A randomized controlled trial of antibiotics on symptom resolution in patients presenting to their general practitioner with a sore throat

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SUMMARY

Background. *Sore throat is a common symptom presented to general practitioners (GPs), and there remains controversy about the appropriate use of antibiotics.*

Aim. *To compare, in a randomized controlled trial, the effectiveness of penicillin, cefixime and placebo on symptom resolution in patients presenting with a sore throat in general practice.*

Method. *Twenty-two GPs in Avon recruited 154 patients, aged 16–60 years, presenting to their GP with a sore throat, and for whom the GP would normally prescribe an antibiotic. Patients were randomized to one of three groups: penicillin V 250 mg four times a day; cefixime 200 mg daily; and placebo. Each was prescribed for five days. The main outcome measures were a diary of symptom resolution over seven days and eradication of group A beta-haemolytic streptococcus (GABHS).*

Results. *Of the 103 (67%) patients who completed symptom diaries, 40 were allocated to receive penicillin, 29 cefixime and 34 placebo. In the analysis including all patients, symptom resolution was greater by day 3 in the cefixime group than in the placebo group. Penicillin did not improve symptom resolution by day 3 compared with placebo, and cefixime was not statistically significantly different from penicillin. There were significant differences in the proportion of patients using analgesia at day 3, with the proportion being lowest in the cefixime group. The results for the subgroup of patients without GABHS were similar to those for all patients; in particular, the only statistically significant difference was between cefixime and placebo. Although numbers were too small for statistical significance, among patients with GABHS the effects of penicillin and cefixime were similarly raised in relation to placebo.*

Conclusion. *Compared with placebo, cefixime can improve the rate of resolution of symptoms in patients with a sore throat who are selected for antibiotic treatment by their GP. The unexpected finding that cefixime was of benefit compared with placebo for patients without GABHS suggests that bacteria other than GABHS may be important in the pathogenesis of sore throat.*

Keywords: sore throat; antibiotics; randomized controlled trial.

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Introduction

SORE throat is a common symptom presented to general practitioners (GPs),[1,2] and there remains controversy about the appropriate use of antibiotics.[3] The prescribing of antibiotics for respiratory complaints varies between doctors[4] and between countries.[5] The prescribing behaviour of GPs is complex,[6] and the decision to prescribe an antibiotic for a sore throat is influenced by social considerations.[7] Few randomized controlled trials (RCTs) have addressed the question of symptomatic resolution for this common condition, although a recent systematic review has concluded that antibiotic treatment does not reduce the symptoms related to the acute illness.[8]

Previous trials carried out in general practice have given conflicting results. One RCT based in general practice, in which the rate of group A beta-haemolytic streptococcus (GABHS) isolation was 7.5%, did not show any benefit from penicillin treatment.[9] Other RCTs, in which the sample population had a higher rate of GABHS isolation, have demonstrated the clinical benefit of antibiotic treatment.[10,11]

This study set out to examine the effect of penicillin and cefixime on symptom resolution in a population selected by GPs for antibiotic treatment. The four ethics committees in Avon approved the study.

Method

Study design

A total of 39 GPs in 22 practices in Avon recruited patients for the study from October 1993 to May 1994. Participating GPs were asked to include patients aged 16–60 years, whose presenting complaint was a sore throat, and for whom the GP would normally prescribe an antibiotic. Patients were not eligible for recruitment if they had received a course of antibiotic in the previous two weeks or if there was a history of rheumatic fever, nephritis or allergy to penicillin and cephalosporins. GPs were asked to keep a log of patients eligible for inclusion in the trial, but who were not recruited.

At presentation, the GP obtained informed consent, completed a record of the signs present in the throat and took a throat swab. GPs were provided with study packs for patients, identified only by number. Each contained instructions together with one course of medication (either antibiotic or placebo) and copies of the questionnaires. Medication was determined by random allocation using blocks of six — two penicillin, two cefixime and two placebo. Each GP was provided with three blocks blinded to both allocation and blocking. The randomization code was kept by the on-call microbiologist in case of treatment failure, and the GP was free to prescribe an antibiotic in such cases. Throughout the trial, patients were allowed to take simple analgesia; the symp-

tom diary asked patients to record whether they were taking any analgesia and how much was taken on each day.

Patients were asked to complete a sociodemographic questionnaire during their initial visit. They were asked to complete a symptom diary daily for seven days beginning on that day. The symptom diary was based on Likert scales,[12] recording the severity of the sore throat, presence of cough, severity of tender lymph glands, and the extent to which patients felt ill and feverish (available from authors on request). At 14 days from presentation, the patient was asked to return to the surgery for a second throat swab and to return the symptom diary. Patient compliance was encouraged by writing to each patient one week after initial recruitment and after the expected follow-up date if the patient had not attended.

The prescribing behaviour of the GPs participating in the trial was compared with a random sample of GPs in Avon by repeating a previous study of prescribing behaviour.[7] GPs were given 16 separate clinical histories of sore throat presentation and asked if they would prescribe an antibiotic, given the picture and the clinical information provided.

Microbiology

Throat swabs were transported in Amies transport medium without charcoal (Sterilin transport swab, Copan, Italy) and processed in the Bristol Public Health Laboratory. Swab contents were inoculated on the tryptic soy blood agar base (Difco, code no. 00369, East Molesey), containing 5% sheep blood and 3% added sodium chloride (final sodium chloride concentration 3.5%).[13] Agar plates were incubated at 37ÞC for 48 hours under anaerobic conditions. Beta-haemolytic colonies were identified as Streptococcus pyogenes using standard laboratory methods.[14]

Statistical methods

For each day, the items of the symptom diary were added to form a summary score. The key outcome measure was the change in symptom score between days one and three, chosen because previous studies had suggested an improvement at this time.[8] An estimate of the sample size suggested that 180 patients (60 in each arm) would need to be recruited to identify a mean change in symptom score of 0.5 standard deviations with a power of 80% and a two-sided significance level of 5%. A small pilot study indicated a standard deviation of about four points on the symptom score.

The characteristics of patients and GPs were compared between the three groups using the Mann–Whitney test, chi-squared test or an exact test, where necessary. The mean change in symptom score from day one to day three between treatment groups was analysed using one-way analysis of variance, with Tukey's multiple comparisons procedure[15] for tests and confidence intervals for the three pairwise contrasts, using the SAS statistical package. The analysis was repeated for the two subgroups of patients with and without GABHS isolated at presentation. Analyses were carried out on an intention-to-treat basis.

Results

Recruitment

A total of 154 patients were recruited to the trial, which was terminated earlier than planned because of local concern about necrotizing fascitis and its association with GABHS.[16] Altogether, 103 symptom diaries were completed (response rate 67%). Questionnaires completed by the GPs were returned for 126 patients (82%), and sociodemographic questionnaires were returned for 118 patients (77%). Given that individual GPs recruited different numbers of patients, the numbers allocated to the three arms of the trial were slightly different: 55 to penicillin; 45 to cefixime; and 54 to placebo.

GPs' records of patients eligible for recruitment, but who were not included in the trial, were not kept completely by the majority of participating GPs. Of the records available, it was clear that some patients declined the offer of taking part in the trial because they felt too ill, or the GP thought they were too ill and needed active treatment. It was also clear that the GP did not have enough time to recruit all the eligible patients seen in the surgery. The number of patients recruited by the GPs varied — the mean number of patients recruited per participating GP was 3.2 (median 2, range 1–9 plus one outlier at 21).

Characteristics of patients

Of the 103 patients who returned the symptom diary, 40 were randomized to penicillin, 29 to cefixime and 34 to placebo. Of the 51 patients who did not complete the study, 15 were randomized to penicillin, 16 to cefixime and 20 to placebo. The isolation rate of GABHS from the responders was 31% (32 out of 103) and from the non-responders was 33% (16 out of 48, three missing). In the group of responders with GABHS isolated, 14 were randomized to penicillin, 10 to cefixime and eight to placebo. In the group of non-responders with GABHS isolated, five were randomized to penicillin, three to cefixime and eight to placebo. Although the numbers are small, there was no statistically significant difference between the responders (those who returned the symptom diary) and non-responders in the randomization to treatment ($\chi^2 = 1.34$ on 2 df, $P = 0.51$) or in the isolation of GABHS ($\chi^2 = 0.08$ on 1 df, $P = 0.78$). The responders to the symptom diary were compared with non-responders for a number of other characteristics (see Table 1). While there was a suggestion that the responders were more likely to be older, married or living as married and non-smokers, none of the differences in Table 1 were statistically significant at the 5% level. The same

Table 1. Characteristics of responders and non-responders to the symptom diary.

Characteristic	Responders*	Non-responders*
Age (median, years)	31.0	24.5
Sex (female)	73/99 (74%)	17/22 (77%)
Sore throat duration (>24 h)	77/97 (79%)	12/17 (71%)
Smoking (non-smoker)	77/97 (79%)	8/17 (47%)
Employment		
Active	63/95 (66%)	13/17 (76%)
Unemployed	8/95 (8%)	2/17 (12%)
Retired	24/95 (25%)	2/17 (12%)
Social class		
Non-manual	54/97 (56%)	6/17 (35%)
Manual	25/97 (26%)	6/17 (35%)
Other	18/97 (19%)	5/17 (29%)
Marital status		
Single	26/97 (27%)	10/17 (59%)
Married	68/97 (70%)	6/17 (35%)
Other	3/97 (3%)	1/17 (6%)
Ethnicity White	96/98 (98%)	16/17 (94%)

*Denominators vary slightly because of missing data.

characteristics were considered across the three treatment groups and, apart from a small excess of non-manual workers and unmarried persons in the penicillin group, there were no marked differences.

Compliance

Patients were asked to record whether they had stopped taking the prescribed medication because of adverse symptoms. On day two, four patients recorded that they had stopped taking the medication. Three of these patients were taking penicillin and one cefixime. On day four, two more patients had recorded that they had stopped taking the medication because of adverse symptoms, both of whom were taking placebo. On day six, no more patients had recorded the need to stop taking their medication. There was no other measure of patient compliance.

Table 2. Prescribing behaviour of GPs in the trial compared with a random sample of GPs in Avon.

Clinical case	Trial GPs (n = 28)	Random sample of GPs (n = 32)
1	7 (25)	8 (28)
2	3 (11)	3 (9)
3	2 (7)	13 (41)
4	21 (75)	24 (75)
5	9 (32)	13 (41)
6	1 (4)	2 (6)
7	5 (18)	3 (9)
8	9 (32)	15 (47)
9	1 (4)	0 (0)
10	5 (18)	2 (6)
11	5 (18)	2 (6)
12	23 (82)	24 (75)
13	13 (46)	10 (31)
14	3 (11)	5 (16)
15	5 (18)	5 (16)
16	2 (7)	3 (9)

Figures given are the number (%) of GPs who would prescribe an antibiotic in each clinical case.

Prescribing characteristics of participating GPs

The prescribing pattern of GPs participating in the trial who returned the questionnaire (n = 28) was similar to the pattern observed in a random sample of GPs in Avon who returned the identical questionnaire (n = 32 out of 60; see Table 2). In only one clinical case out of 16 was there a marked difference between the two groups, that of a 24-year-old mother of three children presenting with a sore throat, for whom GPs participating in the trial were less likely to prescribe.

Symptom diary outcome

Table 3 shows the average daily symptom score, and Table 4 the mean differences in symptom score (day three minus day one) between the three treatments for all patients and the two subgroups of patients. At day three, relative to day one, the overall test for differences between the three treatment arms of the trial was statistically significant (F-statistic on two and 100 df = 5.65, P = 0.0047). The confidence intervals from the multiple comparisons are given in Table 5. The only comparison to reach statistical significance at the 5% level was that between cefixime and placebo. The results of these comparisons repeated for the two subgroups are also given in Table 5. For patients with GABHS isolated at presentation, neither the overall test for differences between the three groups nor any of the comparisons were statistically significant (F-statistic on two and 28 df = 2.24, P = 0.13). However, for patients without GABHS isolated at presentation, the overall test and the comparison between cefixime and placebo were both statistically significant (F-statistic on two and 61 df = 3.57, P = 0.034).

Eradication of GABHS from the throat

In patients with GABHS isolated at recruitment to the study, the proportion of patients who did not have GABHS present after 14 days was four out of 10 patients who received placebo, eight out of 12 patients who received cefixime, and 13 out of 15 patients who received penicillin (P = 0.055 using an exact test).

Table 3(a). Mean symptom scores for all responders (n fluctuates slightly from day to day because of missing values).

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Penicillin	10.5	9.1	7.0	4.0	2.9	1.8	1.5
Cefixime	9.9	7.1	4.3	3.0	2.3	1.4	1.2
Placebo	9.3	8.8	7.0	6.3	4.0	3.5	3.6

Table 3(b). Mean symptom scores for responders with GABHS isolated at presentation (n fluctuates slightly from day to day because of missing values).

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Penicillin	10.6	7.8	5.1	2.0	0.9	0.2	0.0
Cefixime	12.8	9.7	6.2	2.6	1.1	0.0	0.0
Placebo	10.3	10.1	6.6	6.4	4.1	3.6	2.1

Table 3(c). Mean symptom scores for responders without GABHS isolated at presentation (n fluctuates slightly from day to day because of missing values).

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Penicillin	10.4	9.9	8.2	5.4	4.4	2.8	2.5
Cefixime	8.3	5.6	3.2	3.2	3.0	2.3	1.9
Placebo	9.0	8.3	7.1	6.3	4.1	3.5	3.5

Table 4. Mean differences (day 3 – day 1) for the three treatments for all patients, GABHS patients and non-GABHS patients.

	Penicillin	Cefixime	Placebo
All patients	3.53 (n=36)	5.61 (n=28)	2.29 (n=31)
GABHS patients	5.50 (n=14)	6.60 (n=10)	3.57 (n=7)
Non-GABHS patients	2.27 (n=22)	5.06 (n=18)	1.92 (n=24)

Table 5. Confidence intervals (CI) for multiple comparisons — all patients, GABHS patients only and non-GABHS patients only.

Comparison	Penicillin – placebo	Cefixime – placebo	Cefixime – penicillin
All patients			
Difference	1.26	3.19	1.93
95% CI	(-0.83, 3.35)	(0.92, 5.45)	(-0.25, 4.11)
GABHSpatients only			
Difference	1.93	3.03	1.10
95% CI	(-1.41, 5.26)	(-0.52, 6.58)	(-1.88, 4.08)
Non-GABHS patients only			
Difference	0.36	3.14	2.78
95% CI	(-2.49, 3.21)	(0.13, 6.15)	(-0.28, 5.85)

The use of analgesia

At presentation, the proportion of patients who recorded that they were taking analgesia was similar in the three treatment groups. At day three, the proportion of patients recording the use of analgesia was 18/40 (45%) for penicillin, 9/29 (31%) for cefixime, and 23/34 (68%) for placebo ($\chi^2 = 8.73$ on 2 df, $P = 0.013$).

Relapse

A patient was said to have relapsed if the patient returned to the GP within the 14-day study period and the GP prescribed an antibiotic. Nine patients relapsed: three were receiving penicillin, one was receiving cefixime, and five were receiving placebo. The randomization code was broken for two patients: one of the patients receiving penicillin who developed a quinsy, and one patient receiving placebo who complained of worsening symptoms.

Discussion

The characteristics of patients recruited to this study are similar to those of patients with sore throats consulting their GP in previous studies set in general practice,[9,17] and the characteristics of patients in each of the three treatment arms were similar. Nevertheless, the patients recruited to the study were those who were willing to take part in a clinical trial, and whom the GP had selected for antibiotic treatment. The comments from several GPs that there was not enough time during an ordinary consultation to recruit patients, and that the GPs selected a proportion of eligible patients, are in keeping with other research.[18]

This study has shown that, compared with placebo, cefixime improves symptom resolution by day three in patients presenting with a sore throat where the GP selects them for antibiotic treatment. There was also a difference for penicillin compared with placebo, but this did not reach statistical significance; neither, however, did the difference between cefixime and penicillin. Although numbers were too small for statistical significance, among patients with GABHS isolated at presentation, the effects of penicillin and cefixime were raised similarly in relation to placebo. The results for the subgroup of patients without GABHS were similar to those for all patients; in particular, the only statistically significant difference was between cefixime and placebo. Moreover, in this subgroup, the difference between cefixime and penicillin appeared to be greater than for all patients.

Cefixime is considerably more expensive than penicillin V (£6–£85 compared with £0–£30 for the course prescribed in the trial).[19] Although a number of side-effects of cefixime have been noted, they occur with similar frequency to penicillins, and the majority are mild and self-limiting; for example, diarrhoea and stool changes.

The rate of isolation of GABHS in this study (31%) was greater than the 8% observed in the throat swabs taken in general practice and collated by Bristol Public Health Laboratory Service during the study period (M Millar, unpublished observation), and greater than the 7.5% rate reported in a previous study in Bristol.[9] This is not surprising, given the trial inclusion criterion of 'patients for whom you would normally prescribe an antibiotic'. Nevertheless, prescribing decisions for patients with sore throats were similar among trial GPs to those among a random sample of GPs in Avon.

The eradication of GABHS reported in this study needs to be viewed with caution. The numbers are small, and the throat swab does not differentiate between the presence of GABHS as a carrier or a pathogen.[20] Other measures of outcome, in particular the rare complications of streptococcal infection, require clinical trials with very large numbers of patients because the incidence of the complications is so small.

The findings of this study, in particular those for the cefixime-treated group, are consistent with other recent evidence, especially of GABHS tolerance to penicillin.[21] There have also been indications of changes in tonsillar bacteriology in recent years, with an increase in the proportion of beta-lactamase-producing bacteria in tonsillar material.[22] In addition, a meta-analysis of the bacteriological and clinical outcomes of penicillin and cephalosporin treatment of GABHS pharyngitis has demonstrated better efficacy of cephalosporins.[23]

The finding that the beneficial effect of cefixime occurs in patients without GABHS isolated from their throat, requires further explanation. There have been two clinical trials reporting benefit of antibiotic treatment in patients presenting with sore throat who did not have GABHS isolated at presentation.[24,25] Together with the finding from other studies that there is no recognized pathogen identified in 50% of sore throats,[20] this observation suggests that the importance of GABHS as the main bacterial pathogen in such patients could have been overstated. The bacterial flora of the pharynx is complex, and there may be unrecognized bacteria that contribute to the pathogenesis of sore throat. Another possibility is that the isolation of GABHS from a sore throat is a marker for bacterial infection, rather than the cause.

In conclusion, cefixime can improve the rate of resolution of symptoms in patients with a sore throat who are selected for antibiotic treatment by their GP. It should be remembered, however, that in this study cefixime was not statistically significantly different from penicillin, and that penicillin was not statistically significantly different from placebo. Nevertheless, cefixime was of benefit compared with placebo however, even for patients without GABHS. This unexpected finding suggests that bacteria other than GABHS may be important in the pathogenesis of sore throat; further research is clearly needed into the microbiology of this condition.

References

1. Morrell DC, Wale CJ. Symptoms perceived and recorded by patients. *J R Coll Gen Pract* 1976; **26:** 398-403.
2. Royal College of General Practitioners and Office of Population Censuses and Surveys. Morbidity statistics from general practice. *Third national morbidity survey 1981–1982.* London: HMSO, 1986.
3. Little PS, Williamson I, Shvartzman P. Are antibiotics appropriate for sore throats? *BMJ* 1994; **309:** 1010-1012.
4. Howie JGR, Richardson IM, Gill G, Durno D. Respiratory illness and antibiotic use in general practice. *J R Coll Gen Pract* 1971; **21:** 657.
5. Touw-Otten FW, Johansen KS. Diagnosis, antibiotic treatment and outcome of acute tonsillitis: report of a WHO regional office for Europe study in 17 European countries. *Fam Pract* 1992; **9:** 255-261.
6. Bradley CP. Factors which influence the decision whether or not to prescribe: the dilemma facing general practitioners. *Br J Gen Pract* 1992; **42:** 454-458.
7. Howie JGR. Clinical judgement and antibiotic use in general practice. *BMJ* 1976; **2:** 1061-1064.
8. Del Mar C. Managing sore throat: a literature review. II. Do antibiotics confer the benefit? *Med J Aust* 1992; **156:** 644-649.
9. Whitfield MJ, Hughes AO. Penicillin in sore throat. *Practitioner* 1981; **255:** 234-239.
10. Randolph MF, Gerber MA, Demeo KK, Wright L. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *J Pediatr* 1985; **106:** 870-875.
11. Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis: placebo controlled double blind evaluation of clinical response to penicillin therapy. *JAMA* 1985; **253:** 1271-1274.
12. Likert RA. A technique for the development of attitude scales. *Educ Psychol Measurement* 1952; **12:** 313-315.
13. Wat LL, Fleming CA, Hodge DS, Krishnan C. Selective medium for isolation of Arcanobacterium haemolyticum and Streptococcus pyogenes. *Eur J Clin Microbiol Infect Dis* 1991; **10:** 443-446.
14. Fachlam RR, Carey RB. Streptococci and aerococci. In: Lenette EH, Balows A, Hausler WJ, Shadomy HJ (eds). *Manual of clinical microbiology.* Washington DC: American Society for Microbiology, 1992.
15. Zar JH. *Biostatistical analysis,* 2nd edn. New Jersey: Prentice-Hall, 1984.
16. Pini P. Superbug stars in media-made epidemic. *Lancet* 1994; **343:** 1376-1377.
17. Morrell DC. Symptom interpretation in general practice. *J R Coll Gen Pract* 1972; **22:** 297-309.
18. Peto V, Coulter A, Bond A. Factors affecting general practitioners recruitment of patients into a prospective study. *Fam Pract* 1993; **10:** 207-211.
19. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary.* Wallingford: The Pharmaceutical Press, 1996.
20. Del Mar C. Managing sore throat: a literature review. I. Making the diagnosis. *Med J Aust* 1992; **156:** 572-575.
21. Kim KS, Kaplan EL. Association of penicillin tolerance with failure to eradicate group A streptococci from patients with pharyngitis. *J Pediatr* 1985; **107:** 681-684.
22. Timon CI, McAllister VA, Walsh M, Cafferkey MT. Changes in tonsillar bacteriology of recurrent acute tonsillitis 1980 v 1989. *Respir Med* 1990; **84:** 395-400.
23. Pichochero ME, Margolis PA. A comparison of cephalosporins and penicillins in the treatment of group A beta-haemolytic streptococcal pharyngitis: a meta-analysis supporting the concept of microbial copathogenicity. *Pediatr Infect Dis J* 1991; **10:** 275-281.
24. Chapple PAL, Franklin LM, Paulett JD, *et al.* Treatment of acute sore throat in general practice. Therapeutic trial with observations on symptoms and bacteriology. *BMJ* 1956; **1:** 705.
25. Marlow RA, Torrex AJ, Haxby D. The treatment of nonstreptococcal pharyngitis with erythromycin: a preliminary study. *Fam Med* 1989; **21:** 425-427.

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