Definition of Opportunistic Infections in Immunocompromised Children on the Basis of Etiologies and Clinical Features: A Summary for Practical Purposes

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Abstract: Opportunistic Infections (OIs) still remain a major cause of morbidity and death in children with either malignant or nonmalignant disease. OIs are defined as those infections occurring due to bacteria, fungi, viruses or commensal organisms that normally inhabit the human body and do not cause a disease in healthy people, but become pathogenic when the body's defense system is impaired. OIs can also be represented by unusually severe infections caused by common pathogens. An OI could present itself at the onset of a primary immunodeficiency syndrome as a life-threatening event. More often, OI is a therapy-associated complication in patients needing immunosuppressive treatment, among long-term hospitalised patients or in children who undergo bone marrow or solid organ transplantation.

The aim of the present review is to provide a comprehensive and ‘easy to read’ text that briefly summarises the currently available knowledge about OIs in order to define when an infection should be considered as opportunistic in pediatrics as a result of an underlying congenital or acquired immune-deficit.

Keywords: Opportunistic infections, children, immunocompromised host, etiology, pathogenic, immune-deficit, malignant.

1. INTRODUCTION

Opportunistic Infections (OIs) are defined as infections occurring due to bacteria, fungi, viruses, or parasites that normally do not cause a disease, but become pathogenic when the body's defense system is impaired [1]. OIs can also be represented by unusually severe infections caused by common pathogens [1]. In all cases, all these are infections where pathogens take advantage of a host with a weakened immune system and/or with an altered microbiota [1, 2]. OIs can present a wide geographic variability because of different environmental exposures to potential pathogens and intrinsic virulence factors, especially for mycobacteria, fungi and parasites [3, 4]. Moreover, genetic host patterns and the diverse type, grade and timing of iatrogenic immune-suppression can affect both the likelihood and clinical features of OIs [5, 6].

OIs are frequently described in the context of epidemiological surveys in specific patients’ population with a congenital or acquired (e.g. HIV disease, antineoplastic chemotherapy, transplant, etc.) impairment of the immune system. Unfortunately, especially in the case of clinical trials with the administration of immunosuppressive or cytotoxic drugs, pre-defined classifications of OIs are frequently not adopted, but all the infections observed may be reported as OIs [7, 8]. Conversely, the CDC classification of OIs in children living with HIV is available online (at: https://npin.cdc.gov/publication/guidelines-prevention-and-treatment-opportunistic-infections-among-hiv-infected-children). This may generate confusion, especially in children developing specific primary infections. For example, a primary infection due to Varicella-Zoster Virus (VZV) occurring in a patient (most frequently a child) receiving immunosuppressive drugs for rheumatoid arthritis, but without a severe clinical picture or VZV related complications, should not be considered as an OI, since that is an infection that probably would have appeared regardless of the immune-suppression. Similar considerations could be made for primary Tuberculosis (TB). Moreover, common cold, conjunctivitis or upper respiratory infection, for example, related to adenovirus, can occur in a previously healthy individual as well as in immunocompromised children; however, when the...
infection becomes persistently localised and/or disseminated, it may be considered as OI [9].

As a consequence, the definition of OI in children enrolled in clinical trials of immunosuppressive treatments could be misleading.

The aim of the present review is to provide a comprehensive and ‘easy to read’ text, that briefly summarises the currently available knowledge, in order to define when an infection should be considered as opportunistic in pediatrics as a result of an underlying congenital or acquired immune-deficit.

2. MATERIALS AND METHODS

Reviews, meta-analyses, large clinical trials or case series papers reporting clinical description and etiologies of infectious complications in congenital immunodeficiencies or during any type of immunosuppressive therapy in children were selected through a MEDLINE/PubMed search, using the keywords: “opportunistic infections, children, immune-suppression, infections”, restricting the search to the last 10 years. The research was also extended to textbooks on ‘Infectious Diseases’ or ‘Pediatric Infectious Diseases’ published in the last 5 years. Pathogens or clinical pictures strictly related to infections of cystic fibrosis, presence of congenital abnormalities (e.g. of the urinary tract), vascular access devices, prosthetic devices, surgical site infections (superficial or deep) or any surgery-related infection was excluded from the report. The full text of the selected papers and of pertinent references was then retrieved and collectively discussed, with the decision about inclusion in the present narrative review being ultimately made according to the subjective impression of the authors. The text was ultimately organised in the following major paragraphs: (i) “OIs predisposing factors with summary table”; (ii) “bacterial etiology with summary table”; (iii) “fungal etiology with summary table”; (iv) “viral etiology with summary table”; (v) “protozoal etiology with summary table” and (vi) “helminthic etiology with summary table”.

2.1. OIs Predisposing Factors

The most relevant cause of OIs in children is represented by aggressive treatments for malignant diseases. New chemotherapy approaches, resulting from achievements of the last decades in medical science, confer longer survivals to children with disease previously considered untreatable, but could lead to an immunological impairment and, as a consequence, to OIs. Infections remain a major cause of therapy-associated morbidity and death. Neutropenia represents the most important risk factor for OIs, the type and incidence of which directly correlate with its severity and duration (in Caucasians over 1 year is defined as mild if Average Neutrophils Count (ANC) is 1.0 and 1.5 x 10⁹/L, moderate if between 0.5 and 1.0 x 10⁹/L, and severe if less than 0.5 x 10⁹/L). Granulocytopenia exposes to the risk of bacterial infection, but also, if profound and prolonged, the risk of fungal infection [10].

Relatively brief neutropenic periods induced by chemotherapy (7-10 days in solid tumor chemotherapy or 20-30 days in anti-leukemic treatments) could be managed more easily than severe chronic neutropenias because of a longer period of exposure to low neutrophils levels and intrinsic neutrophils qualitative defects of the latter. Box 1. shows conditions predisposing to OIs.

**Box 1. Conditions predisposing to OIs**

| 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. |
|---------------------------------|--------------------------------------------------------------------------------------------------|
| a)                               | Profound neutropenia (>1 week), clinical instability or significant medical co-morbidities.       |
| b)                               | Cancer and/or high intensity chemotherapy (e.g. 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 steroidal treatment or immunosuppressive drugs (e.g. autoimmune disease, transplantation). |
| g)                               | HIV infection.                                                                                  |
| h)                               | ICU                                                                                             |
| i)                               | Prolonged hospitalisation.                                                                     |
| j)                               | Malnutrition.                                                                                   |

HIV infection, steroids, immunosuppressive agents and transplantations alter mainly cell-mediated immunity. Particularly transplantation is an example of iatrogenic impairment in different sectors of immunity, with the consequent risk of a specific opportunistic infection.

Among patients who undergo Hematopoietic Stem Cells Transplantation (HSCT), the early pre-engraftment phase (day 0 to days 15-45) carries the risk of bacterial and/or fungal infection due to neutropenia and mucosal damage. During the early post-engraftment period (engraftment to day 100), the impairment of cell-mediated immunity could cause viral (e.g. CMV, HHV6, EBV) and fungal (Aspergillus, Pneumocystis carinii) infections, while in the late phase (days 100 to 356), in addition to those microorganisms, VZV and encapsulated bacterial infections are observed, the impaired opsonisation being the main mechanism. Asplenia leads to susceptibility to encapsulated bacteria with frequent fulminating progression and intracellular parasites (Plasmodium spp. and Babesia spp.).

Multiple trauma or burn patients in the ICU are exposed to the risk of an infection due to the loss of the first line defense against microbial invasion, and the use of devices (ventilation support, vascular or vesical catheters). Lastly, anatomical and/or physiological anomalies, such as disrupted epithelial barriers (e.g. eczema, IBD), dysfunctional drainage
systems (e.g., cystic fibrosis) and incompetent valves (e.g., vesico-ureteric reflux) could also represent a substrate to OIs. Less frequent than acquired causes, congenital causes of OIs are represented by Primary Immunodeficiency Diseases (PIDs).

In some cases, especially in immune dysregulation syndromes (e.g., IPEX, ALPS), children affected could develop severe infections because of immunosuppressive treatment or disruption of mucosal barriers rather than a primary immunodeficiency [11].

### 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.                                                              |
| *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–Guérin (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. Bacteremia due to other mycobacteria (e.g., *M. iranicum*). |

#### 2.2. Bacterial Etiology

All the pathogens and clinical features reported are referred to patients with congenital immunodeficiencies, HIV disease or iatrogenic immunosuppression (e.g., transplant, antineoplastic chemotherapy, autoimmune diseases). Some of these infections, like invasive group B streptococcal disease or invasive infections due to *Enterobacteriaceae* should be considered OIs only if occurring a few months (in general 3-6) after birth, since infections via vertical transmissions can cause per se severe clinical pictures also in the absence of specific impairment of the immune system.

Table 1 summarises OIs due to bacteria. OIs due to bacteria are generally recurrent, invasive, sometimes with age-specific cut-offs. For example, disseminated bartonellosis, with multiple and prolonged lymphadenitis, may be encountered in transplanted children and/or under steroidal treatment or may present as bacillary angiomatosis in children with HIV infection [12]. Primary *Mycobacterium tuberculosis* infection and disease can be observed also in normal children, and therefore, generally should not be considered an OI in the absence of dissemination or reactivation of an infection documented before the initiation of immunosuppression. On the other hand, dissemination of *Bacillus Calmette-Guérin* (BCG) after vaccination can be observed in children affected with severe T-cell defects that were still not detected at the time of vaccination.

#### 2.3. Fungi

Table 2 summarises OIs due to fungi. Some of these pathogens may present geographical restrictions (so called endemic mycoses), but nowadays, the possibility of these infections must be taken into account in any country, because of increasing traveling and migrations. Classically, invasive fungal disease (IFD) may be present in children with a broad range of congenital immunodeficiencies, malignancies, hematopoietic (HSCT) or solid-organ transplant (SOT) recipients, premature neonates, children in ICU or who underwent important abdominal surgery, with autoimmune and/or autoinflammatory conditions on immunomodulatory agents [12]. Of note, cutaneous localisation of fungal infections may be the first clinical indication of an underlying IFD [13].

#### 2.4. Viruses

Table 3 summarises OIs due to viruses. Primary viral infections and/or re-activation of latent viral infections are the frequent causes of opportunistic infections in immunocompromised hosts (e.g., CMV), but other viruses can cause an opportunistic disease only in the presence of a specific immune deficit (e.g., EBV in patients with *X-linked lymphoproliferative syndrome*).
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). |
| *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 capsulatum* [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. |

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, hepatospleno-lymphomegaly and extensive tissue damage – especially liver and bone marrow - encephalitis and 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 (> 10^35 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 dermatomes; disseminated or invasive: cutaneous lesion in > 3 dermatomes (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).                                                                                                                                                                             |

(Table 3) Contd...
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2.5. Protozoa

Table 4 summarises OIs due to protozoa. These infections can largely vary, due to different geographical distribution and exposure to competent vectors. For example, Trypanosoma cruzi infection may both reactivate in the immune-compromised host previously exposed to the protozoa and may be transmitted through organ transplantation. No clear data are available about Plasmodium spp., however, it is of value to stress the importance of screening for malaria in immune-compromised hosts returning from endemic areas with symptoms and signs compatible with the infections, even in the absence of fever [44].

2.6. Helminths

Table 5 summarises OIs due to helminths. These are not frequently reported as the cause of OIs. However, Strongyloides spp. may cause disseminated disease in immunocompromised patients, especially neutropenic cancer patients, with high morbidity and mortality. Moreover, few case reports highlight the complex interaction between immunocompromised hosts and parasite that may lead to a more severe presentation of Taenia spp. infections.

3. COMMENTS

There is a well known relationship between impairment of the immune system and the type of OIs developed [15, 56, 75]. At the same time, the diagnosis of a possible OI may allow the clinicians to screen for an underlying immunodeficit. A life-threatening opportunistic infection is the most frequent clinical presentation in a PID at the onset. Table 6 lists primary immunodeficiency diseases according to the type of immunity defect and most typical OIs.
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. |
| Onchoerca jakutensis [53]   | Multiple cutaneous nodules.                             |
| Onchoerca volvulus [54]     | More severe skin disease then immunocompetent hosts.    |
| Taenia crassiceps [55]      | Cutaneous infection and/or more severe infection.       |

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                                               | H. influenzae, S. pneumoniae, M. catarrhalis, Staphylococcus spp. including methicillin resistant, P. aeruginosa, M. pneumonia, rhinovirus, adenovirus (severe sinopulmonary or disseminated infections) Enterovirus (meningoencephalitis) Giardia l. (chronic diarrhea) Mycobacterium hominis and avium. |
|                                        | Agammaglobulinaemia                                                 | H. influenzae, S. pneumoniae, M. catarrhalis, Staphylococcus spp. including methicillin resistant, P. aeruginosa, M. pneumonia, rhinovirus, adenovirus (severe sinopulmonary infections). |
|                                        | CVID                                                                | 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 diarrhea) Pneumocystis jiroveci. |
|                                        | Specific antibody deficiency                                         |                                                                                       |
|                                        | Transient hypogammaglobulinemia                                      |                                                                                       |
| Combined T/B cell deficiencies         |                                                                     |                                                                                       |
|                                        | T- B+ SCID                                                           |                                                                                       |
|                                        | T- B- SCID                                                           |                                                                                       |
|                                        | Omenn’s Syndrome                                                    |                                                                                       |
|                                        | Hyper IgM-CD40 ligand deficiency                                     |                                                                                       |
| Defects of innate immunity [63-68]    | Phagocytic disorders                                                | S. aureus, Streptococcus spp (skin ulcers, periodontitis) Candida spp. (skin and pulmonary infections) P. carinii.                                                                                                                     |
|                                        | Chronic granulomatous disease                                       | S. pneumoniae, H. influenzae (recurrent sinopulmonary infections) Neisseria spp. (meningococcal and gonococcal infections).                                                                                                      |
|                                        | Congenital neutropenia                                               | Neisseria spp. (disseminated infections).                                                                                                                    |
|                                        | Leukocyte adhesion deficiency                                       | NT mycobacteria (disseminated infections), fungi (disseminated infections), HPV (recurrent infections).                                                                                                             |
|                                        | GATA2 deficiency                                                    |                                                                                       |
|                                        | Complement deficiencies                                             | S. pneumoniae, Neisseria spp. (disseminated infections).                                                                                                     |
|                                        | C1 and C2 deficiencies                                               | Susceptibility to mycobacteria and Salmonella spp.                                                                                                             |
|                                        | C5-C9 deficiencies                                                  |                                                                                       |
| Defects in intrinsic and innate immunity | IL12/IFN-γ signaling pathway deficiency                            | Aspergillus (invasive) Candida (meningo-encephalitis and/or colitis).                                                                                           |
|                                        | CARD9 deficiency                                                    |                                                                                       |
|                                        | TLR signaling pathway deficiency                                     | S. pneumoniae, S. aureus, P. aeruginosa (recurrent/severe infections).                                                                                           |

(Table 6) Contd…
| Diseases of immune dysregulation [69, 70] | Immuno Deficiency | Most Common Pathogens Causing OIs |
|---|---|---|
| Chediack-Higashi syndrome | Staphylococcus spp., Streptococcus spp (respiratory, muco-cutaneous recurrent infections). Recurrent bacterial infections due to neutropenia. |
| Hermansky-Pudlak syndrome | Staphylococcus spp., Streptococcus spp (respiratory, muco-cutaneous recurrent infections). |
| Griscelli syndrome | |
| 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 (pulmonary absceses, 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: immuno dysregulation polyendocrinopathy enteropathy X-linked; APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy/dysplasia; ALPS: autoimmune lymphoproliferative syndrome.

**CONCLUSION**

The aim of the present review was to give a concise summary on when a specific infectious disease (pathogen and/or clinical picture) could/should be considered (and reported) as an OI, especially in the context of clinical trials where OIs represent severe adverse events that must be registered. Indeed, clinical trials usually do not use the same definitions of infectious complications or sometimes describe a “common” infectious disease without a complicated clinical course as an OI for the only reason that it occurred in an immunocompromised patient [57], or that passing time can cause an opportunistic disease. This may overemphasise the risk of diagnosing OIs in clinical trials, especially in children, where many of the infectious diseases (at least primary episodes) could be considered as not related to immune-compromise in the absence of peculiar, disseminated or severe clinical features.

Considering the wide amount of pathogens (some of them described only in case reports or small case-series) that can cause infection in the presence of disrupted anti-infective defenses, this review can not be considered comprehensive. We acknowledge the limitation of a narrative review compared with a systematic one, but the main aim of this paper was to guide the clinicians in the vast world of OIs in children and to remember to investigate any predisposing condition if OIs are suspected. We believe that its utility can be represented by the summary in a single paper of the most important pathogens and/or clinical pictures that can be certainly defined as OIs, and that this summary could be useful in defining an OI in clinical trials of immunosuppressive drugs in pediatrics.

**CONSENT FOR PUBLICATION**

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

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