

Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice

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SUMMARY

Background. The effect of antibiotic therapy in sore throat is questionable and this dilemma has been complicated by the emergence of multiple resistant strains of micro-organisms.

Aim. A randomized double-blind placebo-controlled clinical trial was undertaken in patients aged 4–60 years to assess the efficacy of penicillin V on the clinical course and bacteriological response in patients with sore throat in general practice.

Method. Two hundred and thirty-nine patients presenting with an acute sore throat to 37 general practices in the Netherlands who were clinically suspected of group A beta-haemolytic streptococci (GABHS) were randomized for treatment with penicillin V ($n = 121$) or placebo ($n = 118$). Resolution of sore throat, fever and return to daily activities were evaluated by the general practitioner 2 days after the start of treatment and by the patients keeping a diary for 7 days. The result of throat culture after 2 days was evaluated.

Results. A difference in resolution of sore throat was present after 2 days in all patients, but was a result of GABHS-positive patients ($n = 111$; 46%) in favour of those randomized for penicillin V (adjusted odds ratio 5.3; 95%CI 1.9–15.1). An effect in the course of fever was also seen in GABHS-positive patients (adjusted odds ratio 5.3; 95%CI 1.02–27.7). A difference of 1–2 days was seen in clinical recovery. No difference was found in daily activities between the treatment groups. After 2 days, 4% of the penicillin-treated patients harboured GABHS compared with 75% of the placebo group.

Conclusion. Only GABHS-positive patients benefit from penicillin V in their clinical cure in the first few days. Therefore, rapid testing is necessary. Treatment may be beneficial with regard to the clinical course, but it is not necessary.

Keywords: sore throat; clinical trials in general practice; group A beta-haemolytic streptococci.

Introduction

A MINORITY of patients presenting with sore throat have acute tonsillitis;^{1,2} one-third appear to harbour group A beta-haemolytic streptococci (GABHS), including carriers.³ The effect of antibiotic therapy is questionable:^{4–7} a quicker recovery, and reductions in complications⁴ and the spread of the infection are mentioned as possible advantages. Negative aspects include allergic reactions, selection of resistant micro-organisms and increased susceptibility to new GABHS infections.⁵ The influence of antibiotics on recurrences of infection is questionable.^{6,7} Several double-blind placebo-controlled studies have been performed,^{6,8–13} but the results of the four in general practice were divergent.^{9,10,12,13} Nowadays, the existing clinical dilemma whether or not to treat sore throat with antibiotics is complicated because of the emergence of multiple resistant strains.^{14,15} Consequently, a more restrictive antibiotic policy is strongly recommended.¹⁵ At the same time, several outbreaks of severe group A streptococcal infections have been observed since the mid-1980s, especially in the USA.^{16,17} However, these outbreaks were limited in comparison with the total of episodes of sore throat. This clinical dilemma explains the wide variation of antibiotic treatment in sore throat in various countries.¹⁸

One way of reducing antibiotic prescribing could be a differentiation on clinical grounds for the presence of GABHS with the help of four clinical features: fever, anterior cervical lymphadenopathy, exudate and absence of cough.^{19,20} The aim of this study is to assess the effectiveness of penicillin V compared with a placebo in patients with sore throat who are clinically more suspected of a GABHS infection.

Methods

Patients

Patients were recruited from 37 general practices during the years 1990 to 1992, with 43 general practitioners participating for 6–18 months. Inclusion criteria were acute sore throat and age 4–60 years. A predictive approach was chosen by including patients with a moderate chance of GABHS who had three or four of the following clinical features:²⁰ fever (history); anterior cervical lymphadenopathy; (tonsillar) exudate; and absence of cough. Exclusion criteria were: imminent quinsy; a concomitant disease or seriously impaired resistance; sore throat for more than 14 days; allergy to penicillin V; the use of antimicrobial drugs during the preceding 4 weeks; or earlier participation in the trial. Both written and verbal information were given to the patients and their informed consent was requested. The study protocol was approved by the Utrecht University Hospital Ethical Committee, Utrecht, the Netherlands.

Base-line characteristics

Degree of sore throat²¹ (grade 1 to 5*), presence or absence of fever (oral temperature of 37.5 °C or higher), degree of limitation of daily activities (grade 1 to 5*), cough, duration of sore throat

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in days, absence from school or work, and number of consultations for a sore throat in the preceding year were registered. Exudate of tonsils or pharynx and tenderness of anterior cervical lymph nodes were registered from participants and non-participants, as well as age, sex, system of health insurance (fee for service or sick fund capitation fee), and the reason for not participating.

Bacteriology

Throat samples were transported in a modified Stuart medium. Seven per cent sheep blood agar (Oxoid) was inoculated and incubated at 37 °C within 48 hours in aerobic and anaerobic conditions overnight. Isolated haemolytic streptococci were typed by using a latex agglutination test (Streptex; Murex Diagnostica Benelux BV, Utrecht, Netherlands). All isolated beta-haemolytic bacterial strains were sent for confirmation to a reference laboratory (National Institute of Public Health and Environmental Protection; Bilthoven, Netherlands).

Follow-up

All patients were asked to return for a follow-up examination after 2 days; the general practitioners registered the degree of sore throat, limitation of activities, absence from school or work, the exudate and anterior cervical lymphadenopathy, and oral temperature while unaware of treatment or throat culture result. Another throat swab was taken for culturing. Patients kept a diary registering the degree of sore throat, limitation of daily activities, body temperature and intake of trial medication. After 14 days, existing complaints were registered by the general practitioner. Encounters which had taken place for sore throat and related conditions were registered with a questionnaire after 6 months.

Treatment

Random and blind allocation was performed for either feneticillin (250 mg for 4–9-year-old patients, 500 mg for subjects who were 10 years and older) or placebo (tablets or capsules, identical in shape and taste), three times a day, for 10 days. Paracetamol was provided for 2 days and could be taken when needed (maximum four times a day). The remaining trial medication tablets and paracetamol tablets were counted. If considered necessary, the reason for breaking the code was registered. Possible adverse effects of the trial medication were registered.

Outcome measurements

Outcome measurements were resolution of sore throat, disappearance of fever and resolution of limitation in daily activities. The percentage of negative cultures after 2 days was assessed. Breaking the code during the first 2 weeks was defined as a treatment failure.

Any suppurative or non-suppurative complications within 4 weeks, or the occurrence of new episodes of sore throat or related upper respiratory tract infections within 6 months of the start of therapy were compared between the treatment and the control group.

Statistical analysis

The concordance between two independent raters (CFD and another physician) of the coding of data collected by the general practitioners was more than 98%. Data were analysed according to intention to treat:²² the patients were analysed according to the treatment which they were originally assigned, whether trial medication was taken or not.

The data were analysed using the SPSS X program. The

EGRET statistical package²³ was used for the calculation of (adjusted) odds ratios and 95% confidence intervals (95% CIs).²⁴ The outcome at the first follow-up visit was expressed in crude odds ratios and was controlled for possible confounding and effect modification with a logistic regression analysis. The odds ratio (OR)²⁵ is the ratio of the odds in favour of getting well, if treated with penicillin, to the odds in favour of getting well, if treated with placebo. We controlled whether the effect of treatment differed for various results of throat culture. The odds ratios of the effect of treatment were adjusted for duration of throat complaints before initial visit, number of clinical features at onset, age category (below 15 years versus 15 years and older), and time lapse between initial and first follow-up visit (e.g. because of weekends).

The course of the sore throat was presented graphically by means of a Kaplan–Meier curve.²⁶ End-points were defined as the day at which the sore throat had reached score 2 or 1. The difference between the two curves was expressed in terms of the hazard ratio, i.e. the chance of a certain outcome per unit of time for patients randomly assigned to penicillin, divided by the chance for those randomly assigned to placebo. The hazard ratio can be interpreted as a relative risk. Hazard ratios were obtained by means of the Cox proportional hazards model, adjusted for incomparability of base-line features,^{23,27} and 95% CIs were calculated.²⁴

Results

Out of the 401 patients fulfilling the inclusion criteria,† 57 (15%) fulfilled an exclusion criterion and 105 patients were not included for the reasons mentioned in Table 1. Informed consent was given by 239 patients. No difference was observed between participants and non-participants with respect to the number of clinical features, age, sex and system of health insurance (Table 2). Excluded patients more often showed four clinical features. No differences were found in the baseline characteristics of the two treatment groups (Table 3). The mean age of the penicillin-treated patients did not differ from the mean age in the placebo group.

Some clinical features were unknown for eight patients (four on placebo and four on penicillin): only two features were registered. According to the intention-to-treat principle, they have not been excluded.

Follow-up

After 2 days, fewer of the patients treated with penicillin (36/117; 31%) than of those with placebo (57/117; 49%) still had a sore throat (OR=2.1; Table 4). This effect only appeared to be present in GABHS-positive patients. A significant difference in the resolution of sore throat was seen (OR=3.8; 95%CI 1.7–8.8) for the GABHS-positive patients ($n = 111$), but not for the GABHS-negative patients. Adjustment for age category and the time lapse between the initial and first follow-up visit made the

Table 1. Patients not participating: reasons for non-inclusion.

Reason	Number
Patient not interested	35
Doctor's reason: follow-up impossible, too busy	22
Practical reasons	22
Follow-up impossible for patient	13
Patient wants penicillin	8
Various other reasons	5
Total	105

Table 2. Characteristics of participants, patients excluded for medical reasons and other non-participants (*n* = 401).

Characteristic	Participants (<i>n</i> = 239)	Other non-participants (<i>n</i> = 105)	Patients excluded (<i>n</i> = 57)
Mean age in years (SD)	26 (12.0)	24 (12.4)	28 (13.5)
Sex (% male)	39	41	32
Presence of three clinical features (%)*	61**	57	43**
Insurance (% Public Health Plan)	69***	67	55***

*Fever (history), anterior cervical lymphadenopathy, (tonsillar) exudate and absence of cough. **Difference of proportion, 18%; 95%CI of difference 4–33%. ***Difference of proportion, 13%; 95%CI of difference -1 to 28%.

Table 3. Baseline characteristics of patients treated with penicillin V versus placebo (*n* = 239).

Characteristic	Penicillin V (<i>n</i> = 121)	Placebo (<i>n</i> = 118)
<i>Demographic</i>		
Mean age in years (SD)	26.6 (11.6)	24.6 (12.3)
Age range	4–59	4–58
Children below 15 years (%)	14.0	21.4*
Sex (% male)	36	42
Insurance (% Public Health Plan)	68	69
<i>Presenting symptoms</i>		
Fever (history) at visit (% yes)	83	85
Degree sore throat** (median)	4	4
Presence of three clinical features (%)***	64	58
Mean number of days stayed at home (SD)	0.92 (1.2)	0.88 (1.0)
Mean duration of sore throat in days (SD)	4.1 (2.2)	4.0 (2.3)
Limitation of daily activities**** (median)	3	3
<i>Culture result</i>		
GABHS (%)	45	47
Children below 15 years (% GABHS)	65	64

*Control for this difference is described in results. ** (1) None; (2) mild; (3) discomforting; (4) distressing; and (5) horrible or excruciating. ***Four clinical features assessed: fever, (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough. **** (1) Normal level; (2) some reduction; (3) moderate reduction; (4) large reduction; and (5) totally incapacitated.

effect of penicillin on the resolution of sore throat in the GABHS-positive patients even more pronounced (adjusted OR=5.3; 95%CI 1.9–15.1). Adjustment for either the prior duration of sore throat or the number of clinical features at onset did not influence the result.

A significant difference in favour of penicillin (OR=5.0; 95%CI 1.3–18.8) was visible for fever in GABHS-positive patients, which remained after adjusting for age and prior duration of sore throat (Table 4). Adjustment for the time lapse between the two visits and for the number of clinical features at onset did not influence the result. No difference was visible for limitation of activities, either in the whole group or in patients with GABHS, even after adjusting for age and prior duration of sore throat. Adjustment for the time lapse between the two visits or the number of clinical features at onset did not influence the result. No difference in the absence from school or work was seen between the two groups. Four per cent (2/56) of the penicillin group compared with 75% (41/55) of the placebo group

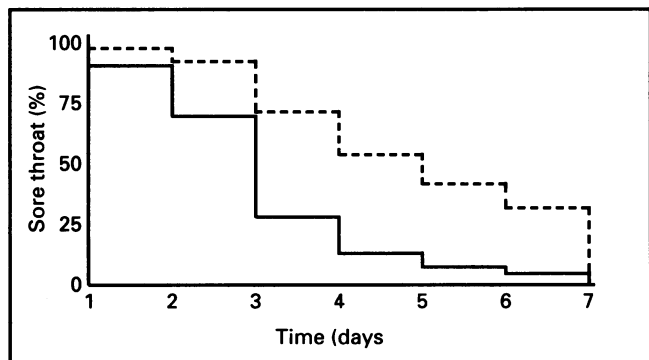


Figure 1. Proportion of group A beta-haemolytic streptococci-positive patients still complaining of sore throat in the penicillin (—) and placebo (---) groups according to diary registration (*n*=103). Twelve patients (four placebo, eight penicillin) had less than moderate (score 1 or 2) sore throats; the curve starts with less than 100% of the patients.

still harboured GABHS at the first follow-up visit (95%CI 59–84).

The course of the sore throat according to diary registration in GABHS-positive patients in the first week is shown in Figure 1. The crude hazard ratio for sore throat was 0.4 (95%CI 0.3–0.7). After controlling for age, the hazard ratio was 0.5 (95%CI 0.3–0.8). This means that patients randomized for penicillin had a 50% lower risk of still having sore throat in the first week than patients randomized for placebo. Other factors had no influence. The hazard ratio in the GABHS-negative group was 1.0 (95%CI 0.7–1.4).

Eight placebo-treated patients (A, B, C, E, F, I, J and L) and four penicillin-treated patients (D, G, H and K) were treatment failures (Table 5). One placebo-treated patient (C) with GABHS developed an arthritis of the elbow after 8 days and recovered in 2 weeks with oral penicillin V (ESR 31 mm in one hour; ASO 338 U; normal \leq 200).

Seven patients in the penicillin group decided not to continue the trial medication because of adverse effects of the trial medication, mostly abdominal complaints. No difference in compliance was seen between the two treatment groups. No difference in the use of analgesics was seen between the two treatment groups, either in the whole group or in GABHS-positive patients.

New episodes of upper respiratory tract infections within 6 months were presented by 15 patients in the placebo group and 14 in the penicillin group. In the 111 patients harbouring GABHS, six out of 55 patients treated with placebo and 10 out of 56 patients treated with penicillin presented a new episode.

Discussion

The administration of penicillin V in patients with an acute sore throat and three or four relevant clinical features reduced the

Table 4. Effect of treatment with penicillin V or placebo on clinical features of all patients, initially GABHS-positive and negative patients at first follow-up visit ($n = 239$). Odds ratios, adjusted odds ratios and 95% confidence intervals (95% CIs).

Outcome	All	GABHS+	GABHS-		
	Crude OR 95% CI	Crude OR 95% CI	Adjusted* OR 95% CI	Crude OR 95% CI	Adjusted* OR 95% CI
Sore throat*	2.1 1.3–3.6	3.8 1.7–8.8	5.3 1.9–15.1	1.3 0.6–2.7	1.3 0.6–3.0
Fever	1.9 0.9–4.0	5.0 1.3–18.8	5.3 1.02–27.7	1.2 0.5–3.2	1.4 0.5–3.9
Limitations***	1.7 1.0–2.9	2.0 0.9–4.4	1.7 0.7–4.1	1.3 0.6–2.7	1.3 0.5–3.1

*Adjustment was performed for age category, prior duration of sore throat, moment of follow-up and number of clinical features. **See Table 3 footnote. ***See Table 3 footnote.

Table 5. Patients with broken treatment code: culture result, initial and final treatment, moment of breaking the code, and reason for breaking.

Patient	Culture (+ = GABHS)	Initial treatment (0 = placebo)	Days after initial visit	Reason for breaking	Final treatment
A	+	0	5	pain lymph-nodes	penicillin V
B	+	0	2	imminent quinsy	bicillin*
C	+	0	8	mono-arthritis	penicillin V
D	+	1	2	not improved	same
E	+	0	3	complaints increased	penicillin V
F	+	0	4	sore throat, fever	erythromycin
G	–	1	2	'enough' (patient)	same
H	–	1	2	wish patient (during on-call)	penicillin V
I	–**	0	2	imminent quinsy	bicillin*
J	–	0	5	increased sore throat	penicillin V
K	–	1	1	headache	same
L	–	0	3	not improved	penicillin V

*Benzathine-procaine penicillin i.m., followed by oral penicillin V. **Group G streptococcus.

duration of sore throat in comparison with placebo. However, this reduction in the duration of sore throat by 1–2 days was only seen in patients with a throat culture positive for GABHS. This difference disappeared within one week. Fever resolved significantly sooner in patients with GABHS. The bacteriological effect was less pronounced than the effect described by Randolph *et al* in a paediatric population: 3% versus 100% difference.⁸ An earlier resolution of sore throat was found in two other randomized, placebo-controlled studies of sufficient size,^{9,10} but not in another placebo-controlled study in general practice.¹² An earlier return to school or work—often given as the reason for treating patients with penicillin—could not be confirmed by our results.

Imminent quinsy was determined in two cases and mono-arthritis in one. The fact that these three cases were all treated with placebo is striking. No non-suppurative complications were seen. Although attention should be paid to the reports of severe group A streptococcal infections,^{16,28} by far the majority of patients with sore throat in general practice should not be considered to be at risk for this serious complication at present. Exceptions may be young people living in crowded situations, such as the Army.¹⁷

Although penicillin eradicates the bacteria within 24–48 hours in patients harbouring group A beta-haemolytic streptococci,^{6,10} a reduction of the spread has never been demonstrated in a clinical study.^{6,29} The persistence of GABHS in untreated patients was not related to more frequent infections afterwards. Studies of

recurrences are inconsistent.^{6,30,31}

Clinical differentiation between GABHS-positive and other patients is only possible to a limited extent.³ Consequently, a diagnostic test could be performed. If the patient turns out to be GABHS positive, a treatment with penicillin would result in an earlier resolution of the sore throat and fever, and in a bacteriological effect; but in the case of overall penicillin treatment, the majority of patients would be treated unjustifiably. Moreover, because complications of a GABHS infection are rarely seen,³² the advantage of treatment with penicillin is limited. Even the relatively low prescription rate of antibiotics for this condition in the Netherlands (74%)³³ might be too high in view of the fight against resistant strains.¹⁵

By registering non-participants, we conclude that our data are capable of generalization to all Dutch patients between 4 and 60 years of age visiting their general practitioner with a sore throat, and having three or four of the specified clinical features and none of the exclusion criteria we used. Our results cannot be generalized to the patients excluded for medical reasons.

As for the clinical course, penicillin treatment is only necessary in cases of imminent complications or in patients at risk of serious complications. In patients with a higher probability of GABHS (three or four clinical features), penicillin is beneficial, but not necessary.

*The McGill-Melzack questionnaire:²¹ Pain today? (1) none; (2) mild; (3) discomforting; (4) distressing; (5) horrible or excruciating. Activities today? (1) normal level; (2) some reduction; (3) moderate reduction; (4) large reduction; (5) totally incapacitated.

†Inclusion criteria: (1) use of antimicrobial drugs < 4 weeks ago, 19; (2) no penicillin allowed (presumed allergy?), 6; (3) need of penicillin according to the physician, 36; and (4) earlier participation in trial, 2. Five patients fulfilled both categories 1 and 2.

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