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Some Opportunistic Infections in Childhood: Causes, Diagnosis and Treatment Methods

Sabina Muradovna Gulieva[1*], Muradovna Akhverdiyeva Galina[1], Eugeny Kalinin[2], Shirvan Emirovna Mameeva[3], Anna Agasievna Harutyunyan[4] and Tatiana Alekseevna Kabanova[4]

[1]Russian National Research Medical University, N. I. Pirogov, st. Ostrovityanova, 1, 117997, Moscow, Russia.
2Tyumen State Medical University, Tyumen, Russian Federation, Russia.
[3]Federal State Budgetary Educational Institution of Higher Education, Astrakhan State Medical University of the Ministry of Healthcare of the Russian Federation, Russia.
[4]I. M. Sechenov First Moscow State Medical University, Bol'shaya Pirogovskaya Ulitsa, 2/4, 119435, Moscow, Russia.

Authors' contributions

This work was carried out in collaboration among all authors. Authors SMG and TAK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MAG and EK managed the analyses of the study. Authors SEM and AAH managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The article discusses the features of the emergence and development of the so-called opportunistic infections that occur in children with weakened immunity.
Such infections are often caused by non-tuberculosis mycobacteria, fungi, and herpesviruses, and such infections can also develop in children who are treated with immunobiological drugs. Since these are serious and rapidly developing diseases, the diagnosis should be made at the earliest stages of the development of the disease and be based on the features of clinical phenomena described in the literature and anamnesis data indicating the presence of such infections. The

**Corresponding author: E-mail: gul675@mail.ru;*

earlier an infection is detected, the faster it will be possible to start appropriate therapy.
The relevance of this topic is due to the fact that, despite the improvement in the diagnosis of opportunistic infections in recent years, they still are a problem for pediatricians, who are not always able to diagnose them in time. Accordingly, the pediatrician should, in case of suspicion of the presence of such an infection in a child patient, contact specialists who have experience in their treatment in order to take timely measures to stop the development of the disease.
The aim of the study is to consider the features of some opportunistic infections in childhood, their causes, diagnosis, and treatment methods.

Keywords: Childhood; pediatrics; infections; weakened immunity; treatment.

1. INTRODUCTION

Along with common infectious diseases, patients in childhood may develop so-called opportunistic infections (OI). They are caused by pathogens (bacteria, viruses, fungi, or protozoa) that are aided by a host with a weakened immune system, altered microbiota, or a violation of skin barriers.

A condition characterized by a balance between several species that make up the microbiota is called eubiosis. Any disorders of eubiosis, known by the broad name dysbacteriosis, can cause infectious and non-infectious diseases. Opportunistic infections occur in situations of dysbiosis, they predispose a person' immune system to exogenous and endogenous infections. They occur in the context of autoimmunity or show reactions of varying intensity, both enhanced (in allergic reactions and conditions of chronic inflammation) and reduced (in cases of immunodeficiency or cancer) [1].

The manifestations of infection vary depending on the patient's accompanying pathology, which, in turn, is associated with not fully functional aspects of the immune system.

In pediatric practice, accompanying diseases or situations that lead to opportunistic infections are increasingly common. Human immunodeficiency virus (HIV) infection, congenital immunity errors (formerly called primary immunodeficiencies), neoplasms, autoimmune conditions, and the use of chemotherapy, radiation therapy, or immunomodulatory drugs are some examples of these accompanying pathologies.

2. RESEARCH METHODS

The paper reviews the literature on the occurrence and development of OI in childhood, and groups such infections into different classes of pathogens. Also, through the use of the analytical method of research, the methods of diagnosis and features of therapy of mycobacterial, fungal, viral infections, as well as infections affecting people using immunobiological agents are considered.

3. RESULTS AND DISCUSSION

Let us consider the features of OI that can develop in childhood with a weakened immune system.

Non-tuberculosis microbacteria are widespread in the environment and can cause diseases known as microbial infections. Most disseminated infections are associated with cellular immunity disorders, for example, in patients with congenital immunity deviations affecting the interferon-gamma axis (IFN)/interleukin (IL) -12 / IL-23 (IL-12 deficiency, IFN-gamma deficiency,- kappa deficiency) [2]. They manifest as respiratory infections, usually in patients with pre-existing pulmonary pathologies (cystic fibrosis, COPD, bronchiectasis) and in patients with skin and soft tissue infections, including lymphadenitis and surgical wound infections, regardless of whether they are associated with device implantation or not. They can also manifest as disseminated infections in immunocompromised patients. According to their phenotypic characteristics, they are divided into two groups: slow-growing and fast-growing microbacteria (Table 1) [3].

Among slow-growing mycobacteria, *Mycobacterium avium* complex mycobacteria is the most common cause of lung infection, as well as the main cause of lymphadenitis in children under 5 years of age. They affect patients living with HIV with a cluster of differentiated 4 (CD4) T-lymphocytes below 50 / mm3 or patients with innate errors of immunity, causing extrapulmonary and disseminated clinical pictures. M. kansasii, another non-tuberculous

mycobacterium, causes pulmonary infection with fibroblast tuberculosis and, less commonly, focal or disseminated infections in patients with HIV or other immunosuppressive conditions.

Fast-growing mycobacteria also cause chronic respiratory infections in children with pre-existing lung lesions, skin and soft tissue infections, many of which are associated with surgical procedures, as well as infections associated with catheters and prostheses. The latter can form biofilms, which makes treatment more difficult, so it is necessary to remove these devices in order to cure the patient. M. abscess of this group is of particular importance, causing respiratory infections and creating great difficulties in the treatment of infections [4].

Final diagnosis of mycobacterial infections requires identification of the pathogen. If there is a clinical suspicion of a non-tuberculosis mycobacterium infection, one should contact the laboratory to ensure proper handling of the samples and culture conditions to isolate the pathogens. As a rule, in adults, two or more sputum samples or one sample of bronchoalveolar lavage should lead to the release of non-tuberculosis mycobacteria for diagnosis. In children, these criteria have yet to be established. Moreover, the isolation of non-tuberculosis mycobacteria from sterile areas indicates infection. At the same time, a tuberculin skin test in the case of a mycobacterial infection is usually positive, because several antigens are common to M. tuberculosis and other mycobacteria.

Also, children with weakened immunity may develop fungal infections with low pathogenicity, which specifically infect a child with weakened immunity. They are caused by fungi that are locally common in the environment, such as mycelial fungi (*Fusarium spp*., Mucorales, etc.) or yeasts that are part of the endogenous or exogenous microbiota of fungi, such as *Candida spp*.

Candida spp. infections are manifested in the form of infections of the bloodstream, urinary tract, bones, skin or surgical site, myocarditis, meningitis and abscesses, the latter being associated with the introduction of a catheter. The most common clinical picture is the onset of a fever that cannot be treated with antibiotics in patients at risk.

It is believed that most cases of cancer occur endogenously as a result of translocation of pathogens through the gastrointestinal tract, in which up to 70% of the immunocompetent healthy population is colonized by *Candida spp*.

Factors that increase colonization of the Candida intestine (use of antibiotics, corticosteroids, paralytic intestinal obstruction, intestinal obstruction) or determine atrophy or damage to the intestinal mucosa (prolonged fasting, complete parenteral nutrition, hypotension, surgery, mucositis secondary to chemotherapy or radiation therapy) may increase the phenomenon of translocation from the gastrointestinal tract. Less often, exogenous infections occur due to medical procedures, contamination of solutions or prostheses, or colonization of the central venous catheter [5].

Among the *Candida spp*. species, C. albicans is most commonly found in clinical practice. However, some non-albic species, such as *C. tropicalis*, *C. parapsilosis* , *C. glabrata*, and *C. krusei*, are involved in increasing the number of invasive infections, with a high proportion of treatment inefficiencies associated with resistance to azoles and echinocandins.

In a retrospective study of pediatric cancer patients with candidaemia, it was observed that patients who had Candida tropicalis isolated had more skin lesions compared to patients with other types of candidaemia.

Table 1. Mycobacterium species and their dissemination

The direction of action of *mycobacteria*	Types of mycobacteria
Mycobacteria that cause leprosy	*M. leprae, M. Lepromatosis*
Slow-growing non-tuberculosis mycobacteria	*M. avium комплекс -M. intracellulare u M. avium M. kansasii, M. xenopi, M. malmoense, M. szulgai, M. ulcerans*
Fast-growing non-tuberculosis mycobacteria	*M. abscessus, M. chelonae, M. fortuitum, M. marinum u* and others.

Some years ago, there were no reports of multi-resistant Candida, but the current scenario includes invasive infections caused by multi-resistant non-albicans Candida, most of them C. glabrata and C. auris.

C. auris is a new species. Discovered in 2009, it has been described in more than 30 countries on six continents. It is highly resistant to antifungal drugs, with an estimated mortality rate of 30-72%. Its isolation is difficult when using conventional biochemical methods, and it can be mistaken for *C. haemulonii*. As with other Candida spp. species containing C. aegis in non-sterile areas may represent colonization, and its detection is very important, since, in addition to the fact that colonization is difficult to eradicate, there is a risk of horizontal transmission.

Invasive aspergillosis occurs in patients with weakened immune systems and severe and persistent neutropenia due to treatment with corticosteroids or chemotherapy, stem cell transplants, or organ transplants, especially lung transplants. It has a high mortality rate, with the most common species being *Aspergillus fumigatus, A. flavus,A. niger*, and *A. terreus*. versicolor. A. fumigatus is the main causative agent of invasive pulmonary aspergillosis, followed by *A. flavus* and *A. terreus.* Research shows that *A. Fumigatus* can form aerosols and can be transmitted to other people.

In invasive aspergillosis, the earliest manifestation is fever in a patient with prolonged neutropenia, respiratory symptoms such as cough and shortness of breath, and poor lung auscultation. Patients with severe immunosuppression can progress to disseminated forms with damage to the central nervous system, which leads to brain abscess and, in rare cases, to meningitis [6].
The diagnosis is based on clinical suspicion, imaging studies, antigen screening (galactomannan and beta-D glucan) , and fungal isolation by microscopy and culture.

Infections caused by Fusarium spp. may clinically manifest as persistent fever that cannot be treated with broad-spectrum antibiotics, in patients with neutropenia and T-cell immunodeficiency, or in patients with acute leukemia. People with weakened immune systems may have skin lesions characterized by painful erythematous spots or papules that develop into necrotic ulcers known as gangrenous ecthyma, which are more common on the extremities and spread quickly. Main entrance for Fusarium spp. these are the airways, followed by damaged or burned skin.
A catheter infection can lead to fungemia.and its removal, associated with an antifungal agent, is crucial for treatment. Fungal isolation can be performed by skin biopsy or blood culture. The diagnosis and treatment of disseminated fusariasis are also described in Table 3.

Pneumocystis jiroveci is known as the causative agent of opportunistic pneumonia in people infected with HIV. The incidence in this group decreased due to combined antiretroviral therapy and prevention of pneumocystosis. On the other hand, there is currently an increased incidence of infections in those who receive immunosuppressants for cancer or autoimmune diseases, in hematopoietic stem cells, or in recipients of solid organ transplants. A recent study of adults and children showed that the most common concomitant diseases in the latter were oncohematological diseases, post-transplant period and weak immune system. The main clinical manifestation was pneumonia with fever, cough, shortness of breath and oxygen desaturation, developing into respiratory failure in adults and children. Radiological examination revealed bilateral consolidation or bilateral interstitial infiltrates. The mortality rate is about 25%.

The diagnosis of *P. jiroveci* infection is based on the imaging of an agent with specific staining in the lung tissue or in samples of respiratory secretions, such as bronchoalveolar la-vazh, induced sputum, or endotracheal aspiration in intubated patients.
The treatment of choice is sulfamethoxazole trimethoprim (SMZ-TMP), administered intravenously for 21 days. Intravenous pendamidine may be an alternative for those who do not tolerate SMT-TMP or who have no response after four to eight days of SMZ-TMP therapy. Patients with partial O2 pressure below 70 mmHg are recommended to take oral prednisone for 21 days.

Cryptococcus, an encapsulated yeast fungus that causes cryptococcosis, is a member of the yeast group and is found mainly in patients with hematological malignant neoplasms, as well as in those who take high doses of corticosteroids, in recipients of solid organ transplants, and in persons infected with HIV and cell immunosuppression [7]. In these children, hematogenic spread can occur in the central

nervous system, bones, and skin. The most common form is cryptococcal meningitis, which is sluggish with fever, headache, and behavioral changes. Common complications are intracranial hypertension and inflammatory immune recovery syndrome. The diagnosis can be made by screening for cerebrospinal fluid or serum antigen, but the final diagnosis depends on the release of the agent in the culture of body fluids or biopsy material [8].

The difference between the two species, *C. neoformans* and *C. gatti*, depends on the use of selective nutrient media. The diagnosis and treatment of cryptococcosis are described in Table 3.

Another deep mycosis, mucormycosis, should be a differential diagnosis of invasive as-pergillosis. Both have similarities in affected patients (cancer patients and patients with diabetes, in the case of mucormycosis), in risk factors (long-term neutropenia), as well as in clinical and radiological signs [9]. A recent study comparing invasive aspergillosis with mucormycosis in cancer patients showed that mucormycosis is more common in children and adolescents than in adults, as well as in patients with acute leukemia and graft rejection, while aspergillosis is more common in patients with lymphoma [10].

3.1 Discussion

The diagnosis and treatment of mycobacterial infections are presented in Table 2.

Table 3 also summarizes the diagnosis and treatment of major opportunistic fungal infections.

Accordingly, following these recommendations will help to reduce the spread of OI among susceptible children and will make the treatment of the underlying disease more effective.

Table 2. Diagnosis and treatment of major infections caused by non-tuberculosis mycobacteria

Pathology	Agents of infection	Diagnostics	Treatment
Lung, nodular infection, or bronchiectasis	*M. avium комплекс*	Culture of respiratory secretions	Clarithromycin or azithromycin + ethambutol + rifampicin or rifabutin
			In the fibrous-cavity or disseminated form: associated streptomycin or amikacin.
Lung infection	*M.kansasii*	Culture of respiratory secretions	Rifampicin + ethambutol + clarithromycin + levofloxacin or moxifloxacin
Lung infection	*M.absces sus*	Culture of respiratory secretions	Imipenem or cefoxitin
			Amikacin, clarithromycin
			Tigecycline or doxycycline (for people over 8 years of age)

Table 3. Diagnosis and treatment of major opportunistic fungal infections

Pathology	Agents of infection	Diagnosis	Treatment
Disseminated candidiasis	***Fungal microorganisms albicans***	Antigen test (β1, 3 glucan) Blood culture	*1st choice: Echinocandins: Micafungin*
			2 nd choice: amphotericin B
			3 rd choice: fluconazole
	Candida glabrata	Antigen test (β1, 3 glucan) Blood culture	*1 st choice: echinocandins*
			2 nd choice: amphotericin B
	Candida auris	Antigen test (β1, 3 glucan) Blood culture	Multi-resistant
			Echinocandin associated with amphotericin B
Invasive aspergillosis	*Aspergillus fumigatus*	Serial computed tomography of the lungs: nodules in the lungs and the sign of	Elimination of immunosuppression and control of the main disease

		the halo, the sign of the air crescent	
		Direct screening and culture of *Aspergillus spp.*	1 st choice: voriconazole
		Galactomannan plasma, bronchoalveolar lavage, or cerebrospinal fluid	Other: itraconazole, posaconazole, ravuconazole.
		Persistently negative values: high negative prognostic value of the disease (β1,3 glucan) in serum.	Liposomal amphotericin
		PCR	Echinocandin
			Caspofungin in combination with voriconazole in refractory invasive disease.
Disseminated fusarium infection	*Fusarium solani* and others	Screening and culture for skin or blood fungus	Amphotericin B Desoxycholate
		β1,3 glucan	Liposomal amphotericin B
		Radiology: Interstitial pulmonary infiltrate and nodules or caves.	Voriconazole
Pneumocystosis	*P. jiroveci*	Direct screening for *P. jiroveci*	Sulfamethoxazole + trimethoprim
		PCR in bronchoalveolar lavage or sputum	
Disseminated cryptococcosis or cryptococcosis of the central nervous system	*C. gatti* and *C. neoformans*	CSF and serum antigen screening	Amphotericin B deoxycholate + 5 flucytosine
		Culture of biological fluids and biopsy material	Fluconazole
Mucormycosis	*Rhizopus* (*R. arrhizus*), *Mucor* (*M. circinelloides*), *Rhizomucor* (*R. pusillus*), *Cunninghamella* (*C. bertholletiae*), *Absidia* (*A. corymbifera*)	Tomography: halo sign, inverted halo sign, pleural effusion, pulmonary nodules	Amphotericin B deoxycholate or liposomal amphotericin
		Direct examination of nasal mucosal scraping, sinus aspiration, sputum, or bronchoalveolar lavage:	Posaconazole
		wide hyaline hyphae without partitions with branches at an angle of 90 °.	
		Anatomical and pathological test; culture (sensitivity: 50%)	

CONCLUSIONS

Despite the improvement in the diagnosis of OI, in recent years, they remain a problem for pediatricians, who do not often face them. Accordingly, at the first suspicion of the occurrence of OI, the pediatrician should get appropriate advice from specialized medical experts and start treatment. Well-conducted consultation and timely measures for diagnosis

and treatment will allow them to provide the necessary medical care for children diagnosed with OI, among whom the mortality rate from such diseases is still high.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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