Πρωτοπαθείς Ανοσοανεπάρκειες:
Οι πολλαπλές κλινικές εκδηλώσεις σε ενήλικες

Λοιμώξεις

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Δομή της παρουσίασης

- Primary Antibody Deficiencies (PADs) - general
- Main clinical features associated with PADs
- Common variable immunodeficiency (CVID)
- Lung Disease in PADs
- Antibiotic prophylaxis in Primary Immune Deficiency Disorders (PIDDs)
- Chronic Granulomatous Disease (CGD)
- Recurrent and sustained viral infections in PIDDs
- Chronic viral skin infections in PIDDs

Primary antibody deficiencies (PADs)

Durandy A, Kracker S and Fischer A
Nature Reviews Immunology 2013
doi:10.1038/nri3466

Primary antibody deficiencies (PADs)

- The most common PIDDs in humans.
- Mostly attributed to B cell-intrinsic defects.
- Can also be caused by functional impairments in other immune cell lineages (includ. innate immune cells and T cells).
- Whereas most PIDs are monogenic, the most prevalent type of PAD - common variable immunodeficiency (CVID) - seems to have a more complex genetic basis.

Pathophysiology of PADs

- **PADs associated with B cell-intrinsic defects**

  (Leads to variable pan-hypogammaglobulinaemia, although the numbers of circulating B cells remain normal)

- **PADs associated with B cell-extrinsic defects**

- **PADs with unknown etiology**

PADs associated with B cell-intrinsic defects - I

- ***Defects in B cell development***

  - X-linked agammaglobulinaemia (**XLA**)

- ***Defects in B cell migration***

  - Warts, hypogammaglobulinaemia, infections and myelokathexis (**WHIM**) syndrome

  - Wiskott–Aldrich syndrome (**WAS**)

- ***Defects in B cell survival***

- ***Defects in immunoglobulin class switch recombination***

  Two key steps in the maturation of B cells

  - class-switch recombination (CSR)
  - somatic hypermutation (SHM)

PADs associated with B cell-intrinsic defects - II

- ***Defects in cytokine signaling***
- ***Defects in B cell activation***

  PADs caused by B cell activation defects are part of combined immunodeficiency (CID) disorders involving both T cells and other cells except those affecting the

  - CD19 complex or
  - CD20

PADs associated with B cell-extrinsic defects - III

- ***Defects in T cell development or activation***

  Genetic impairments of T cell differentiation also lead to secondary B cell defects

- ***Defects in innate immunity***

  The recent description of the role of innate immunity in B cell responses to T cell-independent antigens points to a very new disease mechanism, linking for the first time innate immune cells and B cell immunity.

PADs with unknown aetiology

- Selective IgA deficiency (SIgAD)
- Common variable immunodeficiency (CVID)
- Selective IgG subclass deficiency
- Selective IgM deficiency
- Selective polysaccharide antibody deficiency (SPAD)

Selective IgA deficiency (SIgAD)

It is defined as a serum IgA of less than 7 mg/dL with normal IgM and IgG levels in individuals of 4 years of age or older

- **SIgAD is the most common PAD**, however, its genetic basis has not yet been defined.
- **Two-thirds of individuals are asymptomatic** (suggesting effective compensation by secretory IgM in the mucosae).
- The remaining one-third suffer from bacterial infections, most often of the respiratory tract, as well as gastrointestinal disorders, autoimmunity, and atopy.
- Approximately 25% of symptomatic patients have a family history of either SIgAD or CVID.

Common variable immunodeficiency (CVID)

CVID corresponds to a heterogeneous group of disorders characterized by:

- **low levels of IgG and IgA, ± low IgM levels**
- **with defective antibody responses**

In some cases, is associated with an increased incidence of:

- granuloma,
- autoimmunity
- lymphoid hyperplasia, and
- cancer

CVID - US study: Phenotypes and conditions

Associated condition (N = 473)	n	Percentage
Infections only (no complications)	151	31.9
Chronic lung disease (functional/structural)	135	28.5
Autoimmunity	134	28.6
Gastrointestinal disease	73	15.4
Granulomatous disease	46	9.7
Liver disease/hepatitis	43	9.1
Lymphomas and other lymphoid malignancies	39	8.2
Splenectomy	39	8.2
Other cancers	33	6.9

Resnick ES, et al. Blood. 2012;119:1650-7.

Common variable immunodeficiency (CVID)

- 10–20% of patients have a family history of CVID or IgA deficiency.
- The genetic variations associated with CVID, in over 90% of cases have not yet been defined on a molecular basis.
- As CVID has a late onset, it is probably caused by a **combination of several genetic variations** rather than by a defect in a single gene.

Pathogens affecting CVID patients

- **Encapsulated bacteria**
- *Mycoplasma* and *Ureaplasma.*
- With widespread usage of IgG replacement therapy, the emergence of "non-infectious" complications, which include

  - autoimmune cytopenias,
  - gastrointestinal disease,
  - liver disease,
  - lung disease, and
  - malignancy,

  have emerged as the most important cause of morbidity and mortality in CVID patients

Selective IgG subclass deficiency

- **Selective IgG subclass deficiency is defined as a lack of one or more IgG subclasses with normal overall IgG levels.**
- **IgG2 deficiency** is most commonly reported and is often associated with IgG4 deficiency.
- **IgG3 deficiency**, which is less common, is often associated with another IgG subclass deficiency.
- **Both lead to susceptibility to recurrent bacterial infections.**

Selective IgM deficiency (SIgMD)

- Selective IgM deficiency (SIgMD) is a rare disorder that leads to **recurrent infections (most frequently with encapsulated pathogens)** from infancy onwards.
- Its pathogenesis remains unclear.

Selective polysaccharide antibody deficiency (SPAD)

Patients with SPAD have

- normal immunoglobulin levels (including IgG2), *but*
- lack polysaccharide-specific antibodies,

and are therefore **susceptible to infections,**

especially those caused by encapsulated bacteria.

Congenital agammaglobulinemia

- **Sinopulmonary tract infections** (in 60% of patients).
- **Pyoderma, chronic conjunctivitis, gastroenteritis, arthritis, meningitis, osteomyelitis** and **septicemia** are also seen.
- **Infections with encapsulated bacteria** like *Haemophilus influenzae* and *Streptococus pneumoniae* are the most frequent concern for these patients.
- Susceptibility to certain viral infections, such as **hepatitis** and **enteroviruses**, may also be increased.

Hyper IgM syndrome

Both the X-linked and AR forms of HIGM syndrome predispose to:

- sinopulmonary infections
- gastrointestinal infections
- autoimmune disease
- susceptibility to infections not typical for antibody deficiency alone, like *Pneumocystis*.

The main phenotypes of primary antibody deficiencies

Phenotype	Main clinical features	Main B cell biological features
Pan-agammaglobulinaemia (absence of IgM, IgG and IgA)	**Bacterial infections** (in the respiratory tract) and **enterovirus infections**	Absence of CD19+ B cells
Variable pan-hypogammaglobulinaemia (CVID)	**Bacterial infections** (in the respiratory tract and gut), autoimmunity, cancer and increased risk of granuloma	Decreased frequency of CD27+ memory B cells; defective plasma cells in tissues
CSR deficiencies (absence or decrease in levels of IgG and IgA)	**Bacterial and opportunistic infections**	Decreased frequency of CD27+ memory B cells
Selective IgA deficiency	**Most often asymptomatic**	ND
Selective IgM deficiency	**Frequent infections with encapsulated bacteria**	No IgM antibody production (absence of allohemaglutinins and polysaccharide-specific antibodies)
Selective IgG2 and/or IgG4 deficiency	**Frequent bacterial infections,** diagnosis after 2 years of age; sometimes transient in childhood	Defective polysaccharide-specific antibody production
Selective polysaccharide antibody deficiency	**Bacterial infections** (after 2 years of age)	Normal IgG (including IgG2 and IgG4) levels

Durandy A, et al. Nature Rev Immunol 2013. doi:10.1038/nri3466

Main clinical features associated with PADs

- **Susceptibility to infections**
- **Autoimmunity and autoinflammation**
- **Carcinogenesis**

Susceptibility to infections

The production of different immunoglobulin isotypes with high affinities for antigens is essential for efficient protection against infections.

- **IgM** constitutes the first line of defence against encapsulated bacteria in vascular spaces.
- **IgG** has a longer half-life and diffuses in the extracellular compartment
- **IgA** is transported to mucosal surfaces (especially in the gut)
- **IgE** is involved in immune responses to helminths.

PADs: Type of infections

- Infections predominantly affect the respiratory tracts, leading to the severe complications of **sinusitis** and **bronchiectasis**, if left untreated.

- The most prevalent microorganisms are:

  - *Streptococcus pneumoniae*,

  - non-typeable ***Haemophilus influenzae*** and

  - Gram-negative bacteria

PADs: Type of infections

To a lesser extent, patients with PADs are vulnerable to:

- **Intestinal tract infections**, mainly by:
  - *Giardia spp.*
  - *Campylobacter jejuni*
  - *Salmonella spp.*
  - *Helicobacter pylori*
- **Bacterial cutaneous infections**

PADs: Type of infections

- Some patients with agammaglobulinaemia also suffer from **severe, chronic enteroviral infections**, suggesting a major role for antibodies in preventing the dissemination of enteroviruses from the gut.
- The **absence of vulnerability to fungal infections** shows that antibodies are dispensable for immunity to fungi.
- Antibodies also seem to be less important for antiviral responses, with the notable exception of enteroviruses.

Lung Disease in Primary Antibody Deficiencies

Schussler ED, et al.

Allergy Clin Immunol Pract. 2016;4:1039–52

Interstitial lung disease (ILD) in PAD

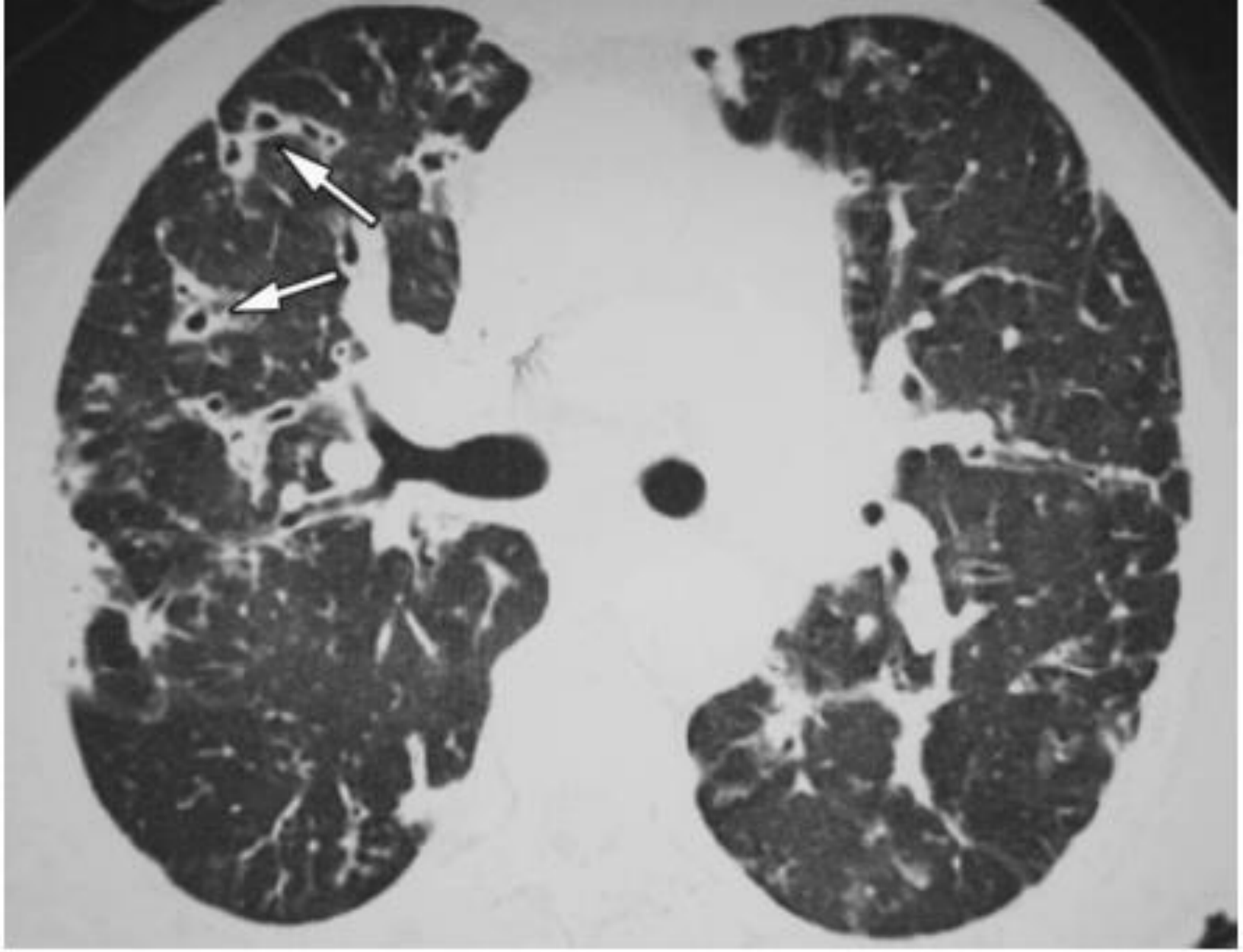
- The development of lung disease in PAD **may not be solely** the result of recurrent bacterial infection or a consequence of bronchiectasis.
- Recent characterization of monogenic immune dysregulation disorders and more extensive study of CVID has demonstrated that ILD in PAD can result from **generalized immune dysregulation** and frequently occurs **in the absence of pneumonia history or bronchiectasis.**

Schussler ED, et al. Allergy Clin Immunol Pract. 2016;4:1039–52

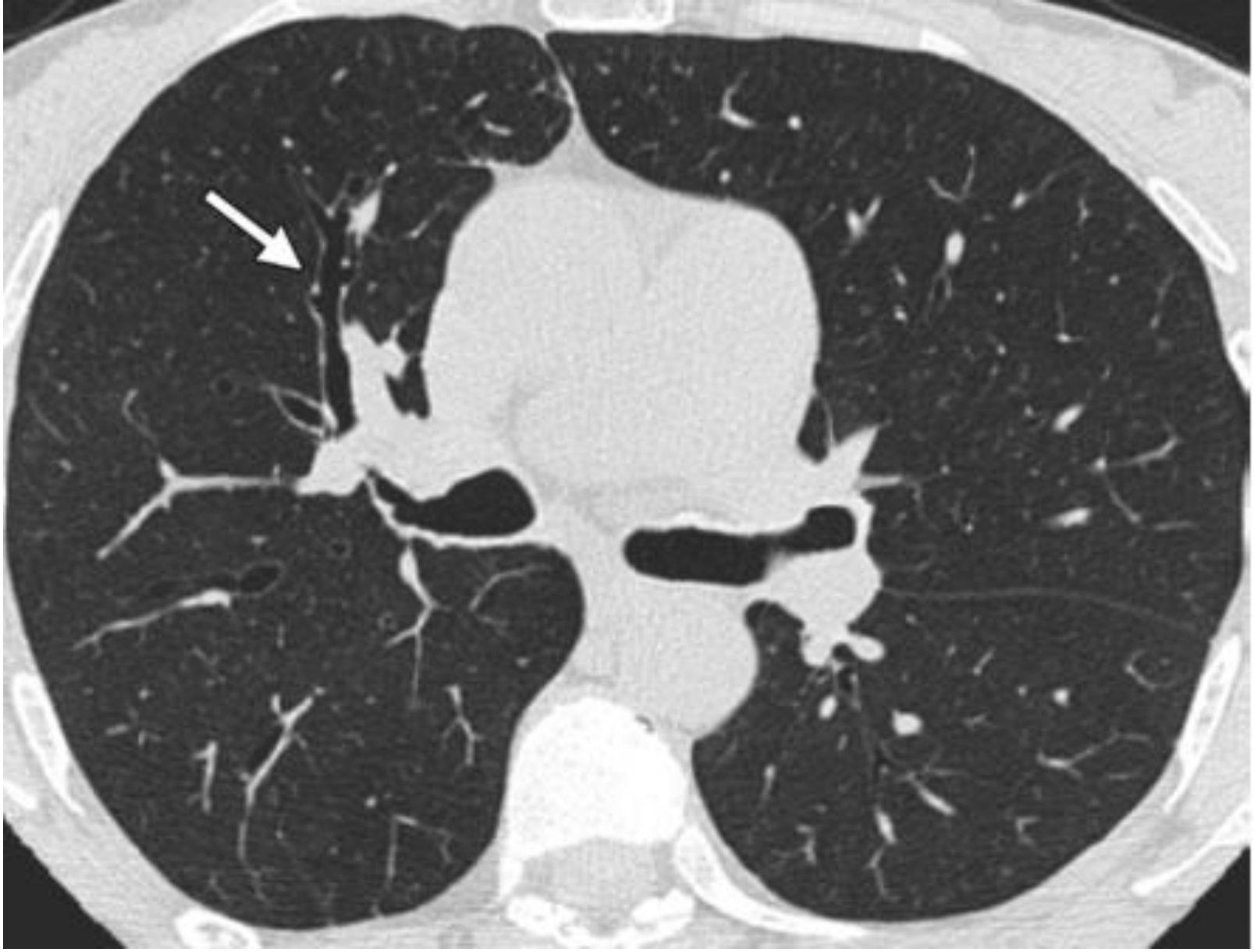
Interstitial lung disease (ILD) in PAD

- While all antibody deficient patients are at risk of developing bronchiectasis, **ILD occurs in some forms of PAD much more commonly than others**, suggesting that distinct but poorly understood immunological factors underlie development of this complication.
- Importantly, ILD can have earlier onset and may worsen survival more than bronchiectasis.

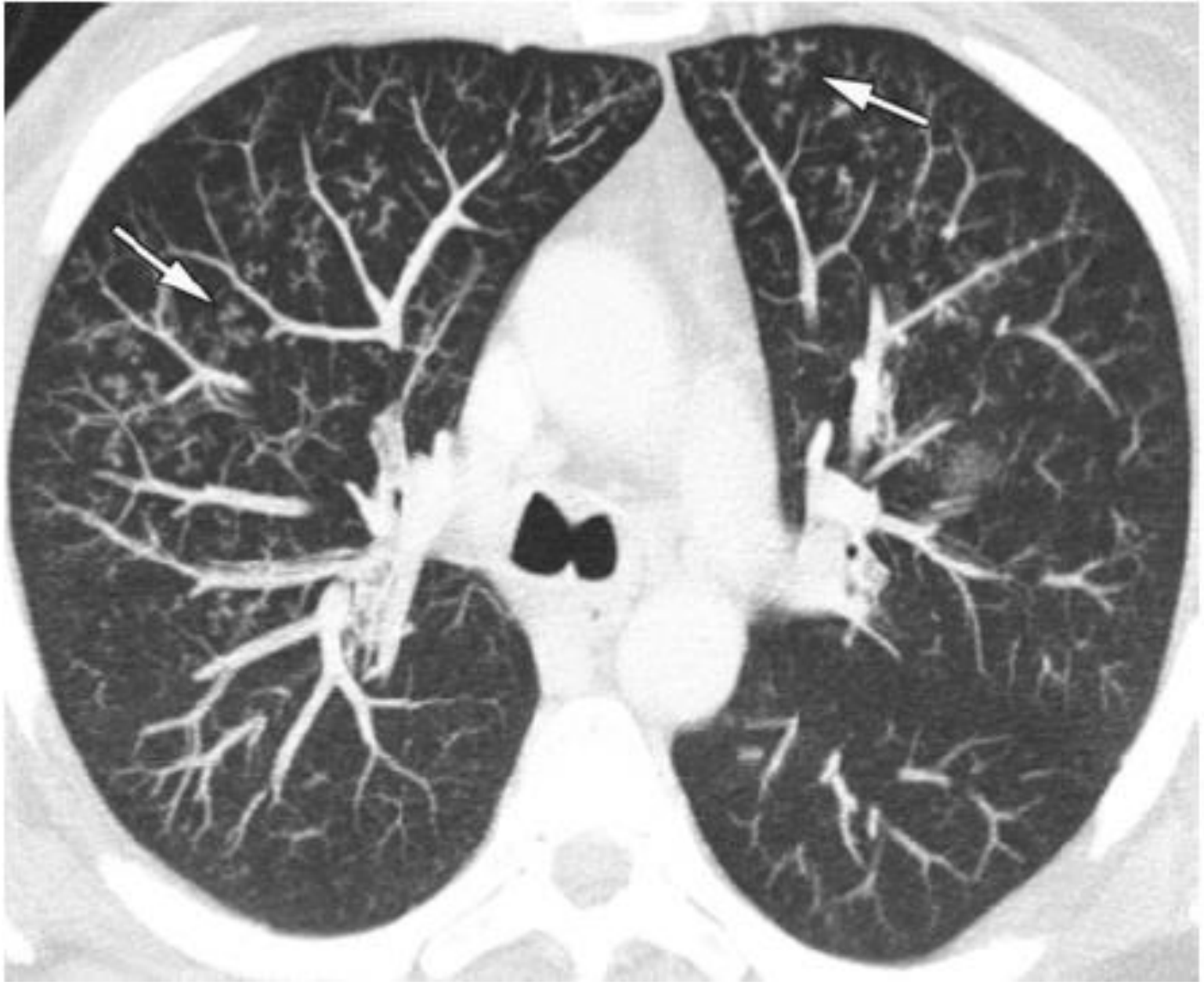
Schussler ED, et al. Allergy Clin Immunol Pract. 2016;4:1039–52



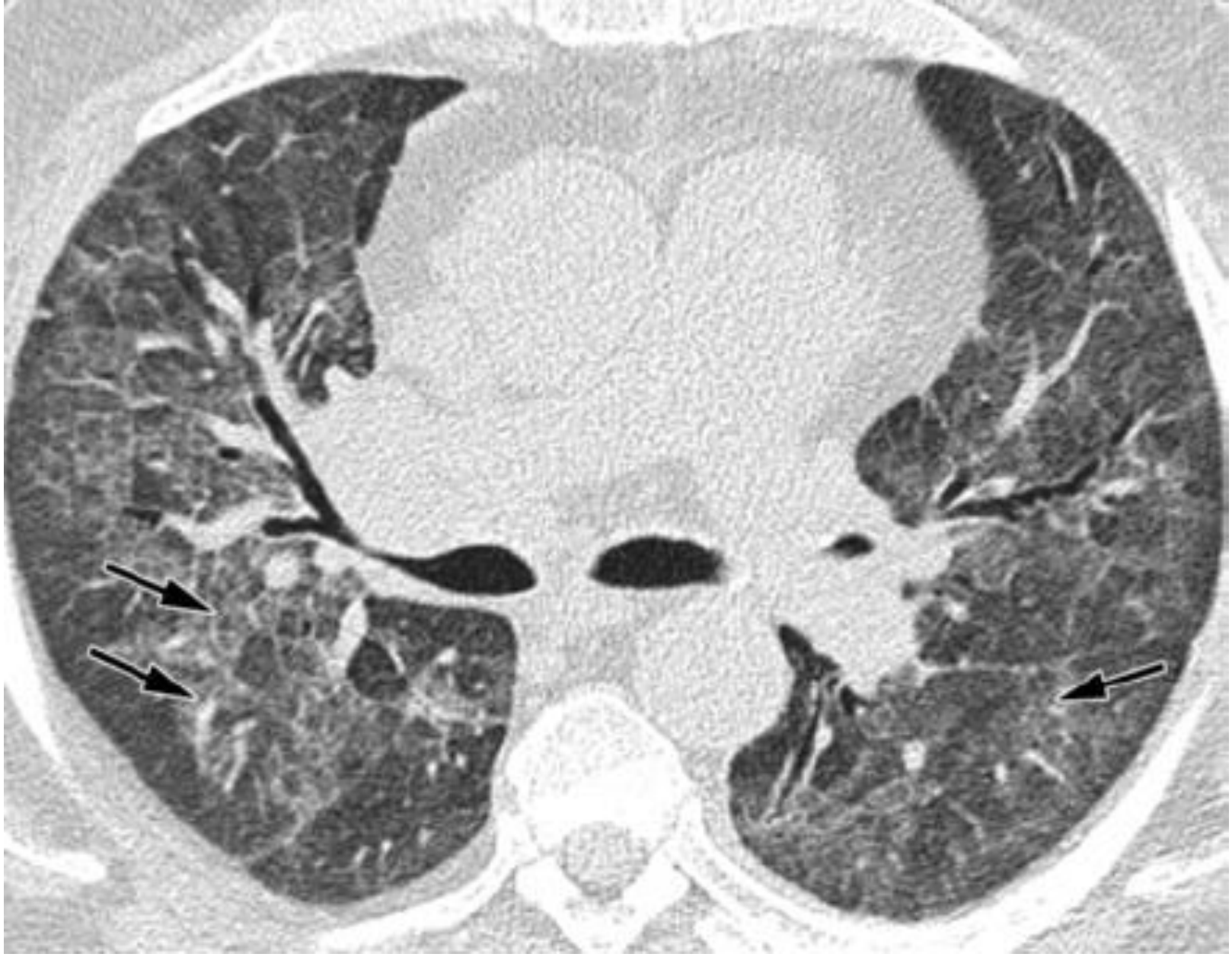
Bronchiectasis and bronchial wall thickening in a 17y. patient with XLA.
CT image shows the diffuse distribution of abnormalities (arrows)



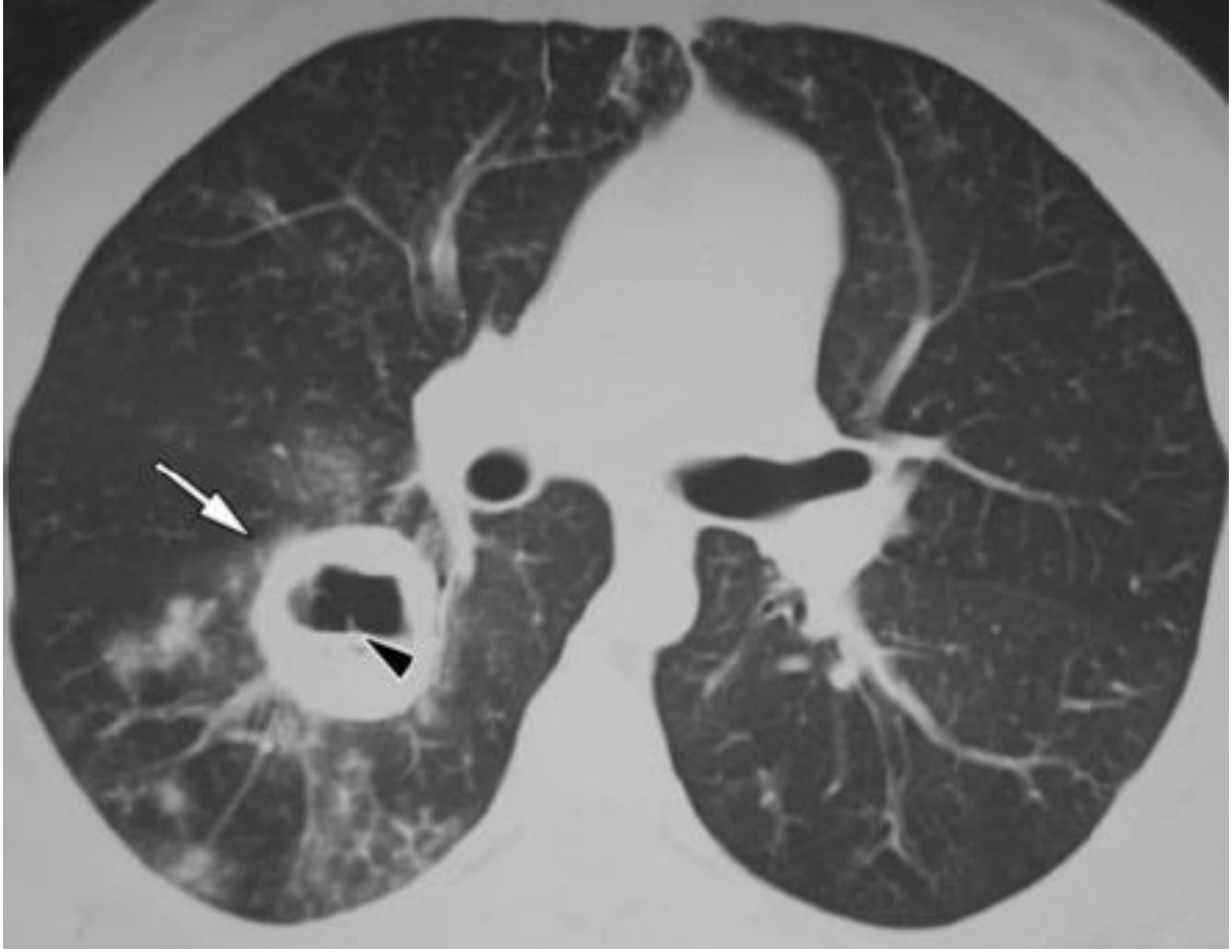
Axial CT image obtained in a 55y. patient with CVID demonstrates cylindrical bronchiectasis in the right upper lung lobe (arrow)



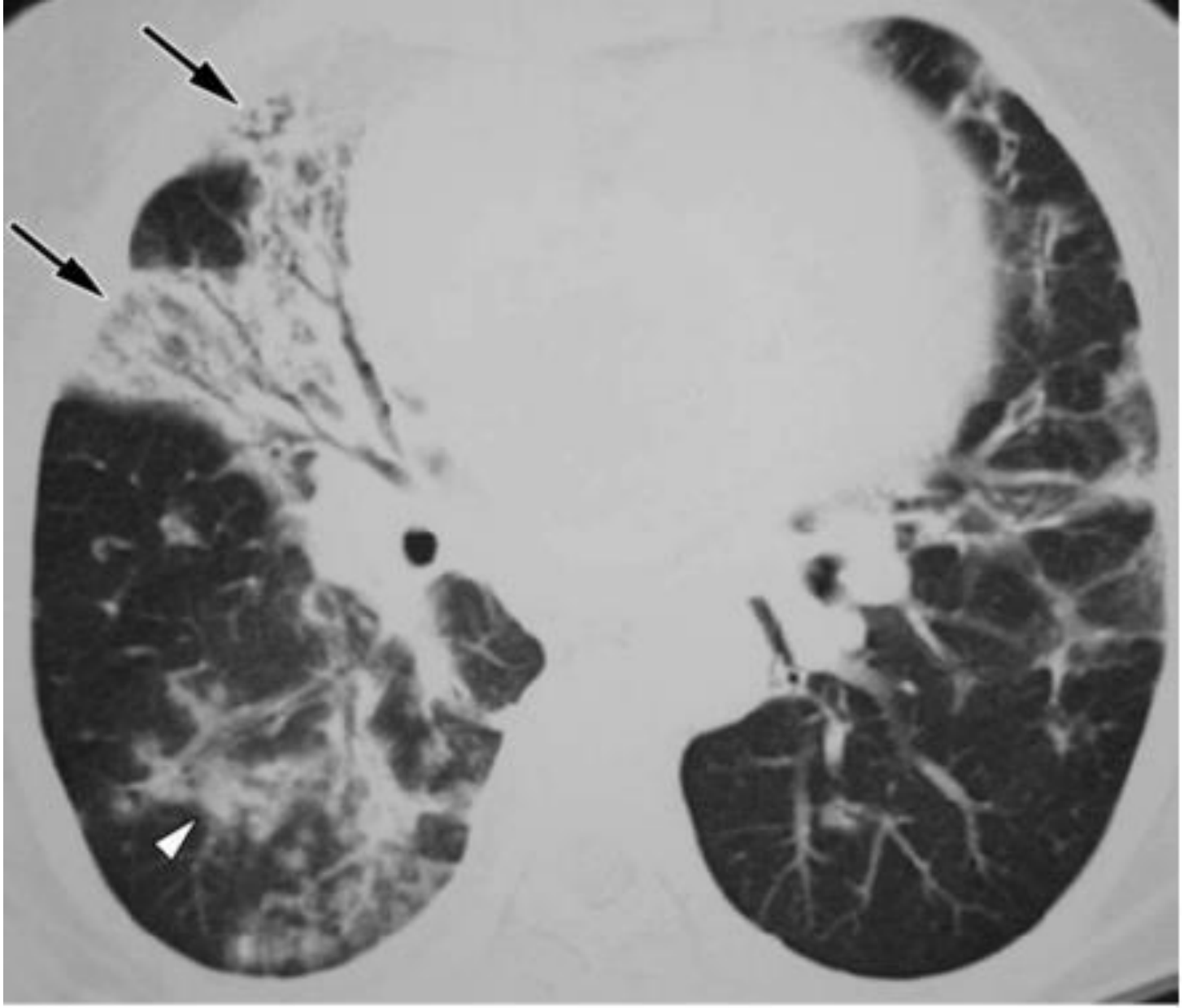
Infectious bronchiolitis in a 24y. patient with CVID. Maximum intensity projection image clearly depicts multiple tree-in-bud nodules in the upper lobes of both lungs (arrows)



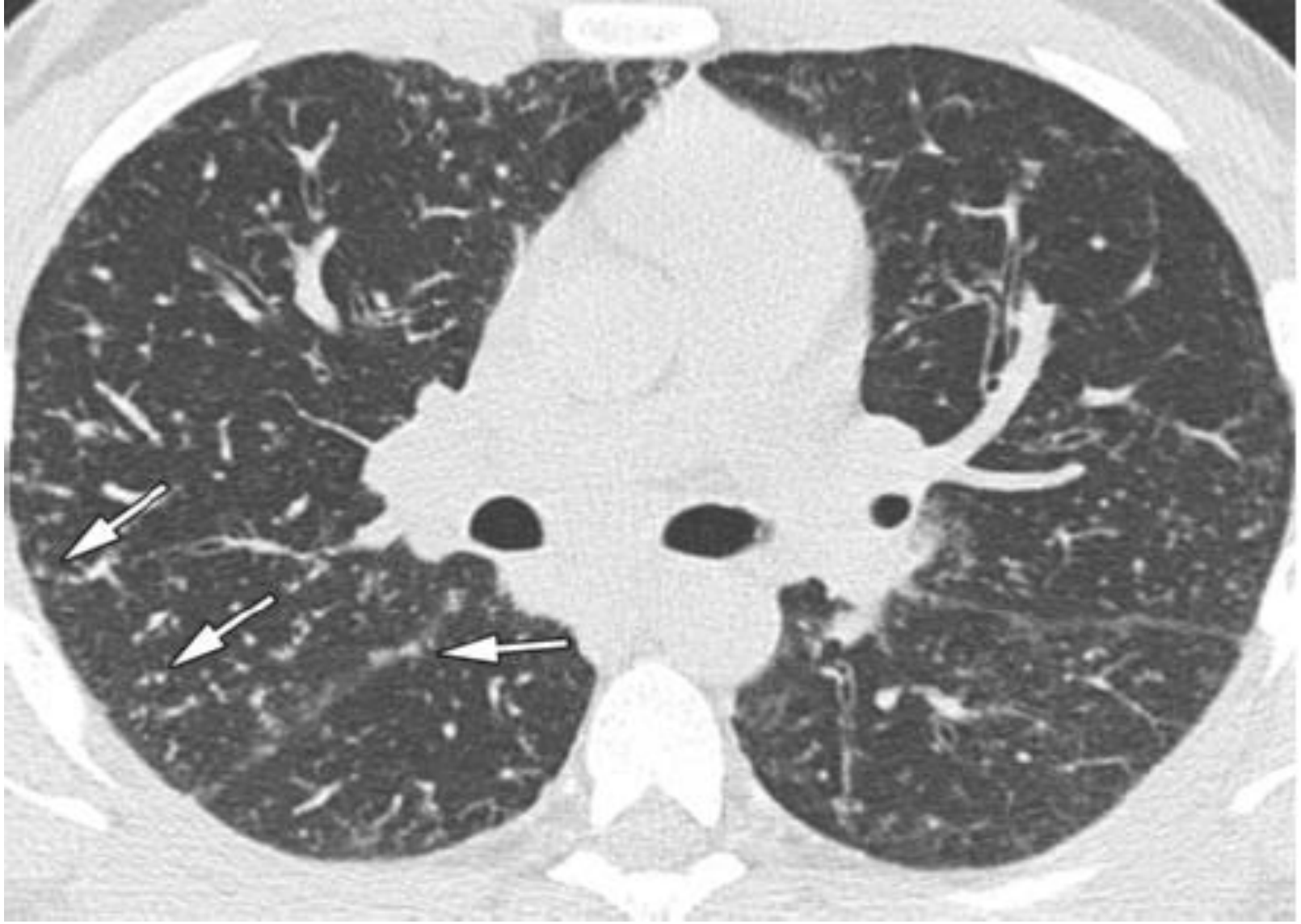
P. jiroveci **pneumonia in a 31-year-old patient with severe hypogammaglobulinemia. Axial CT image shows ground-glass infiltrates with a diffuse bilateral distribution (arrows)**



Aspergilloma in a severely immunocompromised patient with X-linked agammaglobulinemia. Axial CT shows a thick-walled mass (arrow) with an air-fluid level (arrowhead) in the R lower lobe.

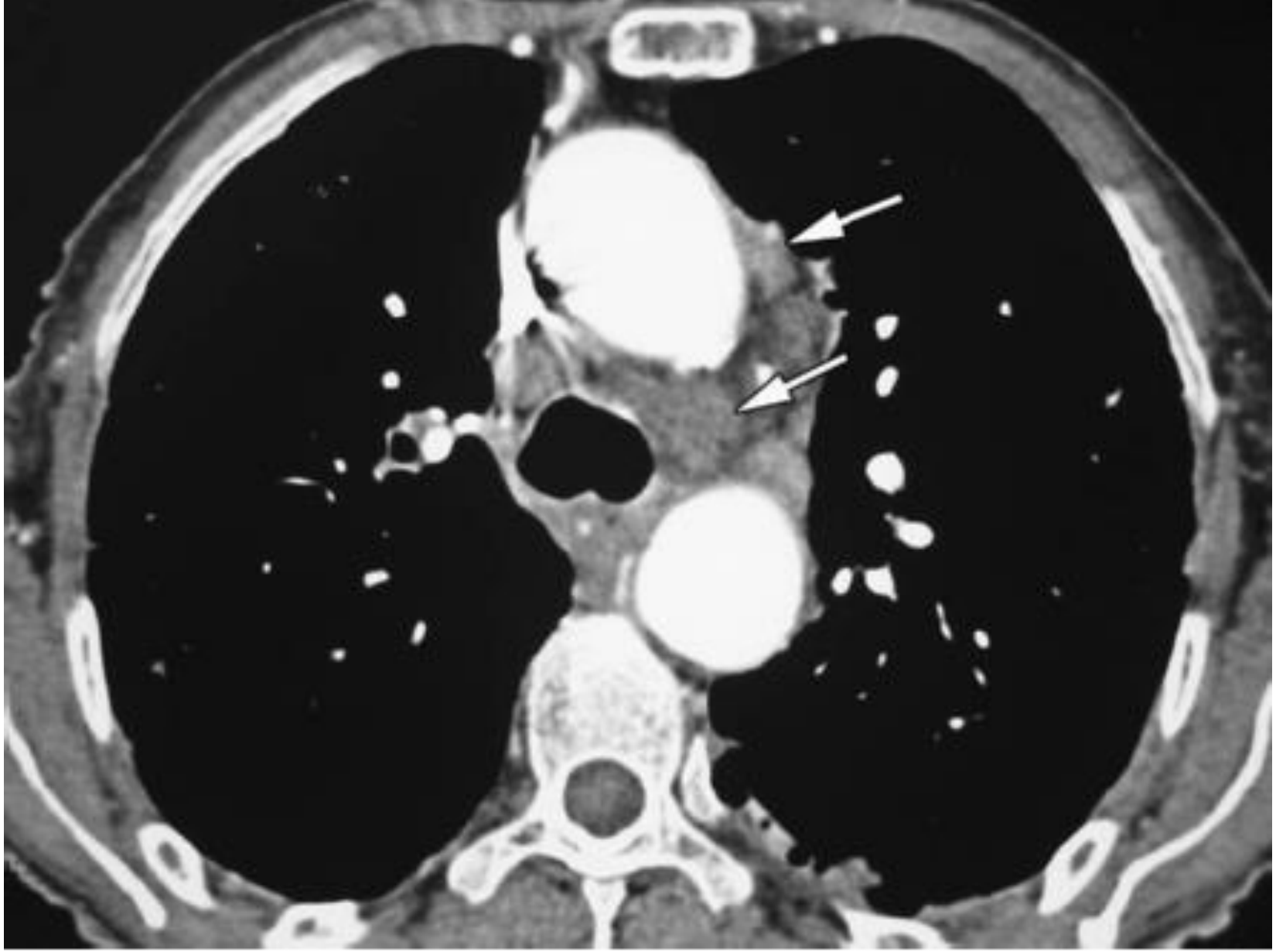


Axial CT image shows massive areas of fibrosis in the right lung with traction bronchiectasis of the middle lobe (arrows).
Alveolar condensation in the lower lobe (arrowhead) is indicative of acute infection.

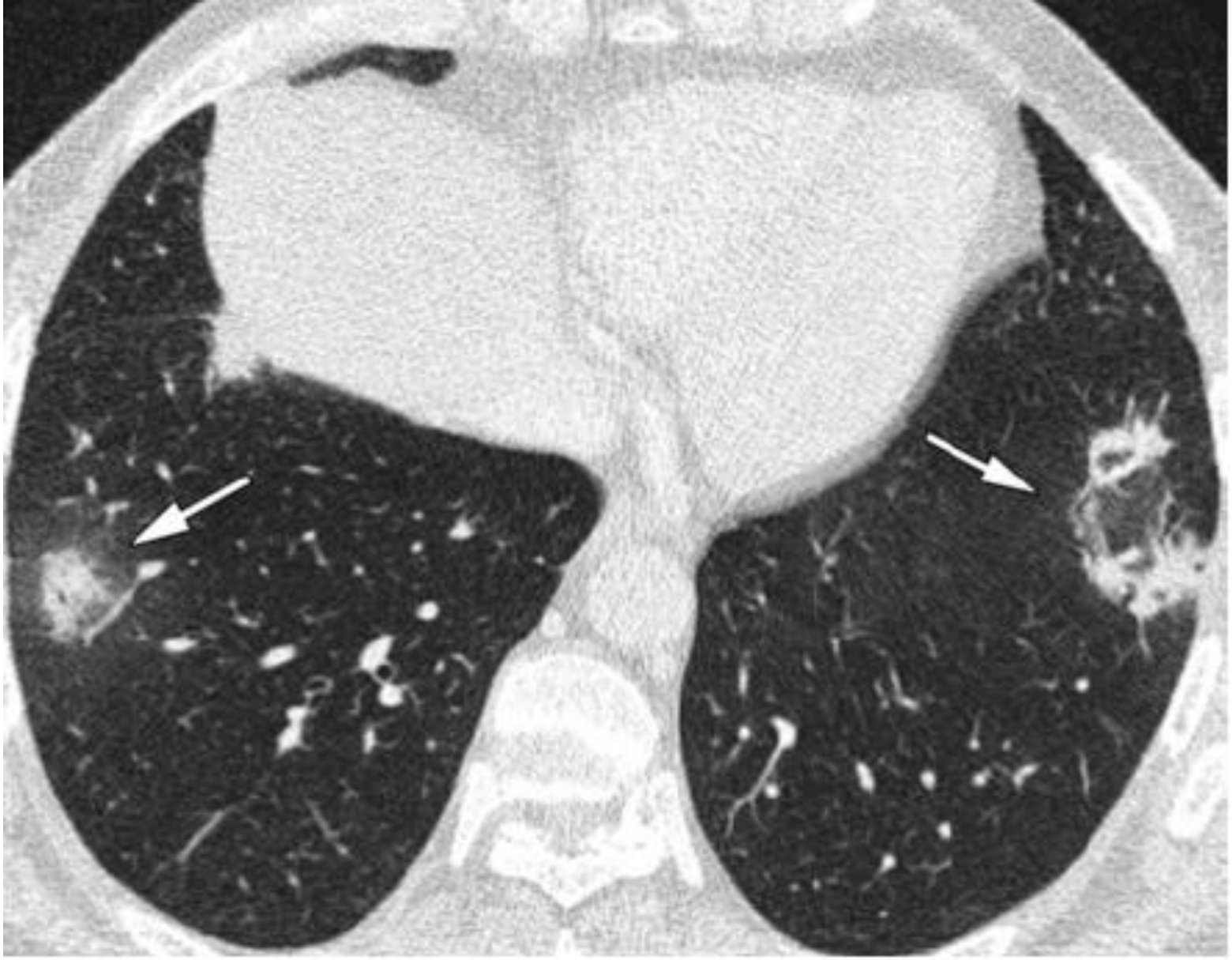


Granulomatosis in a 22-year-old patient with CVID.

Axial CT image demonstrates small nodules with a perilymphatic distribution and irregular thickening of pleura and interlobular septa (arrows), an appearance similar to that of sarcoidosis.



Proved systemic granulomatosis in a 40y patient with CVID.
Axial CT image shows multiple sarcoidlike mediastinal lesions (arrows)



Organized pneumonia in a 40y patient with long-standing hypogammaglobulinemia. Axial CT image shows bilateral focal regions of consolidation (arrows)

IgG replacement

- **All antibody-deficient patients require IgG replacement, with either intravenous or subcutaneous delivery.**
- The use of IgG replacement therapy considerably limits infectious complications and chronic lung lesions.
- However, **IgG replacement treatment is not always sufficient**, as the other immunoglobulin isotypes are not provided.

IgG replacement

- Interestingly, in a prospective study of a cohort of patients with pan-hypogammaglobulinaemia and CSR deficiency who received equal IgG replacement therapy, patients with class-switch recombination (CSR) deficiency had a lower incidence of acute respiratory tract infections and bronchiectasis and a significantly lower risk of infection with non-typeable *H. influenzae* compared with agammaglobulinemic patients.
- These patients carried IgM antibodies specific for non-typeable *H. influenzae* in their serum and saliva.

Micol R, et al. J Allergy Clin Immunol 2012;129:770–7.

IgG replacement

- Interestingly, similar protection has been found in CD40L- and activation-induced cytidine deaminase (AID)-deficient patients (who lack somatic hypermutation - SHM), as well as in other patients with class-switch recombination (CSR) deficiencies, in whom SHM is normal.
- Thus, IgM antibodies that have been actively transported to mucosal surfaces seem to be clinically protective against some microorganisms, irrespective of whether they have undergone somatic hypermutation - SHM.
- This shows that IgG, which cannot be transported to mucosal surfaces as it fails to bind to the J chain, cannot fully substitute for the immunoglobulin isotypes that can be transported to mucosal surfaces (namely, IgM and IgA).

Micol R, et al. J Allergy Clin Immunol 2012;129:770–7.

Antibiotic Prophylaxis in Primary Immune Deficiency Disorders

Kuruvilla M and Maria Teresa de la Morena.

J Allergy Clin Immunol Pract 2013;1:573-82.

Prophylactic antibiotics

- Administration of antibiotics might be required in patients with SIgMD.
- Long-term antimicrobial prophylaxis could be required for patients with agammaglobulinaemia in addition to IgG replacement therapy to compensate for the absence of IgM.
- Patients with class-switch recombination (CSR) deficiencies are protected from infection with some bacteria (such as non-typeable *H. influenzae),* possibly by their IgM antibodies.

Antibiotic prophylaxis regimens in primary antibody deficiency syndromes

PAD	Regimen
XLA or CVID (>3 breakthrough infections or extremely severe infection on IgG)	Azithromycin 5 mg/kg PO 3/wk (alternate days) or 10 mg/kg/wk; SMX-TMP 5 mg/kg TMP component PO daily or 3/wk
THI and selective IgA deficiency (seasonal intermittent during winter or continuous prophylaxis)	Azithromycin 5 mg/kg PO 3/wk or 10 mg/kg/wk; amoxicillin 20 mg/kg PO once or twice daily; SMX-TMP 5 mg/kg TMP component PO daily or 3/wk

XLA: Bruton agammaglobulinemia
CVID: Common variable immunodeficiency
THI: Transient hypogammaglobulinemia of infancy

Kuruvilla M, et al. J Allergy Clin Immunol Pract 2013;1:573-82

Suggested antibiotic prophylaxis regimens in PIDs

PID	Regimen
SCID	*Pneumocystis jirovecii* prophylaxis: SMX-TMP 5 mg/kg TMP component PO once daily 3 days per wk or atovaquone 30 mg/kg once daily; HSV-prophylaxis: Acyclovir 20 mg/kg/dose 3 times a day; Fungal prophylaxis: Fluconazole 6 mg/kg/d PO daily (follow AST and ALT) and Palivizumab (15 mg/kg intramuscularly) during RSV season
Hyper-IgM syndrome	SMX-TMP PO 5 mg/kg TMP component PO 3 times per wk; azithromycin PO (may have a role in CD40L or CD40 deficiency)
CGD	SMX-TMP 5 mg/kg TMP component PO divided twice daily; itraconazole 100 mg daily PO (<13 y or <50 kg); 200 mg daily (>13 y or >50 kg)
Congenital neutropenia (variable recommendation with advent of cytokine therapy)	Penicillin; SMX-TMP
WHIM syndrome	SMX-TMP 5 mg/kg TMP component PO daily

SCID- Severe combined immune deficiency
CGD- Chronic granulomatous disease
WHIM- Warts, Hypogammaglobulinemia, Infections, and Myelokathexis

Kuruvilla M, et al. J Allergy Clin Immunol Pract 2013;1:573-82.

Suggested antibiotic prophylaxis regimens in PIDs

Anhidrotic ectodermal dysplasia with immune deficiency	SMX-TMP 5 mg/kg TMP component PO 3/wk; azithromycin 5 mg/kg PO 3/wk (alternate days); acyclovir 20 mg/kg/dose 3 times a day PO divided 3-4/d; fluconazole 6 mg/kg/d daily PO
TLR defects, IRAK4 and Myd88	SMX-TMP 5 mg/kg TMP component PO daily and/or penicillin V
Mendelian susceptibility to mycobacterial disease	Azithromycin; clarithromycin
Complement deficiency	Penicillins (in the setting of recurrent infections)
Hyper-IgE syndrome	SMX-TMP; cloxacillin (typically for SMX-TMP failures); itraconazole; voriconazole (typically for secondary prophylaxis)
Wiskott-Aldrich syndrome	SMX-TMP 5 mg/kg TMP component PO 3/wk; penicillin V 125 mg (<5 y) to 250 mg (>5 y) PO twice daily (after splenectomy)
DiGeorge syndrome (not required in most instances)	SMX-TMP 5 mg/kg TMP component PO 3/wk

TLR: Inborn errors of Toll Like Receptor pathways:
IRAK4: IL-1 receptor-associated kinase 4
MyD88: Myeloid differentiation primary response gene (88)

Kuruvilla M, et al. J Allergy Clin Immunol Pract 2013;1:573-82.

Antibiotic prophylactic regimens studied in syndromes with recurrent infections

Disease process	Regimens studied
Recurrent AOM	Amoxicillin 20 mg/kg once or twice daily, 6 mo
	Sulfisoxazole 50 mg/kg/d, 6 mo
Chronic sinusitis	Erythromycin 250-500 mg twice daily, 12 wk
	Roxithromycin 150 mg daily, 12 wk
	Azithromycin 500 mg weekly, 8-20 wk
CF bronchiectasis	Azithromycin 500 mg 3 times a wk, 6 mo
Non-CF bronchiectasis	Azithromycin 250 mg 3 times a wk, >3 mo
	Erythromycin 250 mg daily, 12 mo
	Azithromycin 500 mg 3 times a wk, 6 mo
	Azithromycin 250 mg daily, 12 mo

Kuruvilla M, et al. J Allergy Clin Immunol Pract 2013;1:573-82

CHRONIC GRANULOMATOUS DISEASE

GENETICS, BIOLOGY AND CLINICAL MANAGEMENT

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Chronic Granulomatous Disease (CGD)

Inherited disorder of the phagocyte NADPH oxidase.

It is a disease of both:

- **Impaired host defense**

  - increased risk for a distinct spectrum of bacterial infections.

- **Dysregulated inflammation**

  - Crohn-like inflammatory bowel disease,
  - Obstructive inflammation of the genitourinary tract,
  - Pneumonitis resembling sarcoidosis

Infections by *Aspergillus species* and other filamentous fungi are the major causes of mortality in CGD

Bacterial infections in CGD

- *Staphylococcus aureus*
- *Burkholderia cepacia*
- *Serratia spp*
- *Nocardia asteroides, N. farcinica*
- *Salmonella spp*
- *Actinomyces spp*
- *Granulobacter bethesdensis*
- *Mycobacterium tuberculosis*
- BCGitis

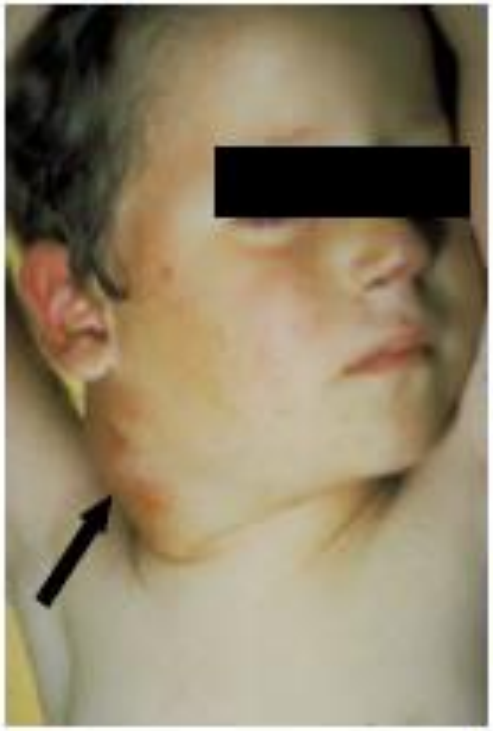
Chronic Granulomatous Disease (CGD)

CGD patients **do not appear to be at increased risk** for several pathogens that are commonly observed in the general population e.g.:

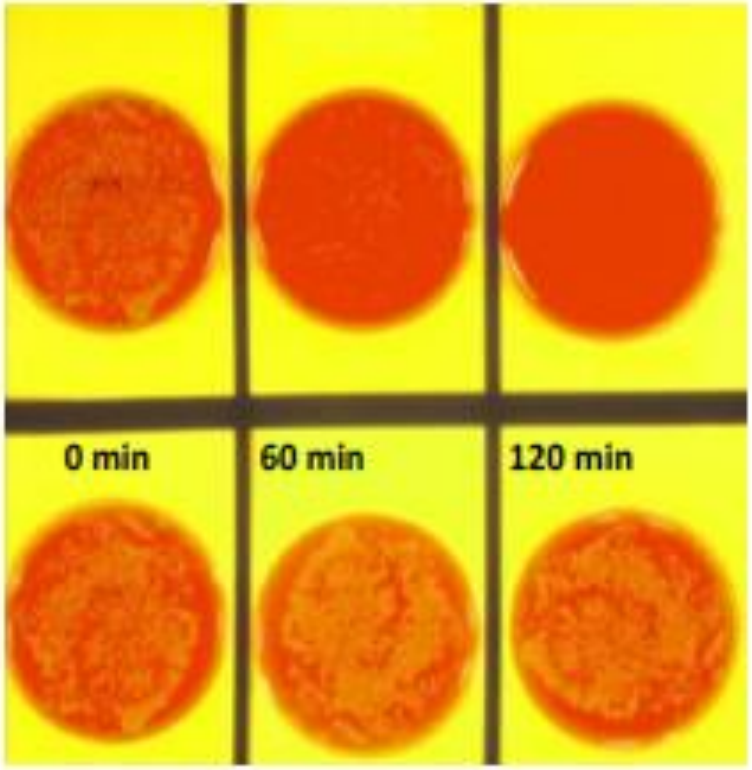
- Streptococcal infections, or
- Opportunistic pathogens that commonly affect other immunocompromised patients, such as:
  - *P. aeruginosa* infections in pts with chemotherapy-induced neutropenia or
  - *Pneumocystis jirovecii* in patients with impaired cellular immunity.

CGD: Defect of Bacterial Killing

Lymph node abscess

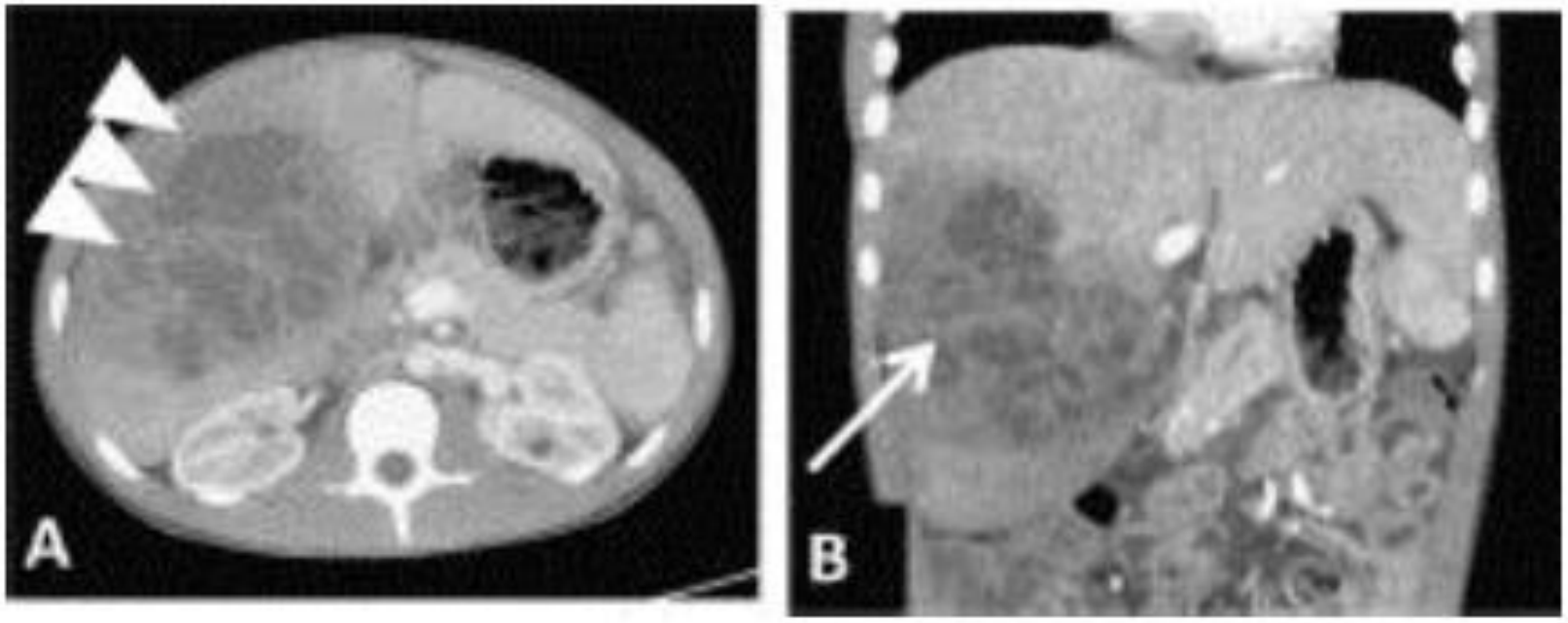


S. aureus killing by neutrophils



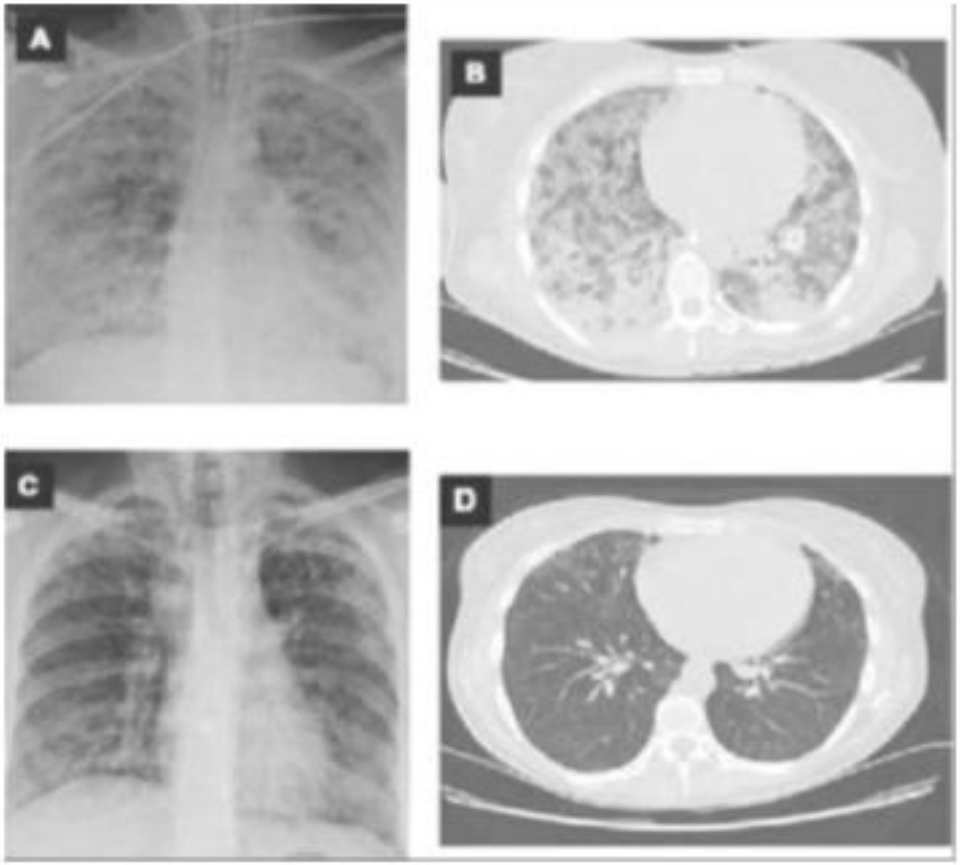
- **Lymph node abscess by *S. aureus* in a CGD patient.**
- **Neutrophil bactericidal assay showing that neutrophils from a CGD patient have defective killing of *S. aureus.***

CGD: Hepatic Abscess



- **CT and MRI imaging of *S. aureus* liver abscesses in an X-linked CGD patient.**
- **The infection responded to IV antibiotics and systemic corticosteroids.**

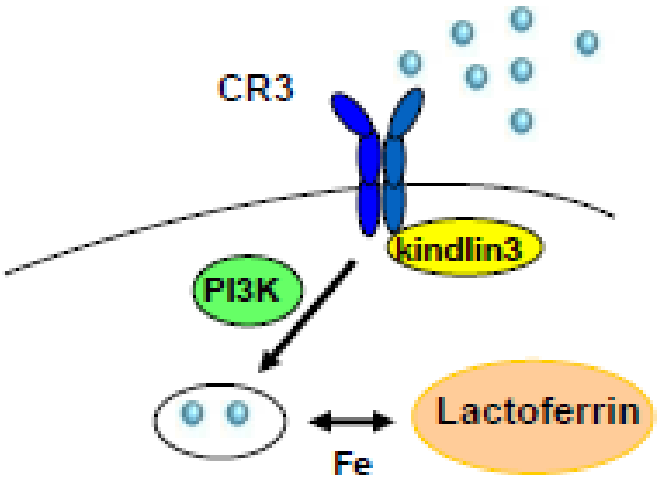
Fulminant Mulch Pneumonitis in CGD



- Chest radiograph (A) and CT scan (B) of a patient with newly diagnosed p47phox-/- CGD with fulminant fungal pneumonitis.
- Thoracoscopic lung biopsy showed intense pyogranulomatous inflammation, with invasive hyphae.
- **Cultures grew *A. fumigatus* and *Rhizopus species.***
- She was treated with **broad spectrum antibacterial and antifungal therapy with corticosteroids** to reduce inflammation.
- Imaging approximately 2 months later (C and D) show resolution of infiltrates.

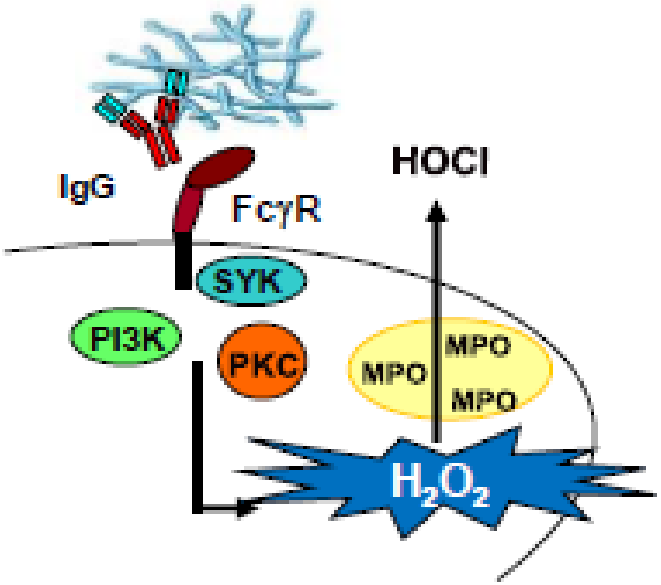
Neutrophil-mediated killing of *Aspergillus hyphae*

Inhibition of *A. fumigatus* germination



Non-oxidative killing mechanisms

Killing of *A. fumigatus* hyphae



NADPH oxidase

• The production of ROS by the NADPH oxidase system and chlorination by MPO into toxic metabolites are involved in the killing of many serum-opsonized bacteria, and some of the stages of Candida (germination) and Aspergillus (hyphae).
• ROS production by the NADPH oxidase system and chlorination by MPO are not involved in the killing of Aspergillus conidia and inhibition of its germination by human neutrophils.
• Neutrophil-mediated killing of *Aspergillus hyphae (but not Candida* hyphae) strictly depends on opsonizing IgGs without the involvement of complement factors or the CD11b/CD18 integrin.

The extreme susceptibility to *Aspergillus* infection in CGD might be twofold

1. **The CGD neutrophils are defective in controlling hyphal growth,**
2. **The CGD monocyte/macrophages are deficient in controlling conidial killing.** Use of anakinra (recombinant IL-1Ra)?

- Excessive inflammatory responses that are characteristic of CGD can also be detrimental to controlling infection.

- **Can blocking of IL-1 be beneficial during infections in pts with CGD?**

  - the use of IL-1 blockade in this setting may need to be a balancing act given the importance of IL-1 in promoting recruitment of neutrophils and other inflammatory cells that contribute to non-oxidative control of pathogens (e.g., IL-1 is crucial for recruitment of the first immune response against lung invading *Aspergillus*).

CGD: European registry

- Analysis of clinical data from 429 European patients with CGD showed that the most frequently cultured pathogens per episode were

  - *Staphylococcus aureus* (30%) and

  - *Aspergillus spp.* (26%)

- *Aspergillus species* (111 cases) was the most common cause of pneumonia.

Van den Berg JM, et al. PLoS ONE 2009; 4: e5234.

Common Severe Infections in CGD - USA

268 pts followed at a single center (NIH) over 4 decades.

Incidence per pathogen:

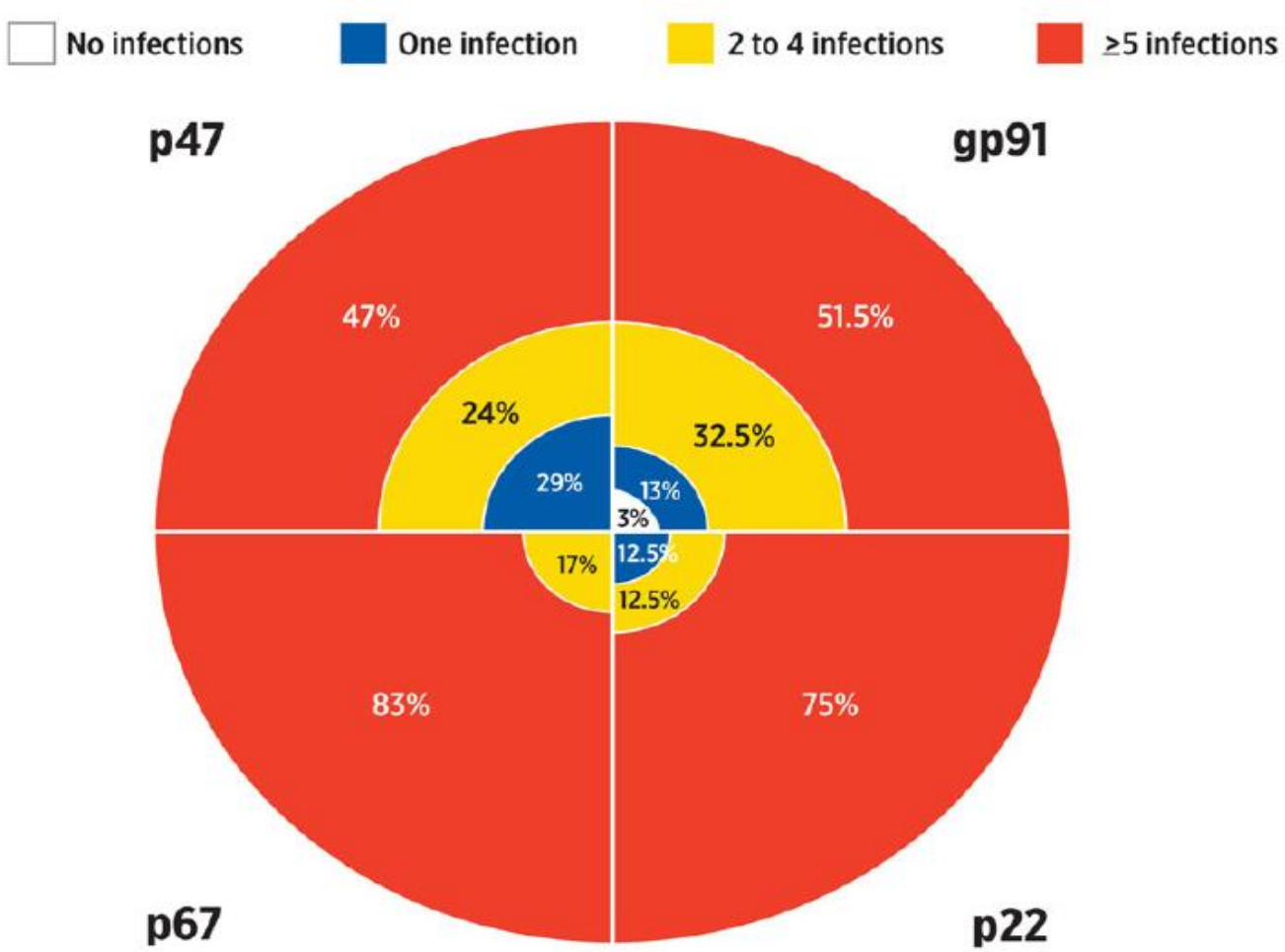
- *Aspergillus*: **2.6** cases /100 patient-years
- *Staphylococcus* (severe infection): **1.44** cases /100 pt-years
- *Burkholderia*: **1.06** cases /100 patient-years
- *Serratia*: **0.98** cases /100 patient-years
- *Nocardia:* **0.81** cases /100 patient-years

Marciano BE, et al. Clin Infect Dis 2015;60:1176–83

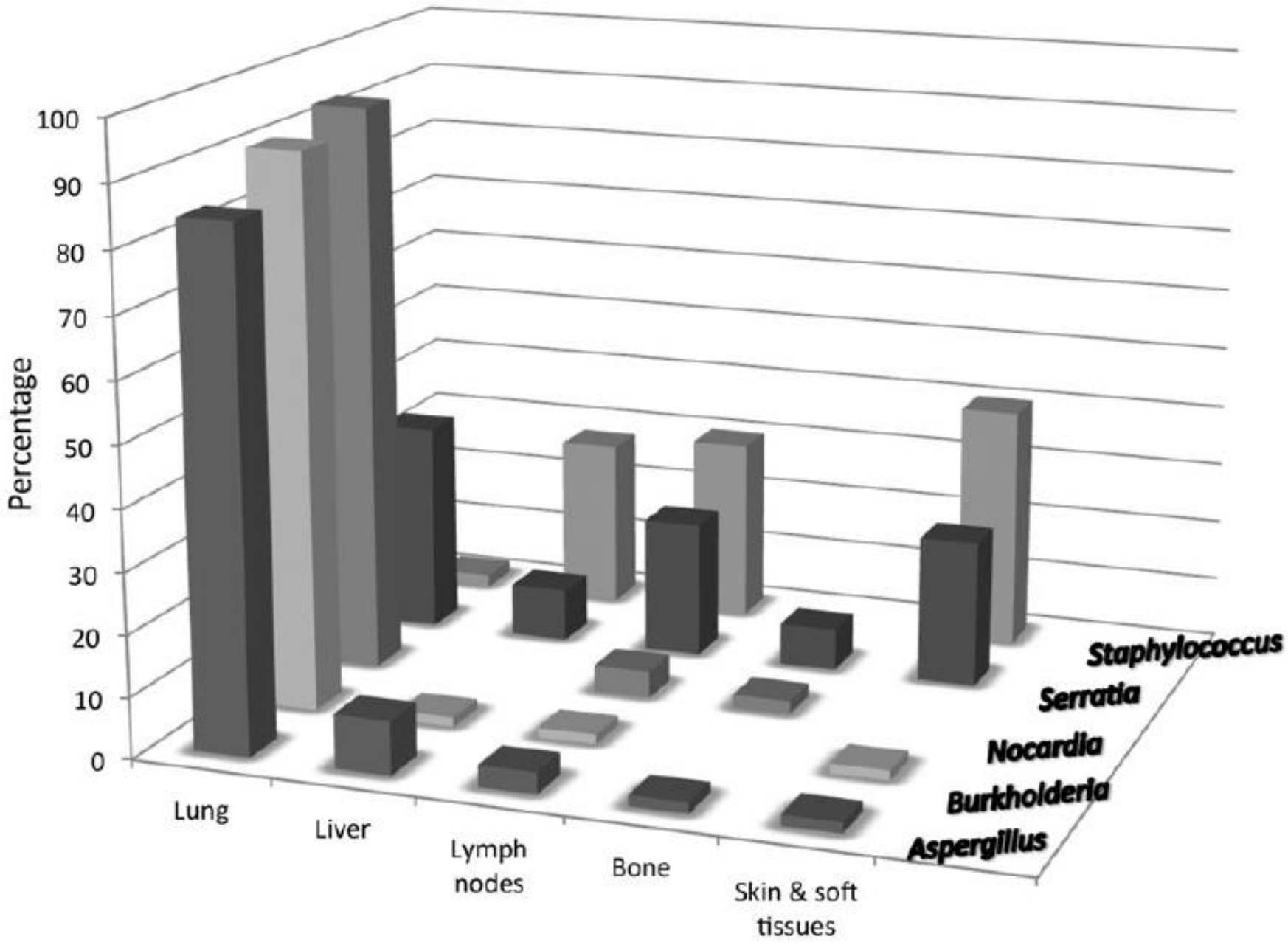
Common severe infections in CGD - USA

- **Lung infection occurred in 87% of patients.**
- **Liver abscess occurred in 32%.**
- *Aspergillus* incidence was 55% in the lower superoxide-producing quartiles (quartiles 1 and 2) but only 41% in the higher quartiles (RR, <0.0001).
- *Aspergillus* and *Serratia* were somewhat more common in lower superoxide producing gp91phox deficiency.

Marciano BE, et al. Clin Infect Dis 2015;60:1176–83



No. patients	No infections	One infection	2 to 4 infections	≥5 infections	Total
p47^{phox}		20	17	33	**70**
gp91	5	24	60	95	**184**
p22^{phox}		1	1	6	**8**
p67^{phox}			1	5	**6**



Marciano BE, et al. Clin Infect Dis 2015;60:1176–83

Mortality in CGD

- The median age at death has increased
  - from 15.53 years before 1990
  - to 28.12 years in the last decade.
- Infection accounts for 80% of the non-transplant-related deaths.
- Fungal infection carried a higher risk of mortality than bacterial infection and was the most common cause of death (55%).
- X-linked patients generally had more severe disease, and this was generally in those with lower residual superoxide production.
- Gastrointestinal complications were **not** associated with either infection or mortality.

Marciano BE, et al. Clin Infect Dis 2015;60:1176–83

CGD – USA: Editorial

- The residual superoxide production is the most important determinant of risk of mortality from infection, rather than the subunit of NADPH oxidase that is affected.
- *Burkholderia* infections recurred more frequently in the $p47^{phox}$ cohort.
- *Aspergillus* infections occurred at an earlier age in the $gp91^{phox}$ cohort.

Gennery AR. Clin Infect Dis 2015;60:1184–5

CGD – USA: Editorial

- **Perhaps the most surprising finding is that 30% of patients did not receive regular antifungal prophylaxi**s.
- Severe invasive infections continue to occur after diagnosis, presumably while taking prophylactic antimicrobial medication.
- **Inflammatory GI symptoms and the use of corticosteroids are not associated with infectious deaths.**

Gennery AR. Clin Infect Dis 2015;60:1184–5

Recurrent and Sustained viral infections in Primary immunodeficiencies

Ruffner MA, et al. Front Immunol. 2017:8:665

Viral infections in Primary immunodeficiencies

- T cell defects are associated with a generally increased predisposition to viral infections.
- All viral infections are typically prolonged in patients with T-cell defects.
- Interferon regulatory factor 7 (IRF7) deficiency is associated with a selective susceptibility to influenza.
- **Any patient with prolonged viral infections is at risk for bacterial superinfection.**

Viral infections in primary immunodeficiencies

- **RSV**
- **Influenza**
- **Rhinovirus** (most prevalent during the respiratory season)
- **Coronavirus**
- **Metapneumovirus**

  (increasingly recognized as causing respiratory infections)

Ruffner MA, et al. Front Immunol. 2017:8:665

Viral infections in patients with SCID

- Patients with **SCID** are extremely susceptible to progressive infection with **CMV** as well as other systemic viral infections.
- Infants with suspected SCID should be protected from exposures such as:
  - breast milk,
  - transfusions,
  - live viral vaccines,
  - potentially infected siblings,
  - caregivers

Ruffner MA, et al. Front Immunol. 2017:8:665

EBV susceptibility

Phenotype	Gene defect	Viral susceptibility	Other features
EBV viremia	*ITK*	EBV	Lymphoma
EBV viremia	*MAGT1*	EBV	Lymphoma
EBV viremia	*CD27*	EBV	Low IgG
EBV viremia	*CORO1A*	Many viruses	Lymphoma
EBV HLH	*SH2D1A*	EBV	Lymphoma, dysgammaglobulinemia, and vasculitis
EBV HLH	*XIAP*	EBV	Hypogammaglobulinemia
EBV lymphoma	*MCM4*	EBV, CMV	Malignancy, short stature, adrenal insufficiency
Primary familial HLH	*PRF1*, *UNC13D*, *STX11*, *STXBP3*	EBV, CMV, others	
Pigmentary dilution with HLH	*LYST*, *RAB27A*, *AP3B1*, *BLOC1S6*	EBV, CMV, others	Pigmentary dilution
EBV susceptibility with broad infectious susceptibility	Leaky SCID, most combined immunodeficiencies, *WASP*, *WIPF1*, *PLCG2*, *PRKCD*, *ORAI1*, *STIM1*, *IKBKG*, *CASP8*, *STAT1* GOF, *DOCK8*, *GATA2*	Many viral susceptibilities	Gene dependent

GOF, gain of function; LOF, loss of function; EBV, Epstein–Barr virus; HLH, hemophagocytic lymphohistiocytosis; CMV, cytomegalovirus; SCID, severe combined immune deficiency; IgG, immunoglobulin G.

Ruffner MA, et al. Front Immunol. 2017:8:665

Management of systemic viral infections

- For CMV, therapy is often begun with ganciclovir or valganciclovir.
- Foscarnet may be added if the virus is resistant or progressive in spite of adequate ganciclovir.
- Bone marrow toxicity from ganciclovir may also require a change to foscarnet.
- EBV in some cases is treated with rituximab to eliminate one important reservoir of virus

Ruffner MA, et al. Front Immunol. 2017:8:665

Hemophagocytic lymphohistiocytosis - HLH

- HLH can occur without an underlying PID, and thus genetic analysis is often central to the management.
- Nearly always an underlying PID will require HSCT as definitive therapy.
- HLH due to uncommon infections such as:

  - *Leishmania*,
  - Influenza viruses, and
  - Arboviruses

  will not require HSCT.

bjh review

Severe Epstein–Barr virus infection in primary immunodeficiency and the normal host

Austen J. J. Worth,[1,2] Charlotte J. Houldcroft[3] and Claire Booth[1,2]

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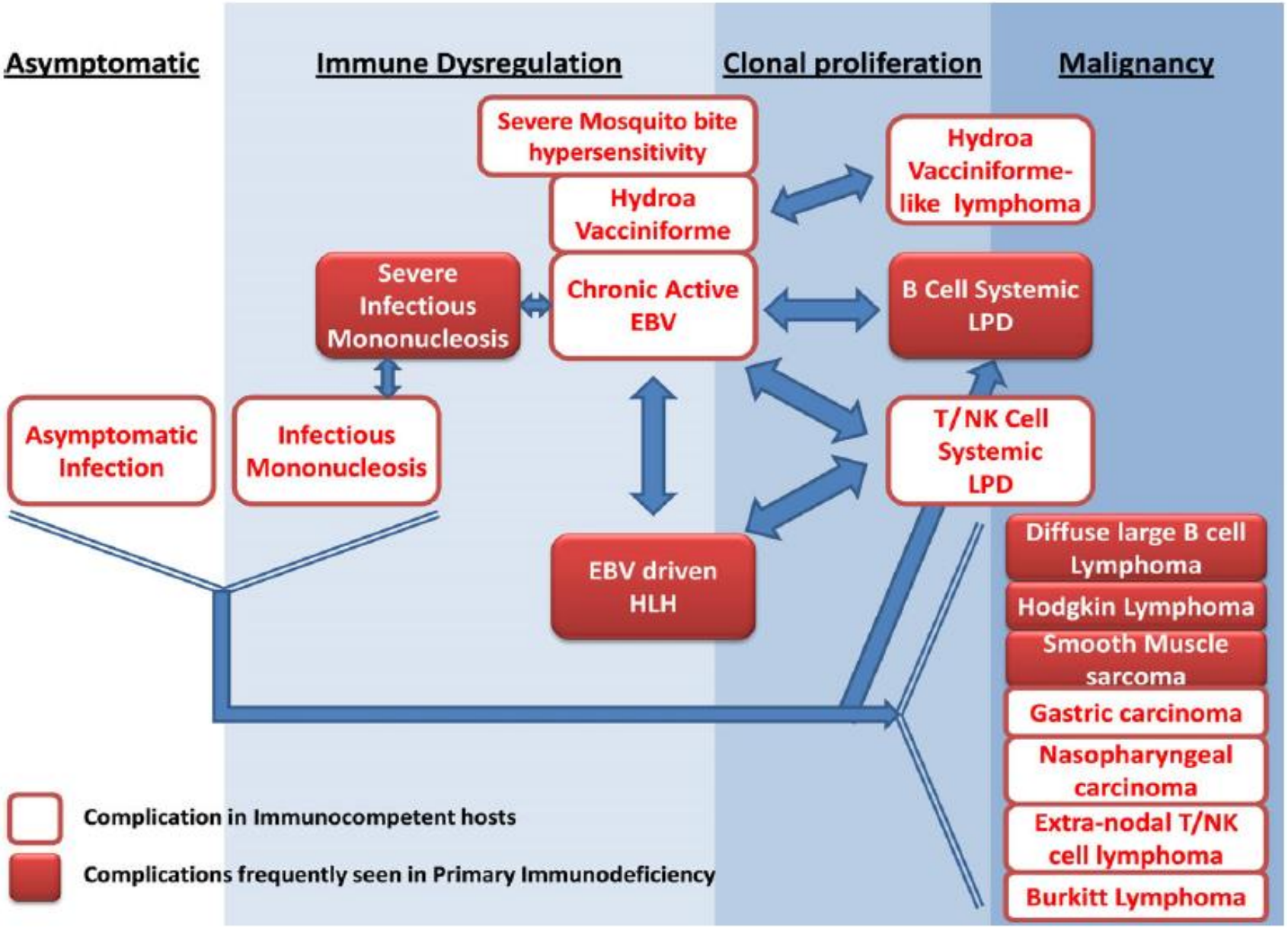
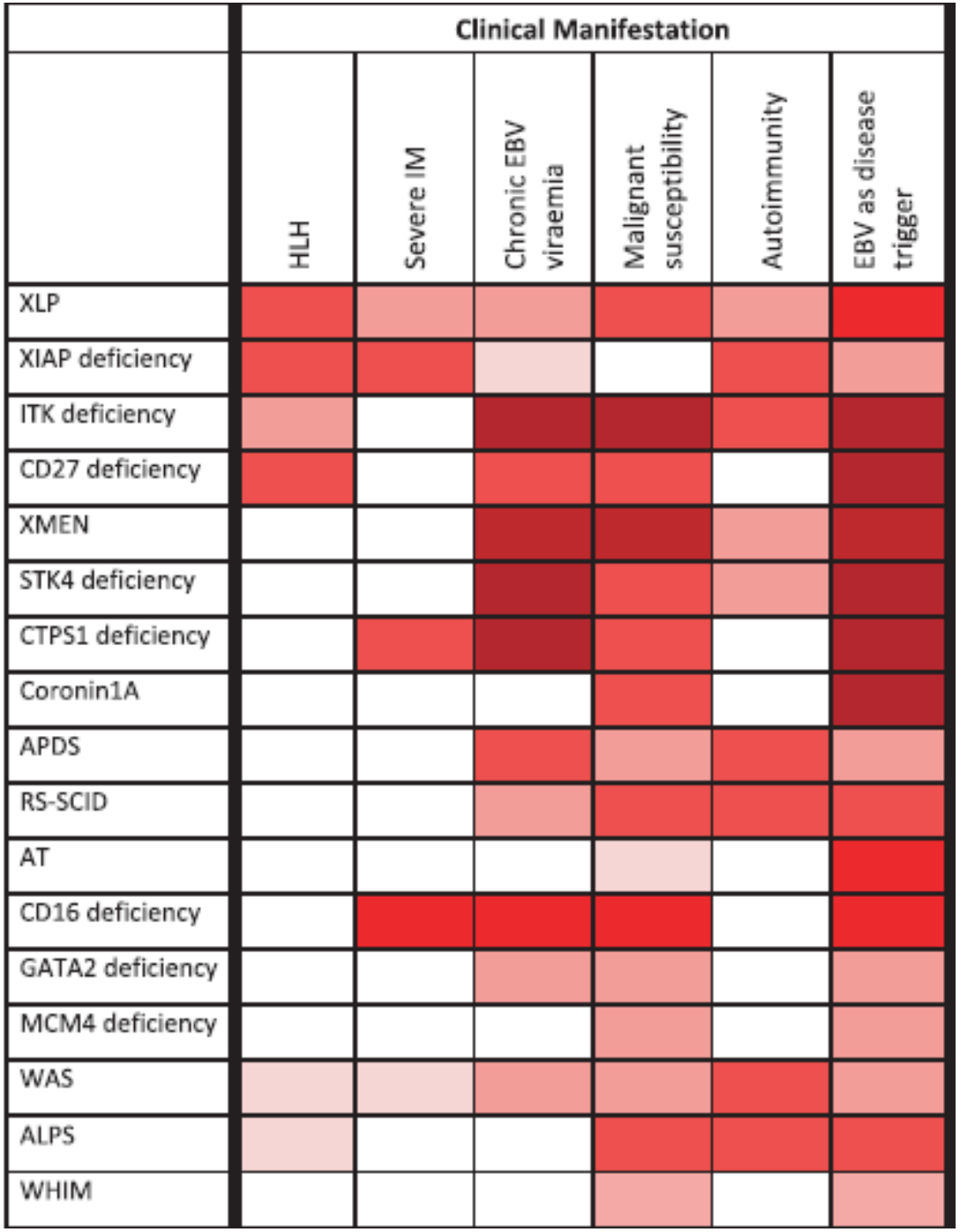
Worth AJJ, et al. Br J Haematol 2016. doi: 10.1111/bjh.14339

Clinical manifestations of EBV infection



Worth AJJ, et al. Br J Haematol 2016 doi: 10.1111/bjh.14339

Severe EBV infection in PIDs



Frequency

	>75% patients
	25 – 75% patients
	<25% patients
	Sporadic cases
	Not described

Worth AJJ, et al. Br J Haematol 2016
doi: 10.1111/bjh.14339

Chronic viral skin infections in primary immunodeficiency

Ruffner MA, et al. Front Immunol. 2017:8:665

Cutaneous manifestations in PIDs

- Cutaneous manifestations are common in PIDs.
- **As many as two-thirds of the patients have cutaneous manifestations at some point**

  - Atopy,
  - Infection,
  - Inflammatory lesions

  have all been described, and there may be interplay between the features.
- Awareness of common skin infections is important both to aid in the early diagnosis and also in the treatment of potentially life-threatening infections that can begin in the skin.

Ruffner MA, et al. Front Immunol. 2017:8:665

Bacterial infections of the skin

- Bacterial infections are one of the most common findings in PIDs.
- **Folliculitis, abscesses, and impetigo are typical in neutrophil defects.**
- A significant subset of PIDs diagnoses is associated with fungal infections.
- Chronic mucocutaneous candidiasis is most often due to defects that affect the Th17 cell production or function.

Viral infections of the skin

- Viral infections of the skin are not nearly as common but are much more suggestive of PIDs.
- **Severe herpes infections and papillomavirus are particularly characteristic of PID and can become the most notable feature in a patient.**
- Chronic herpes virus and papillomavirus, in turn, predispose to cutaneous carcinoma and surveillance becomes important for this evolution.

Gastrointestinal (GI) viral infections

- Chronic diarrhea (>6 weeks) is a frequent finding in PID patients.
- Given that the etiologies of chronic diarrhea in immunodeficient patients can be diverse, it is important to first distinguish if the diarrhea is
  - infectious,
  - malabsorptive, or
  - inflammatory

Gastrointestinal (GI) viral infections

- **Adenovirus, enterovirus,** and **rotavirus** have been isolated from single PID patients with chronic diarrhea, and the true incidence is not known.
- An important consideration is that SCID has been associated with susceptibility to the live rotavirus vaccine.
- CVID and agammaglobulinemia can rarely have prolonged asymptomatic shedding of vaccine-strain polio following immunization with live-attenuated oral polio vaccine.

Norovirus

- In a series of pediatric patients with:
  - SCID,
  - major histocompatibility complex II deficiency,
  - CD40L deficiency, and
  - agammaglobulinemia

  norovirus was the most frequently (20.6%) isolated virus
- **Norovirus shedding can be prolonged in the stool of patients.**

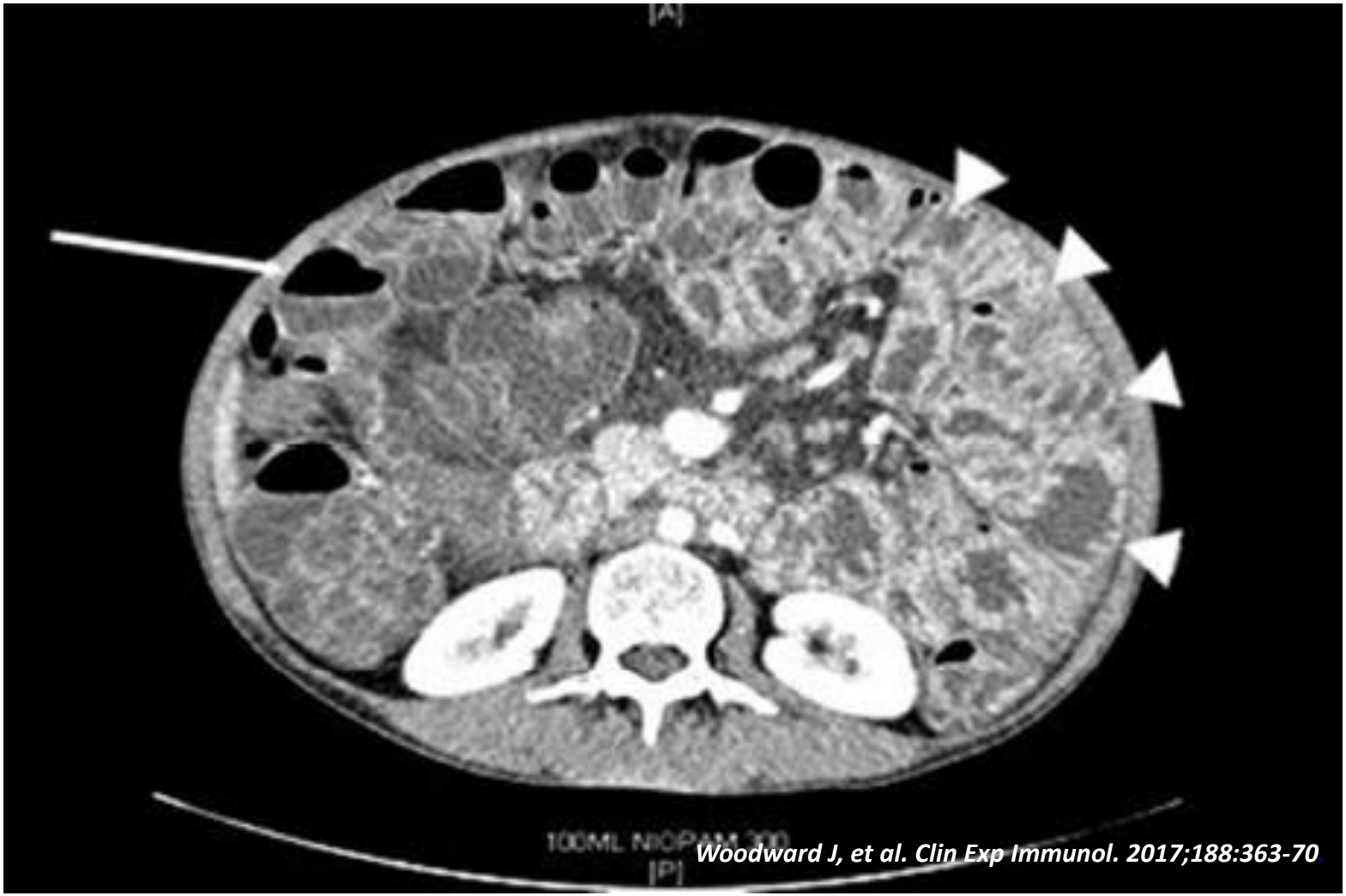
Frange P, et al. J Infect Dis 2012;206:1269–74.

Chronic Norovirus infection and CVID

- A subset of patients with CVID experience a severe Norovirus-associated enteropathy leading to intestinal villous atrophy and malabsorption.
- Symptomatic infection of up to 8 years has been demonstrated with clinical and histological recovery on viral clearance.
- Although oral immunoglobulins and nitazoxanide have been used to treat Noroviral infections associated with immunosuppression, **Ribavirin** is the only agent to date that has been linked to viral clearance in the Noroviral enteropathy associated with CVID.

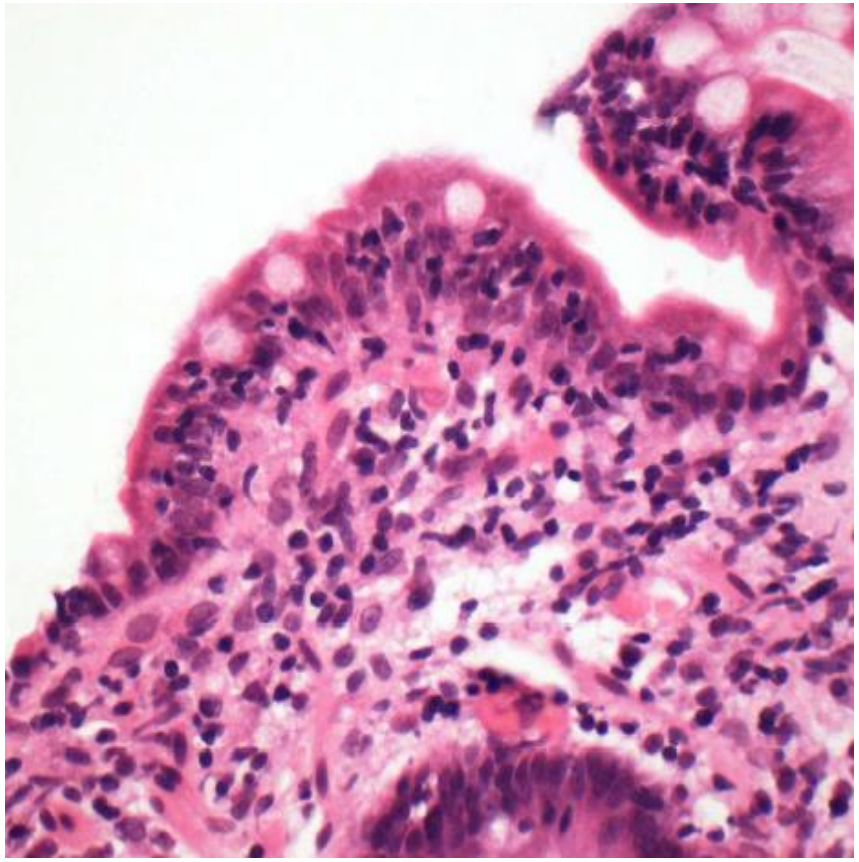
Woodward J, et al. Clin Exp Immunol. 2017;188:363-70.

Abdominal cross sectional contrast-enhanced CT image from a patient with longstanding chronic Norovirus infection with CVID

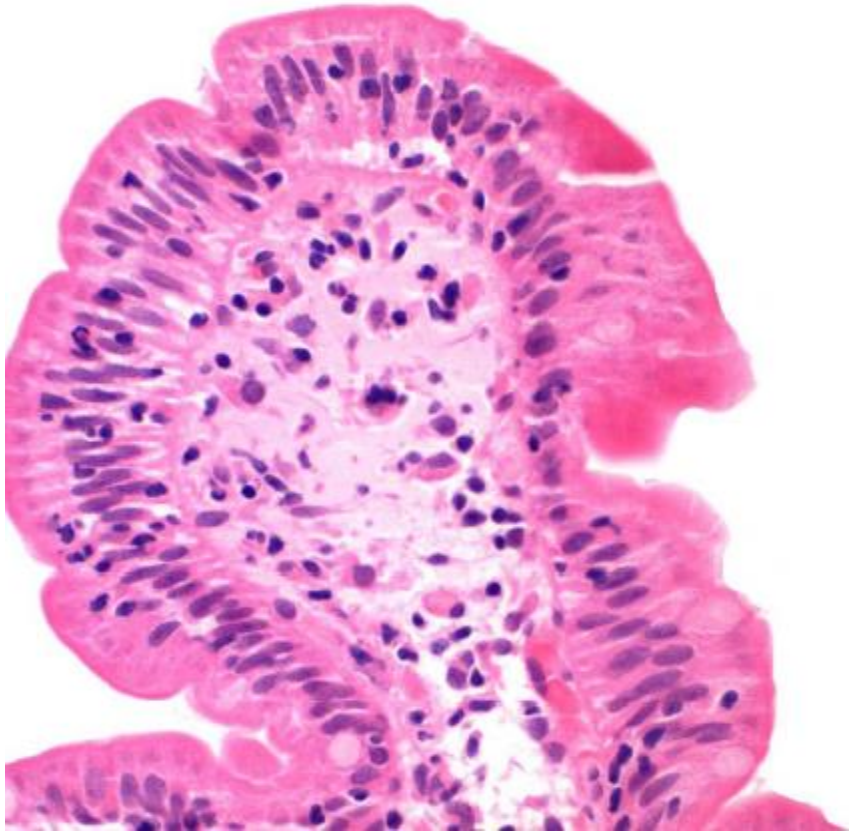


Woodward J, et al. Clin Exp Immunol. 2017;188:363-70

Small bowel loops appear thickened with hyperenhancement of the mucosa (arrowheads), representing a pan-enteritis of the small intestine in contrast to the normal appearance of the colon (arrow)



- Duodenal biopsy in patient with CVID and chronic Norovirus infection (H&E stain, x40).
- Norovirus RNA was detected by PCR in stool and also from the duodenal biopsy specimen.
- Marked villous atrophy is apparent with a chronic inflammatory infiltrate in the lamina propria (lacking plasma cells in view of the immunodeficiency).
- The enterocytes are reduced in height and vacuolated.



- The same patient following Norovirus clearance with a prolonged course of Ribavirin (H&E stain, x40).
- Note that the inflammatory infiltrate in the lamina propria has resolved,
- There is restitution of villous architecture and the enterocytes are columnar.

Woodward J, et al. Clin Exp Immunol. 2017;188:363-70.

Viral family	Virus	Increased susceptibility in which PID	Other features
Papillomaviridae	HPV	Ataxia telangiectasia; *DOCK8*; EV (*EVER1*, *EVER2*, *RHOH*; *LCK*); *GATA2*; Idiopathic T cell lymphopenia; Netherton syndrome; *STK4/MST1*; WHIM (*CXCR4*); WILD, *CARMIL2/RLTPR*, Clouston's syndrome	EV: warts are often flat, appearing as actinic keratosis or seborrhea-like lesions and can have increased susceptibility to unusual HPV strains. No other infectious susceptibility DOCK8, GATA2: also include susceptibility to HSV. Progressive lymphopenia seen
Herpesviridae	HHV8/KSHV	IFNGR1, OX40	Susceptibility to mycobacteria
	HSV	*DOCK8*; *GATA2*; *NEMO*; *STAT1 GOF*; *STK4*; *CXCR4*; Wiskott–Aldrich syndrome (WAS)	*DOCK8*, *NEMO*, *STAT1* GOF: broad infectious susceptibility *CXCR4*: pancytopenia, abnormal neutrophils WAS: thrombocytopenia, eczema
	VZV	*DOCK8*; *GATA2*; *STAT3* GOF; *IFNGR1*; *RHOH*; *STAT1* GOF; *STK4*	*DOCK8*, *NEMO*, *STAT1* GOF: broad infectious susceptibility *CXCR4*: pancytopenia, abnormal neutrophils WAS: thrombocytopenia, eczema
Poxviridae	MCV	*DOCK8*; *GATA2*; *IKBKG*; *STAT1* GOF; *STK4*; *CXCR4*; *CARMIL2/RLTPR*	*DOCK8*, *IKBKG*, *STAT1* GOF: broad infectious susceptibility *CXCR4*: pancytopenia, abnormal neutrophils WAS: thrombocytopenia, eczema
	Orf virus	*STAT1* GOF	Broad infectious susceptibility

GOF, gain of function; LOF, loss of function; HPV, human papilloma virus; HSV, herpes simplex virus; EV, epidermodysplasia verruciformis; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis.

Viral infections of the CNS in PID

- **Atypical herpes simplex encephalitis**
- **CNS enteroviral disease**

Causes of increased susceptibility to HSV encephalitis

TLR3 [autosomal dominant (AD)]
TRIF [autosomal recessive (AR)]
UNC93B1 (AR)
TRAF3 (AD)
TBK1 (AD)
IRF3 (AD)
STAT1 (AR)
IKBKG (XL)

Ευχαριστώ

Αθήνα: 27/4/2018