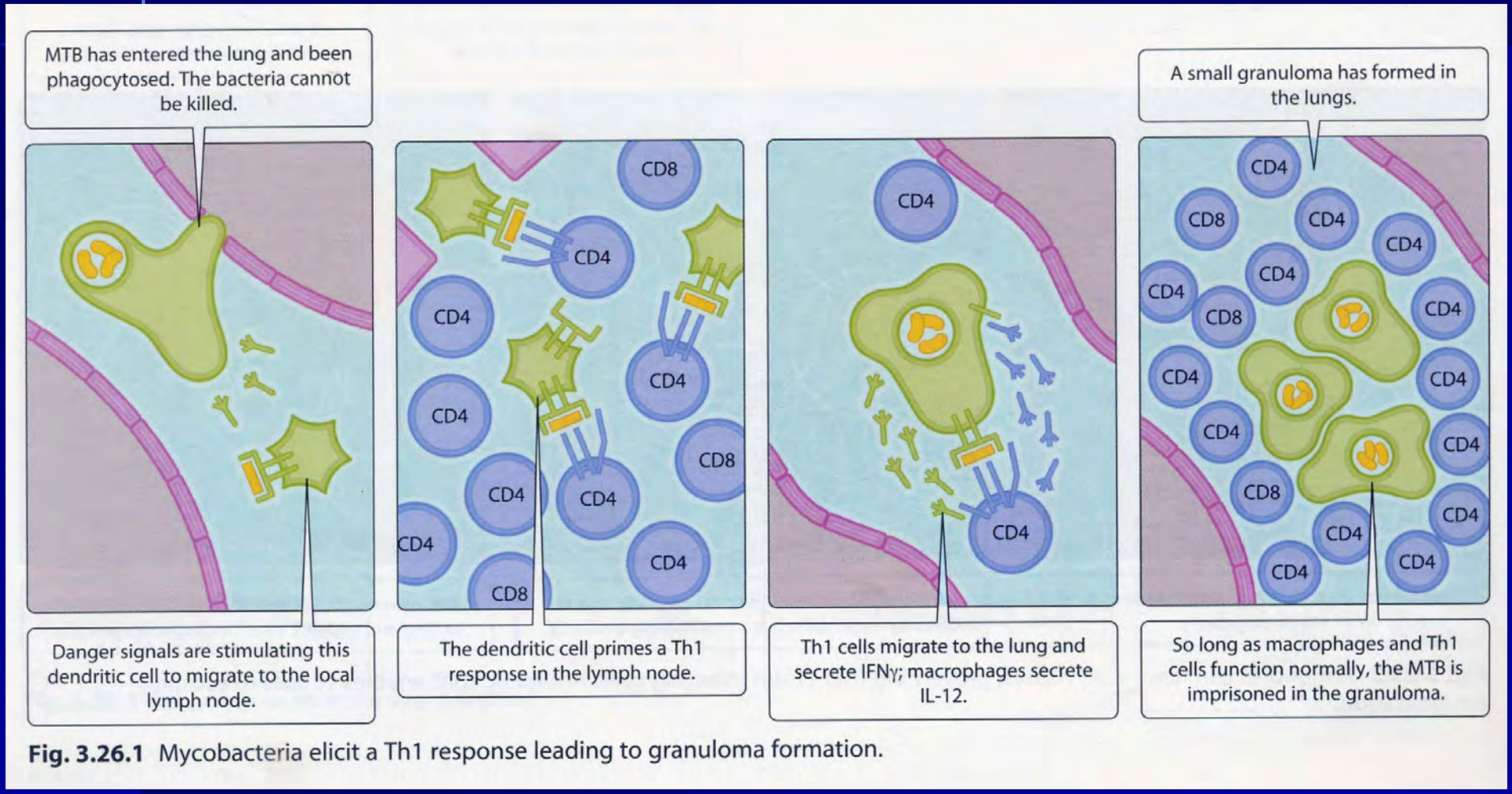
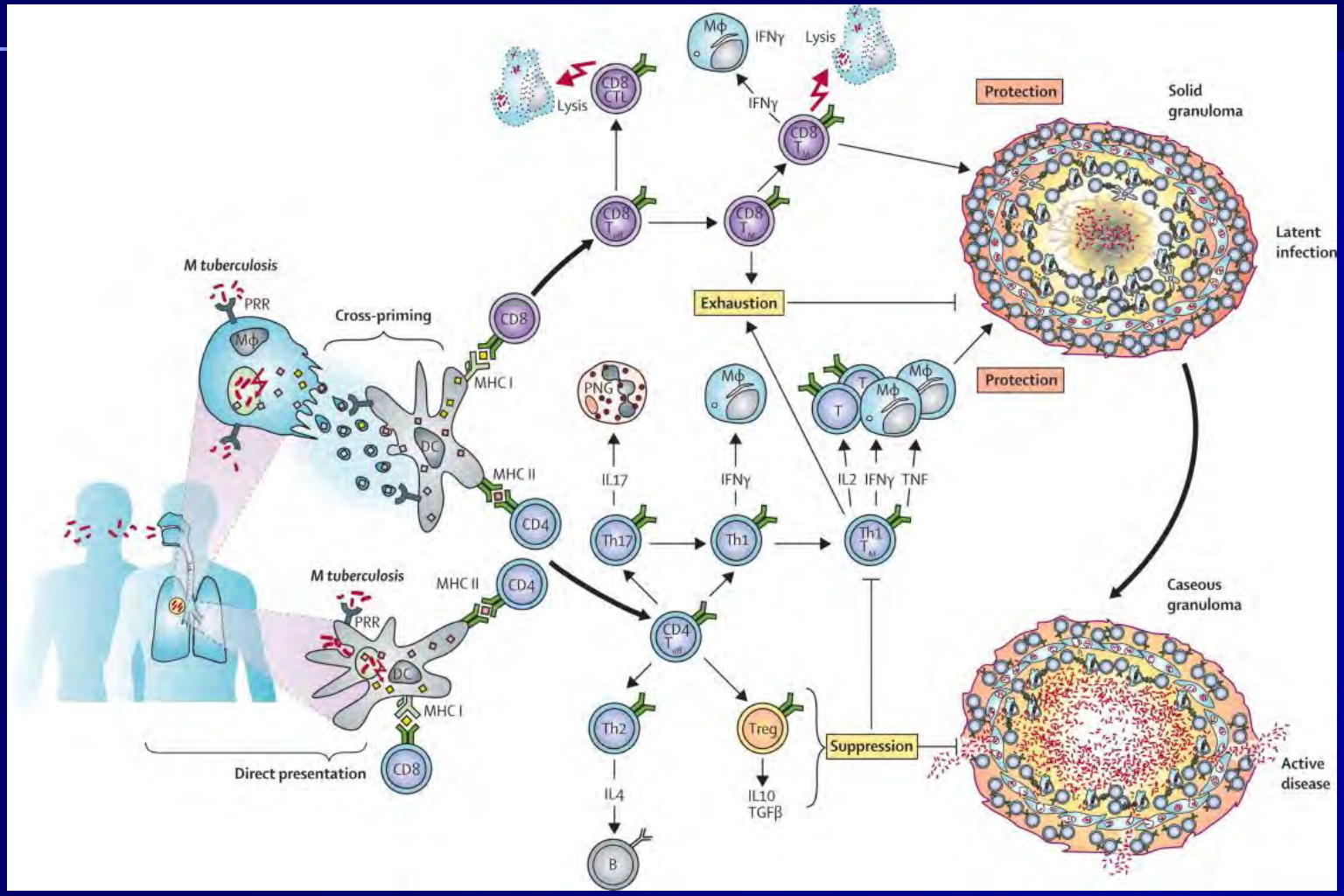


Fig. 3.26.1 Mycobacteria elicit a Th1 response leading to granuloma formation.

Response to chronic/TB infection



New vaccines for tuberculosis, Lancet. 2010 Jun 12;375

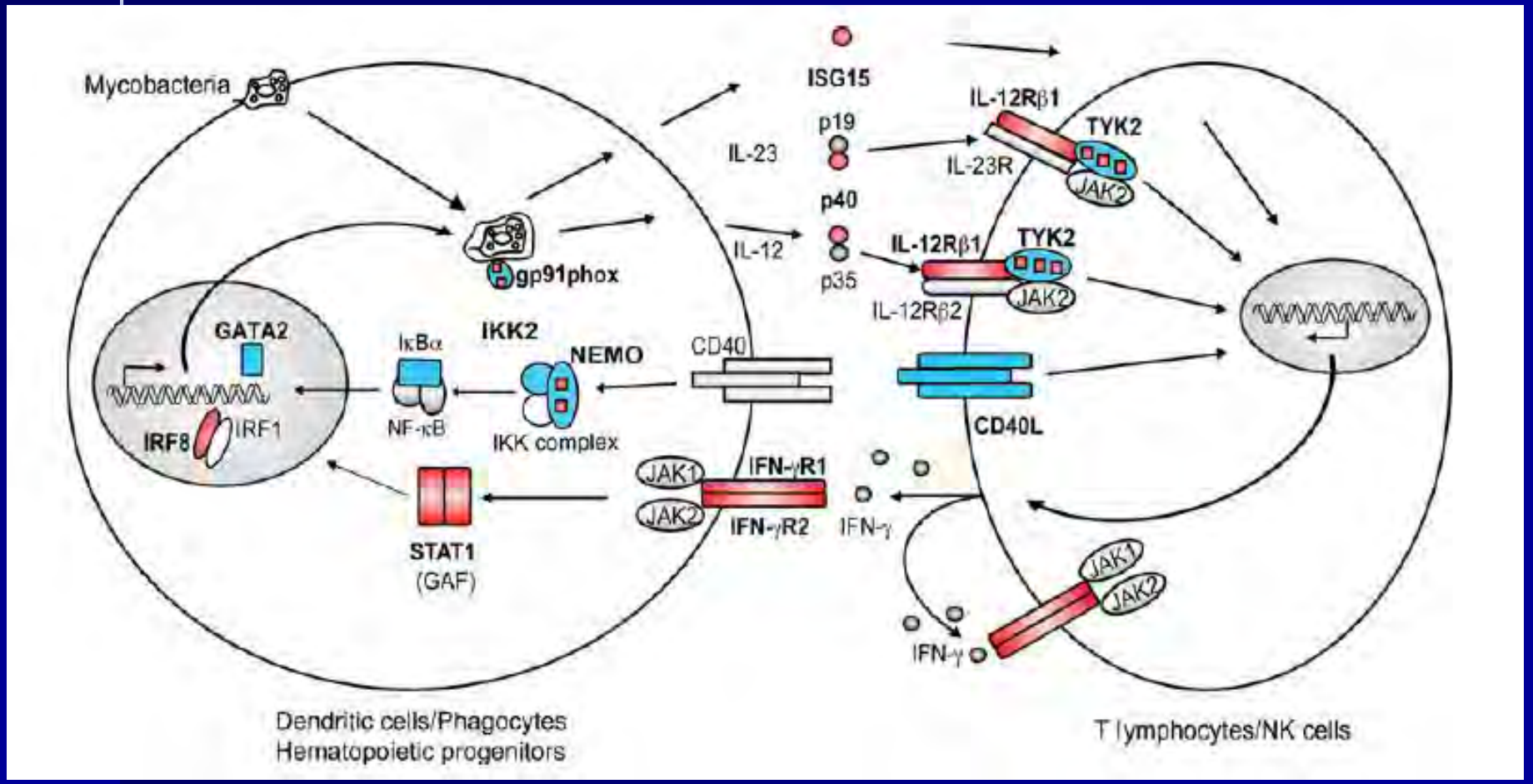
PID with Mycobacterium infections

Table 1. Acquired and inherited conditions with mycobacterial susceptibility to BCG, NTM, or *Mycobacterium tuberculosis*

	NTM	BCG	TB	TB only*	Other infections†	Physiopathology
Acquired ID						
Immunosuppressive treatment/BMT	+	?	+	No	Yes	Impairment of immune cells
HIV	+	+	+	No	Yes	T-cell defect
Anti-IFN-γ antibodies	+	–	+	No	Yes	Impaired IFN-γ response
Anti-TNF-α antibodies	+/–	–	+	Yes	Yes	Impaired TNF-α response
Inherited ID						
Cystic fibrosis	+	–	+	No	Yes	Alteration of the lungs
PID						
SCID	–	+	+	No	Yes	T-cell defect
AD GATA2 deficiency	+	–	+	No	Yes	Quantitative defect of monocytes, DC, and PAP
CGD	+/–	+	+	No	Yes	Respiratory burst defect in all phagocytic cells
EDA-ID	+	+	+	No	Yes	Impaired CD40-dependent IL-12 production
XR CD40L deficiency	+	+	+	No	Yes	Impaired CD40-dependent IL-12 production
AR STAT1 deficiency	+	+	–	No	Yes	Impaired IFN-γ response
AR IRF8 deficiency	–	+	–	No	Yes	Absence of monocytes and DC
AR TYK2 deficiency	–	+	+	Yes	Yes	Impaired IFN-γ production
MSMD						
IFN-γR deficiencies	+	+	+	Yes	No	Impaired IFN-γ response
AD STAT1 deficiency	+	+	+	Yes	No	Impaired IFN-γ response
XR gp91phox deficiency	–	+	+	Yes	No	Respiratory burst defect in macrophages
AD IRF8 deficiency	–	+	–	No	No	Absence of $CD11C^+$ $CD1c^+$ DC
XR NEMO deficiency	+	+	+	No	No	Impaired CD40-dependent IL-12 production
IL-12 and IL-12R deficiencies	+	+	+	Yes	Yes	Impaired IFN-γ production
AR ISG15 deficiency	–	+	–	No	No	Impaired IFN-γ production

Inherited and acquired immunodeficiencies underlying tuberculosis in childhood, Immunol Rev 2015

PID with Mycobacterium infections



Inherited and acquired immunodeficiencies underlying tuberculosis in childhood, Immunol Rev 2015

4 Stages of Immunologic Testing when Primary Immunodeficiency is Suspected

1

- History and physical examination, height and weight
- CBC and differential
- Quantitative Immunoglobulin levels IgG, IgM, IgA (related to age)

√

2

- Specific antibody responses (tetanus, diphtheria)
- Response to pneumococcal vaccine (pre/post)(for ages 3 and up)
- IgG subclass analysis

X

3

- Candida and Tetanus skin tests
- Lymphocyte surface markers CD3/CD4/CD8/CD19/CD16/CD56
- Mononuclear lymphocyte proliferation studies (using mitogen and antigen stimulation)
- Neutrophil oxidation burst (if indicated)

√

4

- Complement screening CH50, C3, C4
- Enzyme measurements (adenosine deaminase, purine nucleoside phosphorylase)
- Phagocyte studies (surface glycoproteins, mobility, phagocytosis)
- NK cytotoxicity studies
- Further complement studies AH50
- Neo antigen to test antibody production
- Other surface/cytoplasmic molecules
- Cytokine receptor studies
- Family/genetic studies

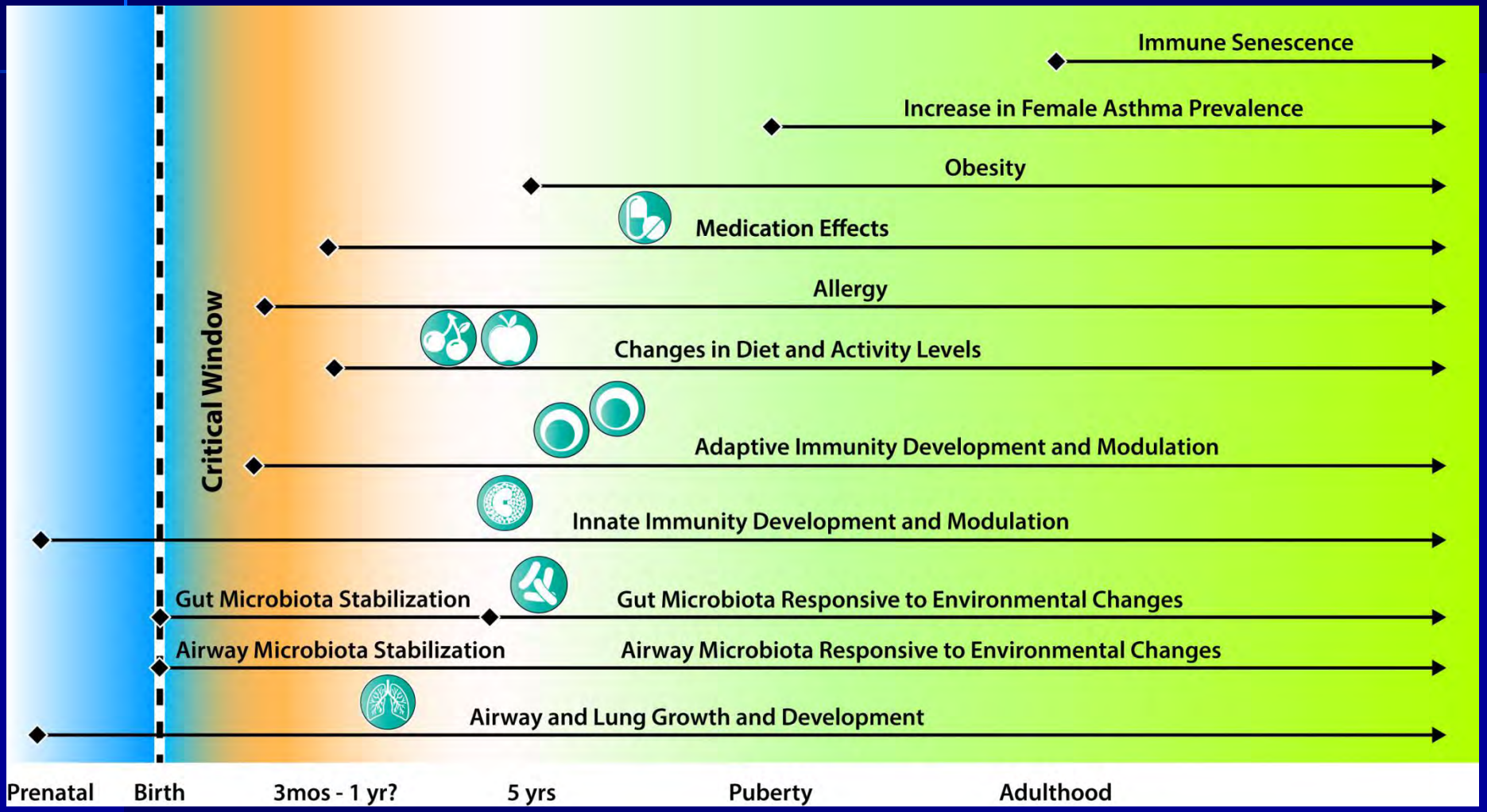
√

X

Recurrent LRTI

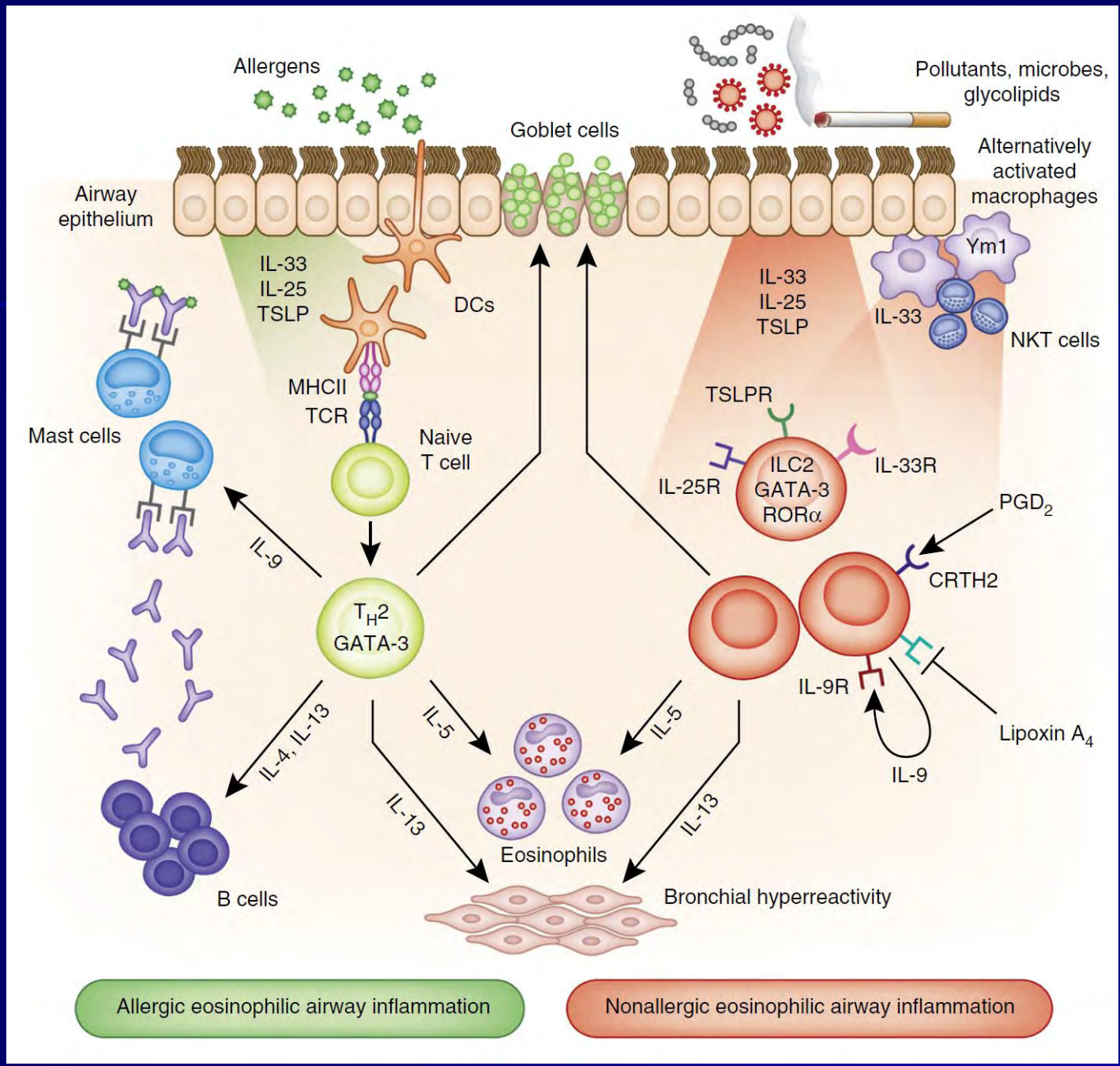
- Impaired respiratory barrier like cystic fibrosis, primary ciliary dyskinesia, CCAM
- Aspiration pneumonia/ GER/ swallowing dysfunction
- Asthma
- Protracted bacteria bronchitis
- PID
  - Antibody defect, Phagocytic defect, HIES, CID, complement deficiency
- Immunology Tests:
  1. FBC, Ig G,A,M,E, C3,C4,CH50
  2. Vaccine antibodies
  3. T/NK lymphocyte subsets if viral/fungal/TB

The Microbiome in Asthma



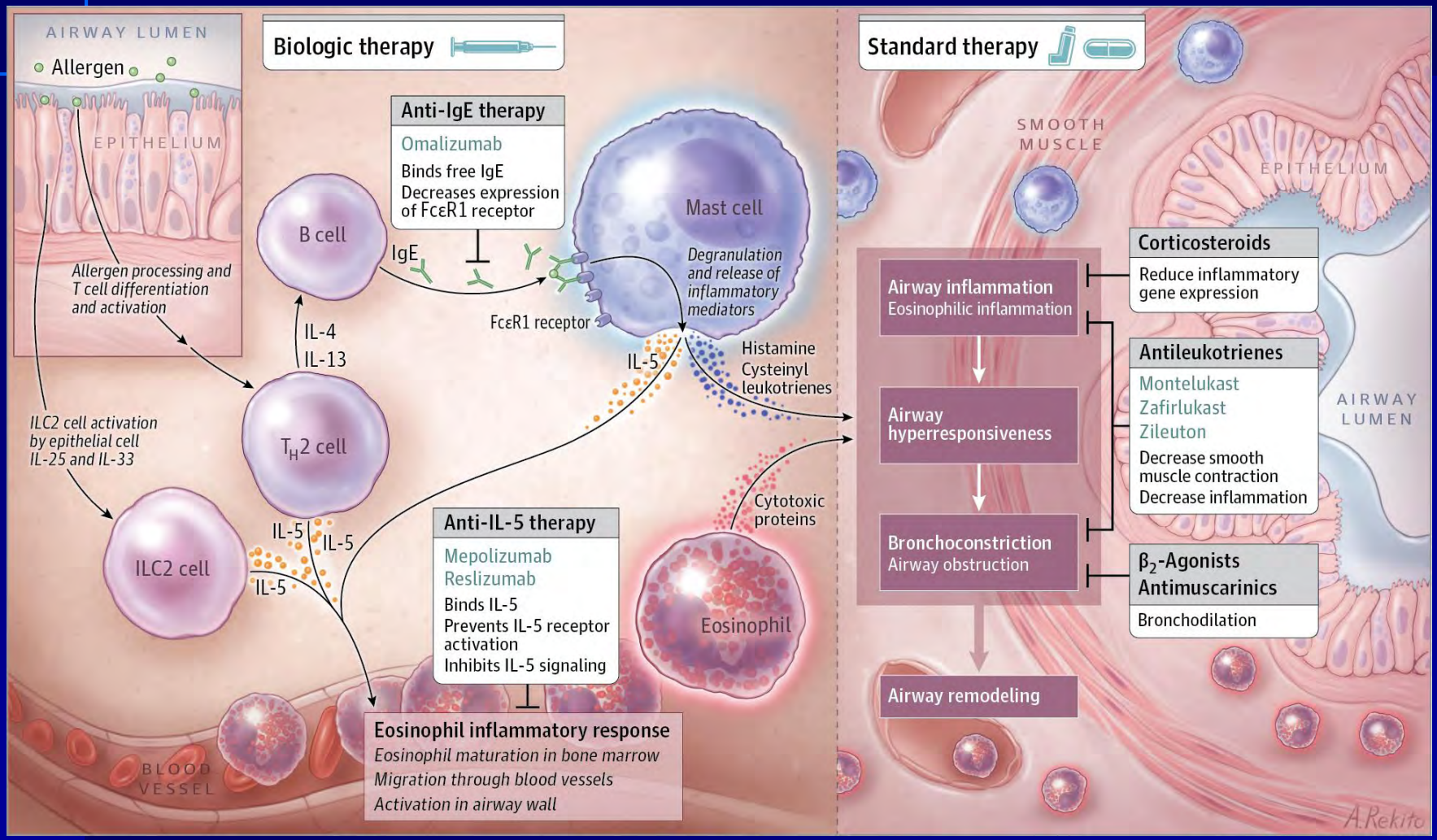
The microbiome in asthma: Role in pathogenesis, phenotype, and response to treatment, Ann Allergy Asthma Immunol 2019 Mar

Immunology of Asthma



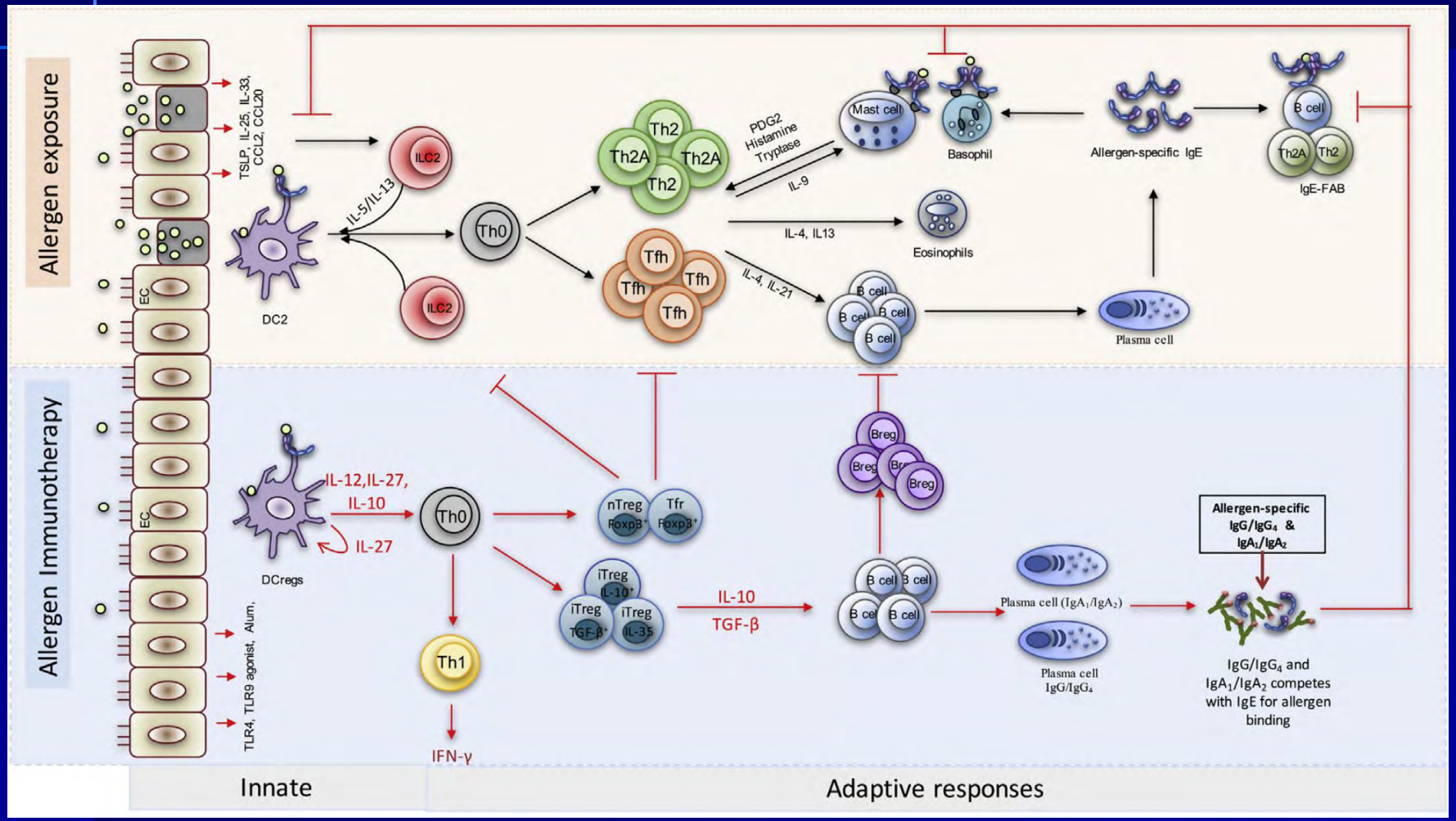
The immunology of asthma, Nat Immunol 2015

Treatment for Asthma



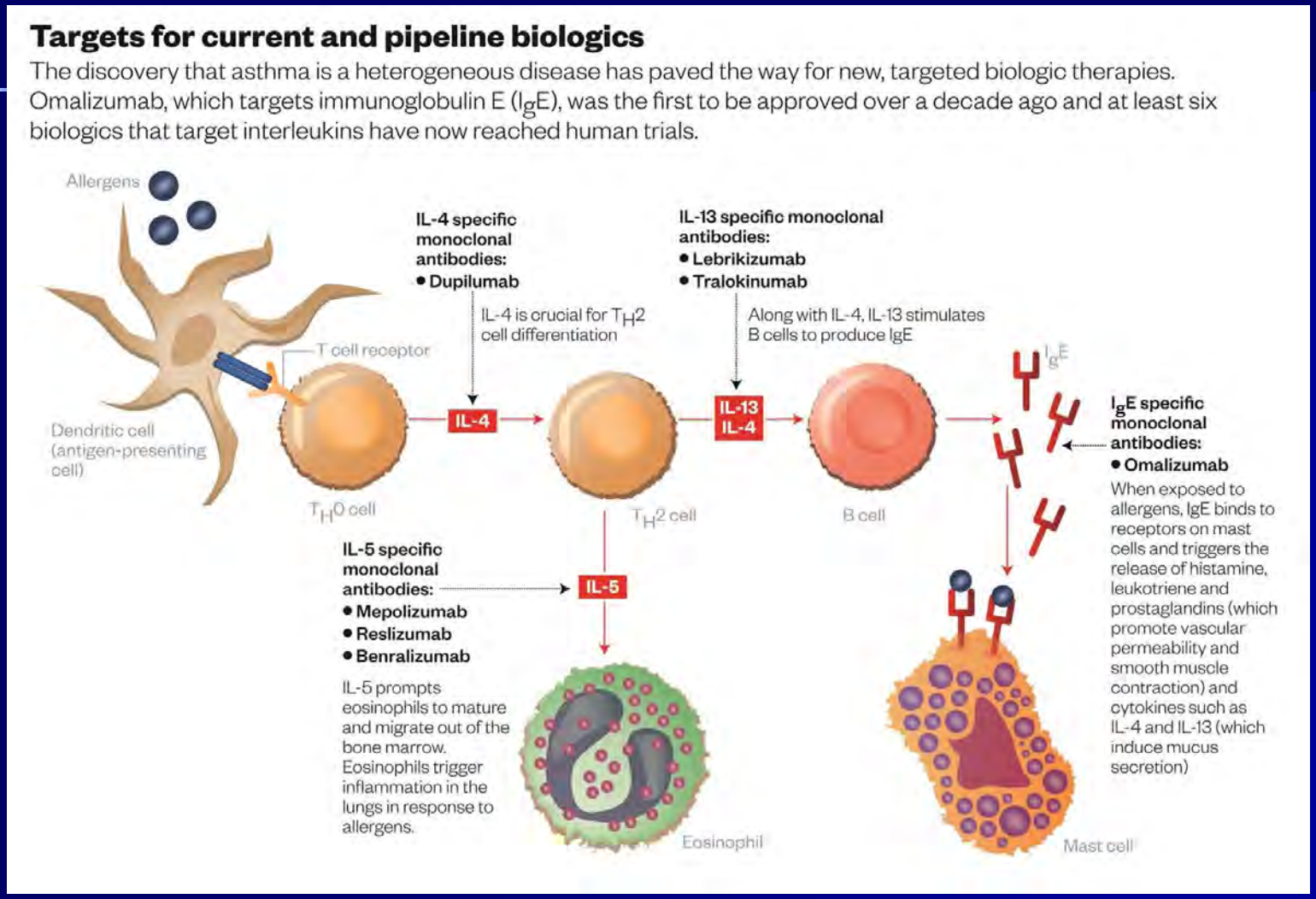
Diagnosis and Management of Asthma in Adults, A Review, JAMA 2017

Immunotherapy for Asthma



Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers, JACI Dec 17

Treatment for Asthma - Biologics



Asthma therapies get personal, The Pharmaceutical Journal Sep 2015

Summary

- PID respiratory infections
  - Bacteria
    - XLA - Streptococcal, Pseudomonas
    - CGD - Staph Aureus, Meiloidosis
    - AD HIES - Staph Aureus lung abscess
  - Viral
    - SCID - viral URTI/ARDS
    - STAT1 GOF – CMV pneumonitis
  - Fungal
    - SCID/XHIGM – PCP
    - STAT1 GOF – Candida, Aspergillus
    - CGD – Aspergillus, Nocardia
    - HIES - Candida
  - Mycobacterium
    - SCID, CGD, MSMD

Suspect PID if:

- Pneumonia ≥ 2 per year
- Sinus infection ≥ 2 per year
- Ear infections ≥ 4 per year
- Bronchiectasis
- ARDS from common respiratory infections

Questions?

Dr Liew Woei Kang
MBBS, MRCPCH (UK), FAMS (Paediatrics), FAAAAI (USA)
Consultant Paediatrician
Paediatric Immunology & Allergy

Allergy

Food allergy – diagnostic tests (SPT and Bld IgE), food challenge, oral immunotherapy
Respiratory allergy – Asthma and AR Tm, SPT, lung function testing, allergen immunotherapy
Skin allergy – Eczema and Urticaria, SPT, skin patch testing
Drug and vaccine allergy – diagnostic tests, drug challenge, drug desensitisation

Immunology

Evaluation of primary immunodeficiency/recurrent infections/periodic fever syndromes
Genetic testing of index case and family
IVIG replacement, SC interferon gamma
Haematopoetic stem cell transplant for PID

Rheumatology

Evaluation of inflammatory disorders/ joint pains and autoimmunity
Juvenile idiopathic arthritis – diagnostics, intraarticular injection, biologics
Vasculitis – Kawasaki, Henoch Scholein Purpura