

What are the clinical indicators of PCP?

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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 are the clinical indicators of PCP?*

The **WHO Pocketbook of Hospital Care for Children** recommends that PCP should be presumptively diagnosed in any child who has severe or very severe pneumonia and bilateral interstitial infiltrates on chest X-ray. Consider the possibility of pneumocystis pneumonia in children, known or suspected to have HIV, whose ordinary pneumonia does not respond to treatment. Pneumocystis pneumonia occurs most frequently in infants and is often associated with hypoxia. Fast breathing is the most common presenting sign, respiratory distress is out of proportion with chest findings, fever is often mild. Peak age is 4–6 months.

(Pocketbook chapter 8.4.2, page 216).

Introduction:

Prior to the introduction of cotrimoxazole prophylaxis, PCP was a common HIV-related disease in children in the US and Europe.^{1,2} As many as 43% of UK children with AIDS had PCP in 1994.² It was thought to be much less common in developing countries, particularly the sub-Saharan African region, where bacterial pneumonia or tuberculosis are the common causes of respiratory morbidity and mortality in HIV-infected individuals. While this is true for adults and older children²⁻⁵, many clinical and autopsy studies have now confirmed that PCP is a very common cause of severe pneumonia and death in HIV-infected infants in many developing

countries.⁶ PCP can often be the first indicator of HIV infection and case-fatality rate is very high in the resource-poor setting. Consequently it is imperative that PCP is diagnosed and treated as early as possible.

Methodology

Articles were identified via the PubMed Clinical Queries Framework. The search strategy used was 'pneumocystis AND (child* OR pedia* OR paedia*) AND (features OR indicators)', which was put through the filters 'diagnosis' and 'broad, sensitive'. This yielded 45 articles in English, of which 19 were selected on titles. 13 of these gave too broad an overview or focussed on adults. Six articles remained, including five prospective trials and one review. Citations listed in the six articles were also hand searched and reviewed, producing six further articles, including two reviews, two prospective patient studies and two prospective necropsy studies. All articles were written in developing countries. Three of the articles presenting prospective data were from the same group of study patients.⁷⁻⁹

Evaluation of diagnostic studies using the Oxford CBM LOE grading system proves more difficult than when assessing treatment studies. In lieu of this, the three reviews were assessed as 2a as they do not state search strategies, and the prospective studies to be 1b or 2b.

Results and Discussion

The three reviews^{6,10,11} discuss many of the studies reviewed here and cover a number of clinical indicators including age of onset, dyspnoea, hypoxia, co-infection, as well as investigative findings such as lower temperature, auscultative findings, radiological changes and biochemical changes. This value of findings in these three reviews is presented together with

evidence of studies that post-date them or are not included.

CLINICAL INDICATORS

Age at presentation

Prospective studies^{7,12-16} and necropsy studies¹⁷⁻²¹ from the sub-Saharan African region have consistently found that most cases of PCP occur in infants, especially those between 2 and 6 months of age. In the largest reported autopsy study of hospitalised children dying with severe pneumonia, Chintu et al reported PCP in 58 Zambian children, of which 51(88%) were younger than one year and 45 (78%) were under six months of age.²⁰ Fatti et al examined clinical indicators of PCP among HIV-infected South African children with pneumonia and found that age less than 6 months was the most significant, independent clinical marker (OR 15.6; 95% CI 2.4-99.8; p=0.004).⁹ The reports from the African region show a similar age-related pattern to that described in USA and UK.^{1,22,23}

Pneumocystis jiroveci is a ubiquitous fungus with low pathogenicity that repeatedly infects humans from early in life. The first clinical description of PCP was by Otto Jirovec in European infants with pneumonia and was associated with death before 6 months of age.²⁴ The most plausible explanation for the age-related incidence and severity of PCP relates to immunity. Most adults and older children will have had prior infection and consequent immunity and so severe immunosuppression is required before the host becomes susceptible to disease. PCP in that group is usually associated with a very low CD4 count. Primary infection is more likely to cause symptomatic disease in infants including in immunocompetent infants because of a lack of innate immunity as well as immaturity of the immune and respiratory systems. PCP is more severe and often fatal in those who are also immunocompromised e.g. HIV-infected or severely malnourished.

HIV status

PCP is strongly associated with HIV infection. PCP is often the first indicator of HIV infection and presentation in infants is not related to CD4 count.^{7,15,22,23} Of 340 HIV vertically-infected children born in UK and Ireland until 1998, PCP was the first AIDS indicator illness in 83 (24%); 82% of PCP cases presented before 6 months of

age and 91% before 12 months of age.²³ Many of these children were born to mothers who did not know their HIV status. In a study by Zar et al of South African infants, only 2 of the 15 cases with PCP were known to be HIV-infected at time of presentation and PCP was the indicator disease in 20% of all HIV-infected infants with pneumonia.^{7,8} Weight-for-age was significantly higher in those with PCP compared to those with pneumonia due to other causes and CD4 count was not different.⁷ An HIV test should be done on any child with suspected PCP if HIV status is unknown. PCP is also described though much less commonly in HIV-exposed but uninfected infants.^{15,20}

Clinical signs

The frequency of presenting clinical features of cough, fever and dyspnoea in infants with PCP is similar to that found in infants with pneumonia due to other causes.^{7,9,13,15}

Graham et al found that Malawian infants with PCP had a significantly lower temperature on admission: 37.8°C (36.2-39.0) compared with 39.0°C (36.0-40.0) in those with bacterial pneumonia (p<0.001) and 38.2°C (35.5-40.5) for others.¹³ Such a difference was not evident in South African infants when PCP was compared with all other cases including viral pneumonia.^{7,8,15}

Respiratory rate is reported to be higher in those with PCP compared to a similar age group with other causes of pneumonia.^{7,9,13} The difference is not so large as to be of clinical relevance and is likely to reflect the degree of hypoxia which is more severe and prolonged in infants with PCP.^{7,13} Cyanosis was significantly more common in one study from South Africa⁷ and oxygen saturation (SaO₂) in air was significantly lower in Malawian infants with PCP (60% [range 30-92]) compared to those with bacterial pneumonia (86% [38-94]) and other cases (89% [28-99]).¹³ Such a difference was not noted in a report from Johannesburg where mean SaO₂ in air was 70% for those with PCP compared to 73% for HIV-infected hospitalised with pneumonia not due to *Pneumocystis* perhaps reflecting the severity of pneumonia in all pneumonia cases.¹⁵

On auscultation, an affected child is more likely to have a clear chest or diffuse signs such as crackles or wheezes, rather than focal abnormalities.^{6,7,15} This is supported by the

radiological changes which also tend to be bilateral and diffuse rather than unilateral or focal which is more common in bacterial pneumonia. No study found chest X-ray changes to be diagnostic of PCP, rather supportive abnormalities include bilateral perihilar infiltrates, hyperinflation, diffuse infiltrates and/or ground-glass opacification.^{6,7,13,15} Clinical and radiological signs can be confused by concurrent disease due to bacteria, viruses or tuberculosis which is especially common in HIV-infected children.^{8,13,15,19,23}

The diagnosis of PCP is often considered when an infant with severe pneumonia is not improving with recommended first-line antibiotics for pneumonia which are usually aimed at the common bacterial causes. A study of Malawian children found that those with PCP had a significantly lower median SaO₂ on day 3 of admission (68% [range 40-96%]) than those with bacterial pneumonia (93% [74-99%]) and were more likely to be still requiring oxygen therapy on day 3 (91% versus 7%: p<0.001).¹³ Hypoxia was more persistent in those with PCP who received oxygen for 96 of a cumulative 105 inpatient days compared with 15 of 94 inpatient days for those with bacterial pneumonia (p<0.0001). Availability of pulse oximetry is very useful as it provides a more objective measure than clinical indicators. For example, on day 3 in these Malawian children, the prevalence of tachypnoea and chest indrawing was not different between the groups even when hypoxia was much more severe in those with PCP.¹³

One study noted that a history of vomiting was significantly less common in those with PCP^{7,9} but this has not been reported or studied elsewhere. Another study of Ugandan children with severe pneumonia, reported that those with PCP had a smaller head circumference compared to those without PCP (41.4cm compared with 44.4cm, p<0.0001).¹⁶ The suggestion was that smaller head circumference may be a clinical indicator of perinatal HIV infection but it is not clear how much of this difference was age-related.

Regression analysis on the study group of 121 Ugandan children showed that a positive HIV test by RNA PCR is indicative of PCP in a child with severe pneumonia.¹⁶ A necropsy study conducted in Botswana found that a child having PCP based on cough, dyspnoea, age less than 12 months and cyanosis had a sensitivity of 50%,

specificity of 79% and a positive predictive value (PVP) of 62%.²¹ If the child had tested HIV positive via ELISA, specificity increased to 91% and PVP to 71%. Retrospective multivariate analysis of 151 HIV-infected South African children with pneumonia⁷ found that four clinical variables were independently associated with a diagnosis of PCP: age <6 months (OR 15.6; 95% CI 2.4-99.8; p=0.004), respiratory rate >59 breaths/min (OR 8.1; 95% CI 1.5-53.2; p=0.018), arterial percentage hemoglobin oxygen saturation (SaO₂) <=92% (OR 5.1; 95% CI 1.0-26.1; p=0.052) and absence of history of vomiting (OR 11.2; 95% CI 1.9-68.0; p=0.008).⁹ The sensitivity and specificity of diagnosing PCP with any two or more of these variables were 1.00 (95% CI 0.74-1.00) and 0.49 (95% CI 0.39-0.59), respectively. Diagnosing PCP with three or more of the indicators had a decreased sensitivity of 0.75 (95% CI 0.43-0.95) and increased specificity of 0.90 (95% CI 0.83-0.95).

INVESTIGATIVE INDICATORS

The laboratory techniques used in Western countries to identify PCP infection are lacking in many developing country hospitals and so it is imperative that such infection can be identified by simple, cost-effective measures.

Neither white cell count and differential nor C-reactive protein were significantly different in those with PCP compared to those without.^{7,15} The only marker to show any significant difference between those with PCP and those with other pneumonias is lactate dehydrogenase (LDH). Zar et al found levels to be elevated in children with PCP, a median of 626 units/l versus 307 units/l for those without PCP (p=0.001).⁷ Similarly, Bakeera-Kitaka et al found mean levels of 816 units/l in PCP compared with 568 units/l in others (p=0.004).¹⁶ Those that died from PCP in this study had significantly higher levels than survivors. This is supported by evidence from developed countries. However in 51 PCP children studied in Johannesburg, no difference was reported¹⁵. LDH may simply be a non-specific marker of lung disease, but nevertheless could be a useful indicator of prognosis.

Identification of the presence of *P.jirovecii* cysts via laboratory techniques is not possible in most developing country hospitals as fluorescent microscopy is required.

Bronchoalveolar lavage (BAL) is the preferred method for obtaining sputum for examination. However, this is an invasive test, very difficult in infants and the equipment and expertise required is not available in most developing countries. In the USA, it has been used to diagnose PCP infection in children as young as two months¹⁷, but BAL in this infant age group could potentially exacerbate a child's respiratory status. Most of the studies reviewed here adopted non-invasive techniques such as sputum induction and/or nasopharyngeal aspiration (NPA). Two used BAL on intubated children only. PCP can be detected in these samples via microscopy using immunofluorescence assay or staining, or alternatively, via the more sensitive polymerase chain reaction (PCR). None of the studies used PCR, so there was no analysis of its sensitivity compared with microscopy techniques.

Zar et al found sputum induction successful in diagnosing 60% (9/15) cases of PCP, seven infants younger than 6 months, but did not find NPA useful⁷. Both Malawian studies diagnosed PCP using NPA but sensitivity of the technique was unknown and may have biased reporting to the more severe cases^{12,13}. More recently, induced sputum and NPA were performed in 105 HIV-positive children in South Africa with severe pneumonia, and the sensitivity and specificity of these tests combined were 75% and 80% when compared to post-mortem histology¹⁵. This study does state that the sensitivity of NPA may be understated due to the limits of their needle biopsy lung sampling technique; the affected lung segments may not have been sampled, and consent for post-mortem was only obtained for 18 of 29 children who died.

Summary

- Pneumocystis pneumonia should be suspected and anti-pneumocystis therapy considered in any HIV-positive infant with severe pneumonia.²⁶
- Age <12 months, absent or low-grade fever, cyanosis, hypoxia that is persistent, poor response to 48 hours of first-line antibiotics, and elevated levels of LDH, all support the diagnosis.
- PCP is often the first clinical indicator of HIV infection.

- Clinical and radiological signs are not diagnostic. However, a clear chest or diffuse chest signs on auscultation are typical with PCP infection, as is the presence of diffuse infiltrates rather than focal signs on chest x-ray.
- Induced sputum and NPA are useful for obtaining sputum for examination when BAL is not possible.

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