Common opportunistic infections in HIV infected infants and children Part 1 - respiratory infections

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Introduction

The prevention and adequate management of respiratory infections is extremely important when taking care of HIV-infected children. The successful use of HAART can drastically reduce the risk of opportunistic infections, which re-emphasizes the importance of making optimal use of this live giving opportunity, as discussed the previous articles in this series. The final topic to be covered is; "Common opportunistic infections in HIV infected infants and children; Part 2 – non-respiratory infections".

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Introduction

Increased susceptibility to infections is the major cause of disease and death in human immunodeficiency virus (HIV)-infected children, with severe respiratory infections consistently reported as the most common cause of death.[1] This manuscript focuses on opportunistic infections that affect the respiratory system, with particular emphasis on tuberculosis (TB). The definition of an opportunistic infection is problematic as immune compromised children are also prone to get common childhood infections more frequently and to a more severe degree than their immune competent peers. Table 1 provides an overview of the most common respiratory infections and non-infectious conditions that occur with increased frequency in HIV-infected children.

Bacterial infections

Child autopsy data from Africa show that bacterial pneumonia is the most common respiratory cause of death in all age groups. *Pneumocystis jiroveci* (PCP) and cytomegalovirus (CMV) pneumonia are most common in infants, especially those less than 6 months of

Table 1: Overview of the most common respiratory infections and non-infectious conditions that occur with increased frequency in HIV-infected children

Infectious	Non-infectious
Bacterial *Streptococcus pneumoniae* *Haemophilus influenza* *Klebsiella pneumonia* *Salmonella spp.* *Escherichia coli* *Staphylococcus aureus* **Viral** Respiratory syncytial virus (RSV) Human metpneumovirus Adenovirus Influenza Parainfluenza Cytomegalovirus (CMV) **Fungal** *Pneumocystis jiroveci* (PCP) Candida species **Mycobacteria** *Mycobacterium tuberculosis* (TB) Non-tuberculous mycobacteria *Mycobacterium bovis* BCG	**Interstitial lung disease** Lymphocytic interstitial pneumonia (LIP) Non-specific interstitial pneumonia **Malignancies** Kaposi sarcoma Lymphoma Leiomyoma **Other** Chronic lung disease due to recurrent/previous severe infections Bronchiectasis Reactive airways Gastro-oesophageal reflux Cardiomyopathy with pulmonary oedema

age, while tuberculosis (TB) becomes more common after this period.[1,2] However, autopsy data does not represent the complete spectrum of disease; more easily diagnosed and treated conditions, such as pneumococcal pneumonia, are often under-represented. *Streptococcus pneumoniae* is the most common bacterial pathogen isolated from HIV-infected children with severe pneumonia; other important bacterial pathogens include *Haemophilus influenzae, Klebsiella pneumonia, Salmonella spp., Escherichia coli* and *Staphylococcus aureus.*[3] New vaccines, such as *H. influenza* type B (Hib) and conjugated pneumococcal vaccine, have demonstrated efficacy to reduce the burden of bacterial pneumonia in HIV-infected children, although the protection provided is less than in immune competent children.[4] Cotrimoxazole prophylaxis also reduces the burden of bacterial pneumonia and other invasive bacterial disease. The most recent South African guidelines for the management of acute community acquired pneumonia include specific recommendations for HIV-infected children;[5] evidence suggest that current WHO treatment guidelines may be inadequate in HIV-infected children, as they are more likely to fail standard case management using penicillin or amoxicillin.[6]

Viral infections

Virus infections are responsible for 30-40% of HIV-infected children hospitalized with acute respiratory tract infections.[7] Respiratory syncytial virus (RSV) is the viral pathogen most frequently identified; other viruses commonly associated with lower respiratory tract infections include influenza, parainfluenza, adenovirus, human metapneumovirus and cytomegalovirus (CMV).[7,8] In addition, it is important to point out that mixed viral and bacterial infections are present in up to two thirds of children with pneumonia.[7] Evidence suggests that HIV-infected children and their caregivers should receive annual flu vaccination if possible; there is a reduced, but measurable protective effect and the transient increase in HIV-viral replication induced by the flu vaccine is not associated with HIV disease progression or other risks.[9]

Cytomegalovirus (CMV)

There is a high prevalence of CMV infection in the general population and CMV is frequently isolated from the respiratory tracts of HIV-infected infants. Therefore a positive CMV culture, from nasopharyngeal aspirates and/or urine, only proves infection and that a child is shedding the virus. The diagnosis of actual target organ disease is more problematic, depending on relevant symptoms together with high levels of CMV viraemia, as indicated by quantitative pp65 antigenaemia or DNA PCR test results. Histopathology remains the most definitive diagnostic test, but it is unfeasible in many settings. CMV and PCP co-infection is common in HIV-infected infants, which makes it difficult to ascertain the contribution of CMV to the underlying lung pathology in children with severe symptoms. Similar disease severity and mortality have been reported in HIV-infected children with CMV and PCP co-infection, compared to those with PCP infection alone, as diagnosed on nasopharyngeal aspirate.[10] Treatment consists of high dose intravenous gancyclovir for 2-3weeks. Valganciclovir, an orally administered prodrug of gancyclovir, seems as effective, but this is not widely available. Due to the risk of immune reconstitution disease, the optimal timing of instituting highly active antiretroviral therapy (HAART) in infants with CMV pneumonia remains a topic of debate; it is best to consult an expert.

Fungal infections

Apart from PCP, fungi are relatively uncommon causes of pneumonia in HIV-infected children. *Candida* frequently colonizes the skin and mucosa, but pulmonary candidiasis is unusual. Other fungi such as *Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immites* and *Aspergillus* species may also cause pneumonia, but usually in conjunction with disseminated disease. Although fungal pneumonia is rare, it is an important differential diagnosis to consider in children with persistent lung disease in whom the most common causes have been excluded.

Pneumocystis jiroveci pneumonia (PCP)

PCP is frequently the first serious illness encountered by the HIV-infected infant who is not on cotrimoxazole prophylaxis.[8] It seems as if cotrimoxazole prophylaxis protects against severe disease rather than infection, as *P. jiroveci* has been isolated from 38% of children considered to have received adequate prophylaxis. However, the provision of prophylaxis was associated with a highly significant reduction in mortality.[9] The first clinical cases of PCP were described among malnourished children housed in orphanages during the Second World War. Cases of "plasma cell pneumonia" were later recognized in a variety of conditions associated with immune compromise and the detection of unusual clusters of PCP in the early 1980's, provided the first indication of the impending HIV epidemic. Substantial reductions in the incidence of PCP occurred with the introduction of cotrimoxazole prophylaxis and HAART. Table 2 highlights the indications for CTX preventative therapy.

In contrast to the dramatic reduction in PCP cases and fatalities achieved in the industrialized world, PCP remains an exceedingly common cause of death among HIV-infected infants in Africa.[10] Autopsy studies from Africa indicate that PCP is the leading cause of death in HIV-infected children <6 months of age; declining in importance after 12-18 months of age.[1,2] PCP also seems to occur with increased frequency in HIV-exposed, but uninfected babies, emphasizing the importance of providing cotrimoxazole prophylaxis to all HIV-exposed infants; at least for the first 12 months in HIV-infected infants and for the first 6 months in HIV-uninfected (PCR negative) exposed infants. Typical presenting features include an HIV-exposed infant with tachypnoea, mild intermittent fever and a dry cough, minimal auscultatory findings with hypoxia and bilateral diffuse alveolar infiltrates on chest radiograph (CXR). The radiographic picture may be highly variable, but significant hypoxia is typical and the lactate dehydrogenase (LDH) level is usually markedly elevated, although this is not specific. The current treatment of choice is high-dose intravenous cotrimoxazole (20mg/kg/day of the trimethoprim component, divided into four doses) for a total duration of 2-3 weeks. Intravenous therapy is recommended in severely ill children; oral therapy is acceptable with mild illness or after clinical improvement. If oral therapy is the only alternative then an oral loading does of 20mg/kg stat is recommended. (personal communication - H Zar) The addition of corticosteroids (prednisone 2mg/kg/day for 1-2 weeks and then tapered) and oxygen supplementation is advised in all children with hypoxia (saturation levels <92% in room air); response to therapy is relatively slow. The emergence of cotrimoxazole resistance is a major long-term concern, but at present cotrimoxazole resistance seems rare. Alternative treatment options include clindamycin and primaquine. Primaquine is associated with haemolysis in patients with G6PD deficiency and if feasible, an attempt should be made to exclude this condition before treatment is initiated. Currently primaquine can be obtained in South Africa with section 21 approval from the Medicine Control Council.

It is common practice to stop cotrimoxazole prophylaxis in adults

following adequate immune reconstitution on HAART. Although this has not been studied in children, discontinuing cotrimoxazole prophylaxis may be considered in children >1 year of age, on HAART for >6 months and with documented sustained immune reconstitution (CD4 count >20%).

Mycobacterial infections

Tuberculosis (TB)

The TB epidemic is sustained in conditions of poverty and crowding, where both exposure to the organism and the vulnerability to progress to disease following infection, are increased.[11] In addition, particularly in sub-Saharan Africa, it is fuelled by the immune compromise that results from HIV infection. Children contribute little to the maintenance of the TB epidemic, but they are greatly affected by it. A recent report from Cape Town, South Africa, indicated that children <13 years of age contribute 13.7% of the total TB disease burden, with a calculated TB incidence rate of more than 400/100 000/year.[12]

Following infection, the risk to progress to disease is mainly determined by the age and immune status of the child. The risk is highest in very young (<3yrs of age) immune immature children and in immune compromised children.[13] Reasons for the high incidence of TB in HIV-infected children are multiple. HIV infected children are not only more vulnerable to progress to disease, but are also more likely to be exposed to TB and become infected/re-infected.[14] The risk increases with severe immune suppression; in a prospective study from Côte d'Ivoire, the risk of TB was 4 times higher in children with CD4 percentage below 15% than in those with CD4 % above 15%.[15]

Diagnosis

The diagnosis of TB in children is a major challenge, owing to the pauci-bacillary nature of the disease and the overlap with other HIV-related diseases.[16] TB can present at any age, even in neonates; an increased incidence of congenital TB has been associated with maternal HIV-infection.

On history, reported contact with an adult index case (including those with sputum smear-negative pulmonary TB) is an important indication of TB exposure; documented in 50-60% of child TB cases. The World Health Organization's (WHO) criteria for the diagnosis of TB (cough >2 weeks, failure to thrive, or weight loss) are less helpful in HIV-infected children in whom these symptoms are common and therefore less specific.[17] In addition, TB-associated symptoms are more frequently acute in HIV-infected children, which reduces the sensitivity of chronic symptoms. However, persistent, non-remitting symptoms or a change in baseline symptomatology, especially if accompanied by unexplained weight loss, should always prompt the clinician to consider a diagnosis of active TB. Previous TB treatment, received by either the child or the adult index case, is associated with drug resistance and therefore culture and drug susceptibility testing is advised to guide optimal management.

On examination, physical signs are often non-specific such as coughing, wheezing, tiredness and/or failure to thrive. As in HIV-uninfected children, the most frequent intra-thoracic disease manifestation is hilar and/or paratracheal adenopathy, but the frequency of advanced and/or disseminated (miliary) disease is increased.[18] Extra-thoracic manifestations are TB cervical adenitis and tuberculous meningitis (TBM); less frequent sites include osteo-articular TB, such as TB spondylitis with vertebral collapse and gibbus formation, and chronic otorrhoea. In general, the spectrum of disease recorded in HIV-infected children, are similar to that seen in very young (<3yrs of age) HIV-uninfected children.[19]

A tuberculin skin test (TST) is of reduced value in HIV-infected children, as the minority of immune compromised children with TB test positive (Mantoux test induration ≥5 mm); severe malnutrition, low CD4 counts and progressive HIV disease are associated with false negative TST results.[20] However, the TST remains a useful test, as a positive result confirms TB infection, which may aid the diagnosis of active TB or indicate the need for preventive therapy. It is important to remember that, due to poor sensitivity, a negative TST result never excludes TB. Novel T-cell based assays seem more specific and especially more sensitive to detect TB infection in immune compromised individuals. However, these assays require fairly large volumes of blood (3-5ml), are very expensive, and fail to confirm or rule out a diagnosis of active TB. The exact role for these tests in resource-limited settings requires further evaluation.[21]

It may be difficult to distinguish TB from other HIV-associated lung conditions on CXR. The most common disease manifestations, hilar and/or paratracheal lymphadenopathy, remain fairly pathonomonic, although it may occur with lymphocytic interstitial pneumonitis (LIP) as well, narrowing of the airways has not been documented with LIP. The typical miliary picture of disseminated (miliary) TB may also be mimicked by the reticulonodular pattern of LIP. Disease in a very young child (<1-2 years) and an evenly spread, fine, nodular pattern on CXR favours a diagnosis of disseminated (miliary) TB, while clubbing, generalised lymphadenopathy and swollen parotids in an older child suggests LIP, but TB and LIP may be present at the same time. The increase in pleural and pericardial effusions observed in adult HIV/TB patients has not been observed in HIV-infected children.

Bacteriologic cultures are the only way of establishing a definite diagnosis. Usually 2-3 fasting, early morning gastric aspirates are collected, but collecting induced sputum and/or samples from any other relevant source should also be considered, including fine needle aspiration (FNA) of peripheral masses, pleural fluid, ear swabs, cerebrospinal fluid, bone marrow aspirates etc. Unfortunately a negative culture result is only reported after 6-12 weeks of incubation and does not rule out the diagnosis of TB. Frequently, TB treatment is instituted on clinical suspicion, but it remains important to perform initial cultures, as well as repeat cultures if the response to treatment is poor.

Prevention

In South Africa, BCG vaccination is routinely given to all newborns, except those with symptomatic HIV-disease, at birth. It has been demonstrated that HIV-infected children are at increased risk of developing BCG associated complications, such as local or disseminated BCG disease,[22,23] while the protection provided by BCG is uncertain. However, in the absence of conclusive risk:benefit estimates, the current recommendation is to vaccinate all children irrespective of HIV-exposure, but to remain vigilant of BCG-associated complications in HIV-infected children.[24]

Preventive chemotherapy is indicated in all HIV-infected children, following household exposure to an adult with pulmonary TB (irrespective of the adult's smear status), once active disease has been excluded. In the absence of previous treatment or symptoms, a positive TST indicates latent TB infection and also requires preventive therapy. Preventive therapy regimens include; isoniazid (INH) daily for 6 months or INH and rifampicin (RMP) daily for 3 months (only if it is given as directly observed therapy).

Curative treatment

The treatment regimen consists of INH,

RMP and pyrazinamide (PZA), given as fixed dose combination therapy, during 2-month intensive phase followed by INH and RMP during the 4-month continuation phase. All TB treatment should be given under direct supervision. Most TB guidelines recommend similar treatment durations for HIV-infected and uninfected TB patients, but due to well-documented cases of disease relapse in HIV-infected children, prolonging the treatment duration to 9 months may have benefit.[25] Clinical and CXR follow-up of all HIV-infected children with TB is indicated. Recurrence of TB (relapse or reinfection) is not uncommon and if response to treatment is poor or a second episode of TB is clinically suspected every effort should be made to confirm the diagnosis on culture and to do drug susceptibility testing. Corticosteroids (prednisone 2mg/kg/day for one month then taper), may be added in cases with TBM, airway compression or pericardial TB.

Treatment for multidrug-resistant (MDR) TB (i.e. resistance to INH and RMP) should be discussed with an expert. A high incidence of extensive (extreme) drug-resistant (XDR) TB has been reported among HIV-infected adults in Kwazulu-Natal, South Africa. The emergence of this highly pathogenic form of TB that is virtually resistant to all treatment poses a grave risk, particularly to vulnerable HIV-infected children.

TB treatment and HAART

All rifamycins including RMP induces the P450 system in the liver and intestinal wall, resulting in increased elimination of protease inhibitors (ritonavir is least affected and its use partially reverses the RMP effect on other drugs), and non-nucleoside reverse transcriptase inhibitors, particularly nevirapine (NVP). RMP also promotes glucuronidation of zidovudine and probably abacavir, but the significance of this interaction is uncertain. (ref)With TB treatment, current recommendations maintain two nucleoside reverse transcriptase inhibitors and only the choice of the third drug is affected:

- children <3 years of age or <10kg: 2 NRTI's and ritonavir or ritonavir-boosted Kaletra® (supplement the ritonavir dose to match that of the lopinavir dose)
- children >3 years of age and >10kg: 2 NRTI's and efavirenz or ritonavir or ritonavir-boosted Kaletra®

Side-effects from TB drugs may be similar to those caused by HAART, but luckily severe side-effects are uncommon. Most side-effects occur within 2 months of starting TB therapy, including hepatotoxicity, skin rashes, nausea and vomiting, leukopaenia and/or anaemia, and peripheral neuropathy. Pyridoxine supplementation is advised for all HIV-infected children on antituberculosis treatment and HAART to reduce the risk of peripheral neuropathy (also see TB and HIV co-treatment in – Initiating anti-retroviral therapy in HIV-infected infants and children).[26]

Immune reconstitution inflammatory syndrome (IRIS)

IRIS describes the temporary exacerbation of TB symptoms and signs (e.g. lymph node enlargement) that may occur when HAART is first introduced. It is mainly ascribed to the effects of immune reconstitution, although a hypersensitivity reaction to antigens released by killed TB bacilli may also contribute. It usually manifests within 2-6 months after the initiation of HAART and subsides spontaneously, although severe cases may require treatment with corticosteroids. This temporary «disease» exacerbation is not an indication of treatment failure.

Non-tuberculous mycobacteria (NTM)

The contribution of NTM to respiratory disease in HIV-infected individuals is an area of intense study at present. *M. avium* complex, an environmentally acquired mycobacterium, is well-described to cause peripheral lymphadenitis, or disseminated disease in children with markedly reduced CD4 counts. Studies among South African gold miners indicate that other mycobacterial species, such as M. kansasii, may be more common in South Africa.[27,28] The clinical presentation is usually non-specific with fever, loss of weight, abdominal pain, and anaemia that are prominent symptoms/signs; respiratory symptoms are uncommon. Diagnosis is by blood or tissue culture and PCR confirmation. Few drugs with proven efficacy are available for the treatment of NTM; the suggested treatment regimen should include ethambutol, RMP and clarithromycin or azithromycin. A fluoroquinolone (ofloxacin or ciprofloxacin) and/or amikacin may be added in severe cases.

Conclusion

The prevention and adequate management of respiratory infections is extremely important when taking care of HIV-infected children. The successful use of HAART can drastically reduce the risk of opportunistic infections, which re-emphasizes the importance of making optimal use of this live giving opportunity, as discussed the previous articles in this series. The final topic to be covered is; "Common opportunistic infections in HIV infected infants and children; Part 2 – non-respiratory infections".

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