What is aetiology of pneumonia in HIV-infected children in developing countries?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is The Aetiology Of Pneumonia In HIV-Infected Children In Developing Countries?*

In 2003, the WHO published a meeting report on the importance of pneumonia in children with human immunodeficiency virus (HIV).[1] The authors stressed difficulty in identifying the aetiology as a major hindrance to delivering appropriate treatment. Based on studies from six African countries the meeting report suggested that Streptococcus pneumoniae and Haemophilus influenzae were the most frequent causes of pneumonia. Pneumocystis jiroveci (previously Pneumocystis carinii) was considered to be the most important pathogen in severe pneumonia.

This systematic review has performed a thorough search amongst the published literature to substantiate or refute the findings from that meeting report.

INTRODUCTION

HIV infection is prevalent among children in many developing countries, particularly in Sub-Saharan Africa where more than two thirds of the global HIV-infected population live.[2] The majority of HIV-infected children develop some form of respiratory disease during the course of their illness and most frequently this is pneumonia.[3,4] Pneumonia has a significant impact on the morbidity and mortality of HIV infected children. It is crucial to identify the pathogens commonly involved and thereby guide patient management and plan preventative measures such as vaccination programmes.

METHODOLOGY

The PubMed data base was searched for English language papers using the 'broad, sensitive scope' and filtered by the category 'etiology'. Both the 'find systematic reviews' and 'search by clinical study category' in the clinical queries section were selected.

The following key words, MeSH terms, synonyms and truncations were used:
("Pneumonia"[MeSH] OR Pneumon* OR pulmon* OR lower respiratory tract infection OR bacteraemia OR sepsis OR septic*) AND ("HIV Infections"[MeSH] OR HIV OR human immunodeficiency syndrome OR AIDS OR acquired immune deficiency syndrome) AND (child* OR pedia* OR paedia* OR neonat* OR infant*)

To obtain additional studies the Cochrane Library, Web of Science, EMBASE and the Global Health Database were searched. Additionally, a cited reference search was performed.

Studies where included provided they identified bacterial, viral or fungal pathogens in children diagnosed with both pneumonia and HIV.

To ensure that the findings were relevant only those conducted in developing countries were included. Due to the limited number of studies available it was decided to also include post mortem studies of HIV-infected children provided a significant proportion had died from a respiratory cause.

This review intended to find whether there was any variation in the range of pathogens causing pneumonia in HIV-infected children when compared to non-infected. Studies were included provided the HIV-status of the children was known.

RESULTS

13 studies from the original search matched the inclusion criteria and a further 3 studies were obtained from the cited reference search, giving a total of 16 studies. There were 8 prospective clinical studies, one of these studies (Ruffini DD et al, 2002) included data on a subset of the children that died.

All the prospective studies had classified pneumonia, severe pneumonia and acute lower respiratory tract infection (LRTI) in accordance with the WHO criteria. For severe pneumonia these criteria are: cough and difficulty breathing with lower chest wall in-drawing and a respiratory rate of >50/min in children aged 2-11 months and >40/min in children aged 12-59 months.[5]

The diagnostic tests used varied widely from blood cultures to a combination of induced sputum (IS), nasopharyngeal aspirate (NPA) and broncho-alveolar lavage (BAL). The validity of nasopharyngeal aspirates (NPA) in determining bacterial aetiology is doubtful and NPA sampling was therefore only included for viral/fungal pathogens. Only BAL and lung aspirates were considered valid respiratory specimens for determining bacterial aetiology.

Bacterial pathogens

Blood culture results from the prospective clinical studies identified S. pneumoniae (7.4%) and S. aureus (2.4%) as the gram positive bacteria most frequently causing pneumonia in the HIV-infected group (Table 1). This was also true for the HIV

negative children although at lower rates (S. pneumoniae 2.8%, S. aureus 1.1%).

Blood cultures probably underestimate the true prevalence of bacterial pathogens, yet only two studies looked at valid respiratory specimens. The study by Zar et al (2001) found S. aureus (14.6%) and S. pneumoniae (1.3%) to be the most prevalent gram positive bacteria using IS and BAL (Table 2). The study by McNally et al (2007) isolated higher rates (S. aureus 17.2%, S. pneumoniae 11.5%) using a wider range of sampling techniques. It is worth noting that the data from the McNally study is based on a subset of children that failed the initial therapy. The post mortem data supported the findings from the clinical studies: again S. aureus (2.3%) and S. pneumoniae (2.3%) were the most commonly found gram positive bacteria. (Table 3)

H. influenzae (1.8%), E.coli (0.8%) and Salmonella species (0.7%) were the gram negative bacteria most frequently isolated in blood cultures from HIV positive children. However, there was a wide spread in occurrence ranging from 3.5% H.influenzae in the study by Madhi et al (2000) to none in the study by Nathoo et al (1993). Interestingly, Klebsiella species was the most frequently isolated gram negative bacteria from valid respiratory specimens in the HIV positive children by both Zar (10.9%) and McNally (9.2%). The post mortem studies confirmed the importance of Klebsiella species (8.3%) whilst also identifying relatively high rates of Pseudomonas species (3.1%) and E .coli (2.6%).

Mycobacterium tuberculosis

Only two clinical studies successfully isolated M. tuberculosis. Zar et al (2001) reported high rates amongst both HIV-positive (7.3%) and HIV negative children (8.1%) and McNally et al (2007) reported even higher rates of M. tuberculosis amongst children who failed standard antibiotic treatment: 20.7% in HIV-positive and 26.1% in HIV-negative children. Overall, the post mortem studies confirmed the importance of M. tuberculosis although there were major variations with Chintu et al (2002) isolating 16.9% in HIV infected and 21.3% in HIV negative children, whilst Lucas et al (1996) identified none in the relevant age group.

Viral pathogens

The few clinical studies that performed virology found cytomegalovirus (CMV), respiratory syncytial virus (RSV) and influenza virus to be the most prevalent (Table 2). Several of the post mortem studies reported on viral pathogens and found CMV to be more prevalent in HIV-positive compared with HIV-negative children.

Fungal pathogens

The clinical study by Zar et al (2001) isolated P. jiroveci in 9.9% of HIV-infected vs. only 4.0% in HIV-negative children, similarly Graham et al (2001) found 17.0% P. jiroveci amongst HIV-infected and no isolates in the HIV-negative children (Table 2). The post mortem studies also found a higher proportion of P .jiroveci in the HIV-positive pneumonia patients (20.6%) when compared with HIV-negative (2.1%).

DISCUSSION

The studies differed greatly in their sampling protocols and this combined with the inevitable variability in the microbiology influences the range of pathogens identified by the studies. Whether the failure to identify a certain pathogen was because it was not present or not recognised due to technical limitations is uncertain.

Obtaining high quality information on the pathogens most likely to cause pneumonia in HIV-infected children is important. It would be valuable to conduct a multi-centre study with standardised sampling and processing methodology. It would also be highly worthwhile to study the aetiology in HIV-epidemic regions outside of Africa.

SUMMARY

Based on the available data it is clear that bacterial pathogens remain the most common cause of pneumonia in HIV-infected children. The WHO makes the following recommendations for management of pneumonia in HIV infected children [1]:

Non-severe pneumonia (0-5yrs)

- Oral amoxicillin as first-line antibiotic. Oral cotrimoxazole is also recommended, but should ideally not be used routinely as this will encourage resistance and diminish its effectiveness against P. jiroveci.
- Regular follow-up to monitor progress.

Severe pneumonia (2-11 months)

- Hospitalise and administer intravenous antibiotic: ampicillin/penicillin + gentamicin or oral amoxicillin + gentamicin.
- Treat for P. jiroveci with intravenous cotrimoxazole.
- If not improving within 72 hrs change to second-line antibiotic: ceftriaxone
- Give oxygen if signs of hypoxaemia

Severe pneumonia (12-59 months)

- Hospitalise and administer intravenous antibiotic: ampicillin/penicillin + gentamicin or oral amoxicillin + gentamicin.
- Treat for P. jiroveci if clinically indicated
- If not improving within 72 hrs change to second-line antibiotic: ceftriaxone
- Give oxygen if signs of hypoxaemia

Health care workers in hospitals where resources are limited are required to investigate and manage children with pneumonia predominantly using clinical guidelines to guide treatment decisions; laboratory based diagnostic technology is rarely available. Treatment guidelines should reflect the pathogens that commonly cause pneumonia in HIV-infected children.

The few studies on the aetiology of pneumonia amongst HIV-infected children in developing countries have identified S. pneumoniae, S. aureus, H. influenzae and Klebsiella species as the major bacterial pathogens in HIV-infected children. HIV-negative children are affected by the same pathogens although at lower rates. The post mortem studies showed similar results except that H. influenzae is slightly less prominent. M. tuberculosis was prevalent regardless of HIV status, reflecting its significance in this region. From the limited data available RSV and parainfluenza appears to be the most prevalent viral causes of pneumonia. P. jiroveci is an additional important pathogen in HIV-infected children.

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