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Original Article

Infectious pathogens in pediatric patients with primary immunodeficiencies

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Background and Purpose: Primary immunodeficiency diseases (PIDs) are rare disorders. Unusual infections often guide the initial investigation for immunodeficiency.
Methods: In order to ascertain the organisms that lead to a predisposition for PIDs, we reviewed the charts of 92 children diagnosed with PIDs at the National Taiwan University Hospital between March 1984 and March 2004.
Results: Pneumonia was diagnosed in 92%, 81%, and 76.5% of patients with antibody, combined, and cellular deficiencies, respectively. Other major illnesses were similar in the 3 groups and included bronchiolitis, acute gastroenteritis, otitis media, and bacteremia. Skin abscess, pneumonia, and lymphadenitis (54.5%, 45%, and 27% of cases, respectively) were the most common infections in patients with phagocyte defects. Organisms were speciated in only 44.8% of infection episodes. Most viral infections were diagnosed by traditional and time-consuming viral culture. Prophylactic antibiotics were prescribed to 9 out of the 92 patients with PIDs.
Conclusions: Early recognition of PIDs requires that practitioners be aware of the infection characteristics, and subsequent reliable and rapid molecular diagnosis are needed in such immunocompromised patients.

Key words: Etiology, infection, immunologic deficiency syndromes, phagocytes

Introduction

Many non-immune manifestations are the first presentation of some primary immunodeficiency diseases (PIDs), such as DiGeorge syndrome and Wiskott-Aldrich syndrome (WAS); however, recurrent or unusual severe infections often prompt the investigation of possible underlying immunodeficiencies.

All immunodeficiency syndromes are associated with a characteristic set of infectious predispositions and some involve the same pathogens. Patients with antibody deficiency have a predisposition to respiratory tract infections caused by encapsulated bacteria as well as enteroviruses [1]. Patients with cellular deficiency are predominantly susceptible to infections caused by intracellular organisms. Patients with phagocytic defects are susceptible to a relatively narrow spectrum of infections, such as catalase-positive organisms in chronic granulomatous disease (CGD) [2] and disseminated nontuberculous mycobacteria in defects of the interferon-gamma (IFN-γ)/interleukin-12 axis [3].

However, the characteristics of infections within the same category of immunodeficiency may vary. Knowledge of the characteristics of these infections is essential for correct diagnoses. Although the association of some infectious organisms with immunodeficiency is reported in the literature, no such data has been reported in Taiwan. In this study, we sought to establish the characteristics of PIDs in Taiwan by retrospectively analyzing the predisposing infectious organisms associated with immunodeficiency in Taiwanese pediatric patients with PIDs treated during the past 20 years.

Methods

Patients

The medical charts of 92 patients with PIDs who were admitted to the pediatric department of the National Taiwan University Hospital between March 1984 and March 2004 were retrospectively reviewed. The PIDs

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Table 1. Summary of pediatric patients with primary immunodeficiency diseases (PIDs) admitted to the National Taiwan University Hospital between 1984 and 2004

PIDs	No. of patients (n = 92)	No. of patients with first admission due to infection (55/92)	Mean age at onset of recurrent infection (range)	Mean age at diagnosis (range)
Antibody deficiencies	25	21/25		
Agammaglobulinemias	10	9/10	4 months (0-8 months)	3.8 years (4 months-10 years)
CVID	8	6/8	3 years (0-10 years)	4.6 years (1 month-10 years)
IgG subclass deficiency	6	5/6	4.2 months (0-8 months)	2.5 years (3 months-6 years)
Selective k chain deficiency	1	1/1	1 month	6 months
Combined deficiencies	21	10/21		
SCID	5	5/5	1.6 months (0-2 months)	4.2 months (2 months-6 months)
Omenn syndrome	2	2/2	2 months	4 months
WAS	8	0/8	6 months (1 month-1.2 years)	2.6 years (2 months-12 years)
Ataxia-telangiectasia	1	0/1	-[a]	2 years
Hyper-IgM syndrome	3	3/3	5.6 months (4 months-7 months)	1.5 years (6 months-3 years)
CID (undefined)	2	0/2	2 months, 5 months	2 months, 5 months
Cellular deficiencies	34	14/34		
NK cell deficiency	1	1/1	7 months	4 years
CD4 lymphopenia	2	1/2	2 years, 15 years	2 years, 15 years
T lymphopenia	2	2/2	2 months, 4 months	9 months
Impaired CMI, undefined	3	2/3	4 months, 2 years	10 years
DiGeorge syndrome	25	8/25	-[b]	-[b]
APECED	1	0/1	8 years	13 years
Phagocyte defects	11	10/11		
CGD	6	6/6	1.3 years (0-5 years)	2.7 years (2 months-8 years)
Hyper-IgE syndrome	2	2/2	1 months, 3 years	15 years, 6 years
Autoimmune neutropenia	2	2/2	2 months, 3 months	8 months, 9 months
Chediak-Higashi syndrome	1	0/1	-[a]	7 months
Complement deficiency				
Complement 4 deficiency	1	0/1	-	7 years

Abbreviations: CVID = common variable immunodeficiency; IgG = immunoglobulin G; SCID = severe combined immunodeficiency; WAS = Wiskott-Aldrich syndrome; Hyper-IgM = hyperimmunoglobulin M; CID = combined immunodeficiency; NK = natural killer cell; CMI = cell-mediated immunity; APECED = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CGD = chronic granulomatous disease; Hyper-IgE = hyperimmunoglobulin E

[a]Data are not shown in ataxia-telangiectasia and Chediack-Higash syndrome because no apparent infection required admission occurred.

[b]Data were not collected in DiGeorge syndrome.

are summarized in Table 1. The PIDs were diagnosed and classified according to the established principles [4,5]. Mutation analyses for Bruton tyrosine kinase (BTK), WAS protein (WASP), autoimmune regulator (AIRE), and CGD (CYBB; cytochrome b-245, beta polypeptide) genes were performed in 3 patients with agammaglobulinemia, 4 patients with WAS, 1 patient with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), and 1 patient with CGD. Chromosome karyotyping or fluorescent in situ hybridization (FISH) analysis was performed for 21 patients with DiGeorge syndrome. Undefined impaired cell-mediated immunity was diagnosed in 3 patients based on an inadequate reaction to skin tests for purified protein derivative, candida, tetanus toxoid, or trychophyton.

Nosocomial infections caused by bacteria that are frequently encountered in intensive care units or hospital wards were not included. Infections occurring after successive bone marrow transplantations in cases of severe combined immunodeficiency, WAS, and Chediak-Higashi syndrome were not included. Records of all infectious episodes as well as identified pathogens were reviewed. The identified organisms were proven to be responsible for the infections by standard culture, virus isolation, serology, polymerase chain reaction,

Table 2. Genetic studies in pediatric patients with primary immunodeficiency diseases

XLA	Mutation in *BTK* gene
Patient 1	1000 T→C (Y 334 H)
Patient 2	IVS11+6T→G
Patient 3	1713 T→G (Y 571 X)[a]
WAS	Mutation in *WASP* gene
Patient 4	121C→T (R 41 X)
Patient 5	37 C→T (R 13 X)
Patient 6	245 C→T (Ser 82"Phe)
Patient 7	IVS1-1g→C
CGD	Mutation in *CYBB* gene
Patient 8	Frame shift mutation with deletion of a G 1691 located 31 nucleotides upstream of the stop codon
APECED	
Patient 9	Normal at exons 2, 6, 8, and 10 in *AIRE* gene
DiGeorge syndrome	
Chromosome karyotyping	
5 patients	del 22q11
3 patients	del 22q11.22
1 patient	del 22q11.21;q11.23
1 patient	del 10p
FISH	
7 patients	del 22q11.2
Gene analysis	
1 patient	Loss of 7 loci in DGCR region; deletion in DGCR region (22q11.2)

Abbreviations: XLA = X-linked agammaglobulinemia; WAS = Wiskott-Aldrich syndrome; CGD = chronic granulomatous disease; APECED = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; FISH = fluorescent in situ hybridization; BTK = Bruton tyrosine kinase; WASP = WAS protein; CYBB = cytochrome b-245, beta polypeptide; AIRE = autoimmune regulator; DGCR = DiGeorge syndrome chromosome region

[a]Mother and sister normal at 1713 T.

biopsy, or clinical features. Failure to identify the cause of an infectious episode was found to be typically due to the absence of microbiological analysis, negative results, or missing data. Records of follow-up examinations were also reviewed; the follow-up period varied between individual patients.

Results

Patient characteristics

A total of 92 pediatric patients with various PIDs were classified into 5 major categories of immunodeficiencies (Table 1). Mutation analyses for the *BTK* gene in 3 patients with agammaglobulinemia, the *WASP* gene in 4 patients with WAS, and the *CYBB* gene in 1 patient with CGD showed positive findings (Table 2). Western blot analysis was also performed for the patient with *CYBB* gene mutation, and the results indicated that gp91phox was 12% of the normal control and p22phox was 48% of the normal control. One patient with APECED displayed an *AIRE* gene having a normal sequence. Deletions in 22q11 (n = 17) and 10p (n = 1) were detected by FISH or chromosome karyotyping in 21 patients with DiGeorge syndrome detected (Table 2). Patients with antibody deficiencies constituted 27.2% (25/92) of the cases, while cellular and combined immunodeficiency disorders represented 59.8% (55/92) of the cases.

Among patients with antibody deficiencies, recurrent infection occurred at a later stage in patients with common variable immunodeficiency (CVID) [3 years] as compared to that in patients with agammaglobulinemias (4 months). Among patients with combined deficiencies, the onset of recurrent infection was within the first 6 months of age, except for patients with ataxia-telangiectasia who had no obvious recurrent infection. In patients with cellular deficiency or phagocyte defects, the onset of infection and age at diagnosis of PID varied widely from patient to patient, ranging from a few months after birth to the first or second decade of life. One patient with a family history of Chediak-Higashi syndrome was diagnosed before the occurrence of any infection. Complement deficiency was the least common PID, and the main manifestation in the only patient with complement 4 deficiency was juvenile rheumatoid arthritis without recurrent infection.

Sixty percent of patients were initially admitted to the hospital due to infection. The reason for the initial admission for most of the remaining patients was the development of symptoms characteristic of WAS, ataxia-telangiectasia, DiGeorge syndrome, APECED, and complement deficiency (Table 1).

Prevalence of infections

As summarized in Table 3, pneumonia occurred at least once in 92% of patients with antibody deficiencies, in 76.5% of patients with cellular deficiencies, and in 81% of patients with combined deficiencies. Other major manifestations were generally similar in these 3 groups of immunodeficiencies, and constituted acute gastroenteritis, bronchiolitis, otitis media, and bacteremia. Patients with phagocyte defects, particularly those with CGD, displayed very different clinical manifestations as compared to the other 3 groups. These manifestations were, in the order of frequency (after taking into account the number of patients and episodes), skin abscess, pneumonia, lymphadenitis, and acute gastroenteritis. The recurrent rate of skin abscess was high (22 episodes in 6 patients). Liver abscess occurred in 1 patient with CGD, but was absent in patients with other types of PIDs (Table 3).

Etiology of infections

Causative pathogens were identified in only 44.8% of the infection episodes. The major categories of pathogens, in order of frequency, were extracellular bacteria, viruses, intracellular bacteria, fungi, and multiple bacteria (Fig. 1). The frequency of unknown pathogens was equally high (50% to 60% by age group), with the frequency of extracellular bacterial infections being markedly higher in patients above 5 years of age (Fig. 2). Viral infections were relatively rare. No obvious seasonally related differences in the categories of pathogens were noted (Fig. 3).

As shown in Fig. 4, the frequency of unknown pathogens ranged from 33% to 66% in the various immunodeficiency disorders. Extracellular bacterial infections were the least common in patients with cellular deficiencies. Viral infections were most evident in the groups of cellular and combined immunodeficiencies,

Table 3. Prevalence of infection by site requiring admission

Type of infection	Antibody deficiency		Cellular deficiency		Combined deficiency		Phagocyte defect	
	Patients (n = 25)[a] No. (%)	Episodes (n = 133)[b] No. (%)	Patients (n = 34)[a] No. (%)	Episodes (n = 107)[b] No. (%)	Patients (n = 21)[a] No. (%)	Episodes (n = 80)[b] No. (%)	Patients (n = 11)[a] No. (%)	Episodes (n = 72)[b] No. (%)
Pneumonia	23 (92.0)	71 (53.0)	26 (76.5)	39 (36.4)	17 (81.0)	31 (38.7)	5 (45.0)	6 (8.3)
Bronchiolitis	7 (28.0)	10 (7.5)	10 (29.4)	20 (18.7)	1 (4.8)	1 (1.3)	3 (27.0)	3 (4.2)
Acute gastroenteritis	10 (40.0)	13 (9.7)	8 (23.5)	9 (8.4)	8 (38.1)	12 (15.0)	3 (27.0)	6 (8.3)
Bacteremia/fungemia	5 (20.0)	5 (3.7)	6 (17.7)	6 (5.6)	4 (19.0)	4 (5.0)	1 (9.0)	1 (1.4)
Otitis media	6 (24.0)	6 (4.5)	4 (11.8)	5 (4.7)	3 (14.3)	1 (1.3)	1 (9.0)	1 (1.4)
Sinusitis	5 (20.0)	5 (3.7)	1 (2.9)	1 (0.9)	-	-	1 (9.0)	1 (1.4)
Skin abscess or cellulitis (also perianal)	4 (16.0)	5 (3.7)	5 (14.7)	6 (5.6)	3 (14.3)	6 (7.5)	6 (54.5)	22 (30.5)
Liver abscess	-	-	-	-			1 (9.0)	1 (1.4)
Meningitis/encephalitis	2 (8.0)	2 (1.5)	3 (8.8)	3 (2.8)	3 (14.3)	3 (3.8)	-	-
Lymphadenitis/suppurative adenitis	-	-	-	-	1 (4.8)	1 (1.3)	3 (27.0)	6 (8.3)
Urinary tract infection	3 (12.0)	3 (2.3)	-	-	2 (9.5)	2 (2.5)	3 (27.0)	3 (4.2)
Peritonitis	-	-	1 (2.9)	1 (0.9)	-	-	1 (9.0)	1 (1.4)
Osteomyelitis	-	-	1 (2.9)	1 (0.9)	1 (4.8)	1 (1.3)	2 (18.0)	3 (4.2)
Varicella	1 (4.0)	1 (0.7)	2 (5.9)	2 (1.8)	3 (14.3)	3 (3.8)	-	-
Herpes zoster	-	-	2 (5.9)	3 (2.8)	-	-	-	-
Herpangina or hand-foot-mouth disease	-	-	1 (2.9)	1 (0.9)	1 (4.8)	1 (1.3)	2 (18.0)	2 (2.8)
Rubella infection	-	-	1 (2.9)	1 (0.9)	-	-	-	-
Mononucleosis	-	-	1 (2.9)	1 (0.9)	2 (9.5)	2 (2.5)	-	-
Others	12 (9.0)		8 (7.4)		12 (15.0)		16 (22.2)	

[a]Patients who had at least 1 episode of the specific infection.

[b]Episodes of specific infection within each category of immunodeficiency.

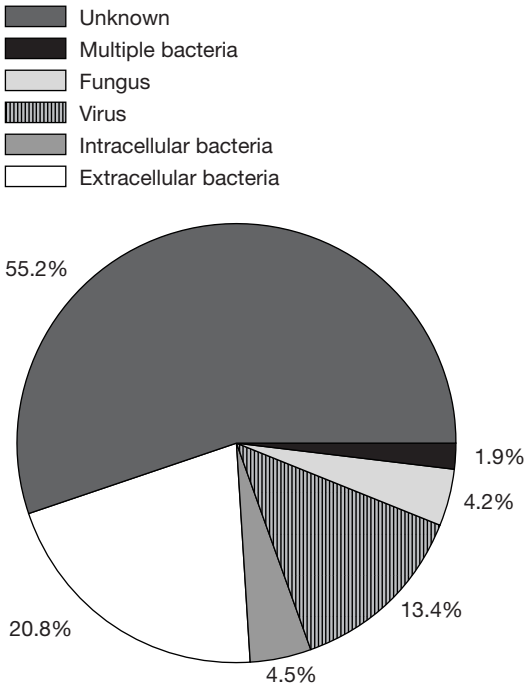

Fig 1. Proportion of infection episodes caused by major categories of pathogens in primary immunodeficiency diseases.

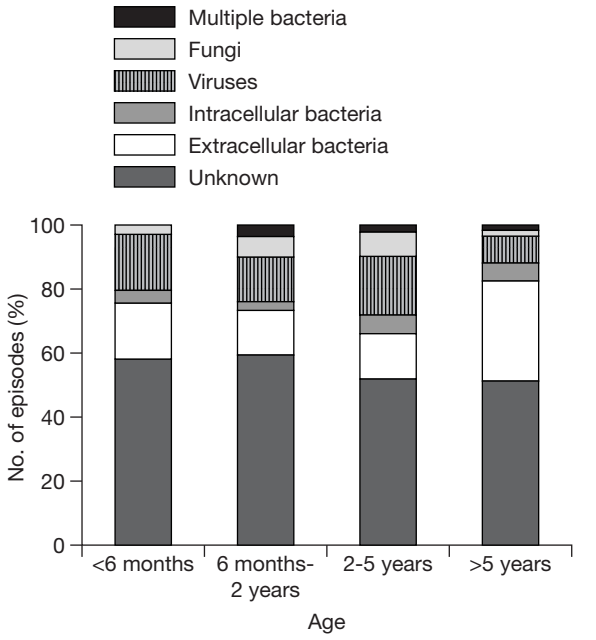

Fig 2. Age distribution of infection episodes caused by major categories of pathogens in primary immunodeficiency diseases.

and fungal infections were particularly prevalent in patients with phagocyte defect (Fig. 4). The pathogens responsible for pneumonia and bacteremia/fungemia are listed in Table 4 and Table 5.

Encapsulated bacteria such as *Haemophilus influenzae*, *Pneumococcus*, and *Haemophilus parainfluenza* were the most common pathogens of pneumonia in patients displaying antibody deficiency (Table 4). In addition, there was a high recurrence rate of pneumonia caused by *H. influenzae* (13 episodes in 3 patients). Among the 11 patients displaying antibody deficiency with known organisms causing pneumonia, 7 patients had agammaglobulinemia. Community-acquired *Pseudomonas aeruginosa* and *Campylobacter coli* infections were particularly evident, in addition to those infections caused by the encapsulated bacteria mentioned earlier (Table 5).

The frequency of viral, fungal, and intracellular bacterial infections was higher in patients with combined and cellular immunodeficiency than in those with antibody deficiency (Fig. 4). As shown in Table 4, the main causative pathogens of pneumonia in these patients included intracellular bacteria such as *Tuberculous bacilli*, *Mycoplasma pneumoniae*, *Chlamydia* spp., viruses such as respiratory syncytial virus (RSV), cytomegalovirus (CMV), influenza virus, and adenovirus, and *Pneumocystis jiroveci* in 2 patients with WAS and hyperimmunoglobulin M (hyper-IgM) syndrome. In addition to cytomegaloviral pneumonitis in patients with WAS (n = 1), undefined combined immunodeficiency (n = 1), T lymphopenia (n = 1), and DiGeorge syndrome (n = 1), 2 siblings with suspected Omenn syndrome had cytomegaloviral mononucleosis.

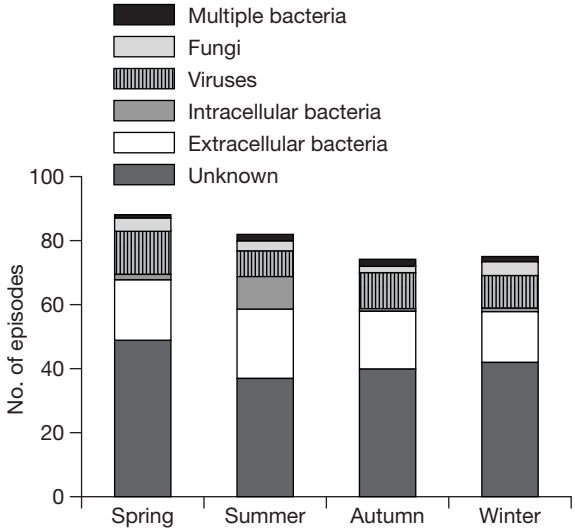

Fig 3. Seasonal distribution of infection episodes caused by major categories of pathogens in primary immunodeficiency diseases.

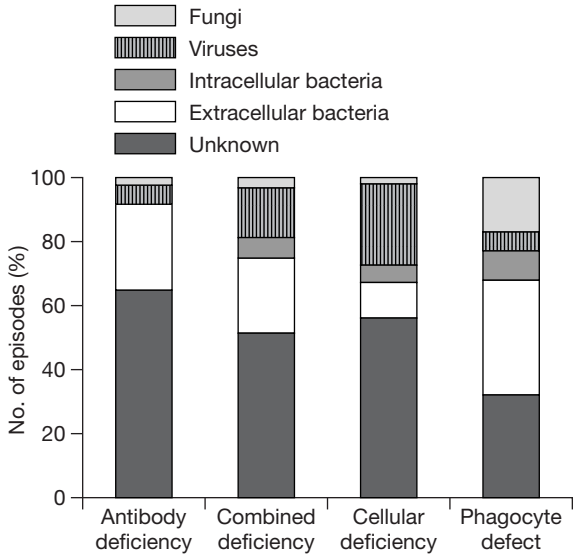

Fig 4. Distribution of infection episodes caused by major categories of pathogens in four groups of primary immunodeficiency diseases.

Sepsis in the patients with cellular deficiency may have been caused by *Salmonella* spp. in 1 patient with impaired cell-mediated immunity, in whom persistent salmonellosis complicated by osteomyelitis was noted, and by *Candida albicans* in another patient with T lymphopenia, although bacteremia could also have occurred in these patients (Table 5). As noted for patients with antibody deficiency, bacteremia caused by encapsulated bacteria and community-acquired *P. aeruginosa* was also evident in 2 patients with suspected hyper-IgM syndrome (Table 5).

Other pathogens of various infections included episodes of herpes zoster and recurrent systemic cutaneous herpes simplex virus (HSV) type I infection in a patient with isolated natural killer (NK) cell deficiency [6], HSV meningoencephalitis in 1 patient with DiGeorge syndrome, cryptococcal meningitis in 1 patient with CD4 lymphopenia, and pneumococcal meningitis in a patient with WAS. Lymphadenitis caused by tubercle bacilli occurred in 2 patients with T lymphopenia and WAS.

Consistent with previous reports [7], catalase-positive pathogens were responsible for the infections in patients with CGD. *Aspergillus fumigatus* pneumonia occurred in 2 patients with CGD, but was absent in patients with other PIDs (Table 4). Another patient with CGD experienced sepsis due to *Burkholderia cepacia*, as documented by bone marrow culture (Table 5). Other complications in CGD patients included subcutaneous abscess caused by *A. fumigatus* and *Serratia marcescens* in 1 patient who also experienced complications due to osteomyelitis, Rhizopus-mediated sinusitis (mucormycosis) [n = 1], peritonitis caused by *Candida pseudotropicalis* with fungal granuloma (n = 1), and lymphadenitis due to *Mycobacteria* spp. (n = 1). In patients with hyperimmunoglobulin E (hyper-IgE) syndrome [8] and autoimmune neutropenia, skin abscesses caused by *Staphylococcus aureus* or *Staphylococcus epidermidis* were noted. One patient was diagnosed early (at 7 months of age) with Chediak-Higashi syndrome due to family history; his brother had died at 2 years of age from Epstein-Barr virus mononucleosis.

Although pneumonia caused by *M. pneumoniae* is prevalent in the general population [9], it was rarely found to occur in the PID patients in this study (Table 4). In all PIDs, acute gastroenteritis was caused mainly by *Salmonella* and rotavirus.

Prophylactic antibiotics

Prophylactic antibiotics/antifungals were prescribed to 9 patients. The regimens were cefpodoxine proxetil (Banan) in a patient with X-linked agammaglobulinemia (XLA); amoxicillin/clavulanic acid (Augmentin) in another patient with agammaglobulinemia; cefixime (Cefspan), cephalexin (Keflex), and amoxicillin/clavulanic acid in a patient with suspected hyper-IgM syndrome (not X-linked immunodeficiency with hyper-IgM); cephalexin in 1 patient with undefined impaired cell-mediated immunity, nystatin (Mycostatin) in a patient with APECED, cotrimoxazole (Baktar) in a patient with CGD, amoxicillin/clavulanic acid and cotrimoxazole in a patient with CGD, and amoxicillin/clavulanic acid in 1 patient with hyper-IgE syndrome.

Discussion

PIDs were traditionally classified into 5 major categories including antibody deficiency, combined T- and B-cell deficiency, cellular deficiency, phagocyte defect, and complement deficiency [4,5]. However, the molecular basis of more than 100 PIDs has been elucidated in the past decades, and PIDs were newly classified into T- and B-cell immunodeficiencies, predominantly antibody deficiencies, other well-defined immunodeficiency syndromes, disease of immune dysregulation, congenital defects of phagocyte number, function, or both, defects in innate immunity, autoinflammatory disorders, and complement deficiencies, according to the latest PIDs

Table 4. Evidences of proven pathogens in primary immunodeficiency diseases

Test	Virus	No.[a]	Bacteria (extracellular)	No.[a]	Bacteria (intracellular)	No.[a]	Fungus	No.[a]
PCR								
	CMV	1	-		-		*Pneumocystis jiroveci*	1
	HSV	1	-		-			
Serology								
	HBV	2	-		*Mycoplasma*	2	-	
	CMV	4	-				-	
	VZV	1	-				-	
Antigen detection								
	Rotavirus	1	-		*Chlamydia*	1	*Cryptococcus neoformans*	1
	RSV	5	-					
Biopsy and stain								
	CMV (inclusion body)	1	-		*Mycobacteria*	4	Hyphae	1
							Aspergillus	1
Culture								
	Adenovirus	3	80 (21 different strains of bacteria)		*Salmonella*	9	*Candida* spp.	10
	CMV	8			*Chlamydia*	1	*Aspergillus*	2
	HSV	1			*Tubercle bacilli*	2	*Penicillium maneffi*	1
	Influenza	3						
	Parainfluenza type 3	2					*Pneumocystis jiroveci*	0

Abbreviations: PCR = polymerase chain reaction; CMV = cytomegalovirus; HSV = herpes simplex virus; HBV = hepatitis B virus; VZV = varicella zoster virus; RSV = respiratory syncytial virus

[a]The number of events using a particular diagnostic method (one specimen or patient can have diagnostic methods).

classification committee convened by the World Health Organization [10]. In order to represent particular immunological features in one major category, the PIDs discussed here were classified according to the general principles established earlier [4,5].

Although defects involving humoral immunity are the most common immunodeficiencies (accounting for about 70% of PIDs) [11], the relatively high proportion of patients with cellular and combined immunodeficiency in this study (Table 1) indicates that defects in T-cell function may lead to susceptibility to infections or other clinical problems that are more severe than those associated with antibody disorders [12].

The relative rarity of viral infections and increased prevalence of bacterial infections in patients older than 5 years (Fig. 2) might be partly explained by the high mortality rate in younger patients with cellular and combined immunodeficiency (data not shown).

It is entirely conceivable that different infection patterns and causative pathogens exist among patients with different major categories of immunodeficiency. Pneumonia is the prevalent infection in nearly all groups of immunodeficiency except in patients with phagocyte defects [13]. Moreover, in patients with XLA, the sinopulmonary tract is a frequent site of infection (60% of patients); other infections include gastroenteritis (35%), pyoderma (25%), meningoencephalitis (16%), septicemia (10%), and osteomyelitis (3%) [14]. Recurrent otitis media, chronic sinusitis, and recurrent pneumonia, often with resulting bronchiectasis, are the most frequent presenting infections in adults with CVID [15]. In approximately half the patients with CVID, the gastrointestinal tract is affected [16]. Presently, pneumonia occurred in 92% of those patients with antibody deficiency, with other infections such as gastroenteritis, bronchiolitis, otitis media, sinusitis septicemia, and skin abscess, in descending order of frequency (Table 3). Consistent with a previous study [17], encapsulated bacteria such as *H. influenzae*, *Pneumococcus*, *P. aeruginosa*, and *S. aureus* were found to be commonly associated with these conditions (Table 4 and Table 5). A high recurrence rate of pneumonia caused by *H. influenzae* was noted in patients (13 episodes in 3 patients). However, the *H. influenzae*

Table 5. Microorganisms associated with pneumonia in primary immunodeficiency diseases (PIDs)

Microorganism	Antibody deficiency		Cellular deficiency		Combined deficiency		Phagocyte defect	
	Episodes (n = 21)[a] No. (%)	Patients (n =11)[b] No. (%)	Episodes (n =10)[a] No. (%)	Patients (n =10)[b] No. (%)	Episodes (n = 7)[a] No. (%)	Patients (n = 7)[b] No. (%)	Episodes (n = 4)[a] No. (%)	Patients (n = 4)[b] No. (%)
Bacteria	20 (95.2)	10 (90.9)	4 (40.0)	4 (40.0)	2 (28.6)	2 (28.6)	2 (50.0)	2 (50.0)
Haemophilus influenza[c]	13 (62.0) [A]	3 (27.3)			1 (14.3) [D]	1		
Pneumococcus[c]	2 (9.5) [A, C]	2 (18.2)	1 (10.0) [M]	1 (10.0)	1 (14.3) [E]	1	1 (25.0) [O]	1 (25.0)
Haemophilus parainfluenza[c]	2 (9.5) [A, C]	2 (18.2)						
Moraxella spp.[c]	1 (4.8) [A]	1 (9.1)						
Enterobacter spp.[c]	1 (4.8) [A]	1 (9.1)						
Mycoplasma spp.[c]	1 (4.8) [B]	1 (9.1)	1 (10.0) [L]	1 (10.0)				
Chlamydia spp.[c]			1 (10.0) [M]	1 (10.0)				
Tuberculous bacilli[c]			1 (10.0) [L]	1 (10.0)			1 (25.0) [O]	1 (25.0)
Virus	1 (4.8)	1 (9.1)	6 (60.0)	6 (60.0)	3 (42.9)	3 (42.9)		
RSV[c]	1 (4.8) [B]	1 (9.1)	2 (20.0) [K, M]	2 (20.0)				
CMV[c]			2 (20.0) [K, M]	2 (20.0)	2 (28.6) [D, G]	2		
Fungi					2 (28.6)	2 (28.6)	2 (50.0)	2 (50.0)
Pneumocystis jiroveci[c]					2 (28.6) [D, E]	2		
Aspergillus fumigatus[c]							2 (50.0) [N]	2 (50.0)

Abbreviations: RSV = respiratory syncytial virus; CMV = cytomegalovirus

[a]Pneumonia episodes caused by the specified organism with in the category of immunodeficiency.

[b]Patients within that category of immunodeficiency whose pneumonia was caused by a specific organism.

[c]Letters in parenthesis denote specific PIDs as follows: A = Bruton's agammaglobulinemia; B = common variable immunodeficiency; C = immunoglobulin G subclass deficiency; D = Wiskott-Aldrich syndrome; E = hyperimmunoglobulin M syndrome; F = Omenn syndrome; G = combined immunodeficiency, undefined; H = severe combined immunodeficiency; I = natural killer cell deficiency; J = CD4 lymphopenia; K = T lymphopenia; L = undefined impaired cell-mediated immunity; M = DiGeorge syndrome; N = chronic granulomatous disease; O = hyperimmunoglobulin E syndrome.

obtained from the patients' sputum cultures may not have been the pathogen responsible for the pneumonia, as *H. influenzae* is a normal resident of the respiratory tract in healthy children [18]. Most cases of sepsis caused by *P. aeruginosa* are nosocomially acquired [19]. In the rare cases of community-acquired *P. aeruginosa* sepsis, approximately 50% of the patients had underlying primary immunodeficiency, mostly congenital agammaglobulinemia and neutropenia [20-23]. Pneumonia may be the first manifestation of PIDs in previously healthy children [20-24]. In this study, in the 3 patients with *P. aeruginosa* sepsis, 2 patients with agammaglobulinemia presented with pneumonia at 8 months of age.

Two patients with Bruton's agammaglobulinemia experienced *C. coli* bacteremia. *C. coli* predominantly causes gastroenteritis, and rarely produces bacteremia or extraintestinal infections [25]. There has been only one reported case of Bruton's agammaglobulinemia with *C. coli* infection presenting with recurrent cellulitis associated with *C. coli* bacteremia [26]. With regard to the gastrointestinal symptoms of lactose intolerance and protein-losing enteropathy, *Campylobacter*, *Yersinia* spp., or *Giardia lamblia* may all contribute to the symptoms [27]. In our study, depending on the culture protocols selected, the isolated pathogens were mainly *Salmonella* or rotavirus. Although enteroviruses and hepatitis viruses cause complications in patients with XLA [28,29], they were not observed in the patients included in our study.

Although the age of onset of recurrent infections in patients with XLA is typically 6 to 12 months of age or later [30], the age of onset of infection in our study was found to be as early as the first few months of life in patients with agammaglobulinemias, even in those patients with a CVID or immunoglobulin G (IgG) subclass deficiency (Table 1).

Patients with inadequate cellular immunity are highly susceptible to opportunistic viral infections such as those associated with herpes viruses, and they often have progressive pneumonia caused by parainfluenza 3 virus, RSV, CMV, or *P. jiroveci* [31]. In herpesviridae, both varicella zoster virus (VZV) and HSV easily reactivate under immunosuppressive conditions and extrapulmonary sites are more likely to be involved, although pneumonitis can occur [32]. The frequency of

Table 6. Microorganisms associated with bacteremia/fungemia in primary immunodeficiency diseases (PIDs)

Microorganism	Antibody deficiency		Cellular deficiency		Combined deficiency		Phagocyte defect	
	Episodes (n = 11)[a] No. (%)	Patients (n =10)[b] No. (%)	Episodes (n = 5)[a] No. (%)	Patients (n = 5)[b] No. (%)	Episodes (n = 5)[a] No. (%)	Patients (n = 5)[b] No. (%)	Episodes (n = 1)[a] No. (%)	Patients (n =1)[b] No. (%)
Pseudomonas aeruginosa[c]	3 (27.3) [A]	3 (30.0)			2 (40.0) [E]	2 (40.0)		
Haemophilus influenza[c]	4 (36.4) [A]	3 (30.0)						
Pneumococcus[c]	1 (9.1) [C]	1 (10.0)			2 (40.0) [E, D]	2 (40.0)		
Campylobacter spp.[c]	2 (18.2) [A]	2 (20.0)						
Enterobacter spp.[c]	1 (9.1) [B]	1 (10.0)	1 (20.0) [M]	1 (20.0)				
Salmonella spp.[c]			1 (20.0) [L]	1 (20.0)				
Other *Streptococcus* spp.[c]					1 (20.0) [D]	1 (20.0)		
Aeromonas spp.[c]			1 (20.0) [M]	1 (20.0)				
MRSA[c]			1 (20.0) [M]	1 (20.0)				
Burkholderia cepacia[c]							1 (100) [N]	1 (100)
Candida albicans[c]			1 (20.0) [K]	1 (20.0)				

Abreviation: MRSA = methicillin-resistant *Staphylococcus aureus*

[a]Bacteremia/fungemia episodes caused by specific organisms within the category of immunodeficiency.

[b]Patients within that category of immunodeficiency whose bacteremia/fungemia was caused by a specific organism.

[c]Letters in parenthesis denote specific PIDs as follows: A = Bruton's agammaglobulinemia; B = common variable immunodeficiency; C = immunoglobulin G subclass deficiency; D = Wiskott-Aldrich syndrome; E = hyperimmunoglobulin M syndrome; F = Omenn syndrome; G = combined immunodeficiency undefined; H = severe combined immunodeficiency; I = natural killer cell deficiency; J = CD4 lymphopenia; K = T lymphopenia; L = undefined impaired cell-mediated immunity; M = DiGeorge syndrome; N = chronic granulomatous disease.

viral infection increased by 15% to 25% in patients with combined and cellular deficiencies (Fig. 4). As in the case of antibody deficiency, pneumonia due to intracellular bacteria, viruses (RSV, CMV, influenza virus, and adenovirus), and *P. jiroveci* was the major infection type in patients with combined and cellular immunodeficiencies (Table 3 and Table 4). The presentations of HSV and VZV infections in our patient with isolated NK cell deficiency [6] are consistent with previously reported cases [33]. Likewise, the occurrence of *Cryptococcus neoformans* in 1 patient with CD4 lymphopenia is the same as that found in individuals infected with the human immunodeficiency virus [34].

There are different variants of hyper-IgM syndrome, and the immunological features as well as the infection predispositions are not the same. X-linked hyper-IgM syndrome (XHIM) results from a mutation in the CD40 ligand gene, leading to T-cell defects and very low or undetectable levels of immunoglobulin A and IgG, and normal to increased serum IgM [35]. XHIM is classified as a T- and B-cell immunodeficiency [10]. The two autosomal recessive forms of hyper-IgM-syndrome, now termed activation-induced cytidine deaminase deficiency and uracil-DNA glycosylase deficiency, are classified as antibody deficiencies [10]. In the X-linked form, opportunistic infections characteristic of T-cell dysfunction such as interstitial pneumonitis caused by *P. jiroveci* and chronic diarrhea caused by *Cryptosporidium parvum* are of special concern except for usual organisms such as encapsulated bacteria encountered in hypogammaglobulinemia [35]. Interstitial pneumonitis caused by *P. jiroveci* affects as many as 20% to 40% of the patients and often marks clinical onset [36,37]. In addition, it is one of the major causes of death [36,38]. Opportunistic infections with *P. jiroveci* are unusual in autosomal recessive forms of hyper-IgM syndrome [39]. In our study, 3 patients with suspected hyper-IgM syndrome were classified as having combined immunodeficiency; however, only 1 patient with defective expression of CD40 ligand after activation of CD4+ T cells was confirmed to have XHIM syndrome [40]. The other 2 patients were clinically suspected of having hyper-IgM syndrome; further genetic study or CD40 ligand expression analysis was not undertaken. The infections in the patient with XHIM syndrome included pneumonia caused by *P. aeruginosa* and *C. albicans* cultured from bronchoalveolar lavage (BAL) at 6 months of age [40] and *P. jiroveci* pneumonia diagnosed by polymerase chain reaction at 6 years of age. The other 2 patients with suspected hyper-IgM syndrome had recurrent bacterial pneumonia characteristic of hypogammaglobulinemia and both experienced community-acquired *P. aeruginosa*

bacteremia, as seen in patients with agammaglobulinemia [21-24].

Although WAS and ataxia-telangiectasia are classified as "other well-defined immunodeficiency syndromes" instead of "T- and B-cell immunodeficiencies" [10], we classified them as combined immunodeficiency in accordance with established classification [4,5,17] based on immunological features. In all 8 patients with WAS, the initial presentation of thrombocytopenia complicated by gastrointestinal bleeding and idiopathic thrombocytopenia was misdiagnosed. The reported infections in patients with WAS are usually those produced by Pneumococci and other encapsulated bacteria and result in otitis media, pneumonia, meningitis, or sepsis during the first year. Opportunistic infections by *P. jiroveci* and herpes viruses become more problematic later in life [12]. However, among the 3 patients with WAS who had never been treated with steroids, one had *P. jiroveci* pneumonia at 3 months of age and one had CMV pneumonitis at 4 months of age before bone marrow transplantation. In the other 5 patients with WAS, 3 had infections while under steroid therapy for suspected idiopathic thrombocytopenic purpura, including *Mycobacteria* lymphadenitis, varicella, pneumococcal septicemia, and meningitis. Only 1 patient with ataxia-telangiectasia exhibited no apparent infection that required hospital admission, which is consistent with a demonstration that severe infections are uncommon in spite of the high prevalence of immunologic abnormalities in these patients [41].

In patients with DiGeorge syndrome, the diagnosis was often made on the basis of other clinical features not related to infection. Of 25 patients, 10 had no apparent infections requiring hospital admission and the remaining 15 patients exhibited variable severities of infections. Both thymus hypoplasia and congenital heart disease may have contributed to the susceptibility to infection. According to a previous study, up to 80% of patients with DiGeorge syndrome have a partial form of the disease (variable degree of hypoplasia of the thymus and parathyroid glands) [42], and it is suggested that no immunological treatment is needed for this partial form [12,31].

CGD patients comprised the majority of patients with phagocyte defects in our study (Table 1). In a large series study, pneumonia was the most common infection (79% of CGD patients), and other infections that were found to occur were abscesses (any kind) [68%], suppurative adenitis (53%), osteomyelitis (25%), bacteremia/fungemia (18%), and cellulitis (5%) [7], in that order of frequency. In a smaller study, lymphadenopathy, pulmonary infections, and skin infections were the most common manifestations of CGD (75.6%, 65.9%, and 63.4%, respectively) [13]. There were only 6 patients with CGD in our study, and the frequency of infections was in the same order as those in the patients with phagocyte defect — skin abscess, pneumonia, lymphadenitis, and acute gastroenteritis (Table 3). Only 5 microorganisms are responsible for the overwhelming majority of infections in CGD in North America and Europe: *S. aureus, B. cepacia, S. marcescens, Nocardia* spp., and *Aspergillus* spp. [43]. Pneumonia and cellulits are usually caused by the Gram-negative members of this collection, and rare bacteremia is usually caused by *B. cepacia* and *S. marcescens* as reported in a previous study and observed in this study [43]. Staphylococcal liver abscesses are almost pathognomonic of CGD and should always prompt screening for CGD [7,44,45].

Evidence of pathogens

Serological testing has limited value in the immunocompromised host. Severely compromised patients may be incapable of mounting an antibody response, and in those receiving immunoglobulin infusions, results may be impossible to interpret [46]. The rare occurrence of pneumonia caused by *M. pneumoniae* in our study was possibly partly due to unreliable serological testing despite its presence in 40% of the general population (Table 4 and Table 5) [9]. Despite this prevalence, macrolide antibiotics were often prescribed in clinically suspected cases in our patients. Culturing of *M. pneumoniae* is often time-consuming and lacks sensitivity as the sole diagnostic method. Unfortunately, commercial polymerase chain reaction (PCR)-based tests are not yet available for detection of *M. pneumoniae* [9].

Most of the viral infections in our study were diagnosed by standard viral cultures (Table 6). Although viral cultures have the advantage of antiviral susceptibility testing, they take longer than most clinical situations allow, particularly in those with immunodeficiency disorders [46]. Currently available methods for rapid diagnosis include immunofluorescence tests for common community-acquired respiratory viruses using upper tract secretions and multiplex reverse transcription PCR enzyme hybridization assays for parainfluenza virus 1, 2, and 3, influenza A and B, and RSV A and B. Quantitative PCR testing of blood and respiratory secretions is also used for identifying the

herpes group viruses and adenovirus. For CMV, an alternate sensitive test involves the detection of pp65 antigen in the blood [46]. Other tests include PCR or calcofluor white staining of BAL material for *P. jiroveci* [47], and *Aspergillus* antigen detection and PCR [48].

More than half of the infection episodes had no proven pathogens in our study (Fig. 1). There are several possible explanations. Firstly, specimens may not have been sent for analysis for a spectrum of microorganisms; for example, gastroenteritis samples tended to be analyzed solely for salmonella, shigella, and rotavirus antigens. Secondly, the specimen collection method may have been inappropriate. Some authorities suggest further invasive diagnostic procedures as soon as possible if the results from the tests listed above are negative [46]. For example, BAL provides a specific diagnosis in 50% to 70% of immunocompromised children [46]. However, lavage was not used widely in our patients with PIDs, even after negative general work-up for pneumonia.

Prophylactic antibiotics

Only 9 out of 92 patients were prescribed prophylactic antibiotics in our study. This is consistent with the non-routine use of prophylactic antibiotics for PID patients. Treatment of XHIM is based on regular administration of intravenous immunoglobulins (IVIG) and use of cotrimoxazole to prevent *P. jiroveci* pneumonia [35]. In our study, the only patient with confirmed XHIM received regular IVIG without any prophylactic antibiotics [40], and the patient suffered from *P. jiroveci* pneumonia several years later.

In addition to prophylactic cotrimoxazole, which significantly reduces the incidence of life-threatening bacterial infections in patients with CGD [49], especially when used with IFN-γ [50], itraconazole prophylaxis has proven to be an effective and well-tolerated treatment that reduces the frequency of fungal infections including *Aspergillus* infection [51]. Among the 3 patients with CGD in our study, two received regular IFN-γ without any prophylactic antibiotics or antifungal medications (one of them was administered itraconazole for treatment of established mucormycosis). The remaining patient was a girl whose nitroblue tetrazolium test showed less severity; she was prescribed prophylactic cotrimoxazole without IFN-γ. One boy who had received prophylactic amoxicillin/clavulanic acid and cotrimoxazole without IFN-γ died of disseminated aspergillosis. It has been reported that patients with X-linked recessive CGD appear to have a more severe clinical phenotype than those with autosomal recessive forms [7]. If a different strategy is used in the administration of IFN-γ, prophylactic cotrimoxazole and itraconazole is indeed necessary between the variants of CGD, and further studies are urgently needed to define the differences.

None of the patients with WAS in our study received prophylactic antibiotics. There is no consensus in the use of prophylactic antibiotics [52]. Prophylactic anti-*S. aureus* has been suggested in hyper-IgE syndrome [53]. Indeed, one of our patients with hyper-IgE syndrome received long-term oral amoxicillin/clavulanic acid due to previous recurrent skin abscess caused by *S. aureus.*

Prophylactic antibiotics are not routinely prescribed in patients with agammaglobulinemia or CVID. In addition to IVIG, rotating antibiotics in treatment dose is suggested in pansinusitis or post-infectious chronic lung disease [31]. Prophylactic cefpodoxine/proxetil and amoxicillin/clavulanic acid were administered to 2 patients with agammaglobulinemia separately in our study because of frequent pneumonia in spite of treatment with a high dose of IVIG.

In conclusion, we identified various infectious organisms among different types of PIDs in Taiwanese pediatric patients. Although 100 or more PIDs have been described, some may not be recognized in these patients because of limited diagnostic tools. Susceptibility to infection is one of the most important clinical characteristics of PIDs that should prompt us to investigate the underlying immunodeficiencies. Knowledge of specific infectious predispositions may guide the physician toward specific diagnostic methods and treatments. Traditional methods of virus isolation are time consuming, and serological diagnosis such as antibody response may not be reliable in states of immunodeficiency. Reliable and rapid molecular diagnosis is needed for such patients.

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