Current Pediatric Reviews, 2019, *15*, 197-206

REVIEW ARTICLE

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

Niccolò Riccardi[1,2,*], Gioacchino Andrea Rotulo[3] and Elio Castagnola[4]

[1]*Infectious Diseases Clinic, Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy;* [2]*Department of Infectious - Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Verona, Italy;* [3]*Infectious Diseases Department, Istituto Giannina Gaslini Children's Hospital, University of Genoa, Genoa, Italy;* [4]*Infectious Diseases Department, Istituto Giannina Gaslini, Children's Hospital, Genoa, Italy*

ARTICLE HISTORY

Received: December 25, 2018
Revised: April 15, 2019
Accepted: April 25, 2019

DOI:
10.2174/1573396315666190617151745

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 occuring 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

*Address correspondence to this author at the Infectious Diseases Unit, Department of Health Sciences (DISSAL), University of Genoa, Policlinico San Martino Hospital, L.go Rosanna Benzi, 10, 16132, Genova, Italy; Tel: +393333618694; Fax: +390105556606; E-mail: niccolo.riccardi@yahoo.it

1875-6336/19 $58.00+.00

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 immunedeficit.

2. MATERIALS AND METHODS

Reviews, meta-analyes, 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) "helimintic 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.
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
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–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. 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-Guèrin* (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 immunomudolatory 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 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.

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 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).

(Table 3) Contd…

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.
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.

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. 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 [51]	Meningoencephalitis, granulomatous amoebic encephalitis.
Naegleria fowleri [51]	Meningoencephalitis, granulomatous amoebic encephalitis.

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 clench 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 immunecompromised 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.
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.

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.
	CVID *Specific antibody deficiency* *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 T- B- SCID *Omenn's Syndrome* *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.*
	CARD9 deficiency	Aspergillus (invasive) Candida (meningo-encephalitis and/or colitis).
	TLR signaling pathway deficiency	*S. pneumoniae, S. aureus, P. aeruginosa* (recurrent/severe infections).

(Table 6) Contd…

-	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

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 that pathogen 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

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] CDC Opportunistic Infections definition. Available at: https://www.cdc.gov/hiv/basics/livingwithhiv/opportunisticinfections.html

[2] De Rosa FG, Corcione S, Raviolo S, *et al.* Candidemia, and infections by Clostridium difficile and carbapenemase-producing Enterobacteriaceae: New enteropathogenetic opportunistic syndromes? Infez Med 2015; 23(2): 105-16. [PMID: 26110290]

[3] Nucci M, Queiroz-Telles F, Tobón AM, Restrepo A, Colombo AL. Epidemiology of opportunistic fungal infections in Latin America. Clin Infect Dis 2010; 51(5): 561-70. [http://dx.doi.org/10.1086/655683] [PMID: 20658942]

[4] Bottieau E. Tropical parasitic diseases and immunosuppression. Clin Microbiol Infect 2014; 20(4): 277. [http://dx.doi.org/10.1111/1469-0691.12590] [PMID: 24529256]

[5] Polvi EJ, Li X, O'Meara TR, Leach MD, Cowen LE. Opportunistic yeast pathogens: Reservoirs, virulence mechanisms and therapeutic strategies. Cell Mol Life Sci 2015; 72(12): 2261-87. [http://dx.doi.org/10.1007/s00018-015-1860-z] [PMID: 25700837]

[6] Lake MA, Ambrose LR, Lipman MC, Lowe DM. "'Why me, why now?" Using clinical immunology and epidemiology to explain who gets nontuberculous mycobacterial infection. BMC Med 2016; 14: 54.
[http://dx.doi.org/10.1186/s12916-016-0606-6] [PMID: 27007918]

[7] B-Lajoie MR, Drouin O, Bartlett G, *et al.* Incidence and prevalence of opportunistic and other infections and the impact of antiretroviral therapy among HIV-infected children in low- and middle-income countries: A systematic review and meta-analysis. Clin Infect Dis 2016; 62(12): 1586-94.
[http://dx.doi.org/10.1093/cid/ciw139] [PMID: 27001796]

[8] Winthrop KL, Novosad SA, Baddley JW, *et al.* Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015; 74(12): 2107-16.
[http://dx.doi.org/10.1136/annrheumdis-2015-207841] [PMID: 26395500]

[9] Ison MG, Hayden RT. Adenovirus. Microbiol Spectr 2016; 4(4) [PMID: 27726766]

[10] Groll AH, Castagnola E, Cesaro S, *et al.* Fourth european conference on infections in leukaemia; Infectious diseases working party of the European Group for Blood Marrow Transplantation (EBMT-IDWP); Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC-IDG); International Immunocompromised Host Society (ICHS); European Leukaemia Net (ELN). Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. Lancet Oncol 2014; 15(8): e327-40.
doi: 10.1016/S1470-2045(14)70017-8. [PMID: 24988936]

[11] Aguilar C, Malphettes M, Donadieu J, Chandesris O, Coignard-Biehler H. Prevention of infections during primary immunodeficiency. Clin Infect Dis 2014; 59(10): 1462-70

[12] Wanat KA, Reid E, Kamiyango W, El-Mallawany NK, Kovarik CL. Tumoral bacillary angiomatosis in a child with human immunodeficiency virus. JAMA Dermatol 2014; 150(9): 1015-6.
[http://dx.doi.org/10.1001/jamadermatol.2013.9128] [PMID: 25076357]

[13] Sionean C, Le BC, Hageman K, *et al.* HIV Risk, prevention and testing behaviors among heterosexuals at increased risk for HIV infection--National HIV Behavioral Surveillance System, 21 U.S. cities, 2010. MMWR Surveill Summ 2014; 63(14): 1-39.
[PMID: 25522191]

[14] Raje N, Dinakar C. Overview of immunodeficiency disorders. Immunol Allergy Clin North Am 2015; 35(4): 599-623. [Review].
[http://dx.doi.org/10.1016/j.iac.2015.07.001] [PMID: 26454309]

[15] Siberry GK, Abzug MJ, Nachman S, *et al.* Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Pediatr Infect Dis J 2013; 32(Suppl. 2): i-KK4.
[http://dx.doi.org/10.1097/01.inf.0000437856.09540.11] [PMID: 24569199]

[16] Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases 8th ed. John E. Bennett, Raphael Dolin and Martin J. Blaser. 2014.

[17] Lanternier F, Tubach F, Ravaud P, *et al.* Incidence and risk factors of *Legionella pneumophila* pneumonia during anti-tumor necrosis factor therapy: A prospective French study. Chest 2013; 144(3): 990-8.
[http://dx.doi.org/10.1378/chest.12-2820] [PMID: 23744173]

[18] Buzzi E, Manzoni P, Castagnola E, Benjamin DK Jr, Beghini R, Dall'agnola A. *Candida pneumonia* in a term infant after prolonged use of inhaled corticosteroids for bronchopulmonary dysplasia (BPD). Early Hum Dev 2013; 89(Suppl. 1): S62-3.
[http://dx.doi.org/10.1016/S0378-3782(13)70018-5] [PMID: 23809354]

[19] Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357(25): 2601-14.
[http://dx.doi.org/10.1056/NEJMra064928] [PMID: 18094380]

[20] Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9(Suppl. 3): S1-S155.
[http://dx.doi.org/10.1111/j.1600-6143.2009.02834.x] [PMID: 19845599]

[21] Lönnroth K, Mor Z, Erkens C, *et al.* Tuberculosis in migrants in low-incidence countries: epidemiology and intervention entry points. Int J Tuberc Lung Dis 2017; 21(6): 624-37.
[http://dx.doi.org/10.5588/ijtld.16.0845] [PMID: 28482956]

[22] Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N. Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. J Infect 2012; 64(6): 543-54.
[http://dx.doi.org/10.1016/j.jinf.2012.03.012] [PMID: 22430715]

[23] Sepkowitz KA. Opportunistic infections in patients with and patients without Acquired Immunodeficiency Syndrome. Clin Infect Dis 2002; 34(8): 1098-107.
[http://dx.doi.org/10.1086/339548] [PMID: 11914999]

[24] Grandjean S, Toro A, Drancourt M. *Mycobacterium iranicum* bacteremia and hemophagocytic lymphohistiocytosis: a case report. BMC Res Notes 2017; 10(1): 372.
[http://dx.doi.org/10.1186/s13104-017-2684-8] [PMID: 28789664]

[25] Green M, Michaels MG. Infections in pediatric solid organ transplant recipients. J Pediatric Infect Dis Soc 2012; 1(2): 144-51.
[http://dx.doi.org/10.1093/jpids/pir001] [PMID: 26619167]

[26] Odio CD, Milligan KL, McGowan K, *et al.* Endemic mycoses in patients with STAT3-mutated hyper-IgE (Job) syndrome J Allergy Clin Immunol 2015; 136(5): 1411-3.e1-2.

[27] Köhler JR, Hube B, Puccia R, Casadevall A, Perfect JR. Fungi that infect humans. Microbiol Spectr 2017; 5(3)
[PMID: 28597822]

[28] Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002; 34(8): 1094-7.
[http://dx.doi.org/10.1086/339329] [PMID: 11914998]

[29] Kruisinga MD, van Tol MJD, Bekker V, *et al.* Risk Factors, Treatment and Immune Dysregulation in Autoimmune Cytopenia Following Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Patients. Biol Blood Marrow Transplant 2018; 24(4): 772-8.

[30] Tangye SG. XLP: clinical features and molecular etiology due to mutations in SH2D1A encoding SAP. J Clin Immunol 2014; 34(7): 772-9.
[http://dx.doi.org/10.1007/s10875-014-0083-7] [PMID: 25085526]

[31] Eligio P, Delia R, Valeria G. EBV Chronic Infections. Mediterr J Hematol Infect Dis 2010; 2(1): e2010022.
[http://dx.doi.org/10.4084/mjhid.2010.022] [PMID: 21415952]

[32] Okano M, Kawa K, Kimura H, *et al.* Proposed guidelines for diagnosing chronic active Epstein-Barr virus infection. Am J Hematol 2005; 80(1): 64-9.
[http://dx.doi.org/10.1002/ajh.20398] [PMID: 16138335]

[33] Tavil B, Cetin M, Tuncer M, *et al.* The rate of hepatitis B and C virus infections and the importance of HBV vaccination in children with acute lymphoblastic leukemia. Hepatol Res 2007; 37(7): 498-502.
[http://dx.doi.org/10.1111/j.1872-034X.2007.00079.x] [PMID: 17539991]

[34] Nimgaonkar I, Ding Q, Schwartz RE, Ploss A. Hepatitis E virus: advances and challenges. Nat Rev Gastroenterol Hepatol 2018; 15(2):96-110.
[PMID: 29162935]

[35] Kim DH, Messner H, Minden M, *et al.* Factors influencing varicella zoster virus infection after allogeneic peripheral blood stem cell transplantation: low-dose acyclovir prophylaxis and pre-transplant diagnosis of lymphoproliferative disorders. Transpl Infect Dis 2008; 10(2): 90-8.
[http://dx.doi.org/10.1111/j.1399-3062.2007.00247.x] [PMID: 17605742]

[36] Hayden RT, Gu Z, Liu W, *et al.* Risk factors for hemorrhagic cystitis in pediatric allogeneic hematopoietic stem cell transplant recipients. Transpl Infect Dis 2015; 17(2): 234-41.
[http://dx.doi.org/10.1111/tid.12364] [PMID: 25648430]

[37] Sujeet K, Vasudev B, Desai P, *et al.* Acute kidney injury requiring dialysis secondary to adenovirus nephritis in renal transplant recipient. Transpl Infect Dis 2011; 13(2): 174-7.

[http://dx.doi.org/10.1111/j.1399-3062.2010.00577.x] [PMID: 20946204]

[38] Lagadinou ED, Marangos M, Liga M, *et al.* Human herpesvirus 6-related pure red cell aplasia, secondary graft failure, and clinical severe immune suppression after allogeneic hematopoietic cell transplantation successfully treated with foscarnet. Transpl Infect Dis 2010; 12(5): 437-40.
[http://dx.doi.org/10.1111/j.1399-3062.2010.00515.x] [PMID: 20561301]

[39] El-Mallawany NK, Villiera J, Kamiyango W, *et al.* Increasing numbers of new kaposi sarcoma diagnoses in hiv-infected children and adolescents despite the wide availability of antiretroviral therapy in malawi. Clin Infect Dis 2017; 64(6): 818-9.
[http://dx.doi.org/10.1093/cid/ciw879] [PMID: 28077522]

[40] Kedia S, Acharya PS, Mohammad F, *et al.* Infectious complications of hematopoietic stem cell transplantation. J Stem Cell Res Ther 2013; S3: 002.

[41] Au WY, Lie AK, Shek TW. Fulminant molluscum contagiosum infection and concomitant leukaemia cutis after bone marrow transplantation for chronic myeloid leukaemia. Br J Dermatol 2000; 143(5): 1097-8.
[http://dx.doi.org/10.1046/j.1365-2133.2000.03859.x] [PMID: 11069530]

[42] Barroso KSN, Kaufman J, Brunetta DM, de Carvalho Araújo FM, Barroso-Duarte F. Dengue encephalitis in allogenic hematopoietic stem cell transplantation recipient. Bone Marrow Transplant 2017; 52(10): 1455-6.
[http://dx.doi.org/10.1038/bmt.2017.152] [PMID: 28714943]

[43] Girão ES, Rodrigues Dos Santos BG, do Amaral ES, *et al.* Chikungunya infection in solid organ transplant recipients. Transplant Proc 2017; 49(9): 2076-81.
[http://dx.doi.org/10.1016/j.transproceed.2017.07.004] [PMID: 29149964]

[44] Gadient Hotz S, Müller DJ, Chaney M, Blum J. No fever, no malaria? A diagnostic challenge in an immunocompromised patient. Travel Med Infect Dis 2015; 13(6): 511-2.
[http://dx.doi.org/10.1016/j.tmaid.2015.11.002] [PMID: 26612047]

[45] Genda J, Negron EA, Lotfipour M, *et al.* Severe babesia microti infection in an immunocompetent host in pennsylvania. J Investig Med High Impact Case Rep 2016; 4(3)2324709616663774
[http://dx.doi.org/10.1177/2324709616663774] [PMID: 27656660]

[46] Krause PJ, Gewurz BE, Hill D, *et al.* Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis 2008; 46(3): 370-6.
[http://dx.doi.org/10.1086/525852] [PMID: 18181735]

[47] Prigione I, Castagnola E, Imberti L, *et al.* Multiple relapses of visceral leishmaniasis in an adolescent with idiopathic CD4+ lymphocytopenia associated with novel immunophenotypic and molecular features. Pediatr Infect Dis J 2009; 28(2): 161-3.
[http://dx.doi.org/10.1097/INF.0b013e318185513d] [PMID: 19106781]

[48] Antinori S, Schifanella L, Corbellino M. Leishmaniasis: new insights from an old and neglected disease. Eur J Clin Microbiol Infect Dis 2012; 31(2): 109-18.
[http://dx.doi.org/10.1007/s10096-011-1276-0] [PMID: 21533874]

[49] Lattes R, Lasala MB. Chagas disease in the immunosuppressed patient. Clin Microbiol Infect 2014; 20(4): 300-9.
[http://dx.doi.org/10.1111/1469-0691.12585] [PMID: 24602129]

[50] Marciano-Cabral F, Cabral G. Acanthamoeba spp. as agents of disease in humans. Clin Microbiol Rev 2003; 16(2): 273-307.
[http://dx.doi.org/10.1128/CMR.16.2.273-307.2003] [PMID: 12692099]

[51] Baig AM. Granulomatous amoebic encephalitis: ghost response of an immunocompromised host? J Med Microbiol 2014; 63(Pt 12): 1763-6.
[http://dx.doi.org/10.1099/jmm.0.081315-0] [PMID: 25239626]

[52] Abanyie FA, Gray EB, Delli KW, *et al.* Donor-derived Strongyloides stercoralis infection in solid organ transplant recipients in the United States, 2009-2013. Am J Transplant 2015; 15(5): 1369-75.
[http://dx.doi.org/10.1111/ajt.13137] [PMID: 25703251]

[53] Koehsler M, Soleiman A, Aspöck H, Auer H, Walochnik J. Onchocerca jakutensis filariasis in humans. Emerg Infect Dis 2007; 13(11): 1749-52.
[http://dx.doi.org/10.3201/eid1311.070017] [PMID: 18217562]

[54] Kipp W, Bamuhiiga J, Rubaale T. Simulium neavei-transmitted onchocerciasis: HIV infection increases severity of onchocercal skin disease in a small sample of patients. Trans R Soc Trop Med Hyg 2003; 97(3): 310-1.
[http://dx.doi.org/10.1016/S0035-9203(03)90157-X] [PMID: 15228250]

[55] Heldwein K, Biedermann HG, Hamperl WD, *et al.* Subcutaneous Taenia crassiceps infection in a patient with non-Hodgkin's lymphoma. Am J Trop Med Hyg 2006; 75(1): 108-11.
[http://dx.doi.org/10.4269/ajtmh.2006.75.108] [PMID: 16837716]

[56] Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. BMC Infect Dis 2014; 14(Suppl. 1): S5.
[http://dx.doi.org/10.1186/1471-2334-14-S1-S5] [PMID: 24564453]

[57] Mody R, Naranjo A, Van Ryn C, *et al.* Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial. Lancet Oncol 2017; 18(7): 946-57.
[http://dx.doi.org/10.1016/S1470-2045(17)30355-8] [PMID: 28549783]

[58] Riccardi N, Rotulo GA, Favilli F, *et al.* Pseudomonas aeruginosa severe skin infection in a toddler with X-linked agammaglobulinemia due to a novel BTK mutation. Infez Med 2019; 27(1): 73-6.
[PMID: 30882382]

[59] Bearden D, Collett M, Quan PL, Costa-Carvalho BT, Sullivan KE. Enteroviruses in X-Linked Agammaglobulinemia: Update on Epidemiology and Therapy. J Allergy Clin Immunol Pract 2016; 4(6): 1059-65.
[http://dx.doi.org/10.1016/j.jaip.2015.12.015] [PMID: 26883540]

[60] Parvaneh L, Sharifi N, Azizi G, *et al.* Infectious etiology of chronic diarrhea in patients with primary immunodeficiency diseases. Eur Ann Allergy Clin Immunol 2019; 51(1): 32-7.
[http://dx.doi.org/10.23822/EurAnnACI.1764-1489.77] [PMID: 30417635]

[61] Flanagan SE, Haapaniemi E, Russell MA, *et al.* Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. Nat Genet 2014; 46(8): 812-4.
[http://dx.doi.org/10.1038/ng.3040] [PMID: 25038750]

[62] de la Morena MT. Clinical Phenotypes of Hyper-IgM Syndromes. J Allergy Clin Immunol Pract 2016; 4(6): 1023-36.
[doi: 10.1016/j.jaip.2016.09.013] [PMID: 27836054]

[63] Berrington JE, Flood TJ, Abinun M, Galloway A, Cant AJ. Unsuspected *Pneumocystis carinii* pneumonia at presentation of severe primary immunodeficiency. Arch Dis Child 2000; 82(2): 144-7.
[http://dx.doi.org/10.1136/adc.82.2.144] [PMID: 10648370]

[64] Marciano BE, Spalding C, Fitzgerald A, *et al.* Common severe infections in chronic granulomatous disease. Clin Infect Dis 2015; 60(8): 1176-83.
[http://dx.doi.org/10.1093/cid/ciu1154] [PMID: 25537876]

[65] Maglione PJ, Simchoni N, Cunningham-Rundles C. Toll-like receptor signaling in primary immune deficiencies. Ann N Y Acad Sci 2015; 1356(1): 1-21.
[http://dx.doi.org/10.1111/nyas.12763] [PMID: 25930993]

[66] Spinner MA, Sanchez LA, Hsu AP, *et al.* GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. Blood 2014; 123(6): 809-21.
[http://dx.doi.org/10.1182/blood-2013-07-515528] [PMID: 24227816]

[67] Vila A, Dapás JI, Rivero CV, *et al.* Multiple opportunistic infections in a woman with GATA2 mutation. Int J Infect Dis 2017; 54: 89-91.
[http://dx.doi.org/10.1016/j.ijid.2016.11.408] [PMID: 27894982]

[68] Lanternier F, Mahdaviani SA, Barbati E, *et al.* Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species-induced meningoencephalitis, colitis, or both. J Allergy Clin Immunol 2015; 135(6): 1558-68.e2.
[http://dx.doi.org/10.1016/j.jaci.2014.12.1930] [PMID: 25702837]

[69] Lozano ML, Rivera J, Sánchez-Guiu I, Vicente V. Towards the targeted management of Chediak-Higashi syndrome. Orphanet J Rare Dis 2014; 9: 132.
[http://dx.doi.org/10.1186/s13023-014-0132-6] [PMID: 25129365]

[70] Rezaei N, Hedayat M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. J Allergy Clin Immunol 2011; 127(6): 1329-41.e2.
[http://dx.doi.org/10.1016/j.jaci.2011.02.047] [PMID: 21514636]

[71] Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM. Immunodeficiency and infections in ataxia-telangiectasia. J Pediatr 2004; 144(4): 505-11. [http://dx.doi.org/10.1016/j.jpeds.2003.12.046] [PMID: 15069401]

[72] Candotti F. Clinical manifestations and pathophysiological mechanisms of the wiskott-aldrich syndrome. J Clin Immunol. 2018; 38(1): 13-27. doi:10.1007/s10875-017-0453-z. [PMID: 29086100].

[73] Al-Shaikhly T, Ochs HD. Hyper IgE syndromes: clinical and molecular characteristics. Immunol Cell Biol 2019; 97(4): 368-79.

[74] Grimbacher B, Holland SM, Gallin JI, *et al.* Hyper-IgE syndrome with recurrent infections--an autosomal dominant multisystem disorder. N Engl J Med 1999; 340(9): 692-702. [http://dx.doi.org/10.1056/NEJM199903043400904] [PMID: 10053178]

[75] Picard C, Bobby Gaspar H, *et al*. International union of immunological societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol. 2018; 38(1): 96-128. doi: 10.1007/s10875-017-0464-9. [PMID: 29226302]