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Clinical indicators of *Pneumocystis jiroveci* pneumonia (PCP) in South African children infected with the human immunodeficiency virus

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Summary
Background: Pneumocystis pneumonia (PCP) caused by *Pneumocystis jiroveci* is common in HIV-infected children, producing substantial morbidity and mortality. Initiation of timely, effective therapy depends on clinical identification of children with PCP.
Objective: To develop a clinical decision rule to diagnose PCP in HIV-infected children for use where diagnostic resources are limited.
Methods: Analysis of data collected during a prospective incidence study of the etiology, features, and outcome of HIV-infected children hospitalized with pneumonia.
Results: Four clinical variables were independently associated with a diagnosis of PCP in multivariate analysis: 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 (SaO_2) ≤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; $p = 0.008$). 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).
Conclusion: Empirical anti-pneumocystis therapy should be considered in HIV-infected infants presenting with tachypnea, hypoxia and absence of vomiting.

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Background

Pneumocystis pneumonia (PCP) caused by *Pneumocystis jiroveci* infection, is an important cause of morbidity and mortality amongst HIV-infected children in Africa. Post-mortem studies have found PCP to be the cause of 29—67% of respiratory related deaths amongst HIV-infected children,[1—3] and in-hospital case-fatality rates for PCP have ranged from 20—63%.[4—8] The prevalence of PCP amongst HIV-infected children hospitalized with pneumonia in Africa has varied from 10—49%.[4—8]

The case-fatality rate of children with untreated PCP approximates to 100%, therefore diagnosing and treating children at risk is essential.[9] Effective, specific first-line therapy for PCP consists of trimethoprim—sulfamethoxazole with or without corticosteroids. Definitive diagnosis of PCP in resource-limited areas is difficult, due to a lack of diagnostic resources and expertise,[1,4,7,8] and management decisions for children with pneumonia must be made primarily on a clinical basis. It is therefore important to define a valid clinical diagnostic technique for PCP that could be used by clinicians in resource-limited areas, enabling timely use of empirical anti-pneumocystis therapy.

Certain presenting clinical characteristics have previously been found in HIV-infected children with PCP compared with pneumonia of other etiologies. Graham and colleagues found Malawian children with PCP had a significantly lower median age, oxygen saturation and body temperature; higher proportions had no abnormality or diffuse abnormality on auscultation, compared with children with pneumonia of other etiologies.[8] South African children with PCP have been reported to have a lower median age, and infants with PCP to have increased respiratory rates.[6] Amongst Botswanan children who died from respiratory disease, age $\leq$1 year and pulmonary infiltrates on chest radiograph were predictive of PCP.[2]

The aim of this study was to develop a clinical decision rule,[10] using a combination of clinical criteria, which could be used in resource-limited areas, to differentiate PCP from pneumonia of other etiologies in HIV-infected children.

Methods

Data collected during a prospective incidence study that aimed to compare the etiology, associated clinical, laboratory, radiological features and outcome of children hospitalized with pneumonia,[4,5] were re-analyzed. Data collection occurred at four hospitals forming part of the University of Cape Town teaching hospitals complex in Cape Town, South Africa. Consecutive children below ten years of age, with a primary diagnosis of pneumonia or severe pneumonia, and who were known to be HIV-infected, were suspected of having HIV infection, or were admitted to the intensive care unit, were included prospectively between January and December 1998.

Socio-demographic and clinical data were obtained on admission and captured on standardized data capture forms. Hematological and serum chemistry parameters, measurement of arterial oxygen saturation in room air, blood bacterial cultures, HIV testing, and chest radiography were performed on inclusion in the study. Induced sputum and nasopharyngeal aspirate specimens were obtained, and non-directed bronchoalveolar lavage was performed in intubated children. Specimens were submitted for detection of *P. jiroveci* using a silver methenamine stain and immunofluorescence, and PCP was diagnosed with positive microscopy using either technique, from either bronchoalveolar lavage fluid or induced sputum. These specimens were also submitted for bacterial, viral, fungal and mycobacterial culture, and the nasopharyngeal aspirate submitted for bacterial culture.

For this analysis, the multivariate associations of clinical, laboratory and radiological variables with respect to PCP were analyzed using logistic regression, to identify the combination of variables that best predicted PCP. The variables thus selected were used to calculate the sensitivity, specificity, predictive values, and interval likelihood ratios for combinations of differing numbers of these variables with respect to a diagnosis of PCP, each variable being assigned an equal weighting. Continuous variables in the final model were categorized, with cut-off values chosen that are clinically easily applicable and that maximized differences in the outcome. Post-test (or post-rule) probabilities of PCP were estimated for varying prevalences of PCP by applying Bayes' theorem. The University of Cape Town research and ethics committee granted ethical approval for this analysis, and for the original data collection study.

Results

One hundred and fifty-one HIV-infected children with a median age of 9 months (Interquartile range 3—23 months) were enrolled. There were 80 (53%) males and 71 females. Fifteen children were found to have PCP, accounting for 9.9% (95% CI 5.9—15.5%) of pneumonia cases in the sample. Other organisms cultured from respiratory secretions included *Staphylococcus aureus* (15.0%), *Klebsiella pneumoniae* (10.9%), *Haemophilus influenzae* (8.8%), *Mycobacterium tuberculosis* (7.4%) and cytomegalovirus (14.3%). Fifty-nine (39.1%) children were taking trimethoprim—sulfamethoxazole prophylaxis.

Four variables were found to be independent risk factors for 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 hemoglobin oxygen saturation $\leq$92% (OR 5.1; 95% CI 1.0—26.1; $p = 0.052$) and absence of history of vomiting at presentation (OR 11.2; 95% CI 1.9—68.0; $p = 0.008$). The final model included 116 children (12 with PCP and 104 without); the remaining participants were not included due to missing observations not recorded during data collection (complete-subjects method of logistic regression). This model had an area under the receiver-operating characteristic curve of 0.92. No laboratory results or radiological features were independently associated with PCP.

Using a dichotomous diagnostic test outcome, the sensitivity and specificity of diagnosing PCP with any two or more of these indicator 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) but increased specificity of 0.90 (95% CI 0.83—0.95).