Opportunistic Infections

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Abstract

Evolution in paediatric HIV management has changed the incidence and prevalence of opportunistic infections and a major reduction has been shown for most opportunistic infections with antiretroviral therapy use in lower and middle-income countries, especially in the first year of treatment. However, the high prevalence of disease still requires adequate management of opportunistic infections, to improve patient quality of life and the impact on burden of disease. Lower CD4 counts were associated with chronic infection and increased risk of opportunistic infections in patients, but some studies have shown that even children with high CD4 counts may have opportunistic infections.

This chapter reviews common opportunistic infections that may infect HIV positive children and adolescents, particularly in sub Saharan Africa.

Keywords

HIV · Opportunistic · Children · Adolescents · Neonates · Paediatrics Immunocompromised · Infections

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14.1 Introduction

The mid-year population estimates from Statistics South Africa reported that there are 7,52 million people living with HIV in 2018 and this approximates to 13% of the country's population [1]. Evolution in paediatric HIV management has changed the incidence and prevalence of opportunistic infections and a major reduction has been shown for most opportunistic infections with antiretroviral therapy use in lower and middle-income countries, especially in the first year of treatment [2]. However, the high prevalence of disease still requires adequate management of opportunistic infections, to improve patient quality of life and the impact on burden of disease. Lower CD4 counts were associated with chronic infection and increase risk of opportunistic infections in patients, but some studies have shown that even children with high CD4 counts may have opportunistic infections [3, 4].

This chapter reviews common opportunistic infections that may infect HIV positive children and adolescents, concentrating on developing countries.

14.2 Bacterial Infections

The presentations of bacterial infections are common to both the HIV unexposed, exposed and infected children. However, earlier in the decade the Centre for Disease Control and Prevention (CDC) added this category to the AIDS defining conditions [5]. Although bacterial infections may be common to all children, the spectra of disease presentations are different and may be more severe in the HIV infected child. More current published data suggest that the HIV exposed uninfected infant has a different immunologic profile from the unexposed infant and hence predisposed to bacterial infections with encapsulated organisms [6].

14.2.1 Pneumonia

Streptococcus pneumonia is the leading bacterial cause of pneumonia and has caused most of the deaths in children <5 in 2015 [7]. A study in South Africa found significant reduction in severe pneumococcal disease, with approximately 130,000 cases and 5000 deaths averted over a 5-year period following HIV management interventions and the introduction of the pneumococcal conjugate vaccine [8].

Community acquired pneumonia has been attributed to various common organisms including group B Streptococcus, Listeria monocytogenes, Escherichia coli, Klebsiella pneumoniae, Respiratory syncytial virus and Mycoplasma pneumoniae. The introduction of vaccines and the use of antimicrobials has changed the face of managing the syndrome over the years.

In a Durban based intensive care unit in South Africa, it was shown that there was no difference in outcomes between HIV positive and negative cohorts requiring ventilation [9]. This is most likely attributed to directed therapy of the pneumonia with the use of highly active anti-retroviral therapy. For decades there was a paucity

of information on aetiology of hospital acquired pneumonias but a study in Tygerberg showed that the main organisms implicated have been *Klebsiella* and *Staphylococcus aureus* [10].

14.3 Fungal Infections

Like all opportunistic infections, fungal infections too have changed in the era of antiretroviral therapy. However, in many developing countries invasive fungal infections remain a problem.

14.3.1 Pneumocystis jirovecii Pneumonia

Pneumocystis jiroveci is an ascomycete yeast, previously known as *pneumocystis carinii*. Although this organism is classified as a fungus, it does not respond to antifungal therapy. It is usually managed empirically if a patient presents with a hypoxaemic pneumonia but diagnosis may be confirmed with imaging and microbiological confirmation. WHO guidelines have been supported by recent evidence that cotrimoxazole prophylaxis reduces mortality in infants less than 6 months by preventing pneumocystis pneumonia. Treatment is with high dose trimethoprim/sulfamethoxazole and corticosteroids.

14.3.2 Candida

The clinical manifestations in children may range from mucosal infections (oral thrush) to multiorgan involvement and dissemination. Candida is part of the normal flora of both the gastrointestinal and genitourinary tracts and candidaemia may occur in the immunocompromised patient or patients in intensive care settings with central catheters.

Oropharyngeal and oesophageal candidiasis is treated with topical antifungal or systemic therapy with azoles. It is important to identify the candida species to aid in management. Candida albicans, commonly encountered, is susceptible to the azoles but others may be resistant and susceptible to either amphotericin or the eichanocandins.

Currently there is not much data available on azole resistance.

14.3.3 Cryptococcosis

Cryptococcus is an encapsulated fungus with a wide geographical distribution. Most HIV- associated cryptococcosis is caused by *C. neoformans* [11]. The highest risk of infection is in patients with CD4 < 100 cells/μl. The incidence of childhood Cryptococcosis is less. Sixty three percent of paediatric patients are

immunocompromised [12]. There is little information on paediatric disease, particularly in Sub-Saharan Africa. The 10 week mortality rate in adults on antiretroviral therapy (ART) is as high as 32% [13]. There is a 30% risk of developing IRIS in adults co-infected with Cryptococcus; there is very little data available in children [14].

14.3.3.1 Clinical Characteristics

The most common clinical manifestation is chronic meningoencephalitis, with progressive symptoms of headache, fever, visual disturbances, altered mental state and seizures. Raised intracranial pressure and communicating hydrocephalus are common complications. Pneumonia is the second most common presentation in immunocompromised children [15]. ARDS is unusual in children.

14.3.3.2 Diagnostic Tests

Diagnosis of cryptococcal meningitis can be made by culture of CSF or India ink stain. A presumptive diagnosis can be made with positive Cryptococcal latex agglutination test (CLAT) on CSF specimen. CSF opening pressure is usually high and few cells are seen with normal glucose and occasionally high protein.

14.3.3.3 Treatment

Treatment consists of induction and consolidation phases.

Induction: 1 week of amphotericin B and flucytosine is the preferred option for all children, adolescents and adults. Alternatives include 2 weeks of either fluconazole and flucytosine or amphotericin B and fluconazole.

Consolidation: 8 weeks of fluconazole [16].

14.3.3.4 Secondary Prophylaxis (Maintenance)

A year of fluconazole is recommended in adolescents and children older than 6 years. This is discontinued if:

- asymptomatic for cryptococcosis,
- a ≥6 month increase in CD4 counts >100 cells/mm^3
- and an undetectable viral load on ART for >3 months.

Secondary prophylaxis should be re-initiated if the CD4 count falls below 100 cells/mm^3. Children younger than 6 years should not discontinue fluconazole prophylaxis [16].

14.3.3.5 Screening for at-Risk HIV Positive Patients

Routine serum plasma or serum Cryptococcal Antigen screening followed by clinical screening and antifungal treatment prior to initiation of ART has been recommended by the WHO since 2011 in adults and adolescents with CD4 counts less than 100 cells/mm^3 in high prevalence countries [16]. This is not recommended for children.

14.4 Viruses

14.4.1 Herpes Simplex Virus (HSV)

Herpesviruses are a double-stranded DNA virus. HIV infected patients may develop serious, life-threatening infections as the viral infection is usually controlled by the cellular immune function. HSV1 is transmitted by contact with oral secretions and HSV2 through infected genital secretions. Primary infections may present with fever, excessive drooling and weight loss. Stress may predispose patients to vesicular eruptions that last 2–4 days.

After primary infection with HSV, the virus is latent within the sensory ganglia. If the host is immunocompromised, reactivation occurs typically on the face or lips for HSV 1 and genital areas for HSV2. In the severely immunocompromised host, viraemic spread to distant sites may occur.

Diagnosis: is made with molecular studies. Detection of HSV DNA by PCR is highly sensitive and specific. CSF analysis may show normal glucose and mild lymphocyte pleocytosis. Red cells are often present.

Treatment: It is critical to institute empiric antiviral therapy with acyclovir in immunocompromised individuals with acute neurological symptoms. Treatment is 14 days of IV acyclovir.

14.4.2 Cytomegalovirus (CMV)

The human cytomegalovirus is a double-stranded DNA virus of the Herpesviridae group. Once infection occurs, the host will experience a lifelong period of latency or disease depending on the immune status.

14.4.2.1 Seroepidemiology

The incidence of CMV is dependent on the population, with developing countries experiencing higher seroprevalence as most of the population will have acquired the disease early in life [17–19]. The seroprevalence i.e. IgG positivity in HIV negative, HIV positive adults, AIDS patients, pregnant women and children in Africa ranges between 81.8% and 94.8% [20, 21].

14.4.2.2 Pathophysiology

The site of inoculation in a healthy host is the mucosal surfaces of the upper respiratory or genital tract from contact with viral containing particles in oropharyngeal secretions, urine, cervical and vaginal secretions, semen, breast milk, tears, faeces and blood. The virus infects trafficking leucocytes, replicates and then results in viraemia which is often asymptomatic. Eventually dissemination to multiple tissues occurs. Within 4–6 weeks after infection, shedding of virus may occur, even in healthy hosts, and may continue for months to years thereafter [22]. A period of latency in myeloid stem cells and circulating monocytes then follows in which the

virus remains dormant. Disease occurs when there is reactivation of latent infection or primary infection in a host with a disabled immune system.

14.4.2.3 Impact of HIV on Congenital CMV

HIV-infected women who are CMV seropositive have more frequent CMV reactivations. This increases the risk for congenital CMV infection in neonates who are HIV exposed. HIV-infected neonates have a threefold higher risk for symptomatic congenital CMV infection [23].

14.4.2.4 The Impact of CMV on HIV Progression

CMV infection may act as a cofactor for HIV disease progression. The risk for infant death is increased in HIV-CMV-coinfected patients and there appears to be an accelerated progression of CNS disease in survivors. The high rate of coinfections in pregnant women with HIV in resource-limited settings may influence the transplacental transmissibility of CMV. Maternal immune status is an important determinant in the above [24].

14.4.2.5 Clinical Disease in Children with HIV Infection

CMV is a multisystemic disease. The clinical spectrum of congenital CMV includes in-utero growth retardation, prematurity, jaundice, hepatosplenomegaly and neurological abnormalities [25].

Respiratory presentation is that of an interstitial pneumonitis. The outcome in HIV positive patients requiring ventilation for CMV-related pneumonia is poor [26].

CMV GI disease includes colitis, hepatitis, oral ulceration and gastritis. Colitis is the commonest with patients presenting with bloody diarrhoea, malabsorption and intestinal perforation.

CMV retinitis in children is a less common than in adults, especially in the post ART era. Infection results in necrotic, rapidly progressing brushfire retinitis. Younger children often present with strabismus or failure to fix-and-follow as compared to older children and adolescents who present with visual disturbances. CMV encephalopathy also occurs in children but may be difficult to distinguish from HIV encephalopathy.

14.4.2.6 Diagnostic Tests

Diagnosis of congenital CMV in an infant is based on serology. CMV IgG indicates past infection or transplacental transfer of maternal antibodies. CMV IgM usually indicates an acute (within 3 weeks) or recent infection but may be only weakly positive in neonates. Viral detection in body fluids by PCR may be performed within the first 3 weeks of life to confirm neonatal infection. Urine samples are the most specific means to diagnose infection. Should these tests be positive after 3 weeks of age, it is difficult to ascertain if there is congenital vs postnatally acquired infection.

Diagnosis in HIV positive children or adolescents would include CMV PCR to confirm viraemia and or urine CMV PCR. This is usually present in end-organ

disease. Organ specific diagnosis of tissue and body fluid will aid diagnosis. Diagnosis of retinopathy is dependent on fundoscopy and PCR of vitreal fluid.

14.4.2.7 Treatment

Current recommendation for treatment of children diagnosed with congenital CMV within the first month of life is with Ganciclovir or Valganciclovir for a total of 6 months.

HIV positive patients should be assessed on the need for treatment by the severity of the end organ affectation. CMV viral load of >10,000 copies/ml may be helpful in deciding on need for treatment in patients with clinically symptomatic disease. Systemic therapy for other end-organ disease is Ganciclovir or Valganciclovir for a total of at least 6 weeks. CNS disease is for a total of 6 weeks as above. However, maintenance therapy is recommended until the CD4 count rises to above 100 cells/mm^3 on ART. Current recommendations for retinitis are intravitreal Ganciclovir or Foscarnet [27].

14.4.3 Varicella Zoster Virus (VZV)

VZV is a member of the Herpesviridae group of viruses which results in both primary infection (varicella or chickenpox) and reactivation (Herpes Zoster) in the HIV infected child and adolescent. The virus is transmitted via the air-borne route in droplets and is highly contagious. Herpes Zoster is, however, less contagious.

The incubation period of varicella is on average 14 days and disease may begin with a prodrome followed by typical lesions starting on the face.

Severe disease manifestations are more common in HIV infected patients, especially those who are ART naive and may include neurological abnormalities, hepatitis, pneumonia, and multi-organ dysfunction with disseminated intravascular coagulation [28–30]. Infection may also become chronic and lesions may be severe in the HIV positive.

The herpes zoster rash is preceded 2–3 days by pain and the rash then appears in a dermatomal distribution. Disseminated Zoster may occur and encephalitis and retinitis have been reported as complications in children and adolescents with HIV [31–33].

14.4.3.1 Diagnosis and Treatment

Diagnosis is clinical. PCR may be required only if the course of the disease is atypical, severe, or unresponsive to standard therapy. Severe chickenpox is treated with acyclovir for 7 days.

14.4.4 Hepatitis B

Hepatitis B is a double stranded DNA virus which is part of the Hepadnaviridae family.

14.4.4.1 Epidemiology

The prevalence of Hepatitis B and HIV co-infection in pregnant African women ranges from less than 1%–7% [34]. The seroprevalence in children may range between 1.2% and 29.7% from region to region [35].

14.4.4.2 Aetiology and Pathogenesis

Transmission occurs via the same means as HIV i.e. horizontal, vertical and parenteral. The majority of children and adolescents who have chronic infection with hepatitis B have acquired this by vertical transmission. This depends on the presence of HBeAg, the Hepatitis B viral load and genotype as well as the maternal CD4 count. Progression to chronicity depends on age of acquisition with 90% of infants and up to 50% of children aged 1–5 years old developing chronic hepatitis B after acute infection [34]. Adolescents with sexually acquired HIV infection run a higher risk than HIV negative adolescents of acquiring hepatitis B infection. This may be due to ongoing risky sexual behaviour.

14.4.4.3 Clinical Characteristics

Acute infectious symptoms range from a completely asymptomatic course to fulminant hepatitis developing, on average, 3 months after transmission of the virus.

Chronic infection is a serological diagnosis based on persistence of hepatitis surface antigen (HBsAg) for at least 6 months after acute infection has occurred. Chronic infection is usually asymptomatic. The serious complication of liver cirrhosis and hepatocellular carcinoma occur in 25% of chronically infected children and usually occur in the second or third decade of life. The lifetime risk of developing hepatocellular carcinoma in a child with chronic hepatitis B is 15–40% [35].

14.4.4.4 Diagnosis

Serological Diagnosis

	Vaccinated	Acute infection	Past infection (recovered)	Chronic hepatitis B
HBsAb	+	–	+	–
HBsAg	–	+		+
IgM anti HBc	–	+	_	–
IgG anti HBc	–	–	+	+
HBeAg	–	±	–	+
Anti-HBeAb	–	–	+	

HBsAb (anti-hepatitis B surface antibody), HBsAg (hepatitis B surface antigen), IgM anti HBc (anti-hepatitis core immunoglobulin M), IgG anti HBc (anti-hepatitis core immunoglobulin G), HBeAg (hepatitis B e antigen), anti-HBeAb (anti-hepatitis B e antigen)

Adapted from: Ordering and interpreting hepatitis B serology: Scott A Davison, Simone I Strasser *BMJ* 2014;348:g2522. https://doi.org/10.1136/bmj.g2522
Chronic infection is marked by persistent HBsAg positivity and anti HBc. HBeAg is a marker of active replication, infectivity and liver disease severity.

Molecular Methods

Hepatitis B DNA is not used for diagnostic purposes but to determine if treatment is required and as a means to determine treatment success.

14.4.4.5 Screening

All newly diagnosed HIV positive patients should be screened routinely with an HBsAg test.

14.4.4.6 Treatment

Indications for treatment in children is the same for adults and adolescents.

1. Children with evidence *over 6 months* of ongoing viral replication i.e. Hepatitis B DNA positivity (>10,000 IU/ml) with or without e antigen positivity AND Persistent transaminitis (>2× normal) OR
2. Liver biopsy indicating chronic hepatitis

Treatment of HIV positive adolescents older than 12 years should include a regimen containing tenofovir + lamivudine or emtricitabine. To prevent flare-ups the patient should remain on both drugs for life unless grade 3 or 4 laboratory abnormalities are present that can only be attributed to one of the drugs [27].

Treatment Options for Children [27]

HIV status	Recommended treatment
HIV uninfected >2 years and <12 years	Interferon α (IFN-α), IFN-2a or IFN-2b
HIV uninfected >12 years	IFN-α OR Adefovir OR tenofovir (TDF)
HIV/HBV co-infected <12 years not requiring ART	IFN-α
HIV/HBV co-infected >12 years not requiring ART	Adefovir
HIV/HBV co-infected requiring ART	Lamivudine (or Emtricitabine) plus TDF if >2 years

Note: Lamivudine and Emtricitabine are interchangeable, not additive

14.4.4.7 Prophylaxis

Hepatitis B vaccines are composed of the HBsAg. The dosing schedule differs from country to country but should include a 3 dose series of intramuscular injections. The second dose should be administered at least 1 month after the first. The first dose can be administered at birth.

14.4.4.8 Prophylaxis in Infants Born to HBsAg Positive Mothers

These infants should receive hepatitis B vaccine and hepatitis B immune globulin within 12 h after birth and should then follow the routine vaccination schedule.

14.4.5 HPV

The more than 100 human papillomaviruses (HPV) result in disease in skin or mucous membranes only. The HPV types of concern in patients with HIV are those that have tropism for mucosal membranes. These are classified into high risk or low risk depending on their link to cancers.

14.4.5.1 Clinical Manifestations

Include genital warts, recurrent respiratory papillomatosis, cervical cell abnormalities and anogenital squamous cell carcinomas.

14.4.5.2 Main Types Associated with Significant Disease

Types 16, 18, 31, 33, 35 and 45 especially are associated with anogenital cancers. Type 16 causes 50% and types 16 and 18 combined cause 70% of cervical cancers worldwide. Type 16 is the most carcinogenic and most likely to persist. Cervical cancer is defined as an AIDS -defining disease [36].

14.4.5.3 Epidemiology

Almost 25% of women are infected with HPV. The HPV prevalence in some Sub-Saharan African adolescents reaches 80% [37, 38]. In 2018, there were over 300,000 estimated cervical cancer deaths worldwide, the majority in Sub-Saharan Africa and South East Asia [39].

14.4.5.4 Risk Factors for Developing Cervical Cancer

Most infections with HPV are transient. Risk factors for persistence include sexual debut before 16 years of age, bacterial vaginosis, and HIV positivity in both adults and adolescents [38, 40–42].

14.4.5.5 Screening Recommendations

The American college of Obstetricians and Gynaecologists advise that adolescents with sexually transmitted HIV have cervical cytology twice in the first year following diagnosis, then annually, and at least once within the first year of sexual debut in perinatally infected adolescents [43]. Screening in developing countries varies e.g. South Africa recommends screening of all women from the age of 25 if HIV negative or at HIV diagnosis with repeated screening every 3–5 years [44]. Newer tests include genotyping of HPV to assess risk of progression to cancer.

14.4.5.6 Diagnosis

Diagnosis is based on cytology and histology of pap smears.

14.4.5.7 Prophylaxis

Three vaccines against HPV have been developed: Gardasil ™ (Merck & Co., Inc), Cervarix ™ (GlaxoSmithKline) and Gardasil 9 ™ (Merck & Co., Inc) all of which are effective against types 16 and 18. They have been found to be safe and effective in HIV positive women [45–47].

14.4.6 Rotavirus

Rotavirus has been identified as a common cause of gastroenteritis in children internationally. Many countries have seen a decrease in incidence with the introduction of the vaccine.

Clinical spectrum in children includes fever, and a watery diarrhoea and, if severe, may lead to dehydration, shock and death [48]. More than 50% of patients present with respiratory symptoms and 2–3% with neurological manifestations (seizures, encephalitis and encephalopathy) [49, 50]. Rotavirus is not a cause of prolonged diarrhoea in the HIV infected child [51].

Diagnostic tests include enzyme-linked immunoassays (Elisa) and molecular tests such as polymerase chain reaction (PCR) [52, 53].

The disease is self-limiting and management is supportive with fluid repletion and correction of electrolyte abnormalities.

14.5 Parasitic Infections

14.5.1 Giardiasis

Giardia duodenalis (also known as *Giardia lamblia* and or *intestinalis*) is one of the parasites that causes prolonged, chronic diarrhoea in both HIV positive and negative patients. The clinical spectrum includes watery diarrhoea and epigastric pain, which may last 1–2 weeks. If the symptoms last for months, they may cause malabsorption and weight loss [54]. Giardiasis is typically is an infection of the small bowel. Chronic sequelae include irritable bowel syndrome, chronic fatigue, childhood growth faltering, failure to thrive, and cognitive impairment [55]. Treatment is with metronidazole.

14.5.2 Syphilis

Syphilis is caused by the spirochete, *Treponema pallidum.*

The rate of transplacental transmission of syphilis may be greater in HIV infected vs uninfected mothers [56, 57]. Risk of mother to child HIV transmission in adequately treated mothers with syphilis infection does not appear to be increased. One third of affected live-born infants are symptomatic at birth. Typical early signs of congenital infection include cutaneous lesions, hepatosplenomegaly, jaundice, haemolytic anaemia, bony and joint changes and CNS abnormalities. Signs of late congenital infection include bony abnormalities and abnormalities of cranial nerve VIII.

Sexually transmitted syphilis in HIV positive adolescents mimics that in HIV negative individuals; however, patients with early syphilis have an increased risk of neurological sequelae [58].

14.5.2.1 Diagnosis, Screening and Treatment

Diagnosis is based on Treponemal and Nontreponemal serological tests.

Screening of all pregnant women is recommended at antenatal booking and includes, in high-risk pregnancies, repeat tests at 28 weeks and delivery. Mothers with syphilis diagnosed antenatally should receive a three dose course of Benzathine Penicillin G weekly for 3 weeks. Treatment of congenital syphilis is 10 days of Penicillin G [59].

14.5.3 Malaria

Malaria is a life threatening, mosquito-borne infectious disease caused by parasitic protozoans. There are four different human malaria species Plasmodium falciparum, P. vivax, P. malariae and P. ovale. P. knowlesi is a zoonotic parasite that is known to infect humans.

14.5.3.1 The Effect of HIV on Malaria

HIV has effects on both cellular and humoral immunity thus affecting the immune response to malaria resulting in more severe disease and altered response to treatment in HIV infected individuals. This is especially evident in patients with low CD4 counts [60]. Malaria infection in mothers may result in increased transplacental transmission of HIV through upregulation of CCR5 receptors as well as immune upregulation in foetuses exposed to malaria in-utero [61].

Children with HIV have a higher prevalence of clinical malaria with worse clinical disease and outcome. Malaria does not appear to have any effect on response to ART [62].

14.5.3.2 Diagnosis

Diagnosis is based on identification of the parasite on thick and thin blood smears. Rapid diagnostic tests are also available which can detect up to 4 different parasitic species.

14.5.3.3 Treatment

The WHO recommendation for treatment of uncomplicated P. falciparum is artemether-lumefantrine. The recommendation for treatment of complicated malaria is artesunate. Should this not be available IV quinidine gluconate plus either doxycycline OR clindamycin OR tetracycline may be used [63]. Patients receiving protease inhibitors may need dosage adjustments or an alternative anti-malarial regimen.

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