

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 children¹:

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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Table 1 Blood cultures from pneumonia patients in clinical studies (%)

	Madhi SA ^{6,§}		Graham SM ⁷		Nathoo KJ ^{8,π}		McNally LM ^{9,ψ}		Zar HJ ^{10,χ}		Total [∂]	
Pathogen	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ N (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)
No of patients	548	617	93	57	219	485	242	116	151	99	1102	1275
Age (months)	2-60	2-60	2-60	2-60	1-60	1-60	1-59	1-59	3-23•	2-7•		
Gram +ve												
<i>S. pneumoniae</i>	41 (7.5)	17(2.8)	4 (4.3)	4 (7.0)	12(5.5)	13 (2.7)	24 (9.9)	2 (1.7)			81 (7.4)	36 (2.8)
<i>S. aureus</i>	10 (1.8)	4 (0.6)			5 (2.3)	5 (1.0)	11 (4.5)	5 (4.3)			26 (2.4)	14 (1.1)
Group B strep	1 (0.2)	1 (0.2)	1 (1.1)	0 (0)							2 (0.2)	1 (0.1)
Other Gram +ve					4 (1.8)	8 (1.6)	18 (7.4)	14(12.1)			22 (2.0)	22 (1.7)
Total Gram +ve	52 (9.5)	22 (3.6)	5 (5.4)	4 (7.0)	21(9.6)	26 (5.4)	53 (21.9)	21 (18.1)	11(7.3)	8 (8.1)	131 (11.9)	73 (5.7)
Gram –ve												
<i>H. influenzae</i>	19 (3.5)	11(1.8)			0 (0)	3 (0.6)	1 (0.4)	1 (0.9)			20 (1.8)	15 (1.2)
<i>E. coli</i>	7 (1.3)	1 (0.2)					2 (0.8)	1 (0.9)			9 (0.8)	2 (0.2)
<i>Salmonella spp</i>	3 (0.5)	3 (0.5)	3 (3.2)	4 (7.0)	1 (0.5)	3 (0.6)	1 (0.4)	0 (0)			8 (0.7)	10 (0.8)
Coliforms					6 (2.7)	21 (4.3)					6 (0.5)	21 (1.6)
<i>Klebsiella spp</i>	0 (0)	2 (0.3)			2 (0.9)	8 (1.6)	1 (0.4)	1 (0.9)			3 (0.3)	11 (0.9)
<i>H. influenzae B</i>			2 (2.2)	1 (1.8)							2 (0.2)	1 (0.1)
<i>Pseudomonas spp</i>					1 (0.5)	2 (0.4)	0 (0)	1 (0.9)			1 (0.1)	3 (0.2)
<i>N. meningitidis</i>	1 (0.2)	2 (0.3)									1 (0.1)	2 (0.2)
Other Gram –ve			2 (2.2)	0 (0)	1 (0.5)	4 (0.8)	3 (1.2)	0 (0)			6 (0.5)	4 (0.3)
Total Gram –ve	30 (5.5)	19 (3.1)	7 (7.5)	5 (8.8)	11 (5.0)	41 (8.5)	8 (3.3)	4 (3.4)	9 (6.0)	7 (7.1)	56 (5.1)	69 (5.4)
Fungi												
<i>C. albicans</i>							0 (0)	1 (0.9)			0 (0)	1 (0.1)

[§] Study excluded 50 children with 'indeterminate HIV-status'

^π HIV diagnosed on clinical grounds

^ψ HIV negative includes 41 children that were HIV exposed but uninfected.

^χ Study did not give specific blood culture results according to HIV status, but stated that findings were similar in both groups. Overall, they found *S. pneumoniae* in 12 children (4.8%) and *S. aureus* in 5 children (2.0%).

• 25th-75th percentile

∂ Excluding the Zar study as this only provided blood culture results grouped as total Gram +ve and Gram –ve

Table 2 Respiratory samples from pneumonia patients in clinical studies (%)

	Zar HJ ^{10,x}		Madhi SA ^{11,λ}		Graham SM ^{7,λ}		McNally LM ^{9,δ}		Ruffini DD ^{12,∞}		Bakeera-Kitaka S ^{13,∞}		Total	
Pathogen	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)
No of patients	151	99	442	548	93	57	87	23	105	0	43	78	921	805
Age (months)	3-23•	2-7•	2-60	2-60	2-60	2-60	1-59	1-59	2-24		2-60	2-60		
M. tuberculosis Gram +ve	11 (7.3)	8 (8.1)					18 (20.7)	6 (26.1)					29 (3.1)	14 (1.7)
S. aureus	22 (14.6)	3 (3.0)					15 (17.2)	5 (21.7)					37 (4.0)	8 (1.0)
S. pneumoniae	2 (1.3)	4 (4.0)					10 (11.5)	2 (8.7)					12 (1.3)	6 (0.7)
Other Gram +ve							8 (9.2)	1 (4.3)					8 (0.9)	1 (0.1)
Gram –ve														
Klebsiella spp	16 (10.9)	14 (14.1)					8 (9.2)	1 (4.3)					24 (2.6)	15 (1.9)
H. Influenzae	13 (8.6)	12 (12.1)					5 (5.7)	4 (17.4)					18 (2.0)	16 (2.0)
Pseudomonas spp	12 (7.9)	3 (3.0)											12 (1.3)	3 (0.4)
E. coli							7 (8.0)	1 (4.3)					7 (0.8)	1 (0.1)
M. catarrhalis	4 (2.6)	5 (5.1)											4 (0.4)	5 (0.6)
Salmonella spp							2 (2.3)	0 (0)					2 (0.2)	0 (0)
Legionella spp							1 (1.1)	0 (0)					1 (0.1)	0 (0)
Other Gram –ve	2 (1.3)	8 (8.1)					10 (11.5)	3 (13.0)					12 (1.3)	11 (1.4)
Virus														
CMV	21 (13.9)	10 (10.1)					40 (46.0)	4 (17.4)					61 (6.6)	14 (1.7)
RSV			23 (5.2)	90 (16.4)			8 (9.2)	5 (21.7)					31 (3.4)	95 (11.8)
Influenza virus			22 (5.0)	48 (8.8)									22 (2.4)	48 (6.0)
Parainfluenza			17 (3.8)	32 (5.8)									17 (1.8)	32 (4.0)
Adenovirus			7 (1.6)	10			6 (6.9)	3					13 (1.4)	13

Other virus	2 (1.3)	4 (4.0)	(1.8)		9 (10.3)	2 (8.7)	(13.0)			11 (1.2)	6 (0.7)	(1.6)
Fungi												
<i>P. jiroveci</i>	15 (9.9)	4 (4.0)		16 (17.0)	0 (0)	26 (29.9)	3 (13.0)	51(48.6)	18(41.9)	2 (2.6)	126 (13.7)	9 (1.1)
<i>Aspergillus</i> spp						1 (1.1)	0 (0)				1 (0.1)	0 (0)
Other fungi						2 (2.3)	0 (0)				2 (0.2)	0 (0)

• 25th-75th percentile

χ Bacteria isolated from IS and BAL. Viral/*P. jiroveci*/mycobacterium culture from combination of NPA, IS and BAL.

λ Isolated from NPA

∂ Only includes the subset of study population that failed to respond to therapy. Combined results from blood culture, NPA, gastric washing, non-bronchoscopic BAL, lung aspirate, pleural aspirate. Excluded bacterial isolates from nasopharyngeal swabs and IS.

∞ Isolated from NPA and IS

Table 3 Pathogens identified from lung in post mortem studies (%)

Pathogen	Chintu C ^{14,§}		Nathoo KJ ^{15,π}		Wolf BH ^{16,β}		Jeena PM ^{17,ψ}		Lucas SB ^{18,§}		Ansari NA ^{19,§}		Rennert WP ^{20,§}		Ikeogu MO ^{21,γ}		Ruffini DD ^{12,π}		Total	
	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)	HIV+ n (%)	HIV- n (%)
No of patients	130*	61*	24	0	122	90	36	36	36**	29**	35	12	93	0	122	62	18	0	616	290
Age (months)	1-17	1-17	<6		0-60	0-60	1-18	1-18	1-14	1-14	1m-13y ^λ	1m-13y ^λ	1-70		1-55	1-42	2-24			
<i>M. tuberculosis</i>	22 (16.9)	13 (21.3)	0 (0)	0 (0)			1 (2.7) [§]	0 (0) [§]	0 (0)	0 (0)	4 (11.4)	1 (8.3)	4 (4.3)	-	6 (4.9)	2 (3.2)	1 (5.6)	-	38 (6.2)	16 (5.5)
Gram +ve																				
<i>S. aureus</i>			3 (12.5)	-	2 (1.6)	3 (3.3)	1 (2.8)	4 (11.1)							8 (6.6)	4 (6.5)			14 (2.3)	11 (3.8)
<i>S. pneumoniae</i>					3 (2.5)	1 (1.1)	0 (0)	1 (2.8)							10 (8.2)	4 (6.5)	1 (5.6)		14 (2.3)	6 (2.1)
Group A strep					3 (2.5)	2 (2.2)									3 (2.5)	2 (3.2)			6 (1.0)	4 (1.4)
Group B strep					1 (0.8)	0 (0)													1 (0.2)	0 (0)
Other Gram +ve					12 (9.8)	6 (6.7)	2 (5.6)	0 (0)							5 (4.1)	3 (4.8)			19 (3.1)	9 (3.1)
Gram -ve																				
<i>Klebsiella</i> spp			2 (8.3)	-	19 (15.6)	12 (13.3)	2 (5.6)	1 (2.8)							28 (23.0)	16 (25.8)			51 (8.3)	29 (10.0)
<i>Pseudomonas</i> spp					7 (5.7)	1 (1.1)	6 (16.7)	4 (11.1)							6 (4.9)	1 (1.6)			19 (3.1)	6 (2.1)
<i>E. coli</i>			4 (16.6)	-	11 (9.0)	4 (4.4)	1 (2.8)	0 (0)											16 (2.6)	4 (1.4)
Coliforms															8 (6.6)	7 (11.2)			8 (1.3)	7 (2.4)
<i>H. influenzae</i>					0 (0)	3 (3.3)	0 (0)	1 (2.8)							2 (1.6)	3 (4.8)	1 (5.6)	-	3 (0.5)	7 (2.4)
<i>Salmonella</i> spp					3 (2.5)	0 (0)	0 (0)	1 (2.8)									1 (5.6)		4 (0.6)	1 (0.3)
<i>Salmonella typhi</i>					1 (0.8)	0 (0)													1 (0.2)	0 (0)
<i>H. influenzae</i> B							0 (0)	1 (2.8)											0 (0)	1 (0.3)
Other Gram -ve					2 (1.6)	2 (2.2)	2 (5.6)	2 (5.6)							2 (1.6)	1 (1.6)			6 (1.0)	5 (1.7)
Virus																				
CMV	39 (30.0)	2 (3.3)	2 (8.3)	-			16 (44.4) [§]	1 (2.8) [§]	16 (44.4)	3 (10.3)	8 (22.9)	0 (0)	18 (19.4)	-	9 (7.4)	0 (0)	8 (44.4)	-	115 (18.7)	6 (2.1)
RSV							2 (5.6)	1 (2.8)			4 (11.4)	0 (0)					1 (5.6)		7 (1.1)	1 (0.3)
Parainfluenza							3 (8.3)	1 (2.8)											3 (0.5)	1 (0.3)
Adenovirus							2 (5.6) [§]	5 (13.8) [§]	0 (0)	1 (3.4)	1 (2.9)	0 (0)							3 (0.5)	6 (2.1)
Other virus							7 (19.4)	12 (33.3)					13 (14.0)						20 (3.2)	12 (4.1)

Fungi																			
<i>P. jiroveci</i>	47 (36.2)	6 (9.8)	6 (25.0)	-			16 (44.4) [§]	0 (0) [§]	11 (30.6)	0 (0)	10 (28.6)	0 (0)	10 (10.7)	-	19 (15.6)	0 (0)	8 (44.4)	127 (20.6)	6 (2.1)
<i>C. albicans</i>					1 (0.8)	0 (0)	1 (2.8) [§]	0 (0) [§]										2 (0.3)	0 (0)

* Subset of cohort (age 1-17months)

** Subset of cohort (age 1-14months)

§ Post mortem biopsy

β Post mortem blood culture

π Post mortem biopsy/blood culture

γ Post mortem biopsy/percutaneous lung aspirate

ψ Ante mortem blood culture

λ Median age 10 month

