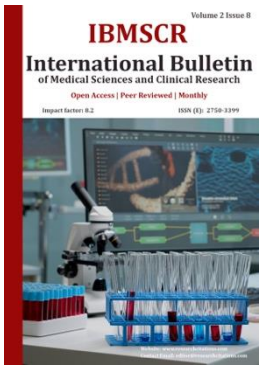


# OVERVIEW OF OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED CHILDREN: ETIOLOGIES AND CLINICAL CHARACTERISTICS FOR PRACTICAL USE

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**Abstract**

Opportunistic infections (OIs) continue to be a significant cause of illness and mortality in children with malignant or nonmalignant conditions. OIs are defined as infections caused by bacteria, fungi, viruses, or normally harmless commensal organisms that inhabit the human body, but become pathogenic when the immune system is compromised. They may also present as unusually severe infections from common pathogens. In some cases, an OI can manifest as a life-threatening event at the onset of a primary immunodeficiency syndrome. More commonly, OIs arise as complications from immunosuppressive therapies, prolonged hospitalization, or in children undergoing bone marrow or organ transplants.

This review aims to provide a concise, accessible summary of the current understanding of OIs, particularly in pediatric patients, to clarify when an infection should be classified as opportunistic in the context of congenital or acquired immune deficiencies.

**Keywords**: Opportunistic infections, Pediatrics, Immunocompromised children, Etiology, Pathogens, Immune deficiency, Cancer

## 1. INTRODUCTION

Opportunistic Infections (OIs) are infections caused by bacteria, fungi, viruses, or parasites that are typically non-pathogenic in healthy individuals but become harmful when the immune system is weakened [1]. They can also manifest as unusually severe infections from common pathogens [1]. OIs exploit a host's compromised immune system or altered microbiota [1, 2]. These infections can vary by region due to environmental exposures and the virulence of certain pathogens, particularly mycobacteria, fungi, and parasites [3, 4]. Moreover, genetic predispositions and the type, severity, and timing of immune suppression caused by medical treatments can influence both the likelihood and clinical characteristics of OIs [5, 6].

OIs are frequently studied in populations with congenital or acquired immunodeficiencies (e.g., HIV, chemotherapy, or post-transplant treatments). However, clinical trials involving immunosuppressive or cytotoxic therapies often do not use clear definitions for OIs, and many infections may be labeled as opportunistic [7, 8]. In contrast, the CDC provides a classification for OIs in children living with HIV, accessible online (https://npin.cdc.gov/publication/guidelines-prevention-and-treatment-opportunistic-infections-among-hiv-infected-children). This can cause confusion, especially when primary infections develop in children. For example, a Varicella-Zoster Virus (VZV) infection in a child on immunosuppressive drugs for rheumatoid arthritis, without severe symptoms or complications, should not necessarily be classified as an OI, as it may have occurred even without immune suppression. The same logic can apply to primary tuberculosis (TB). Common infections like colds or conjunctivitis, often caused by adenovirus, can affect both

healthy and immunocompromised children; however, if the infection becomes persistent or spreads, it may be considered opportunistic [9].

This lack of clarity can lead to confusion in classifying OIs in pediatric patients involved in clinical trials for immunosuppressive treatments.

The purpose of this review is to provide a clear and concise summary of the current understanding of OIs, specifically aimed at defining when an infection should be considered opportunistic in pediatric patients with congenital or acquired immune deficiencies.

## 2. MATERIALS AND METHODS

A MEDLINE/PubMed search was conducted to select reviews, meta-analyses, large clinical trials, or case series papers that reported on the clinical features and etiologies of infectious complications in congenital immunodeficiencies or during any form of immunosuppressive therapy in children. The search was limited to studies from the last 10 years and used the following keywords: "opportunistic infections, children, immune suppression, infections." Additionally, textbooks on "Infectious Diseases" or "Pediatric Infectious Diseases" published within the last 5 years were reviewed.

Infections specific to cystic fibrosis, congenital abnormalities (e.g., urinary tract), vascular access devices, prosthetic devices, superficial or deep surgical site infections, or any surgery-related infections were excluded from this report. The full texts of selected studies and relevant references were retrieved and collectively analyzed. The final decision to include each source in this narrative review was based on the authors' subjective assessment.

The review is organized into the following key sections: (i) "Predisposing factors for OIs with summary table"; (ii) "Bacterial etiologies with summary table"; (iii) "Fungal etiologies with summary table"; (iv) "Viral etiologies with summary table"; (v) "Protozoal etiologies with summary table"; and (vi) "Helminthic etiologies with summary table."

### 2.1. Predisposing Factors for OIs

The primary cause of opportunistic infections (OIs) in children is aggressive treatment for malignant diseases. Advances in chemotherapy over recent decades have significantly improved survival rates for previously untreatable conditions, but these treatments often impair the immune system, increasing the risk of OIs. Infections remain a leading cause of therapy-associated morbidity and mortality.

Neutropenia, a condition characterized by low levels of neutrophils, is the most significant risk factor for OIs. The type and incidence of infections directly correlate with the severity and duration of neutropenia. In Caucasian children over one year old, neutropenia is classified as mild if the Absolute Neutrophil Count (ANC) is between 1.0 and 1.5 x $10^9$/L, moderate if between 0.5 and 1.0 x $10^9$/L, and severe if below 0.5 x $10^9$/L. Granulocytopenia, a decrease in granulocytes, increases the risk of bacterial infections, and when profound and prolonged, it also increases the risk of fungal infections [10].

Short neutropenic periods induced by chemotherapy (e.g., 7-10 days for solid tumor treatment or 20-30 days for leukemia treatments) are generally easier to manage than chronic severe neutropenia, which involves longer exposure to low neutrophil levels and can include qualitative defects in neutrophil function. Box 11 outlines conditions that predispose individuals to OIs.

**Box 1. Conditions predisposing to OIs**

| Characteristic of the infection: |
|---|

| |
|---|
| Characteristic of the infection: |
| Microorganism that normally do not cause disease or |
| common pathogen with an unusual complicated clinical course or |
| recurrence/persistence of same clinical features. |
| Characteristic of the host: |
| a) Profound neutropenia (>1 week), clinical instability or significant medical co-morbidities. |
| b) Cancer and/or high intensity chemotherapy (eg, induction for acute leukemia or HSCT). |
| c) Diagnosis or clinical suspicion of PID. |
| d) Diagnosis or clinical suspicion of cystic fibrosis. |
| e) Anatomic anomalies or cateterism. |
| f) Prolonged steroideal treatment or immunosuppressive drugs (e.g. autoimmune disease, transplantation). |
| g) HIV infection. |
| h)ICU<br>i) Prolonged hospitalisation.<br>j) Malnutrition. |

HIV infection, the use of steroids, immunosuppressive agents, and organ transplants primarily impact cell-mediated immunity. Transplantation, in particular, exemplifies iatrogenic immune impairment, increasing the risk of specific opportunistic infections.

In patients who undergo Hematopoietic Stem Cell Transplantation (HSCT), different stages carry varying risks for OIs. During the early pre-engraftment phase (day 0 to days 15-45), neutropenia and mucosal damage increase the likelihood of bacterial and fungal infections. In the early post-engraftment phase (up to day 100), impaired cell-mediated immunity raises the risk of viral infections such as CMV, HHV6, and EBV, as well as fungal infections like Aspergillus and Pneumocystis carinii. The late phase (days 100 to 356) introduces additional risks, including VZV and encapsulated bacterial infections, largely due to impaired opsonization. Asplenia also increases vulnerability to encapsulated bacteria, which can cause rapidly progressing infections, as well as intracellular parasites like *Plasmodium spp.* and *Babesia spp.*

Patients with multiple trauma or burns in the ICU are susceptible to infections due to compromised skin barriers, along with the use of devices like ventilators and catheters. Moreover, anatomical or physiological abnormalities—such as disrupted epithelial barriers (e.g., eczema, inflammatory bowel disease), dysfunctional drainage systems (e.g., cystic fibrosis), or valve incompetency (e.g., vesico-ureteric reflux)—can also predispose individuals

to OIs. Although less common, congenital causes of OIs, such as Primary Immunodeficiency Diseases (PIDs), are also significant.

In some instances, especially with immune dysregulation syndromes like IPEX or ALPS, children may develop severe infections due to immunosuppressive treatments or compromised mucosal barriers, rather than the underlying primary immunodeficiency itself [11].

**2.2. Bacterial Etiology**

The bacterial pathogens and clinical characteristics described pertain to patients with congenital immunodeficiencies, HIV, or iatrogenic immunosuppression (such as those undergoing transplants, antineoplastic chemotherapy, or being treated for autoimmune diseases). Certain bacterial infections, like invasive group B streptococcal disease or infections caused by Enterobacteriaceae, should only be classified as opportunistic if they occur within the first few months after birth (typically 3-6 months), as infections transmitted vertically can lead to severe clinical presentations even in the absence of immune system impairments.

Table 1 provides a summary of bacterial OIs. Bacterial OIs tend to be recurrent and invasive, sometimes showing age-specific characteristics. For instance, disseminated bartonellosis, which presents with multiple and prolonged lymphadenitis, may occur in children who have undergone transplantation, are receiving steroid treatments, or may manifest as bacillary angiomatosis in children with HIV [12].

Primary *Mycobacterium tuberculosis* infection can occur in healthy children as well, and therefore, it should not be considered an OI unless the infection disseminates or reactivates after immunosuppressive treatment. Conversely, dissemination of Bacillus Calmette-Guérin (BCG) after vaccination is seen in children with severe undetected T-cell deficiencies at the time of vaccination.

Table 1

**Clinical features and pathogens defining the presence of a bacterial OI.**

| **Pathogen** | **Clinical Condition** |
|---|---|
| *Staphylococcus aureus* [13], *Streptococcus pneumoniae* [13, 14], *Listeria monocytogenes* [13], *Nocardia spp* [14], *Pseudomonas aeruginosa* [15], *Burkholderia cepacia* [16], *Escherichia coli* [16], *Klebsiella spp* [16], *Haemophilus influenzae* [16], *Serratia spp* [16]. | Multiple and recurrent infections (≥ 2 or more episodes within 12 months) in patients < 6 years: otitis media, pneumonia, sinusitis, skin-soft tissue. Recurrent pneumonia in patients aged ≥ 6 years. Invasive infections (bacteremia, osteomyelitis/arthritis, meningitis). |
| *Salmonella spp* [13] | Recurrent bacteremia. |

| Pathogen | Clinical Condition |
|---|---|
| *Bartonella spp* [14] | Disseminated disease, only. |
| *Legionella pneumophila* [17] | Pulmonary infection. |
| *Mycobacterium tuberculosis* [13, 14, 16, 19-21] | Reactivation of latent infection. Meningeal tuberculosis. Disseminated or extrapulmonary tuberculosis. |
| Bacillus Calmette–Guèrin (a live, attenuated strain of *Mycobacterium bovis*) [22] | Disseminated disease. |
| *Non-tuberculous mycobacteria* [13, 14, 16, 23, 24] | *M. avium* or *M. kansasii*, disseminated or extrapulmonary disease.<br>Bacteremia due to other mycobacteria (*e.g. M. iranicum*). |

### 2.3. Fungi

Table 2 provides a summary of opportunistic infections (OIs) caused by fungi. While some fungal pathogens may have geographical limitations (endemic mycoses), it is now essential to consider these infections globally due to the rise in international travel and migration. Invasive fungal disease (IFD) commonly affects children with a wide range of conditions, including congenital immunodeficiencies, malignancies, recipients of hematopoietic stem cell transplants (HSCT) or solid-organ transplants (SOT), premature neonates, ICU patients, those who have undergone major abdominal surgery, and children with autoimmune or autoinflammatory conditions receiving immunomodulatory agents [12]. Notably, cutaneous fungal infections may serve as the initial clinical sign of an underlying invasive fungal disease [13].

Table 2

**Clinical features and pathogens defining the presence of a fungal OI.**

| Fungi | Clinical Condition |
|---|---|
| *Candida spp*. [13, 14, 16, 18] | Severe oropharyngeal candidiasis, esophagitis, candidiasis of trachea and bronchi. Pulmonary candidiasis secondary to tracheobronchial infection is not considered as possible outside some specific neonatal conditions. Invasive candidiasis (end-organ disease, including hematogenous pneumonia). |

| Fungi | Clinical Condition |
|---|---|
| *Aspergillus* spp. [13, 14, 16, 19, 25] | Invasive disease only. |
| *Pneumocystis jirovecii* [13, 14, 16, 19, 25] | Pneumonia or disseminated infections. |
| *Cryptococcus* spp. [13, 14, 16, 23, 26, 27] | Cryptococcosis, extrapulmonary: fungemia, meningitis, osteoarticular, disseminated cutaneous. |
| *Coccidioides immitis* [13, 14, 16, 26] | Coccidioidomycosis, disseminated or extrapulmonary. |
| *Histoplasma capsultum* [13, 14, 16, 26] | Histoplasmosis, disseminated or extrapulmonary. |
| Other fungi: [13, 14, 16] *Mucormycosis* (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii, Fusarium, Thalaromyces* spp (previously Penicillium marneffei) *Geotrichum spp., Saprochaete* spp., Magnusiomyces spp. | Invasive disease. |

### 2.4. Viruses

Table 3 outlines opportunistic infections (OIs) caused by viruses. Primary viral infections or the reactivation of latent viral infections are common causes of OIs in immunocompromised individuals (e.g., cytomegalovirus [CMV]). Other viruses, however, only cause opportunistic diseases in the presence of a specific immune deficiency. For example, Epstein-Barr Virus (EBV) can lead to opportunistic infections in patients with X-linked lymphoproliferative syndrome.

Table 3

**Clinical features and pathogens defining the presence of a viral OI.**

| Viruses | Clinical Condition |
|---|---|
| *Cytomegalovirus* (CMV) [13, 14, 16, 23, 28, 29] | Cytomegalovirus disease onset at age > 1 month: pneumonia (CMV-DNA in bronchoalveolar lavage), colitis, central nervous system disease (CMV in cerebrospinal fluid), liver, retinitis (confirmed by an ophthalmologist), nephritis, myocarditis, pancreatitis other. In all cases, typical histological lesions and histopathological detection of the virus must be present. A positive PCR on tissue specimens is not sufficient for the diagnosis (exceptions are shown in parenthesis). |
| *EBV* [30-32] | EBV-induced fulminant infectious mononucleosis with the presence of diffuse lymphadenopathy, hepatosplenomegaly and extensive tissue damage – especially liver and bone marrow - encephalitis and |

| Viruses | Clinical Condition |
|---|---|
| | haemophagocytic-lympho-histiocytosis, B-cell lymphoma and dysgammaglobulinaemia. Chronic active EBV infection: persistent or recurrent infectious mononucleosis-like syndrome with additional complications including hematological, digestive tract, neurological, pulmonary, ocular, dermal, and/or cardiovascular disorders (comprising aneurysm and valvular disease), with very high viral load (> $10^{2.5}$ copies/microgr DNA). |
| *Hepatitis B* Virus [15, 19, 33] | Reactivation |
| *Hepatitis C* Virus [15, 19, 33] | Reactivation/progression |
| *Hepatitis E* Virus [34] | Chronic hepatitis |
| *HSV* [15, 16, 19] | Herpes simplex: chronic ulcers (orolabial or cutaneous or genital > 1 month duration) or bronchitis, pneumonitis or esophagitis, encephalitis or other visceral involvement (onset at age > 1 month). |
| VZV [15, 16, 19, 35] | Varicella with systemic involvement (onset at age > 1 month): neurologic manifestations (encephalitis, ataxia transverse myelitis), hepatitis, pneumonia, multi-organ failure with disseminated intravascular coagulation. Persistent chronic infection: appearance of new lesions for a period > 1 month after primary or recurrent infection, evolving in non-healing ulcers or necrotic, crusted and hyperkeratotic, verrucous lesions. Herpes zoster: uncomplicated herpes zoster: vesicles limited to no more than 3 dermatomers; disseminated or invasive: cutaneous lesion in > 3 dermatomers (disseminated cutaneous) and/or evidence of deep organ involvement. |
| *Adenovirus* [15, 16, 19, 36, 37] | Disseminated disease: hepatitis, hemorrhagic cystitis, persistent gastroenteritis. |
| *Influenza* [15, 16, 19] | Pneumonia, encephalitis. |
| *RSV* [15, 16, 19] | Pneumonia (with onset at age > 6 months). |
| Viruses | Clinical Condition |
| hMPV [15, 16, 19] | Pneumonia, acute respiratory distress syndrome. |
| HHV6, HHV7 [15, 16, 19, 38] | Pneumonia, encephalitis. |
| HHV8 [15, 16, 19, 39] | Kaposi sarcoma. |
| Parvovirus B19 [15, 16, 19] | Chronic/persistent pure red cell aplasia. |

| Viruses | Clinical Condition |
|---|---|
| Rotavirus, Norovirus [15, 16, 19, 40] | Chronic (>1 month duration) diarrhea. |
| JC virus [15, 16, 19] | Progressive multifocal encephalopathy. |
| Molluscum contagiosum virus (poxvirus) [41] | Chronic molluscum contagiosus. |
| BK virus [15, 16, 19, 40] | Polyomavirus nephropathy (PVAN), hemorrhagic cystitis. |
| HPV [15, 16, 19] | Disseminated warts. |
| Enterovirus [14] | Chronic encephalitis. |
| West Nile, Usutu, Chikungunya, O'nyong nyong virus [16, 42, 43] | Encephalitis. |

### 2.5. Protozoa

Table 4 summarizes opportunistic infections (OIs) caused by protozoa. These infections can vary widely based on geographic distribution and exposure to specific vectors. For example, *Trypanosoma cruzi* infection may reactivate in immunocompromised individuals previously exposed to the protozoa and can also be transmitted through organ transplantation. While there is no clear data regarding *Plasmodium spp.*, it is crucial to emphasize the importance of screening for malaria in immunocompromised individuals returning from endemic areas who present with symptoms consistent with infection, even in the absence of fever [44].

Table 4

**Clinical features and pathogens defining the presence of a protozoan OI.**

| Protozoa | Clinical Condition |
|---|---|
| Babesia spp [45, 46] | Severe disease with anemia, pulmonary and renal involvment; persisting and relapsing disease. |
| Toxoplasma gondii [15, 16, 19] | Toxoplasmosis of the central nervous system with onset at age ≥ 1 month.<br>Visceral disseminated toxoplasmosis, (*e.g.* lungs). |
| Cryptosporidium [15, 16, 19] | Cryptosporidiosis, chronic diarrhea (>1 month duration). |
| Giardia [14, 15] | Giardiasis, chronic intestinal diarrhea >1 month duration). |
| Isospora [14, 15] | Chronic diarrhea (>1 month duration). |
| Microsporidium [14, 15] | Chronic diarrhea (>1 month duration) *Anncaliia algerae* myositis. |
| Leishmania [47, 48] | Recurrent, atypical visceral leishmania. |
| Trypanosoma cruzi [16, 49] | Reactivation of American trypanosomiasis: Meningoencephalitis, central nervous system mass, myocarditis. |
| Acanthamoeba spp. [50] | Meningoencephalitis, granulomatous amoebic encephalitis. |
| Balamuthia mandrillaris | Meningoencephalitis, granulomatous amoebic encephalitis. |

| Protozoa | Clinical Condition |
|---|---|
| [51] | |
| Naegleria fowleri [51] | Meningoencephalitis, granulomatous amoebic encephalitis. |

### 2.6. Helminths

Table 5 summarizes opportunistic infections (OIs) caused by helminths. Although they are infrequently reported as the cause of OIs, *Strongyloides spp.* can cause disseminated disease in immunocompromised patients, particularly in neutropenic cancer patients, leading to high morbidity and mortality. Additionally, a few case reports emphasize the complex interactions between immunocompromised hosts and parasites, which can result in more severe presentations of *Taenia spp.* infections.

Table 5

**Clinical features and pathogens defining the presence of a helminthic OI.**

| Helminths | Clinical Condition |
|---|---|
| Strongyloides spp [16, 19, 52] | Hyperinfection, septic shock with multiorgan system failure. |
| Onchocerca jakutensis [53] | Multiple cutaneous nodules. |
| Onchocerca volvulus [54] | More severe skin disease then immunocompetent hosts. |
| Taenia crassiceps [55] | Cutaneous infection and/or more severe infection. |

## 3. COMMENTS.

There is a well-established connection between immune system impairment and the types of opportunistic infections (OIs) that develop [15, 56, 75]. Moreover, the diagnosis of an OI can often prompt clinicians to investigate for an underlying immunodeficiency. In fact, life-threatening opportunistic infections are frequently the initial clinical presentation in patients with primary immunodeficiencies (PID). Table 66 categorizes primary immunodeficiency diseases based on the type of immune defect and the most commonly associated OIs.

Table 6

**Primary immunodeficiency diseases according to the type of immunity defect and related most typical OIs (Adapted from Picard C. *et al.*, Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018).**

| - | Immuno Deficiency | Most Common Pathogens Causing OIs |
|---|---|---|
| **Defects of adaptive immunity** [58-62] | **Antibody deficiencies** | |
| | *Agammaglobulinaemia* | *H. influenzae, S. pneumoniae, M. catarrhalis, Staphylococcus spp.*including methicillin resistant, *P. aeruginosa*, *M. pneumonia*, rhinovirus, adenovirus (severe sinopulmunar or disseminated infections) Enterovirus (meningoencephalitis) Giardia l. (chronic diarrea) *Mycobacterium hominis* and avium. |

| - | Immuno Deficiency | Most Common Pathogens Causing OIs |
|---|---|---|
| | CVID<br>*Specific antibody deficiency*<br>*Transient hypogamma of infancy* | *H. influenzae, S. pneumoniae, M. catarrhalis, Staphylococcus spp.*including methicillin resistant, *P. aeruginosa, M. pneumonia*, rhinovirus, adenovirus (recurrent sinopulmunar infections). |
| | **Combined T/B cell deficiencies** | |
| | T- B+ SCID<br>T- B- SCID<br>*Omenn's Syndrome*<br>*Hyper IgM-CD40 ligand* deficiency | Pyogenic bacteria, *Campylobacter, Listeria,* Herpesvirus, RSV, CMV, parainfluenzae virus type 3 (severe respiratory) Rotavirus (severe diarrhea following immunisation with rotavirus vaccine) Candida (persistent/recurrent oral and perineal infection) Giardia l., Cryptosporidium spp. (chronic diarrea) *Pneumocystis jirovecii*. |
| **Defects of innate immunity** [63-68] | **Phagocytic disorders** | |
| | *Chronic granulomatous* disease | *Staphylococcus spp, Burkholderia, Serratia, Nocardia* (abscesses, pneumonia, granulomatous enteritis) Aspergillus (pneumonia, invasive) Candida spp. (sepsis, adenitis). |
| | *Congenital neutropenia* | *Staphylococcus spp., E. coli, P. aeruginosa* (sepsis, pneumonia, mucocutaneous chornic infections). |
| | *Leukocyte adhesion* deficiency | *S. aureus, Streptococcus spp* (skin ulcers, periodontitis) Candida spp. (skin and pulmonary infections) P. carinii. |
| | *GATA2 deficiency* | NT mycobacteria (disseminated infections), fungi (disseminated infections), HPV (recurrent infections). |
| | **Complement deficiencies** | |
| | *C1 and C2* deficiences | *S. pneumoniae, H. influenzae* (recurrent sinopulmunar infections) *Neisseria spp.* (meningococcal and gonococcal infections). |
| | *C5-C9* deficiences | *Neisseria spp.* (disseminated infections). |
| | **Defects in intrinsic and innate immunity** | |
| | *IL12/IFN-γ signaling pathway* deficiency | Susceptibility to mycobacteria and *Salmonella spp.* |

| - | Immuno Deficiency | Most Common Pathogens Causing OIs |
|---|---|---|
| | *CARD9* deficiency | Aspergillus (invasive) Candida (meningo-encephalitis and/or colitis). |
| | *TLR signaling pathway* deficiency | *S. pneumoniae, S. aureus, P. aeruginosa* (recurrent/severe infections). |
| - | **Immuno Deficiency** | **Most Common Pathogens Causing OIs** |
| **Diseases of immune dysregulation** [69, 70] | *Chediack-Higashi syndrome* | *Staphylococcus spp., Streptococcus spp* (respiratory, muco-cutaneous recurrent infections). |
| | *Hermansky-Pudlak syndrome* | Recurrent bacterial infections due to neutropenia. |
| | *Griscelli syndrome* | *Staphylococcus spp., Streptococcus spp* (respiratory, muco-cutaneous recurrent infections). |
| | *IPEX* | *S. aureus* (skin) Candida spp. |
| | *IL10-IL10R deficiency - XLP syndrome* | EBV (fulminant infections), bacteria and virus (recurrent respiratory infections). |
| | *APECED* | Candida spp (chronic mucocutaneous). |
| | *ALPS* | Bacterial and viral infections due to immunosuppressive drugs. |
| **Others syndromes** [71-74] | *Ataxia-teleangectasia* | *H. influenzae, S. pneumoniae, Staphylococcus spp* (recurrent sinopulmunar infections) herpesvirus. Candida spp (esophagitis). |
| | *Wiskott Aldrich syndrome* | Encapsulated bacteria (recurrent infections) P. jirovecii (pneumonia), Candida spp. (invasive). |
| | *Hyper IgE syndromes* | *S. aureus, P. aeruginosa* (pulmunary abcsesses, pneumatoceles), P. jirovecii (pneumonia), Candida spp (chronic mucocutaneous). |
| | *Di George syndrome (Del 22q11.2)* | *H. influenzae, S. pneumoniae, Staphylococcus spp* (recurrent sinopulmunar infections) CMV, EBV (viremia). |

CVID: Common variable immune deficiency; SCID: Severe combined immunodeficiency; NT: non-tuberculosis; IPEX: immunodysregulation polyendocrinopathy enteropathy X-linked; APECED: autoimmune polyendocrinopathy-candidiasis–ectodermal dystrophy/dysplasia; ALPS: autoimmune lymphoprolipherative syndrome.

## CONCLUSION

This review aimed to provide a concise overview of when specific infections (pathogens and/or clinical manifestations) should be classified and reported as opportunistic infections (OIs), particularly in the context of clinical trials where OIs are severe adverse events that

must be recorded. Clinical trials often do not consistently define infectious complications and sometimes classify common infections without a severe clinical course as OIs simply because they occurred in an immunocompromised patient [57], or because the pathogen has the potential to cause an opportunistic disease. This can lead to an overestimation of OI risk, particularly in pediatric trials, where many infections (especially primary episodes) may not be related to immune compromise unless they present with specific, severe, or disseminated symptoms.

Given the wide range of pathogens (some only mentioned in case reports or small case series) that can cause infections when anti-infective defenses are compromised, this review does not aim to be exhaustive. We recognize the limitations of a narrative review compared to a systematic one, but our primary goal was to guide clinicians through the complex landscape of OIs in children and to remind them to investigate any underlying conditions when OIs are suspected. We believe that the utility of this review lies in summarizing the most relevant pathogens and clinical features that can definitively be considered OIs, and that this summary could prove helpful in defining OIs in pediatric clinical trials involving immunosuppressive therapies

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