# *Pneumocystis carinii* pneumonia in vertically acquired HIV infection in the British Isles

D M Gibb, C F Davison, F J Holland, S Walters, V Novelli, J Mok

**Abstract**

**In order to review the clinical course, laboratory findings, and outcome of children with vertically acquired HIV infection and *Pneumocystis carinii* pneumonia, questionnaires were sent to paediatricians in the British Isles who had reported *P carinii* pneumonia and HIV infection through the British Paediatric Surveillance Unit (BPSU). Paediatric reports from the BPSU are linked to reports of pregnancies in HIV positive women and laboratory reports. *P carinii* pneumonia was the most frequently reported AIDS indicator disease at AIDS diagnosis, occurring in 22/56 (40%) children born in the British Isles; in a further two children *P carinii* pneumonia occurred after another AIDS indicator disease. The median age at *P carinii* pneumonia diagnosis was 4·1 (1·4–27·3) months and in 48% it occurred with other AIDS indicator diseases. Despite intensive treatment the three month survival was only 38%. The nine children surviving *P carinii* pneumonia subsequently developed further AIDS indicator diseases, in particular HIV encephalopathy and four have since died. *P carinii* pneumonia was present at AIDS diagnosis in 65% of children developing AIDS in the first year of life and caused 82% of infant deaths. Most children were not known to be at risk of HIV until they presented with *P carinii* pneumonia. Children with HIV infection develop *P carinii* pneumonia at an early age and have a poor outcome. Increased awareness of the condition is required to initiate early treatment. Prevention may be a compelling incentive for screening in pregnancy, but further study is required to quantify the risks and benefits of initiating early *P carinii* pneumonia prophylaxis as well as the impact this might have on life expectancy.**

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**Department of Epidemiology and Biostatistics, Division of Public Health, Institute of Child Health, London**
D M Gibb
C F Davison
F J Holland

**Department of Paediatrics, St Mary's Hospital, London**
S Walters

**Hospital for Sick Children, London**
V Novelli

**City Hospital, Edinburgh**
J Mok

Correspondence to:
Dr D M Gibb, Epidemiology and Biostatistics Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

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The clinical spectrum and outcome of AIDS in children with vertically acquired infection with HIV type I has been well described in a number of hospital based cohorts.[1 2] *Pneumocystis carinii* pneumonia has been identified as the most common and serious AIDS indicator disease.[3 4] However, most of these studies were based on the experience of a single centre which may have an unrepresentative referral pattern. Paediatric HIV surveillance in the British Isles (United Kingdom and Republic of Ireland) includes reports of children born to seropositive women as well as children presenting with symptomatic HIV disease.[5] This paper describes the clinical course, laboratory findings, and outcome for children with HIV infection who developed *P carinii* pneumonia.

## Methods

In the British Isles, active surveillance of pregnant women and children with HIV infection is carried out through two confidential reporting schemes. HIV positive pregnant women are reported through the Royal College of Obstetricians and Gynaecologists and paediatricians report HIV seropositive children through an active monthly reporting scheme at the British Paediatric Surveillance Unit (BPSU). Details of the two linked schemes, which have been operating since 1989 and have over 90% response rates, have been reported previously.[5] Each report is followed up using a standard questionnaire. Clinical data collected on infected children include details and dates of AIDS indicator diseases, other HIV related signs and symptoms, antiretroviral treatment, prophylaxis, and T cell subsets. The definitions of AIDS and HIV related manifestations are printed on the back of the questionnaire and follow the definition of the Centers for Disease Control in Atlanta with modifications to the definitions of failure to thrive, encephalopathy, and lymphocytic interstitial pneumonitis (see table 1). Reports

*Table 1 AIDS indicator diseases* in children with AIDS born in the British Isles*

| | *Present at AIDS diagnosis* | | *Onset after AIDS diagnosis* | *Median (range) age (months)* |
|---|---|---|---|---|
| | *Alone* | *With others* | | |
| Opportunistic infections | | | | |
| *P carinii* pneumonia | 11 | 11 | 2 | 4·1 (1·4–27·3) |
| Disseminated cytomegalovirus | 0 | 6 | 0 | 3·5 (2·2–5·5) |
| Cryptosporidiosis | 2 | 0 | 1 | 52·9 (16·7–53·4) |
| Oesophageal candidiasis | 0 | 0 | 3 | 40·6 (9·9–61·9) |
| Atypical mycobacterium | 0 | 0 | 0 | – |
| Extrapulmonary tuberculosis | 0 | 0 | 1 | 57·4 |
| Toxoplasmosis, herpes simplex, coccidiomycosis | 0 | 0 | 0 | – |
| Failure to thrive† | 4 | 14 | 3 | 8·1 (3·4–77·2) |
| Recurrent bacterial infection | 5 | 6 | 9 | 20·2 (5·6–77·2) |
| Encephalopathy‡ | 3 | 4 | 7 | 15·5 (0·3–72·3) |
| Neoplasms | | | | |
| Lymphoma | 1 | 0 | 1 | 29·9 (26·0–33·8) |
| Kaposi's sarcoma | 0 | 0 | 0 | – |
| Lymphoid interstitial pneumonitis§ | | | | |
| Mild or asymptomatic | 7 | 3 | 1 | 16·0 (2·8–56·5) |
| Severe | 0 | 2 | 0 | 15·1 (9·0–21·3) |
| Total No of AIDS indicator diseases | 33 | 46 | 28 | |
| Total No of children | 33 | 22 | 13 | |

*Some cases had multiple diagnoses.
†Crossing two weight for age centiles (97, 90, 75, 50, 25, 10, 3).
‡Two or more of: acquired microcephaly, loss of milestones, progressive motor deficits; all over a period of at least three months.
§Severe: respiratory failure, oxygen dependence, exercise intolerance with oxygen intolerance. Mild: chest radiograph without respiratory signs or symptoms.

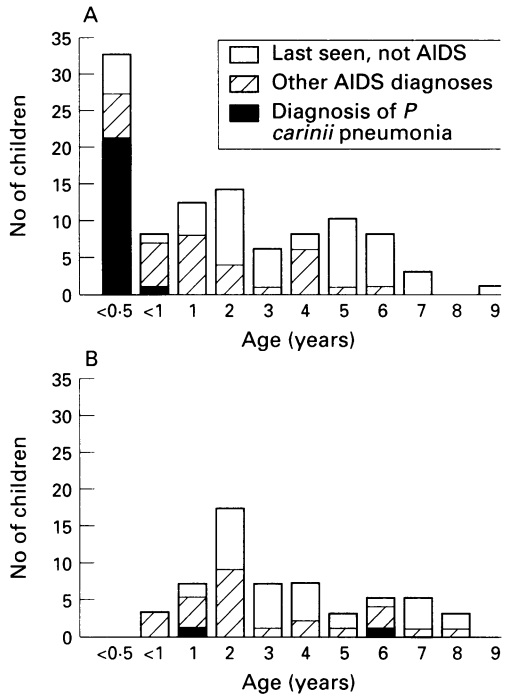


*Figure 1 Details of 160* children with vertically acquired HIV infection – ages at AIDS diagnosis or age last seen but not yet AIDS. (A) born in the British Isles: 55 AIDS, 48 other infected and (B) born abroad: 27 AIDS, 30 other infected. *In nine children the country of birth and clinical data were not available.*

are followed up annually to monitor clinical progression, age at onset of AIDS, and age at death. Paediatricians are requested to report if a child develops AIDS or dies in the interim.

Further details on the clinical illness in children reported with *P carinii* pneumonia were sought from the paediatricians using a standard questionnaire, maintaining confidentiality. Data were collected on the presenting illness, method of diagnosis, treatment, use of ventilation, and outcome of the illness. These data were combined with data collected through the surveillance scheme.

*Table 2* P carinii *pneumonia in children born in the British Isles: clinical manifestations*

| | *HIV risk first ascertained* | | |
|---|---|---|---|
| | *Before* P carinii *pneumonia illness* | *After* P carinii *pneumonia illness* | *Total* |
| No of children | 8 | 16 | 24 |
| Race | | | |
| White | 6 | 7 | 13 |
| Black or mixed | 2 | 9 | 11 |
| Median (range) age at *P carinii* pneumonia onset (months) | 3·8 (1·3–27·4) | 4·3 (2·0–8·3) | 4·1 (1·4–27·4) |
| Interval between onset of symptoms and starting treatment (days) | 13 (3–49) | 11* (2–42) | 11 (2–49) |
| No (%) with *P carinii* pneumonia diagnosis: | | | |
| Presumptive | 2 | 4 | 6 (25) |
| Definitive | 6 | 12 | 18 (75) |
| Nasopharyngeal aspirate | 3 | 8 | |
| Bronchoalveolar lavage | 2 | 1 | |
| Lung biopsy | 0 | 2 | |
| At postmortem examination | 1 | 1 | |
| No (%)ventilated | 2 (25) | 12 (75) | 14 (58) |
| No (%) died of *P carinii* pneumonia illness | 5 (63) | 10 (63) | 15 (63) |
| No (%) survived to three months | 3 (38) | 6 (38) | 9 (38) |

*In one child information was not available.

## Results

By October 1992, 169 children with vertically acquired HIV infection had been reported. Eighty two had developed AIDS, of whom 40 had died. Figure 1 shows the age at AIDS diagnosis or the age last seen for children without an AIDS diagnosis. Further details of the AIDS indicator diseases occurring in those children born in the British Isles are shown in table 1.

Twenty seven children were initially reported to have *P carinii* pneumonia. However, after questionnaires on the clinical details were returned, the diagnosis had been revised in three children. In two of these children, a confirmed diagnosis of cytomegalovirus and adenoviral pneumonia respectively had been made, and in the third, it was not possible to obtain any information about the diagnosis, but the child is alive and well, with a high CD4 count at age 5 years.

Among the 55 children with AIDS born in the British Isles, *P carinii* pneumonia was observed only in infancy and occurred in 22 (40%) at AIDS diagnosis; among the 27 born abroad, only two (7%) had *P carinii* pneumonia at AIDS diagnosis and both were over a year of age (fig 1). Two children born in the British Isles developed *P carinii* pneumonia after an earlier AIDS defining illness (table 1).

Of the 24 children with *P carinii* pneumonia, who were born in the British Isles, a definitive diagnosis was made in 18 (75%), based on the demonstration of pneumocystis with either silver stain or immunofluorescence with monoclonal antibodies (table 2); in six (25%), the diagnosis was made on clinical and radiological grounds.

In 11 children, *P carinii* pneumonia was the sole indicator disease at the time the child fulfilled the paediatric AIDS definition, and in 11 it occurred with other indicator diseases (table 1). These included severe failure to thrive (n=6), cytomegalovirus (n=3), severe failure to thrive and cytomegalovirus (n=1), and severe failure to thrive with encephalopathy (n=1). In three children, both cytomegalovirus and *P carinii* pneumonia were isolated from bronchial secretions, and in one cytomegalovirus was isolated with *P carinii* pneumonia from lung tissue at postmortem examination. Only three children, all under 4 months of age, had no manifestations of HIV infection at or before *P carinii* pneumonia diagnosis. In the remainder other manifestations included failure to thrive (not meeting the AIDS definition), oral candida, bacterial infections, hepatosplenomegaly, and thrombocytopenia.

T cell subsets were measured within a month (before or after) of *P carinii* pneumonia diagnosis in 15 children, and in all but two were less than 1500/mm$^3$, the level below which *P carinii* pneumonia prophylaxis is recommended in infants.[6] However, of the eight children known to have HIV before *P carinii* pneumonia diagnosis, only four had CD4 counts measured before the *P carinii* pneumonia illness and in two these were below the threshold for prophylaxis.

*Table 3 Outcome of children surviving* P carinii *pneumonia illness*

| *Child* | P carinii *pneumonia diagnosis* | *Subsequent AIDS indicator diseases* | *Survival (months)* | *Cause of death* |
|---|---|---|---|---|
| 1 | Presumptive | sFTT, CNS, cryptosporidiosis | 22 | Sepsis |
| 2 | Presumptive | sFTT, CNS, lymphoma | 9* | - |
| 3 | Definitive | CNS, liver disease, sFTT, recurrent bacterial infections | 10* | - |
| 4 | Presumptive | CNS, bacterial infections | 50 | Sepsis |
| 5 | Definitive | sFTT | 2* | - |
| 6 | Definitive | sFTT, CNS | 4 | Died of metabolic problems secondary to severe diarrhoea |
| 7 | Definitive | sFTT | 13* | - |
| 8 | Presumptive | sFTT, CNS, bacterial infections | 16 | Sepsis |
| 9 | Definitive | CNS | 52* | - |

CNS=HIV encephalopathy; sFTT=severe failure to thrive.
*Children still alive by 31 October 1992.

PROPHYLAXIS AND TREATMENT

In 16 (67%) of the 24 children, the diagnosis of HIV infection was made after presentation with *P carinii* pneumonia. Only one of the eight children known to be HIV positive before the development of *P carinii* pneumonia had received *P carinii* pneumonia prophylaxis. This child received inhaled pentamidine and was one of the two who was diagnosed as having AIDS before developing *P carinii* pneumonia. After *P carinii* pneumonia diagnosis all children received treatment with high dose trimethoprim-sulphamethoxazole (TMP-SMX) which was started on the day of admission to hospital in eight children and between one and 22 days later in the remainder. Five children (all white) had allergic skin reactions to TMP-SMX; in one child this was severe with fever, rash, and raised liver transaminases. Eleven children also received pentamidine treatment after TMP-SMX had commenced and 15 received steroids. All children required oxygen treatment and 14 were ventilated (see table 2). Pneumothorax developed in five children, in one before starting ventilation.

OUTCOME

All 24 children have been followed up for at least three months since *P carinii* pneumonia. The three month survival rate was 38% (table 2). All nine children who survived *P carinii* pneumonia subsequently developed further AIDS indicator diseases, in particular HIV encephalopathy which developed in seven (78%) (table 3).

Figure 2 compares survival of children after *P carinii* pneumonia with that of children developing other AIDS indicator diseases in the first year of life. Of the 34 children developing AIDS in infancy, 22 (65%) had *P carinii* pneumonia as the first AIDS indicator disease, occurring either alone or in combination. Of the 12 children who developed other AIDS indicator diseases, two subsequently developed *P carinii* pneumonia from which one child died. Among the children who presented with *P carinii* pneumonia as their first AIDS indicator disease and who survived the first three months, the subsequent survival pattern was similar to those who first developed other AIDS diagnoses. *P carinii* pneumonia accounted for 14/17 (82%) deaths occurring in the first year of life among children with vertically acquired HIV infection born in the British Isles.

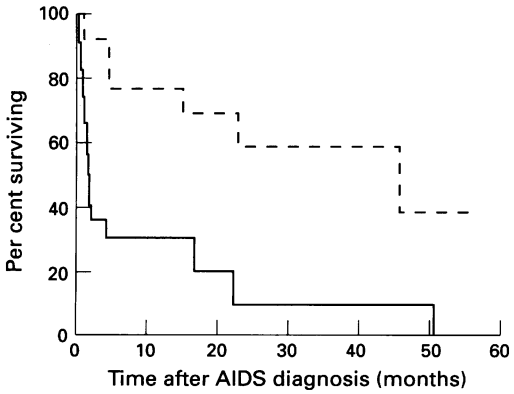


*Figure 2 Survival of children born in the British Isles after first AIDS indicator disease in the first year of life; solid line indicates* P carinii *pneumonia as first AIDS indicator disease (n=22) and dotted line other first AIDS indicator diseases (n=12). (The first AIDS diagnoses in these 12 children were severe failure to thrive, lymphocytic interstitial pneumonitis, severe recurrent bacterial infections, HIV encephalopathy, and cytomegalovirus.)*

## Discussion

The spectrum of AIDS and clinical pattern of *P carinii* pneumonia in children with vertically acquired HIV infection in the British Isles is similar to that reported elsewhere.[1-4 7 8] Findings are similar to those in USA where 39% of children with AIDS presented with *P carinii* pneumonia which was the most common AIDS indicator disease.[6] As in other studies,[3 4 9] the outcome was poor despite availability of intensive care support and the use of specific antimicrobial treatment and steroids. All children in our series were young and two developed symptoms under 6 weeks of age. The poor prognosis may be explained, in part, by the fact that *P carinii* pneumonia is likely to be a primary infection in young infants rather than a reactivation disease, and may be particularly severe in the presence of a damaged or immature immune system and immature lungs. In children with other congenital immunodeficiencies *P carinii* pneumonia also occurs most often in infancy.[10]

In a third of children in this series, *P carinii* pneumonia was associated with severe failure to thrive. It is difficult to determine whether severe failure to thrive was secondary to *P carinii* pneumonia itself, or whether it was due to other HIV related manifestations, such as undiagnosed HIV encephalopathy or gastrointestinal problems. Cytomegalovirus infection was reported as a coincident AIDS indicator disease in four children with definitive *P carinii* pneumonia, based on finding cytomegalovirus in bronchial secretions. However, as cytomegalovirus is frequently cultured from asymptomatic HIV infected children, demonstration of cytomegalovirus infected cells in histological specimens is often considered necessary to diagnosis cytomegalovirus infection. Indeed, Glaser *et al* observed no difference in outcome or survival from *P carinii* pneumonia in children when cytomegalovirus was isolated from bronchoalveolar lavage fluid or lung biopsy specimens

and not specifically treated.[11] The association between *P carinii* pneumonia and subsequent HIV encephalopathy, which was reported in 78% of children surviving *P carinii* pneumonia in this series, has also been observed by others.[1]

All children in this study were treated with high dose TMP-SMX and five (all white) developed adverse reactions. Van der Ven *et al* have suggested that adverse reactions to TMP-SMX may be related to a genetically determined production of 'toxic metabolites'.[12] There are few data on the relationship between adverse reactions to TMX-SMP and race and this could have implications for management.

Altogether 79% of the children with *P carinii* pneumonia who required ventilation died, a figure similar to the 84% mortality reported by Vernon *et al*.[4] The numbers in both series are small, making it difficult to identify clinical features which might characterise those children with a better chance of surviving and who might benefit from ventilation. Children were ventilated for as long as 34 days before death, and in addition to the poor outcome, this raises the question as to whether it is appropriate to ventilate children with severe *P carinii* pneumonia and HIV at a very young age.

In this series, children had symptoms for a median of 11 days before the diagnosis of *P carinii* pneumonia or initiation of treatment. There is a need for increased awareness of *P carinii* pneumonia in young infants so that early treatment, which in adults with HIV infection and *P carinii* pneumonia has been shown to improve survival, can be initiated.

The predictive value of the CD4 count, upon which recommendations for prophylaxis are based[6] is problematic. *P carinii* pneumonia has been described in a 19 day old infant with HIV infection[13] and even with frequent CD4 count measurements from birth, children at risk of *P carinii* pneumonia may not qualify to receive prophylaxis. In this series only two of the four children who had CD4 counts measured before *P carinii* pneumonia had CD4 counts below the threshold recommended for prophylaxis,[6] and this has been reported by others.[9 14] Where facilities for early diagnosis of HIV are available, it may be appropriate to give TMP-SMX early to all HIV infected children, with the additional advantage of helping to prevent bacterial infections.[15] If early diagnosis of HIV infection or frequent follow up of the child are not possible, it may be preferable to offer *P carinii* pneumonia prophylaxis to all children born to HIV positive mothers until HIV infection status is clarified,[16] while recognising that many children would receive TMP-SMX unnecessarily, with the accompanying possibility of haematological or allergic toxicity. At present the uncertainty in this area is reflected in clinical practice. In this series, only one of eight children developing *P carinii* pneumonia and known to be at risk had received prophylaxis. In the British Isles, of the 218 children followed up prospectively from birth, only 13 had been reported to have received prophylaxis; three of these had definitive HIV infection, two are now uninfected, and eight are of indeterminate infection status. However, some centres in the British Isles are now giving prophylaxis at 2–3 weeks of age to all children born to HIV positive women until the child is shown to be uninfected (personal communication). The risks and benefits of this and other strategies for *P carinii* pneumonia prophylaxis require further study.

Whatever policy for primary prophylaxis is implemented, children at risk of developing *P carinii* pneumonia require identification and intensive follow up from birth. In London, only 17% of babies born to positive women are recognised before delivery.[5] Along with advice about the risks of transmitting HIV through breast feeding, prevention of *P carinii* pneumonia is another compelling incentive for offering HIV screening in pregnancy.

**Addendum**

Between October 1992 and October 1993 a further 12 children born in the British Isles developed *P carinii* pneumonia. Of these, 9/12 (75%) did not have HIV risk ascertained before the development of *P carinii* pneumonia.

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