

Phagocyte immunodeficiencies and their infections

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Primary immunodeficiencies (PIDs) primarily affecting the phagocytes (neutrophils and macrophages) typically predispose patients to infections. However, one of the most clinically important features of these disorders is their relatively narrow spectrum of disease-specific infections. Invasive aspergillosis in the absence of immune suppression is essentially seen only in chronic granulomatous disease; disseminated nontuberculous mycobacterial infection in the absence of immune suppression is seen predominantly in patients with defects of the IFN- γ /IL-12 axis. In contrast, infections that are relatively common in some of the PIDs affecting the lymphoid system (*Pneumocystis jirovecii* and *Streptococcus pneumoniae*) are extremely uncommon in PIDs affecting phagocytes. Therefore careful attention to the microbiology laboratory early in the course of evaluation of a patient with recurrent infections and suspected of having a PID will help steer the workup in the appropriate direction. Over the last few years, there have been major advances in the molecular and cellular understandings of PIDs affecting phagocytes. As the field of PIDs becomes broader and more clinical and molecular definition becomes available, it is increasingly important to be able to identify likely pathways for investigation early in the evaluation. Here we have updated some of the more rapidly evolving aspects of PIDs affecting phagocytes, with a special emphasis on the associated microbiology. (J Allergy Clin Immunol 2004;113:620-6.)

Key words: Chronic granulomatous disease, leukocyte adhesion deficiency, IFN- γ , IFN- γ receptor, E-selectin, Aspergillus species, Mycobacteria species, Staphylococcus aureus, IL-12, granuloma

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is caused by defects in the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, the enzyme complex responsible for the generation of superoxide. CGD is characterized by recurrent life-threatening infections caused by catalase-positive bacteria and fungi and exuberant granuloma formation (Table I).¹ The NADPH oxidase is composed of a heterodimeric membrane-bound complex embedded in the walls of secondary granules (gp91^{phox} and p22^{phox}, forming cytochrome b₅₅₈) and 4 cytosolic proteins (p47^{phox}, p67^{phox}, p40^{phox}, and rac;

Abbreviations used

AD:	Autosomal dominant
AR:	Autosomal recessive
CDG-IIc:	Congenital disorder of glycosylation type IIc
CGD:	Chronic granulomatous disease
IFN- γ R:	IFN- γ receptor
IL-12R:	IL-12 receptor
LAD:	Leukocyte adhesion deficiency
NADPH:	Reduced nicotinamide adenine dinucleotide phosphate
Phox:	Phagocyte oxidase
PID:	Primary immunodeficiency
STAT:	Signal transducer and activator of transcription

Fig 1). On cellular activation, the secondary granule fuses with the phagolysosome, depositing cytochrome b₅₅₈ in the membrane. The cytosolic components associate with each other and then with the cytochrome to form the intact NADPH oxidase. This complex transfers an electron from NADPH (thus oxidizing it) to molecular oxygen, producing superoxide. Superoxide is highly reactive and is converted into hydrogen peroxide by means of superoxide dismutase. Hydrogen peroxide is converted to hypohalous acid (bleach when the halide is chloride) by myeloperoxidase in the phagosome.¹ Until recently, the metabolites of superoxide themselves were thought to be the critical mediators of bacterial killing. However, Reeves et al² showed that phagocyte production of superoxide activates the primary granule proteins neutrophil elastase and cathepsin G inside the phagocytic vacuole. It is these proteins, in turn, that are necessary to kill microbes. This new paradigm for NADPH oxidase-mediated microbial killing suggests that the reactive oxidants are critical intracellular signaling molecules that activate other microbicidal pathways rather than exerting a microbicidal effect per se.

CGD can be caused by mutations in any of the 4 structural genes of the NADPH oxidase (gp91^{phox}, p22^{phox}, p47^{phox}, and p67^{phox}). Most cases (65%) involve mutations in gp91^{phox} and are inherited in an X-linked recessive manner (Table II). The remainder are autosomal recessive (AR). The frequency of CGD in the United States is at least 1:200,000 live births and is likely higher.³

The majority of patients are given diagnoses as toddlers and young children because of infections or granulomatous lesions. The lung, skin, lymph nodes, and liver are the most frequent sites of infection. Only 5 microorganisms are responsible for the overwhelming majority of infections in CGD in North America and Europe:

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Staphylococcus aureus, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* species, and *Aspergillus* species. Pneumonia and cellulitis are usually caused by the gram-negative organisms listed above. Bacteremia is uncommon, but when it occurs, it is usually caused by *B cepacia*, *S marcescens*, or the much less common gram-negative rod *Chromobacterium violaceum*, an organism that inhabits warm brackish water and soil. Staphylococcal liver abscesses are almost pathognomonic of CGD.^{1,3,4} Bacterial and *Nocardia* species infections in CGD tend to be symptomatic and associated with increased erythrocyte sedimentation rates and leukocytosis.⁵ In contrast, lack of fever, normal sedimentation rate, and few symptoms are more common in *Aspergillus* species infections.⁶ Therefore normal laboratory values and a paucity of symptoms offer scant reassurance that a patient with CGD is not infected.

The diagnosis of CGD is made on the basis of assays that rely on superoxide production. Currently, we prefer the dihydrorhodamine flow cytometry–based test because of its relative ease of use and ability to readily distinguish X-linked from autosomal forms of CGD.^{7,8}

Trimethoprim-sulfamethoxazole prophylaxis has reduced the frequency of bacterial infections in general and staphylococcal infections in particular. On prophylaxis, staphylococcal infections are essentially confined to the liver and cervical lymph nodes.³ Liver abscesses encountered in CGD are almost always staphylococcal and are dense, caseous, and difficult to drain, requiring surgery in almost all cases.⁴ The diagnosis of a staphylococcal liver abscess should always prompt screening for CGD. With the great successes in antibacterial prophylaxis and therapy, fungal infections, typically caused by *Aspergillus* species, are now the leading cause of mortality in patients with CGD.³ A large, multinational, multicenter, placebo-controlled study proved a marked clinical benefit for patients receiving subcutaneous recombinant IFN- γ . Recipients had 70% fewer and less severe infections than did placebo-treated patients. These benefits held true regardless of inheritance pattern of CGD, sex, or use of prophylactic antibiotics.⁹ Recently, Gallin et al¹⁰ proved that antifungal prophylaxis with itraconazole reduced the risk of fungal infections in patients with CGD. Therefore our current practice is to use prophylaxis with trimethoprim-sulfamethoxazole (5 mg $\cdot$ kg⁻¹ $\cdot$ d⁻¹ given in 2 divided doses), itraconazole (100 mg/d for <50 kg, 200 mg/d for $\geq$ 50 kg), and IFN- γ (50 μ g/m² subcutaneously thrice weekly) in all patients with CGD. This should be done for all patients with CGD regardless of genotype.

Both myeloablative and nonmyeloablative HLA-matched bone marrow transplantations have been performed in patients with CGD.¹¹ Of interest has been a series of cases in which transplantation has been done in the setting of active and refractory infection, such as aspergillosis.¹² Bone marrow transplantation in these cases has been surprisingly effective, and survival has been relatively high. In addition, underlying debilitation has largely resolved in these successful bone marrow transplant recipients, suggesting that bone marrow trans-

plantation might have a significant role in the management of CGD. However, procedure-related toxicities, acute and chronic graft-versus-host disease, and death mandate a careful consideration of risks and benefits.

LEUKOCYTE ADHESION DEFICIENCIES

Leukocyte adhesion to the endothelium, to other leukocytes, and to bacteria is critical in the ability of leukocytes to travel, communicate, inflame, and fight infection. Leukocytes roll along the venular wall by using a series of molecules on the endothelium (selectins) that interact with carbohydrate moieties on the leukocyte to migrate toward sites of inflammation or infection. After sensing activated endothelium, leukocytes use integrins to tightly adhere to adhesion molecules on endothelial cells. Finally, they use a different series of receptors for migration between endothelial cells out into the tissue. Different families of adhesion molecules mediate these discrete processes of rolling, sticking, and emigration or diapedesis, critical among which are the integrins and selectins. Defects in these pathways lead to the general phenomenon of poor inflammation because of poor recruitment of neutrophils into the infected or inflamed site. Several new syndromes that affect leukocyte adhesion have been reported recently.

Leukocyte adhesion deficiency type 1

Leukocyte adhesion deficiency type 1 (LAD-1) is an AR disorder caused by mutations in the common chain of the β 2 integrin family CD18, which is located at 21q22.3. LAD-1 usually presents with recurrent severe infections, impaired pus formation, and impaired wound healing.¹³

Each of the β 2 integrins is a heterodimer composed of an α chain (CD11a, CD11b, or CD11c) noncovalently linked to CD18. CD11a/CD18 is lymphocyte function-associated antigen-1, CD11b/CD18 is macrophage antigen 1 or complement receptor 3, and CD11c/CD18 is p150,95 or complement receptor 4.¹⁴ Because CD18 is required for normal expression of all the α - β heterodimers, defects in CD18 expression lead to either very low or no expression of CD11a, CD11b, and/or CD11c.^{15,16}

Clinically, patients with the severe phenotype (<1% of normal expression of CD18 on neutrophils) have delayed umbilical stump separation (>30 days), omphalitis, persistent leukocytosis (more than 15,000/ μ L), and severe destructive gingivitis and periodontitis leading to tooth loss and alveolar bone resorption.^{15,17,18} Recurrent infections of the skin, upper and lower airways, bowel, and perirectal area are common, usually caused by *S aureus* or gram-negative bacilli, and tend to be necrotizing and ulcerate. Typically, little inflammation is seen surrounding these lesions, and there is an almost complete absence of tissue neutrophils on histopathology. Impaired wound healing is common in LAD-1, leaving scars with a “cigarette-paper” appearance. Aggressive medical management, including debridement and grafting, is often necessary.

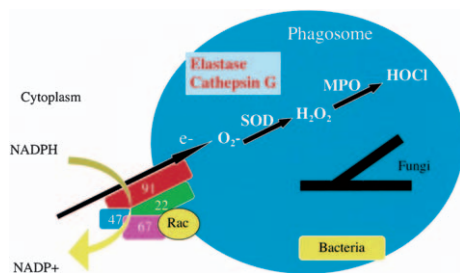


FIG 1. The NADPH oxidase comprises the 4 structural molecules shown, as well as the regulatory components p40^{phox} (not shown) and Rac. NADPH donates an electron to molecular oxygen, thereby creating superoxide. This is converted to hydrogen peroxide (H₂O₂) by superoxide dismutase (SOD). Hydrogen peroxide, in turn, is converted to hypohalous acid (HOCl, bleach) by myeloperoxidase (MPO). The generation of the negative charge by the creation of superoxide leads to a rapid influx of potassium that liberates and activates primary granule contents, such as neutrophil elastase and cathepsin G. Mutations in any of the 4 structural molecules (gp91^{phox}, p22^{phox}, p47^{phox}, and p67^{phox}) lead to CGD. Mutation of Rac2, the predominant G protein in neutrophils, leads to defects in superoxide production, as well as chemotaxis.

The moderate phenotype of LAD-1 (1% to 30% of normal expression of CD18 on neutrophils) is milder and tends to be diagnosed later in life. Normal umbilical separation, lower risk of life-threatening infections, and longer life expectancy are common.^{15,17,18} However, leukocytosis, periodontal disease, and delayed wound healing are still the rule.

As predicted from the adhesion defect, patients with LAD-1 have diminished neutrophil migration in vivo (Rebuck skin windows) and in vitro.^{15,17} Granulocyte adherence to each other, complement-mediated phagocytosis, and antibody-dependent cell-mediated cytotoxicity are also diminished in patients with LAD-1.^{15,17} However, IgG-mediated phagocytosis, superoxide production, and primary and secondary granule release are unaffected.^{15,17} Bone marrow transplantation is the only definitively corrective treatment.^{19,20,21} Human gene therapy studies have been performed in patients with LAD-1 but are not yet of clinical benefit.^{22,23}

Flow cytometric analysis of LAD-1 blood samples shows significant reduction (moderate phenotype) or near absence (severe phenotype) of CD18 and its associated molecules (CD11a, CD11b, and CD11c) on neutrophils and other leukocytes.

However, patients with normal β 2 integrin expression but without functional activity have been described.^{24,25} Therefore expression of CD18 alone is not sufficient to exclude the diagnosis of LAD-1: functional assays (usually in research laboratories) must be performed if the clinical suspicion is high.

Leukocyte adhesion deficiency type 2 or congenital disorder of glycosylation IIc

An AR disease first recognized because of its association with recurrent infections and impaired leukocyte adhesion, among other traits, was named leukocyte

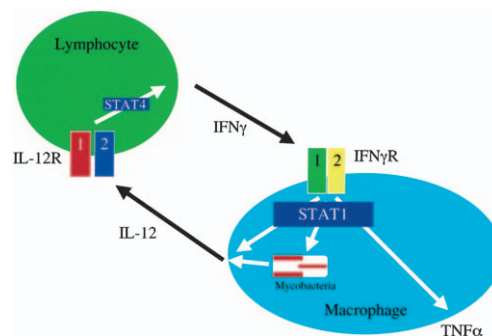


FIG 2. The ingestion of mycobacteria by the macrophage leads to the elaboration of IL-12. This stimulates T and natural killer lymphocytes through IL-12 receptors β 1 and β 2 to signal through STAT4 to produce IFN- γ . IFN- γ acts on its receptors 1 and 2 to signal through STAT1 for the upregulation of TNF- α , the killing of mycobacteria, and the upregulation of IL-12. Mutations in either chain of the IFN- γ R lead to severe susceptibility to mycobacteria and are very difficult to treat. Mutations in IL-12p40 or IL-12R β 1 are milder clinically and can be treated with IFN- γ because that receptor is still intact. Complete recessive mutations in STAT1 are more severe than any of the others because they affect both IFN- γ and IFN- α signaling (not shown). Not shown is the sharing of IL-12R β 1 with the IL-23 receptor, a complex that also signals through STAT4 and upregulates IFN- γ .

adhesion deficiency type 2 (LAD-2).²⁶ However, it is now known that this disease is due to an inborn error in fucose metabolism caused by mutations in the guanosine diphosphate—fucose transporter gene.^{27,28} Therefore this disease is also now known as congenital disorder of glycosylation type IIc (CDG-IIc). CDG-IIc/LAD-2 leads to impaired expression of sialyl-Lewis X (CD15s) and other fucosylated proteins that function as selectin ligands.^{14,26} The CDG-IIc/LAD-2 phenotype includes immunologic and somatic features: increased infection susceptibility, leukocytosis, and poor pus formation, as well as severe mental retardation, short stature, distinctive facies, and the Bombay (hh) blood phenotype. Infections of the skin, lungs, and gums resemble those seen in the moderate phenotype of LAD-1, but the frequency and severity of infections tend to decrease with age.^{26,29} Prolonged oral fucose replacement reduced infectious episodes and neutrophil baseline counts and improved psychomotor capabilities in one report.³⁰ However, fucose treatment was not effective in other patients with CDG-IIc/LAD-2.³¹ To date, this disease is extremely rare, with only a handful of cases identified. The diagnosis is easily established by means of flow cytometry for CD15s.

LAD with abnormal E-selectin expression

A young girl with *Pseudomonas* omphalitis, recurrent ear and urinary tract infections, severe soft tissue infections, and impaired pus formation had deficient endothelial expression of E-selectin.³² In contrast to patients with LAD-1, she had mild chronic neutropenia but appropriate leukocyte increases in response to infections or GM-CSF. Although no alterations in the E-selectin cDNA were detected, her circulating E-selectin

TABLE I. Infections in phagocyte immunodeficiencies

	Microorganisms	Localization
CGD	Common: <i>Staphylococcus aureus</i> ; <i>Serratia marcescens</i> ; <i>Burkholderia cepacia</i> ; <i>Nocardia</i> species; <i>Aspergillus</i> species Less common: <i>Chromobacterium violaceum</i> ; <i>Paecilomyces</i> species; <i>Exophiala</i> species; <i>Scedosporium</i> species	Lung, liver, lymph nodes, skin sepsis (<i>Chromobacterium</i> species, <i>Burkholderia</i> species)
LADs	<i>Staphylococcus aureus</i> ; gram-negative rods (enteric)	Cutaneous, gastrointestinal tract, sepsis
IFN- γ /IL-12 deficiencies	Common: <i>Mycobacteria</i> species (nontuberculous and TB complex); <i>Salmonella</i> species Less common: <i>Listeria monocytogenes</i> , viruses, <i>Histoplasma capsulatum</i>	Disseminated, bone (AD IFN- γ R1), lymph nodes

TABLE II. Selected genetic phagocyte disorders

Disease	Gene affected; chromosomal location	Protein affected	Functional consequence
CGD	<i>CYBB</i> ; Xp23 <i>CYBA</i> ; 16q24 <i>NCF1</i> ; 7q11.23 <i>NCF2</i> ; 1q25	gp91 ^{phox} p22 ^{phox} p47 ^{phox} p67 ^{phox}	Absence of cytochrome b; X-linked CGD; ~70% of cases Absence of cytochrome b; AR-CGD; <5% of cases Cytochrome-positive AR-CGD; ~25% of cases Cytochrome-positive AR-CGD; <5% of cases
LADs	<i>ITGB2</i> ; 21q22.3 <i>FUCT1</i> ; 11	CD18 GDP-fucose transporter 1	LAD-1; loss of expression of CD11a, CD11b, or CD11c; loss of tight adhesion LAD-2; impaired leukocyte rolling; loss of fucosylation of CD15s
IFN- γ R1 deficiency	<i>RAC2</i> ; 22q12.3 <i>IFNGR1</i> ; 6q23	Rac2 IFN- γ R1	Impaired chemotaxis, phagocytosis, oxidative burst Loss of IFN- γ binding; both AR and AD forms
IFN- γ R2 deficiency	<i>IFNGR2</i> ; 21q22	IFN- γ R2	Loss of IFN- γ signaling
STAT1 deficiency	<i>STAT1</i> ; 2q32	STAT1	Impairment of IFN- γ signaling (AD form); impairment of both IFN- γ and IFN- α signaling (AR form)
IL-12 p40 deficiency	<i>IL12B</i> ; 5q31.1	IL-12p40	Impaired IL-12 signaling; reduced IFN- γ production
IL-12RIFN- β 1 deficiency	<i>IL12RB1</i> ; 19p13	IL-12R β 1	Impaired IL-12 signaling; reduced IFN- γ production

levels were increased. Because she had normal intrinsic neutrophil function, significant infections, signs of impaired inflammation, and a suggestive family history for a genetic disorder, this likely represents a defect in E-selectin tethering or secretion.

LAD caused by Rac2 deficiency

A boy born to unrelated parents had delayed umbilical cord separation, perirectal abscesses, failure to heal surgical wounds, and absent pus at sites of infection in the setting of neutrophilia. His neutrophils had defective phagocytosis and primary granule release, as well as significantly reduced stimulated superoxide production.^{33,34} His disease was shown to be due to an autosomal dominant (AD) mutation in the Rho GTPase Rac2 at an amino acid needed for proper interaction with other intracellular proteins. Rac2 comprises more than 96% of the critically important G protein Rac in neutrophils and is necessary for regulation of the actin cytoskeleton (chemotaxis and degranulation) and NADPH oxidase (superoxide production) function. Bone marrow transplantation has been curative.³⁴

LAD with impaired integrin rearrangement and bleeding diathesis

Two brothers were recently reported with profound leukocytosis, recurrent infections, and bleeding.³⁵ The older brother died after bone marrow transplantation, and the younger died at 1 week of life from sepsis. In vitro, leukocytes showed normal rolling along endothelial cell cultures but defective tethering and tight adhesion. Defects in both leukocyte and platelet functions that are biochemically and molecularly distinct from the adhesion disorders previously described suggest a mutation in an early myeloid pathway. This defect is associated with regulation of the GTPase activating protein Rap-1.³⁶ However, its exact mechanism and the connection between the leukocyte and platelet dysfunctions are still unclear.

IFN- γ /IL-12 PATHWAY DEFECTS

The mononuclear phagocyte is critical to antigen presentation, lymphocyte stimulation, lymphocyte proliferation, and cytokine production and response, especially against intracellular microorganisms. Macrophage-engulfed mycobacteria lead to the production of IL-12.

IL-12 stimulates T cells and natural killer cells through its receptor (IL-12R) to produce IFN- γ .^{37,38} IFN- γ acts through its receptor, a heterodimer composed of IFN- γ receptor 1 (IFN- γ R1) and IFN- γ receptor 2 (IFN- γ R2), to activate the latent cytosolic signal transducer and activator of transcription 1 (STAT1), which upregulates numerous genes and activities.³⁹ IFN- γ increases the production of the phagocyte TNF- α and further upregulates IL-12, especially in the presence of LPS.⁴⁰ IFN- γ is necessary for the killing of mycobacteria and certain other intracellular microorganisms, but the mechanism or mechanisms remain elusive (Fig 2).⁴¹ Patients with defects in IFN- γ R1, IFN- γ R2, IL-12R β 1, IL-12 p40, and STAT1 have been identified through their extreme susceptibility to nontuberculous mycobacteria and BCG.^{42,43} These defects, all of which have been identified because of mycobacterial infection, have been grouped as Mendelian susceptibility to mycobacterial disease.

Patients with AR mutations leading to complete loss of IFN- γ R1 or IFN- γ R2 expression have the most severe phenotypes.^{40,44-46} They present early in life with disseminated severe infections, especially if they have received BCG vaccination, and have poor to absent granuloma formation. Salmonella and certain viral infections (herpes simplex virus, cytomegalovirus, parainfluenza, and respiratory syncytial virus) are also seen.⁴⁷ Mortality in these children is high, and infections are severe and recurrent.

In contrast to the complete loss of function typically associated with recessive mutations, there is a less severe common AD mutation in IFN- γ R1.⁴⁸ This mutation occurs just beyond the transmembrane domain and therefore preserves the extracellular ligand-binding aspects of the molecule but removes the intracellular Jak1 and STAT1 binding sites, as well as the IFN- γ R1 domain that allows for the removal of the receptor from the cell surface. Therefore the mutant IFN- γ R1 protein remains stuck on the cell surface, where it binds IFN- γ and the normal IFN- γ R1 and IFN- γ R2 molecules but cannot signal appropriately. These AD mutations are usually at base 818, and almost all are due to a similar 4-bp deletion (818del4).⁴⁸ Patients with AD mutations in IFN- γ R1 usually present in childhood or adolescence and have excellent survival. In North America one crucial clue should be the diagnosis of multifocal mycobacterial osteomyelitis. This presentation in a child or young adult is almost pathognomonic for AD IFN- γ R1 deficiency. Interestingly, mycobacterial osteomyelitis is far less common in the complete recessive forms of IFN- γ R1 deficiency. The diagnosis of defects in the IFN- γ R1 is most rapidly made with flow cytometry looking for surface display of IFN- γ R1. Surface expression is typically absent in AR IFN- γ R1 deficiency and 5- to 10-fold more than normal values in the case of AD IFN- γ R1 deficiency caused by overaccumulation of the cytoplasmically truncated receptor on the cell surface.

Patients with IL-12p40 deficiency have a milder phenotype than that of complete IFN- γ R1 and IFN- γ R2

deficiency.⁴⁹ In IL-12R β 1 deficiency, the risk of environmental nontuberculous mycobacteria infection appears to wane after the age of 12 years, and the clinical penetrance appears to be incomplete.⁵⁰ A dominant form of STAT1 deficiency appears to have affected only antimycobacterial defenses and preserved antiviral immunity.⁵¹ In contrast, recessively inherited complete STAT1 deficiency led to disseminated mycobacterial infections and fatal viral infections in infancy.⁵²

Direct detection of IFN- γ R2 and IL-12R β 1 require cell proliferation in culture. Detection of intracellular phosphorylated STAT1 after IFN- γ stimulation or phosphorylated STAT4 after IL-12 stimulation demonstrate the functional integrity of the respective receptors.^{53,54} Direct detection of IL-12p40 or IL-12p70 can be used for the diagnosis of IL-12p40-deficient patients.⁴⁹ Defects in STAT1 can be detected by using intracellular flow cytometry as well.⁵³

Recently, Höflich et al⁵⁵ and Doffinger et al⁵⁶ have identified potent anti-IFN- γ -neutralizing antibodies in patients with disseminated *Mycobacterium chelonae* infections. Although they could not prove a causal relationship of the autoantibodies to the clinical syndromes, these cases strongly suggest that an acquired immunodeficiency caused by anticytokine antibodies occurs.

Treatment of infections in these patients must take the underlying molecular defect into account. In patients with AD IFN- γ R1 deficiency, IL-12 defects, or IL-12R defects, subcutaneous IFN- γ is effective.⁵⁷ For patients with complete IFN- γ R defects, there is no benefit to the use of IFN- γ . Bone marrow transplantation for IFN- γ R defects must be carefully considered because mortality in the setting of active infection is high.⁵⁸ Currently, we recommend long-term prophylaxis against environmental mycobacterial infections with azithromycin or clarithromycin after infection has been cleared.

CONCLUSIONS

Primary immunodeficiencies affecting phagocyte cells are still being discovered. Phagocyte disorders should be suspected on the basis of clinical infections: staphylococcal liver abscesses are almost pathognomonic of CGD, and multifocal mycobacterial osteomyelitis suggests dominant IFN- γ R1 deficiency. Therefore pathogen isolation has both diagnostic and therapeutic value. There are undoubtedly more phagocyte defects to be identified. Although we have attained molecular knowledge of many of the classically described defects, we remain ignorant about some of the most basic aspects of their pathophysiology, and we still need to sort out the mechanistic implications of the mutations we have found. These defects and mutations exist at the interface between microbes and the adaptive immune response and will continue to inform us about how we survive the constant microbial assault of the real world.

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