

Treating Opportunistic Infections In HIV-Infected Children

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Summary

These guidelines have been prepared in recognition of the unique complexities of HIV infection in infants, children and adolescents. HIV-1 infection has a heterogeneous spectrum of clinical course. Compared to HIV-1-infected adults, survival times are considerably shorter for children who acquire the virus perinatally or during infancy. Factors contributing to accelerated disease progression in infants and children are poorly understood but may include relative immunological immaturity, thymic HIV-1-mediated destruction at a time of active thymopoiesis, and HLA class sharing between mother and infant. Opportunistic infections in adults are often secondary to reactivation of pathogens acquired before HIV infection. In contrast opportunistic infections in infants and children with vertical infection may reflect primary acquisition of host pathogens during ongoing HIV replication and advancing immunosuppression, and contrast clinically in children compared to adults. For example, young children with active tuberculosis more often present with miliary disease. Adult and paediatric treatment guidelines must also reflect differences in respect to drug pharmacokinetics, dosing, preparations and formulations, administration, and toxicities. The following guidelines reflect the current recommendations on treatment of opportunistic infections that are common to HIV-infected infants, children, and adolescents in the United Kingdom. These guidelines were developed using a full review of Medline and have been approved by the CHIVA Steering Committee.

Introduction

Scale of the HIV Epidemic among Children in Europe and Globally

Within a 20-year period HIV infection has spread from a few high-risk groups to become a worldwide pandemic. According to statistics released from UNAIDS and the WHO more than 60 million people have been infected with HIV-1. An estimated 14,000 new infections occur daily. 95% of these occur in developing

nations where access to newer medical treatments are not readily available or affordable.

HIV infection is now the leading cause of death in sub-Saharan Africa. Vertical transmission is the primary means by which infants become infected with HIV either *in utero*, during delivery or by breast-feeding. At the end of 2003 between 2.1-2.9 million children (<15 years) were infected with HIV globally [1].

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In the UK since 1999, there have been more diagnoses of heterosexually acquired infection than of infections acquired through sex between men with an increase in the numbers of women diagnosed. A few HIV-infected women remain undiagnosed until testing is prompted by HIV-related symptoms late in the course of illness. Women who remain unaware of their infection status are unable to benefit from interventions, which can reduce the risk of mother-to-child-transmission (MTCT) of HIV to under 1%. Perinatal transmission rates remain high within Eastern Europe, and older children migrating from countries where HIV infection is endemic continue to present to paediatricians with advanced HIV disease. For these reasons and because HIV-infected children are living much longer with highly active antiretroviral therapy (HAART), the number of children under care has increased in many European countries including the United Kingdom.

The Clinical Course of HIV-1 Infection in Children before HAART

20% of AIDS deaths globally are in children. There is a bimodal distribution: 25% develop AIDS within 1 year, with a median time for 75% ~ 7 years. Perinatally infected infants and children with HIV have accelerated disease progression (compared with adults) as a result of a higher viral set-point and an active thymus (with a larger pool of cells permissive to HIV-infection). In addition, naïve T cells with an impaired functional phenotype are unable to process pathogens

effectively. HIV-1-related symptoms and/or CD4+ T cell depletion therefore develop in most untreated children within the first few years of life [2].

HIV-1 infection in children causes a broad spectrum of disease. The frequency of opportunistic infections (OI's) in HIV-infected children in the absence of HAART, vary with age, pathogen and previous pathogen exposure, and degree of immunosuppression. A history of a previously AIDS-defining OI is a predictor of developing a new infection and most often occurs in children with advanced immunosuppression; however serious bacterial infections and reactivation of TB and herpesviruses may occur across the spectrum of immunologic status complicating HIV-1 infection [3].

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Without HAART the most common OIs in children include serious bacterial infections namely pneumonia and bacteraemia. Common co pathogens and OIs that are difficult to eradicate without successful immune reconstitution include chronic mucosal or disseminated infections with herpesviruses namely CMV, HSV and VZV. Primary disseminated and reactivated tuberculosis is a major cause of morbidity and mortality among HIV-infected children from communities where infection with the pathogen is endemic. Disseminated disease with *Mycobacterium avium* complex may occur in HIV-infected children with advanced immunologic deterioration. *Pneumocystis jirovecii* (formerly *carinii*) pneumonia (PCP) is a common and serious OI associated with a high mortality. The pneumonia most often manifests between 3 to 6 months of age in infants with vertically-acquired infection. Candidiasis (topical, oral, esophageal and tracheobronchial) is the most common fungal infection in HIV-infected children. Causes of acute and chronic CNS infections include *Cryptococcus neoformans*, and *Toxoplasma gondii*. Less commonly observed OIs include cryptosporidiosis and systemic fungal infections. Clinical presentations include hepatosplenomegaly, failure to thrive, oral candidiasis, recurrent diarrhoea, parotitis, cardiomyopathy, hepatitis, nephropathy, developmental delay and

encephalopathy, lymphoid interstitial pneumonitis, recurrent bacterial infections and specific malignancies. The latter include non-Hodgkin's B-cell Burkitts-type lymphomas, leiomyosarcomas and Kaposi's sarcoma, which is not uncommonly described in HIV-infected children of African ethnicity.

The Paediatric HIV Classification

The CDC clinical categories and paediatric classification system for children younger than 13 years of age, known to be HIV-infected, are presented in Tables 1 and 2. Table 2 emphasizes the importance of the CD4+ T-lymphocyte count and percentage as an immunologic surrogate and marker of prognosis but does not use information on viral load (VL) as quantitated by RNA polymerase chain reaction (PCR) assay.

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Table 1 adapted from CDC. 1994 revised classification system for HIV in children less than 13 years of age. *MMWR*1994;43: RR-12 [3]

Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. USA: National Pediatric and Family HIV Resource Center and Health Resources and Services Administration; August 8, 2001.

	Clinical categories			
Immunologic Categories	N: No signs/symptoms	A: Mild signs /symptoms	B: Moderate signs /symptoms	C: Severe signs/symptoms
1: No evidence of suppression	N1	A1	B1	C1

2: Evidence of moderate suppression	N2	A2	B2	C2
3: Severe suppression	N3	A3	B3	C3

Table 2: Immunologic categories based on age-specific CD4+ T-lymphocyte counts and percent of total lymphocytes.

Immunologic Category	Age of Child					
	<12 mos		1-5 yrs		6-12 yrs	
	μL	(%)	μL	(%)	μL	(%)
1: No evidence of suppression	>1,500	(>25)	>1,000	(>25)	>500	(>25)
2: Evidence of moderate suppression	750-1,499	(15-24)	500-999	(15-24)	200-499	(15-24)
3: Severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

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CD4% and VL are now usually measured every 3–4 months in children under follow up in the United Kingdom which permit calculation of short-term risk estimates of disease progression. These values are useful in knowing when to commence or change ART [4]. Successful implementation and maintenance of

HAART, resulting in immune reconstitution has been pivotal in offsetting OIs and arresting disease progression in HIV-infected children [5].

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Treatment Guidelines by OI; Mycobacteria *Mycobacterium tuberculosis*

Epidemiology

HIV infection is an important risk factor for the development of active tuberculosis, including in children. In sub-Saharan Africa up to half of hospitalized children with culture-proven TB are also HIV-infected [1].

In 2002, 6794 new cases of TB disease were diagnosed in England, Wales and Northern Ireland. Of these, 401 (6%) were among children aged <15 years. The number co-infected with HIV is uncertain because only a limited number of UK children who have TB have been tested for HIV infection. The largest proportion of newly diagnosed HIV-infected children in the UK are foreign-born and at higher risk of exposure to TB. Children with TB are almost always infected by an adult most commonly a household contact and their infection represents primary infection rather than the reactivation disease observed among adults.

Clinical Manifestations

Clinical presentation of TB disease among children with HIV infection is similar to that in children without HIV infection. Most tuberculosis infection is usually asymptomatic. Early clinical manifestations of disease include fever, weight loss, cough, night sweats and chills. Children with pulmonary TB may have little or no symptoms. Chest x-ray may show hilar lymphadenopathy, segmental involvement, cavitary lesions or a miliary pattern. Radiological changes may be less well-defined in HIV-infected children. Older HIV-infected children and adolescents may have adult-type reactivation pulmonary disease with cavitation. Multiple lobes are involved in up to 25% of children. Extrapulmonary disease in children will include lymphadenitis, disseminated (miliary) disease, CNS, bone/joint disease, and abdominal disease.

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Diagnosis

Diagnosis of TB has traditionally relied on microscopy of clinical samples using Ziehl-Neelsen or auramine-rhodamine staining. Children with pulmonary TB are less likely to have positive smears because they may not produce sputum voluntarily and have lower quantities of bacteria in sputum. Acid-fast stains of early morning gastric aspirates are positive in <20% of children with TB [2]. Samples from extrapulmonary sites, such as lymph node, CSF, and joint fluid, also have lower yields on acid-fast staining.

Microbiological isolation of *M. tuberculosis* on culture represents the gold standard for diagnosis of TB. Three consecutive morning gastric aspirates yield a positive culture of *M. tuberculosis* in up to 70% of infants and 30-50% of children with clinical pulmonary TB [3]. Gastric lavage samples, collected on three consecutive mornings, has a higher yield on culture (50%) than a single sample collected by bronchoalveolar lavage (10%) [4]. Recently, sputum induction with hypertonic saline has been shown to be safe and equivalent in terms of culture

yield to the collection of three early morning gastric aspirates [5]. The culture yield from other fluids and tissues from extrapulmonary sites is lower, even with optimal samples.

Drug sensitivity testing should be performed on all *M. tuberculosis* isolates in order to identify resistant strains. In some instances, sensitivity of the source case may be known and useful when deciding drug combinations especially in the presence of MDR TB.

Tuberculin skin testing (TST) using PPD (SSI - 2 tuberculin units) has traditionally been used as a diagnostic tool. However TST suffers from significant false positives and negatives. Approximately 10% of immunocompetent children with culture proven TB disease will have a negative TST [6]. Children with HIV co-infection will be even less likely to have a positive TST, particularly those with CD4 counts <15% or 200 cells/L. This limits the usefulness of TST as a diagnostic tool especially since a negative test will not exclude TB if negative in an HIV infected child.

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PCR amplification techniques have been used for the rapid identification of TB through amplification of specific regions of mycobacterial DNA in clinical samples. These tests suffer from low sensitivity (45-83%) and specificity (80%) in gastric aspirates from children compared to adults with TB disease. Sensitivity and specificity is also poor for extrapulmonary samples, such as CSF, where numbers of bacteria is likely to be lower.

Species identification using molecular probes may be useful, particularly in the very immunosuppressed child where atypical mycobacteria may cause clinical disease and which may be hard to clinically differentiate from *M tuberculosis*. These tests are most effective when applied to samples in which mycobacteria have been detected microscopically.

Interferon gamma-based tests are currently licensed and available for use in the UK, although not yet widely available. These assays measure interferon-gamma production by lymphocytes in response to TB antigens (PPD, ESAT-6, CFP-10) and may allow differentiation from atypical mycobacteria and BCG. Data from children with TB disease in South Africa show better sensitivity than tuberculin skin testing (83% and 63%, respectively), especially in HIV-infected children (73% and 36%) respectively [7]. The role of these assays in identifying TB infection is less clear, particularly since there is no gold standard for the presence of infection. Further studies are presently being done.

Treatment

The basic principles of treatment of a child with TB and HIV will be the same as that for an HIV-uninfected child. Due to drug interactions between some anti-tuberculous and antiretroviral drugs, the treatment of children being treated for both HIV and TB may be complex and may require specialist care. Refer to BHIVA adult TB guidelines 2005 interaction table at www.bhiva.org. It is recommended that initial empiric treatment of a child with active TB disease should consist of a daily 4-drug regimen including isoniazid, rifampicin, pyrazinamide, and ethambutol (the latter due to the possibility of a drug-resistant organism) [8]. Ethionamide can be used as an alternative to ethambutol in cases of TB meningitis because of better CNS penetration. Prothionamide is more widely available and is interchangeable with ethionamide and maybe better tolerated than ethionamide.

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Specific Doses

Drug dosage, adverse reactions and interactions with antiretroviral therapy is summarized in the table below:

Drug	Dose	Adverse Reactions	Interaction with ART
Isoniazid	5-10mg/kg/day	Elevation of hepatic enzymes, hepatotoxicity, peripheral neuritis	No
Rifampicin	10mg/kg/day	Gastrointestinal upset, hepatotoxicity	Yes, mainly PI and NNRTI's.
Pyrazinamide	35mg/kg/day	Hepatotoxicity	No
Ethambutol	15mg/kg/day	Optic neuritis	No

For active pulmonary disease, antituberculous drug treatment should be for a total of 6 months (2 months of quadruple therapy followed by 4 months of dual therapy with isoniazid and rifampicin). Children with extrapulmonary disease such as CNS, or miliary disease, should be treated for a total duration of 12 months (2 months of quadruple therapy followed by 10 months with isoniazid and rifampicin).

Optimal timing of commencement of HAART in newly diagnosed HIV-infected children with TB disease remains unclear. In general, antiretroviral therapy should be commenced at least 1-2 months after commencement of antituberculous therapy. For children already on HAART when TB is diagnosed, treatment should be continued however alteration of drug combinations may be required to minimize potential toxicities and drug-drug interactions.

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The main interaction between treatment for HIV and TB is with the use of rifamycins. Rifampicin induces hepatic cytochrome Cyp3A enzymes and can accelerate clearance of drugs metabolized by the liver (particularly PI's and NNRTIs), resulting in subtherapeutic levels of the latter. Data from adults on boosted PI's suggest increased hepatotoxicity and need to increase the dose of the PI (with therapeutic drug monitoring). Concomitant administration of rifampicin and efavirenz will require a dose increase of efavirenz. Caution should be

exercised with concomitant administration of rifampicin and nevirapine due to significant hepatotoxicity. Rifabutin is a less potent inducer of cytochrome Cyp3A enzymes and can be used as an alternative to rifampicin in children on HAART. A decrease in rifabutin dosage by 50% is required when coadministered with ritonavir, indinavir, nelfinavir, amprenavir, or ritonavir-boosted saquinavir; an increased dose (by 50%–100%) of rifabutin is needed when coadministered with efavirenz. Rifabutin should not be administered with delavirdine or hard gel capsule saquinavir without ritonavir boosting because of decreases in protease inhibitor drug levels [9]. An oral suspension of rifabutin is available from special order manufacturers. Therapeutic drug monitoring (TDM) of PI/NNRTI's is recommended when combined with rifampicin/rifabutin.

Drug-resistant TB should be treated with a minimum of three effective anti-tuberculous drugs to which the isolate is susceptible. Additional drugs used for treatment of MDR-TB include fluoroquinolones (ciprofloxacin, moxifloxacin), aminoglycosides, ethionamide/prothionamide. These medications should be used in consultation with an ID or TB specialist.

Adjunctive treatment with corticosteroids has been shown to be beneficial in children with tuberculous meningitis with lower morbidity and mortality [10]. Other situations where steroids may be beneficial include pleural or pericardial effusions, severe miliary disease, and bronchial obstruction. A dose of 1 to 2 mg/kg/day of prednisolone or its equivalent is recommended for 6--8 weeks.

An immune reconstitution syndrome in patients receiving anti-TB therapy who are on HAART has been reported in HIV-infected adults [11]. Symptoms of high fever, expanding CNS lesions, worsening lymphadenitis and pulmonary infiltrates may occur after commencing TB treatment. Optimal treatment remains unclear although non-steroidal anti-inflammatory drugs and systemic corticosteroids have been used.

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Treatment Guidelines by OI; Mycobacteria

Disseminated *Mycobacteria avium* complex (MAC) Disease

Epidemiology

MAC organisms (including *M. avium*, *M. intracellulare*, *M. paratuberculosis*) are common in many environmental sites and may be acquired by inhalation or ingestion. Person-to-person spread has not been observed. Environmental sites harbouring MAC are diverse and include water, soil, and animals. Disseminated MAC occurs almost exclusively in persons with advanced HIV disease, however higher CD4+ T cell counts have been recorded in younger HIV-infected children (< 2 years of age). Disseminated MAC rarely occurs during the first year of life [1, 2, 3]. Age-related CD4+ cell counts levels considered as high risk for MAC warranting consideration of prophylaxis are <750/ μ L in HIV-infected children <1 year old; <500/ μ L for children aged 1–2 years; <75/ μ L for children aged 2–6 years; and <50/ μ L for children aged >6 years [4].

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Clinical Manifestations

It is difficult to separate the clinical and laboratory features directly attributable to MAC from abnormalities attributable to advanced HIV disease. In early reports of HIV-infected children with disseminated MAC high fever, weight loss with failure to thrive, chronic diarrhoea and malabsorption, night sweats, neutropenia and/or severe anemia were most often described [5-8]. Other features included persistent or recurrent abdominal pain, intra-abdominal lymphadenopathy, hepatosplenomegaly, and an elevated serum alkaline phosphatase level.

Organ-specific localizing signs and symptoms may present as a manifestation of disseminated MAC. The most commonly involved organs include the spleen, lymph nodes, liver, intestines, colon, bone marrow, and less commonly, lungs, adrenals, stomach, and central nervous system [9]. Isolated pulmonary disease is rare [10] although presentation with isolated parenchymal pulmonary disease

is a marker of high risk for dissemination [11]. When lung disease does occur, the chest radiograph may reveal alveolar infiltrates, nodules, or cavitations.

Immune Reconstitution Syndrome

Local manifestations of disseminated MAC may occur in severely immunosuppressed HIV-infected children following immune reconstitution with HAART. Local symptoms develop secondary to an inflammatory response to MAC antigens as cell-mediated immunity is restored. Most often, patients exhibit lymphadenopathy, occurring within 1 to 12 weeks of initiating HAART; abdominal pain and hepatosplenomegaly are also reported. Fever may be present, but other constitutional symptoms (weight loss and night sweats) usually are absent, and blood cultures usually do not grow MAC. Biopsy may be required to establish an accurate diagnosis and to exclude other processes [12, 13].

Diagnosis

Definitive diagnosis of disseminated disease requires isolation of the organism from blood or biopsy specimens from normally sterile sites including bone marrow. Several mycobacterial blood cultures over time may be required to yield a positive result. Blood cultures are highly sensitive in recovery of MAC. Caution must be exercised in the interpretation of cultures obtained from nonsterile sites, such as gastric washing specimens, stool, urine or respiratory tract secretions, which may suggest transient colonization and not invasive disease. Repeated isolation of numerous colonies of a single species is more likely to indicate disease than culture contamination or transient colonization.

Treatment

Combination therapy with a minimum of 2 drugs is recommended: clarithromycin or azithromycin plus ethambutol. In patients with more severe symptoms rifabutin can be added as a third drug but can cause a number of drug interactions by increasing CYP3A activity. If rifabutin cannot be administered, ciprofloxacin,

levofloxacin and/or amikacin or streptomycin can be considered. The most effective way to prevent disseminated MAC in HIV-infected children is to preserve or improve immunity with optimal antiretroviral therapy. Lifelong suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. The safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied.

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Specific Doses

Initial treatment (at least 2 drugs):

Clarithromycin 7.5–15 mg/kg (max: 500 mg/dose) PO BD + ethambutol 15–25 mg/kg (max: 2.5 gm/day) PO OD followed by chronic suppressive therapy. For severe disease, add: Rifabutin 10–20 mg/kg (max: 300 mg/day) PO OD.

If rifabutin cannot be administered (or if a fourth drug is needed for patients with more severe symptoms or disseminated disease): Ciprofloxacin 20–30 mg/kg/day (max: 1.5 gm/day) IV or PO OD; or levofloxacin 500 mg PO OD; or amikacin 15–30 mg/kg IV in one or two divided doses (max: 1.5 gm/day), although we generally start with 15mg/kg/day and adjust according to plasma levels (cBNF 2006)

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Treatment Guidelines by OI; Invasive and Recurrent Bacterial Infections

Epidemiology

Invasive bacterial infections are the most common OIs in HIV-infected children with lower respiratory tract infections (LRTIs) most often diagnosed (with an event rate of 15 per 100 child years), followed by bacteraemia (11 per 100 child years) and urinary tract infection (3 per 100 child years) [1]. Other serious bacterial infections, include osteomyelitis, meningitis, abscess, and septic arthritis, which occurred at rates <0.2 per 100-child years.

LRTI is presumptively diagnosed in young children who most often present with fever, chest symptoms with or without an abnormal chest x-ray, unless an accompanying bacteraemia is present (reported as 14.9% and 6.5% in HIV-infected and non-HIV-infected children, respectively from South Africa). Common isolates including *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Staphylococcus aureus* and *Escherichia coli* were more likely to be resistant to common antibiotics in HIV-infected children, who had a higher associated mortality (13.1% versus 2.1%, respectively) [2].

Globally *Streptococcus pneumoniae* accounts for >50% of all bacteraemic episodes in HIV-infected children who have an increased risk of invasive pneumococcal infection compared to non-HIV-infected children [3-6]. Before *Haemophilus influenzae* type B (Hib) conjugate vaccine became widely available, HIV-infected children were at greater risk for developing bacteremic pneumonia from Hib [7]. Bacteraemia with other gram-negative isolates is commonly described to include *Pseudomonas aeruginosa*, nontyphoidal *Salmonella* and *Escherichia coli*.

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Clinical Manifestations

Signs and symptoms are organ/system-specific and similar in HIV-infected and non-HIV-infected children with an acute presentation, fever and leucocytosis; the latter may be absent in very immunosuppressed children [8]. Recurrent lower and upper RTI and meningitis are commonly described in HIV-infected children.

Diagnosis

LRTI is diagnosed clinically and supported by radiographic findings. In older children sputum culture may support the diagnosis [9]. Isolation of the pathogen from blood or pleural fluid should be attempted. Other investigations to identify occult foci including CT and ultrasound for bronchiectasis and abscesses.

Treatment

If an organism is identified, antibiotic susceptibility testing should be performed and therapy based on the results of susceptibility testing. HIV-infected children who are not severely immunosuppressed or neutropenic can be expected to respond similarly to HIV-uninfected children and should be treated with antimicrobial agents recommended for the most likely bacterial isolates. Severely immunocompromised children presenting with invasive or recurrent bacterial infections may require empiric antimicrobial treatment covering a broad range of resistant organisms pending results of diagnostic evaluations and cultures.

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Prevention

HIV-infected children aged <5 years should receive Hib and 7-valent pneumococcal conjugate vaccines. Children aged >2 years also should receive the 23-valent pneumococcal polysaccharide vaccine (>2 months after their last conjugate vaccine dose), with a single revaccination with the pneumococcal polysaccharide vaccine 3–5 years later if the child is aged <10 years or after 5 years if the child is aged >10 years [10, 11].

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Treatment Guidelines by OI; Fungi

***Pneumocystis jirovecii* (formerly *carinii*) Pneumonia (PCP)**

Epidemiology

PCP remains one of the most commonly reported opportunistic infections in children with AIDS and is associated with a high mortality rate. Because over half of all cases of PCP in children with perinatally acquired HIV occur in infants 3 to 6 months of age, early identification of HIV-infected infants is essential so that prophylaxis can be initiated. Prophylaxis for PCP is recommended for all infants born to HIV-infected women, beginning at 4 to 6 weeks of age irrespective of the CD4⁺ T-cell count, since many young infants with PCP have CD4⁺ cell counts >1,500/ μ L [1].

Clinical Manifestations

Infants and children may develop a subacute or an abrupt diffuse pneumonitis with non-specific symptoms (mild non-productive cough, dyspnea at rest, poor feeding, weight loss). Clinical signs include tachypnea and respiratory distress, oxygen desaturation, bilateral basal crackles and fever [2]. The magnitude and prevalence of these signs and symptoms is variable, although tachypnea is universal by the time radiographic changes become apparent. The latter often shows bilateral diffuse interstitial disease with a reticulogranular appearance; rarely, lobar, miliary, pneumothorax or pneumomediastinum and nodular lesions occur as well. Occasionally, the chest roentgenogram at the time of diagnosis appears normal [3]. Most children with PCP have substantial hypoxia with low arterial oxygen pressure and an alveolar-arterial oxygen gradient of >30 mm/Hg. The disease may be far advanced before it is diagnosed and associated with a high mortality rate (5% to 40% with treatment, and 100% if untreated) [2, 4, 5]. Extrapulmonary manifestations of *Pneumocystis jiroveci* infection occur rarely in HIV-infected children [6] and can present without concurrent pneumonia at multiple noncontiguous sites.

Diagnosis

Definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids from induced sputum after inhalation of nebulized 3% hypertonic saline. Sensitivity of induced sputum analysis ranges from 25%–90%; because negative predictive value is only 48%, it may be necessary to follow a negative induced sputum sample with bronchoscopy and bronchoalveolar lavage - the diagnostic procedure of choice in infants. Sensitivity ranges from 55%–97% and might be positive for at least 72 hours after PCP treatment has been initiated; treatment should not be delayed while awaiting results.

Three types of stains can be used to diagnose *P. jiroveci* organisms in specimens. Gomori's methenamine-silver stains the cyst wall brown or black. Toluidine blue stains the cyst wall blue or lavender and also stains fungal elements. Giemsa or Wright's stains stain the trophozoites and intracystic sporozoites pale blue with a punctate red nucleus unlike the other stains, this does not stain the cyst wall

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Treatment

Co-trimoxazole or Trimethoprim-sulfamethoxazole (TMP/SMX) is the treatment of choice for PCP. After the acute pneumonitis has resolved, children with mild to moderate disease who do not have malabsorption or diarrhoea can be given oral treatment with the same dose of TMP/SMX in 3–4 divided doses to complete a 21-day course. Adverse reactions to TMP/SMX reported in children include rash (including erythema multiforme and rarely Stevens Johnson syndrome), haematologic abnormalities (neutropenia, thrombocytopenia, megaloblastic, or aplastic anaemia), gastrointestinal complaints, hepatitis, and renal disorders [7]. For mild or moderate skin rash, TMP/SMX can be temporarily discontinued and

restarted when the rash has resolved. If an urticarial rash or Stevens-Johnson syndrome occurs, TMP/SMX should be discontinued and not readministered.

Pentamidine isothionate is recommended for patients intolerant of TMP/SMX or who demonstrate clinical treatment failure after 5–7 days of TMP/SMX therapy. In patients with clinical improvement after 7–10 days of intravenous therapy with pentamidine, an oral regimen (atovaquone) might be considered to complete a 21–day course. The most common adverse drug reaction to pentamidine is renal toxicity, which usually occurs after 2 weeks of therapy and can be averted by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if infused rapidly), prolonged QT interval (torsades de pointes), and cardiac arrhythmias can occur. Hypoglycemia (usually after 5–7 days of therapy) or hyperglycemia, hypercalcemia, hyperkalemia, pancreatitis, and insulin-dependent diabetes mellitus have also been reported.

Atovaquone, dapsone/trimethoprim and Clindamycin/primaquine are alternatives for treatment of mild to moderately severe PCP in adults. Data are limited in children. Trimetrexate glucuronate with leucovorin (folinic acid) has also been used as initial therapy in severe PCP in adults.

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A course of corticosteroids might be beneficial in some cases of PCP of moderate or great severity, started within 72 hours of diagnosis. Several studies in children have demonstrated a reduction in acute respiratory failure, decreased need for ventilation, and a decrease in mortality with early use of corticosteroids [8-10]. Indications for corticosteroid include a PaO₂ value of <70 mm Hg or an alveolar-arterial gradient of >35 mm Hg. A few case reports in children have documented improved pulmonary function with use of surfactant in cases of severe disease [11, 12].

Prophylaxis

Prophylaxis should be continued after 1 year of age for HIV-infected children who have had any CD4⁺ T-cell determination in the first 12 months of life indicating immunosuppression (CD4⁺ T lymphocyte percentage is less than 25% of total circulating lymphocytes). For HIV-infected children aged 1 to 5 years, PCP prophylaxis should be administered if [1] the CD4⁺ T-cell percentage is less than 15% of total lymphocytes or <500 cells/ μ L; [2] a rapid decline in CD4⁺ T-cell count or percentage occurs; or [3] if severely symptomatic HIV disease (category C) is present. For children 6 years of age or older, any CD4⁺ T-cell count of < 200 cells/ μ L is an indication for chemoprophylaxis [13].

The recommended drug regimen for prophylaxis in all immunocompromised patients (whether from HIV infection, malignancy, or other causes) is

TMP/SMX administered orally once daily three times per week. In patients who cannot tolerate TMP/SMX, aerosolized pentamidine is considered to be an alternative for those children 5 years of age or older; daily oral dapsone is another alternative drug for prophylaxis in children, especially those younger than 5 years. Intravenous pentamidine has also been used, but it appears to be less effective and potentially more toxic than other prophylactic regimens. Other drugs with potential for prophylaxis include pyrimethamine with dapsone, pyrimethamine-sulfadoxine, and oral atovaquone. Experience with these drugs in children is limited. These agents should be considered only in unusual situations in which the recommended regimens are not tolerated or cannot be used [13].

Although prophylaxis substantially reduces the risk of PCP, pulmonary and extrapulmonary *P. jirovecii* infections have occurred in HIV-infected adults and children receiving prophylaxis.

For previously immunocompromised children who have undergone immune reconstitution with HAART, prophylaxis can be discontinued if CD4⁺ T cell counts > 200 cells/ μ L are sustained for at least 6 months. However the safety of

stopping secondary prophylaxis following immune reconstitution has not been studied extensively.

Specific Doses

PCP treatment: Co-trimoxazole 120mg/kg/day IV in three to four divided doses or PO three or four times daily (after acute pneumonitis has resolved). In mild to moderate disease, I/V TMP/SMX may be changed to PO X 21 days followed by chronic suppressive therapy.

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Alternative therapeutic regimens (if TMP/SMX intolerant or clinical treatment failure after 5–7 days of TMP/SMX therapy):

Pentamidine 4 mg/kg IV once daily (pentamidine might be changed to atovaquone after 7–10 days IV therapy; or Atovaquone 15–20 mg/kg (max: 750 mg/dose) PO; infants 3–24 months of age may require a higher dose of 45 mg/kg/day.

Primaquine base 0.3 mg/kg PO once daily (max: 30 mg/day) + clindamycin 10 mg/kg IV or PO (max: 600 mg given I/V and 300–450 mg PO) every 6 hours has been used in adults, but data in children are not available.

Trimetrexate 45 mg/m² body surface area I/V OD + leucovorin 20 mg/m² body surface area I/V or PO every 6 hours (leucovorin or Calcium Folate

continued for 3 days after discontinuation of trimetrexate) in adults. Data in children are limited.

The role of Corticosteroids:

Prednisone dose: 1 mg/kg PO BD X 5 days, then 1 mg/kg PO daily for 5 days, then 0.5 mg/kg PO daily for days 11–21. The recommended regime is I/V methyl prednisolone at 0.5 mg/kg/dose, four times a day for 7 days, then twice daily for 7 days and finally once daily for 7 days. This can be changed to oral prednisolone in the same doses (2 mg/kg OD for a week, then 1 mg/kg for a week, then 0.5 mg/kg for a week) when oral feeding starts.

PCP prophylaxis:

Infants < 1 year 120 mg TMP/SMX OD three times a week usually on Monday, Wednesday and Friday; the dose for average sized children aged 1-3 is 240 mg TMP/SMX;

for 4-9 years 480 mg TMP/SMX,

and for 10 years and over 960 mg TMP

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Treatment Guidelines by OI; Fungi

Candida species

Epidemiology

Candida are normal inhabitants of the human gastrointestinal tract and may be recovered from up to a third of the mouths of normal individuals and two thirds of those with advanced HIV disease [1].

Candida albicans most often causes mucocutaneous candidiasis in HIV-infected children with low or declining CD4+ T cell number (or percentage). Related risk factors include neutropenia, treatment with corticosteroids and/or broad-spectrum antibiotics, the presence of indwelling vascular catheters and prolonged intravenous infusions particularly with parenteral alimentation and lipids. Such patients are also at risk of invasive infection [2, 3]. Common complications of disseminated disease include endophthalmitis, hepatosplenic and renal candidiasis, and osteomyelitis. A significant percentage of reported cases of fungaemia in HIV-infected children are caused by non-*albicans* *Candida* species. Isolates include *C. tropicalis*, *C.pseudotropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei* and *C. dubliniensis* [4].

The introduction of HAART has resulted in a significant decline in the incidence of a number of opportunistic illnesses including mucocutaneous candidiasis [5].

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Clinical Manifestations

Mucocutaneous infection may result in variable clinical symptoms including burning pain, altered taste sensation, and difficulty swallowing. However, many patients are asymptomatic. Most patients present with pseudomembranous candidiasis or thrush (white curdlike plaques on the buccal mucosa, palate, gums, or tongue with inflamed underlying mucosa). Angular cheilitis (inflammation and cracking at the corners of the mouth) may be noted. Acute

atrophic candidiasis (flat erythematous mucosa) or chronic hyperplastic thrush (raised white plaques that appear on the lower surface of the tongue, palate and buccal mucosa, and cannot be removed), present less frequently.

Vulvovaginal candidiasis may present with itching, watery to curd-like discharge, vaginal erythema with adherent white discharge, external dysuria, erythema, and swelling of labia and vulva with discrete pustulopapular peripheral lesions.

Mucocutaneous infection may also involve intertriginous areas of the gluteal folds, neck, groin, and axilla and the nailbed. Oesophageal candidiasis is usually accompanied by the presence of oropharyngeal candidiasis but may be absent.

Typically, dysphagia and odynophagia are described, although children may present with nausea and vomiting alone.

Diagnosis

Diagnosis is usually suggested by a characteristic clinical appearance. Recovery of an organism is not diagnostic since colonization is common. However a 10% potassium hydroxide (KOH) slide preparation of a scraping of an active lesion can be confirmatory. Pseudohyphae and budding yeast are characteristic findings. In patients with poorly responsive mucosal candidiasis, a culture should be obtained to look for drug-resistant yeast or identification of isolates that respond poorly to azoles (*C kruseii* or *C glabrata*). Barium swallow or upper GI endoscopy can confirm a suspicion of oesophageal involvement. The latter should be performed to rule out other causes of oesophagitis (HSV, CMV, MAC).

The diagnosis of candidemia can be made with blood cultures. Additional investigations include retinal examination for endophthalmitis, echocardiogram for cardiac vegetations, abdominal CT or ultrasound for hepatic or renal involvement, and bone scans if osteomyelitis is suspected.

Treatment

Classes of antifungal agents include polyenes (nystatin and amphotericin B), azoles including the imidazoles (clotrimazole) and triazoles (ketoconazole, itraconazole, fluconazole, voriconazole and posaconazole), and pyrimidine synthesis inhibitors, including 5-flucytosine. Newer agents include the candins (caspofungin and V-echinocandin).

As a result of inhibitory activity on cytochrome P-450-dependent hepatic enzymes, azole compounds have substantial drug interactions that may result in decreased plasma concentration and increased metabolism of the azole and the unexpected toxicity of the coadministered drug.

Adverse effects of amphotericin B are primarily related to nephrotoxicity with hypokalemia from renal tubular damage. Permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity can be ameliorated by hydration with 0.9% saline intravenously over 30 minute before infusion. Infusion-related fevers, chills, nausea, and vomiting can occur. Pretreatment with acetaminophen (paracetamol) and/or diphenhydramine (or chlorphenamine) may alleviate such reactions.

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Oropharyngeal candidiasis:

Topical therapy with nystatin suspension for 7 to 14 days is effective [6]. Systemic regimens that are indicated with failure of topical therapy include the oral azole compounds particularly fluconazole [7]. Ketoconazole or itraconazole can also be administered but usually as 2nd-line to fluconazole because of variable absorption. Intravenous amphotericin B is 3rd-line in patients with severe, refractory oropharyngeal candidiasis [8].

Oesophageal candidiasis:

Systemic therapy with fluconazole 14-21 days is effective. For refractory disease, alternative agents include oral itraconazole, low-dose intravenous amphotericin B

for a minimum of 7 days, intravenous voriconazole and caspofungin [9], although data and experience in children are limited for the latter.

Invasive Disease:

Despite the frequency of mucosal candidiasis, invasive disease is uncommon in HIV-infected subjects. Risk factors include the presence of indwelling intravenous catheters, neutropenia, chemotherapy, and parenteral alimentation. Central venous catheters should therefore be removed [4].

Intravenous amphotericin B is the drug of choice [10]. The duration of therapy is determined by the presence of deep tissue foci, patient clinical response, and presence of neutropenia. For candidaemia, treatment is recommended until 2–3 weeks after the last positive blood culture and signs and symptoms have resolved. In patients with persistent candidaemia despite appropriate therapy, investigation for a deep tissue focus of infection should be conducted including echocardiogram, renal or abdominal ultrasound, and ophthalmologic evaluation. Flucytosine has been used in combination with amphotericin B in some patients with severe invasive candidiasis, particularly in patients with CNS disease. Levels should be monitored and doses adjusted to keep the level between 40–60 ug/mL, particularly in patients with renal impairment where toxic levels can result in bone marrow suppression.

High dose fluconazole is an alternative to amphotericin B for treatment of invasive disease in patients with uncomplicated candidaemia with albicans species who have not recently received azole therapy or prophylaxis [6]. Fluconazole should not be initiated in the treatment of resistant candida species including *C. krusei* and *C. glabrata*.

Three lipid formulations [amphotericin B lipid complex (Abelcet), liposomal amphotericin B lipid complex (AmBisome), and amphotericin B cholesteryl sulfate complex] have a role in treatment of invasive disease that is refractory to conventional amphotericin B in children who are at risk for nephrotoxicity. Lipid preparations appear to be as efficacious as conventional amphotericin B for treatment of invasive disease [11], but their use is limited by cost.

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Vulvovaginal Candidiasis:

The standard treatment includes topical clotrimazole or miconazole for 7 days. However, shorter courses of topical medication for 3 days may be equivalent to treatment with 7 days. Either topical or systemic therapy appears effective for women with HIV infection, but clinical relapse commonly occurs [12].

Prophylaxis

Immune reconstitution with HAART accompanied by a reduction in plasma HIV-1 viraemia is the best intervention to reduce the rate of candida colonization and clinical disease [5, 13]. Other possible interventions include good oral hygiene, avoidance of unnecessary antibiotics and steroids, and specific antifungal medications. However the indications for continuous prophylactic antifungal therapy remain uncertain and may result in the emergence of resistant and refractory infections [1]. Universal primary antifungal prophylaxis is therefore not currently recommended and the indications for secondary prophylaxis should be individualized.

Specific Doses

Oropharyngeal treatment:

Fluconazole 3–6 mg/kg (max: 400 mg/dose) PO OD X
7–14 days

OR Itraconazole cyclodextrin oral solution 2.5 mg/kg
PO BD (max: 200 mg/day) X 7–14 days

OR Clotrimazole trouches: 10 mg troche PO four times daily X 14 days(Not available in UK amphotercin or nystatin lozenges nearest alternative)

OR Nystatin suspension: 4–6 ml PO four times daily or one to two 200,000 U pastilles four to five times daily X 7–14 days. Usually 1ml qds (upto 5ml max in

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severe disease) Nystatin pastilles only available as 100,000 unit.

Oropharyngeal (fluconazole resistant):

Itraconazole cyclodextrin oral solution X 7-14 days

OR Amphotericin B oral suspension 1ml (100 mg/ml) four times daily for 14 days

Oesophageal disease: Fluconazole 6 mg/kg PO once on day 1, then 3–6 mg/kg (max: 400 mg/dose) X 14–21 days

OR Itraconazole cyclodextrin oral solution 2.5 mg/kg PO BD or 5.0 mg/kg PO OD X 14–21 days

OR Amphotericin B 0.3–0.5 mg/kg IV OD for a minimum of 7 days

Invasive disease:

Amphotericin B 0.5–1.5 mg/kg IV OD.

Mild to moderate disease: Initiate at doses of 0.25–0.5 mg/kg IV OD then increase as tolerated to 0.5–1.5 mg/kg IV OD.

Severe disease: Initiate treatment at target daily dose. Following stabilization and resolution of fever on daily therapy in children with invasive disease, amphotericin B may be given as 1.5 mg/kg IV once every other day.

In uncomplicated catheter-associated *C. albicans* candidaemia, an initial course of amphotericin B followed by fluconazole 5–6 mg/kg IV to complete treatment can be used.

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Amphotericin B + flucytosine 100–150 mg/kg PO divided into 4 doses for severe invasive disease, especially involving the CNS. Flucytosine dose should be adjusted to keep drug levels between 40–60 ug/ml.

Lipid formulations of amphotericin B: Lipid Complex (Abelcet): 5 mg/kg IV OD X 2–4 weeks, Liposomal (AmBisome): 3–5 mg/kg IV OD X 2–4 weeks

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Treatment Guidelines by OI; Fungi

Cryptococcus neoformans

Background

Meningoencephalitis is the most frequent manifestation of cryptococcosis and pneumonia the most frequent fungal pneumonia encountered in individuals with AIDS. The incidence had fallen before HAART became widely available with the more frequent use of azole antifungals [1, 2]. *Cryptococcus neoformans* is an encapsulated oval yeast. Inhalation of unencapsulated forms may result in colonization of the airways and respiratory infection [3] with a propensity to invade the CNS.

Cryptococcus grows readily from soil contaminated with avian excreta, particularly those of pigeons. The overall incidence is higher among HIV-infected subjects from Africa and Southeast Asia [4]. Cryptococcosis in children with AIDS appears less common, with a prevalence rate of approximately 1.4% [5]. More than 75% of the cases associated with AIDS develop when the CD4 T-lymphocyte count falls below 50 cells/mm³ [6].

Clinical Manifestations

CNS invasion may be secondary to haematogenous infection or may represent reactivation disease. Infection typically presents as a subacute process characterised by headache, fever, and, less often, altered mental status; however, presentations characteristic of acute meningitis can occur with up to 70% of children. In a study from Zimbabwe presenting with nuchal rigidity, 40% with seizure activity, and approximately 20% with focal neurologic signs [7]. Cranial nerve palsies and papilloedema are the most common ocular manifestations secondary to CNS invasion. Complications include hydrocephalus, motor or sensory deficits, cerebellar dysfunction and seizures.

Cryptococcal pneumonia may be either asymptomatic or symptomatic, with or without evidence of dissemination. It is unclear if disseminated disease represents a progression or reactivation of pulmonary disease. Children with pulmonary cryptococcosis, without dissemination, present with cough and recurrent fever. Chest radiographs may reveal focal or diffuse infiltrates and intrathoracic lymphadenopathy.

Cutaneous cryptococcosis is a sign of dissemination and may precede life-threatening disease by several weeks [8]. The lesions may appear as papules, tumours, vesicles, plaques, abscesses, cellulitis, purpura, ulcers, or bullae, and have previously been misdiagnosed as molluscum contagiosum [9].

Diagnosis

The CT scan is usually nonspecific but may show signs of increased intracranial pressure, hydrocephalus, or focal lesions, especially in the basal ganglia.

Abnormal CSF findings, including pleocytosis, low glucose, and high protein concentrations, are seen in approximately 40% of patients although in HIV-infected children with CNS disease these parameters may be normal. However the opening pressure is usually elevated [10]. The India ink stain on wet mount preparation that outlines the polysaccharide capsule is positive on direct examination of the CSF in over 80% of patients with cryptococcal meningitis secondary to AIDS. Cryptococcal antigen can be detected in CSF, serum, or bronchoalveolar lavage fluid by latex agglutination. Cryptococcal antigen detection in the serum is usually indicative of systemic disease but does not correlate with clinical response to treatment. In contrast cryptococcal antigen titres in CSF can be helpful in evaluating response to therapy. False negative titres may occur as a result of high (prozone effect) or low antigenic concentration, or the presence of nonencapsulated strains [11]. Fungal cultures from CSF, sputum and blood might identify the organism. In selected cases, such

as in patients with refractory disease or relapse, susceptibility testing of the *C. neoformans* isolate can be helpful.

Treatment

Recommendations for treatment of severe cryptococcal disease in children have been extrapolated from adult data to include induction therapy with amphotericin B combined with a minimum of 2 weeks of flucytosine [12]. Consolidation therapy involves a replacement of amphotericin B and flucytosine with high dose IV or oral fluconazole for a minimum of 8 weeks or until CSF cultures are stable.

Following induction and maintenance therapy, maintenance suppressive therapy with a low oral dose of fluconazole. Itraconazole can also be instituted, however relapse rates may be higher [13]. Lipid formulations of amphotericin B have been used for treatment of cryptococcal meningitis in adults and may be useful in patients with impaired renal function, although the optimal dose has not been determined [14,15]. Prior to the introduction of HAART, patients with AIDS-associated cryptococcal meningitis had to continue chronic suppressive therapy for their lifetime. There are no clear guidelines on discontinuation of secondary prophylaxis in adult and paediatric patients following immune reconstitution with HAART [16]. In our centres we discontinue maintenance therapy in patients with sustained CD4 T-cell counts >200 cells/ μ L following immune reconstitution with HAART. The aggressive management of acute cerebral edema and increased intracranial pressure is pivotal in the management of acute cryptococcal meningitis. Mannitol and corticosteroids have been used to treat signs of acutely increased intracranial pressure but their role remains controversial.

Children with severe pulmonary disease can be treated with amphotericin B induction therapy combined with flucytosine for 2 weeks. Following acute treatment, maintenance therapy with fluconazole or itraconazole is recommended. For children with mild-to-moderate pulmonary cryptococcosis

fluconazole alone can be used for treatment followed by lifelong suppressive therapy with fluconazole (in the absence of immune reconstitution). Itraconazole is a suitable alternative.

Specific doses

Meningeal and extrameningeal disseminated disease:

Acute therapy (minimum 2 week induction followed by consolidation therapy): IV amphotericin B 0.7–1.5 mg/kg OD

OR IV Liposomal amphotericin B (AmBisome) 3–5 mg/kg OD (in children with renal insufficiency or infusion-related toxicity to amphotericin B) + PO flucytosine 25 mg/kg four times daily.

Consolidation therapy (followed by chronic suppressive therapy): IV or PO

Fluconazole 5–6 mg/kg BD (max: 800 mg/day)

OR IV or PO Itraconazole 2–5 mg/kg (max:200 mg/dose) BD for a minimum of 8 weeks or until CSF cultures are sterile.

Severe, isolated pulmonary disease:

IV Amphotericin B 0.7–1.5 mg/kg OD + PO flucytosine 25 mg/kg four times daily followed by chronic suppressive therapy with fluconazole or itraconazole.

Mild, isolated pulmonary disease:

Oral fluconazole 3–6 mg/kg OD followed by chronic suppressive therapy

OR oral itraconazole 2–5 mg/kg OD (max: 400 mg/day), followed by chronic suppressive therapy.

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Treatment Guidelines by OI; Fungi

Histoplasmosis

Background

Disseminated histoplasmosis is recognized as a common AIDS-defining opportunistic infection in endemic areas (Americas, Africa, East Asia) but is infrequently documented in HIV-infected subjects native to Europe. Most reports are in individuals returning from endemic regions, or following endogenous reactivation of a latent infection imported previously from overseas. Reports of autochthonous cases in Europe suggest the possible endemic presence of *Histoplasma capsulatum* in some regions, such as the South of France or the Po valley in Italy [1]. However, there are no reports of regionally acquired disease among HIV-infected children in Europe. In contrast the incidence of disseminated histoplasmosis in HIV-infected children residing in the United States is 0.4% and remains the most frequently diagnosed systemic fungal disease in that country with an estimated 500,000 cases per year [2]. The diagnosis of disseminated histoplasmosis should therefore be considered in children with AIDS who have previously resided in endemic regions.

H. capsulatum exists in mycelial form in soil contaminated by bird droppings or other organic material. Primary infection in the respiratory tract is commonly asymptomatic in immunocompetent hosts since cell-mediated immunity prevents dissemination, which occurs as a result of either reactivation and newly acquired infection in subjects with severe immunosuppression or during infancy.

Clinical manifestations

Most symptomatic children with acute pulmonary histoplasmosis develop an influenza-like illness with non-pleuritic chest pain, hilar adenopathy, and mild pulmonary infiltrates; symptoms persist for 2 days to 2 weeks. Intense exposure

to spores can cause severe respiratory tract symptoms and diffuse nodular pulmonary infiltrates, prolonged fever, fatigue, and weight loss. Erythema nodosum can occur in adolescents. Primary cutaneous infections can occur after trauma.

A primary pulmonary focus frequently results in widespread dissemination in children with AIDS which is most often characterized by prolonged fever in association with weight loss and a nonproductive cough [3]. Frequent physical findings include hepatosplenomegaly, diffuse adenopathy and failure to thrive. Cutaneous lesions that are erythematous and nodular may develop. Mucosal ulceration, pancytopenia, disseminated intravascular coagulopathy, and gastrointestinal bleeding can ensue in association with elevated liver transaminases. Manifestations of CNS involvement include chorioretinitis, meningitis, and brain abscesses [4].

Diagnosis

Fungal culture from bone marrow, blood, sputum, and tissue specimens is the definitive method of diagnosis. The lysis-centrifugation method is preferred for blood cultures. Identification of *H. capsulatum* can be shortened in cultures through the use of a DNA probe. Demonstration of typical intracellular yeast forms by examination with Gomori methenamine silver of tissue, blood, bone marrow, or bronchoalveolar lavage specimens strongly support the diagnosis of histoplasmosis when clinical, epidemiologic, and other laboratory studies are compatible.

Detection of *H. capsulatum* polysaccharide antigen (HPA) in serum, urine, or bronchoalveolar lavage fluid by radio or enzyme immunoassay is a rapid, sensitive (particularly during acute pulmonary and disseminated infection) and

specific diagnostic method and can be detected before culture positivity and antibody detection [5]; a negative test does not exclude infection. Antigen concentration can be used to monitor treatment response and to identify relapse. Cross reactivities occur in patients with blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infection. Meningitis can be diagnosed by testing CSF for Histoplasma antigen, antibody and culture: a diagnostic yield of 40%–70%, 70%–90% and 20%–60% respectively, is reported [5]. Serologic tests are not useful for the diagnosis of acute histoplasmosis and might be undetectable in immunosuppressed patients [6]. Histoplasmin skin tests are not sensitive for the diagnosis of disseminated disease [3].

Treatment and Specific Doses

Pediatric treatment recommendations for HIV-infected children are extrapolated from data in the adult literature. Erythema nodosum, arthritis, and pericarditis do not necessitate therapy. Pericarditis is treated with indomethacin. HIV-infected patients should always receive antifungal therapy; untreated disseminated histoplasmosis is usually fatal.

Itraconazole is effective in the treatment of mild disseminated histoplasmosis in HIV-infected patients and immunocompetent children [7]. High-dose fluconazole is an alternative but is less efficacious and the organism may develop drug resistance [8]. Amphotericin B at a dose of 1 mg/kg for 4 to 6 weeks is recommended for severe disseminated disease in children with AIDS [9]. Amphotericin B therapy should be continued for 12–16 weeks in children with histoplasma meningitis. Liposomal amphotericin B is an alternative for patients who cannot tolerate conventional amphotericin.

Patients with HIV infection and disseminated histoplasmosis or meningitis require chronic suppressive therapy (secondary prophylaxis) with itraconazole to prevent relapse; fluconazole is a suitable alternative if itraconazole is not tolerated. Safety

of discontinuation of secondary prophylaxis following immune reconstitution with HAART in children has not been studied extensively.

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Treatment Guidelines by OI; Protozoa

Toxoplasmosis

Epidemiology

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T gondii is one of the most common causes of chronic infection with an intracellular organism in humans. Acute infection in immunocompetent individuals is usually asymptomatic. A chronically infected individual with impaired cell-mediated immunity is at risk for reactivation of the infection, which manifests primarily as encephalitis and usually occurs in HIV-infected subjects with CD4+ T cell counts $<100/\mu\text{L}$ [1]. Older children, adolescents, and adults typically acquire infection by ingestion of poorly cooked meat or contaminated vegetables that contain parasitic cysts, or by direct contact with cat feces. AIDS-defining *Toxoplasma* encephalitis is uncommon in HIV-infected children ($<1\%$ of paediatric AIDS cases even before the advent HAART) [2].

Clinical Manifestations

Toxoplasma encephalitis should be considered in all HIV infected children with new neurologic findings. Although focal findings are more typical, the initial presentation can be variable and reflect diffuse CNS disease. Characteristically *toxoplasma* encephalitis has a subacute onset with focal neurologic abnormalities often accompanied by headache, altered mental status, and fever [3]. Common focal neurologic signs include motor and speech disturbances. Patients can also present with seizures, cranial nerve abnormalities, visual field defects, sensory disturbances, cerebellar dysfunction, meningismus, movement disorders, and neuropsychiatric manifestations [3].

Manifestations of extracerebral toxoplasmosis in HIV-infected children include ocular toxoplasmosis, which occurs most often in association with *toxoplasma* encephalitis necessitating neurologic examination. Patients with chorioretinitis present with blurred vision, pain or photophobia. Rarely manifestations of

reactivated chronic toxoplasmosis include systemic toxoplasmosis, pneumonitis, hepatitis, and cardiomyopathy/myocarditis [4].

Diagnosis

A presumptive diagnosis of toxoplasma encephalitis is based on clinical symptoms, serologic evidence of infection, and the presence of a space-occupying lesion on imaging studies.

Individuals with AIDS who are infected latently with *T gondii* have variable IgG titres and rarely possess IgM antibody. Although seroconversion and fourfold increases in IgG antibody titers may occur, the ability to diagnose active disease in patients with AIDS is commonly impaired by immunosuppression. IgM antibodies typically disappear a few months after infection but can remain elevated for more than 1 year confounding the differentiation of acute and remote infection [5].

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Additional investigations to support the diagnosis of toxoplasma encephalitis include CT scanning of the brain that might indicate multiple, bilateral, hypodense, focal ring-enhancing lesions especially in the basal ganglia and cerebral corticomedullary junction in 70-80% of patients [6]. Magnetic resonance imaging is more sensitive and will confirm basal ganglia lesions in most patients [7]. Although toxoplasmic encephalitis can occasionally cause a single brain lesion on MRI, such a finding suggests an alternative diagnosis (primarily CNS lymphoma and tuberculoma) [8].

Definitive diagnosis of *Toxoplasma* encephalitis requires histologic confirmation by brain biopsy, and can be considered when early neurologic deterioration is present despite empiric treatment or in children who fail to respond to anti-toxoplasma therapy after 10–14 days. If lumbar puncture is not contraindicated, PCR of CSF should also be considered. Ocular toxoplasmosis is diagnosed on

the basis of observation of characteristic retinal lesions in conjunction with serum specific antibodies.

Treatment

HIV-infected children with acquired CNS, ocular, or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin (calcium folinate) plus sulfadiazine for 6 weeks, assuming clinical and radiological improvement. Longer courses of treatment might be required in cases of extensive disease or sub-optimal response after 6 weeks.

Pyrimethamine is associated with reversible bone marrow suppression (neutropenia, anaemia, and thrombocytopenia), rash (including Stevens Johnson Syndrome) and nausea. A full blood count should be performed weekly during daily treatment with pyrimethamine. Increased doses of leucovorin may be required in the event of marrow suppression and continued 1 week after discontinuation of acute therapy.

The combination of pyrimethamine plus clindamycin is as effective as pyrimethamine plus sulfadiazine during the acute phase of therapy [9] and is indicated in patients who develop sulphonamide hypersensitivity.

Trimethoprim-sulphamethoxazole (Co-trimoxazole) may be as effective as pyrimethamine plus sulphadiazine for the treatment of toxoplasmic encephalitis [10]. Alternative regimens reported in adults include azithromycin with pyrimethamine and leucovorin (calcium folinate) (in subjects with allergies to sulphur-containing drugs), atovaquone plus pyrimethamine and leucovorin (calcium folinate), or atovaquone with sulphadiazine alone, or atovaquone as a single agent in patients intolerant to both pyrimethamine and sulphadiazine.

Corticosteroids (dexamethasone or prednisone) can be administered to patients with toxoplasmic encephalitis with cerebral oedema and intracranial hypertension, or when CSF protein is very elevated (>1,000 mg/dL). Duration of corticosteroid administration should be as short as possible because of the potential immunosuppressive effects of steroids. In the absence of effective HAART, 50-80% of patients with AIDS who do not receive maintenance therapy experience a relapse of toxoplasmic encephalitis at 12 months [11].

Trimethoprim-sulphamethoxazole (Co-trimoxazole), when administered for PCP prophylaxis, provides primary prophylaxis against toxoplasmosis. Atovaquone or dapsone combined with pyrimethamine may be suitable alternatives [12]. The safety of discontinuing primary or secondary prophylaxis among HIV-infected children receiving HAART has not been studied extensively. In adults with AIDS a sustained increase (>6 months) in CD4 count >200 cells/ μ L is an indication to discontinue prophylaxis, and should be restarted if CD4 count decreases to < 200 cells/ μ L.

Specific Doses

Acquired toxoplasmosis, acute induction therapy (followed by chronic suppressive therapy):

Pyrimethamine: loading dose, 2 mg/kg (max: 50 mg) PO OD X 3 days, then 1 mg/kg (max: 25 mg) PO OD + sulphadiazine 25–50 mg/kg (max: 1.0–1.5 gm/dose) PO four times daily + leucovorin 10–25 mg PO OD, followed by chronic suppressive therapy. Treatment duration (followed by chronic suppressive therapy): at least 6 weeks

For sulphonamide-intolerant patients:

Clindamycin 5.0–7.5 mg/kg (max: 600 mg/dose) PO or IV four times daily can be substituted for sulphadiazine combined with pyrimethamine and leucovorin

Notes:

Trimethoprim-sulphamethoxazole (Co-trimoxazole) (5 mg/kg TMP plus 25mg/kg SMX IV or PO BD) i.e 30mg/kg is an alternative to pyrimethamine-sulphadiazine in adults. Other alternative regimens in adults include atovaquone (1.5 gm PO BD) combined with pyrimethamine/leucovorin; with sulphadiazine alone; or as a single agent in patients intolerant to both pyrimethamine and sulphadiazine. Azithromycin (900–1,200 mg/day) has also been used in adults combined with pyrimethamine-sulfadiazine.

Secondary prophylaxis in the absence of effective HAART:

Consult an expert.

Primary prophylaxis: TMP (Trimethoprim) when administered for PCP prophylaxis, provides primary prophylaxis against toxoplasmosis.

Atavaquone or dapsone combined with pyrimethamine may be suitable alternatives

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Treatment Guidelines by Opportunistic Infection; Protozoa

Cryptosporidiosis and microsporidiosis

Background

Cryptosporidium hominis (formerly *C. parvum* genotype 1 or human genotype) causes self-limited enteric illness in immunocompetent hosts. Other species that infect humans include *C. parvum* (formerly *C. parvum* genotype 2 or bovine genotype), and *C. meleagridis*. Infection is initiated when ingested oocysts excreted in the feces of infected animals and humans, excyst and release sporozoites which attach to and invade intestinal epithelial cells particularly in the jejunum and terminal ileum [1]. This can result in profuse, nonbloody, watery diarrhoea with dehydration and malnutrition in immunocompromised hosts. Outbreaks have been associated with ingestion of contaminated drinking water and public swimming pools. Foodborne and person-to-person spread also have been documented particularly in toddlers attending day care centres [1, 2].

Microsporidia are also small, sporeforming, obligate intracellular parasites that cause moderate to severe diarrhoea in HIV-infected children. The parasites are transmitted by the faecal-oral route, develop in enterocytes and are excreted in faeces [3]. Jejunal enterocytes are most commonly infected [4]. Microsporidiosis has been reported in up to 7% of HIV-infected Thai children with acute and chronic diarrhea [5].

Clinical manifestations

In immunocompetent hosts, *Cryptosporidium* infection results in a self-limited diarrhoeal illness that lasts from 4 to 20 days and is associated with abdominal cramping, nausea, vomiting, low-grade fever, and anorexia [6]. Disease caused by microsporidiosis is much more common to the immunocompromised host with clinical manifestations that are indistinguishable from the manifestations of isosporiasis and cryptosporidiosis.

In HIV-infected children frequent and persistent, watery diarrhoea is the most common presentation of both cryptosporidial and microsporidial infection, associated with abdominal cramps, fever, vomiting, anorexia, weight loss, and poor weight gain [7]. Untreated chronic severe diarrhoea may cause malnutrition, failure to thrive, and/or severe dehydration.

Extraintestinal complications of cryptosporidiosis include gallbladder and biliary tree involvement with acalculous cholecystitis, and sclerosing cholangitis.

Symptoms include fever, vomiting and right upper abdominal pain associated with elevated alkaline phosphatase in the absence of elevated bilirubin and transaminase levels [8]. Biliary cryptosporidiosis is diagnosed by finding the organism in bile or on histologic examination of tissue from the biliary tree [9].

Pulmonary or disseminated cryptosporidial infection, are also documented.

Extraintestinal complications of microsporidia species include hepatitis, peritonitis, keratoconjunctivitis, myositis, cholangitis, sinusitis, and disseminated

CNS disease.

Diagnosis

The detection of oocysts on microscopic examination of stool specimens is diagnostic. Routine laboratory examination of stool for ova and parasites will not detect *C parvum* so this organism should be specified to laboratory personnel and at least three stool samples submitted on three separate days since oocyst excretion can be intermittent. Organisms also can be identified in intestinal biopsy tissue or intestinal fluid.

Microsporidia species spores can be detected in thin unconcentrated smears of formalin-fixed stool specimens or duodenal aspirates stained with a chromotrope-based stain (a modified trichrome stain).

Treatment

HAART is the treatment of choice since immune reconstitution frequently results in clearance of these organisms [10]. No consistently effective therapy is available for treatment of either cryptosporidiosis or microsporidiosis, and duration of treatment in HIV-infected subjects is uncertain.

Nitazoxanide may have efficacy in decreasing the severity of symptoms of diarrhoea caused by *Cryptosporidia* in children [11, 12]. Other agents for the treatment of cryptosporidiosis in HIV-infected children may include paromomycin and azithromycin [13]. Albendazole may be useful in decreasing diarrhoea secondary to some microsporidial species [14,15]. The treatment duration is unknown for both cryptosporidiosis and microsporidiosis.

Specific Doses

Cryptosporidiosis

Microsporidiosis

Nitazoxanide (data from immunocompetent children, treatment period, 3 days)

1–3 yr: 100 mg PO BD

4–11 yr: 200 mg PO BD;

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OR Paromomycin 25–35 mg/kg

2 to 4 divided doses PO

(max: 2 gm daily)

OR Azithromycin 10 mg/kg PO on day 1,

then 5 mg/kg body PO daily (max: 600 mg daily).

Albendazole 7.5 mg/kg
(max: 400 mg/dose) PO
BD for intestinal or
disseminated infection by
microsporidia
other than *Enterocytozoon
bienuesi*

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Treatment Guidelines by OI; Viruses

Cytomegalovirus (CMV)

Background

As with other herpesviruses, human CMV remains latent in the infected host throughout life, but rarely reactivates to cause clinical illness except in subjects with impaired cell-mediated immunity. The clinical manifestations vary with the age and host immunocompetence. Acquisition can occur in infancy, early childhood, or adolescence and reflects either vertical or horizontal transmission. The former occurs during the intrapartum or postpartum periods particularly by breast-feeding and is rarely symptomatic. Horizontal transmission may occur by contact with virus-containing saliva, urine, or semen; or through transfusion of

infected blood or transplantation of infected organs. In developing countries, most children acquire CMV infection early in life, with seroprevalence approaching 100% by early adulthood. HIV-infected children appear to be at higher risk for CMV acquisition during early childhood than children without HIV infection [1].

Clinical manifestations

Asymptomatic infections are the most common, particularly in children. An infectious mononucleosis-like syndrome with prolonged fever and mild hepatitis, occurring in the absence of heterophil antibody production, can occur in adolescents and adults. In the immunocompromised host infection may occur secondary to reactivation of latent viral infection or may be newly acquired. In children with extraocular CMV disease, fever and loss of developmental milestones in association with anaemia, thrombocytopenia and elevated lactic dehydrogenase are initially observed. Viral dissemination results in multiple organ system involvement, with the most important clinical manifestations consisting of pneumonitis, gastrointestinal disease, and retinitis.

CMV retinitis

CMV retinitis is the most frequent severe manifestation of CMV disease in HIV-infected children, accounting for approximately 25% of CMV AIDS-defining illnesses. Peripheral lesions are frequently asymptomatic, and even advanced disease does not cause pain. In younger children, strabismus or failure to fix and follow objects, are useful signs. Older children may complain of floaters, loss of peripheral vision, or reduction in central vision. The disease can progress to total blindness and retinal detachment if left untreated. CMV produces a necrotic rapidly progressing retinitis with characteristic white perivascular infiltrate and retinal haemorrhages. Older HIV-infected children with CD4+ T cell counts <100/ μ L are more likely to develop CMV retinitis than those with higher CD4+ T cell counts, but CD4+ number is less predictive in young infants [2,3].

CMV gastrointestinal disease

GI tract disease caused by CMV can include oesophagitis, gastritis, pyloric obstruction, hepatitis, pancreatitis, colitis, ascending cholangitis and cholecystitis. Signs and symptoms may include nausea, vomiting, dysphagia, epigastric pain, icterus, and watery diarrhoea. Stools may be bloody. Sigmoidoscopy in CMV colitis is nonspecific, showing diffuse erythema, submucosal haemorrhage, and diffuse mucosal ulcerations. Endoscopy and biopsy may demonstrate cytomegalic inclusion cells in GI endothelium or epithelium.

CMV pneumonitis

CMV in pulmonary disease is often isolated with other organisms (e.g., *P. jiroveci*). CMV pneumonitis begins with fever and a dry, nonproductive cough, which can progress acutely resulting in retractions, dyspnea, and hypoxia. Bilateral interstitial infiltrates are noted radiographically.

CNS manifestations

Co-infection with CMV appears to accelerate HIV disease progression and associated neurological disease [4, 5]. Manifestations include subacute encephalopathy and myelitis. CSF findings are nonspecific and may show a polymorphonuclear predominance, elevated protein, and low glucose. However, many children have normal CSF.

Diagnosis

It is often difficult to distinguish asymptomatic infection from disease. CMV can be isolated by viral culture from virtually any body fluid or tissue. A positive blood

buffy-coat culture establishes a diagnosis of CMV infection and increases the likelihood that disease or symptoms are caused by CMV because children with positive blood cultures are at higher risk for developing end-organ disease.

Viral antigen (specifically pp65 antigen) or DNA can be detected directly by qualitative and quantitative PCR and DNA hybridization. These techniques are more sensitive than buffy-coat or cultures for detecting CMV and can be used to identify patients at higher risk of disease. Quantitation by DNA PCR can be used as a marker of disease progression and to monitor response to therapy [6]. Histopathology demonstrates characteristic “owl’s eye” intranuclear and smaller intracytoplasmic inclusion bodies in biopsy specimens.

Treatment

The drug of choice for initial treatment of disseminated CMV disease, including CMV retinitis, in HIV-infected children is ganciclovir. Prolonged therapy is associated with the emergence of ganciclovir-resistant CMV strains. Major side effects include myelosuppression (anaemia, neutropenia, and thrombocytopenia which may necessitate dose reduction or interruption or the use of granulocyte colony-stimulating factor) and renal toxicity.

Foscarnet is an alternative drug to treat CMV disease or for use in ganciclovir-resistant CMV infections. Foscarnet should be given slowly over the course of 2 hours (no faster than 1 mg/kg/minute). Infusing foscarnet with saline fluid loading can minimize renal toxicity. Doses should be modified in patients with renal insufficiency. Major side effects include renal toxicity and electrolyte imbalances. Valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for HIV-infected adults with CMV retinitis however an appropriate dosage of this drug for children is not currently available. The major adverse effect is myelosuppression. Cidofovir is also effective in treating CMV retinitis in adult patients who are intolerant of other therapies. Major side effects include nephrotoxicity by

producing proximal tubular dysfunction including Fanconi syndrome and acute renal failure and neutropenia.

TDM of ganciclovir may be useful especially in infants without immune reconstitution as they may require higher doses of ganciclovir.

Prophylaxis

Severely immunocompromised children with HIV/CMV coinfection should have a dilated retinal examination performed every 4–6 months. Prophylaxis with oral ganciclovir or valganciclovir can be considered for HIV-infected adolescents who are CMV-seropositive with CD4+ T lymphocyte count of <50 cells/ μ L but must be balanced with the risks of (val)ganciclovir-induced neutropenia, anaemia, conflicting reports of efficacy, lack of proven survival benefit, risk for emergence of ganciclovir-resistant CMV, and cost. Oral Valganciclovir suspension is available and has been used successfully in BMT prophylaxis.

Neither aciclovir nor valaciclovir should be used for CMV infection.

Specific Doses

Disseminated disease and retinitis:

Induction therapy (followed by chronic suppressive therapy): Ganciclovir 5 mg/kg IV every 12 hours X 14–21, then 5mg/kg per day for 5–7 days per week for chronic suppression

OR

Foscarnet 60 mg/kg IV every 8 hours X 14–21 days, then 90–120 mg/kg OD for chronic suppression

OR

Older children: Oral valganciclovir 900 mg OD

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Treatment Guidelines by OI; Viruses

Herpes Simplex Virus 1 and 2 (HSV 1 & 2)

Background

Due to the high universal prevalence of HSV infection, many individuals infected with HIV are also infected with HSV-1 and/or HSV-2. Following primary infection, HSV establishes latent infection in sensory root ganglia that correspond with the site of inoculation, from which symptomatic recurrences develop intermittently. Primary HSV-1 infection often occurs during childhood and is subclinical, as a result of direct inoculation of infected droplets from orolabial or nasal secretions onto susceptible mucosal surfaces. HSV-2 infection is usually acquired from sexual activity. In orolabial infection, HSV develops latency in the trigeminal ganglia, whereas latency develops in sacral ganglia for the latter. There is an association between increased frequency and severity of HSV reactivation and asymptomatic viral shedding with advancing immunosuppression in HIV-infected adults [1, 2, 3]. Recurrent HSV infection is AIDS-defining in approximately 6% of HIV-infected children who may also have more severe episodes associated with prolonged viral shedding [4].

Clinical manifestations

The most common presentation of HSV infection in children is orolabial disease characterized by a painful vesicular eruption with a few or as many as 20 distinct vesicles appearing on the lips, tongue, or buccal mucosa [5]. Fever, irritability, tender submandibular lymphadenopathy, and superficial, painful ulcers in the gingival, oral mucosa and perioral area characterize primary HSV gingivostomatitis. In immunosuppressed HIV-infected children, primary HSV co-infection is associated with extensive tissue destruction, poor healing of ulcerative lesions, prolonged viral shedding, and occasional dissemination [6]. The latter includes visceral involvement and generalized skin lesions. Other sites of involvement include the esophagus, genitalia, liver, adrenals, lung, kidney, spleen and CNS.

Diagnosis

The diagnosis is clinically based on the appearance of vesicles and ulcers. The virus can be isolated from mucocutaneous lesions by culture. Other sensitive detection methods include direct staining of infected cells for virus antigen, antibody detection, and identification of virus particles by electron microscopy [7]. HSV serology is not useful because prevalence rates of HSV antibodies in subjects with HIV are high. For children with suspected HSV encephalitis, detection of HSV DNA by PCR in the CSF is the diagnostic test of choice since CSF cultures for HSV are usually negative [8]. Definitive diagnosis of HSV oesophagitis requires endoscopy with biopsy and culture.

Treatment and Prophylaxis

Parenteral or oral acyclovir is the drug of choice for treatment of HSV infection in

infants and children, irrespective of underlying immunity. HIV-infected children with symptomatic HSV gingivostomatitis should receive IV or oral acyclovir for 7–14 days. Disseminated HSV disease or encephalitis should be treated with IV acyclovir for 21 days. HIV-infected children with severe oral recurrences (more than 3–6 severe episodes a year) or previous disseminated disease may benefit from prophylaxis with oral acyclovir [9].

Valacyclovir is a prodrug of acyclovir with improved bioavailability but is not active against acyclovir-resistant HSV. It is approved for use in adults and adolescents for treatment of genital herpes and may be used in children although data are limited. Acyclovir-resistant HSV infection should be treated with IV foscarnet until infection resolves.

Specific Doses

Central nervous system or disseminated disease in children outside the neonatal period:

Aciclovir 20 mg/kg IV three times daily X 21 days.
(Surface area dosing 500mg/m² tds more accurate).

Moderate to severe symptomatic gingivostomatitis:

Aciclovir 10 mg/kg IV three times daily X 7–14 days.
(Surface area dosing 250mg/m² tds).

For genital herpes (adults and adolescents):

Aciclovir 20 mg/kg (max: 400 mg/dose) PO three times daily X 7–10 days. Valaciclovir is approved for use in adult and adolescents with genital HSV - 1 gram PO BD X 7–10 days. 800mg max single dose

Mild symptomatic gingivostomatitis:

Aciclovir 20 mg/kg (max: 400 mg/dose) PO three times daily X 7–14 days.

Acyclovir-resistant HSV infection:

Foscarnet 40 mg/kg IV three times daily or 60 mg/kg IV twice daily.

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Treatment Guidelines by OI; Viruses

Varicella Zoster Virus (VZV)

Epidemiology

VZV, a neurotropic member of the herpesvirus family causes acute primary infection and lifelong latency resulting in varicella (chickenpox) and zoster (shingles), respectively. In temperate climates, varicella commonly occurs in childhood resulting in a benign self-limited illness in children with intact cellular immunity. In adults and all subjects with impaired cellular immunity, varicella can be more severe resulting in disseminated cutaneous disease and visceral involvement. VZV infection (zoster) typically recurs with advancing age in immunocompetent hosts or secondary to impaired humoral or cell-mediated immunity particularly in children with low CD4 count (< 15%) at the time of primary infection [1]. Current CD4+ cell count correlates with the frequency of recurrences [2]. An episode or recurrences of zoster in a young individual warrant consideration of underlying HIV infection.

Infectivity usually begins 1-2 days before the onset of rash, and patients remain infectious until all vesicular lesions are crusted. In the immunocompetent host, the period of infectiousness is usually 5 - 7 days after the lesions first appear. In immunocompromised hosts, prolonged viraemia and shedding occur and can be accompanied by an extended duration of new lesion formation (>1 month after primary or recurrent infection) [3, 4].

Clinical Manifestations

A generalized severe pruritic vesicular rash and fever is diagnostic. Lesions appear first and are most numerous on the trunk, neck, and face. The vesicles contain fluid, rest on an erythematous base and ulcerate and dry to form crusts and scabs. Lesions in all stages of development (macules, papules, vesicles, ulcers, and crust) are characteristic of varicella. Lesions during chronic VZV

infection are varicelliform at onset but may evolve into non-healing, necrotic and crusted ulcers that become hyperkeratotic [5].

The classical clinical presentation of zoster (a painful localized cutaneous vesicular eruption along one or more contiguous dermatomes) is diagnostic. Lesions evolve over 1 to 2 days to form vesicles, pustules, and crusts. In HIV-infected patients, zoster may be bullous, haemorrhagic, necrotic, and particularly painful. Blisters and crusts usually last 2- 3 weeks, although necrotic lesions may last up to 6 weeks and heal with severe scarring. Zoster in HIV-infected children may also present as an atypical rash that extends beyond dermatomal boundaries or is bilaterally distributed or generalized, or as multiple episodes of a disseminated rash more similar in appearance to chickenpox than zoster [3].

Varicella pneumonitis in HIV-infected children is associated with severe pulmonary manifestations resulting in hypoxaemia and diffuse reticulo-nodular densities on radiography. Encephalitis occurs more frequently with zoster in the ophthalmic distribution, and cerebellar findings are typical; prominent symptoms include ataxia, tremors, and dizziness. Cerebral involvement results in fever, headache, vomiting and lethargy [6].

Diagnosis

The diagnosis of VZV infection is often suspected from the clinical presentation. Direct immunofluorescence expressed on the surface of infected cells from scrapings obtained from the base of skin, conjunctiva, or mucosal lesions allow VZV antigen detection, and is the diagnostic procedure of choice. Direct and indirect immunofluorescence or immunoperoxidase methods can also detect antigen in VZV-infected cells in tissue sections of lung, liver, brain, or other organs.

Treatment

Aciclovir is the drug of choice for treatment of VZV infection in HIV-infected children. With primary varicella, acyclovir should be initiated as soon as initial lesions appear and may be administered intravenously in moderate to severely immunosuppressed children with high fever or numerous or deep, necrotic, or haemorrhagic skin lesions. Oral acyclovir should be used only for treatment of primary varicella in HIV-infected children with normal or only slightly decreased CD4+ cell counts. Oral aciclovir is the treatment of choice for zoster in HIV-infected children since disseminated disease occurs less often with zoster than varicella. Intravenous administration can be considered for severely immunosuppressed children with trigeminal nerve involvement or extensive multidermatomal zoster.

Children who continue to develop lesions or whose lesions fail to heal may be infected with aciclovir-resistant VZV and can be treated with intravenous foscarnet. Valaciclovir is not active against acyclovir-resistant VZV strains but is approved for treatment of zoster in adults. Data are limited for use in children.

Specific Doses

Varicella

Children with moderate or severe immune suppression, high fever or necrotic lesions IV:

Acyclovir: 10-20 mg/kg three times daily X 7 days after no new lesions.

Surface area dosing tds more accurate: 10mg/kg or 250mg/m² and 20mg/kg or 500mg/m².

Children with mild immune suppression and mild oral disease:

Acyclovir 20 mg/kg oral (max: 200 mg/dose) four times daily X 7 days after no new lesions.

Zoster

Children with severe immune suppression, trigeminal nerve involvement or extensive multidermatomal zoster IV:

Aciclovir: 10-20 mg/kg IV three times daily X 7–10 days.

Children with mild immune suppression and mild disease oral:

Aciclovir: 20 mg/kg PO (max: 200 mg/dose) four times daily X 7–10 days.

For patients not responding to acyclovir:

Foscarnet 40–60 mg/kg IV three times daily X 7–10 days.

Valaciclovir is approved for use in adult and adolescents with zoster at a dose of 1 gram PO BD X 7–10 days; data on dosing in children is limited.

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Treatment Guidelines by OI; Molluscum Contagiosum

Background

Is caused by a poxvirus, which is spread by direct contact or by fomites, such as towels. Lesions may disseminate by autoinoculation. Infectivity is generally low,

but occasional outbreaks can occur. The eruption is common to immunocompetent children whose lesions are scattered widely over the face, arms, and trunk. Immunocompromised children tend to develop more intense and widespread eruptions. The prevalence among HIV-infected subjects ranges from 10-20% [1].

Clinical Manifestations

Molluscum contagiosum is characterized by usually 2-20 discrete, 5 mm-diameter, flesh-coloured, dome-shaped papules, some with central umbilication. Lesions commonly occur on the trunk, face, and extremities. An eczematous reaction encircles the lesions in approximately 10% of patients. In HIV-infected children the lesions often number greater than 100 with a predilection for the eyelids [2].

The diagnosis usually can be made clinically. Wright or Giemsa staining of cells expressed from the central core of a lesion reveals characteristic intracytoplasmic inclusions.

Treatment

Children with single or widely scattered lesions need not be treated as lesions usually regress spontaneously. Mechanical removal of the central core of each lesion may result in more rapid resolution with application of a topical anesthetic before the procedure. Alternatively, topical application of cantharidin (0.7% in collodion); peeling agents, such as salicylic and lactic acid preparations; electrocautery; or liquid nitrogen may also remove the lesions. Treatment may prevent autoinoculation and spread to other people. Scarring occurs rarely. No control measures are known for isolated cases. For outbreaks, which are common in the tropics, restricting direct person-to-person contact and sharing of potentially contaminated fomites may decrease spread.

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