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

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Declaration

I, Geoffrey Libero Fatti hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATED TO MY WIFE LIZA, WHO HAS GIVEN ME

CONSTANT SUPPORT AND ENCOURAGEMENT

THROUGHOUT THE DEGREE

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ABSTRACT

Background

Pneumocystis pneumonia (PCP) is an important cause of morbidity and mortality amongst HIV-infected children in Africa. Definitive diagnostic resources for PCP in Africa are limited due to their expense and technical difficulty, however recognising and treating children at risk is essential. As management decisions for children with pneumonia are made primarily on a clinical basis in many African regions, it is important to attempt to define a valid clinical diagnostic technique for PCP that could be used by clinicians to determine the use of correct empirical antibiotic therapy. The objectives of this study were to identify clinical features associated with PCP in HIV-infected children hospitalised with pneumonia, to determine the combination of features that best predicts PCP in these children, and to calculate the diagnostic accuracy of these features.

Methods

This study was a re-analysis of a database of a prospective study. Consecutive children below ten years of age, with a primary diagnosis of pneumonia or severe pneumonia, and who were known to be HIV-infected or were suspected of having HIV infection, were included prospectively over a 12 month period. Clinical data and diagnostic testing for PCP were obtained on admission. Bi- and multivariate analysis of associations of the clinical variables with PCP were performed using logistic regression, to identify the combination of variables that best predicted PCP. The diagnostic accuracy of the best predicted features were calculated.

Results

151 children were enrolled, of whom 15 were diagnosed with PCP. Four clinical variables were found to be independently associated with a diagnosis of PCP. These were: 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 haemoglobin oxygen saturation ≤ 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 sensitivity and specificity of diagnosing PCP with any two or more of the four clinical indicators was 1.00 (95% CI 0.74 – 1.00) and 0.49 (95% CI 0.39 – 0.59) respectively; with three or more of the indicators the sensitivity and specificity was 0.75 (95% CI 0.43 – 0.95) and 0.90 (95% CI 0.83 – 0.95) respectively. The interval likelihood ratio (iLR) associated with none or any one of the indicators being present was zero, with an associated post-test probability of PCP of 0%. Presence of any three of the variables had an iLR of 5.0 (95% CI 2.0 – 12.5) with a post-test probability of PCP of 36% (95% CI 18% - 58%) in the sample. All four variables being present had an iLR of 36.0 (95% CI 4.4 – 96.5) with a post-test probability of PCP of 80% (95% CI 33% - 97%).

Discussion

This analysis provides preliminary evidence in the clinical prediction of PCP in HIV-infected children hospitalised with pneumonia, and has identified four easily measured clinical indicators that are independently associated with PCP. The presence of none, or any one of the clinical indicators is associated with low post-test probabilities of PCP, and any three or all four indicators with increased probabilities. The diagnostic tool is however unable to conclusively identify children at the population level that do not require specific anti-pneumocystis treatment. The measures of test diagnostic accuracy are imprecise indicating a lack of statistical power, and design-related biases may have influenced the results.. Further studies should be undertaken to validate these findings, and to quantify measures of diagnostic accuracy with greater precision.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION AND LITERATURE REVIEW

1.1 Background

Pneumocystis pneumonia (PCP) caused by *P. jiroveci* infection (previously classified as *P. carinii*), is a common life-threatening complication of HIV infection in children. In a developed setting, PCP has been found to be the most frequent reason for admission of HIV-infected children to a paediatric intensive care unit, accounting for 45% of admissions over a ten-year period in the United Kingdom (Lubis 2004). The burden of PCP in HIV-infected African children was previously poorly described, as a result of a lack of resources to adequately diagnose PCP, and adult data suggesting it to be rare in the African region (Abouya 1992, Batungwanayo 1994). Post-mortem studies since the turn of the century have however found PCP to be the cause of respiratory-related deaths in 29% of HIV-infected children in Zambia, 32% in Botswana, and 67% in Zimbabwe (Chintu 2002, Ansari 2003, Nathoo 2001).

Investigators have used varying diagnostic methods and sample selection criteria in ante-mortem studies of the burden of PCP in African children. The proportion of PCP amongst HIV-infected children hospitalised with pneumonia has been found to be 10% in Cape Town using bronchoalveolar lavage (BAL) and induced sputum (IS) samples, and 11% in Malawi using nasopharyngeal aspirates (NPA) (Zar 2000, Graham 2000). Children with severe pneumonia as defined by the World Health Organization clinical criteria (WHO 1994) were found to have PCP in 44% and 49% of episodes in two studies from Johannesburg using IS and NPA samples (Madhi 2002, Ruffini 2002).

PCP in HIV-infected children has a high mortality, with in-hospital case-fatality rates ranging from 20% - 63% in Africa (Madhi 2002, Ruffini 2002, Zar 2000, Graham 2000). Developed countries had similar mortality rates at earlier stages of the HIV epidemic, with reported mortality rates of 22% - 64% (Bye 1994, Sleasman 1993).

In South Africa, HIV-infected children account for 60% of children hospitalised with pneumonia, and 45% of patients with severe pneumonia (Zar 2001, Madhi 2002). HIV-associated PCP is therefore a common and important cause of morbidity and mortality amongst children in this country.

1.2 Diagnosis of PCP

Histological diagnosis following percutaneous lung aspiration biopsy, is the gold standard for the ante-mortem identification of aetiological pathogens in pneumonia (Zar 2003). It is however an invasive procedure, and is associated with the risk of pneumothorax and clinical decompensation, especially in children with severe respiratory illness. Lower respiratory tract secretions obtained from BAL is considered the best alternative method of diagnosing PCP (Ruffini 2002, Behrman 2004), and has been shown to produce yields for PCP of 40% in a developed country (Gibb 1994) and 30% in Durban (McNally 2004). BAL is performed non-bronchoscopically in infants (NB-BAL), by lavaging the distal airways with a suction catheter passed down the endotracheal tube, as the paediatric bronchoscope would obstruct airflow in the infants' airway (Morrow 2001). PCP is diagnosed from microscopy of lavage fluid, with visualization of cysts exhibiting typical *P. jiroveci* morphology using a direct monoclonal antibody immunofluorescent (IF), or silver methanamine stain. BAL is however invasive, and

reported adverse events have included arterial desaturation (63%), significant bradycardia (17%), and pulmonary haemorrhage (4%) (Morrow 2001, McNally 2004). The procedure also requires resources, including skilled personnel and specialised equipment, that are limited in most developing countries (Chokephaibulkit 1999, Zar 2000, Graham 2000, Chintu 2002).

Non-invasive, simpler and inexpensive alternative diagnostic methods include obtaining IS samples and NPA's. IS samples are collected after administering nebulized hypertonic saline solution to the child, and obtaining sputum either by expectoration or suctioning. An NPA is obtained by instilling sterile saline into the nostrils and suctioning the nasopharynx with a catheter attached to a mucus trap (Zar 2001). One study only has reported the accuracy of these methods in the diagnosis of PCP. The sensitivity and specificity of IS was 65% and 100% respectively, and for NPA's found to be 38% and 80% respectively (Ruffini 2002).[1] Reliable estimates of the diagnostic accuracy of these methods from larger studies have however not been produced as yet.

Definitive diagnosis of PCP in resource-limited countries is especially difficult as BAL, and the laboratory infrastructure required to perform the specialised staining techniques are limited or unavailable.

[1] Post-mortem lung histology from limited tru-cut biopsy specimens were used as a reference, obtained in a subset of 18 children who died (eight of whom had evidence of PCP and 10 of whom did not).

1.3 Prevention of PCP

Cotrimoxazole (CTX), a combination of trimethoprim (TMP) and sulfamethoxazole, is a cheap antibiotic with a broad spectrum of activity that is used to prevent PCP in HIV-infected children. Improved survival was found amongst HIV-infected infants taking CTX prophylaxis in non-randomised retrospective cohort studies (Thea 1996, Rigaud 1994), and historical comparison studies have shown large reductions in the incidence of PCP in HIV-infected infants following the introduction of CTX prophylaxis in the United Kingdom and Thailand (Duong 1999, Chokephaibulkit 1999). Ruffini and colleagues (2002) found Johannesburg children with PCP to be less likely to have taken CTX prophylaxis compared with children with pneumonia of other aetiologies, in a non-randomised prospective study. Randomised control (RCT) studies of CTX prophylaxis in HIV-infected children had not been performed prior to 2003 (Grimwade 2003). A placebo-controlled RCT reported in the *Lancet* in November this year showed reduced mortality (across all age groups and baseline CD4 cell counts) and a reduced overall hospital admission rate in the CTX group (Chintu 2004). A specific reduction in PCP incidence could however not be shown, as only one trial participant (placebo group) developed PCP. The trial did also not include infants younger than six months of age, who are a high-risk group for developing PCP (Graham 2000, Madhi 2002, Chintu 2002).

Selik and colleagues have analysed death certificate data in the United States, to report a reduced proportion of HIV-related childhood deaths due to PCP (from 19.0% to 7.5%) between 1987 – 1999, that was temporally associated with the advent of combination antiretroviral therapy (Selik 2003). The WHO has recently recommended the scaling up of the delivery of highly active antiretroviral therapy (HAART) in resource-limited settings (WHO 2004). Reports of the initial

effect of HAART in HIV-infected African children have demonstrated a decreased incidence of pneumonia, tuberculosis, acute diarrhoea, an increase in median CD4 cell percentage and mean weight-for-age score, and a significant drop in median viral load in children while taking HAART, compared with their observation period prior to HAART (Kouakoussui 2004, Fassinou 2004, Eley 2004). Data on specific changes in the incidence of PCP are however lacking, due to the small number of infants that have been included in African studies. The use of HAART is not yet widely available in Africa, and complicated by the difficulties of diagnosing HIV-infection in infants, complex dosing schedules, adverse drug effects, and the cost of drugs and programme implementation. It is therefore unlikely at this stage to significantly affect the burden of childhood PCP, unless widespread HAART programmes are realised.[2]

1.4 Management of PCP

The case-fatality rate of untreated children with PCP approximates 100%, therefore recognizing and treating children at risk is essential (Hughes 1991). The treatment of PCP differs from that of other organisms producing pneumonia, and is effective but has complications and potential adverse effects. Treatment of PCP involves the following:

1. CTX given as an intravenous loading dose of 10mg/kg TMP followed by a maintenance dose of 20mg/kg/day TMP in four divided doses for 2-3 weeks. This is larger than the usual dose, and therefore has increased potential to produce adverse effects. Intravenous therapy is preferable for severely ill children, but oral treatment can be substituted for mild illness, or

[2] A full discussion on the use of HAART and CTX prophylaxis is not included, as this is not central to the aim of the dissertation.

once clinical improvements occur. Significant adverse events are common, occurring in approximately 15% of children with HIV-infection. The most common include urticarial rash, potential for fluid overload in ill children, and neutropenia (Behrman 2004, Zar 2001). Difficulties and complications associated with intravenous therapy include the high cost of the injectable drug, skill and resources needed to provide intravenous access, and the need for hospitalisation (Zar 2001).

2. Corticosteroid administration produces improved outcome in the treatment of hypoxic HIV-infected adults with moderate to severe PCP, when administered within 72hrs of onset (Hughes 1991). Use of corticosteroids has also been shown to improve short-term survival, and reduce the need for mechanical ventilation in children with PCP from non-randomised, before-after studies (Bye 1994, Sleasman 1993). Randomised control studies have not been performed in children, however administration of corticosteroids is recommended in children with moderate to severe illness as part of PCP therapy. A suggested regimen is prednisone 2mg/kg for 7 days, then tapering doses over the next 10-14 days (Pickering 2000, Ruffini 2002). Steroids have powerful immunosuppressive properties, and concern about cytomegalovirus (CMV) co-infection after initiating of steroids has been expressed. Overwhelming CMV infection in HIV-infected children occurring within weeks of initiation steroid therapy has been reported (McLaughlin 1995), and in a necropsy study of 16 children with PCP, 11 had CMV co-infection (Jeena 1997). Chintu and colleagues (2002) found CMV co-infection in over 40% of PCP cases. Conclusive data indicating causality due to steroid therapy is however lacking.

3. Oxygen therapy should be given to hypoxic children with a room air arterial oxygen saturation of less than 92% (Zar 2001, b).

It is important to accurately diagnose PCP in children, as treatment is different from that of other organisms causing pneumonia, timely treatment is necessary to prevent death, but it is expensive and has potential to produce adverse effects. A diagnostic test is required that is sensitive (i.e. does not leave cases of PCP undetected), and reasonably specific to prevent unnecessary treatment of children who do not have PCP. As definitive diagnostic procedures for PCP are expensive and limited in most African countries, diagnoses and management decisions are made primarily on a clinical basis. It is therefore important to attempt to define a valid clinical diagnostic technique for PCP that could be used by clinicians to determine empirical antibiotic therapy for HIV-infected children with pneumonia.

1.5 Clinical indicators of PCP

Certain presenting clinical characteristics have been found in HIV-infected children hospitalised for PCP compared with other pneumonias: Graham and colleagues found that children with PCP had a significantly lower median age, median body temperature, median percentage haemoglobin oxygen saturation; and higher proportions had no abnormality or diffuse abnormality on auscultation, in comparison with children with pneumonia of other aetiologies (Graham 2000). Ruffini and colleagues found *P. jiroveci* was more likely to be isolated in children who had not received CTX prophylaxis (Ruffini 2002). Madhi and colleagues found children with PCP to have a lower median age, and infants to have a higher respiratory rate (Madhi 2002).

A useful clinical diagnostic tool that can be used in a resource-limited setting to distinguish HIV-infected children with PCP from those with pneumonia of other aetiologies has however not yet been developed.

1.6 Study Purpose, Aim and Objectives

1.6.1 Purpose:

To identify clinical criteria that may predict PCP in HIV-infected children with pneumonia, as opposed to pneumonia of other microbiological aetiology.

1.6.2 Aim:

To develope a diagnostic tool that can be used in a clinical setting to distinguish between children with and without PCP amongst HIV-infected hospitalised with pneumonia.

1.6.3 Objectives:

i) To identify clinical, x-ray, and laboratory features that may be associated with PCP in HIV-infected children hospitalised with pneumonia.

ii) To determine the feature or combination of features (if any), that best predicts *P. jiroveci* infection in these children, and to calculate the diagnostic accuracy of those features.

1.7 Measures of diagnostic accuracy

Investigators have reported the diagnostic accuracy of clinical decision rules (CDR's) in two principal ways (McGinn 2000). The sensitivity and specificity of a rule can be calculated when the rule has a dichotomous (disease/no disease) outcome, and all patients above a chosen cut-off are assigned the same risk of disease. If a CDR has multiple outcome levels however, the calculation of sensitivity and specificity involves combining categories of test results, and information is therefore lost.

The usefulness of a CDR is largely determined by the accuracy with which it identifies its target disorder, and the interval likelihood ratio's (iLR's) of hierarchical levels of test results are of greater value for informing on the accuracy of a multilevel test than are sensitivity and specificity (Jaeschke 1994, Mayer 2004, Buchsbaum 1991). The iLR's of each level of outcome of the CDR are used to calculate the post-test (or post-rule) probability of the target disorder. This is a function of the iLR and the pre-test (pre-rule) probability of disease, (which equals the prevalence or burden of disease in the population at risk, Buchsbaum 1991). The calculated post-test probabilities of disease may allow patients to be stratified into multiple categories of disease risk, e.g. low, intermediate or high.

2 METHODS

Data have been collected, as detailed by Zar HJ and colleagues, in a study that aimed to compare the aetiology, associated features and outcome of HIV-infected children hospitalised with pneumonia. Data collection methods of the initial study have been summarised, and included as parts of sections 2.3 –2.4 (Zar 2000, 2001). The current study has re-analysed data from the existing database.

2.1 Study Design

This study was a re-analysis of a database of a prospective study.

2.2 Source population

HIV-infected children below 10 years of age in the drainage area of the University of Cape Town teaching hospitals complex, who have access to healthcare, and who would make use of public hospital facilities.

2.3 Setting and sample population

The study sample comprised children admitted to four hospitals (Groote Schuur, Red Cross War Memorial Children's, Somerset and Conradie) between January and December 1998. Consecutive participant sampling was performed as defined by the following selection criteria:

Children with a primary diagnosis of pneumonia or severe pneumonia, (defined as the presence of tachypnoea or lower chest indrawing according to World Health Organization criteria (WHO 1994), and who were known to be HIV infected, were suspected of having HIV infection, or were admitted to the intensive care unit (ICU) were entered prospectively. A suspicion of HIV infection was based on the presence of two or more of the following: generalised lymphadenopathy, weight below the 3rd percentile for age, hepatomegaly, splenomegaly, oral candidiasis, enlarged parotids or chronic diarrhoea.

Exclusion criteria were:

- previous admission to hospital within a month before the study
- cystic fibrosis
- known immunodeficiency, cardiac or neurological disease except if this was HIV-associated.
- Current admission to hospital for greater than 48 hours.

2.4 Data collection

2.4.1 Measurement of potential clinical predictors

Eligible children were enrolled during working hours from Monday to Friday. A history and physical examination were performed by a doctor (intern or registrar) for each child on admission at the hospitals. Socio-demographic and clinical data were abstracted from the admission records by a trained research nurse and captured on a standardised data capture form.

Blood tests including HIV testing, bacterial culture, a complete blood count, lymphocyte phenotyping, and chemistry were performed. HIV infection was confirmed by two positive ELISA tests in children older than 18 months, or by a positive ELISA and polymerase chain reaction (PCR) in those younger. Chest radiography was performed on inclusion in the study.

2.4.2 Measurement of outcome (PCP)

Sputum was induced in non-intubated patients using nebulized hypertonic saline by a physiotherapist or research nurse. Physiotherapy techniques were then applied, and sputum was obtained either by expectoration or suctioning. A NPA was obtained by instilling four drops of sterile saline into the nostrils and suctioning the nasopharynx with a sterile suction catheter attached to a mucus trap. In intubated children, non-directed BAL was performed.

Sputum, NPA and BAL fluid were submitted for detection of *P. jiroveci.* Specimens were liquefied, washed with sterile water, then concentrated by centrifugation. The resuspended deposit was used to make two smears and fixed with acetone. One smear was stained by a silver methenamine technique, the other was stained with monoclonal antibody and scanned using a fluorescent microscope. A positive result on IF was regarded as visualization of five or more typical cysts characteristic of *P. jiroveci* morphology at 100x magnification. A child was classified as having PCP when BAL fluid or sputum demonstrated *P. jiroveci* using either staining technique.[3]

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[3] Refer to Section 3.2 for outcome classification of children who were positive for PCP on microscopy of NPA only.

IF was performed by one medical technologist in the microbiology laboratory and silver staining by a medical technologist in the pathology laboratory, both situated at Red Cross Children's Hospital. Most of these tests were performed within 24 hours of admission, the remaining tests were performed at a maximum of 48 hrs after admission. The readers of these reference tests were blind (masked) as to the clinical symptoms of the child.

Sputum and BAL fluid were also submitted for bacterial, viral, fungal and mycobacterial culture, and the NPA submitted for bacterial culture. One to three early morning gastric lavages were performed and specimens stained for acid-fast bacilli and cultured for *M. tuberculosis*.

Children were evaluated and treated by the admitting doctor. When PCP was suspected, a standard treatment regime of intravenous CTX, and corticosteriods was started. Children were switched to oral CTX following clinical improvement for a total of 21 days of therapy. Use of oxygen, antibiotics or other therapy was at the discretion of the ward doctor and consultant paediatrician.

2.5 Statistical analysis

Data were entered into an Epi-Info 6 (CDC, Atlanta, USA) database during the initial study by two trained research nurses. For this analysis, data was imported into Stata versions 6 and 7 (Stata corporation, Texas, USA). Continuous variables are expressed as means ± SD or as median and inter-quartile range.

Bivariate analyses of the association of clinical, laboratory and radiological features with PCP (as the outcome variable) were performed using logistic regression. Multiple logistic regression was used to determine the independent contribution of variables associated with PCP. Variables with a p-value of < 0.2 in the bivariate analyses were considered as eligible for inclusion in the multivariate analyses. The final variables were selected using forward and backward stepwise logistic regression, and confirmed with model-building procedures using the likelihood-ratio test (maximum-likelihood estimation). The best predictive clinical variables thus selected were combined, and the sensitivity, specificity, predictive values, and iLR's of combinations of these variables calculated, with each variable being assigned an equal weighting. Likelihood ratio confidence intervals were calculated as described by Simel and colleagues, 1991 (Appendix 3). Post-test probabilities of PCP were calculated for different prevalences of *P. jiroveci* infection by applying Bayes' theorem (Mayer 2004, Appendix 4). An illustrative clinical decision rule (CDR) based on post-test probabilities of PCP was derived, and its accuracy in the sample assessed.

Missing observations in the study database were approached in the regression analyses using the complete-subjects method, in which only subjects with all values recorded for all covariates were retained in the analysis (Greenland 1995). Methods such as weighted estimating equations and multiple imputation were not used due to their complexity and unavailability in commonly used statistical software packages.

2.6 Ethical issues

Ethical approval for this analysis was granted by the Research and Ethics Committee of the University of Cape Town (Ref no. 035/2004). The original data collection study was also approved by the University of Cape Town Research and Ethics Committee (Ref no. ERC 183/97). Informed consent for enrolment in the study and for HIV testing was obtained from a parent by a research nurse. Patient names in the database were removed for the purposes of the study, and individual participants were identifiable as study numbers only.

3 RESULTS

3.1 Sample population characteristics

One hundred and fifty one HIV-infected children were enrolled in the study, of whom 71 (47%) were female. Table 1 indicates demographic features, microbial pathogens isolated, and hospital course of children included in the sample.

Table 1 Demographic features, microbial pathogens isolated, and hospital course of sample population (n=151)

Age in months, median (IQR)	9 (3 – 23)
Female, *n* (%)	71 (47)
First admission, *n* (%)	59 (39)
Newly diagnosed with HIV, *n (%)*	64 (42)
Microbial pathogens, *n* (%)	
P. jiroveci	15 (9.9)
S. aureus	22 (15.0)
K. pneumoniae	16 (10.9)
H. influenzae	13 (8.8)
P. aeruginosa	12 (8.2)
M. tuberculosis	11 (7.4)
M. catarrhalis	4 (2.7)
S. pneumoniae	2 (1.4)
A. baumanii	2 (1.4)
CMV	21 (14.3)
Other viruses (HSV, RSV, parainfluenza)	2 (1.4)
Days in hospital, median (IQR)	14 (9 – 20)
ICU days, median (IQR)	6 (5 – 8)
Hospital death, *n* (%)	31 (20.5)

3.2 Diagnosis of PCP

BAL was performed in nine children, IS samples were obtained from 139, and NPA's obtained from 140 children. BAL specimens were positive for PCP in six children, and IS in a further nine. Two children had positive NPA specimens; both were however negative on IS (neither had BAL), and it was concluded by the investigators of the original study to classify these children as negative for PCP.[4] Fifteen children were therefore classified as having PCP, accounting for 9.9% (95% CI 5.9% - 15.5%) of episodes of pneumonia in the sample. Thirteen (86.6%) children with PCP were younger than 6 months of age, and 43 (28.5%) children without PCP were younger than 6 months of age.

Other common pathogens included *S. aureus* (15.0%), *K. pneumoniae* (10.9%), *H. influenzae* (8.8%), *M. tuberculosis* (7.4%) and cytomegalovirus (CMV, 14.3%). The median length of hospital stay was 14 days, and 31 (20.5%) children died while in hospital.

Empirical broad-spectrum antibiotic treatment was commenced in 150 (99%) of children prior to laboratory diagnostic results being available. Specific anti-pneumocystis treatment was started in 25 (17%) of the sample, and in 6 (40%) of children who were later diagnosed as having PCP.

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[4] The sensitivity and specificity associated with IS in the diagnosis of paediatric PCP has been reported as superior to that of NPA's (Ruffini 2002, see Section 1.2). It has been suggested that NPA's produce a poorer reflection than IS samples of infective pathogens at the lower respiratory tract level (Zar 2003), as NPA's may produce increased numbers of false negative results by failing to detect pathogenic *P. jiroveci* present in the lower airways, as well as producing more false positive results by detection of non-pathogenic commensal *P. jiroveci* cysts located in the nasopharynx of some children (Zar HJ, personal correspondence).

Adverse events to BAL included arterial desaturation, mild self-resolving bronchial haemorrhage, and bradycardia. Obtaining induced sputum produced no serious adverse events, however minor events that occurred included marked increase in coughing, mild epistaxis, and wheezing that was responsive to an inhaled bronchodilator.[5]

3.3 Clinical characteristics of sample

Clinical, laboratory and radiological features, stratified by the presence of PCP, are shown in table 2. Results of each subsection of the table have been ranked according to the bivariate p-value.

[5] Adverse events to BAL and IS were captured in separate databases that included additional children, that were unavailable for this analysis. BAL performed in 35 children produced a drop in SaO_2 to below 90% in 22 (62.9%) children, mild haemorrhage in one, and bradycardia (heart rate below 85 beats per min) in six (17.1%) children (Morrow 2001). IS obtained from 210 children resulted in marked increase in coughing in 8 (5.6%), mild epistaxis in 6 (4.2%), and wheezing that was responsive to an inhaled bronchodilator in 3 children (2.1%) (Zar 2003).

Table 2a Demographic and clinical features of the sample population stratified by the presence of PCP with bivariate odds ratio's of PCP

Clinical variable	PCP (n=15)	Without PCP (n=136)	Odds ratio (OR)	95% confidence interval (95% CI) of OR	
Prior admission, n (%)	2 (13.3)	88 (63.2)	0.08	0.02 – 0.38	0.001
Newly diagnosed with HIV, n (%)	13 (86.7)	51 (37.5)	10.83	2.35 – 49.96	0.002
CTX prophylaxis, n(%)	1 (6.6)	58 (42.6)	0.09	0.01 – 0.70	0.022
Age (months)	3 (3-4)	10 (4-24)	0.88	0.78 – 0.99	0.027
Male gender, n (%)	12 (80)	68 (50)	4.00	1.08 – 14.81	0.038
Symptoms, n (%)					
Vomiting	2 (13.3)	64 (47)	0.16	0.03 – 0.74	0.019
Rhinnorrhea	6 (40)	81 (59.5)	0.35	0.12 – 1.07	0.058
Diarrhoea	1 (6.7)	38 (27.9)	0.17	0.02 – 1.30	0.088
Fever	12 (80)	96 (70.6)	1.50	0.40 – 5.63	0.548
Fast breathing	13 (86.7)	105(77.2)	1.24	0.26 – 5.91	0.789
Cough	15 (100)	129 (94.9)	-	-	-
Vital signs,median(IQR)					
Resp. rate (breaths/min)					
Age < 6 months	63 (60-72)	55 (48-62)	1.06	1.01-1.12	
Age > 6 months	62 (50-74)	48 (40-60)	1.07	0.97-1.18	
Heart rate (beats/min)					
Age < 6 months	160 (140-180)	150 (136-160)	1.03	0.99-1.06	
Age > 6 months	130 (120-140)	130 (120-150)	0.99	0.92-1.06	
Axillary temp (°C)					
Age < 6 months	37.0 (36.5-37.5)	36.8 (36.4-37.4)	1.21	0.59-2.46	
Age > 6 months	37.2 (36.8-37.5)	37 (36.5-38.0)	0.89	0.20-3.91	

Clinical variable	PCP (n=15)	Without PCP (n=136)	Odds ratio (OR)	95% confidence interval (95% CI) of OR	
Physical exam, n (%)					
Cyanosis	8 (53.3)	35 (25.7)	3.27	1.10-9.66	0.025
SaO_2	92.5 (88-95)	94 (92-97)	0.89	0.79-0.99	0.032
Splenomegaly	13(86.7)	85 (62.5)	3.90	0.85 - 17.99	0.081
Clubbing	1 (6.7)	29 (21.3)	0.26	0.03 – 2.07	0.205
Crepitations	7 (46.7)	96 (70.5)	0.42	0.09 – 2.02	0.279
Bronchial breathing	3 (37.5)	47 (52.2)	0.55	0.12 – 2.43	0.430
Hepatomegaly	14 (93.3)	131 (96.3)	0.53	0.59 – 4.90	0.579
Oral candida	8 (53.3)	81 (60.0)	0.76	0.26 – 2.22	0.619
Wheeze	3 (33.3)	37 (38.5)	0.80	0.19 – 3.83	0.759
Lower chest indrawing	6 (40)	76 (55.9)	1.13	0.27 – 4.75	0.866

Table 2b Laboratory and radiological results of the sample population stratified by the presence of PCP with bivariate odds ratio's of PCP

Clinical variable	PCP (n=15)	Without PCP (n=136)	Odds ratio (OR)	95% confidence interval (95% CI) of OR	p-value
Blood tests					
LDH (U/1)	626 (450.5-1098.5)	307 (243-465)	1.002	1.00 – 1.004	0.003
Potassium (mmol/l)	4.8 (0.6)	4.2 (0.8)	2.62	1.21 – 5.68	0.014
Haemoglobin (g/dl)	9.8 (8.5-11.4)	8.8 (7.8-9.9)	1.30	1.02 – 1.64	0.029
Glucose (mmol/l)	6.2 (0.8)	5.2 (1.4)	1.53	0.93 – 2.50	0.091
CD4/CD8	0.4 (0.2-0.7)	0.3 (0.2-0.4)	1.67	0.91 – 3.05	0.096
Magnesium (mmol/l)	0.9 (0.1)	0.9 (0.1)	39.88	0.28 – 5576	0.144
Protein (g/l)	67.5 (56-75)	78.5 (63-88.5)	0.99	0.96 – 1.02	0.416
CD4/T cells (%)	16.4 (12.7-27.6)	23.6 (14.5-38.7)	0.98	0.91 – 1.05	0.530
Lymphocytes (10^9/l)	4.6 (3.3-8.2)	4.4 (2.5-6.7)	1.03	0.91 – 1.17	0.571
Neutrophils (10^9/l)	6.7 (3.8-8.6)	5.6 (3.4-9.4)	0.98	0.89 – 1.09	0.753
WCC (10^9/l)	12.4 (10.5-19.4)	12.7 (9.3-17.9)	0.99	0.93 – 1.06	0.818

CD4 (cells/μl)	871 (290-1150)	667 (360-1120)	1.01	0.73 – 1.40	0.962
Platelets (10^9/l)	367 (173-446)	337 (219-444)	1.00	1.00 – 1.00	0.977
Radiology, n (%)					
Adenopathy *	0 (0)	23 (19.5)	0	-	-
Diffuse alveolar pattern	11 (73.3)	106 (89.8)	2.52	0.31 – 20.37	0.386
Pleural effusion	0 (0)	14 (11.9)	0	-	-
Consolidation	15 (100)	108 (91.5)	-	-	-
Diffuse nodular pattern	0 (0)	9 (7.6)	0	-	-
Hyperinflation	11 (73.3)	73 (61.9)	1.70	0.51 –5.64	0.390
Cavity	0 (0)	3 (2.5)	0	-	-
Normal Xray	0 (0)	3 (2.5)	0	-	-
Disease severity					
ICU admissions, n (%)	8 (53)	13(10)	10.81	3.37 – 34.64	<0.001
In-hospital death, n (%)	7 (47)	24 (18)	1.21	0.99 – 1.47	0.008

Continuous variables are median (25^{th} – 75^{th} percentile)
* hilar or mediastinal

The following presenting clinical features were associated with a diagnosis of PCP on bivariate (unadjusted) analyses: Younger age, increased respiratory rate amongst children aged < 6 months, child newly diagnosed with HIV, decreased arterial percentage haemoglobin oxygen saturation (SaO_2, room air, at presentation, cyanosis, male gender, and increased serum LDH. The following were associated with pneumonia's other than PCP: Child on CTX prophylaxis, prior hospital admission, and history of vomiting and diarrhoea at presentation.

PCP was closely associated with increased disease severity as reflected by ICU admissions and in-hospital death. No radiological, or other laboratory features were associated with PCP.

3.4 Multivariate analysis and final model characteristics

Multiple logistic regression was performed, and the following model was selected with the best statistical fit (Table 3). This model included the results of 116 children (12 with PCP and 104 without PCP); the remaining participants were not included due to missing observations not recorded during data collection (complete-subjects method of logistic regression).

The following emerged as independent predictors of PCP: Respiratory rate > 59 breaths/minute, age < 6 months, $SaO_2 \leq 92$, and absence of history of vomiting at presentation. Other variables that were significant on bivariate analyses fell out of the adjusted model.

Table 3 Final multivariate model of indicators of PCP

Clinical variable	Adjusted odds ratio	95% confidence interval (95% CI)	p-value
Respiratory rate >59 breaths/min	8.1	1.5 – 53.2	0.018
Age < 6 months	15.6	2.4 – 99.8	0.004
Absence of history of vomiting	11.2	1.9- 68.0	0.008
$SaO_2 \leq 92$	5.1	1.0 – 26.1	0.052

Continuous variables in the final model were categorised, with cut-off values chosen in order to be easily clinically applicable, and that maximised differences in the outcome, i.e. PCP. Box plots of these variables stratified by PCP are shown in Appendix 1. Children with an SaO_2 of ≤ 92 would be considered as having significant respiratory compromise. Children aged < 6 months had respiratory rates higher than children aged > 6 months (table 2), however the

confounding effect of age on respiratory rate would be "adjusted for" by the multivariate modelling.

The multivariate model has the following characteristics: Area under the receiver-operating characteristic (ROC) curve: 0.92 (a measure of the predictive ability of the model). Aikaike's Information criteria (AIC): 54.86 (used to compare models that are not nested).

There was no interaction amongst the variables, as all interaction terms were non-significant. Model checking: The form of the linear predictor and the link function were adequate. There were no strongly influential or outlying observations (Appendix 2).

Table 4 shows the findings of the bivariate associations of the variables included in the final model with PCP, with categorization of the continuous variables. CTX prophylaxis is also included for comparison, as this variable was included in a different multivariate model as discussed in section 3.7. Sensitivity and specificity (including confidence intervals) with respect to the diagnosis of PCP are shown for each clinical variable.

Table 4 Bivariate analyses of categorised variables that were independently associated with PCP

Clinical variable		PCP n (%)	Without PCP n (%)	Odds ratio (95% CI)	p-value	Sensitivity (95% CI)	Specificity (95% CI)
Respiratory Rate (breaths/min)	> 59	11 (85)	46 (34)	10.5	0.003	0.85	0.66
	≤ 59	2 (15)	88 (66)	(2.2-49.4)		(0.55-0.98)	(0.57-0.73)
Age	< 6 months	13 (87)	44 (32)	13.5	0.001	0.87	0.68
	≥ 6 months	2 (13)	92 (68)	(2.9-62.8)		(0.60-0.98)	(0.59-0.75)
History of vomiting	Yes	2 (13)	64 (49)	0.2	0.019	0.87	0.49
	No	13 (87)	67 (51)	(0.03-0.7)		(0.60-0.98)	(0.40-0.58)
SaO_2 (%)	> 92	7 (50)	73 (66)	1.9	0.253	0.50	0.66
	≤ 92	7 (50)	38 (34)	(0.7-5.8)		(0.23-0.77)	(0.56-0.75)
CTX prophylaxis	Yes	1 (7)	58 (43)	11.7	0.019	0.93	0.46
	No	14 (93)	78 (57)	(1.5-91.5)		(0.68-0.99)	(0.37-0.54)

Eighty-five percent of children with PCP had a respiratory rate of > 59 breaths per minute, and 87% of children with PCP were under 6 months of age. Eighty-seven percent of children with PCP had no history of vomiting at presentation, and 93% of children who developed PCP were not taking CTX prophylaxis.

Absence of CTX prophylaxis had the highest individual sensitivity for the diagnosis of PCP of 0.93 (95% CI 0.68 – 0.99), but a low specificity of 0.46 (95% CI 0.37 - 0.54). Age < 6 months had the highest individual specificity of 0.68 (95% CI 0.59 – 0.75).

The weakest of the four variables associated with PCP in the multivariate model was SaO_2. There was a significant association with PCP on bivariate analysis with SaO_2 as a continuous variable (p=0.032, table 2), and in the final model when categorised (table 3). Addition of this variable to the other three variables in the multivariate model also strongly improved model fit (likelihood ratio test p-value = 0.007). Categorisation of continuous variables may however result in reduced significance of associations, as was evident on bivariate analysis when SaO_2 was categorised (p=0.253, table 4).

3.5 Measures of diagnostic accuracy of the final predictive model

Two methods of calculating measures of diagnostic accuracy of combinations of the best predictive variables were employed, as discussed in section 1.7. Firstly, table 5 indicates the sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and likelihood ratio's (LR's) for positive and negative tests according to the number of clinical indicators present (of the final four clinical indicators selected). The calculation of these measures assumes that the clinical test has a dichotomous outcome i.e. positive or negative with respect to PCP. The third row of the table will for example, indicate the values when the presence of any two or more indicators are used to assign the child as having PCP. If none, or any one of the indicators were present, the child would be assigned as not having PCP.

Each clinical variable has been assigned an equal weighting. Mathematical methods which are used to incorporate varying weights for each variable such as recursive partitioning and

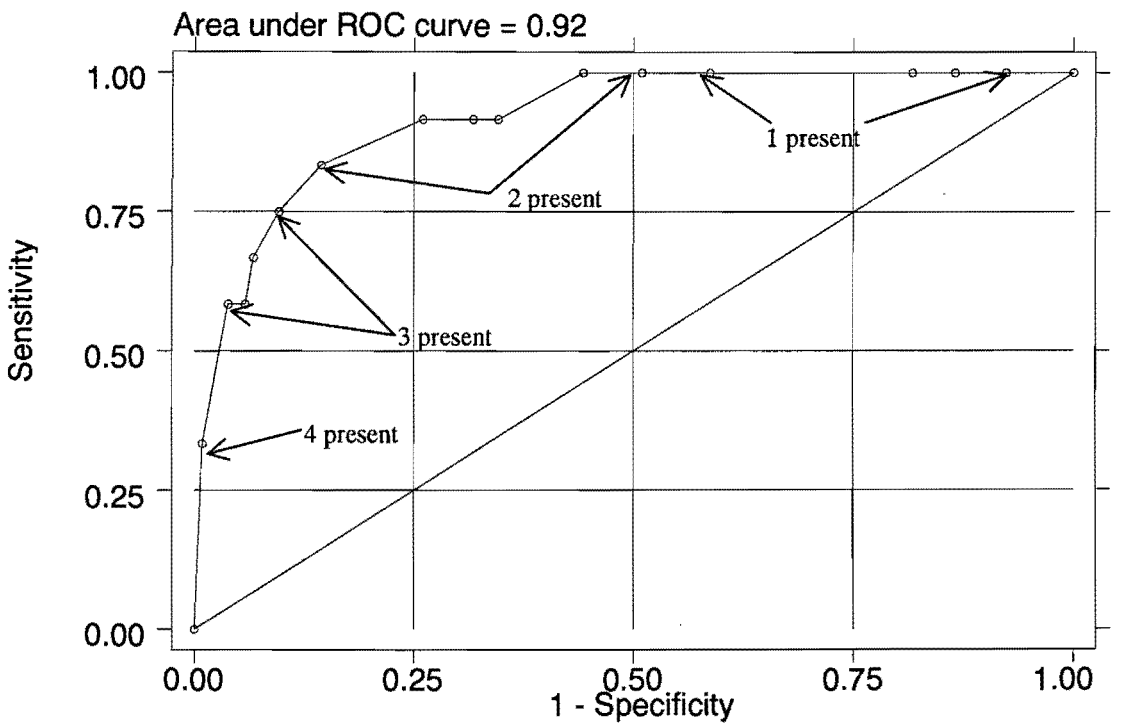
classification and regression trees (CART) analysis (Wasson 1985, Mayer 2004) are, due to their complexity, beyond the scope of this analysis.

Table 5 Sensitivity and specificity of diagnosing PCP according to the number of the best clinical indicators

No. of indicators present	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR +ve test (95% CI)	LR -ve test (95% CI)
0	1.00 (0.74- 1.00)	0 (0- 0.35)	0.10 (0.10-0.28)	–	–	–
Any 1	1.00 (0.74- 1.00)	0.08 (0.03- 0.14)	0.11 (0.06-0.19)	1.00 (0.63-1.00)	1.1 (1.0- 1.1)	0
Any 2	1.00 (0.74- 1.00)	0.49 (0.39- 0.59)	0.18 (0.10-0.30)	1.00 (0.93-1.00)	2.0 (1.6- 2.4)	0
Any 3	0.75 (0.43- 0.95)	0.90 (0.83- 0.95)	0.47 (0.24-0.71)	0.97 (0.91-0.99)	7.8 (4.0- 15.2)	0.3 (0.1- 0.7)
All 4	0.33 (0.10-0.65)	0.99 (0.95-1.00)	0.80 (0.28-0.99)	0.93 (0.86-0.97)	34.8 (4.3-279.4)	0.7 (0.5-1.0)

In order to help guide the choice of the most appropriate cut-off point to use to delineate normal or abnormal results for a test with multiple outcomes, the ROC curve, where sensitivity is plotted against 1-specificity for all combinations of test results, is used. The part of the curve closest to the top left hand corner maximizes sensitivity and specificity. Figure 1 shows the ROC curve of the final predictive model.

Figure 1: Receiver-operating characteristic curve for final predictive model, showing points according to the number of clinical indicators present



Tables six and seven are two-by-two tables showing the diagnostic ability of the clinical model when using two potential cut-off values for a positive test for PCP:

i) two or more indicators diagnosing PCP (table 6).

ii) three or more indicators diagnosing PCP (table 7).

Table 6 **Diagnostic ability of the final model using a cut-off value of any two or more indicators diagnosing PCP.**

	PCP confirmed by IF/staining (*n*)		
	PCP	**No PCP**	**Total**
Clinical Diagnostic test +	12	53	65
-	0	51	51
Total	12	104	116

Using this cut-off value, sensitivity is 1.00 (95% CI 0.74 – 1.00), with all children with PCP being correctly classified as having PCP. The specificity of 0.49 (95% CI 0.39 – 0.59) is however low, with 51 of 104 children without PCP being correctly classified as not having PCP. Assuming a prevalence of PCP as measured in the study, the probability of having PCP with a positive test result (PPV) is low (0.18 (95% CI 0.10 – 0.30), with 53 of 65 children classified as positive by the test not having PCP.

Table 7 **Diagnostic ability of the final model using a cut-off value of three or more indicators diagnosing PCP**

	PCP confirmed by IF/staining (*n*)		
	PCP	**No PCP**	**Total**
Clinical Diagnostic test +	9	10	19
-	3	94	97
Total	12	104	116

A cut-off value of three or more indicators diagnosing PCP improves specificity to 0.90 (95% CI 0.83 – 0.95), with 94 of 104 children without PCP being correctly classified as not having PCP. Sensitivity, 0.75 (95% CI 0.43 – 0.95) is however decreased, with three of 12 children with PCP being misclassified as negative. PPV (0.47 (95% CI 0.24 – 0.71) is modestly improved, but is still low. NPV values for both cut-points are >0.90.

Confidence interval's surrounding the estimates of test diagnostic accuracy are wide, as discussed in section 4.5.

3.6 Interval likelihood ratio's of the final predictive model

Table 8 indicates the iLR's for each level of test outcome, i.e. according to the number of clinical indicators present in a child. This table differs from Table 5 in that the diagnostic test has multiple outcomes instead of a simple dichotomous outcome, which has the advantage that categories of test outcomes are not collapsed, resulting in greater test information being available.

Post-test probabilities of PCP vary according to the pre-test probability of PCP and the iLR of each level of test outcome. The pre-test probability of the disorder of interest for a clinical rule, is the prevalence of the disorder in the population at risk (HIV-infected children hospitalised with pneumonia), which was 10% in this sample. The proportion of PCP in HIV-infected children in Africa has been reported to be as high as 49% amongst children with severe pneumonia (as discussed in sections 1.1 and 4.1). Post-test probabilities of PCP have been calculated using these values as pre-test probabilities of PCP. For comparison, the lower limit of

the 95% CI of the proportion of PCP in the sample (6%) has also been included as a pre-test probability.

Table 8 Interval likelihood ratios and post-test probabilities of PCP with varying pre-test probabilities, according to the number of clinical indicators present

No. of indicators present	Interval Likelihood ratio (95% CI)	Post test probabilities, % (95% CI) of PCP according to pre-test probabilities of PCP		
		6%	10%	49% (severe pneumonia)
0	0	0	0	0
Any 1	0	0	0	0
Any 2	0.6 (0.2- 1.7)	4 (1-10)	7 (2-16)	38 (18-62)
Any 3	5.0 (2.0- 12.5)	24 (11-44)	36 (18-58)	83 (66-92)
All 4	36.0 (4.4- 96.5)	70 (22-86)	80 (33-97)	97 (81-100)

Three pre-test probabilities of PCP have been used, viz. the samples' proportion of PCP point estimate (10%) and lower 95% CI limit (6%), and the maximum reported proportion of PCP amongst HIV-infected children hospitalised with pneumonia (49%).

The iLR when none, or any one clinical indicator is present is zero, with resulting post-test probabilities of PCP being zero, irrespective of the pre-test probability. When all four indicators are present, the iLR is 36.0 (95% CI 4.4-96.5), with post-test probabilities of PCP that are significantly increased from the pre-test probability. This is seen to a greater extent as the pre-

test probability of PCP increases, with a post-test probability of PCP of 97% (95% CI 81% - 100%) when the pre-test probability is 49%.

Table 9 shows illustrative implications of a clinical decision rule (CDR), based on the confidence interval limits of the post-test probabilities of PCP (for all pre-test probabilities) from table 8. A threshold post-test probability of PCP of ≥ 10% has been used to indicate initiation of specific anti-pneumocystis treatment (as discussed further in section 4.4.2).

Table 9 Illustrative implications of a clinical decision rule for PCP according to the number of clinical indicators present

Number of indicators present	Children per row category (%)	Post-test probabilities of PCP, % (95% CI limits)	Management action
Zero or one	43.9	Low, 0 (–)	Withhold specific treatment
Two	39.7	Intermediate, 4–38 (1–62)	Indeterminate (Further investigation if available)
Three or four	16.4	High, 24–97 (11–100)	Initiate specific treatment

Zero or one clinical indicator in a child is associated with a post-test probability of PCP of < 10%, indicating withholding of specific anti-pneumocystis treatment. Three or four indicators being present has a post-test 95% CI lower limit of >10%, indicating initiation of specific treatment. Two indicators are associated with post-test probability 95% CI limits on both sides of the threshold probability; therefore management is indeterminate. Table 10 illustrates the accuracy that use of this CDR would have in the study sample.

Table 10 Implications of the CDR in the study sample

	PCP (n=12) n (%)	No PCP (n=104) n (%)	Total (n=116) n (%)
Correctly managed	9 (75.0)	51 (49.0)	60 (51.7)
Incorrectly managed	0 (0.0)	10 (9.6)	10 (8.6)
Indeterminate (two indicators)	3 (25.0)	43 (41.3)	46 (39.7)

Seventy-five percent of children with PCP would correctly receive specific anti-pneumocystis treatment, and 0% would not receive treatment, however 25% would fall in the indeterminate group. Only 9.6% of children without PCP would unnecessarily receive anti-pneumocystis treatment, and 49% of children without PCP would correctly not receive specific treatment.

The iLR's of a diagnostic test are useful, if they alter the pre-test probability to cross the threshold value in which treatment (or further investigation) is either initiated or withheld. Table 11 shows prevalence scenarios in which use of this CDR would produce changes in management decisions in children, in areas where definitive diagnosis of PCP is unavailable. Pre-test probabilities of 6–10%, and $\geq$ 10% have been used.

Table 11 Prevalence scenarios that would produce changes in management decision with use of the CDR

No. of indicators present	Pre-test probability of PCP (%)	Post-test probabilities of PCP, % (95% CI limits)	Specific treatment started without CDR (Yes/No)	Specific treatment started using CDR (Yes/No)	Indicator of CDR changing management (treatment threshold crossed)
zero or	6 < 10	0	N	N	
one	≥10	0	Y	N	**
three or	6 < 10	24 – 80 (11–97)	N	Y	**
four	≥10	36 – 97 (18–100)	Y	Y	

Use of the CDR would produce a change in management to not initiate PCP treatment when zero or one indicator is present, when the pre-test probability of PCP is ≥10%. A change in management to start treatment is produced when three or four indicators are present, when the pre-test probability is between 6 and 10%.

3.7 Other models evaluated

1. A multivariate model with the next best statistical fit (model 2), included the variable absence of CTX prophylaxis instead of SaO_2, as shown in table 12.

Table 13 Characteristics of the best predictive model and model 2

	AIC	Area under ROC curve
Best predictive model	54.86	0.92
Model 2	58.80	0.91

The AIC of model 2 is higher, indicating poorer data fit than the first model, and the area under the ROC curve is marginally lower. The first model that included SaO_2 is therefore statistically the better model.

Table 14 Further models evaluated

	Clinical variables included in model	Comment
	RR >59 age <6 months $SaO_2 \leq 92$ absence of vomiting no CTX prophylaxis	No CTX prophylaxis was not significant in this model (p=0.214), and did not improve the goodness-of-fit when added to the other four variables (LR test chi-square p-value = 0.168).
4	RR >59 age < 6 months $SaO_2 \leq 92$ no CTX prophylaxis	No CTX prophylaxis was also non-significant in this model (p=0.224) and did not improve the goodness-of-fit when added to the other three variables (LR test chi-square p-value = 0.174).
5	Specifically including serum LDH with combinations of the other variables, as increased serum LDH was strongly associated with PCP on univariate analysis.	LDH was however not significant on multivariate analysis (p=0.151) and did not improve goodness-of-fit of the models.

4 DISCUSSION

4.1 Patient characteristics

One hundred and fifty one children were included in the sample, which compares favourably in size with other investigators who have compared the presentation of HIV-infected children with pneumonia (Ansari 2003: 35 participants, Ruffini 2002: 105 participants, Graham 2000: 150 participants). Only Madhi and colleagues (2002) had a larger sample size consisting of 231 episodes of pneumonia (101 episodes of PCP) amongst 185 children.

The proportion of PCP in the sample (9.9%) was similar to the Malawian sample of 10.6% (Graham 2000), but lower than was found in the two studies from Johannesburg (43.7% and 48.6%, Ruffini 2002, Madhi 2002). Investigators however used differing sample selection criteria, diagnostic techniques, and diagnostic criteria for PCP. It is therefore difficult to interpret if these varying measurements reflect true geographic variation in the burden of PCP, or are due to the differing study methods used. The following may have influenced the lower proportion of PCP found in this study:

i) Patient selection was different in the two studies from Johannesburg, as children with only severe pneumonia as defined by the World Health Organization clinical criteria (WHO 1994) were included. Children with PCP have pneumonia's of increased severity than children with pneumonia of other aetiologies, as reflected by increased rates of ICU admission and in-hospital death (table 2). The incidence of PCP in these samples would therefore be expected to be higher.

ii) This study diagnosed PCP with visualisation of five or more cysts on microscopy, while the studies from Johannesburg diagnosed PCP with visualisation of two or more cysts. This would further contribute to the higher proportions of PCP reported there.

iii) Due to resource constraints, it was not possible in the Cape Town study to perform post-mortem examinations to detect PCP in children who died, as was done in the Johannesburg studies. The sensitivity of IS samples for PCP is 65% compared with post-mortem histology, therefore possible cases of PCP in this sample may not have been diagnosed.

4.2 Clinical indicators of *P. jiroveci* infection

Four clinical features were found to be independently associated with PCP in the sample:

- **Age at presentation**

Children with PCP were significantly younger than those without PCP. This has similarly been found by three other investigators (Ansari 2003, Graham 2000, Madhi 2002).

- **Respiratory Rate**

Children aged < 6 months with PCP had significantly higher respiratory rates than those without PCP. Madhi and colleagues (2002) found a similar association amongst children aged < 1 year. Graham and colleagues (2000) found no association between respiratory rate and PCP, however statistical power was low as differences were tested on a total of only 37 children. From this

analysis, respiratory rates of >59 breaths/min would only have significance in identification of children with PCP if they were also below 6 months of age.

- **Absence of history of vomiting at presentation**

This symptom was strongly associated with PCP in both bivariate and multivariate analyses. Other researchers have not measured history of vomiting at presentation. Vomiting may be a feature of lower respiratory tract infections where hyperinflation predominates, resulting in a flattened diaphragm and a compressed stomach, whereas hyperinflation is not usually associated with PCP. Another possible reason may be that children who have had vomiting are more likely to have aspiration pneumonia as opposed to PCP. The association may also be due to chance, considering that a large number of clinical variables were compared with the presentation of PCP from the database. Further research however needs to be performed in this area.

- **Median arterial percentage haemoglobin oxygen saturation in room air**

As in this study, Graham and colleagues found a reduced median SaO_2 amongst children with PCP ($p = 0.003$, Graham 2000). Children with PCP therefore have greater respiratory compromise than children with pneumonia of other aetiologies. A cut off value of <92% is clinically meaningful to use if an oximeter is available, and suggests increased repiratory compromise.

4.3 Multiple logistic regression results

Many of the clinical variables that were significant on bivariate analyses were non-significant on multivariate analyses, i.e. they were not independent predictors of PCP. The final model included

four variables, as further increases in the number of variables did not improve prediction of the outcome, and would increase the difficulty of clinical use.

The final model had a lower AIC and a higher area under the ROC curve than model 2 (which included absence of CTX prophylaxis), indicating that it was more effective in predicting outcome. The AIC is a measure of comparing model fit in non-nested models. The model with the lower AIC generally fits the data best, and it is used to help select the most appropriate predictor variables (Collet 1994). The ROC curve is a plot of sensitivity vs. 1-specificity for a specific diagnostic test (Altman 1991). A perfectly predictive model has an area under the curve of 1.0, with lower values indicating poorer predictive power, and an area of 0.50 indicating no discriminatory value.

Absence of CTX prophylaxis was significantly associated, and sensitive in the diagnosis of PCP in bivariate analyses, however it failed to reach significance at the 5% level in the multivariate analyses. As discussed in section 1.1, numerous studies have demonstrated the benefit of CTX in preventing PCP (Thea 1996, Rigaud 1994, Duong 1999, Chokephaibulkit 1999, Ruffini 2002, Chintu 2004), and CTX is currently "recommended for primary prophylaxis against PCP in all infants born to HIV-infected women in industrialised and resource-poor countries, from six weeks of age and continuing until HIV-infection status is negative. In HIV-infected children after infancy, CTX is recommended if CD4 counts are less than 15% of total lymphocyte count." (Chintu 2004). Concerns have however been expressed that CTX prophylaxis may lead to bacterial resistance to antibiotics, resistance of malaria parasites to sulfadoxine-pyrimethanamine, and that it may be ineffective in areas that demonstrate high levels of bacterial resistance to PCP. Madhi and colleagues (2002) found CTX prophylaxis was not associated with

a significant reduction in PCP among children considered to have received adequate prophylaxis, and Gill and colleagues (2004) consider that a policy of mass CTX prophylaxis may be counterproductive in certain circumstances.

This analysis has failed to show an independent protective effect of CTX prohylaxis in relation to PCP. The validity of this observation is however questionable, as the study was not specifically designed to measure the drugs' effect, subjects were non-randomised, use of CTX was measured by questioning on retrospective use, and adherence could not be validated.

4.4 Measures of diagnostic accuracy and their clinical relevance

4.4.1 Sensitivity and specificity

The sensitivity of a diagnostic test is the proportion of subjects with the target disorder in whom the test result is positive. Specificity is the proportion of subjects without the target disorder in whom the result is negative. These measures are useful to evaluate diagnostic tests in groups of subjects, but less helpful in applying results to individual patients. In a diagnostic test with multiple outcomes, a cut-off value needs to be chosen to divide test results into normal and abnormal. There is usually a trade-off involved between sensitivity and specificity when selecting a cut-off level, which is shown in the ROC curve of the final model (Figure 1). The part of the curve closest to the top left-hand corner indicates maximum sensitivity and specificity.

The prognosis of an HIV-infected child with untreated PCP is extremely poor, so children with the disease should not be left undiagnosed, i.e. sensitivity of the diagnostic test needs to be

maximised. A cut-off value of any three or more indicators producing a positive test has an unacceptably low sensitivity of 0.75 (95% CI 0.43-0.95). Alternatively, using a cut-off value of any two or more indicators producing a positive test has a higher sensitivity of 1.00 (95%CI 0.74–1.00), but the specificity of 0.49 (95%CI 0.39 – 0.59) is poor. A PPV of 0.18 (using this studies' prevalence of PCP) would also result in an acceptably high proportion of children who would be classified as positive by the test who do not have PCP (82%). These children would receive specific treatment unnecessarily, with its resultant potential for adverse effects.

4.4.2 Likelihood ratio's and post-test probabilities of PCP

LR's are alternate measures of diagnostic accuracy that indicate the magnitude that a diagnostic test (or rule) will raise or lower the pre-test probability of the target disorder. The LR can be calculated for each level of test outcome (the iLR), and diagnostic tests may therefore have more then simply positive or negative results (Mayer 2004). An iLR of 1 indicates no alteration in the pre-test to post-test probability of the target disorder. The higher the iLR is above 1, the greater the increase in probability that the disorder is present. Alternately, the lower the iLR is below 1, the greater the decrease in probability of the disorder.

In order to attach meaning to this diagnostic measure, the following categories are used as a guide to the strength of the usefulness of an iLR: iLR > 10 or < 0.1: conclusive change in pre-test to post-test probability; iLR 5-10 or 0.1 – 0.2: moderate change in probability; iLR 2-5 or 0.2 – 0.5: small change in probability (may be important); iLR 1-2 or 0.5-1: small, mostly unimportant change (Jaeschke 1994).

The iLR is used to calculate the post-test probability of the condition from the pre-test probability. Differing pre-test probabilities will produce differing post-test probabilities for the fixed iLR of each outcome. For an iLR to be useful it should alter the pre-test probability to cross a threshold value, in which treatment (or further investigation) is either initiated or withheld.

Published threshold values based on clinical suspicion, for the initiation of specific treatment for suspected PCP in HIV-infected children with pneumonia, have not as yet been produced, and attending physicians working in areas where definitive diagnosis is not available must use their own discretion, considering the risks and benefits of treatment, when making management decisions. A suggested threshold value, however, is to start specific treatment if the probability of PCP is considered to be ≥10% (Zar HJ, personal interview, September 2004), as used in the illustrative example for the CDR (tables 9 and 10). The nature of the CI's of the post-test probabilities of PCP (for all pre-test probabilities), would however allow threshold values ranging from 1% - 11% without the structure of the CDR being altered.

Use of the CDR in this sample would result in no children with PCP being incorrectly excluded from receiving specific treatment, and fewer than 10% of children without PCP would unnecessarily receive specific treatment. In order to confidently place children in the category of not receiving specific treatment, the upper limit of the confidence interval of the post-test probability of PCP also needs to be below the treatment threshold. The upper confidence limit of the iLR and post-test probability of zero cannot however be calculated, and PCP can therefore not be confidently excluded at the population level, when zero or one indicator is present in a child. The results of this analysis can therefore not be used to inform on clinical management decision-making at this stage.

The usefulness of a diagnostic test is also influenced by the proportion of patients suspected of having the target disorder, whose test results have high or low iLR's which move patients across a treatment threshold (Jaeschke 1994). The proportion of children in this sample with categories of iLR's that potentially produce clinically relevant changes in the probability of PCP is 60.3% (zero, any one, three, or four indicators present, table 9). 39.7% of children in the sample however fell in the indeterminate category of the CDR (children with two indicators present). The category contained 3(25%) of those who had PCP. This category of children may however be suitable for further diagnostic investigation for PCP in areas that have access to diagnostic equipment, but due to geographical distance or resource constraints, are able to investigate only a limited number of children. Laboratory investigations revealed PCP in 3 (6.5%) of 46 children in this category; this is nevertheless an important diagnostic yield due to the serious nature of the disease.

It is interesting to note that in the clinical management of children in the sample, all except one child received empirical broad-spectrum antibiotic treatment prior to laboratory diagnostic results becoming available. A low proportion (17%) of the sample however received anti-pneumocystis treatment empirically, and only 6 of 15 children later confirmed to have PCP received specific treatment empirically. The proportion of the sample started on anti-pneumocystis treatment empirically may be expected to be higher with a pre-test probability of PCP (9.9%) which approximates the suggested treatment threshold (10%). A clinical prediction method for PCP had however not yet been investigated at the time of the study, and children were hospitalised in tertiary centres, where clinicians could generally expect diagnostic investigative results for PCP within 48hrs of admission, and may therefore have been more

cautious about starting specific therapy. The burden of paediatric PCP in Africa had also been poorly described at that time, and may have been expected to be lower than it actually was.

4.5 Strengths and weaknesses of the final predictive model

In summary, the strengths of the final predictive statistical model are as follows:

1. Four clinical indicators have been identified that are independently associated with PCP in HIV-infected children hospitalised with pneumonia.
2. Ease of clinical use, as all indicators are easily measured.
3. The post-test probability of PCP, based on the number of these indicators in an individual child, can be roughly estimated.

The weaknesses of the final model are:

1. Confidence intervals (CI's) for the estimates of diagnostic accuracy (iLR's, post-test probabilities, sensitivity and specificity) of the model are large, due to:
    i) Small numbers of children with PCP in the sample (type II error). Theoretical analyses have shown that the sample should contain at least five subjects (Wasson 1985), but preferably twenty (Mayer 2004) with the outcome of interest, for each predictive finding in the clinical rule. This rule has four predictive clinical findings, therefore the sample should have at least 20, but preferably 80 cases of PCP, in order to increase precision of the estimates of diagnostic accuracy.

ii) Missing observations amongst certain of the clinical indicators resulted in 35 children (three with PCP) being excluded from the final multivariate model, which further contributed to reduced statistical power of the analysis.
The imprecision of the effect measures make it difficult to base firm conclusions or consequent clinical recommendations upon these results.

2. The biological explanation of history of vomiting in relation to PCP is as yet unsure.

4.6 Final predictive model conclusions

1. This predictive model provides preliminary evidence in the clinical prediction of PCP in HIV-infected children hospitalised with pneumonia, and can estimate the posterior probability of PCP based upon four easily measured clinical criteria.
2. It is most useful to use the iLR of categories of test outcome to calculate the post-test probability of PCP. Using a single cut-off to demarcate a dichotomous positive or negative test outcome produces a loss of useful information.
3. An illustrative CDR has been derived that divides children into three categories to either receive or to not receive specific treatment for PCP, and children that require further diagnostic investigation (where available).
4. This CDR can however not be recommended for clinical use at this stage, as it cannot confidently be estimated that children with zero or one clinical indicator will not have PCP at the population level. The imprecision of the measures of test accuracy also make it difficult to base firm conclusions on the results. The CDR has not been validated, and may therefore be described as a level four CDR

according to McGinn and colleagues (2000), that has been derived but not validated. It would need to be re-evaluated in further adequately designed studies with larger sample sizes, in order to quantify measures of diagnostic accuracy with greater precision, before it can be suggested to aid in clinical decision making, if appropriate.

4.7 Strengths of Study

- "The optimal design for assessing the accuracy of a diagnostic test is considered to be a prospective blind comparison of the test and the reference test in a consecutive series of patients from a relevant clinical population. A relevant clinical population is a group of patients covering the spectrum of disease that is likely to be encountered in the current or future use of the test" (Lijmer 1999). This study was a prospective study, and enrolment of consecutive patients is likely to have included subjects with a clinically meaningful spectrum of disease. (The study population however consisted of children admitted to secondary and tertiary hospitals, therefore the results of the study cannot be generalised to include children presenting with pneumonia at primary care levels.)

- Interpretation of the reference test results by the laboratory staff was done without knowledge of the results of the clinical diagnostic test under study, i.e. it was a blind (masked) study.

- Verification bias did not occur, i.e. the decision to perform the reference test was not based on the results of the clinical diagnostic test.

4.8 Limitations of study

This study has the following limitations:

- Admitting doctors did not have a standardised assessment protocol or data-capture form at admission of each child. The number of admitting doctors was not recorded, and admitting doctors were not necessarily briefed on aspects of the study and the need for complete data capture. A person other than the doctor who first examined the child captured the clinical data on the study data capture form from the admission notes. Standard definitions of all potential clinical predictive findings were also not detailed prior to the study. The quality of clinical data is therefore questionable. Inter-observer variation in the assessment of the clinical variables is cosequently likely, which would produce a non-differential misclassification bias of index variables, biasing study estimates towards the null, i.e. produce an under-estimate of accuracy of the test (Wasson 1985, Katzenellenbogen 1997). Inter-observer agreement of the presenting clinical observations between two or more clinicians was not measured, therefore the magnitude of the bias cannot be quantified.

- A non-differential misclassification bias of the outcome (PCP) in the sample is possible, as due to resource constraints of the original study, post-mortem lung biopsy and BAL examination of all children could not be performed. Cases of PCP may therefore have been misdiagnosed, as IS samples have a lower sensitivity and specificity than BAL in the diagnosis of PCP. This would similarly produce a bias toward an under-estimate of test accuracy.

- The post-hoc selection of the cut-off points for the categorisation of the continuous variables in the predictive model may be a source of type I statistical error, and bias toward an over-estimate of accuracy of the diagnostic test (Mayer 2004).

- Provision was not made during data collection for multiple infective pathogens. Prior to the study in 1998, there had been case reports and series of viral and bacterial co-infections with *P. jiroveci* infection. Prospective evaluations of the frequency of this occurrence have subsequently found co-infections with PCP to be relatively common (Madhi 2002, Chintu 2002).

- The number and clinical details of eligible children excluded from the study were not recorded. Children excluded from the study may differ systematically from the study participants in terms of the index clinical variables or the outcome, potentially biasing outcome measures in either direction.

- The rates of misclassification of the test have not been estimated for a new theoretical population using statistical cross-validation techniques, such as the split-sample, jacknife or bootstrap methods (Wasson 1985).

- Many clinical features were compared in children with and without PCP, and statistical power of this study was low due to the small number of children with the outcome. The likelihood of spurious outcomes therefore needs to be considered.

4.9 Reporting of study

The reference test, the clinical diagnostic test, and the study population have been described with sufficient detail to "allow for replication, validation and generalisation of the study," as recommended by Lijmer and colleagues (1999). Descriptions of diagnostic tests are considered sufficient if clear definitions of positive and negative test results are mentioned. Description of the study population is considered sufficient if two of the following characteristics are described: age of participants, female to male ratio, or distribution of symptoms – the former two were described in this study.

This report also includes 22 of 25 criteria recommended for the reporting of diagnostic accuracy studies, according to the Standards for Reporting of Diagnostic Accuracy (STARD) steering group (Bossuyt 2003). The items not included were: Report estimates of variability of diagnostic accuracy between readers, centres or participant subgroups if done (item 23); and report estimates of test reproducibility if done (item 24). Neither were measured in the original study. Item 10 (describe the number, training and expertise of the persons executing and reading the index tests and the reference standard) was partially fulfilled (the number of doctors admitting the sample children was not measured).

4.10 Future studies

Further studies are needed in order to attempt to define a valid CDR. These studies would need to be specifically designed for this purpose, and would require the following features:

- Sample size and power: The sample should contain a minimum of 20, but preferably 80 cases of PCP in order to increase precision of the estimates of diagnostic accuracy, as discussed previously. Assuming a 10% proportion of PCP amongst HIV-infected children hospitalised with pneumonia, the total sample size required would therefore be 200 – 800 children. At the rate of enrolment of children at the four hospitals that were used in the original study, it would however take over five years to achieve a sample size of 800.

- Explicit definitions of all potential clinical predictive findings should be stated, with standardised and complete data capture methods used by the doctors on hospital admission of the child. Inter-observer agreement should ideally be measured, and only those observations with a high inter-observer reliability (kappa statistic) should form part of the final rule.

- Post-mortem lung biopsies should be performed on children who die during the study, as this is the most accurate method for identifying the aetiological agent responsible for the pneumonia (Chintu 2002). These results should be correlated with ante-mortem diagnoses.

- Detection and evaluation of multiple infective pathogens should be incorporated in the study.

- A mathematical model to create a rule that incorporates varying weights for each of the clinical predictors may be used.

- Statistical cross-validation techniques may be used to validate the rule in the study population from which the rule was derived.

The CDR derived in this analysis may also be evaluated in a different setting and population, with prospective measuring of the rate of misclassification.

Future research should also aim to produce explicit treatment threshold values for the initiation of anti-pneumocystis treatment in HIV-infected children based on clinical criteria, for use in areas where laboratory diagnostic measures for PCP are limited.

The relationship between vomiting and PCP should be evaluated in further epidemiologic and pathophysiological research.

5 CONCLUSION

This study has shown that four presenting clinical features are independent indicators of the risk of PCP amongst HIV-positive children hospitalised with pneumonia in South Africa, namely respiratory rate > 59 breaths/per minute; age < 6 months; $SaO_2 \leq 92$; and absence of history of vomiting at presentation.

A multivariate model has been described that estimates interval likelihood ratio's and post-test probabilities of PCP for differing numbers of these indicators. There is a low probability of PCP with zero or one clinical indicator in a child, and increasing probabilities with the presence of any three or all four of the indicators. The derived CDR may have use in assigning children to treatment categories, and in identifying children that require further diagnostic investigation should this be available for a limited number of children.

This analysis provides preliminary evidence in the clinical prediction of PCP in HIV-infected children with pneumonia. The CDR is however unable to conclusively identify children at the population level that do not require specific anti-pneumocystis treatment. The important measures of test diagnostic accuracy are also imprecise, and design-related biases may have influenced the results. Conclusions or clinical recommendations can therefore not be based on the results at this stage. Further studies that are specifically designed to validate clinical predictors of PCP in HIV-infected children should be undertaken, in order to quantify measures of diagnostic accuracy with improved precision and validity.

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APPENDIX 1: Box plots of continuous variables in the final model indicating categorisation cut-off values.

Figure 3: Respiratory Rate according to PCP status

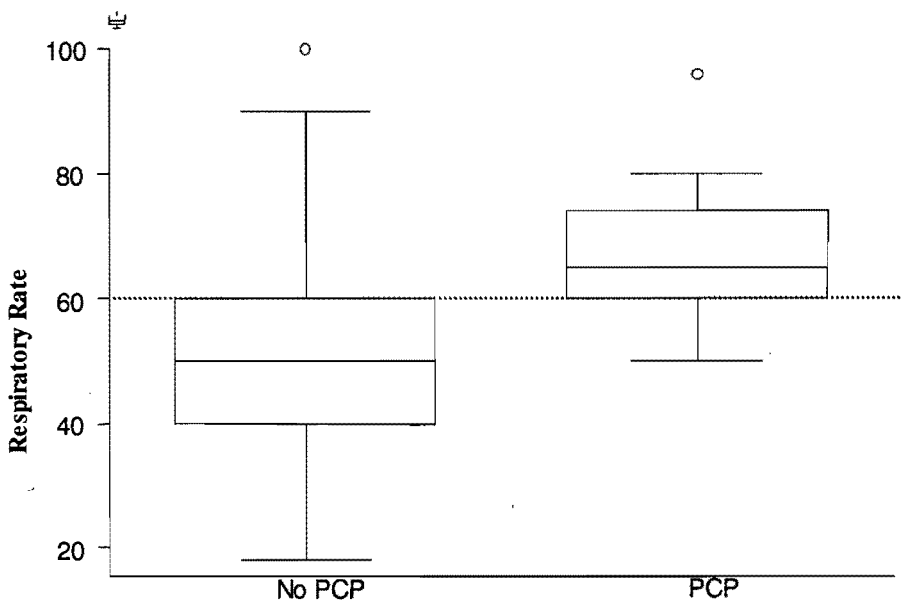


Figure 4: Age according to PCP status

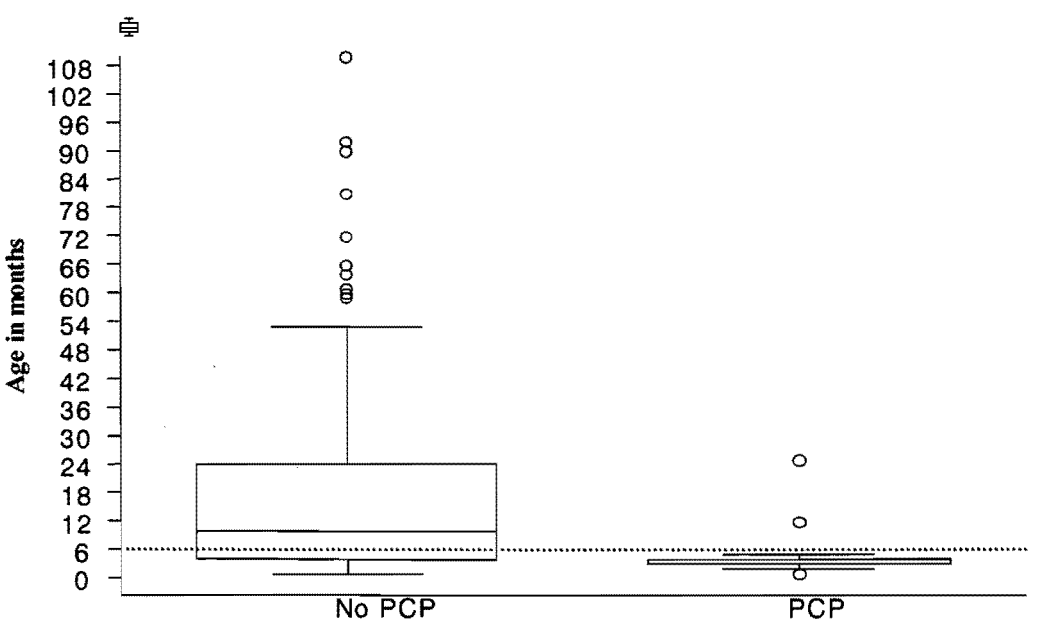
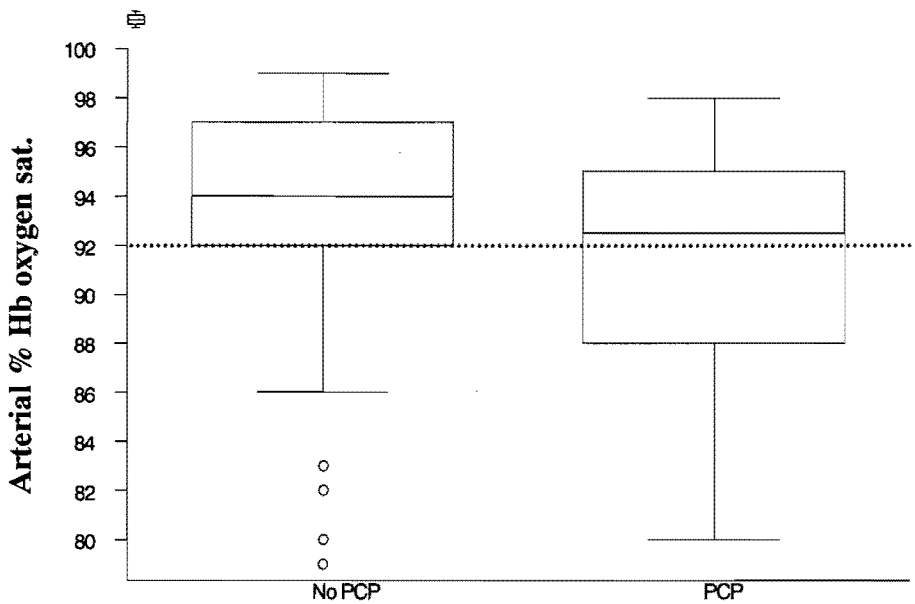


Figure 5: Arterial percentage haemoglobin oxygen saturation according to PCP status



APPENDIX 2: Model-checking procedures for the final model.

Four aspects of the final statistical model were checked, namely:

1. Assessment of the form of the linear predictor.
2. The appropriateness of the link function.
3. Detection and description of outlying observations.
4. Detection and description of influential observations.

1. Assessment of the form of the linear predictor.

i Plots of standardised deviance and Pearson residuals were plotted against the observation number (index plots, Figures 6 and 7). A systematic pattern in these plots would indicate that the model is incorrect.

ii Standardised deviance residuals were plotted against the linear predictor (Figure 8). Two distribution curves are typically seen for binary data, which would indicate adequacy of the linear predictor.

Figure 6: Plot of standardised deviance residuals vs. study-number

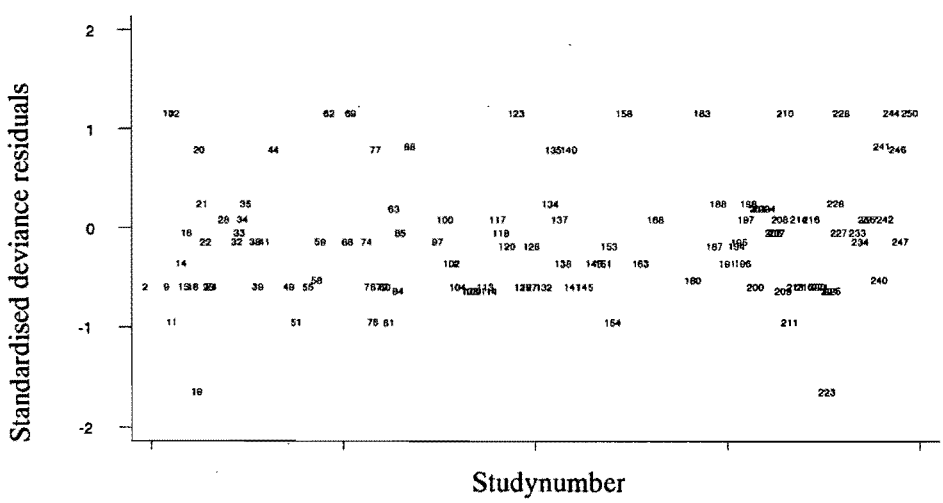
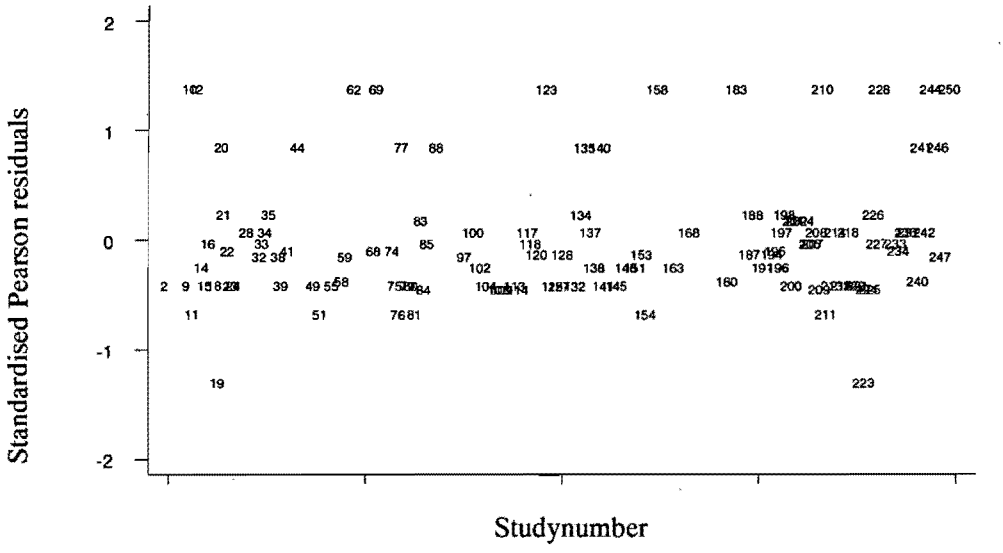
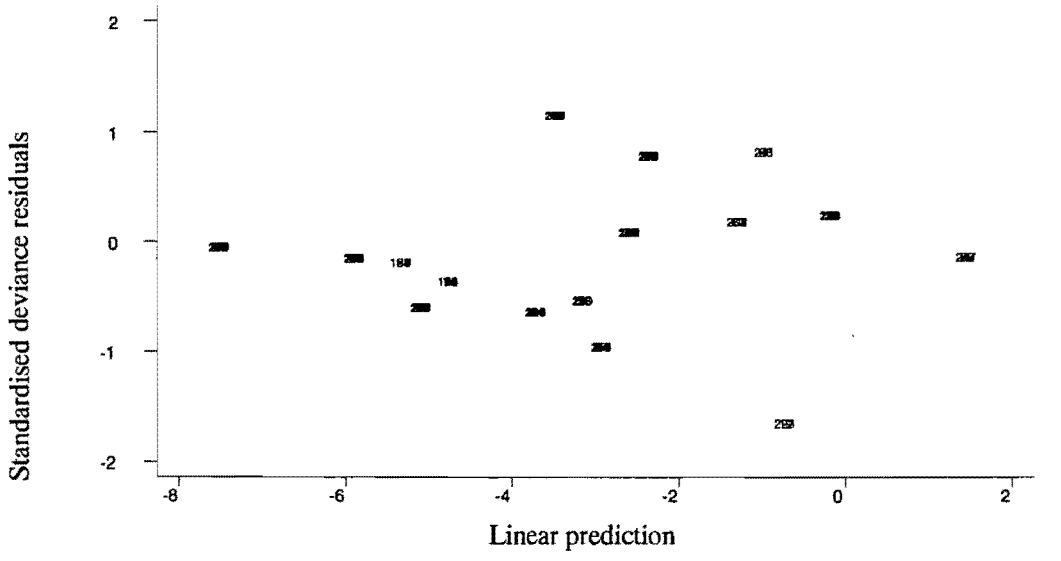


Figure 7: Plot of standardised Pearson residuals vs. study-number



No systematic pattern is detectable in either of these plots, indicating that the linear component of the model is adequate.

Figure 8: Plot of standardised deviance residuals vs. linear predictor



The form of the linear predictor is adequate, as seen by the typical distribution for binary data.

2. The LOGIT transformation is always appropriate for a binary response as used in this analysis, and therefore does not need checking.

3. Outlying observations.

   Figures 6 and 7 are also used to detect outlying observations with residuals >|2|.

Two subjects are identified as potential outliers, namely study-numbers 19 and 223, however their standardised residuals are < |2| indicating that they are weak outliers.

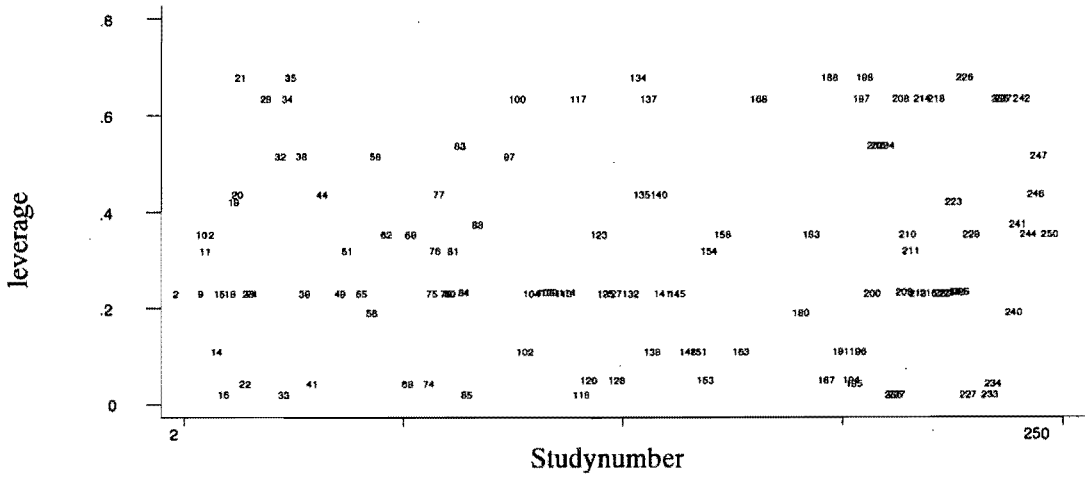
Description of these subjects:

Study-number 19: Did not have PCP despite having a respiratory rate of 50, age of 3 months, SaO_2 of 90%, and no history of vomiting.

Study-number 223: Did not have PCP despite having a respiratory rate of 18, age of 3 months, SaO_2 of 90%, and no history of vomiting.

4. In order to identify observations with high leverage (influential observations), a plot of the leverage statistic (h_I) is drawn against the observation number (Figure 9). Observations with a high leverage would have a high h_I value compared to the other observations.

Figure 9: Plot of leverage statistic (h_i) vs. study-number



No subjects with high leverage are observed.

Model Checking Conclusions:

1. The form of the linear predictor is adequate.
2. The link function is adequate.
3. There are no strong outlying observations.
4. There are no influential observations.

APPENDIX 3: Calculation of interval likelihood ratio's and their confidence intervals

(Simel 1991)

		Disease	
		Present	**Absent**
Test	Level 1	A	B
Result	Level 2	E	F
	Level 3	G	H
	Level 4	C	D
	Total	n1	n2

Matrix when obtaining multilevel test results

The point estimate of the interval likelihood ratio of level 2 is given by the equation:

$$LR_2 = \frac{p_1}{p_2} = \frac{E/(A+E+G+C)}{F/(B+F+H+D)} = \frac{E/n_1}{F/n_2}$$

Where p_1 = proportion of diseased patients with a given test result

p_2 = proportion of non-diseased patients with the same test result

The 95% confidence interval of the interval likelihood ratio is calculated as follows:

$$LR_2 = \exp\left(\ln\frac{p_1}{p_2} \pm 1.96 \cdot \sqrt{\frac{1-p_1}{p_1 n_1} + \frac{1-p_2}{p_2 n_2}}\right)$$

APPENDIX 4: Calculation of post-test probabilities using Bayes' theorem

(Adapted from Buchsbaum 1991, Mayer 2004)

$$P2 = \frac{\frac{iLR \ . P1}{1 - P1}}{1 + \frac{iLR \ . P1}{1 - P1}}$$

Where P1 = pre-test probability of disease

P2 = post-test probability of disease

iLR = interval likelihood ratio

Confidence interval limits of the post-test probabilities of disease are calculated using the confidence interval limits of the iLR.

PAIN MANAGEMENT IN CHILDREN WITH CANCER

Dissertation by

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INDEX

INTRODUCTION

Pain is an important problem in the care of children with all stages of cancer but especially in the 'end of life' phase. The World Health Organization (WHO) confirms that palliative care serves to affirm life through the active total care of patients whose disease is not responsive to curative treatment. Cancer pain management in the child requires an in-depth knowledge of both the gene management of children and the manifestations of paediatric pain. It is ethically wrong to allow a child to suffer uncontrolled pain. Every child deserves to have adequate and safe pain control. Th goal of management is to achieve the best quality of life (QOL) for patients and their families duri illness and bereavement. The child with cancer is usually part of a larger family unit; the needs an input of parents, siblings, and extended family members need to be addressed in order to achieve optimal relief for the child.

The assessment and measurement of paediatric pain requires the understanding of normal development and behaviour, recognition of age-appropriate verbal and behavioural manifestations pain, and the knowledge of the tools currently available for the assessment and treatment of paediatric pain.

Drugs for pain and symptom control in children, the dosing guidelines and specific toxic manifestations need to be understood by the caregivers.

In South Africa (SA) there are 9 paediatric oncology units (POU) which treat children with cancer therefore are involved in the management of cancer pain in children.

Each POU has its own pain and symptom management regimen and it is unknown whether there any conformity in the management of pain by the different units in the country. If there is no consensus on pain management in children in the RSA, physicians who move from one Province another, probably manage pain as they were taught in the unit where they previously worked, wh can lead to continued diversification.

LITERATURE REVIEW

Almost all children with cancer will experience pain. It could either be as a direct result of the disease, as a side effect of treatment, as the result of invasive clinical procedures, or as an aspec psychological distress. In 70% of cases, pain will at some stage become severe. Although the means to relieve pain are widely available, in developed and developing countries alike, their use children has often been very limited. There is a need to address the lack of knowledge of children perception of pain and illness. Non-drug, supportive measures need to be evaluated again, and u in the daily management of pain control. Reasons for inadequate pain control could include inappropriate drug doses, and the fears of drug 'addiction' resulting in the fact that the general ke principles of analgesic drug administration ('by the ladder', 'by the clock', by the child' and 'by the mouth') are not followed.

We need emphasis on a holistic approach. Management of pain should not be in isolation but as p of a comprehensive palliative care plan.

and answer their questions with honesty.

The value of involving family members in treatment and support must be appreciated.

KEY PRINCIPLES

The general principles of analgesic administration which is advocated by health professionals are **'by the ladder'**, **'by the clock'**, **'by the child'**, and **'by the mouth'**.

The World Health Organization (WHO) initially developed the ladder approach.

'BY THE LADDER'

'By the ladder' refers to a three-step approach for selecting progressively stronger drugs progressing from paracetamol to codeine to morphine to correspond to the child's pain level which may progress from mild to moderate to strong.

STEP 1
Non-opioid analgesic (for example, paracetamol, NSAID)
+/- Adjuvants (antidepressants, anticonvulsants, steroids)
If pain persists or increases

STEP 2
Weak opioids analgesic (for example, codeine)
+/- Non-opioid analgesic
+/- Adjuvant drugs
If pain persists or increases

STEP 3
Strong opioid analgesic (for example, morphine, diamorphine)
+/- Non-opioid analgesic
+/- Adjuvant drugs

The use the World Health Organization (WHO) ladder of treatment allows for a systemic approach to pain control. The WHO ladder is applicable to the management of long term pain

dose, and dosing schedule, children should receive the next more potent analgesic.

'BY THE CLOCK'

'By the clock' refers to the timing for administering analgesic medications. Analgesics should be administered on a regular schedule (e.g. every 4 or 6hours, based on the drugs duration of actior and the severity of the child's pain) not on a pro re nata basis, unless the pain episodes are truly intermittent and unpredictable.

On a pro re nata basis, children must first experience pain before they can obtain pain relief. Chil should receive analgesics at regular times, 'by the clock', to provide consistent pain relief and prevent breakthrough pain.

'BY THE CHILD'

'By the child' refers to the specific needs of the individual child. There is no perfect, universal do that will be appropriate for all children with pain. The goal is to keep the child pain free and to sele a specific dose, which will prevent a particular child from experiencing pain before he/she receive the next dose.

'BY THE MOUTH'

'By the mouth' refers to the route of drug administration. Medication should be administered to children by the simplest, least painful and most effective route, usually by mouth.

COMMUNICATION WITH PARENTS

Parents want to be actively involved in making decisions about their child's care. They value hone accuracy, clarity and compassion in their providers.

Parents should be informed about pain relief and they should be aware that pain control plans are individual to every child and his or her family. The family's coping ability is of great importance.

team members, the child, and the family.

Every unit should have information leaflets available for the parents, care team members and far involved in the pain management of the individual patient. A general information leaflet about can pain, the ladder approach, adverse effects of analgesics used and contra indications of the NSAII are very helpful and valuable to the unit and the parent. Every unit should compose information leaflets to suit their circumstances. The leaflet will have to be translated in to all the most frequent used languages. See Appendix F as an example of a patient leaflet on morphine.

ROUTE OF ADMINISTRATION OF PAIN RELIEF

The preferred route for drug administration is orally. The rectal, subcutaneous or intravenous rout should be used for patients with persistent vomiting, post operative GIT dysfunction or depressed level of consciousness. Disadvantages of difficult routes are the following: pain and discomfort, operator experience required, unpredictable absorption, costs and maintenance of the specific rou Verbal consent should, whenever possible, be obtained from the parents and child when the recta route is used for drugs. The use of syringe pumps for subcutaneous or intravenous delivery of analgesic agents is well documented. This provides the options of a continuous 24hr infusion reaching steady state levels or intermittent bolus of which the pharmacokinetics is less predictable further advantage is the possibility of adding the following drugs with morphine as part of a continuous subcutaneous or intravenous infusion:

Cyclizine
Dexamethasone
Haloperidol
Hyoscine hydrobromide
Metoclopramide
Midazolam

Routes of administration of analgesics should be discussed with the child and parents.

LOCAL ANAESTHETIC DRUGS

Procedure-related pain is a significant problem for many children receiving cytotoxic chemotherap Eutectic mixture of local anaesthetics (EMLA) consists of lignocaine 2,5% plus prilocaine 2,5%. T topical cream (5%) provides effective superficial anaesthesia, and promises to be extremely usefu for pain relief during percutaneous access procedures in cancer patients. EMLA cream needs at least 45min (ideally 60-90min) to work; onset is slower in non-Caucasians, because its absorption impeded by melanin in the skin. It constricts capillaries in the skin, causing blanching. The constriction resolves 15min after removal of the cream, although the analgesia persists for 1h. Sk irritation may occur if the cream is left on for more than two hours. A study by AW Miser and TS G (1994) showed a statistically significant decrease in pain intensity scores ($P < 0.002$), recorded by both children and investigators, during the use of EMLA cream as compared with placebo.

Amethocaine gel (Ametop) contains 40mg/g of amethocaine. It is used in the same way as EMLA but, unlike EMLA, may dilate capillaries making the siting of cannulae easier. There is adequate analgesia after 30min. for venepuncture and after 45min. for venous cannulation.

Lignocaine and bupivacaine can both be used as infiltration to provide local analgesia. Lignocaine has a pH of 5 to improve its shelf life, and for this reason can be painful when injected. Warming th solution to body temperature and injecting it very slowly can reduce the local stinging. Aspiration before each injection and constant movement of the needle are useful ways to avoid intravascular injections. This method of providing local anaesthesia is not popular in children (for procedures su as siting an IV cannula) as the administration of the local is almost as painful as the procedure itse

SEDATIVES AS ADJUVANTS TO ANALGESIA

Sedatives are particularly valuable when lengthy and repeated procedures are undertaken.

Sedatives may result in unpredictable responses in some children who may become disinhibited, agitated, restless or over-sedated.

Sedatives relieve anxiety, not pain. During their administration appropriate monitoring should be undertaken and skilled individuals should be available to manage the airway if a problem develop

Chloral hydrate is a pure sedative/hypnotic with no analgesic effect. Midazolam is an amnesic sedative, but also not an analgesic drug. These drugs should not be used alone for painful procedures. Ketamine may produce laryngospasm, particularly in infants. It is a potent analgesic a well as a dissociative anaesthetic. Ketamine can produce nightmares and hallucinations, especial in older children. It is a very useful agent given orally rectally, intravenous or intramuscularly (exception only).

NSAIDS

NSAIDS are very useful agents for pain management, either alone or in combination with other analgesics. Used in combination with an opioid, NSAIDS allow the use of a lower dose of opioid to achieve equivalent analgesia ('opioid-sparing effect'). They are also useful as a 'step across' or a 'step down' analgesic when weaning a patient up or down the WHO ladder of pa control.

One should be aware of the side effects and contraindications of the NSAIDS. NSAIDS are not licensed to be used in infants and should be used with care in this age group or in children weighir less than 10kg. They need to be used with care in children who are thrombocytopenic as they inhil platelet action. NSAIDS are especially good for pain with an inflammatory component, and for bon pain, for example, diclofenac, either orally, via gastrostomy or as suppositories.

ADJUVANT ANALGESIC AGENTS

NEUROPATHIC PAIN

Neuropathic pain, which is usually due to nerve infiltration or compression, is only partially responsive to opioids. It should be considered particularly if the pain has an unusual nature, for example burning or shooting.

Two classes of drugs are valuable in the management of neuropathic pain and should be started early on if possible:

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants such as amitriptyline may be helpful, especially in treating the burning pa caused by nerve compression, invasion by tumour or from neuropathy (for example, caused by vincristine). The starting dose of amitriptyline is 500 micrograms/kg at night (increasing if needed mg/kg twice daily).

ANTICONVULSANTS

Anticonvulsants such as carbamazepine may be helpful, especially when neuropathic pain is shooting or stabbing. Start with a low dose of 2,5mg/kg twice a day, and increase gradually by 2,5 5mg/kg/h (consider using controlled release tablets). Therapeutic blood levels range from 4-14mg/

NON-PHARMACOLOGICAL INTERVENTIONS

ENVIRONMENTAL FACTORS

The treatment room on a paediatric ward can often be a frightening place for a child. Every attemp should be made to minimize or to remove the negative aspects of these areas, such as an overly

environment decorated with toys, mobiles and pictures.

SUPPORTIVE AND DISTRACTIVE TECHNIQUES

Age appropriate distraction strategies which may be used in the treatment room during procedure include:

- Holding a familiar object (comforter), such as a pillow or soft cuddly toy
- Singing; concentrating on nice things; telling jokes; games and puzzles
- Going on imaginary journeys
- Blowing out air or bubbles
- Reading pop-up books
- Playing with a kaleidoscope or 3D viewer
- Breathing out (but nor hyperventilation, which may increase anxiety and induce venoconstriction)
- Looking in a mirror to see the view through a nearby window
- Watching television or a video, playing interactive computer games
- Listening through headphones to stories or music.

Parents can assist with many of these activities. Not all children are helped by distraction; some prefer to focus on the procedure. It is important to identify each child's coping mechanism and hel the child to use it.

It is becoming more common for parents to stay with their child during an invasive procedure. However, this depends on the experience of the doctor and the type of procedure. Less experienc doctors are uncomfortable with parents present, and many doctors will allow parents to be present for venepuncture or lumbar puncture but would exclude them during more invasive procedures, fo example, insertion of a chest drain.

helped most' was to have their parents present during a painful procedure. It is not enough just to allow parents to be present; they need guidance on how to support their child during the procedur Studies suggest that talking to and touching a child during a procedure is both soothing and anxie relieving. The child and parents should be adequately prepared for the procedure. Explaining to th parents why the procedure is needed, how it will be done and how long it will take may help reduc anxiety.

In a few children, especially those who require repeated procedures and long stay in hospital, a ch psychologist and/or a child psychiatrist form part of the valuable multidisciplinary team in oncology Music and art therapy techniques may also be of value.

RATIONALE FOR THIS STUDY

Pain management does not appear in the textbook most recommended for South African undergraduate paediatric medical students. Hospitalised children with chronic pain are most likely be patients in a POU. In SA there is no formal unified regimen for pain control in children with terminal cancer.

Pain in children is therefore managed according to the experience and expertise of the paediatricia of the local POU. It is unknown what facilities are available or what methods are used by the differe POU's for pain management. Paediatric Oncology Units are responsible for all paediatric cancer management and for this reason it was decided to start a survey in this section of paediatrics.

AIM

The **AIM** of this study is to evaluate the present situation of pain management in the 9 POU's of SA and to suggest an optimal practical pain management regimen for children in these 9 paediatric oncology units.

METHODS

Study design: A cross-sectional study was used to assess the management of pain in the nine Paediatric Oncology Units (POU's) in SA.

A questionnaire with both open-ended and closed response questions was the two major formats used.

As a group, cross-sectional studies fall between purely descriptive studies and those that can be used for testing hypotheses. Cross-sectional studies are also useful for describing the clinical spectrum of a disease. However, in modified forms cross-sectional studies are sometimes employ to do some analytical work. In cross-sectional studies all observations are made on a single occasion. Surveys are a form of cross-sectional study aimed at describing accurately the characteristics of a given population. They are often used for assessing attitudes, opinions or beli of persons concerning health related issues. The information is obtained by questionnaires and interviews. The questionnaire is an important device for gathering research data. In order to obtai accurate, valid and reliable responses it is necessary to have a well-designed questionnaire. A variety of comparisons can be made using survey data. Variables may need to be controlled. The researcher needs to measure differences between the groups.

One great advantage with the self-administered questionnaire is financial. There is a marked reduction in costs because of savings in the number of interviewers to be employed, and in time. There is the additional advantage of standardized response, because the variability of different interviewing techniques and the interaction between the subject and the interviewer are eliminated One problem with this method is that it can only be used in situations where literacy rates are sufficiently high and postal services are reliable. The disadvantages are higher rejection rates, the inability to obtain clarifications or details, and less control over how the form is filled. The

acceptable answers.

The principal considerations before commencing the development of a questionnaire are the following:

1) Does a suitable questionnaire already exist?
2) Who will complete the questionnaire?
3) What format will be used? Open-ended and closed responses are the two major formats. Open-ended has the advantage of eliciting more detailed answers. The respondent is free answer without any limitations imposed by the interviewer. The disadvantage is that greate time is taken to complete the questionnaire; respondents get tired; difficulty in analyzing answers. Closed response question have the advantage of being tightly structured; respons is easy to code and analyze; less time is taken in filling the questionnaire. The disadvantag are that the answers have less depth. The respondent is led in pre-determined direction leaving him less choice to express his own potentially unique answers.

☐ A questionnaire (Appendix B) on the teaching and practical management of pain in children with terminal cancer was sent to each of the Paediatric Oncology Units in the RSA. Questio 26.1 and 26.2, on the teaching will not be dealt with in this research, but the information is included for future analysis. Open-ended and closed response questions were asked and a the end of the questionnaire there was enough space left for comments.

An information sheet (Appendix A) accompanied the questionnaire.

This method was suitable for this study: i) all persons that completed the questionnaire are literate open-ended responses have the advantage of eliciting more detailed answers iii) closed response

completed at a paediatric congress which the 9 POU's attended.

The information received from the POU's is confidential, patient identity or the name of the reporti unit is not revealed and no ethical issues apply to this study.

The information was recorded and analysed to determine similarities, most common practices, an useful additions.

The questionnaires were completed by the most experienced person from each POU. No previous questionnaires were used to collect any of the questions.

There are only 9 POU's in SA and therefore the sample size was limited. Fortunately all 9 POU's responded and completed the questionnaire.

RESULTS: ANALYSES

QUESTIONS ASKED		REPLY BY POU'S		
		Y	**N**	**N/A**
Q1:	**Do you use visual analogue scales for pain assessment?**	**2**	**7**	
Q2:	**Do you use the 'by the ladder' approach for analgesic administration?**	**6**	**3**	
Q3:	**Do you use 'by the clock' analgesic management?**	**5**	**4**	
Q4:	**Do you provide any info on cancer to the patients?**	**6**	**3**	
Q5:	**Do you provide the parents with info about the side effects**	**7**	**2**	
Q6:	**Do you discuss the 'by the ladder' approach?**	**5**	**4**	
Q7:	**Do you explain your choice of analgesic?**	**7**	**2**	
Q8:	**Do you have any input from parents? (e.g. pain assessmen Pain control)**	**4**	**3**	**2**
Q9:	**Do you use intramuscular analgesic?**	**0**	**9**	

Q11:	Do you use S/C morphine syringe drivers?	4	5	
Q12:	Do you use intravenous syringe drivers?	7	2	
Q13:	Do you use rectal suppositories for pain? • 1 – morphine • 1 – Voltaren	2	7	
Q14:	Do you use local anaesthetic before performing LP's • 1 – not done • 1 – EMLA • 1 – lignocaine • 1 – EMLA & lignocaine • 1 – IV sedation	6	2	
Q15:	Do you use local anaesthetic before siting an IV cannula? 4 – EMLA	4	5	
Q16:	Do you use sedation for intrathecal chemotherapy? • 1 – general anaesthetic • 1 – Dormicum & Vallergan forte & Inapsin • 1 – Ketamine • 1 – Dormicum • 1 – Dormicum & Ketalar • 1 – Midazolam & Valoron • 1 – Dormicum & Atropine & Ketalar • 1 – not done	7	1	
Q17:	Do you make use of a child psychiatrist to evaluate Emotional pain?	4	5	
Q18:	Do you give accurate age-appropriate info about pain to the child?	6	3	
Q19:	Do you find that situational factors can lead to inadequate pain control?	9	0	
Q20:	Do you evaluate contributing situational factors?	9	0	

Q21:	Do you measure/revise the child's pain regularly? • 6 – daily • 2 – 4 to 6 hourly	8	1	
Q22:	Do you use the child's physical parameters as pain measure?	4	5	
Q23:	Do you use Valoron drops?	9	0	
Q24:	Do you use adjuvant analgesic drugs? • 1 – Corticosteroids/Anti-epilepticums • 2 – Steroids/Anti-depressants • 1 – Tegretol • 1 – Solucortef • 1 – Anti-depressants • 1 – Steroids/Tegretol/Amitriptilene • 1 – no drugs mentioned	8	1	
Q25:	Do you make use of NSAIDS? • 1 – Doxyphene • 1 – Ponstan/Brufen • 1 – Voltaren • 1 – Brufen • 1 – Aspirin • 1 – drug not mentioned	6	3	
Q26:	Do you feel you have optimal pain control for children?	7	2	
Q27:	Do you make use of attention distractions?	1	8	
Q28:	Do you make use of music when performing procedures or for relaxation?	2	7	
Q29:	Do you have a separate room to perform procedures and to lessen the traumatic experience for the child?	9	0	

Over 80% of children with advanced cancer will experience pain, regardless of the underlying diagnosis. The child with cancer may experience pain of several etiologies (See table 1).

Table 1: ETIOLOGIES OF PAIN IN CHILDREN WITH CANCER

ETIOLOGY	EXAMPLES
Cancer-related	
• **Direct**	• **Bone and/or bone marrow invasion** • **Soft tissue invasion, capsular distension, hollow viscus obstruction** • **Invasion/compression of central or peripheral nervous systems**
• **Indirect**	• **Bed sores**
• **Debility**	• **Infection**
Treatment-related	• **Mucositis** • **Postoperative state** • **Infection** • **Radiation dermatitis** • **Abdominal pain from protracted vomiting** • **Prolonged post-lumbar puncture headache** • **Neuropathy: drug-induced, phantom limb**
Procedure-related	• **Bone marrow aspiration and biopsy** • **Lumbar puncture**
Incidental	• **Trauma** • **Pre-existing medical condition**

Careful assessment of pain should be undertaken before commencing treatment. In 1987 Wong a

Baker described the **QUESTT** approach to pain assessment.

- Question the child
- Use pain rating scales
- Evaluate behavioural and physiological changes
- Secure the parents' involvement
- Take the cause of pain into account
- Take action and evaluate the results

effect pain assessment.

The results of the questionnaire :

The visual analogue scales are only used by two of the 9 POU's.

Six of the 9 POU's make use of the 'by the ladder' approach, and 5 of the 9 POU's make use of t 'by the clock' analgesic approach.

All professionals involved with any kind of pain management should use the 'by the ladder' appro for analgesic administration. In SA two thirds of the POU's make use of the 'by the ladder' approa 'By the clock' analgesic administration is used by 5 of the units. Analgesics given at regular times provide consistent pain relief and prevent breakthrough pain.

All the POU's avoid intramuscular analgesic administration and are aware that this method has a very limited role to play in the pain management of children. The intramuscular route is not appropriate and there is little place for IM pain relief, particularly as a repeated treatment.

Intravenous (IV) analgesics are used by 8 of the POU's. Four make use of subcutaneous morphin syringe driver and seven make use of an intravenous syringe driver. Two of the units use rectal suppositories. Local anaesthetic is used by four of the nine POU's before IV cannulation.

A subcutaneous morphine syringe driver could be a very helpful method of managing pain in the terminally ill child, as it would allow some individuals to go home with a syringe driver. A hospice could be involved with the further care and management of these individuals.

It appears that the POU's have good communication with parents and their patients. Information about pain, analgesic management and side effects of the treatment(s) is being discussed by most the units. Seven of them explain the choice of analgesics, and seven of the units give parents information on adverse effects of the pain treatment. Four of seven units have input from parents o pain control/pain assessment (2 did not answer the question).

The majority of the units use sedation before performing intrathecal chemotherapy. One unit does not administer intrathecal chemotherapy.

Six of these units use local anaesthetic before performing lumbar punctures. These are very goo results, but the units not using any anaesthetic or sedation should be encouraged to review their protocols and consider an appropriate form of sedation.

A positive aspect from this survey shows, that the pain management teams are aware that contributing and situational factors can increase the level of pain in these children.

Valoron drops (all 9 units use these drops) and adjuvant analgesic drugs (8 of the units use these analgesics) play a valuable role in pain management.

Three of the POU's do not use NSAIDS. NSAIDS usually form part of STEP 1 of the 'by the ladde approach. Thrombocytopaenia may be one reason why so few units use this group of drugs, but t aspect was not determined in this study.

Supportive and distractive techniques are of great value to limit the traumatic experiences of these children. These children need to deal with multiple procedures, for example IV cannulations, intrathecal chemotherapy, lumbar punctures and other investigations.

Two units make use of music when performing procedures or for relaxation and only 1 unit makes use of attention distractions. All nine units have a separate room to perform procedures. Seven of the POU's feel they have effective, controlled pain management. Six of the 9 POU's provide the parents with information on cancer pain. Five of the 9 discuss the ladder approach.

The study confirms suspicion that an optimal practical pain management regimen for children in S is needed.

IMPLEMENTATION OF SELF-REPORT SCALES

The selection of a self-report scale should be based on:

- The age of the child
- His/her cognitive ability
- The time available for education about the scale
- The knowledge of nursing staff about the scale
- The preference of children who have used the different scales in the past.

In practice very few, 2 of the 9 POU's, make use of a visual analogue scale. It may be that the paediatric units are too busy or that it simply takes too long for staff to explain and assess the child pain. It could be that the scales are too difficult or dull for patients to use. Cultural differences could also play a major role in POU's in SA. A pain scale should be equally applicable to all cultures, or at least allow modification for different cultural contexts. This problem is more obvious where visual scales are used with photographs of children's faces. Black children will not identify with photos of white children. In children between 3-6 years of age, a combination of verbal report and behavioural mechanisms is more reliable and a more accurate way for pain assessment. In children under the age of 3 years one has to rely only on behavioural mechanisms because communication is not primarily verbal. Scales selected should be simple, clear and easy to use. Self-report scales provide a subjective, quantitive measure of pain. They are generally considered suitable only for children over age 6 years of age, as they all rely to some extent on the child having some idea of relative size and number.

Self-report scales require the child's co-operation and understanding, and may be interpreted differently by different cultural groups. In practice they are said to be more useful in the assessment of response to analgesia.

infrequently. Scales selected should be simple, clear and easy to use. Available scales for the self reporting of pain in children are listed in appendix C. The CHEOPS behavioural scale is easy to le and use. Six observed behaviours, crying, facial expression, verbal expression, torso position, leg position and touch are scored. The CHEOPS scale was originally used for postoperative pain and needle pain. The disadvantage is that the scale is insensitive for long-term pain.

Behavioural measures are the option to use in very young children (4 years or younger). The faces scale is a good option to use in the child 6-8 years old. The visual analogue scale (VAS) can be us in the child that understands numbers and proportions (age 5 years and over). The vertical scale may be better than the horizontal scale.

Many children are incapable of completing a Visual Analogue Scale before they are 5 years old. Observation is therefore often the only way to establish whether a child is in pain and to measure t intensity of the pain. This is why it is important to find a system for clinical grading of child pain tha could be implied by medical staff. The DEGR scale (Gauvain-Piquard A.) includes anxiety and depression-like items. This scale was designed to diagnose and grade pain evoked by cancer in children aged 2-6 years. This scale is based on behavioural observation.

The scale consisted of the following 17 items.

ITEM SCALE

1- Nervousness, anxiety
2- Antalgic rest position
3- Ability to protest
4- Spontaneous protection of painful areas
5- Child retires "into his shell"
6- Somatic complaints
7- Lack of expressiveness
8- The child points out painful areas
9- Moodiness, irritability

11-Lack of interest in surroundings

12-Control exerted by the child when moved

13-Slowness and rarity of movements

14-Emotional reactions to medical examination of painful regions

15-Signs of regression

16-Social withdrawal

17-Tendency to cry

Seven items concerned with pain (items 2,4,6,8,10,12 and 14), six items concerned with depressi

(items 5,7,11,13,15,and 16), and four items concerned with anxiety (items 1,3,,9 and 17).

OBSERVATION OF PHYSIOLOGICAL MEASURES +/- BEHAVIOURAL CHANGE

Only 4 of the 9 Paediatric Oncology Units evaluate physiological measures to assess pain.

The following behavioural and physiological measures may be indicators of pain:

- Facial changes, acute or chronic- for example frozen watchfulness
- Crying
- Sweating
- Withdrawal from environment, not interacting and playing
- Sleep disturbance
- Poor appetite
- Unwilling/less interested to play; decreased motor activity
- Decreased concentration
- Increased heart rate and blood pressure
- Nursing staff should monitor the oxygen saturation, respiratory rate, blood pressure, heart ra

CONCLUSION

There is no conformity in the management of pain in children with cancer by the 9 different POU's SA. Some units have limited access to certain drugs. Cultural issues, language barriers and socio-economic differences exist in some of these units. There are also limitations at some units for supporting services, such as hospice care.

RECOMMENDATIONS

There is a need for a formal unified regimen for pain control in children with cancer in SA. Guidelines should be available at every POU in SA. Physicians at these units, as well as the nursir staff and the rest of the multidisciplinary team involved with these children, should have teaching o pain management in children with cancer.

Prior to treatment cancer pain should be classified according to the method proposed by Ljungmar et al., who suggest that cancer pain can be reduced to one or more of four basic etiologies as follows:

- ✓ Cancer related (e.g. pain due to infiltration of the tumour in various organs or tissues)
- ✓ Treatment related (e.g. pain as side-effect of chemotherapy and radiation- for example, mucositis, radiation dermatitis, drug-induced peripheral neuropathy, prolonged post-lumbar puncture headache)
- ✓ Procedure related (e.g. due to finger-prick, venepuncture, lumbar puncture, bone marrow aspiration and trephine, or post-operative pain)
- ✓ Pain of other etiology (e.g. growth pains, trauma)

SUGGESTED REGIMEN FOR PAIN MANAGEMENT IN SA

It might not be possible to use the suggested regimen at all the POU's, but each unit could adapt suggested regimen so that it would work best for their circumstances. Adaptations would need to made where some units have limited access to certain drugs, cultural issues and socio-economic differences exist and where supporting services (e.g. hospice) are limited. Each unit should revie their guidelines and make the proper adjustments to have effective and controlled pain managem for their children. The following are guidelines and recommendations to have optimal pain management control in children with cancer:

1. Make use of a **PAIN ASSESSMENT TOOL/SELF-REPORT SCALE** to assess the child's pain. The following are recommended:

AGE	MEASURE	DESCRIPTION
< 3 years	CHEOPS	Six observed behaviors : crying facial expression verbal expression, torso position, leg position, touch
3 - 6 years	Faces scale	Faces indicating pain intensity were derived from children's drawings
> 6 years	Visual analogue scale (VAS)	Vertical or horizontal line with verbal, facial or numerical anchors on continuum of pain intensity
Adequate cognitive & communicative abilities	Self report measure	Child is asked about intensity, rhythm & variation pain

Methods for assessment of pain

- Use the **QUESST approach**

assessment for neonates, infants, and children under four years of age or for children with developmental disabilities.

Behavioural scales may under represent the intensity of persistent pain, compared with self-report The CHEOPS (Children's Hospital of Eastern Ontario pain scale) was originally used for postoperative pain and needle pain. This scale is easy to learn and use. The one disadvantage is that it is insensitive to long-term pain. The CHEOPS scale (see Appendix E) is recommended and very practical to use. Behavioural scales do not on the whole depend on the child's desire or ability communicate. The observational rating scale (DEGR scale) is also of value in children between2-6 years.

2. Use the **'BY THE LADDER, BY THE CLOCK, BY THE MOUTH AND BY THE CHILD'** key principles.

3. **PRESCRIBING AND ADMINISTERING PAEDIATRIC ANALGESIA:**

PAIN ASSESSMENT	DRUG	DOSE
MILD TO MODERATE	PARACETAMOL • tabs & soluble tabs 500mg • Paediatric elixir 120mg/5ml • Suppositories 60mg, 125mg, • 240mg & 500mg	• 10-20mg/kg • Repeat 4-6 hourly • Max 80mg/kg in 24 hours
	IBUPROFEN • Tabs 200mg & 400mg • Suspension 100mg/5ml	• not recommended <1 yr • 2,5-20mg/kg
	DICLOFENAC • Tabs 25mg & 50mg • Suppositories 12,5mg	• 0,5-1mg/kg • 2-3 times a day with food • Max 3mg/kg in 24 hours
MODERATE TO SEVERE	PARACETAMOL/CODEINE • 4-6 hrly . • Syrup 5mg codeine, 120mgparacetamol/5ml Tabs 8mg codeine 500mg paracetamol	• Codeine dose: 0,5-2mg/kg

		Increase the dose by 30-50% until the pain is controlled
	MST tablets or suspension	• Calculate MST dose at 6x4 hrly dose: • =dose in 24 hours divided by 2 =12 hourly MST dose
	MORPHINE S/C or IM	• 0,1-0,2mg/kg/dose 3-4 hourly Max dose 15mg

A very effective analgesic regimen is to use valoron and paracetamol in alternating doses, giving each every 6 hours, but not together (e.g. valoron at 6 & 12 and paracetamol at 9 & 3).

VALORON (1mg/kg/dose 6hourly: 1 drop = 2,5 mg). The weight of patient divided by 2,5 = numb of drops per dose. The old regimen of giving 1 drop per year of age under-doses most children. O drop per year of age +2 drops every 4-6 hourly is the suggested Valoron dosage. The maximum dosage should not exceed 1mg/kg/dose. Valoron should not be used in neonates and children unc 10kgs outside of the hospital setting.

4. Use a **STEPWISE PAIN MANAGEMENT**. Multimodal treatment may be necessary. Start simple with the correct dose and step up if pain persists. For moderate to severe pain use paracetamol and valoron and then add NSAID if necessary (if no contra-indication present).
5. Appropriate analgesics for age, size of the child, procedure and illness should be used.
6. Use EMLA/AMETOP prior to cannulation, lumbar punctures, blood sampling. In some children where prolonged intravenous therapy is needed, a central venous line is advised. This can be done as a peripherally inserted long line. Broviac lines or port lines are recommended in children that will need long periods of chemotherapy. Topical anaesthetic cream (EMLA or Ametop) can be used to numb the port area before a needle is inserted for access.
7. Intrathecal chemotherapy can be a very frightening and painful experience for the child with cancer. Ideally it should be performed under generalized anaesthetic. Unfortunately this mig

experience to the patient. Ketamine is a potent analgesic as well as a dissociative anaesthetic. Onset is rapid (1 min) and as is recovery (15-20 min) The dose for procedure is 1-4 mg/kg intravenously over a minimum of 60 seconds, to produce 5-10 min of anaesthetia. Midazolam and dormicum are also good choices, but unfortunately they only g an amnestic sedative effect and are not analgesic drugs. Midazolam can also be given orall or intranasally using the injection solution at a dose of 400-500 microgram/kg. Onset is afte 15 min and recovery after 1 hour. The maximum dose is 15 mg and in heavier children temazepam may be a good alternative. In some children, midazolam causes respiratory depression and hyperexcitability. These can be reversed by flumazenil 10 microgram/kg.

8. Bone-marrow aspiration and trephine (biopsy) should be performed under general anaesthetic. If not possible Ketamine or Midazolam plus analgesic as advised above.

Individualize every child. There is no final dose that will be appropriate for all children with pain. T **'by the child'** refers to the need to adjust analgesic doses based on the individual child.

- Medication should be administered to children by the simplest and most effective route, usually by mouth. Key principle, **'by the mouth'**, refers to the route of drug administration.

Suggested pain regimen for procedures:

PROCEDURE	ANALGESIC	DOSE
Blood sampling Cannulation	Ametop / EMLA. If not available : ice cube inside finger of a plastic glove (applied for 1 min)	

	If respiratory depression: use flumazenil	10 microgram/kg
Intrathecal chemo-therapy Bone marrow biopsy	General anaesthetic recommended If not possible: Ketamine Premedication with oral atropine may reduce secretions and prevent laryngo-spasm	 1-4 mg/kg IV over 60 at least seconds 40 microgram/kg

- Practice **verbal and non-verbal communication** strategies, appropriate to children at vari developmental stages that may help the management of acute and chronic pain. For examp
  - ✓ Find something positive to say about an aspect of the child's physical state
  - ✓ Give a message that the child can be helpful or can master something in his situation, fo example, allow them to choose how they will lie or where their mother will sit
  - ✓ Use a distraction approach: speak in terms of going home, or going playing after a painf procedure is over.
  - ✓ Accept some crying or shouting, which can be a form of distraction for the child.

For inpatient care, where possible, a comfortable bed or chair for the parent next to the child shoul be offered. In selected cases it may be appropriate for parent and child to sleep together in the san bed. A majority of children sleep with their parents when they are ill at home and there is increasin evidence that it may have beneficial effects on the child.

- Communication with parents and patients form a very valuable and important part pain management. The choice of drugs, side effects of treatment, and general information on pain should be discussed.

assessment. They exacerbate the experience of pain. Management of anxiety is therefore an essential part of pain management. The major drugs used to treat anxiety are the **benzodiazepines**. The commonest benzodiazepines used to trea anxiety are diazepam (long half-life), lorazepam (intermediate half-life) and midazolam (short half-life). Lorazepam has some amnestic effect, but it is midazolam that displays such an effect most consistently and effectively.

- The **memory** of the procedures, which were performed during a child's illness oft cannot be erased. The long-term adverse impact of repeated interventions in paediatric oncology is associated with cumulative experiences, as one painful and frightening procedure succeeds another, each made worse by the memory of the last and the fear of the next one. Drugs such as midazolam (100-200microgram/k IV), that can attenuate the memory of an unpleasant procedure are useful. They must, however, never be used alone in the management of painful procedures, as they are not analgesic and their anxiolytic effect is very short-lived.

- **CONSCIOUS SEDATION**: the most widely used combination is that of midazolam combined with morphine, fentanyl or ketamine. Ketamine may produce laryngospasm, particularly in infants. A trained anaesthetist or intensivist able to deal safely with upper airway obstruction should therefore administer the drug.

- Where deep sedation or general anaesthesia is unavailable or inappropriate, **sedative medications** are often used. Barbiturates or chloral hydrate will often he

to modify anxiety caused by the procedure.

Chloral hydrate is often used as sedation prior to performing minor procedures. The drug is administered orally but does not always have a pleasant taste, and can provoke nausea in some children. Furthermore, in older children the volume required, may be intolerable. Chloral hydrate is contra-indicated in children with liver failure or renal impairment.

ADJUVANT DRUGS

MAJOR ANALGESIC INDICATIONS FOR ADJUVANT DRUGS

INDICATION	SUGGESTED DRUG (S)	COMMENTS
Neuropathic pain	Tricyclic antidepressants, e.g. Amitriptyline, Carbamazepine Amitriptyline: 500 micrograms/kg at night Increase to 1 mg/kg twice a day if needed Carbamazepine: 2,5mg/kg twice a day and increase gradually by 2,5-5mg/kg/day at weekly intervals Maintenance dose: 10-20mg/kg/24hr Therapeutic blood levels range from 4-14mg/l	Pain improvement in 3-5 days
Compression or invasion of central or peripheral nervous systems	Corticosteroids, particularly dexamethasone Dexamethasone: 250-500 microgram/kg/24hr in 2-3 divided doses	Indicated for tumour-asscociated raised ICP, cord compression, plexus & nerve invasion; Mannitol or acetazolamide may also be indicated for raised ICP
Muscle spasm	Benzodiazepines Diazepam: start with 100 microgram/kg every 6-12 hr and titrate for effect	Lorazepam or oxazepam are the drugs of choice; alternative is diazepam
Widespread bone pain	Corticosteroids Dexamethasone: as above	High doses frequently give pain relief, often of brief duration

Africa

- **REVIEW**

It is of great importance to **review** the patient as well as the pain management treatment for the individual on a regular basis. A pain assessment every 12 hours should be adequate to assure tha your patient's pain is under control. Every child deserves to have adequate and safe pain control.

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APPENDIX A

Dear Colleague

I am enrolled in the Palliative Medicine programme, MPhil degree through UCT, and would appreciate your input and help for my mini-dissertation for this course. Prof G Wessels is acting as my supervisor.

I would like to compare pain management regimens used by SA Paediatric Oncology Units.

The aim of this research is to compare above regimens and comments on pain management in children with cancer and to suggest an optimal regimen for our local conditions.

I will appreciate your input and time for this project.

Attached you will find a questionnaire on pain management in children with cancer.

Please be so kind to complete and fax to 021 - 9307382.

Once again thank you for your interest and time.

Dr Lizette Pieterse

PAIN MANAGEMENT

APPENDIX B

Please be so kind to answer the following questions.

Please answer the questions by choosing YES or NO

The information that you provide will remain strictly confidential.

At your centre:	YES	NO
1 Do you use visual analogue scales for pain assessment?		
2 Do you use the "by the ladder" approach for analgesic administration?		
3 Do you use "by the clock analgesic management"?		
4 Do you provide any information on cancer pain to the parents?		
4.1 Do you provide the parents with information about the adverse effects of pain Rx?		
4.2 Do you discuss the "by the ladder" approach?		
4.3 Do you explain your choice of analgesic?		
5 Do you have any input from parents? (eg. Pain assessment, pain control)		
6 Do you use intramuscular analgesics?		
7 Do you use intravenous analgesics?		
8.1 Do you use a S/C morphine syringe driver?		
8.2 Do you use an intravenous syringe driver?		
9 Do you use rectal suppositories for pain? If "YES" what do you use?		
10 Do you use local anaesthetic before performing lumbar punctures? If "YES": what do you use?		
11 Do you use local anaesthetic before siting an IV cannula? If your answer is "YES": what do you use?		

	YES	NO
12 Do you use sedation for intrathecal chemotherapy? If "YES": what drug(s) do you use? _____ _____		
13 Do you make use of a child psychiatrist to evaluate emotional pain?		
14 Do you give accurate age-appropriate information about pain to the child?		
15 Do you find that situational factors can lead to inadequate pain control? (eg.cognitive, behavioural, and emotional factors)		
16 If yes, do you evaluate contributing situational factors?		
17 Do you measure / revise the child's pain plan regularly? If "YES" how often, eg. Daily, 6-hourly, etc _____ _____		
18 Do you use the child's physical parameters (eg. Heart rate, sweat index, blood pressure, cortisol level) as pain measure?		
19 Do you use Valoron drops?		
20 Do you use adjuvant analgesic drugs? (eg. Anti-depressants, anti-convulsants, Cortico steroids, neuroleptics, etc). If "YES" what do you use? _____ _____		
21 Do you make use of NSAID's? If "YES" which NSAID(s) do you use? _____ _____		
22 Do you feel you have optimal pain control for children?		
23 Do you make use of attention distractions (eg. "Pop-up" books, etc)?		
24 Do you make use of music when performing procedures or for relaxation?		

	YES	NO
25 Do you have a separate room to perform procedures and to lessen the traumatic experience of the child?		
26.1 Do you teach pain management in children to undergraduates?		
If "YES": For which year students (eg. ? II, ?III, ?IV, ?V, ?VI)		
How many periods in one year?		
26.2 Do you teach pain management in children to postgraduates?		
If "YES": Is it part of the official teaching program?		
Is the training during ward rounds?		

Please write short notes on the different drugs and dosages you use for pain control

COMMENTS

Thank you for your time

Appendix C SELF REPORT SCALES FOR PAIN ASSESSMENT

Measure	Description	Indications for use	Advantages	Disadvantages
Self report measure	Child is asked re. Intensity, rhythm and variations in pain	Adequate cognitive and communicative abilities	Simple, efficient, easily administered	Subject to bias (e.g. demand characteristics, inaccurate or selective memory)
Poker Chip Tool	Child chooses 1-4 chips (Chips = "piece of hurt")	Age 4-8 years	Correlates with overt behaviours during injections; adequate convergent validity; partial support for discriminant validity	May seem childish to older children
Faces scale	Faces indicating pain intensity were derived from children's drawings	Age 6-8 years	Strong agreement among children re. Pain severity of faces and consistency of intervals. Adequate test-retest reliability	Younger child may tend to choose happiest face; may also choose extremes
Visual analogue scale	Vertical or horizontal line with verbal, facial or numerical anchors on a continuum of pain intensity	Age 5 years and older	Reliable and valid (child report correlates with behavioural measures and with parent, nurse, physician ratings). Versatile (can rate different dimensions-pain and affect-on same scale)	Child must understand proportionality. Intervals on numerical scales may not be equal from a child's perspective. Vertical scale may be better than horizontal.
Oucher scale	Six photos of children's faces indicating intensity; 100-point corresponding vertical scale	Age 3-12 years	Reliable; adequate content validity; corelates with other scales. Pictorial plus numerical scales, so applicable to broader age range	

Appendix D BEHAVIOURAL SCALES FOR PAIN ASSESSMENT

Measure	Description	Indications for use	Advantages	Disadvantages
Behavioural measures	Direct observation of overt behaviours, usually measured repeatedly at regular intervals, according to time or phase of procedure	Very young children. Used with self-report scale. Best reliability and validity are for short, sharp pain	Useful when child is unable to rate pain; less subject to bias than self report	Not as well validated for longer lasting pain or for subtle behaviours (e.g. guarding wound). Difficult to discriminate
Procedural rating scale and observational scale of behavioural distress (OSBD)	10 observed behaviours: Crying, screaming, need for physical restraint, verbal resistance, requests for emotional support, muscular rigidity, verbal pain expression, flailing, nervous behaviour, information-seeking	Originally used for bone marrow aspiration and lumbar puncture, but appropriate for any short, sharp pain	Satisfactory inter-rater reliability; OSBD correlates with self report of pain and anxiety	Requires training of observers
Children's Hospital of Eastern Ontario pain scale (CHEOPS)	Six observed behaviours: Crying, facial expression, verbal expression, torso position, leg position, touch	Originally used for postoperative pain and needle pain	Easy to learn and use. Inter-rater reliability = 80% concurrent validity	Insensitive to long term pain
Gauvain-Piquard rating scale	15 behaviours divided into three subscales: pain behaviours (e.g. guarding wound), anxiety behaviours (e.g. nervousness), psychomotor alterations (e.g. withdrawal)	Validated with 2-6 year olds. Used for long term pain in children with cancer	Preliminary studies show adequate inter-rater reliability and sensitivity to differences in children	Validity studies not yet completed

Item	Behaviour	Score	Definition
Cry	1	No cry	Child is not crying
	2	Moaning	Child is moaning or quietly vocalising; Silent cry
	2	Crying	Child is crying, but the cry is gentle or whimpering
	3	Scream	Child is in a full-lunged cry; sobbing; may be scored with complaint or without complaint
Facial	1	Composed	Neutral facial expression
	2	Grimace	Score only if definite negative facial expression
	0	Smiling	Score only if definite positive facial expression
Child verbal	1	None	Child not talking
	1	Other complaints	Child complains, but not about pain; e.g. "I ant to see Mummy" or "I am thirsty"
	2	Pain complaints	Child complains about pain
	2	Both complaints	Child complains about pain and about other things; e.g. "It hurts; I want Mummy"
	0	Positive	Child makes any positive statement or talks about other things without complaint
Torso	1	Neutral	Body (not limbs) is at rest; torso is inactive
	2	Shifting	Body is in motion in a shifting or serpentine fashion
	2	Tense	Body is arched or rigid
	2	Shivering	Body is shuddering or shaking involuntarily
	2	Upright	Child is in vertical or upright position
	2	Restrained	Body is restrained
Touch	1	Not touching	Child is not touching or grabbing at wound
	2	Reach	Child is reaching for but not touching wound
	2	Touch	Child is gently touching wound or wound area
	2	Grab	Child is grabbing vigorously at wound
	2	Restrained	Child's arms are restrained
Legs	1	Neutral	Legs may be in any position but are relaxed; includes gentle swimming or serpentine-like
	2	Squirming/kicking	Definitive uneasy or restless movements in the legs and/or striking out with foot or feet
	2	Drawn up/tensed	Legs tensed and/or pulled up tightly to body and kept there
	2	Standing	Standing, crouching or kneeling
	2	Restrained	Child's legs are being held down

Appendix F

Patient leaflet: morphine

QUESTIONS ABOUT MORPHINE

Questions and concerns about medicines used to control pain are normal. We hope that this handout will answer your questions about your child's pain relief. The medicines we use are safe and very effective. They will help your child recover more easily and quickly from his or her surgery. If you have questions that are not answered in this handout, please ask to speak to one of the staff dealing with your child's pain management.

SOME COMMON QUESTIONS

Is morphine too strong for children?

Will my child become addicted to morphine?

Will my child have unpleasant side effects from morphine?

WHY DO WE USE MORPHINE?

Your child may have some pain after certain procedures.

Morphine and some morphine-like medicines are some of the most effective treatments to control this pain. These medicines are very safe when used properly. Your child should be able to move or cough without discomfort. If your child is to have physiotherapy after surgery and has good control, the treatment will be more effective. Recovery and healing should take place more quickly.

IS MORPHINE TOO STRONG?

The pain relief effects of morphine depend on the dose given. In this hospital the doses are worked out for each child according to his or her weight and age. The children are watched carefully by the nurses and doctors in the wards. Special charts are filled in every hour by the ward nurses. These nurses check the dose of medicine that your child is receiving and how effective it is. As your child's pain gets less, he or she is given less medicine.

CAN MORPHINE FOR PAIN CONTROL CAUSE ADDICTION?

Your child will not become addicted to the morphine that he or she is given to control the pain. Addiction does not occur, even if a child needs more morphine for a long time.

WILL MY CHILD HAVE UNPLEASANT SIDE EFFECTS FROM MORPHINE?

Sometimes morphine may make your child feel slightly sick or itchy. These side effects can be reduced by:

Adjusting the dose of morphine.

Giving other medicines to treat the side effects such as antisickness medicine.

Over-sleepiness is rare and should not be confused with your child 'catching up' on sleep that he or she may have lost if very unwell before surgery.

WILL MY CHILD BE SORE WHEN MORPHINE IS STOPPED?

We often give regular doses of milder pain relief medicines, such as paracetamol or diclofenac, at the same time as morphine. These can be given as a tablet, syrup or suppository. They can help us to use less morphine and to stop the morphine sooner. When morphine is stopped, these milder drugs are given in adequate amounts to keep pain well controlled.