

MINIREVIEW

Immunity to Microbes: Lessons from Primary Immunodeficiencies[∇]

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Primary immunodeficiency diseases (PIDs) represent a large and heterogeneous group of more than 120 different entities, most of which have now been genetically characterized (77). Increased susceptibility to infections is the predominant manifestation of almost all forms of PID, particularly in infants and children, demonstrating the paramount importance of the immune system in defense against infection. It has long been known that the nature of an immune defect is related to the etiology of an infection. Prime examples are recurrent respiratory infections with pyogenic bacteria in patients with antibody deficiencies, opportunistic infections with fungi and viruses in infants with SCID (severe combined immunodeficiency), *Neisseria meningitidis* infections as a hallmark of defects in late-complement components, recurrent staphylococcal infections in patients with neutrophil disorders, and susceptibility to weakly virulent mycobacterial diseases and to *Salmonella* in patients with deficiencies of the interleukin-12 (IL-12)/IL-23-gamma interferon (IFN- γ) axis. Studies of PID patients have actually contributed to clarification of the anti-infection roles of several mechanisms and components of the immune response, as PIDs offer unique opportunities to link phenotypes to immunological functions and to ascribe various classes of immunity to defenses against different microbes. Thus, studies of agammaglobulinemic patients were crucial in elucidating the role of antibodies in immunity to extracellular bacteria and enteroviruses, as were studies of children with Kostmann's syndrome (congenital severe neutropenia) and chronic granulomatous disease (CGD) in defining the critical role of neutrophils and studies of SCID patients in showing the relevance of T-cell immunity in resistance to intracellular pathogens. More recently, as clinical phenotypes are being mapped to gene defects, respective pathophysiologies can be better understood, often with the help of murine knockout models.

Here we offer an observational approach to host/parasite relationships, based on clinical features of PID patients. After an exhaustive review of the main infectious manifestations of PID patients described in large published series as well as in our own series, we propose a novel classification of PIDs according to the degrees of clinical susceptibility to infectious

agents observed with PID patients, attempting to link selective susceptibility to specific mechanisms and to established genetic defects. Evidence for a causal association between a particular infection and a given PID is available in some cases, but in others, only a small number of patients have been studied. The data were organized in tables that classify susceptibility to each infection as high (when it is a major manifestation of disease), intermediate (when it appears in some cases but not as a rule), and low (when it is seldom seen). We believe that organizing available information in this manner may also be helpful for the physician, whose identification of a given infection may help determine a putative immunodeficiency.

SUSCEPTIBILITY TO EXTRACELLULAR BACTERIAL INFECTIONS

Streptococcus pneumoniae and *Haemophilus influenzae*. *S. pneumoniae* is frequently an infectious agent for PID patients and immature infants, while *H. influenzae* b has become rare among immunocompetent children since a vaccine has been available. The presence of a polysaccharide capsule that impedes phagocytosis is a relevant virulence factor in both cases. Infections usually present in PID patients as recurrent pneumonia, sinusitis, and otitis media and occasionally as arthritis and cellulitis and may be life threatening as septicemia and meningitis. As shown in Table 1, most, if not all, patients with antibody deficiencies are highly susceptible to infections with pneumococci (87), as is true of X-linked (XL) agammaglobulinemia (19, 64, 88), common variable immunodeficiency (CVID), IgG2 deficiency, and anti-polysaccharide antibody deficiency (8, 18, 22, 46, 84, 98). Surprisingly, *S. pneumoniae* has not been frequently isolated from patients with hyper-IgM syndrome, even the type 2 form, in which defects in activation-induced cytidine deaminase (AID) dampen class switch recombination and somatic hypermutation (66, 72, 91, 114). However, as these patients are very prone to recurrent otitis media and sinopulmonary infections, representation of *S. pneumoniae* (and *H. influenzae* b) may be underestimated due to the rarity of microbiological diagnoses in such conditions. For patients with selective IgA deficiency, a higher predisposition to pneumococcal infections is not consistently found (21, 54, 89) except when deficiencies of either IgG2 or anti-capsular antibody production are also present (8, 46, 84).

Patients with deficiencies of the earliest components of the classical complement pathway (C1q, C1r, C1s, C4, and C2), as well as of C3, factors D and I, show increased susceptibility to *S. pneumoniae* and *H. influenzae* b (43, 107), as may also be the

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TABLE 1. Susceptibility of patients with different PIDs to *Streptococcus pneumoniae* and *Haemophilus influenzae* infections

PID with indicated level of susceptibility:		
High	Intermediate	Low
XL-agammaglobulinemia (19, 64, 88)	SCID (105)	Chronic granulomatous disease (1, 15, 113)
CVID (18, 22)	X-linked hyper-IgM syndrome (CD40L deficiency) (66, 114)	Leukocyte adhesion deficiencies (LADs) (97)
IgG2 deficiency (8, 46, 84, 101)	Hyper-IgM type 2 (AID deficiency) (72, 91)	Deficiencies of MAC components (C5-9) and factor H of complement system (43, 107)
Selective anti-polysaccharide antibody deficiency (46)	Selective IgA deficiency (21, 46, 54, 89)	IL-12/IL-23-IFN- γ axis deficiencies (33, 36, 42, 85, 96)
Deficiencies of early components of classical pathway of complement system (C1, C4, C2), C3, factors I and D (43, 107)	Ataxia-telangiectasia syndrome (79)	
IRAK-4 deficiency ^a (23, 38, 61, 70, 86)	MHC-II deficiency (45, 57)	
Defects of NEMO-dependent NF- κ B activation (XL-EDA-ID) (60, 61, 83)	Neutropenias (9, 25)	
Asplenia (48, 99)	Hyper-IgE syndrome (10, 50, 51)	
MHC-I deficiencies (due to TAP-1 or TAP-2 deficiencies) (32, 45, 47)		

^a *H. influenzae* b was not isolated from IRAK-4-deficient patients (61).

case for patients with defects in the mannan-binding lectin pathway (e.g., mannan-binding-associated serine protease 2) (104).

Overwhelming systemic *S. pneumoniae* infections are the main clinical manifestations of congenital asplenia, as is also true when it is associated with other defects (such as Ivemark syndrome) (48, 99). Life-threatening *H. influenzae* infections have also been observed in patients with congenital asplenia (48).

The susceptibility of IL-1 receptor-associated kinase 4 (IRAK-4)-deficient patients to pneumococcal infections is extreme (23, 38, 61, 70, 86), and susceptibility of patients with PIDs due to defects in NF- κ B essential modulator (NEMO)-dependent NF- κ B activation (X-linked anhydrotic ectodermal dysplasia with immunodeficiency [XL-EDA-ID] and other milder phenotypes) (60, 61, 83, 108) is also high but not extreme, as in IRAK-4-deficient patients. This demonstrates the relevance of innate immunity in protection against *S. pneumoniae*. Interestingly, while patients with NEMO defects do not produce antipneumococcal capsular polysaccharide antibodies, some IRAK-4-deficient patients do (108, 110). Patients with inherited NF- κ B-mediated inflammation disorders may fail to show clinical (high body temperature) and laboratorial (leukocytosis, high C-reactive protein levels in serum) signs of inflammation, even in the face of ongoing systemic infections (110).

It is noteworthy that pneumococcal infections are rare with all forms of CGD and even with neutropenias (9, 87, 97, 113) and that they are not a common initial manifestation in SCID infants (11, 12, 105). In the case of SCID infants, infections with opportunistic agents such as *Mycobacterium bovis* BCG (BCG), *Pneumocystis carinii*, *Candida* species, and cytomegalovirus (CMV) occur first, when passively acquired maternal antipneumococcal antibodies still afford protection. Thereafter, administration of broad-spectrum antibiotic therapy following the diagnosis of SCID can prevent the onset of bacterial infections.

The level of susceptibility to *H. influenzae* is very similar to that for *S. pneumoniae* (see Table 1). In contrast to *S. pneumoniae*, *H. influenzae* was not isolated from any of the IRAK-4-deficient patients described by Ku et al. (61) and was associated with only a few cases of NEMO mutations (60, 61).

Interestingly, NEMO patients may produce anti-*H. influenzae* b antibodies at normal levels in sera while remaining unresponsive to *S. pneumoniae* after receiving conjugate vaccines (60).

Studies of PID patients show that protective immunity to *S. pneumoniae* and *H. influenzae* b requires opsonization by IgG2 anti-capsular polysaccharide antibodies and complement, in addition to recruitment of inflammatory mechanisms involving Toll-like receptor (TLR)-dependent-activation of NF- κ B. The spleen plays a crucial role in the clearance of opsonized bacteria from the blood and as the site for T-cell-independent antibody responses to bacteria in marginal zones (59, 111).

Staphylococcus aureus. Despite advances in antimicrobial therapy, *S. aureus* remains a major problem for patients with phagocyte disorders. High susceptibility to staphylococcal infections (Table 2) is observed in patients with (i) defects in microbial killing mechanisms, as in CGD; (ii) phagocyte adhesion defects, as in leukocyte adhesion deficiency (LAD) type 1; (iii) quantitative phagocyte disorders (cyclic and persistent neutropenias); and (iv) composite conditions, as in Chédiak-Higashi syndrome (1, 9, 15, 25, 55, 97, 100, 113). Deep-seated infections in CGD patients are often caused by *S. aureus*, liver abscesses being a hallmark of the disease. Susceptibility to *S. aureus* (Table 2) is also characteristic of hyper-IgE syndrome, defined by the triad of very high levels of IgE in the serum, recurrent skin abscesses (possibly facilitated by widespread scratching of lesions), and pneumonias that often evolve to pneumatocoele formation (10, 50, 51). While hyper-IgE syndrome remains a rare example of a PID with an unknown genetic basis, susceptibility to *S. aureus* has been related to abnormal neutrophil function, as defective chemotaxis was observed in some patients, yet phagocytosis, bacterial killing, and oxidative metabolism are all conserved.

In regard to CGD patients, it is noteworthy that the most frequent etiological agents isolated from their lesions are catalase-positive microorganisms, both bacteria (*S. aureus*, *Burkholderia cepacia*, *Serratia marcescens*, and *Nocardia* species) and fungi (*Aspergillus fumigatus* and *Aspergillus nidulans*), but they do not present abnormal susceptibility to catalase-negative pathogens (e.g., *S. pneumoniae*, *Candida* species, or *P. carinii*) (1, 15, 97, 100, 113). The hitherto-accepted view is that the catalase in microorganisms could be a virulence factor that

TABLE 2. Susceptibility of patients with different PIDs to *Staphylococcus aureus* infections

PID with indicated level of susceptibility:		
High	Intermediate	Low
Hyper-IgE syndrome (10, 50, 51, 65)	SCID (105)	Complement deficiencies (43, 107)
Chronic granulomatous disease (1, 15, 113)	Defects of NEMO-dependent NF- κ B activation (EDA-ID) (60, 61, 83)	Asplenia (48, 99)
Neutropenias (9, 25)	XL-hyper-IgM (CD40L deficiency) (66, 114)	IL-12/IL-23-IFN- γ axis deficiencies (33, 36, 42, 96)
Leukocyte adhesion deficiencies (LADs) (97)	MHC-II deficiency (45, 57)	
Chédiak-Higashi syndrome (55)	Wiskott-Aldrich syndrome (106)	
IRAK-4 deficiency (61, 86)		
XL- and AR-agammaglobulinemia (19, 40, 52, 64, 67, 88)		
IPEX syndrome (80, 112)		

further impairs defective microbial killing of CGD cells. However, recent experimental data suggest that the critical defect in CGD patients is a failure to activate phagocyte granular proteases and that generation of reactive oxygen species and myeloperoxidase activity are not by themselves sufficient to kill engulfed microorganisms (93). Thus, the role of microbial catalase as a virulence factor within phagolysosomes is still a controversial issue meriting further investigation with humans.

S. aureus is a frequently occurring pathogen for patients with IRAK-4 deficiencies (26, 61) but has rarely been isolated from patients with XL-EDA-ID associated with NEMO defects (60, 61, 83).

Somewhat surprisingly, *S. aureus* and *Pseudomonas aeruginosa* are among the etiological agents most frequently isolated from XL-agammaglobulinemia patients (19, 64, 65, 88). Although episodes of neutropenia are not rare in either XL- or autosomal recessive (AR)-agammaglobulinemic patients, there is no clear association between low neutrophil counts and *S. aureus* or *Pseudomonas* species infections (40, 52, 64, 67). These findings demonstrate that specific antibodies are relevant for protection against *S. aureus* and *Pseudomonas* species, in addition to the crucial role of neutrophil activation by the TLR-IL-1/IRAK-4/NEMO pathway. Antibodies may contribute to resistance by neutralizing bacterial exotoxins or exoenzymes that are highly destructive for tissues, as seen in scalded-skin syndrome. Antibodies may also act by opsonization, as the presence of a polysaccharide capsule in most *S. aureus* isolates could require antibodies for opsonization.

Staphylococcal species (and enterococci) have been described as frequent causes of septicemia and death in infants with an immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome, due to mutations in the Foxp3 gene (80, 112). Foxp3 is essential for the development of regulatory T cells. Since most IPEX patients present conserved neutrophil counts, immunoglobulin levels, and antibody production capacity, it is unclear whether high susceptibility results directly from the genetic defect or is secondary to the very frequent skin and gut lesions or even to immunosuppressive therapy. On the other hand, it is striking that staphylococcal infections are frequent and severe with two PIDs in which deficits of regulatory T cells are either demonstrated (IPEX) or suspected (hyper-IgE syndrome). This has also been a frequent finding with scurfy mice (J. Demengeot, personal communication), but a putative protective effect of a "suppressor" cell type will remain paradoxical as long as the respective molecular basis is not established.

Neisseria meningitidis. High susceptibility to *N. meningitidis* is a very peculiar manifestation and is usually the only clinical problem of patients with deficiencies of the membrane attack complex (MAC; C5 to C9 components of the complement system) (43, 107). MAC-deficient patients have an estimated 5,000- to 10,000-fold-greater risk of contracting meningococcal disease than controls, and 50 to 60% actually suffer recurrent episodes (44). Systemic *N. gonorrhoeae* infections in C6- and C8-deficient individuals have been sporadically described. Surprisingly, susceptibility to *Neisseria* species is selective, and these patients are not particularly prone to other infections. Complement-dependent bacteriolysis is thus critical for defense against *Neisseria* species, while it is likely a redundant mechanism in protection against other microbes, including gram-negative bacteria that are lysed by complement in vitro. Patients with properdin deficiencies also present high susceptibility to meningococcal infections, and *Neisseria* species infections in patients with deficiencies of C3 and the alternative pathway (factors D, H, and I) have been described (43, 107). In contrast, patients with deficiencies of the early components of the classical pathway (C1q, C1r/C1s, C4, and C2) do not present particular susceptibility to *Neisseria* species.

Recently, Smirnova et al. (102), studying a large group of patients with meningococcal disease, found a strong association with rare heterozygous missense mutations of TLR4 (Toll-like receptor 4), but only one case of *N. meningitidis* infection was found among 13 IRAK-4 deficient patients, in agreement with the fact that TLR4 activation involves intracellular signaling pathways other than IRAK-4 (61).

SUSCEPTIBILITY TO INTRACELLULAR BACTERIAL INFECTIONS

As shown in Table 3, few PIDs impart susceptibility to mycobacteria, but patients with mycobacterial infections characteristically develop severe, disseminated, sometimes life-threatening diseases, even with low-virulence strains such as BCG and environmental nontuberculous mycobacteria (NTM) (1, 11, 12, 15, 33, 63, 94, 96, 97, 103, 105). There are differences in susceptibility to mycobacteria with different PIDs. In patients with IL-12/IL-23-IFN- γ axis defects, BCG and NTM are the most frequently identified, but there are also reports of *Mycobacterium tuberculosis* infections in this group (14, 33, 36, 42, 85, 96). In CGD, BCG and *M. tuberculosis* have been isolated from patients living in areas where these diseases are endemic (1, 15, 63, 65, 74), whereas BCG has been the pre-

TABLE 3. Susceptibility of patients with different PIDs to mycobacterial infections

PID with indicated level of susceptibility:		
High	Intermediate	Low
Defects of IL-12/IL-23-IFN- γ axis ^{a,b,c} (14, 33, 36, 42, 85, 96)	X-linked hyper-IgM syndrome (CD40L deficiency) (66)	Predominantly antibody deficiencies (19, 21, 22, 64, 67, 72, 91)
All SCID types ^a (11, 12, 105)		Complement deficiencies (43, 107)
Idiopathic CD4 lymphocytopenia ^b (103)		Neutropenias (9, 25)
Defects of NEMO-dependent NF- κ B activation (X-EDA-ID) ^b (83)		Leukocyte adhesion deficiencies (LADs) (97)
Chronic granulomatous disease ^{a,c} (1, 15, 63, 65, 74)		MHC-I deficiencies (32, 47, 69, 73, 119)
		IRAK-4 deficiency (23, 38, 61, 70, 86, 110)
		Asplenia (48, 99)

^a The most frequently isolated mycobacterium with this PID was BCG.

^b The most frequently isolated mycobacterium with this PID was NTM.

^c The most frequently isolated mycobacterium with this PID was *M. tuberculosis*.

dominant mycobacterium isolated from SCID patients (11, 12, 105) and NTM is the most common in children affected by NEMO defects (83) and idiopathic CD4 lymphocytopenia (45, 103). These differences may result from both different degrees of exposure and distinct defective resistance mechanisms.

Defects in the IL-12/IL-23-IFN- γ axis, grouped as Mendelian susceptibility to mycobacteria disease, are characterized by selective susceptibility to mycobacteria and *Salmonella* species. They include, in order of frequency, defects of (i) IFN- γ R1, which binds IFN- γ onto macrophages; (ii) IFN- γ R2, the signaling chain of the same receptor; (iii) the common p40 subunit of IL-12 and IL-23; (iv) the common β 1 receptor subunit of IL-12 and IL-23; and (v) the signal transducer and activator of transcription 1 (STAT-1) (33, 42, 85, 96). In addition to disseminated BCG infections, the two known unrelated homozygous patients with STAT-1 defects are prone to viral infections, certainly due to defects of the IFN- α and IFN- β signaling pathways, as discussed below (36).

Patients with all types of SCID are very susceptible to BCG, disseminated disease being observed in approximately one-third of vaccinated children (11, 12, 94, 105). Thus, the practice of compulsory administration of BCG early in life, as performed in many countries, represents a relevant risk for these infants.

Patients with three other PIDs also show marked susceptibility to NTM, *Mycobacterium avium* in particular, but not to BCG. They are idiopathic CD4 lymphocytopenia (103), XL-EDA-ID, and NEMO hypomorphic mutations (61, 83), the

latter two result in inability to produce IL-12 and tumor necrosis factor alpha in response to CD40L signaling (96, 108).

Mycobacterial infections are rare among American CGD patients (113) but occur frequently in countries where there is a high prevalence of tuberculosis and where BCG is compulsory. A high proportion of CGD patients from Iran, Hong Kong, and Taiwan had severe recurrent *M. tuberculosis* and BCG infections (63, 65, 74). Brazilian CGD patients are also highly susceptible to BCG, although no case of tuberculosis has been identified (1, 15).

These observations indicate that protective immunity to mycobacteria relies on the IL-12/IL-23-IFN- γ axis, possibly mediated by enhanced respiratory burst and intracellular killing in phagocytes following the production of IFN- γ by CD4⁺ T lymphocytes in response to IL-12/IL-23 secreted by infected macrophages, processes that are known to involve NF- κ B signaling.

SUSCEPTIBILITY TO FUNGAL INFECTIONS

Levels of susceptibility of PID patients to fungi are shown in Tables 4 and 5. *Candida* species and *P. carinii* are the most common fungi that infect pediatric patients, as they colonize infants early in life. In contrast, exposure to environmental *Aspergillus* species, *Histoplasma* species, and *Cryptococcus neoformans* occurs later in life and is more sporadic.

Infants with SCID are very susceptible to fungal infections, oral candidiasis and *P. carinii* interstitial pneumonia being the

TABLE 4. Susceptibility of patients with different PIDs to *Pneumocystis carinii* infections

PID with indicated level of susceptibility:		
High	Intermediate	Low
All SCID types (11, 12, 105)	XL agammaglobulinemia (19, 64, 88)	Predominantly antibody deficiencies (except some cases of XLA and CVID) (21, 46, 84, 91, 101)
MHC-II deficiency (45, 57)	CVID (22)	MHC-I deficiencies (TAP-1 and TAP-2 defects) (32, 47, 69, 73, 119)
ZAP 70 deficiency (37, 45)	Wiskott-Aldrich syndrome (106)	Complement deficiencies (43, 107)
Idiopathic CD4 lymphocytopenia (45, 103)	XL-EDA-ID (NEMO defects) (61, 83)	IL-12/IL-23-IFN- γ axis deficiencies (33, 36, 42, 85)
X-linked hyper-IgM syndrome (CD40L deficiency) (65, 66, 114)	Hyper-IgE syndrome (50, 51)	Neutropenias (9, 25)
AR-hyper-IgM type 3 (CD40 deficiency) (68)		Chronic granulomatous disease (1, 15, 113)
		Chédiak-Higashi syndrome (55)
		IRAK-4 deficiency (23, 38, 61, 70, 86, 110)
		Ataxia-telangiectasia syndrome (79)
		Asplenia (48, 99)

TABLE 5. Reported clinical associations between PIDs and different fungal infections

PID associated with indicated fungus:			
<i>Candida</i>	<i>Aspergillus fumigatus</i>	<i>Cryptococcus neoformans</i>	<i>Histoplasma capsulatum</i>
APECED (2, 6)	Chronic granulomatous disease (3, 15, 113)	Idiopathic CD4 lymphocytopenia (103)	Idiopathic CD4 lymphocytopenia (103)
Other forms of chronic mucocutaneous candidiasis (45)	Hyper-IgE syndrome (3, 50)	Hyper-IgE syndrome (10, 50)	XL hyper-IgM syndrome (CD40L deficiency) (114)
Hyper-IgE syndrome (10, 50, 65)	SCID ^a (117)		Hyper-IgE syndrome (50)
SCID (11, 12, 105)	Leukocyte adhesion deficiencies (LADs) (97)		Autosomal dominant form of IFN- γ receptor 1 deficiency ^a (118)
MHC-II deficiency (57)	Idiopathic CD4 lymphocytopenia (45)		
Idiopathic CD4 lymphocytopenia (103)			
XL-EDA-ID (defects of NEMO) (60, 83)			
Myeloperoxidase deficiency in diabetic patients (97)			
Wiskott-Aldrich syndrome (106)			

^a Only one case has been reported.

most frequently diagnosed (11, 105). No significant differences in susceptibility to infections are reported with the various SCID types, all characterized by severely reduced numbers or absence of functional T cells and usually classified according to lymphocyte phenotype: (i) T⁻B⁺NK⁻ (X-linked γ chain, Janus kinase 3 [JAK-3], and CD45 deficiencies), (ii) T⁻B⁺NK⁺ (IL-7R α and CD3 δ deficiencies), (iii) T⁻B⁻NK⁺ (recombination activating gene 1 [RAG-1] and RAG-2 deficiencies, Omenn's syndrome, and *Artemis* defects), and (iv) T⁻B⁻NK⁻ (adenosine deaminase deficiency and reticular dysgenesis) (11, 45, 77, 105). Patients with ZAP-70 (zeta-associated protein-70) deficiency (decreased CD8, normal numbers of functionally deficient CD4) also frequently suffer from *P. carinii* and *Candida* species infections (37, 45). Although not included in the SCID group, patients with major histocompatibility complex class II (MHC-II) deficiencies ("bare lymphocyte syndrome," characterized by defective expression of HLA class II, variable reduction of HLA class I expression, decreased levels of CD4⁺ cells, and normal/elevated levels of CD8⁺ cells) are also highly susceptible to *P. carinii* pneumonia (45, 57), while idiopathic CD4 lymphocytopenia imparts elevated susceptibility to fungal infections (45, 103) (Tables 4 and 5).

Patients with either CD40L (X-linked or type 1 hyper-IgM syndrome) or CD40 (type 3 hyper-IgM syndrome) defects are very prone to *P. carinii* pneumonia (66, 68, 114), but patients with hyper-IgM syndrome type 2 (AID mutations) show normal resistance to all fungi, as expected (72, 91).

Recent reports described patients with defects of the IL-12-IL-23-IFN- γ axis with disseminated fungal infections. An autosomal dominant form of IFN- γ receptor 1 deficiency (118) and a homozygous missense mutation in the gene encoding IL-12/IL-23R β 1 (29) presented recurrent disseminated *Histoplasma capsulatum* osteomyelitis and a severe form of *Paracoccidioides brasiliensis* infection, respectively. These cases suggest a causal link between mycosis and the defect of the IL-12/IL-23-IFN- γ axis, reinforcing the notion that the spectrum of susceptibility in such patients is broader than originally described.

These data highlight the pivotal function of CD4⁺ T lymphocytes in protection against *P. carinii* and other fungal infections, thus confirming observations of patients with human immunodeficiency virus infection, and indicate a critical role of CD40-CD40L interactions in the mechanisms of immunity. This contrasts with the generally conserved resistance to *P.*

carinii and other fungi in severe phagocytic defects, with the notable exception of catalase-producing *Aspergillus* species. In addition, defects of the IL-12/IL-23-IFN- γ axis are conspicuous by their lack of marked susceptibility to fungus infections. In other words, it is very surprising that resistance to intracellular infections shows such a great disparity in mechanisms, as seen by the relative incidence of *Pneumocystis* or *Mycobacteria* species infections with several PIDs.

The mechanisms responsible for the selective susceptibility to *Candida* species of patients with APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) due to *AIRE* (autoimmune regulator gene) mutations and with as-yet-uncharacterized diseases such as chronic mucocutaneous candidiasis and hyper-IgE syndrome, are not fully understood (2, 6, 45, 50, 51). Interestingly, however, as discussed above for *S. aureus*, defects of regulatory T cells are suspected in these conditions.

Patients with both X-linked and AR forms of chronic granulomatous disease are typically susceptible to *Aspergillus* species infections (Table 5) (3, 97, 113). *Aspergillus* species, together with *S. aureus*, *B. cepacia*, *Serratia* species, and *Nocardia* species, are responsible for the overwhelming majority of infections in CGD patients, *Aspergillus* species being the most common isolate from patients with pneumonia and the leading cause of mortality in these patients (113). Surprisingly, CGD patients are resistant to *P. carinii* infections (Table 4) (1, 15, 97, 113).

SUSCEPTIBILITY TO VIRAL INFECTIONS

The first and most striking observation concerning the frequency and severity of viral infections in PID patients (Table 6) is the consistent absence of susceptibility in patients with seriously compromised systems of MHC-I/cytolytic CD8⁺ T cells. This contrasts with classical observations of murine models (120) which demonstrate that antiviral defense is ensured by class I-restricted CD8⁺ T cells. Thus, patients with low levels of expression of MHC-I molecules (transporters associated with antigen processing 1 [TAP-1], TAP-2, and tapasin deficiencies) (47, 69, 73, 115, 119), as well as those with low numbers of cytotoxic CD8⁺ $\alpha\beta$ T cells (inherited CD8 deficiency) (28), are not particularly susceptible to viral diseases. Equally surprising, patients with either TAP deficiencies or familial CD8 deficiency due to a mutation in the CD8 α gene

TABLE 6. Susceptibility of patients with different PIDs to viral infections

PID with indicated level of susceptibility:		
High	Intermediate	Low
All forms of SCID (11, 12, 24, 49, 90, 105)	IFN- γ receptor defects (13, 34, 78)	MHC-I deficiencies due to TAP-1 and TAP-2 defects (32, 47, 69, 73, 119)
MHC-II deficiency (57)	X-EDA-ID (NEMO defects) (61, 83)	MHC-I deficiency due to tapasin defect ^d (115)
Idiopathic CD4 lymphocytopenia (45, 103)	CVID (19, 22)	CD8 ⁺ cell deficiency ^d (28)
Selective NK-cell deficiency (7, 39, 82)	X-linked hyper-IgM syndrome (114)	Perforin deficiency (41, 71)
Complete STAT-1 deficiency (homozygous patients) (36)	Ataxia-telangiectasia syndrome (79)	ALPS (due to Fas, FasL, and caspase 10 defects) (4, 81)
ALPS (due to caspase 8 deficiency) ^d (17)	Wiskott-Aldrich syndrome (106)	IL-12/IL-23 deficiencies (42, 78, 85)
XL- and AR-agammaglobulinemia ^a (64, 67, 88)		IRAK-4 deficiency (23, 38, 61, 70, 86, 110, 116)
WHIM syndrome ^b (31, 53)		Chronic granulomatous disease (1, 15, 113)
Epidermodyplasia verruciformis ^b (92)		Neutropenias (25, 97)
X-linked lymphoproliferative syndrome ^c (62, 75)		Hyper-IgE syndrome (10, 50, 51)
		Complement deficiencies (43, 107)
		Asplenia (48, 99)

^a Patients with these PIDs are characteristically susceptible to enteroviruses.

^b Patients with this PID are characteristically susceptible to human papillomavirus.

^c Patients with this PID are characteristically susceptible to EBV.

^d Only one case or family has been reported.

present a striking homogeneity of clinical manifestations: recurrent sinopulmonary infections with extracellular bacteria (*H. influenzae*, *S. pneumoniae*, *S. aureus*, *P. aeruginosa*, and *Klebsiella* species), which evolve to bronchiectases (28, 32, 45, 47). Serology positive for a variety of common pathogenic viruses clearly indicated that these patients had contact with viruses, as expected for most herpesviruses that are usually contracted early in life, such as cytomegalovirus, herpes simplex virus (HSV), and varicella virus (32). Their serology was also positive for live-vaccine viruses, such as polioviruses, measles, and mumps. While a respiratory viral infection might have preceded bacterial disease, as in patients with antibody deficiencies, it remains surprising that the clinical manifestations of MHC-I/CD8 deficiencies resemble those of humoral deficiencies (28, 32, 65, 69, 119).

Along the same lines, perforin defects do not seem to impart increased susceptibility to viral infections (41, 71). Perforin deficiency is detected in about 30% of children with familial hemophagocytic lymphohistiocytosis, a severe and often fatal disease characterized by overwhelming activation and proliferation of T cells (resulting in wide-spread infiltrates), activation of macrophages, and high levels of IL-1, tumor necrosis factor alpha, IFN- γ , and IL-6 in the blood, with multiple deleterious effects (41). The disease seems to result from "uncontrolled" lymphocyte proliferation, possibly in response to a pathogen (41, 56, 71). Although viral infections (CMV, respiratory syncytial virus, other respiratory viruses, and enteroviruses) have been associated with the onset of the disease, the same has been described for *Klebsiellae* species and *Plasmodium falciparum* (41). Increased susceptibility to viral infections has not been described with other defects in cytolytic activity; patients with ALPS (autoimmune lymphoproliferative syndrome), a less-severe perturbation of lymphocyte homeostasis associated with Fas, FasL, and caspase-10 defects, show no increased susceptibility to any infection (4, 81). In contrast, two ALPS patients carrying caspase-8 mutations had severe mucocutaneous herpes simplex virus infections (17).

It is also somewhat surprising that PID patients with IL-12/IL-23 defects do not seem more susceptible to viruses (42, 78,

85, 96), while IFN- γ R-deficient patients show only a moderate incidence of viral infections (13, 34, 78). In contrast, patients with homozygous mutations in STAT-1 (and STAT-5) are highly vulnerable to viruses, seemingly as a consequence of impaired responses to type I IFN (35, 36, 58). Again in contrast to murine models (109), in humans the antiviral role of IFN- γ seems to be redundant (except perhaps against CMV and human herpesvirus 8) (13, 34, 78), IL-12 being entirely redundant, since patients with IL-12R β 1 and IL-12p40 subunit deficiencies do not present abnormal susceptibilities to viral infections (42, 78, 85).

Highly increased susceptibility to often-fatal viral infections is instead seen in all PID patients with compromised CD4⁺ T-cell/MHC-II functions. Thus, as seen in Table 6, all SCID patients are very susceptible to viruses, mainly those of the herpesvirus group (CMV, Epstein-Barr virus [EBV], and varicella-zoster virus [VZV]), but also to respiratory syncytial virus, parainfluenza virus type 3, adenovirus, and enteroviruses (11, 12, 24, 49, 90, 105). Interestingly, extreme susceptibility to viral infections is similar with all forms of SCID, with or without NK cells, and is also characteristic of patients with defective MHC-II expression (persistent CMV, enterovirus, adenovirus, and herpes simplex virus infections, in order of frequency), which caused bronchopulmonary infections, meningoencephalitis, diarrhea, hepatitis, and all the early deaths (11, 57, 105). Similarly, patients with idiopathic CD4 lymphocytopenia are also vulnerable to viruses, severe zoster infections being the most frequent among affected adults (45, 103). The clinical phenotype of ZAP-70 deficiency also shows the relevance of a conserved CD4⁺ T-cell function in viral defense. Thus, while as seen above, CD8⁺ T-cell-deficient patients do not show particular susceptibility to viruses, those with ZAP-70 mutations, harboring functionally deficient CD4⁺ T cells, present high susceptibility to viruses early in life, as do other SCID patients (37, 45, 76).

Viral susceptibility is typically seen in patients with agammaglobulinemia and hypogammaglobulinemia, particularly to viruses that enter by the gastrointestinal tract and disseminate hematogenously (18, 64, 67, 88). High incidence and severity of enteroviral

diseases has been reported for patients with X-linked agammaglobulinemia and AR-agammaglobulinemia due to defects in the μ heavy-chain gene, chronic viral meningoencephalitis being the most severe complication (64, 67, 88). These patients are also at risk for developing vaccine-associated poliomyelitis paralysis after live oral poliovirus vaccination (64, 88). Enteroviral meningoencephalitis has also been described as a complication for X-linked hyper-IgM patients (20, 114). Overtly abnormal susceptibility to enteroviral infections has not been described for either selective IgA deficiency or for patients with hyper-IgM syndrome due to AID deficiency (16, 21, 72, 89, 91). This is quite surprising, given the fact that AID-deficient patients lack affinity maturation mechanisms, suggesting that “germ line” antibodies are sufficient to ensure normal antiviral defense.

Equally unexpected is the observation that IRAK-4-deficient patients are not abnormally susceptible to viruses or other intracellular pathogens (23, 38, 61, 70, 86, 116). Intact resistance is possibly due to conserved IFN- α and IFN- β responses, which might be ensured by IRAK-4-independent activation through TLR-3 or TLR-4 and/or by TLR-independent mechanisms (116). In contrast, NEMO-deficient patients resemble those with combined immunodeficiencies, presenting high susceptibilities to HSV, CMV, and papillomavirus infections and to extracellular bacteria, mycobacteria, and *P. carinii* (61, 83). This is likely due to the defective NK function (but with normal counts and phenotype) that was observed in all patients tested (83), as there is evidence for a critical involvement of NEMO and NF- κ B signaling pathways in NK-cell function and for the role of NK cells in antiviral protection. While extremely rare and not fully recognized yet as PIDs (77), selective NK deficiencies have been described; overall, recurrent life-threatening herpesvirus infections (VZV, CMV, and HSV) were the paramount manifestations (7, 39, 82), as was the case with a distinct, mixed defect of NK cells with low CD8⁺ T-cell and neutrophil counts (5) and in individuals homozygous for a polymorphism of Fc γ R11a that is expressed in NK cells and neutrophils (27, 30). While these observations indicate that NK cells are critical in resistance to viruses of the herpes group (82), high susceptibility to viral infections is scored for all SCID types, irrespective of normal numbers of NK cells (IL-7R deficiencies, CD3 δ deficiency, and RAG-1 and RAG-2 deficiencies) or low numbers of NK cells (X-linked γ -chain defects, JAK-3 deficiency, and adenosine deaminase deficiency) (11, 24, 49, 90, 105). MHC-II-deficient patients, who present normal NK cell numbers, are also very susceptible to several viral infections (11).

There are some examples of PID patients with selective susceptibility to viruses, namely to papillomaviruses in patients with epidermodysplasia verruciformis (associated with mutations in *EVER1* and *EVER2*) (92) and WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokatexis, and neutropenia, associated with increased response of the receptor CXCR4 to its ligand, CXCL12) (31, 53) and to EBV in patients with X-linked lymphoproliferative syndrome (62, 75). The pathophysiology of such selective viral susceptibility is not yet fully understood.

In short, the clinical evidence from PID patients provides several challenging lessons on protective antiviral immunity. (i) T-cell-mediated immunity is essential for resistance to viruses.

TABLE 7. Susceptibility of patients with different PIDs to *Protozoa* species infections

PID associated with indicated <i>Protozoa</i> species:	
<i>Giardia lamblia</i>	<i>Cryptosporidium parvum</i>
XL-agammaglobulinemia (64)	X-linked hyper-IgM syndrome (CD40L deficiency) (65, 66, 95, 114)
CVID (22)	Hyper-IgM syndrome type 3 (CD40 deficiency) (68)
IgA deficiency (54)	MHC-II deficiency (57, 95)
Hyper-IgM syndrome type 2 (AID deficiency) (72, 91)	
X-linked hyper-IgM (CD40L deficiency) (66)	
MHC-II deficiency (57)	
XL-EDA-ID (NEMO defects) (83)	
APECED (6)	

(ii) Antiviral T-cell resistance is essentially ensured by CD4⁺ MHC-II-dependent cells. (iii) A critical role of CD8⁺ MHC-I-dependent T cells in human antiviral protective immunity is questionable, and this issue needs to be better understood. (iv) Neutralizing antibodies are crucial for preventing hematogenic dissemination of enteroviral infections. (v) Efficient neutralization by antibodies does not seem to require affinity maturation. (vi) The IFN- α and IFN- β pathways seem to be crucial for antiviral protection, whereas IFN- γ (and IL-12) seems not to be particularly relevant for most viruses in humans. (vii) Selective defects of NK cells impart susceptibility to herpesviruses, but NK cells do not restore normal resistance in CD4⁺ T-cell/MHC-II deficiencies. The question raised by these findings is whether TAP-1-, TAP-2-, and tapasin-dependent presentation of antigens by HLA class I molecules to CD8⁺ cytotoxic lymphocytes is crucial for antiviral protective immunity in humans, as is described for the response to noncytotoxic viruses in mice (120). It is possible that CD8 T lymphocytes do not actually play equivalent roles in antiviral immunity in humans and mice or that perhaps humans, naturally outbred and exposed to infectious agents, have more (or additional) redundant mechanisms of protection.

SUSCEPTIBILITY TO PROTOZOA

The infectious intestinal protozoa most frequently isolated from patients with PIDs are *Giardia lamblia* (19, 64, 72, 88, 91) and *Cryptosporidium parvum*, a frequent cause of chronic diarrhea in patients with combined T- and B-cell defects (Table 7). High susceptibility to *G. lamblia* infections is associated with impaired production of mucosal IgA antibodies, seen in all the antibody-deficient patients (21, 22, 64, 66, 72, 91). Patients with hyper-IgM syndromes due to CD40L/CD40 deficiencies are very prone to *Cryptosporidium* species infections and often develop sclerosing cholangitis in consequence of the infection (66, 68, 95, 114). Increased susceptibility to *Cryptosporidium* species infections and sclerosing cholangitis is also seen in patients with MHC-II deficiencies (57, 95).

Unlike adult patients with acquired immunodeficiencies, pediatric PID patients do not frequently have problems with *Toxoplasma gondii*, even those with T-cell defects (11, 57, 65, 105, 114). One explanation may be the lower exposure of infants and young children to this pathogen, usually transmitted by raw meat and environmental exposure to cat feces. Alternatively, the widespread use of antibiotics in PID pa-

tients, mainly trimethoprim-sulfamethoxazole, may well prevent *T. gondii* infections.

FINAL COMMENTS

We should start with a word of caution. It must be emphasized that some PID patients may have apparent resistance to a given set of infectious agents that is not due to intact immunological competence but to deliberate restriction of exposure to those pathogens. Alternatively, a false impression of conserved resistance may arise from the fact that such patients receive prophylactic or therapeutic broad-spectrum antibiotic coverage as soon as an infectious agent is suspected. This may explain, for instance, the rarity of pneumococcal and some fungal infections in SCID patients and of *Toxoplasma* species infections in PID patients overall.

Our first general conclusion concerns the singularity of host/pathogen interactions. Despite the great variety of cell types and molecular mechanisms of innate and adaptive immunity participating in anti-infection defense, the susceptibility of groups of PID patients to selective infections shows that, for each pathogen or group of pathogens, there are essential, nonredundant mechanisms of protection. Immune responses are systematically scored in such infections and may even contribute to the overall protection, but not all of these other mechanisms are critical in ensuring immunity.

This review of PID patient characteristics as a whole also reveals many surprises compared to those for current models essentially constructed on observations of mice. Antiviral immunity provides the most challenging differences to current convictions. Thus, few of the critical mechanisms of protection, as identified in experimental mice, seem to be essential for resistance in human beings. This applies, first, to the relevance of MHC-I-restricted CD8⁺ T cells with cytolytic effector functions. Surprisingly, deficits in MHC-I expression and peptide presentation are associated with susceptibility to respiratory infections by extracellular bacteria but not to viruses. An apparently normal resistance to viruses is also seen with CD8⁺ T-cell defects, with humans with perforin mutations suffering, instead, from uncontrolled lymphocyte proliferation (41, 56). Furthermore, if a few conditions suggest a critical role for NK cells in the defense against herpesviruses, others demonstrate that NK cells require "help" from lymphocytes and, alone, afford no protection (11, 24, 49, 57, 82, 90, 105). Moreover, if PIDs confirm the role of antibodies in the defense against enteric viruses, they also show, contrary to expectations, that somatic hypermutation and affinity maturation of specific antibodies might not be essential to ensure protection. Finally, IL-12 and IFN- γ are not critical in antiviral defense, in contrast to type I IFNs, which, as expected, are fundamental for resistance to viral infections. One argument that may conciliate the different observations from humans and mice would invoke the rarity of CD8⁺ T-cell- or MHC-I-deficient patients precisely to conclude that they play critical roles in viral protection, postulating exceptionally robust "second-line" mechanisms in the few surviving mutants. Although studies with mice have contributed to advancements in the field, the information they provide is limited. Results are often influenced by the strain and background of gene-targeted mutants. In addition, mouse studies are based on null mutants, whereas gene defects can be

studied in humans in the context of hypomorphic mutations and allelic series.

Another general comment derives from the uniqueness of the immune protection against each pathogen. For some, it is surprising that essential mechanisms of protection to intracellular pathogens are so widely variant for bacteria and fungi, for various types of gram-negative and gram-positive bacteria, for capsulated and uncapsulated bacteria, and for fungi and protozoa, often in the same apparent environment. For us, the take-home lesson is that much is yet to be understood and that the clinical characteristics of PIDs will continue to offer an excellent field of inquiry and source of learning.

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ADDENDUM IN PROOF

After acceptance of the manuscript, a study by E. Kekalainen, H. Tuovinen, J. Joensuu, M. Gylling, R. Franssila, N. Pontynen, K. Talvensaaari, J. Perheentupa, A. Miettinen, and T. P. Arstila (J. Immunol. **178**:1208–1215, 2007) provided a solid demonstration for a Treg cell deficit in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients, as we had hypothesized in our paper; however, an explanation for their specific susceptibility to *Candida* species remains speculative.

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