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Treatment and prophylaxis of *Pneumocystis carinii* pneumonia

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Introduction

In recent decades there has been a distinct shift in emphasis in the etiology of infectious diseases. Organisms formerly regarded as non-pathogenic or hardly pathogenic are increasingly being identified as agents of severe infections. Among them is *Pneumocystis carinii*, a ubiquitous saprophyte recognized as the causative agent of a life-threatening form of interstitial pneumonia.

Epidemiology

There are two main forms of the disease (Fernex, 1980; Kernbaum et al., 1978):

1. Endemic, epidemic or sporadic outbreaks of interstitial plasma-cell pneumonia occurring in infants in nurseries or hospitals. Particularly at risk are infants with immune deficiencies or those suffering from malnutrition and gastroenteritis.
2. Sporadic outbreaks of pneumonitis occurring in immunodeficient patients of all ages: cancer patients who have been treated with cytostatics or corticosteroids or organ transplant recipients.

   Infants under one year are at highest risk for the disease, followed by children from 1 to 10 years of age and adults between 50 and 59 years.

According to investigators such as Hughes et al. (1975) and Harris et al. (1980) untreated infection is fatal in 90–100% of cases. Larter et al. (1978) estimate mortality at 50%, Hughes (1976) and Ackers (1978) at 50% in children and 100% in adults.

Therapy

Pneumocystis carinii pneumonia does not respond to antibiotics. The therapy of choice was formerly pentamidine isethionate, given intramuscularly in a

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daily dosage of 4 mg per kg bodyweight for two to twenty-five days (Lipson et al., 1977).

According to several authors, survival rates between 42% and 95% have been obtained. However, pentamidine has a high rate of irreversible, occasionally fatal, side effects. Trin Dinh et al. (1976) report an incidence of 46.8% in 404 patients, whereas Parving et al. (1976) speak of 50%.

In the search for an equally effective but better tolerated drug, co-trimoxazole (trade name Bactrim) has been used with success. Co-trimoxazole has the advantage that it can be given orally, or parenterally.

The combination sulfadoxine/pyrimethamine (trade name Fansidar) is less effective for therapy, but ideal for prophylaxis.

Dosage of co-trimoxazole

Today, the accepted and life-saving dosage is 20 mg trimethoprim (TM) and 100 mg sulfamethoxazole (SMZ) per kg daily, in two to four divided doses.

Clinical experience with co-trimoxazole

Therapy with co-trimoxazole was pioneered by Hughes et al. (1975), mainly in children. In one study in two groups of 21 children these authors compared co-trimoxazole and pentamidine (Table 1) in the dosages mentioned. The duration of therapy was 14 days, with crossover to the alternate drug if there was no response after three days. In patients not crossed over, therapy was successful in 15 patients in the co-trimoxazole group and in 12 in the pentamidine group. One patient in the pentamidine group died. If the results of primary therapy are added to those achieved after crossover, the cure rates are as follows: co-trimoxazole 83%; pentamidine 74%. Table 2 shows the incidence of side effects with the two treatments. Co-trimoxazole is markedly better tolerated than pentamidine.

In another publication Hughes et al. (1978) report on a randomized comparative study in 50 patients with *Pneumocystis carinii* pneumonia carried out from 1975 to 1976. These children, average age 6 years, all had underlying neoplastic diseases, mainly leukemia.

The results, under similar conditions as in the study previously described, show a cure rate of 77% in the 26 children treated with co-trimoxazole and 75% in the 24 who received pentamidine.

Several investigators have reported on their experience with co-trimoxazole in children. All of them obtained good results with co-trimoxazole, both with regard to therapeutic success and side effects. Experience with refugee children from Vietnam (Gleason et al., 1975; Hodson et al., 1976) illustrate that children suffering from malnutrition are at high risk for *Pneumocystis carinii* pneumonia and a careful watch must be kept. Mortality can be reduced by treating both the malnutrition and the infection.

Table 1. Comparative study of co-trimoxazole and pentamidine in children (Hughes et al., 1976)

	'Bactrim'	Pentamidine
Study design and results		
Number of patients	21	21
Dosage	oral 20 mg TM + 100 mg SMZ per kg daily, in four divided doses	intramuscular 4 mg/kg daily in a single daily dose
Duration of therapy	14 days, crossover after 3 days if no response	
Results:		
Cure	15	12
Died	–	1
Crossover necessary	6	8
Results in patients crossed over		
Number of patients	8	6
Cure	4	2
Overall cure rate		
Number of patients	23	19
Cure	19	14
Percent	83%	74%

Table 2. Side effects (Hughes et al., 1976)

	'Bactrim' oral	Pentamidine intramuscular
Rash	6	1
Flush	0	1
Nausea and vomiting	2	0
Vomiting	3	0
Induration*	–	8
Erythema*	–	1
Pressure pain*	–	1
BUN (>20 mg%)	0	4
Eosinophilia	2	0
Decreased serum folic acid	1	1
SGOT	0	2
SGOT and SGPT	1	3
Hypoglycemia	0	5
Hypocalcemia	0	1
Total	15	28

* at injection site

Table 3. Effect of co-trimoxazole in *Pneumocystis carinii* pneumonia in adults (Lau and Young, 1976)

Patients	8 hospital patients, aged 19 to 72 years, with cancer of kidney or bone marrow transplantations
Dosage	960-1200 TM + 4800–6000 mg SMZ daily for 10 to 16 days
Results	– 5 patients sucessfully treated – 2 patients died of the underlying disease after 3 and 6 days' treatment respectively, no evidence of *Pneumocystis carinii* pneumonia at autopsy – 1 patient died after 12 days of therapy, not evaluable, no autopsy
Side effects	1 patient developed thrombocytopenia and leukopenia, blood count became normal when therapy was stopped and supplementary folic acid given

Studies have also been carried out in adults with *Pneumocystis carinii* pneumonia. Lau and Young (1976) treated 8 patients with cancer, kidney transplants or bone marrow transplants with oral co-trimoxazole. The dosage was 960–1200 mg trimethoprim and 4800–6000 mg sulfamethoxazole daily, given in three divided doses for ten to sixteen days. The results are listed in Table 3.

Winston et al. (1979) treated 11 adult patients who could not be treated orally with intravenous infusions of cotrimoxazole. The daily dosage was 10–15 mg trimethoprim and 50–75 mg sulfamethoxazole per kg bodyweight, given in four divided doses. Duration of treatment varied from two to sixteen days. In the 7 patients successfully treated (64%), clinical improvement became apparent after an average of 3.6 days and could be confirmed by radiography after 7.6 days.

Prophylaxis

Co-trimoxazole

Prophylaxis with co-trimoxazole does not require a high dosage. Hughes et al. (1977) (Table 4) divided 160 children with cancer who were being treated with immunosuppressive drugs and radiation therapy into two groups: 80 children received 150 mg trimethoprim and 750 mg sulfamethoxazole per square meter body surface daily; the other 80 children were given placebo. After an average of 14 months treatment none of the children given co-trimoxazole had contracted *Pneumocystis carinii* pneumonia, whereas 17 cases occurred in the placebo group.

Feldman et al. (1978) report on a field study carried out by 25 doctors from 1975 to 1976 in 1000 children with cancer at risk for *Pneumocystis carinii* pneumonia. 484 who were considered to be at highest risk received co-trimoxazole in a prophylactic dosage. The incidence of *Pneumocystis carinii* pneumonia during this period was 0.3%, compared with 3 to 6% before prophylaxis with co-trimoxazole was available. The drug was well tolerated.

Table 4. Co-trimoxazole for the prophylaxis of *Pneumocystis carinii* pneumonia (Hughes et al., 1976)

	'Bactrim' group	Placebo group
Number of patients	80	80
Type of cancer:		
Acute lymphatic leukemia	66	70
Rhabdomyosarcoma	10	7
Others	4	3
Dosage	150 mg TMP_2 + 750 mg SMZ per m^2 and day, in two divided doses	placebo
Duration of treatment	14.2 months	14.1 months
Result		
Number of patients developing infection	0 (0%)	17 (21%)

Side effects: Skin rash, vomiting, diarrhea, abdominal pain, nausea, jaundice, anemia, megaloblastic changes, were not more frequent in the 'Bactrim' group than in the placebo group.
Note: The cancer therapy was not impaired.

Table 5. Co-trimoxazole prophylaxis for *Pneumocystis carinii* pneumonia in children with leukemia or other cancers (Harris et al., 1980)

Group	Prophylaxis	Number of patients	Developed *Pneumocystis carinii* pneumonia
High risk	+	229	–
Low risk	–	19	–
High risk	–	10	5
Died		8	–

Harris et al. (1980) also achieved favourable results with prophylaxis using a dosage of 4 mg trimethoprim and 20 mg sulfamethoxazole per kg daily for six months to over a year. A summary of these results is given in Table 5.

A study by Wolff and Baehner (1978) shows that long-term prophylaxis with low doses gives substantially better results than short-term prophylaxis with a higher dosage.

Sulfadoxine and pyrimethamine

In a orphanage in Shiraz, Iran, *Pneumocystis carinii* pneumonia was epidemic from 1961 to 1968 and an important cause of death in infants between 3

and 9 months of age. The disease usually developed after prolonged diarrhea. From October 1968 to October 1969, Post et al. (1971) carried out a prospective double-blind study with sulfadoxine/pyrimethamine and placebo. The prophylactic dosage was 40 mg sulfadoxine and 2 mg pyrimethamine per kg bodyweight every week or every fourteen days. None of the 22 children who received the prophylaxis became ill, but 7 (25%) of the 28 untreated children developed the disease. At the end of the study, there was no difference in folate levels in the two groups.

Conclusions

Co-trimoxazole is as effective as pentamidine isethionate for the treatment of *Pneumocystis carinii* pneumonia, but is better tolerated, even in the high dosage required. It is therefore currently regarded as the drug of choice. Co-trimoxazole therapy also prevents the occurrence of most other bacterial infections.

Both co-trimoxazole and the combination sulfadoxine/pyrimethamine are suitable for prophylaxis. However, whereas daily doses of 2 to 4 tablets of co-trimoxazole are required, sulfadoxine/pyrimethamine has the advantage that 1 to 2 tablets every fourteen days are sufficient.

Bibliography can be obtained from the author on request.