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The spectrum of infectious pathogens in patients with primary or secondary immunodeficiency

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Abstract

Many non-infectious diseases have as a common complication the secondary development of infections, which are most likely to occur in immunocompromised individuals. Immunodeficiency (ID) is classified into primary and secondary ID (SID). Primary ID results from fundamental defects in proteins and cells that are critical for specific immune responses. Extrinsic factors, such as long-term use of immunosuppressive drugs and chronic diseases, can also affect immune responses, leading to a state of SID. In this review, we summarized the spectra of potential infectious pathogens in primary and SID, which are very different from those in immunocompetent individuals. We hope that this review will help clinicians with empirical management of infections in immunocompromised individuals caused by different etiologies and lead to better patient outcomes.

Keywords

Primary immunodeficiency. Secondary immunodeficiency. Infections. Pathogens.

Introduction

Immunodeficiency (ID) is a group of diseases caused by quantitative and/or functional abnormalities in innate and adaptive immunity[1]. It is classified into primary ID (PID), if the disease is genetically inherited, and secondary ID (SID), if the disease is acquired later in life. The most common PIDs include humoral deficiency, combined ID and phagocyte dysfunction[2], while SIDs are often secondary to hematological disorders and long-term use of immunesuppressives et al.[3]. Patients with either PID or SID are susceptible to a variety of infections, many of which are life-threatening. To assist clinicians rapidly initiate empirical treatment of infections in these patients, this review summarizes the most common infectious pathogens in PID and SID.

The spectrum of infectious pathogens in patients with PID

The spectra of infectious pathogens commonly occurring in the patients with humoral deficiency, combined ID or phagocyte dysfunction are described with some PIDs as examples.

Humoral ID

X-linked agammaglobulinemia (XLA)

XLA, one of the most common X-linked PIDs in children, is characterized by severe hypogammaglobulinemia and loss of peripheral circulating B cells. Children with XLA develop symptoms between 6 and 12 months of age as maternal immunoglobulin G dis-

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appears[4]. Study shows that most patients present with recurrent infections. Other common infections include otitis media, sinusitis, conjunctivitis, urinary tract and gastrointestinal infections. XLA-associated infections are usually caused by cystic purulent bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Streptococcus pyogenes,* and *Pseudomonas aeruginosa* et al. *Giardia lamblia* is often isolated from stool samples of these patients with chronic diarrhea and malabsorption. *Campylobacter jejuni* is another pathogen often causing gastrointestinal, skin, and bloodstream infections in patients with XLA. Without immunoglobulins, XLA patients are susceptible to invasive infections from encapsulated bacteria, have an increased incidence of enterovirus infections and chronic diarrhea.

Selective IgA deficiency (SIgAD)

SIgAD is one of the most common congenital immunodeficiencies in which patients lack IgA secretion both in serum and on mucosal surfaces. The disease can be familial or acquired. Although most individuals with SIgAD are asymptomatic, some patients develop various clinical infections such as pulmonary, gastrointestinal, urogenital, skin, and mucosal infections[5-7]. The majority of these lung infections are caused by *S. pneumoniae*, *H. influenzae*, *Candida albicans,* and *Staphylococcus aureus*. Pathogens responsible for infections at other sites include *Salmonella*, *Shigella*, *Escherichia coli,* and *Klebsiella*.

Cellular ID

DiGeorge syndrome

DiGeorge syndrome is associated with developmental abnormalities of the third and fourth branchial arches with a prevalence of 1:4000-1:6000[8]. Malformations of the heart, palate, and face are characteristic. Bacterial, viral, and fungal infections of the upper and lower respiratory tract are common. The main associated pathogens include *S. pneumoniae*, *H. influenzae*, Moraxella, rhinovirus, coronavirus and respiratory syncytial virus et al.[9].

Chronic granulomatous disease (CGD)

CGD is an inborn error of immunity. Pathogenic variants in the cytochrome B (CYB)-B, CYBA, CYBC1, neutrophil cytosolic factor (NCF)-1, NCF2 and NCF4 genes of the NADPH oxidase enzyme complex are responsible for the clinical phenotype of CGD. NADPH oxidase is an enzyme complex that produces various reactive oxygen species such as superoxide anion and hydrogen peroxide. CGD has an X-linked or autosomal recessive inheritance pattern[10]. Patients with CGD frequently present with a variety of inflammatory and infectious diseases[10]. The most common sites of infection are the lung, gastrointestinal tract, skin, lymph node, liver, bones, kidney, and brain. The most common pathogens in CGD patients are *Aspergillus* spp. accounted for 35% of all deaths from infection in patients with chronic kidney disease (CKD), *S. aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* spp., *Salmonella* spp., *E. coli,* and *Klebsiella* spp.[11,12].

Combined immune deficiency

Purine nucleoside phosphorylase deficiency (PNPD)

PNPD is an autosomal recessive disease. PNP deficiency upregulates blood levels of guanosine and hypoxanthine, resulting in increased levels of guanosine deoxytriphosphate in lymphocytes. The primary characteristic of PNPD is a deficiency in cellular immunity, with suppressor T cells exhibiting a greater degree of impairment than helper T cells, given the heightened sensitivity of T lymphocytes to PNP deficiency. In 79 children with PNPD, 54 patients had recurrent viral, bacterial and fungal infections. The most common etiological viruses include cytomegalovirus (CMV), Epstein-Barr virus (EBV) and varicella[13]. The most common bacteria include *S. pneumoniae*, *S. aureus*, *Mycobacterium,* and *E. coli*. The most common fungus include *Candida*, *Aspergillus* and *Cryptococcus*.

Ataxia telangiectasia (AT)

AT is caused by deleterious mutations in the gene encoding the AT mutated serine/threonine protein kinase. Combined immunodeficiencies occur in about 70% of the patients carrying the mutation. In addition to the eponymous symptoms, patients with AT often present with impaired immunity, hypersensitivity to ionizing radiation, neurological dysfunction, and an increased risk of malignancy[14]. Patients typically present with recurrent sinopulmonary infections, predominantly caused by *S. pneumoniae*, *H. influenzae*, *Aspergillus*, respiratory syncytial virus, and influenza virus.

Major histocompatibility complex class II (MHC-II) deficiency

A deficiency of MHC-II on antigen-presenting cells results in a reduction in the number and impaired function of CD4+ T-cells, rendering the patient highly susceptible to infections caused by a diverse range of bacteria, fungi, viruses and protozoa. The typical clinical manifestations include recurrent respiratory and gastrointestinal infections. Pneumonia was the most common observed symptom that the incidence rate was 82.9% in 29 patients; followed by recurrent diarrhea that the incidence rate was 74.3% in 26 patients, severe infections (such as sepsis, meningitis, encephalitis, and acute respiratory distress syndrome) that the incidence rate was 74.3% in 26 patients, viral infections that the incidence rate was 62.9% in 22 patients, recurrent moniliasis that the incidence rate was 57.1% in 20 patients, and failure to thrive that the incidence rate was 48.6% in 17 patients[15].

Severe combined ID (SCID)

SCID is a group of disorders characterized by severe T-cell deficiency with or without B-cell abnormality. In SCIDs the development of lymphoid stem cells into T cells is affected and the disease is typically characterized by severe hypoplasia of secondary lymphoid organs, thymic abnormalities, loss of lymphoid components, and failure of normal epithelial differentiation. In addition, Hassal's corpuscles may be absent[14]. Patients may have a family history of unexplained infant death and present early in life with a history of developmental failure, oral candidiasis, unexplained diarrhea, interstitial pneumonia and other recurrent bacterial, viral, fungal, or protozoal infections. Liver and spleen tumors may also be present. The present study describes the clinical, immunological, and molecular manifestations of 57 patients diagnosed with SCID from India. Among the most common clinical manifestations in patients are recurrent pneumonia (66%), stunting (60%), chronic diarrhea (35%), gastrointestinal infections (21%), and oral candidiasis (21%)[16]. The bacteria most commonly associated with SCID include Bacillus Calmette-Guerin, Yersinia pestis, *S. aureus*, *Klebsiella pneumoniae*, *P. aeruginosa*, *B. cepacia,* and *Bacillus crystallis*. The most commonly identified viruses are rotavirus, CMV, rubella, respiratory syncytial virus, and varicella.

Wiskott-Aldrich syndrome (WAS)

WAS is an X-linked syndrome characterized by the clinical trial of recurrent infections, thrombocytopenia, and eczema. The gene responsible is the WAS protein (WASP) gene. Sepsis, pulmonary tuberculosis (TB), and *Candida* infections are common in this patient population. Patients with WAS are susceptible to a range of infectious diseases, including candidiasis and molluscum contagiosum, aspergillosis, and *Pneumocystis jiroveci* pneumonia. These patients are also at risk of infection by a variety of bacterial, viral, and fungal pathogens. Bacterial otitis media, sinusitis, and pneumonia are common occurrences, as are impetigo, cellulitis, and abscesses. Other frequently reported bacterial events include small bowel colitis and urinary tract infections, as well as meningitis and sepsis. Viral infections, including varicella-zoster virus (VZV), herpes simplex virus (HSV), EBV, CMV, and human papillomavirus, can have a significant impact on the patient's health[17].

Nezelof syndrome

Nezelof syndrome, also known as thymic hypoplasia syndrome, is a type of immune deficiency in the production of T lymphocytes due to thymic hypoplasia. Immunoglobulin levels may be normal or elevated, and there may be one or more selective defects in certain types of immunoglobulin. Sometimes even immunoglobulin levels are normal, specific antibody responses are impaired. The primary causative agents are *C. albicans*, viruses, *P. aeruginosa* and non-tuberculous mycobacteria.

The spectrum of infectious pathogens in patients with SID

SID occurs as a result of a variety of medical conditions and the use of certain medications, and is becoming increasingly common. Disease-related conditions include tumors, severe infections, and organ or system failure. Long-term use of glucocorticoids, cyclophosphamide, cyclosporine A, and tacrolimus is the most common iatrogenic etiology of SID.

Cancer/Malignancy

There is increasing evidence that post-operative infectious complications (PICs) are associated with

poor prognosis in cancer patients. A large proportion of cancer-related deaths are due to post-operative infections. Inappropriate use of antimicrobials is one of the most common causes of ineffective or failed treatment of infections.

Although the underlying mechanisms of tumor progression associated with PICs are still unknown, three mechanisms have been proposed. First, molecular patterns of pathogens may be directly involved in tumor growth; second, factors released by immune cells during infection may affect tumor progression; third, tumor suppressor factors may inhibit host tumor immunity. In addition, cancer patients may require long-term chemotherapy, which will inevitably compromise host immunity and lead to infection. Another factor to consider is the peripherally inserted central catheter, which is usually implanted in cancer patients for chemotherapy. Repeated invasive surgery compromises the protective barrier of the skin and mucous membranes. The respiratory tract is another common site of infection in cancer patients and is associated with significant morbidity and mortality. Most upper respiratory tract infections are caused by viruses (HSV, CMV, and EBV). The main pathogens causing bloodstream infections in cancer patients are Gram-negative bacteria, most commonly *E. coli* and *K. pneumoniae*. Bloodstream infection of Gram-positive bacteria can also occur in cancer patients, such as *S. aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium,* and *Enterococcus faecalis*.

Hematological malignancy is the most common malignancy causing SIDs,[12] in which infections are typically caused by encapsulated bacteria, Gram-negative and -positive bacteria, opportunistic fungi, and viruses. In addition, since the clinical use of immunomodulatory drugs such as bortezomib, there has been an increase in the incidence of VZV infection in cancer patients.

Transplantation

CMV is highly prevalent, with 60-80% of the adult population testing positive. Most patients are infected at a young age and most initial infections are mild. The most important factor determining the risk of developing overt CMV infection after transplantation is the CMV serum status of both the donor and the recipient. The greatest risk is associated with transplantation of organs from CMV-infected donors into uninfected recipients[18].

Overt TB infection may develop as a result of reactivation of latent TB in the recipient or acquisition from the donor. Common risk factors for TB acquisition are associated with the recipients themselves[19].

Allogeneic bone is widely used for bone reconstruction in clinical practice. The estimated risk of bacterial infection for large and non-large allogeneic bone was 11.7% and 0.7%, respectively. Several bacteria have been associated with allograft infection, including *S. aureus*, *S. epidermidis*, *Clostridium*, *Enterobacter,* and *Mycobacterium tuberculosis*[20].

Anti-interferon gamma autoantibody

Interferon gamma (IFN-γ), a cytokine produced predominantly by Th1 cells and natural killer cells, plays a critical role in immune responses against intracellular pathogens, particularly non-tuberculous mycobacterium (NTM) species. The presence of pathological anti-IFN-γ autoantibodies neutralizes IFN-γ activity and can lead to disseminated NTM infections. Anti-IFN-γ patients typically experience a chronic clinical course characterized by recurrent and persistent infections, with reported incidence rates ranging from 13% to 75%. Multiple opportunistic infections affecting various organs have been documented, including NTM infections observed in 85.5% of anti-IFN-γ patients and 18.8% of salmonellosis[21]. Anti-IFN-γ autoantibodies should be sought in otherwise immunocompetent hosts with recurrent or disseminated NTM infections, particularly in patients of East Asian descent. Therefore, under certain circumstances, anti-TB or NTM treatment may be given to the patients positive for anti-IFN-γ autoantibodies with unexplained infections[22-30].

CKD

CKD is a slowly progressive disease characterized by changes in the structure and function of the kidneys. Management of CKD-associated infections is critical given the burden of these complications and the associated morbidity and mortality, as well as the role of non-routine risk factors in CKD. Studies have shown that *P. jiroveci* and HSV are predominant in CKD. The clinical manifestations of *P. jiroveci* pneumonia (PJP) are attributable to two primary factors. Firstly, *P. jiroveci* is capable of direct attachment to type I alveolar epithelial cells, where it rapidly transitions from a small trophic form to a larger cystic form. This process ultimately results in diffuse lung injury. On the other hand, the injury is caused by the body's defense mechanism against foreign pathogens, which results in an inflammatory response that ultimately leads to

severe lung injury and a significant limitation of lung function. This, in turn, causes hypoxia and even respiratory failure. The administration of PJP in its early stages can be mitigated through empirical treatment, thereby reducing the associated harm.

Dialysis

Dialysis mainly includes hemodialysis and peritoneal dialysis. In the hemodialysis, due to the possible sharing of dialysis equipment and blood contact between patients, there is an increased risk of infection with some blood-borne pathogens, such as hepatitis B virus (HBV), hepatitis C virus and HIV[31]. Nevertheless, the prevalence of the condition has decreased markedly. A study in South Korea found that Gram positive bacteria were the main pathogens causing peritoneal dialysis related peritonitis, with *S. epidermidis* and *S. aureus* being the most common pathogens. Gram-negative bacteria such as *E. coli* and *K. pneumoniae*, and fungi such as *Candida* and Cryptococcus were also the common pathogens found in the patients having peritoneal dialysis, although the infections caused by them occurred less frequently than those by Gram-positive bacteria[32].

The susceptibility of patients undergoing dialysis to pathogens is influenced by various factors, including immune dysfunction, age, obesity, prolonged dialysis time, comorbidities, catheter-related factors, residual renal function, and hyponatremia. Understanding these factors can help take targeted preventive measures and reduce the risk of infection in dialysis patients.

Diabetes

Diabetes is easy to be complicated with various infections, and poor blood sugar control is one of most important risk factors for serious infections. Pyelonephritis and cystitis are more common in female diabetic patients with recurrent attacks. In severe cases, they can lead to renal and peri-renal abscesses, as well as necrosis of the renal papilla. This is mainly related to *E. coli*, *K. pneumoniae*, *Enterococcus*, and coagulase negative *Staphylococcus*[33]. Purulent skin infections such as boils and abscesses can recur and sometimes cause sepsis. The etiological bacteria usually include *S. aureus, S. pyogenes, P. aeruginosa, E. coli and Clostridium difficile*. *Candida* barbicans often cause diabetic skin infection. Other fungal skin infections such as tinea pedis and tinea corporis are also common. Fungal vaginitis and balanoposthitis are common complications in female patients, mostly caused by *C. albicans*. The incidence of pulmonary TB in diabetic patients is significantly higher. In addition, diabetic foot is also a common complication of diabetes.

Table 1. Infectious pathogens in different types of primary immunodeficiency

Disease	The major pathogen species
X-linked agammaglobulinemia	*Streptococcus pneumoniae, Haemophilus influenzae* type B, *Streptococcus pyogenes, Pseudomonas aeruginosa*
Selective IgA deficiency	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Salmonella, Shigella, Escherichia coli, Klebsiella, Escherichia coli, Klebsiella*
DiGeorge syndrome	*Streptococcus pneumoniae, Haemophilus influenzae*, Moraxella
Chronic granulomatous disease	*Aspergillus* spp., *Staphylococcus aureus, Burkholderia cepacia*
Purine nucleoside phosphorylase deficiency	CMV, EBV, *Streptococcus pneumoniae, Staphylococcus aureus, Candida, Aspergillus, Cryptococcus*
Ataxia telangiectasia	*Streptococcus pneumoniae, Haemophilus influenzae, Aspergillus*
Major histocompatibility complex class II deficiency	CMV, HSV, *Pseudomonas* species, *Staphylococcus* species, *Streptococci*
Severe combined immunodeficiency	*Carselia, Yersinia, Staphylococcus aureus, Klebsiella pneumonia*
Wiskott-Aldrich syndrome	VZV, HSV, EBV, CMV, HPV
Nezelof syndrome	*Candidiasis albicans, Pseudomonas aeruginosa*

VZV: varicella-zoster virus; HSV: herpes simplex virus; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HPV: human papillomavirus.

Table 2. Infectious pathogens in different types of secondary immunodeficiency

Disease	The major pathogen species
Cancer	HSV, CMV, *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus*
Transplantation	Herpes viral infections, CMV, TB, *Staphylococcus aureus*
Anti-interferon gamma autoantibody	NTM
Chronic kidney disease	PJP
Dialysis	*Staphylococcus epidermidis, Staphylococcus aureus, Candida, Cryptococcus*
Diabetes	*Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa, Escherichia coli*
Liver failure	*Cryptococcus*
Corticosteroids	*Staphylococcus aureus, Escherichia coli*

HSV: herpes simplex virus; CMV: cytomegalovirus; PJP: *Pneumocystis jiroveci* pneumonia; NTM: nontuberculous mycobacterium; TB: tuberculous.

Liver failure

Liver failure is defined as a severe acute or chronic hepatic insufficiency caused by a variety of reasons, which can lead to dysfunction or loss of hepatic synthesis, detoxification, excretion and biotransformation[34-37]. Further clinical symptoms may also manifest, including coagulation disorders, jaundice, hepatic encephalopathy, and ascites. In our country, HBV infection is the leading cause of liver failure. Furthermore, patients with liver failure often also suffer from ID, which increases the risk and severity of infectious disease. Studies have demonstrated that patients with chronic liver failure have a significantly higher prevalence of cryptococcal infections. This is due to a number of factors, including impaired phagocytosis, reduced complement levels, impaired immune regulation, invasive procedures, the use of corticosteroids and antibiotics, and gastrointestinal hemorrhage associated with liver disease.

Corticosteroids

Glucocorticoids are a class of steroid anti-inflammatory drugs widely used in clinical practice. Due to their immunosuppressive effects, long-term use of glucocorticoids will cause SID and increase the risk of infection in the patients. Corticosteroid use (prednisone ≥ 20 mg/day for 14 days or cumulative prednisone dosage over 600 mg or other equivalent regimen) causes ID and increases the risk of infection[38,39]. Common infection sites include urogenital tract, respiratory tract, skin and gastrointestinal tract with the first three sites accounting for 86% of all infections. The pathogens causing skin infections are mainly *S. aureus* and mixed anaerobic bacteria, while those causing urogenital tract infections are mainly *E. coli* and *K. pneumoniae*. The pathogens causing respiratory infections are mainly *S. aureus*, mixed anaerobic bacteria, *Haemophilus influenza* and *Enterobacter*. Opportunistic infections account for 7% of all infections, with the main pathogens being *Candida*, *Pneumocystis carinii*, herpes zoster virus, CMV, and *Aspergus*.

Conclusions

Due to the impaired immune function of the body, ID patients are significantly more susceptible to various infectious diseases. The occurrence, development, treatment, and prognosis of their infections are therefore special, as they deviate from the typical patterns observed in immunocompetent individuals.

With regard to bacterial infections, patients with impaired immunity are susceptible to infections with relatively low virulence or opportunistic pathogenic bacteria. These infections are frequently chronic, recurrent, and difficult to eradicate entirely, which can result in the emergence of drug-resistant bacterial strains. The development of an antimicrobial therapy plan must consider the specific pathogenic bacteria, the drug sensitivity results, and the patient's immune status to create a comprehensive program. The course of treatment is often longer as a result.

In patients with impaired immune function, such as those with HIV infection who have developed acquired immunodeficiency syndrome, the progressive destruction of the immune system can result in a variety of serious opportunistic viral infections. These include CMV and HSV, which not only exacerbate the patient's condition but also involve multiple organs and systems, thereby significantly impairing the patient's quality of

life and survival period. Despite the capacity of antiviral therapy to control viral replication to a certain extent, the complete removal of the virus remains challenging. Furthermore, there is an inherent risk of adverse drug reactions and the development of drug resistance.

Fungi represent a significant infectious agent in immunodeficient patients, with *Candida* and *Aspergillus* being particularly prevalent. Deep fungal diseases have a high incidence in such patients, which is difficult to diagnose. Furthermore, the types of antifungal therapeutic drugs are relatively limited, with some of the drugs being more toxic. Therefore, it is necessary to closely monitor adverse drug reactions and therapeutic efficacy throughout the course of treatment, and adjust the treatment program in a timely manner.

It is imperative to consider the possibility of parasitic infections in immunodeficient patients, such as *P. carinii* pneumonia. This can develop when the immune system is severely impaired, with rapid disease progression and a high mortality rate if not treated promptly.

In conclusion, the management of infectious diseases in immunodeficient patients is a complex and long-term process that necessitates the involvement of multiple disciplines, including infectious diseases, immunology, and clinical microbiology. An early and accurate diagnosis, a rational anti-infective treatment plan, monitoring and regulation of immune function, and implementation of preventive measures are essential to improve the prognosis of immunodeficient patients. However, due to space constraints, only a limited number of primary immunodeficiency diseases (PEDs) and states of immunosuppression (SIS) and their associated infectious agents have been summarised in tables 1 and 2 in this paper. Further basic and clinical studies are necessary to identify other pathogens in the future.

Author contributions

W. Zou designed the research; S. Zou and Q. Li operated the literature retrieval, and data extraction; S. Zou and Q. Li wrote the paper. All authors read and approved the final manuscript.

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Conflicts of interest

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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