The Child with HIV and Respiratory Illness

Author: Andrew Riordan, updated by Steve Welch
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Content
1. Introduction
2. HIV staging
3. Past medical history
4. Highly active antiretroviral therapy
5. Examination
6. Causes of respiratory illness
7. Initial investigations
8. Management
   8.1. Fungal infections
      8.1.1. *Pneumocystis jiroveci* Pneumonia
   8.2. Bacterial infections (non-mycobacterial)
      8.2.1. Pneumonia
   8.3. Viral infections
      8.3.1. Cytomegalovirus (CMV)
      8.3.2. Influenza
      8.3.3. Other viral infections
   8.4. Mycobacterial disease – *Mycobacterium tuberculosis*
   8.5. Non-tuberculous mycobacterial disease
   8.6. Lymphocytic interstitial pneumonitis
9. Nursing care
10. References

1. Introduction
Children with HIV infection are told to come to hospital if they become unwell. This is usually either because they have a fever, vomiting and diarrhoea, or a chest infection. These guidelines are for the child with respiratory illness.
Children with HIV have a considerably increased risk of bacterial infections. General principles are: treat with antibiotics earlier, with higher doses for longer courses.

2. HIV staging
   - Note the stage of the child’s HIV disease
   - The more severely immunosuppressed the more likely to have minimal signs and serious pathology
   - Look in notes or on results system for recent letters and CD4 count
   - All infants (<12 months) are at risk of severe respiratory illness irrespective of CD4 count
   - In older children the risk of severe infection may be assessed by the child’s CD4 count and age

<table>
<thead>
<tr>
<th>Classification of HIV-associated immunodeficiency</th>
<th>Age-related CD4 Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 11 months</td>
</tr>
<tr>
<td>None or not significant</td>
<td>&gt; 35</td>
</tr>
<tr>
<td>Advanced</td>
<td>25–29</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 25</td>
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</tbody>
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3. Past medical history
   - Past history from parents or clinic letters (parents may find it difficult to reiterate history due to stigma)
   - Take a good history of the current illness
   - Immunisation history
   - Ask about known TB contact
• Travel history (including malaria prophylaxis)
• Is the child on prophylaxis against PcP, and has adherence been good?

4. **Highly active antiretroviral therapy**
   • It is important to ensure that antiretroviral drugs have been given and tolerated while the child is unwell.
   • What medication is child taking?
   • Has child missed any doses?
   • Has child vomited doses? If vomited within 1 hour of dose – should be given again. If unable to take, or keep down medication, need to admit and give via NGT. Ondansetron can be given prior to dose in order to give best chance of tolerating medication.
   • Liquid medication is often large in volume – if not tolerating liquids with ondansetron consider use of crushed tablets.
   • Viral load will increase and resistance to drugs will develop if antiretroviral drugs are not given regularly.

5. **Examination**
   • Examine the child thoroughly
   • Signs of other pathology may be masked

6. **Causes of respiratory illness**

   Co-infection is common in HIV. Children with advanced HIV and serious respiratory disease are more likely to have multiple pathogens than a single organism.

   See table below
### Minimal immunosuppression

**Pneumocystis jiroveci Pneumonia (PcP)**

### Bacterial Pneumonia

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*

### Mycobacterial disease

**Mycobacterium Tuberculosis**

### Viral infections

- Cytomegalovirus
- Measles
- Adenovirus
- Parainfluenza
- Influenza
- Respiratory syncitial virus (RSV)
- Varicella
- Herpes Simples

### Lymphocytic Interstitial Pneumonitis

Medication (see below)

### In severe immunosuppression also

**Bacterial pneumonia**

- *Staphylococcus aureus*
- Gram-negative infections
- esp *Pseudomonas aeruginosa*

**Non-Tuberculous Mycobacterial Disease**

- *Mycobacterium avium complex* (MAC)

**Fungal infections**

- Aspergillosis
- Histoplasmosis
- *Candida*
- Nocardia

**Congestive cardiac failure**

- Cardiomyopathy/cor pulmonale

**Malignancy**

- Kaposi’s Sarcoma
- Leiomyoma
- Leimyosarcomas
- Lymphoma

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**WHO Stage IV (AIDS-defining) illnesses include**

- Pneumocystis pneumonia
- Recurrent severe bacterial infections (e.g. empyema, but excluding pneumonia)
- Extrapulmonary/disseminated tuberculosis
- Kaposi’s sarcoma

**Cytomegalovirus infection**
- Disseminated non-tuberculous mycobacteria infection
- HIV associated tumours

**HIV-associated cardiomyopathy**

**Medication**

Children recently started on HAART may develop respiratory symptoms. Abacavir hypersensitivity may present as a respiratory illness soon after starting the drug, but the frequency of this is greatly reduced with HLA testing before starting abacavir therapy.

Respiratory symptoms may be caused by immune reconstitution inflammatory syndrome (IRIS) in children after starting ART.

7. **Initial investigations**

All HIV-infected children with respiratory symptoms should have the following investigations:

- Chest x-ray
- Oxygen saturations
- FBC
- CRP
- Blood cultures

Other investigations should be conducted depending on the clinical situation (see management below).

8. **Management**

8.1. **Fungal infection**

Severe fungal respiratory infections should be considered in children with HIV infection and severe immunosuppression however, samples may be falsely positive, and expert advice should be sought before starting prolonged potentially toxic treatments.

8.1.1. *Pneumocystis jiroveci* Pneumonia (PcP)

PcP is life-threatening in children with HIV.

PcP accounts for 40-50% of category C diagnoses.
PcP is more common in children less than 1 year (72% of cases), at which age CD4 count is not a good indicator of PcP risk. PcP is less common in older children without severe immune suppression. In susceptible children, cotrimoxazole prophylaxis is highly effective at preventing PcP ONLY IF adherence is good. PcP may often be the presenting illness in a child not previously known to have HIV.

- **Clinical**

The clinical features of PcP are tachypnoea, dyspnoea, cough and fever. The onset may be insidious over 1-2 weeks with slowly increasing tachypnoea. All will be tachypnoeic by the time the CXR is abnormal. Coughing is not usually prominent until the full clinical picture develops with severe dyspnoea. Physical findings are usually limited to fine crepitations. Fever is often low grade. Hypoxia is common, with saturations in air often 80-90%. A rapidly progressive course of disease leading to respiratory failure in a few days has also been described. The CXR may be normal or hyperinflated early in the disease, but there are usually perihilar infiltrates. The aevolar infiltrates progress peripherally with late apical sparing. Occasionally bullae, cysts and pneumothoraces may be seen.

- **Diagnosis**

In infants the diagnosis can sometimes be obtained from an NPA, but bronchoscopy with bronchoalveolar lavage (BAL) is the optimum method for diagnosing PcP in children. If BAL cannot be performed straight away, then start treatment pre BAL (can obtain positive results up to 72 hours after starting treatment doses of Cotrimoxazole). Microbiology must be informed prior to the BAL/NPA and the specimen must be sent there directly.
As PcP is a category C defining diagnosis, it is very important to make a definitive diagnosis even after commencing treatment.

- **Treatment**

The recommended initial treatment of PcP is intravenous cotrimoxazole 60mg/kg given 12 hourly, infused over one hour (See BNFc).

It is not unusual for the child to deteriorate clinically for a few days after commencing therapy, and then significantly improve by one week. Beware of the slow onset of pneumothorax, and maintain a low threshold for repeat CXR if there is clinical deterioration.

The course is 21 days and the cotrimoxazole should ideally be given intravenously for at least 2 weeks (Consider long line insertion).

Side effects from cotrimoxazole are not infrequent, an erythematous rash being the commonest which resolves on stopping the drug. An urticarial rash or signs of Stevens-Johnson syndrome, require immediate discontinuation of the drug forever. Gastrointestinal disturbance and bone marrow suppression also occur, so monitor FBC.

If there is failure to respond to Cotrimoxazole after 5-7 days, or a hypersensitivity reaction to the drug, treatment should be changed to intravenous pentamidine isethionate (once daily, 4 mg/kg/day) by slow infusion, for 3 weeks. Side effects include renal impairment, neutropenia, thrombocytopenia, hepatitis and early hypoglycaemia with late development of insulin dependent diabetes.

Other treatments are less well studied in children (e.g. dapsone and trimethoprim, inhaled pentamidine, clindamycin and primaquine, atovaquone). Discuss these with an HIV paediatrician.

- **Steroids**

Studies in adults and children have demonstrated a reduced morbidity and mortality in PcP with early use of corticosteroids. Methyl prednisolone should be given to children with PcP and moderate or severe pulmonary dysfunction (PaO2 <70 mm Hg or an alveolar-arterial gradient of >135 mm Hg). The recommended regimen for intravenous methyl prednisolone is 1 mg/kg/dose.
twice daily for 5 days, then 0.5 mg/kg/dose twice daily for 5 days then 0.5 mg/kg/dose once daily for 5-10 days. This can be changed to oral prednisolone in the same doses when oral feeding starts.

- **Other Pathogens**

Failure to respond to cotrimoxazole alone should raise the possibility of a second treatable infection and repeat BAL or lung biopsy should be considered. Coinfection with CMV or respiratory viruses is common.

8.2. Bacterial Infections (non-mycobacterial)

8.2.1. Pneumonia

The commonest clinically diagnosed serious bacterial infections are acute pneumonia and bacteraemia. The frequency of bacterial infection increases with HIV disease progression and immunosuppression. Even with successful antiviral treatment, bacterial infections, especially pneumococcal pneumonia, remain more common than in uninfected children.

- **Clinical**

The clinical presentation of acute bacterial pneumonia in children with early HIV infection is similar to non-infected children. Clinical signs may be less obvious in children with HIV and fever and WBC may be lower. It is always important to obtain blood cultures.

- **Treatment**

Initial treatment should be with IV cefotaxime 200 mg/kg/day until there is a clinical response. If the child does not improve quickly (24 hours) add azithromycin (10 mg/kg/OD for 5 days). If there is hypoxia or no clinical improvement in 48 hours then a bronchoscopy should be organised. If there is a good clinical response, continue the IV antibiotics for at least 10 days. Relapses, especially with pneumococcal infection are common. Co-amoxiclav, or a five-day course of azithromycin, is a good option if there are concerns about compliance. Always use the highest antibiotic dose for age.

8.3. Viral Infections

8.3.1. Cytomegalovirus (CMV)
CMV is shed asymptomatically in secretions by one third of HIV infected children. Disseminated CMV infection is an important category C defining diagnosis in HIV-infected children. Patients with disseminated CMV disease are viraemic and may have retinitis, radiological evidence of CMV pneumonia, a rash and hepatitis. CMV viraemia should be sought for by sending a blood PCR for CMV. The role of CMV in respiratory infection is unclear as it is often found with other pathogens (PcP). Patients with proven disseminated CMV disease should be treated with Ganciclovir. A two-week induction phase of 5mg/kg every 12 hours intravenously, is followed by a prolonged maintenance phase of 5 mg/kg/day given 3-7 days/week or consider oral valganciclovir. Monitor regular FBC as neutropenia is common with ganciclovir.

8.3.2. Influenza
HIV-infected individuals were not severely affected during the 2009 H1N1 swine flu pandemic, but they probably do mount suboptimal immune responses. Making a diagnosis of influenza of any type should be considered early in the course of a respiratory illness in an HIV-infected child, and samples should be taken for diagnosis, and treatment with oseltamivir offered according to the results or whilst they are pending if there is a high clinical suspicion and the child is significantly unwell.

8.3.3. Other Viral Infections
Common respiratory viruses may cause mild or severe disease in children with HIV, depending on age and CD4 count. It is important to consider coinfection with PcP (see above) in a child with disease that does not improve. Measles or varicella may cause severe pneumonitis, and varicella should be treated with intravenous aciclovir. RSV infection may result in prolonged shedding of the virus, and may be complicated by bacterial superinfection requiring antibiotic treatment. Ribavirin is not highly effective, but may be considered in severe RSV.

8.4. Mycobacterial Disease – *Mycobacterium tuberculosis*
• **Clinical**

HIV infected children have an increased risk of TB. The diagnosis of TB in children remains difficult whether or not they are infected with HIV. Symptoms may be non-specific (fever, weight loss) and range from a persistent cough to apathy and lethargy in disseminated disease. CXR signs include hilar lymphadenopathy, segmented or lobar disease, atelectasis, effusions or miliary shadowing. Extrapulmonary disease is rare.

Every attempt should be made to obtain sputum for mycobacterial culture if TB is suspected. Culture is the gold standard for TB diagnosis, allowing drug sensitivity patterns to be established but culture positive rates of only 30-50% are usual. Three gastric lavage cultures are more sensitive than 1 broncho-alveolar lavage culture.

*Mantoux* and gamma interferon tests may help in making a diagnosis, but neither test is sensitive or specific enough to confirm or refute a diagnosis of active TB.

• **Management**

Treatment for TB is the same as for HIV negative children; rifampicin and isoniazid for 6 months with pyrazinamide and ethambutol for first 2 months only. Check sensitivities of the organism (from the adult contact or the child). If there is resistance to one of the 4 drugs used, seek advice.

If the child is on anti-retroviral therapy, discuss with an HIV paediatrician.

**8.5. Non-tuberculous mycobacterial disease**

Disseminated non-tuberculous mycobacterial disease (DNTM), is associated with severe immunosuppression (CD4 count <50/mm³). 90% of cases are due to *Mycobacterium avium* intracellulare complex (MAC). Median survival of children from diagnosis is 6 months.

These children should be discussed with an HIV paediatrician.

Respiratory symptoms are uncommon. The clinical features usually include prolonged fever, bone marrow suppression, weight loss and chronic GI symptoms. In patients with DNTM, MAC may be isolated from the lungs.
Radiological presentation can occur with enlarged hilar lymph nodes. Treatment should be discussed with an HIV paediatrician. It involves a complex multi drug regime of ethambutol, rifabutin and clarithromycin. If the clinical presentation is suspected then mycobacterial blood cultures should be taken using the special bottles available from microbiology. Also send sputum and stool for mycobacterial culture.

8.6. Lymphocytic Interstitial Pneumonitis

- **Clinical**

  The onset of LIP is usually **slow**, characterised by a chronic cough in children, often with evidence of generalised lymphadenopathy, bilateral parotid enlargement and hepatosplenomegaly. Many children are asymptomatic initially and the diagnosis is most frequently made on a routine CXR, or a CXR taken when the child presents with an acute lower respiratory tract infection (ALRTI). Having LIP leads to an increased frequency of ALRTI. Although a definitive diagnosis of LIP requires a lung biopsy, the presence of a widespread reticulonodular shadowing (1-5 mm diameter) in a well child, with or without hilar lymphadenopathy, persisting on a CXR for greater than 2 months, which does not respond to antibiotics can be considered as presumptive evidence for LIP.

9. **Nursing care**

- Ensure the paediatric HIV team are aware the child/young person is being seen at the earliest possible time point.
- Find out from notes/HIV team or parent/carer (alone without child) if child/young person is aware of their HIV diagnosis. Ensure other team members are aware.
- Check if the child is on HAART and has their medications with them.
- Ensure child or young person and parent understands the information they have been given.

10. **References**

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