

Trimethoprim- Sulphamethoxazole in the Treatment of Pneumonia

A CLINICAL TRIAL

BY

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Pneumonia is a common condition in Rhodesia, accounting for approximately 6.5 per cent. of all adult admissions to Harare Central Hospital, Salisbury. The great majority of cases respond well to treatment with crystalline penicillin on an inpatient basis, but a recent investigation has indicated that other treatment regimes are satisfactory and could well be used on an outpatient

basis (Sutton *et al.*, 1969). These included a single intramuscular dose of long-acting penicillin, a single intramuscular dose of mixed long-acting and crystalline penicillins and a single day's therapy with oral penicillin.

Trimethoprim-sulphamethoxazole, a synergistically acting combination of antibacterial drugs, is well established in the treatment of infections of the urinary tract (Grünberg and Kolbe, 1969; Reeves *et al.*, 1969), chronic bronchitis (Hughes, 1969) and, more recently, typhoid (Kamat, 1970; Farid *et al.*, 1970; Stamps and Wicks, 1970). Its use against respiratory tract infections has been largely limited to the treatment of chronic bronchitis, probably because acute infections are already well provided for by penicillin and other antibiotics. However, its range of activity is wide and includes the pyogenic cocci, so it should be effective in the treatment of acute infections of the lower respiratory tract.

Table 1
PATIENTS WITHDRAWN FROM TRIAL (ALL MALES)

Case No.	Treatment Group	Reason for Withdrawal
6	Trimethoprim-sulphamethoxazole	Associated severe hypertension with cardiac failure and hypertensive encephalopathy. Patient died 15 hours after admission.
16	"	Patient discharged himself against medical advice 2 days after admission.
33	"	Found on bronchography to have cystic lung disease.
53	"	Died on admission.
55	"	Erroneous diagnosis; patient found to have acute nephritis with uraemia.
60	"	Erroneous diagnosis; patient found to have amoebic liver abscess with spread to lower lobe of right lung.
8	Penicillin	Erroneous diagnosis; patient found to have malabsorption syndrome.
13	"	Pneumonia unconfirmed; patient had upper respiratory tract infection only.
18	"	Pleural effusion with underlying bronchial carcinoma.

PENICILLIN TREATED

TRIMETHOPRIM-SULPHAMETHOXAZOLE TREATED

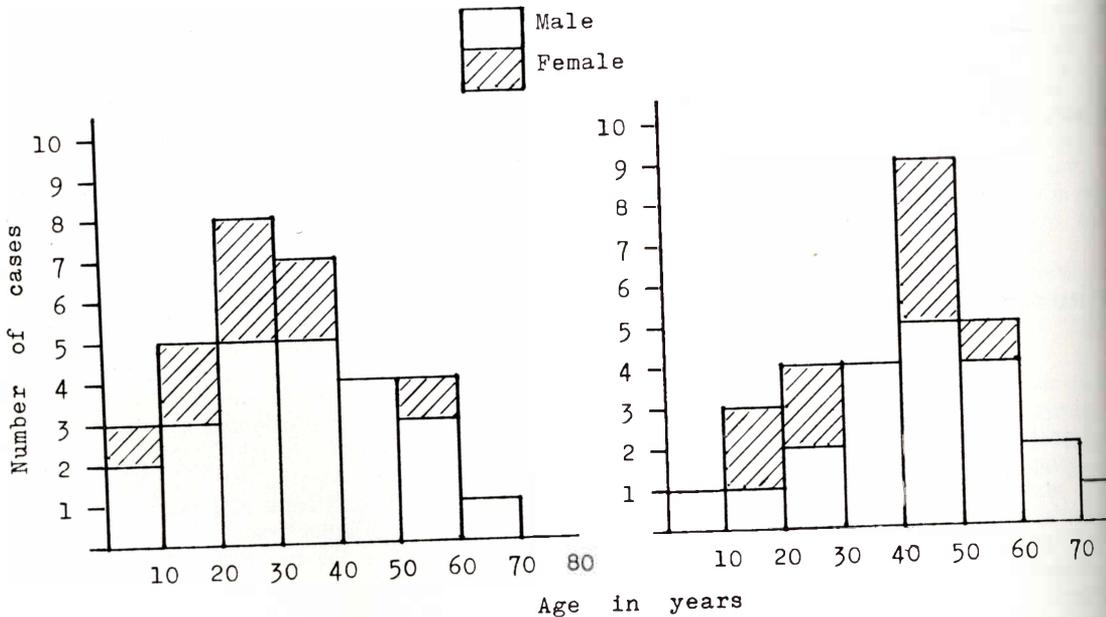


Figure 1. Age distribution.

PENICILLIN TREATED

TRIMETHOPRIM-SULPHAMETHOXAZOLE
TREATED

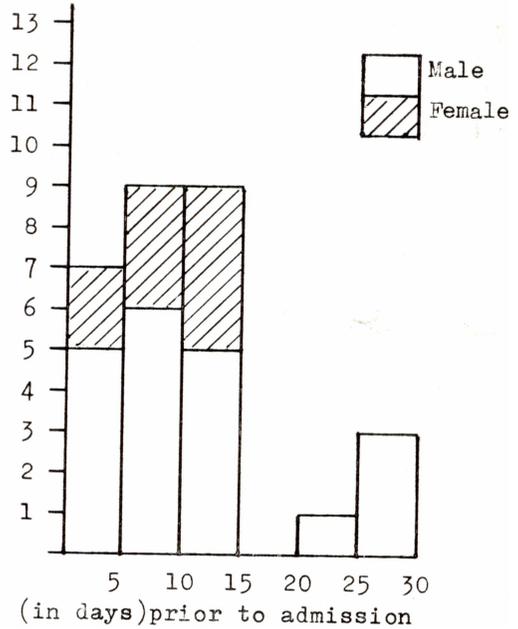
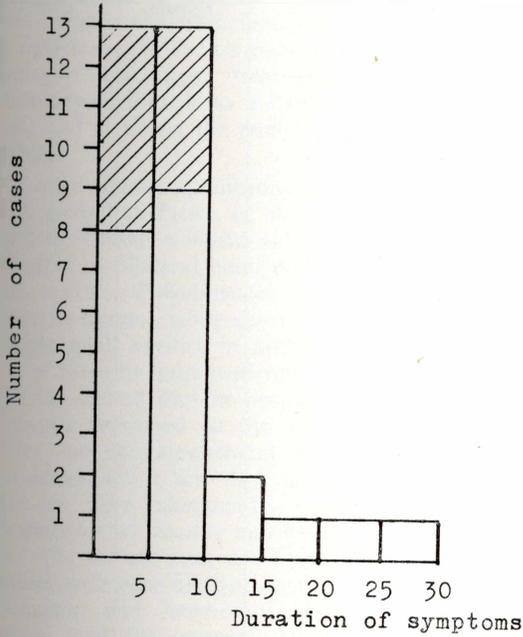


FIGURE 2. Symptom Duration.

The present trial was undertaken to compare trimethoprim-sulphamethoxazole with crystalline penicillin in the treatment of pneumonia.

METHOD

Seventy consecutive patients admitted to two medical wards (male and female) with the diagnosis of pneumonia were allocated to treatment with penicillin or trimethoprim-sulphamethoxazole (t-s) according to a previously arranged randomised table. The initial allocation was 26 males and nine females to each group, but nine males were subsequently withdrawn from the trial (Table 1), leaving 23 males and nine females in the penicillin-treated group and 20 males and nine females in the t-s-treated group. The mean age of patients treated with penicillin was 30.1 years (6-62), while it was rather higher at 39.6 years (7-79) in those treated with trimethoprim-sulphamethoxazole (Fig. 1).

It should be emphasised that in several cases the length of history indicated that the pulmonary infection was not acute. Nonetheless, with an admission diagnosis of "pneumonia", such patients

were included in the trial. The duration of symptoms before admission ranged from 1-28 days (average 6.8) in the penicillin group and from 2-30 days (average 10.2) in the t-s group (Fig. 2).

In each case a throat swab, cough plate and specimen of sputum were submitted for culture on admission, and before commencement of treatment. A chest radiograph was taken and a blood count was done as soon as conveniently possible. The standard treatment for pneumonia prior to the trial had been intramuscular penicillin 1 mega unit 6-hourly and this regime was continued for those patients allocated to penicillin treatment. Patients allocated to trimethoprim-sulphamethoxazole treatment were given 2 tablets twice daily. Patients in both groups were discharged as soon as they were considered clinically cured, while, if pulmonary signs persisted, the chest radiograph was repeated after one week of treatment and other investigations were carried out as seemed indicated. Where the treatment of any patient appeared ineffective it was discontinued and alternative therapy was instituted.

Table II
COMPARISON BETWEEN PATIENTS TREATED WITH PENICILLIN AND PATIENTS TREATED WITH TRIMETHOPRIM-SULPHAMETHOXAZOLE

	PENICILLIN GROUP			T-S GROUP		
	Male	Female	Total	Male	Female	Total
NUMBER OF PATIENTS	23	9	32	20	9	29
AGES in years	32.4 (6-62)	24.1 (6-50)	30.1 (6-62)	42.1 (7-79)	34.1 (14-53)	39.6 (7-79)
DIAGNOSIS Lobar pneumoniae	18	8	26	15	7	22
Bronchopneumonia	5	1	6	5	2	7
ORGANISM RECOVERED						
Streptococcus Pneumonia	2	1	3	5	1	6
Haemolytic Streptococcus ...	4	—	4	1	—	1
Klebsiella species	2	1	3	1	—	1
(not pneumoniae)						
Staphylococcus pyogenes	1	—	1	—	—	—
Haemophyllus Influenza	1	—	1	—	—	—
Monilia	1	—	1	1	1	2
TREATMENT RECORDED BEFORE ADMISSION						
1 mega units I.M. crystalline penicillin on day of admission	—	2	2	1	2	3
1 mega units crystalline penicillin and 900,000 units procaine penicillin I.M. one week before admission	—	—	—	1	—	1
Oral penicillin V 250 mg. 6 hourly for 2 days	—	—	—	1	—	1
COMPLICATIONS						
Failure of resolution	2	—	2	6	—	6
Abscess formation	1	—	1	—	—	—
Meningitis	—	—	—	2	—	2
DEATHS	1	—	1	2	1	3
CHANGE OF THERAPY REQUIRED	4	—	4	8	—	8
TIME TAKEN (in days) FOR TEMPERATURE TO FALL TO NORMAL	2.8	1.6	2.5	4.2	1.7	3.4
LENGTH OF STAY IN HOSPITAL (days)	14.8 (3-46)	9.3 (7-14)	13.4 (3-46)	20.2 (3-45)	8.0 (3-24)	16.3 (3-45)

RESULTS

The results of treatment are summarised in Table II. 79 per cent. of all patients had lobar pneumonia and 21 per cent. had broncho-pneumonia; there was no significant difference in this respect between the two groups. A positive bacterial culture was obtained from only 12 of the penicillin group cases and from eight of the t-s group cases (33 per cent. of all cases), while monilia was recovered from three cases. Lung puncture has been shown to be a safe and efficient method of recovering organisms in lower respira-

tory tract infections (Sinha & Hughes, 1966) and will be used for bacterial diagnosis in a further trial of trimethoprim-sulphamethoxazole that being undertaken.

Only seven patients (two in the penicillin group and five in the t-s group) were recorded as having received treatment before admission. However, in view of the duration of symptoms (in excess of 10 days in 18 cases) it seems possible that others had been treated privately before coming to Harare Hospital.

Treatment with penicillin apparently produced

a distinctly better response than treatment with t-s. Failure of resolution occurred in two patients in the penicillin group, necessitating a change in therapy, and a third case progressed to multiple abscess formation. This patient died on the sixth day after admission (the only death in this group) and was found at autopsy to have carnification with multiple abscesses involving the whole of the right lung. In the t-s group, six cases showed failure of resolution; treatment was changed either to penicillin or to a broad spectrum antibiotic, and in all six the pneumonia subsequently resolved.

Of more serious significance was the meningitis which complicated two of the t-s treated cases. The first of these, a 9-year-old boy, was admitted with signs of bilateral basal pneumonia and right otitis media. Pneumococci were grown from culture of sputum, while chest radiograph showed multiple small cavities in both lower zones. In view of these findings penicillin was added to t-s from the second day in hospital, despite which meningitis developed on the sixth day. Sulphadiazine and chloramphenicol in full doses were then added, and a few days later ampicillin and cloxacillin were substituted. The child's condition deteriorated steadily and he died on the 18th day. The second case, a 50-year-old male, was admitted with signs of right upper and lower lobar pneumonia, and haemolytic streptococci were cultured from his sputum. He had been given an injection of 1 mega unit crystalline penicillin with 900,000 units procaine penicillin one week before admission. Treatment with t-s was commenced, but, on the fifth day in hospital, he developed meningitis and, despite an immediate change to penicillin, sulphadiazine and chloramphenicol, he died four days later.

The third death in the t-s treatment group occurred in a 26-year-old female who was admitted with right upper lobar pneumonia three days after delivery. Her pneumonia appeared clinically to be responding well to treatment, but, after three days in hospital, she developed puerperal psychosis, jumped from a third floor window and died of multiple injuries.

Initial therapy was changed in eight t-s treated patients—namely six with failure of resolution and two who developed meningitis. Only four of the penicillin treated patients required a change of treatment; in addition to two with failure of resolution and one with multiple abscesses there was a 30-year-old male who was admitted with bilateral bronchopneumonia, a subnormal temperature and in a state of shock. In view of his serious condition, streptomycin was added to his penicillin therapy and he was also given intra-

venous hydrocortisone. Response was excellent and within five days he was clinically cured.

As shown in the table, the time taken for the temperature to fall to normal was, on average, a day longer in patients treated with t-s than in those treated with penicillin. Patients who were afebrile from the start (three penicillin treated and four t-s treated cases) were excluded in making this calculation.

The length of stay in hospital was on average three days longer in t-s treated patients, though a further breakdown indicated that t-s treated females were discharged earlier than any other single group.

CONCLUSIONS

Trimethoprim-sulphamethoxazole is effective in the majority of cases in the treatment of lobar and bronchopneumonia. However, at a dosage of two tablets twice daily, it has been found to be clearly less effective than penicillin, 1 mega units 6-hourly. Patients treated with t-s responded more slowly and stayed in hospital longer; a change of therapy was more frequently necessary, and they developed more complications than those treated with penicillin. In recording these differences a number of points should be stressed:

The trimethoprim-sulphamethoxazole treated patients as a group were older (mean difference of nine years) than the penicillin treated patients and the duration of their symptoms was longer (mean difference of 3.4 days).

An average dosage of trimethoprim-sulphamethoxazole was compared with a fairly large dosage of crystalline penicillin.

One of the trimethoprim-sulphamethoxazole treated patients, who developed meningitis on the sixth day in hospital, had also been on penicillin since the second day. In this case it would seem that penicillin failed no less than trimethoprim-sulphamethoxazole to prevent this complication and the subsequent death.

A further trial of trimethoprim-sulphamethoxazole is being undertaken with a dosage of three tablets twice daily. It is hoped to improve the rate of bacterial diagnosis by routine culture of pre-treatment lung puncture aspirates.

Acknowledgments

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