TREATMENT OF ACUTE SORE THROAT IN GENERAL PRACTICE

THERAPEUTIC TRIAL, WITH OBSERVATIONS ON SYMPTOMS AND BACTERIOLOGY

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Sore throat is a common complaint in general practice, but doctors do not agree on the best method of treatment. Earlier trials of sulphonamide drugs gave conflicting results (Rhoads and Afremow, 1940; Freis, 1944; Clodfelter, 1945; Commission on Acute Respiratory Disease, 1945), but more recently MacDonald and Watson (1951) and Landsman and her colleagues (1951) both concluded that the sulphonamide treatment they used was not effective. As with many of the earlier trials, the patients treated by MacDonald and Watson were young Service men, and their findings are not necessarily applicable to younger patients or to those living in their own homes. Furthermore, although there was little difference between the average duration of symptoms and signs in treated and control cases, a statistically significant preponderance of patients making a good recovery after 72 hours' treatment had received sulphonamide. Landsman's patients were of all ages and were treated in general practice, but the total number of cases was too small to put the question beyond doubt.

Evaluation of penicillin in the treatment of sore throat has been bacteriological rather than clinical. Investigations by Plummer *et al.* (1945), Keith *et al.* (1945), and Denny *et al.* (1953) confirmed that penicillin eradicated streptococci from the throat and strongly suggested that clinical recovery was also accelerated. A controlled trial of penicillin in sore throat in this country was reported by Gardner (1953), who treated 102 cases of food-borne streptococcal tonsillitis with penicillin, sulphadimidine ("sulphamezathine"), or aspirin. The average recovery time in the penicillin group was similar to that in the sulphadimidine group and about half as long as that in the aspirin group, but as the numbers were small the differences were not statistically significant.

The problem that faces the general practitioner, however, is not the treatment of streptococcal tonsillitis but of acute febrile sore throats, of which only a proportion may be streptococcal. Though certain broad differences between large groups of cases of streptococcal and non-streptococcal sore throat have been observed (Commission on Acute Respiratory Diseases, 1944, 1947; Landsman *et al.*, 1951), the classification of an individual case on clinical grounds alone is not practicable. Probably most doctors prescribe intramuscular penicillin if the illness is severe, but find more difficulty in deciding whether to use penicillin or sulphonamide, with the attendant risk and discomfort, for less severe infections. Because it was felt that no adequate evaluation of sulphonamide or of oral penicillin in the treatment of cases of this kind had been made, the investigation described below was undertaken.

Outline of Investigation

Selection of Cases

Patients aged more than 2 years seen in general practice were considered for inclusion in the investigation if their doctor thought them to be suffering from an acute infection of the throat or middle ear, provided that the illness had not already lasted for more than 48 hours. Only those cases that were of such severity that they would previously have been given penicillin or sulphonamide were then accepted. There were periods when the doctor decided that pressure of work would prevent him from carrying out the requirements of the trial. During these periods he did not admit any case, and so far as he was concerned the trial was temporarily suspended. Apart from these occasions, every suitable case seen by the five of us in general practice between February, 1954, and September, 1955, was included and a record kept of symptoms, treatment, and progress.

On seeing a case for the first time the doctor recorded the history and his clinical observations on a standard record card. He then decided whether or not the patient should be included in the therapeutic trial, in which he would be allocated to one of three treatments at random. If he did not think that random treatment should be given he recorded his reasons and the treatment actually prescribed. The nature of the investigation was explained to all patients to whom the doctor proposed to give the random treatment, and very few objected to taking part.

Preparations Used in the Trial

Three preparations were used—potassium penicillin, sulphadimidine, and a placebo (barium sulphate). They were supplied in powder form by Glaxo Laboratories, each in bottles of three sizes—6 oz. (170 ml.), 8 oz. (225 ml.), and 10 oz. (280 ml.). The 6-oz. (170-ml.) bottles were suitable for patients aged 2 to 4 years, the 8-oz. (225-ml.) bottles for patients aged 5 to 9, and the 10-oz. (280-ml.) bottles for patients aged 10 and over.

The bottles were completely filled with water immediately before being given to the patients; the resulting suspensions of each of the three preparations then had the same percentage composition irrespective of bottle size. The three preparations were as nearly as possible identical in appearance and flavour, and the doctors did not know which medicament was in any particular bottle.

Each bottle bore a label giving instructions to the patient on the dose to be taken and was inscribed with a number from a random series to indicate to the doctor the order in which the bottles were to be issued to patients. Three random series were used, one for each age group. The key to the random series was the only guide to the contents of each bottle, and no copy of this was held by the practitioners.

A patient admitted to the therapeutic trial was given the bottle bearing the lowest unused serial number in the appropriate age group. The serial number of the bottle used was recorded at once in the space allocated for the purpose on the back of the patient's record card. The patient or patient's mother was told that the treatment was to be taken at 7 a.m., 12 a.m., 5 p.m., and 10 p.m. for five days as shown on the label on the bottle, and was given instructions on the accurate measurement of the dose. The content of the daily dose of the three preparations is shown in Table I for each age group. All patients receiving one of the three trial preparations were given, in addition, a fixed dosage of soluble aspirin tablets in water twice a day for three days.

In July, 1955, a sample of the penicillin mixture was re-assayed by Glaxo Laboratories and reported to be at full potency.

TABLE I.—*Content of Daily Dose* of the Three Treatments Under Trial*

Age Group	Daily Dose*		
	Sulphadimidine	Penicillin	Placebo (Barium Sulphate)
2–4 years ..	2 g.	1,200,000 units	2 g.
5–9 ,, ..	3 ,,	1,800,000 ,,	3 ,,
10 years and over	4 ,,	2,400,000 ,,	4 ,,

* A quarter of each daily dose was administered four times a day for five days.

The Follow-up

For the purposes of the investigation each patient was seen three times—on the first occasion, again three days later, and for the third time 10 to 14 days after the start of treatment. On each occasion a description of the patient's condition was recorded on the card in a standard manner, and nose and throat swabs were taken. Cotton-wool swabs on wooden sticks used for this purpose were broken off into the gonococcal transport medium of Moffett *et al.* (1948) in bijou bottles, and posted to the laboratory. At the beginning of the investigation specimens of urine collected at the third visit were also posted to the laboratory, but it was soon found more convenient to limit the examination to a test for protein performed by the doctor himself. At the second visit the bottles of medicine were inspected to see whether the mixture was being taken adequately.

Change of Treatment

If the doctor was at any time dissatisfied with the progress of his patient he could change from random treatment to one of his choice. This change of treatment and the reasons for it were recorded on the card. If in the interest of such patients he wished to know the treatment that had been given under the investigation he telephoned the laboratory, where the key to the random series was held, and this information was at once available. This was done on five occasions.

Laboratory Methods

On arrival at the laboratory 24 to 48 hours after being taken, nose and throat swabs were plated on horse-blood–agar plates. In the early stages of the investigation a further attempt was made to isolate haemolytic streptococci by enrichment in blood broth containing 1/500,000 crystal violet followed by plating on blood–agar plates. Later, this enrichment was abandoned, owing to pressure of work and the relatively small number of additional positive findings.

All haemolytic streptococci were grouped and the majority tested for sensitivity to penicillin and sulphonamide. A record was also kept of other organisms growing on the original plate, with particular reference to those known to be penicillin-resistant. It is probable that the bacteriological results were not so good as they would have been if the swabs had been plated as soon as they were taken, but we believe that the difference is not likely to have been serious.

General Findings

During the 20-months period of the investigation 339 patients were studied and 308 of these were regarded as suitable for admission to the therapeutic trial. Most of the remaining 31 were excluded because of the presence of other medical conditions or for socio-economic reasons and two because they were unwilling to participate. None was excluded solely on account of the gravity of the throat infection. Of the 308 treated at random, 69 were aged 2 to 4 years, 120 aged 5 to 9, and 119 aged 10 or more. Haemolytic streptococci were isolated from acute-stage throat swabs from 11 patients in the youngest age group, 61 in the middle age group, and 60 in the highest age group. The reason for the low proportion of streptococcal isolations from children under 5 years is unknown. In 22 of 132 patients with positive throat swabs haemolytic streptococci were also isolated from the nose swab, but the nasal swab was positive in only 2 of the 176 patients with negative throat swabs. No clue to the aetiology of the 176 non-streptococcal illnesses was obtained from the acute-stage throat swabs.

The presenting symptoms and signs were analysed in relation to the presence or absence of haemolytic streptococci in the acute-stage throat swabs of the 239 patients aged 5 years or more. The youngest age group was excluded because the proportion positive was so different and because symptoms were probably less reliable. The frequency with which various symptoms and signs were noted in the two groups is presented in Table II, where it may be seen that there were few differences. Sore throat, shivering, sweating, anorexia, and abdominal pain were slightly more frequent

TABLE II.—*Clinical Findings in Patients Aged 5 Years or More With and Without Haemolytic Streptococci in Acute-stage Throat Swabs*

	Proportion in Whom Symptom or Sign was Noted	
	Haem. Strep. Present	Haem. Strep. Absent
Presenting symptoms:	(121)	(118)
Sore throat	93%	79%
Running nose	20%	28%
Cough	27%	33%
Abdominal pain	33%	20%
Anorexia	76%	63%
Shivering	60%	43%
Sweating	56%	47%
Muscular pains	35%	34%
Earache	31%	28%
Signs when first seen:		
Throat swelling	77%	63%
,, redness	93%	86%
,, exudate	55%	38%
Tonsils absent	7%	14%
,, normal	56%	48%
,, enlarged	34%	35%
,, grossly enlarged	4%	4%
Tonsillar glands enlarged	74%	68%
,, ,, tender	40%	43%
Eardrums red	7%	19%
,, bulging	2%	3%
,, discharging or perforated	5%	3%
Scarlatiniform rash	7%	3%
Conjunctivitis	0%	2%

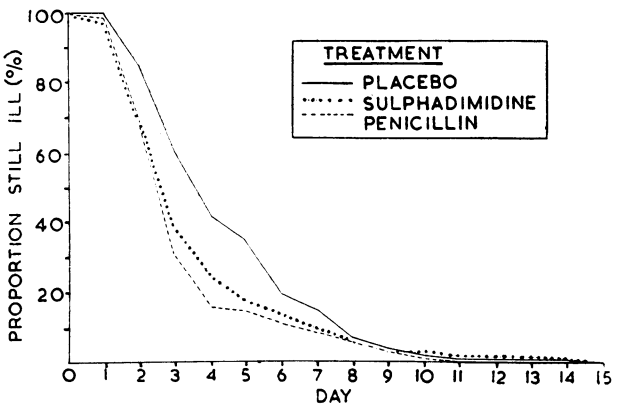
TABLE III.—*Proportion of Patients Still Ill on the Third Day in Relation to Bacteriology, Age, and Treatment (based on Patient's or Patient's Mother's Estimate of Duration of Illness)*

Haem. Strep. in Acute-stage Throat Swabs	Treatment	2–4 Years		5–9 Years		10 Years or More		All Ages	
		No.	Still Ill (On 3rd Day)	No.	Still Ill (On 3rd Day)	No.	Still Ill (On 3rd Day)	No.	Still Ill (On 3rd Day)
Present	Placebo	6	50%	24	46%	21	71%	51	57%
	Sulphadimidine	3	33%	18	22%	15	53%	36	36%
	Penicillin	1	0%	19	26%	20	35%	40	30%
Absent	Placebo	10	40%	17	59%	19	84%	46	65%
	Sulphadimidine	15	47%	20	30%	16	44%	51	39%
	Penicillin	23	39%	18	33%	18	22%	59	32%
All patients	Placebo	16	44%	41	51%	40	78%	97	61%
	Sulphadimidine	18 } 58	44% } 41%	38 } 116	26% } 36%	31 } 109	48% } 52%	87 } 283	38% } 43%
	Penicillin	24	38%	37	30%	38	29%	99	31%

in the streptococcal group and a running nose slightly commoner in the non-streptococcal group. Local signs in the throat were a little more frequent in those from which streptococci were isolated and there were rather more red eardrums in those with negative swabs. It is clear that a clinical differentiation of individual patients would be impossible.

Clinical Results of Treatment

In analysing the results of treatment 25 of the 308 patients admitted to the trial were excluded, 19 because treatment was not adequately taken and 6 because follow-up was incomplete. The remaining 283 were fairly evenly divided among the three treatment groups (Table III), the slightly lower number on sulphadimidine apparently being due to chance. Many methods of assessing the efficacy of treatment were available, but that which seemed to us most important was the patient's or the patient's mother's estimate of the duration of illness. The results observed, using this criterion on all 283 patients, are given in the Chart, which shows the proportion in each of the three groups still ill day by



Rate of recovery of 283 patients of all ages in the three treatment groups (based on patient's or patient's mother's estimate of duration of illness).

day until all had recovered. The curves for the penicillin- and sulphadimidine-treated patients are similar, but they differ greatly from that of the control group, particularly three to five days from the beginning of treatment. This result is shown in greater detail in Table III, where the proportions still ill at the time of the second follow-up visit, on the third day of treatment, are set out. The third day was chosen because it proved necessary to change the treatment of 17 patients on or after the third day, and these would have been lost if a later day had been chosen. Furthermore, information obtained by the doctor at the time of his second visit was likely to be accurate.

If age and bacteriological findings are disregarded it may be seen that, whereas 61% of patients in the control group were still ill on the third day, the corresponding proportions in the sulphadimidine and penicillin groups were 38% and 31% respectively. The difference in proportion between control and sulphonamide groups is statistically significant $\left(\frac{\text{Difference}}{\text{Standard error}} = \frac{23}{7.2} = 3.2\right)$ and the effect of penicillin was even greater. However, the difference between 38% and 31% could well have occurred by chance $\left(\frac{\text{Difference}}{\text{Standard error}} = \frac{7}{7.0} = 1.0\right)$. A close examination of the figures in Table III shows that the presence or absence of haemolytic streptococci in the acute-stage throat swabs made little difference to the results of treatment and that the advantage of penicillin and sulphadimidine over the placebo was confined to those over 4 years of age. But whereas both drugs were equally effective in children aged 5 to 9 years, penicillin was apparently better than sulphadimidine in those aged 10 years and over, though the difference did not quite reach the usually accepted level of statistical significance $\left(\frac{\text{Difference}}{\text{Standard error}} = \frac{19}{11.6} = 1.6\right)$

Other methods of assessing the results of treatment were also available. These included the doctor's estimate of the duration of illness—usually but not always the same as the patient's—and the duration of sore throat and of physical signs in the throat. An analysis of these criteria, again based on the doctor's findings at the time of his visit on the third day, is shown in Table IV. All methods gave essentially the same answer. A red or bulging eardrum was observed at the first examination of 48 patients included in the therapeutic trial. At the third day 10 out of 16 (63%) of those given the placebo still had abnormal drums, compared with 4 out of 13 (31%) of those given sulphadimidine and 6 out of 19 (32%) of those given penicillin. Though these numbers are small they follow the same trend as that shown for signs in the throat. In two patients the eardrum perforated on the day after treatment began but healed completely before the final visit. They were both in the penicillin group.

A further indication of the value of a given treatment may be obtained from an examination of its more obvious failures. Thus, of the 17 patients who were still so ill on the third day that the doctor was forced to take them out of the trial and change the treatment, 11 were having the placebo, 4 sulphadimidine, and 2 penicillin. Symptoms recurred after apparent recovery in a further 20 patients; 6 of these were having the placebo, 11 sulphadimidine, and 3 penicillin. If relapses and treatment failures are combined, 17 were in the control group, 15 in the sulphadimidine group, and only 5 in the penicillin group. Ten of these failures were due to the presence of acute otitis media—5 on the placebo, 4 on sulphadimidine, and 1 on penicillin. On the other hand, three patients on penicillin developed a sore mouth or tongue and two patients on sulphadimidine complained that the medicine made them vomit; there were no complaints of this kind with the placebo. Five patients were found to have transient proteinuria when tested between the 10th and 14th days; four of these had received penicillin and one sulphadimidine. No cases of rheumatic fever or of persistent discharging ears were found during the follow-up.

TABLE IV.—*Effect of Treatment Assessed by Various Methods*

Haem. Strep. in Acute-stage Throat Swab	Treatment	Doctor's Estimate of Duration of Illness		No. with Sore Throat		No. with Swollen Throat		No. with Red Throat		No. with Exudate in Throat	
		No.	Still Ill on 3rd Day	On 1st Day	Still Present on 3rd Day	On 1st Day	Still Present on 3rd Day	On 1st Day	Still Present on 3rd Day	On 1st Day	Still Present on 3rd Day
Present	Placebo	51	65%	41	54%	38	42%	46	59%	25	24%
	Sulphadimidine	36	47%	31	29%	28	18%	34	50%	21	5%
	Penicillin	40	45%	37	19%	33	30%	38	45%	23	13%
Absent	Placebo	46	70%	26	62%	35	40%	39	56%	22	32%
	Sulphadimidine	51	43%	32	19%	28	25%	44	27%	21	24%
	Penicillin	59	42%	35	20%	36	19%	48	31%	20	25%
All patients	Placebo	97	67%	65	57%	73	41%	85	58%	47	28%
	Sulphadimidine	87 (283)	45% (52%)	63 (202)	24% (33%)	56 (198)	21% (30%)	78 (249)	37% (44%)	42 (132)	14% (20%)
	Penicillin	99	43%	72	19%	69	25%	86	37%	43	19%

It was thought possible that the state of the patient's tonsils might influence the speed of recovery or the effect of chemotherapy or antibiotic treatment, but this was not so. The proportion of patients still ill on the third day of treatment in those with normal tonsils or tonsils removed was 62% in the control group, 39% in the sulphadimidine group, and 30% in the penicillin group. The corresponding figures for those with tonsils enlarged or grossly enlarged were 59%, 37%, and 33%.

Bacteriological Results of Treatment

All but four of the strains of haemolytic streptococci isolated belonged to group A and all were sensitive to penicillin and sulphadimidine. Penicillin was apparently much more effective than sulphadimidine in eradicating the organism as judged by throat swabs taken on the third day of treatment. There were 121 patients in whom haemolytic streptococci were isolated from acute-stage throat swabs and who were fully treated and followed up. Sixteen out of 35 patients (46%) given sulphadimidine were still positive at the third day, compared with 27 out of 47 (57%) given the placebo, but none of the 39 who received penicillin was positive at this examination. The proportion of positive swabs taken between the 10th and 14th days was placebo 32%, sulphadimidine 29%, and penicillin 21%. It seems possible that penicillin may have inhibited the growth of streptococci in the throat sufficiently to produce a sterile throat swab but not eradicated the organism completely. Alternatively, the patients may have been reinfected subsequently from other members of their family.

Penicillin-resistant Gram-negative bacilli were found quite often in third-day nose or throat swabs. Persistent infection of the throat with penicillin-resistant organisms was not observed. *Candida albicans* was isolated from only four throat swabs during the investigation : two taken on the third day from patients—one on the placebo and one on sulphadimidine—and two taken in convalescence from patients who had been treated with penicillin.

Discussion

The results of this trial indicate that both oral penicillin and sulphadimidine reduced the length of illness in patients aged 5 years and over. Why similar beneficial results were not found in those under 5 is not clear. Possibly the aetiology of infections in the younger age group is different—certainly a lower proportion were streptococcal—or possibly the duration of illness was less easy to assess accurately in those too young to describe their symptoms well. Though no statistically significant difference between penicillin and sulphadimidine was demonstrated, such differences as there were, particularly in those aged 10 years or more, together with the greater frequency of relapse and treatment failure in those who received sulphadimidine, suggest that penicillin was the better of the two. Penicillin was unquestionably more effective in eradicating haemolytic streptococci as judged by throat swabs taken on the third day, and it is interesting that its clinical efficacy was not so definitely superior. No information was obtained on the value of penicillin and sulphadimidine in the prevention of the more serious complications of throat infection—rheumatic fever and nephritis—and relatively little of their value in otitis media. Inflamed eardrums returned to normal more rapidly with penicillin and sulphadimidine than with the placebo, but the only two perforations that occurred were in children receiving penicillin.

The equal response of both streptococcal and non-streptococcal throat infections was an unexpected finding that deserves further study. It seems unlikely that many streptococcal infections were missed and included in the wrong group, as the proportion of patients from whom streptococci were isolated (45%) was about what one would expect. It is usual to attribute most non-streptococcal throat infections to viruses, of which the recently discovered adenoidal-pharyngeal-conjunctival group is at present chiefly under suspicion. Possibly virus infection was responsible for most of the illnesses in younger children, and this would explain their failure to respond to treatment, but it is difficult to explain the results in older patients in the same way. Bacteriological findings did not suggest that any accepted bacteriological pathogen was responsible for the non-streptococcal illnesses, but perhaps not all "normal pharyngeal flora," or certain varieties of them, are as innocent as they appear.

It seems reasonable to conclude from this trial that patients with acute sore throat will probably benefit from sulphadimidine or penicillin treatment. It may be questioned whether reduction in duration by a day or two of a relatively trivial illness justifies such potential disadvantages as reactions and the development of drug-resistant strains, but virtually no reactions to treatment were observed in this trial, and certainly no insensitive strains of streptococci were found after treatment. Furthermore, there is evidence that the treatment of acute throat infections with penicillin prevents rheumatic fever (Wannamaker *et al.*, 1951).

Summary

A clinical and bacteriological survey of cases of acute sore throat in general practice and the results of a strictly controlled trial of oral penicillin, sulphadimidine, and a placebo in its treatment are described.

Whereas 61% of patients receiving the placebo were still ill on the third day of treatment the corresponding rates for those on sulphadimidine and penicillin were 38% and 31% respectively. The difference between 61% and the other two rates was statistically significant, but that between 38% and 31% was not. However, the difference between penicillin and sulphadimidine in those 10 years of age and over was greater than in those under 10 years. Fewer failures of treatment occurred in those who received penicillin.

The unexpected observation was made that the results of treatment were practically the same in streptococcal and non-streptococcal sore throats.

Analysis of the presenting symptoms and signs in patients with and without haemolytic streptococci in pre-treatment throat swabs showed only minor differences between the two groups. No clue to the aetiology of the non-streptococcal illnesses was found, apart from their apparent response to both sulphadimidine and penicillin.

We are much indebted to Glaxo Laboratories for supplying the three preparations used in the trial and to the Medical Department, Imperial Chemical (Pharmaceuticals) Limited, for providing them with the sulphadimidine. We should like to thank Dr. J. Knowelden, of the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, for providing lists used in the random allocation of treatment.

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