

Treatment of pneumocystis carinii pneumonia in children

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SUMMARY Eighteen children with pneumocystis carinii pneumonia diagnosed over a period of 16 years at a children's hospital are reviewed. All had an underlying disease, either congenital immunodeficiency or a malignancy. 15 patients were treated, 10 with pentamidine isethionate alone, 2 with both pentamidine and co-trimoxazole, and 3 with co-trimoxazole alone. 12 of the treated group recovered and the 3 untreated patients died. The 3 deaths after treatment occurred in children receiving pentamidine alone, and in whom secondary factors contributed. The side effects of treatment with pentamidine were high, and included local reactions, hypoglycaemia, and uraemia. However, our results confirm that pentamidine is an effective treatment for pneumocystis carinii pneumonia in childhood. Co-trimoxazole may be an effective and relatively nontoxic alternative treatment.

Pneumocystis carinii was first recognized as a serious lung pathogen when it was found to be the aetiological agent of epidemics of interstitial pneumonia in malnourished preterm infants from Eastern Europe in the 1940s and 1950s (Gajdusek, 1957). In Western countries it is now recognized as a rare pneumonia occurring almost exclusively in patients with immunodeficiency or malignant disease. *Pneumocystis carinii* is thought to be a protozoan because of its morphological appearances; it infects the terminal respiratory passages of both man and a number of animals causing diffuse alveolar disease and interstitial pneumonitis (Robbins, 1967).

Patients

Eighteen children with histologically proven pneumocystis carinii pneumonia have been diagnosed at this hospital in the 16 years from January 1959 to December 1975 (Fig. 1). Diagnosis in each case was made by examination of lung tissue by histological methods including Gomori's methenamine silver stain. All patients had an underlying disease, either congenital immunodeficiency or a malignancy.

Fifteen children were treated with either pentamidine isethionate alone, co-trimoxazole alone, or both pentamidine and co-trimoxazole. Details of these patients are given in the Table, and are grouped according to the treatment they received. 3 patients were not treated. The first was a boy aged

6 months with variable immunodeficiency who had a post-mortem diagnosis in 1959 before treatment became available generally. The second was a boy aged 6 months with severe combined immunodeficiency who was transferred from another hospital moribund and died within 2 days, and the third was a girl aged 7 months with Letterer-Siwe disease who died unexpectedly before this diagnosis was made and specific treatment given.

Patients with malignancy. No particular treatment combination appeared to predispose these patients to the infection. Each of the 6 children with acute lymphocytic leukaemia received radiotherapy, one for a mediastinal lymphoma (Case 3), 2 for central nervous system (CNS) relapse (Cases 8, 13), and 3 (Cases 9, 10, 12) as prophylaxis. Both patients who had radiotherapy for CNS relapse had pneumonia within 11 months and 5 months of the treatment. Prednisone therapy was suspended within one month

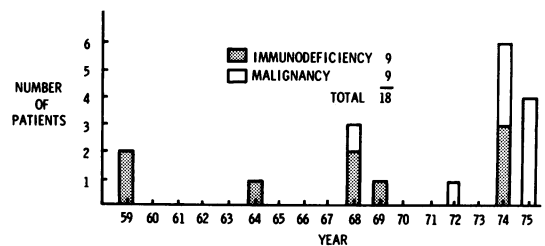


Fig. 1 *Pneumocystis carinii* pneumonia. The Hospital for Sick Children, Great Ormond Street, 1959-1975.

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of presentation in 4 cases, 3 within a week of diagnosis. Peripheral white cell counts at presentation of the pneumonia showed severe lymphopenia in 5 patients and neutropenia in 1.

Patients with immunodeficiency. A family history of an affected male sib was noted in Case 11, but as 7 out of 9 of this group were boys, an X-linked disorder is probable. The episode of pneumonia in Case 2 probably represents a second infection with pneumocystis as he was first seen at the age of 7 months with a pneumonitis which responded to a combination of drugs, including pentamidine (Rodgers and Haggie, 1964). As there was no histological proof of the diagnosis, this patient's initial episode has not been included in the data.

Clinical findings and investigations

The mean duration of symptoms before presentation was 2.5 weeks, range 2 days to 6 weeks. When first seen all of the patients were tachypnoeic; and 10 had a cough, 6 a fever, and 4 patients with a history of less than 3 weeks had finger clubbing. All but 3 patients had clear chest to auscultation. Auscultatory signs when present were reported as scattered râles and crepitations throughout both lung fields. Arterial blood gases, taken in air at presentation in 12 patients, showed a uniform pattern of severe hypoxia and hypocapnia with little acid-base disturbance (Fig. 2). Many of the older patients, though cyanosed and tachypnoeic, had little toxicity or prostration at presentation. Chest x-ray changes in all were bilateral and showed similar features of a diffuse, progressively coalescing pneumonia that often spared the peripheral lung fields in the early stages.

In 14 patients diagnosis was confirmed by the histology of an open lung biopsy. Pneumothorax occurred after lung biopsy in one child. It was non-tension in type, occurring 2 days after the procedure,

and was successfully treated by underwater drain. A second child required postoperative ventilation as a result of oversedation from anaesthetic premedication. 4 patients were diagnosed by post-mortem histology of lung tissue.

Deaths in treated patients

Three patients died, 2 during and one 2 weeks after a course of pentamidine isethionate. The first (Case 3) was a child with leukaemia who had initial cytotoxic drug treatment for a presumed malignant infiltration of the lungs, and died 2 days after pentamidine treatment was started. The second (Case 5), who also had leukaemia, had the lowest P_{O_2} recorded at presentation (2.92 kPa (22 mmHg) in air) and who died of hypoxia and renal failure on the 10th day of treatment. Histology of the lung at necropsy showed unresolved pneumocystis pneumonia and an adenovirus was grown from post-mortem lung. The third (Case 8) was a child with severe combined immunodeficiency who died 2 weeks after a 14-day course of pentamidine was completed. During this period he was malnourished with a serum albumin of 8 g/l. Post-mortem lung histology showed a bronchopneumonia superimposed on a resolving pneumocystis pneumonia.

Seven of the 12 patients who recovered from the pneumonia have since died of their underlying disease. Of the 5 survivors, 4 have acute lymphocytic leukaemia in remission and one has variable immunodeficiency. This latter patient is now aged 17 and was the first child reported with immunodeficiency successfully treated with pentamidine (Marshall *et al.*, 1964).

Discussion

Our data confirm that pentamidine isethionate is an effective drug for the treatment of pneumonia caused by *Pneumocystis carinii*, and compares

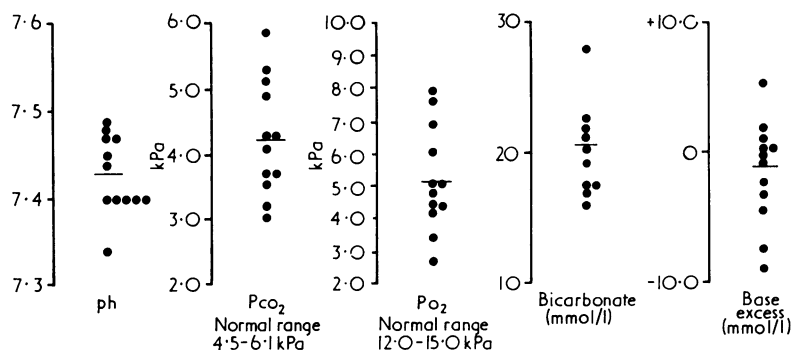


Fig. 2 Blood gases (in air) at presentation in 12 patients. Conversion—SI to traditional units: 1 kPa \approx 7.5 mmHg. Bicarbonate and base excess: 1 mmol/l \approx 1 mEq/l.

Table Children with pneumocystis carinii pneumonia 1959-1975

Case no.	Age at onset of pneumonia	Sex	Underlying disorder	Treatment of underlying disease	Duration of treatment of underlying disease	Dose and duration	Complications of treatment	Outcome
<i>Treatment with pentamidine isethionate (daily IV)</i>								
1	2 yr 4 m	M	Variable immunodeficiency	Immunoglobulin	2 w	4 mg/kg per day-10 d	Nil	Recovered from pneumonia; alive aged 17 yr
2	1 yr 3 m	M	Variable immunodeficiency	Immunoglobulin	9 m	4 mg/kg per d-10 d	Nil	Recovered from pneumonia; died aged 7 yr of degenerative disorder of CNS; no post mortem
3	5 yr 6 m	M	Acute lymphocytic leukaemia	Radiotherapy for mediastinal lymphoma; CP, VCR, 6MP, MTX, Pred	9 m	4 mg/kg per d-2 d	Nil	Died of pneumocystis pneumonia
4	6 m	M	Severe combined immunodeficiency	Immunoglobulin	1 w	4 mg/kg per d-35 d	Transient leucopenia and thrombocytopenia	Recovered from pneumonia; died of septicaemia 5 m later
5	9 m	M	Severe combined immunodeficiency	Immunoglobulin	1 w	4 mg/kg per d-14 d	Nil	Died 2 w after treatment; post mortem—resolving pneumocystosis and bronchopneumonia
6	4 m	M	Erythrophagocytic reticulosis	VBL, Pred	6 w	4 mg/kg per d-10 d	Bilateral buttock abscesses, raised urea (17.9 mmol/l; 108 mg/100 ml) 1 m after treatment started but returned to normal	Recovered from pneumonia; died 5 m later of underlying disease
7	3 yr 5 m	M	Disseminated neuroblastoma	VCR, CP, ADR, Pred	1 yr	4 mg/kg per d-9 d	Bilateral buttock abscesses	Recovered from pneumonia; died of underlying disease 1 yr later; no post mortem
8	8 yr 2 m	F	Acute lymphocytic leukaemia	VCR, Pred, MTX, 6MP; radiotherapy and intrathecal MTX for CNS relapse	4 yr	4 mg/kg per d-9 d	Raised urea (31.3 mmol/l; 189 mg/100 ml) hypotension, renal tubular necrosis	Died on 9th d of treatment; pneumocystis in post-mortem lung; adenovirus from post-mortem lung
9	11 yr 4 m	M	Acute lymphocytic leukaemia	Prophylactic CNS, radiotherapy and intrathecal MTX, VCR, Pred, CP, ASP, CA, MTX, 6MP	2 yr	150 mg/m ² -5 d; 100 mg/m ² -5 d	Nil	Recovered from pneumonia; now off anti-leukaemia therapy for 1 yr without relapse

10	8 yr 1 m	M	Acute lymphocytic leukaemia	Prophylactic CNS radiotherapy and intrathecal MTX, VCR, Pred, CP, ADR, ASP, 6MP, MTX, CA	1 yr 6 m	150 mg/m ² -10 d	Transient hypoglycaemia on 9th d	Recovered from pneumonia; continues on antileukaemia therapy without relapse	
Treatment with co-trimoxazole (oral)									
11	11 m	M	Severe combined immunodeficiency	Immunoglobulin thymic and fetal liver transplant (unsuccessful)	10 m	TMP 40 mg, SMX 200 mg twice daily 14 d	Nil	Recovered from pneumonia; died of septicæmia 2 m later; no pneumocystis seen in lung at post mortem	
12	6 yr 2 m	M	Acute lymphocytic leukaemia	Prophylactic CNS radiotherapy and intrathecal MTX; VCR, Pred, MTX, 6MP, ASP, ADR, CP, CA	10 m	20 mg TMP, 100 mg SMX/kg per d twice daily 14 d	Nil	Recovered from pneumonia; continues on antileukaemia therapy without relapse	
13	7 yr 11 m	M	Acute lymphocytic leukaemia	CNS radiotherapy and intrathecal MTX for CNS relapse; VCR, Pred, MTX, 6MP, ASP, ADR, CP, CA	4 yr	20 mg TMP, 100 mg SMX/kg per d twice daily 14 d	Nil	Recovered from pneumonia; continues on antileukaemia therapy	
Treatment with (a) pentamidine (daily IV) and (b) co-trimoxazole (oral)									
14	5 m	F	Severe combined immunodeficiency	Immunoglobulin	Diagnosed together	(a) 4 mg/kg per d (b) TMP 40 mg, SMX 200 mg twice daily (a) 14 d (b) 14 d	Nil	Recovered from pneumonia; died 8 m later of infection	
15	6 m	M	Variable immunodeficiency	Immunoglobulin	Diagnosed together	(a) 150 mg/m ² (b) TMP 20 mg, SMX 100 mg twice daily (a) 7 d, 3 d (b) 10 d	Hypoglycaemia 3 d after stopping therapy; raised urea 9.9 mmol/l (60 mg/100 ml) in 2nd week returned to normal after treatment stopped; urticaria at site of penitamide injection on one occasion	Recovered from pneumonia; retarded and spastic quadriplegic, possibly as a result of hypoglycaemia, as normal developmentally until onset; died 18 m later of pneumonia and debilitation	

VCR = vincristine; Pred = prednisolone; MTX = methotrexate; 6MP = 6-mercaptopurine; ASP = asparaginase; ADR = doxorubicin; CA = cytosine arabinoside; TMP = trimethoprim; SMX = sulphamethoxazole; VBL = vinblastine; CP = cyclophosphamide.

favourably with the response to this drug seen in other series (Johnson and Johnson, 1970; Geelhoed *et al.*, 1973; Hughes *et al.*, 1973; Walzer *et al.*, 1974; Western *et al.*, 1975). Secondary factors in the 3 children who died reduced the possibility of a favourable response to this drug. One was given initial cytotoxic therapy in error, the disease progressing to a fulminating picture from which the patient died after 2 days' treatment (Case 3). A second child who died on the 9th day of therapy had the most severe initial picture as judged by blood gas analysis, and had recurrent episodes of hypotension and hypoxia in addition to renal tubular necrosis (Case 8). A superimposed adenovirus infection might have further compromised this patient. The third child died after a course of therapy was complete (Case 5). He was malnourished with the extremely low terminal serum albumin of 8 g/l. Severe malnutrition in itself can predispose to pneumocystis pneumonia (Hughes *et al.*, 1974a) and might have perpetuated it in this child. There was also a bilateral bronchopneumonia which would have contributed to his demise. These 3 patients received pentamidine 4 mg/kg per day, which is a slightly lower dosage regimen than that recently suggested of 150 mg/m² for 3 days followed by 100 mg/m² for 7 days (Hughes *et al.*, 1973), particularly in the younger age groups.

Pentamidine has significant side effects and those noted in this series are comparable with other reports (Johnson and Johnson, 1970; Wang *et al.*, 1970; Geelhoed *et al.*, 1973; Hughes *et al.*, 1973; Walzer *et al.*, 1974; Western *et al.*, 1975). In experimental animals pentamidine is quickly cleared from the blood and preferentially stored in the kidney and liver. It is slowly excreted in the urine and bile, traces still being detected up to 8 months later (Waalkes *et al.*, 1970). It is a diamidine, one of a group of drugs first developed as hypoglycaemic agents and used in tropical protozoal infections such as trypanosomiasis (Schoenbach and Greenspan, 1948). Ivády *et al.* (1967) first reported its efficacy in pneumocystis pneumonia. The extremely slow excretion could have accounted for a late onset of hypoglycaemia seen in one patient (Case 15) in whom it occurred 3 days after treatment was stopped. Renal tubular necrosis has been associated with the drug (Wang *et al.*, 1970; Hughes *et al.*, 1973; Western *et al.*, 1975), but we are reluctant to attribute the tubular necrosis seen in Case 8 solely to renal toxicity of pentamidine, because of the associated severe hypoxia and hypotension and the fact that regeneration was seen at necropsy despite continuing therapy. A transient rise in blood urea was seen in 2 patients (Cases 6, 15). Hypotension is reported as a complication of pentamidine therapy,

usually acutely after intravenous therapy. The neutropenia and thrombocytopenia seen after a prolonged treatment regimen of 35 days in one patient (Case 4) was probably secondary to a disturbance in folate metabolism which has been described with the use of pentamidine (Robbins, 1967).

Co-trimoxazole was proposed as a therapeutic agent in pneumocystis pneumonia when it was shown to be effective in animal studies (Hughes *et al.*, 1974b), and when early clinical studies with the related combination of pyrimethamine and sulphadiazine showed promise (Kirby *et al.*, 1971). A recent report confirms its efficacy, particularly in a high-dose regimen early in the course of infection (Hughes *et al.*, 1975). Co-trimoxazole has many attractions as a preferred form of therapy in pneumocystis carinii pneumonia. It seems to have a rapid onset of action, a response often occurring in the first few days; and a low incidence of toxic side effects when compared with pentamidine. However, because of pentamidine's proven efficacy in this otherwise fatal infection, comparisons with co-trimoxazole are necessary before it can be discarded. The 3 patients treated with co-trimoxazole alone all recovered without side effects. 2 were treated by a high dose and one by a standard dose regimen. Co-trimoxazole might also be useful in prophylaxis, such as in the treatment of at risk contacts of a known case.

No specific cytotoxic drug combination was associated with the onset of disease. Radiotherapy was used in all the leukaemic patients. The recorded association of the onset of infection after the use of prednisone is confirmed (Rifkind *et al.*, 1966; Johnson and Johnson, 1970; Western *et al.*, 1975). The reason for this is not certain but might be due to a temporary suppression of the inflammatory response of the alveoli to the organism, a pre-existing infection becoming manifest after stopping this drug.

The frequent insidious onset of the symptoms of lung disease, the relative lack of toxicity, and an absence of auscultatory signs in the chest often resulted in late presentation of these children. 4 of the children had finger clubbing after cough and dyspnoea of less than 2 weeks' duration. This possibly indicates significant lung involvement before symptoms became evident.

There was no evidence, such as simultaneous clinic visits or common ward residence, to suggest cross infection in these cases. However, as man to man transmission has been strongly implied in some reports (Ruskin and Remington, 1967; Brazinsky and Phillips, 1969; Singer *et al.*, 1975) patients with suspected infection should be isolated from other susceptible children.

The increased numbers of patients in whom this infection has been diagnosed in recent years (Fig. 1) could be due to a greater awareness of the condition in addition to the more aggressive treatment regimens of children with malignancy by both chemotherapy and radiotherapy, resulting in a greater and sustained immunosuppression. The possibility, however, cannot be excluded that it represents an increased prevalence of the infection. Little is known of the epidemiology of *Pneumocystis carinii* though it is of interest to note that the epidemic form of the infection seen in Eastern Europe two and three decades ago has declined in recent years.

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Addendum

Since the preparation of this paper 4 additional cases of pneumocystis carinii pneumonia, confirmed by lung biopsy, were seen between March and August 1976. 3 were children with acute lymphocytic leukaemia who were receiving maintenance chemotherapy for the disease and had been in remission between 9 and 15 months: their total lymphocyte counts were low, 3 ranging between 400 and 700/mm³ (0.4-0.7 × 10⁹/l). The fourth patient, a male aged 6 months, had an immunodeficiency disorder (low IgG and IgA, normal IgM, normal tests for cell-mediated immunity) and presented with respiratory symptoms, the immunodeficiency and lung infection being diagnosed during the same admission. All 4 children have recovered after treatment with co-trimoxazole (120 mg/kg per d) administered orally twice daily for 14 days. The infant with immunodeficiency also received immunoglobulin replacement therapy.