Sore Throat in General Practice

A Diagnostic and Therapeutic Study

Keelpijn in de huisartspraktijk

Een diagnostisch en therapeutisch onderzoek

Carien F. Dagnelie

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PROEFSCHRIFT

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door

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geboren op 25 juni 1955 te Rotterdam

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Aan mijn ouders

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CONTENTS

Chapter 1

GENERAL INTRODUCTION

Het grootste deel van het leven
wordt beheerst door het vanzelfsprekende.
Wie in dat vanzelfsprekende blijft steken,
wie nooit een stap buiten de betreden paden durft te gaan,
wie niets meer wil
dan het vol goede trouw aanhangen van tradities
en het napraten van frasen
kan alle goede eigenschappen ter wereld hebben,
maar één ding ontbreekt: moed.

Clara Wichmann

1.1 Introduction

Sore throat is a common complaint in the general population. However, most people experiencing a sore throat do not consult a physician, as Evans and colleagues concluded[1]. They found that five percent of a study population asked to keep a diary of their complaints over a period of three months had experienced a sore throat on one or more days, but only 16% of these patients had contacted a health professional[1]. In a Dutch study covering the years 1959-1964, Valkenburg and colleagues similarly found that only nine percent of patients with a streptococcal sore throat had consulted a physician[2]. Evidently, general practitioners only encounter the 'tip of the iceberg' of sore throat complaints[3,4].

Even though so many cases are not presented, sore throat is nevertheless one of the complaints most often presented. Hansen reported that, during one year, eight percent of the patients attending surgery during daytime complained of a sore throat[5]. A minority of patients with sore throat have acute tonsillitis, or acute pharyngitis*,[6]. The most common diagnoses are: common cold, acute tonsillitis, unspecified sore throat, scarlet fever and (proven) strep throat[7]. Together with common colds and acute sinusitis, acute tonsillitis is one of the top ten of presented diseases in Dutch general practice[8]. Dutch morbidity studies show incidences of presented cases of acute tonsillitis varying from 20/1000 persons per year[9] to 25/1000 persons per year[10], with a peak in the age category 15-24[10]. The Dutch incidence of acute tonsillitis has decreased significantly during the last few decades[11] for reasons which are not clear. The present incidence means that a general practitioner in an average practice sees at least one patient with acute tonsillitis each week. Although upper respiratory tract infections (URTIs) are common illnesses in general practice, many aspects concerning diagnosis and treatment appear to be unknown. Physicians vary considerably in the way they manage patients with URTIs[12].

The main question for a general practitioner is whether to treat sore throat with an antimicrobial drug. One issue is the assessment of the cause of sore throat, especially group A beta-haemolytic streptococci (GABHS). Another issue is the balance of the advantage of an antimicrobial treatment weighed against the possible risk of that

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* In the USA the term pharyngitis is used for both acute pharyngitis and acute tonsillitis (ICPC codes R74.2 and R76.1), the former being of viral origin and the latter viral or bacterial[6].

treatment. Guidelines for a more rational and uniform policy were developed for the management of URTIs in general practice. One of the guidelines related to acute sore throat. A decision analysis was carried out based on the results of a literature study[13,14]. In this analysis, the advantages and disadvantages of a particular strategy were weighed and the influence of variation in chances and outcome assessed. The result of the decision analysis was to treat without testing when the prior probability of group A beta-haemolytic streptococci (GABHS) was more than 88% and complaints had been present for less than two days; not to treat with a prior probability below 40%, and to perform a rapid test in the intermediate range[13,14]. If complaints had been present for more than two days, antimicrobial treatment was not advised.

While carrying out the decision analysis, it became clear that there was a lack of data. Most data originated from studies in hospital settings[15,16,17] where study populations are often a mixture of referred patients and visitors to emergency clinics. This implies that a selection of more serious cases was probably studied. The management advice in such situations could be different from that of everyday general practice.

Besides patients with sore throat, little information appeared to be available about microbial throat flora in healthy people in the Netherlands. The most recent Dutch data about the prevalence of GABHS derives from the study of sore throat by Bots and colleagues in 1960[18]. Since then, a number of factors may have influenced the throat flora, such as the increased use of antimicrobial drugs, a change in illness behaviour, and changes in socio-economic circumstances. Since Dutch general practitioners (GPs) do not use throat cultures in daily practice, the present bacterial throat flora in Dutch patients with sore throat is unknown. Similarly, the significance of a number of micro-organisms found in studies of sore throat patients in other countries was also unknown[19,20,21,22,23,24,25,26], and required further study. The importance of GABHS was acknowledged decades ago, since it was recognized as causative in acute rheumatic fever and acute glomerulonephritis[2].

There are several possible diagnostic procedures for assessing the presence of GABHS in patients with sore throat. A major disadvantage of the most important one - the throat culture - is the delay before the result is known, especially in countries where cultures are not performed in an office setting. In the USA, treatment is often started blind and is discontinued should the culture appear to be negative[27,28,29]. A better strategy would be to postpone treatment for a few days.

Alternative tests were developed in the 1980s, introducing a variety of rapid streptococcal antigen detection tests appropriate for use in a general practice setting,

and providing a result at short notice. Many studies have assessed the diagnostic value of various tests[30,31,32,33,34,35,36,37]. They were most often compared with the throat culture and seldom with antibody titres[37]. Until now, little experience has been acquired with these rapid tests in the Netherlands[38].

Apart from their diagnostic value, further questions concern the relationship between costs and benefits, and the influence the introduction of a rapid group A streptococcal antigen detection test may have on the management of patients[27,39]. A lack of knowledge was also encountered regarding the management of patients with sore throat in general practice. For decades, penicillin V has been considered a useful and effective drug in GABHS-tonsillitis, with the particular aim of preventing complications[40]. More recently, the decreased incidences of suppurative and non-suppurative complications have rendered other factors more important. The influence of penicillin on the eradication of the GABHS and on the clinical course of a GABHS-infection have been studied more recently[17,41,42,43,44,45,46]. In a number of studies, penicillin appeared to shorten the duration of some signs and symptoms[17,41,42,43,44], although other authors reported different results[45] and some stressed the importance of a symptomatic treatment[46].

The guideline for sore throat was completed in 1988. It contained many precautions[38,47]. While the guideline was being developed, the decision was made to collect new data regarding the diagnosis and treatment of sore throat from patients in a Dutch general practice setting. A registration of management strategies in daily practice[48] showed that antimicrobial drugs were being prescribed in 74% of the presented cases of sore throat - a lower percentage than in most other countries[12] (but much higher than that advised by the Dutch guidelines). As a consequence of this lower prescription rate, the Dutch microbiological flora may differ from that in countries where prescription rates are higher.

Dutch GPs seldom use diagnostic tests for sore throat. The Dutch College of General Practitioners' practice guideline 'Acute sore throat'[49] does not indicate a rapid test or throat culture. Instead, they use four clinical features helpful in predicting the chance of a GABHS-infection as described by Centor and colleagues[50]: fever (history), anterior cervical lymphadenopathy, (tonsillar) exudate, and absence of cough. When all four features were present, the chance of a positive throat culture for GABHS in a U.S. study in adults was more than 50%; with three features, the chance was 33%[50]. In the Dutch guideline, treatment with penicillin is advised, but is not

obligatory, for patients with four clinical features, except for special cases*. Since these four clinical features have not been evaluated in a Dutch general practice setting, their use needs evaluation, particularly since Dutch GPs are used to relying on the clinical picture rather than using cultures or rapid tests.

The lack of knowledge with regard to the microbiological flora, the diagnostic value of a rapid streptococcal antigen detection test and the effectiveness of penicillin V in patients with sore throat led to the following objectives for this study.

1.2 Aims of the study

The study had the following **aims**:

1. To obtain knowledge about the current microbiological flora in patients presenting with sore throat in Dutch general practice.
2. To assess the diagnostic value of a rapid group A streptococcal antigen detection test in general practice.
3. To determine the effectiveness of penicillin V in patients aged 4-60 presenting with sore throat in general practice and suspected of GABHS.

This thesis addresses the following **research questions** related to these **aims**:

1a. How often are GABHS, and non-group A, *Corynebacterium haemolyticum*, and other micro-organisms cultured from throat specimens of patients visiting their GPs with a sore throat?

1b. Are the four clinical features: fever (history) ≥38.5°C rectally, (tonsillar) exudate, anterior cervical lymphadenopathy and absence of cough, predictive for the presence of GABHS?

2. What is the diagnostic value of a rapid group A streptococcal antigen detection test in general practice:
   a. with a throat culture as a reference test in patients aged 4-60, and
   b. with an antibody titre as a reference test in patients aged 11-60 presenting with sore throat?

3. What is the effectiveness of penicillin V compared with placebo in patients

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* Scarlet fever, imminent quinsy, history of acute rheumatic fever, seriously impaired immune system, or an epidemic of streptococcal infections in a closed community[49].

with sore throat, suspected of a GABHS infection, in: (i) the clinical improvement of the patient: course of sore throat, ability to perform daily activities, fever, anterior cervical lymphadenopathy and exudate; (ii) reducing the number of suppurative complications; (iii) eradicating the GABHS, and (iv) reducing the occurrence of new episodes of upper respiratory tract infections in the first six months after the treatment?

1.3 A guide to the reader

In **chapter 2** the current knowledge about the epidemiology of sore throat is reviewed. Etiology, diagnostic procedures, clinical course, and current management strategies are described.
In **chapter 3** a general outline of the study procedures and the study populations in the different parts of the study are described.
In **chapter 4** the results of the study concerning the microbiological flora in patients presenting with sore throat in general practice are described and discussed.
The diagnostic value of the rapid group A streptococcal antigen detection test compared with other tests is presented in **chapter 5**.
In **chapter 6** the results of the randomized double blind clinical trial in patients suspected of a GABHS infection are presented and discussed.
In **chapter 7** the overall conclusions of the study are drawn and discussed. Recommendations are given for the management of sore throat in general practice and some proposals for future research are suggested.

Some repetition has been unavoidable since certain chapters (namely 4, 5 and 6) were written with a view to separate publication.

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Chapter 2

AN OVERVIEW OF THE SUBJECT:

'Wat is er?' vraagt Floortje.
'Ik heb keelpijn,' zegt Eddie.
'Keelpijn?'
Frans is er ook bij komen staan. Hij hoort het woord keelpijn. 'Dan kijken we even in zijn keel,' zegt hij. 'Heeft hij een rode keel, dan heeft hij keelpijn. Heeft hij geen rode keel, dan zijn het smoesjes. Dan is hij bijvoorbeeld schoolziek!'

'What's the matter?' asked Floortje.
'I've got a sore throat,' answered Eddie.
'Sore throat?'
Frans came over to join them. He had heard the words 'sore throat'. 'Let's have a look,' he said. 'If he's got a red throat, then he's got a sore throat all right. But no red throat, then it's just excuses. Planning to play hookie, eh!'

Uit: Cok Grashof, Floortje Bellefleur vindt een poes.

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2.1 Introduction

This chapter provides a general overview of the literature relevant to the subject of the study. In section 2.2, the epidemiology of sore throat, and of acute tonsillitis in particular is described. The etiology of throat complaints and the microbiological flora found in patients with sore throat is reviewed in section 2.3. The diagnostic procedures available, that is to say throat culture, rapid group A streptococcal antigen detection test and antibody titres, are reviewed in section 2.4. The clinical course and the influence of treatment with antimicrobial drugs is reviewed in section 2.5. The final section (2.6) reviews the current management of patients with sore throat and describes several of the management strategies encountered in other publications.

2.2 Epidemiology

Sore throat is a frequently presented complaint in general practice, even though most people experiencing a sore throat do not consult a physician[1]. In a study population keeping a diary of their complaints for three months, only 16% of the patients experiencing a sore throat had consulted a health professional[1].

A minority of patients with a sore throat have acute tonsillitis, or acute pharyngitis*[,2], the percentage depending on the terminology used, the country and certain other factors. Two Dutch morbidity registration systems indicate that the incidence of acute tonsillitis is especially high in the age categories 15-24[3], and 25-44[4], and relatively low in children aged 0-4 and in people aged 65 or older[3]. School-aged children are also often affected, according to other studies[5]. The fraction of cases of acute tonsillitis caused by group A beta-haemolytic streptococci (GABHS) depends on the prevalence in the population described[6], and may vary from 5 to 30% according to age, setting (hospital or primary care) and geographic region[7,8]. In several studies, about one-third of patients with sore throat had a streptococcal infection[9,10,11]. The incidence of GABHS is also said to vary according to season, although authors differ widely in their observations. Some reported a peak incidence in autumn[12,13], some in winter[11,14], while others indicated spring as the main season[9,15]. A Danish study reported a peak incidence in March and an even distribution during the rest of the

* In the USA the term pharyngitis is used for both acute pharyngitis and acute tonsillitis (ICPC codes R74.2 and R76.1), the former being of viral origin and the latter viral or bacterial[2].

year[10]. Two Belgian studies showed a peak in summer[5,16]. The Dutch morbidity registrations reveal an increase in the incidence of acute tonsillitis during the year, from spring until winter[4]. In conclusion, it has to be said that there is no major seasonal influence.

Symptoms are often less pronounced in patients with sore throats who do not have tonsillitis. Viruses and other micro-organisms may be responsible; often the cause remains unknown[14]. Dutch morbidity studies showed incidences of presented cases of acute tonsillitis varying from 20/1000[17] to 25/1000[4] persons per year. The Dutch incidence of acute tonsillitis has decreased significantly during the last few decades[18]. Whether this has been caused by a decreased incidence in the population, or a decrease in the cases presented, is not known. The present incidence means that, on average, a general practitioner sees at least one patient with acute tonsillitis each week. Differences in culture, terminology, methods of collection of data and diagnostic categories make a reliable international comparison of epidemiology and causes of acute tonsillitis difficult.

The main reason for diagnosing GABHS infections has always been the risk of non-suppurative complications, such as acute rheumatic fever (ARF). The incidence of ARF has declined gradually during the last century[19]. In Denmark, between 1862 and 1962[20] the annual incidence of ARF fell from 200 to 10/100,000 persons. In the United States in the early sixties, the annual incidence of ARF among children was about 25/100,000[21]. The Dutch annual incidence of ARF in the same period was 19/100,000[22]. Twenty-five years later, the annual incidence in the USA was estimated at 0.5/100,000[22,23,24,25] or even lower: 1-2 cases per million[26]. This figure is consistent with Howie's figure for Scottish children in 1980: 0.6/100,000 per year[27]. Dutch registration systems showed around 50 hospital admissions per year for ARF between 1983 and 1987[28]. However, by far the majority of cases were recurrences, and no separate number of new cases is available. Since 1976, no deaths due to ARF have been reported in the Netherlands[28]. The decline of ARF in most developed countries is considered to be related to an improved socio-economic situation with better hygiene and food, and to changes in the immunopathogenicity of the streptococci[20,24,25]. The introduction of penicillin came much later, and has probably hardly contributed to the decline[26].

The resurgences of ARF observed in the mid eighties in the USA [21,29,30,31], and later on in Europe[32], signified an impressive relative increase, but the absolute number of rheumatic fever cases was not large[33]. By 1992, the number of reported cases had decreased, although the rate had not yet returned to the low levels observed

during the 1970s or early 1980s[34]. In earlier studies, the occurrence of rheumatic fever as a non-suppurative complication has been shown to be reduced when penicillin was given intramuscularly[35]. In the 1970s, Tompkins estimated a reduction to 10% of the original risk[36]. For oral penicillin, this effect has never been established[37]. Many years later, Howie calculated that only a small difference was observed for the chance of ARF in patients with a streptococcal infection treated with penicillin (1:30,000) compared with patients not so treated (1:40,000)[27]. More importantly, in most cases absolute prevention is impossible, because at least one third of ARF cases follow streptococcal infections that are asymptomatic[22,34,38], or are not presented to a physician.

The incidence of another important non-suppurative complication - acute glomerulonephritis (AGN) - has also decreased considerably. In a Dutch study undertaken in the early sixties, the annual incidence of AGN was 20/100,000[22]. Between 1983 and 1987 Dutch registration systems showed 140 hospital admissions per year for new and old cases of AGN[28]. Of these, two-thirds were males; a peak was seen for 9-15 year olds. During the years 1985-1987 three deaths due to AGN were reported in the Netherlands[28]. A reduction in the occurrence of acute glomerulonephritis by treating patients with penicillin has never been demonstrated[39]. As with ARF, the majority of patients with AGN were first seen for these late complications, one third having had no history of pharyngitis[22].

Assessment of the risk of suppurative complications in patients with a streptococcal infection is not easy. In a study performed in the early sixties by Haverkorn and colleagues[40], suppurative complications such as otitis media and quinsy developed in approximately 2% of the patients. In a study by Pichichero and his colleagues[41], no difference was reported between patients immediately receiving penicillin and patients receiving a placebo for the first two days. Some other studies also failed to show a reduction in suppurative complications[5,42,43,44]. In the past few years, several publications have described a 'toxic shock-like syndrome' apparently following a GABHS infection in many countries, including the Netherlands[33,45,46,47]. These severe infections have been associated with mortality rates as high as 30%[33]. In 10% of 20 cases GABHS were found in a throat culture, whereas in most cases a skin infection was traced[46]. In comparison with the incidence of sore throat in general practice, the numbers of serious complications are extremely low. Although a watchful eye is advised, until now no change in strategy for general practice seems to be needed.

After the non-suppurative complications had decreased in significance, other

aspects, such as clinical cure, bacteriological cure, and recurrences were studied as arguments to support the continued use of penicillin.

In conclusion, acute tonsillitis is present in a minority of cases of sore throat. Group A beta-haemolytic streptococci (GABHS) are considered most important because of the potential (non)suppurative complications. Nevertheless, GABHS are only found in a minority of patients with acute tonsillitis.

2.3 Etiology

A variety of causes may be found for sore throats and a variety of micro-organisms may be responsible. In acute tonsillitis, several micro-organisms are found; viral, bacterial, or other. Differences in the results of various studies may be derived from differences in terminology, the population studied, help-seeking behaviour or patients' expectations. A major part of acute tonsillitis is caused by respiratory viruses[48]. The remaining patients harbour bacteria such as group A beta-haemolytic streptococci (GABHS). Some throat infections prevail in certain age categories. For instance, GABHS infections are found in children more frequently than in adults[14]. In an American study published in 1975, the prevalence of GABHS in patients with pharyngitis was 31% for children and 15% for adults[49]. Pichichero reported a prevalence of below 30%[50] for children. Several European studies reported a prevalence of GABHS of 25 to 30% in populations of both children and adults with sore throat[5,51,52]. In one study in a population of patients selected for their clinical picture*[,53], a prevalence of 40% was assessed. In an American study in adults with pharyngitis published in 1983 the prevalence was only 9%[54]. The GABHS have always been considered the most important micro-organisms studied in patients with acute tonsillitis and pharyngitis because of the relatively high frequency of GABHS and the potential complications, such as rheumatic fever.

The question as to whether in the Netherlands other bacteria cause sore throat is not easily answered. This is because there is no tradition of culturing throat swabs in Dutch general practice, except for difficult cases. Some studies from other countries describe the occurrence of other micro-organisms and assess their significance. The relevance of the growth of non-group A beta-haemolytic streptococci is not clear. In

* inclusion criteria at least four of the following: sore throat, reddening or swelling of tonsil(s), pus on tonsil(s), enlarged regional lymph nodes, or fever[53].

several international studies in adults, group C streptococcus was described as a pathogen with a prevalence of 6 to 7%[55,56]. The clinical picture is said to be similar to that of GABHS, but it may be less severe. Other authors concluded that group C usually represents only a minor factor in the pathogenesis of pharyngitis[57,58,59].

Of group G streptococci, less is known and their relevance is not very clear[56,60,61]. McMillan and colleagues did not find any difference between patients and controls in the pediatric age group[62]. On the other hand, Gerber and colleagues[63] have described a community-wide outbreak of group G streptococcal pharyngitis in patients aged three to 21. Group B and F streptococci are not recognized as pathogens in the throat.

In two studies[64,65] *Corynebacterium haemolyticum* was described as a pathogen, especially in adolescents, with a clinical picture mimicking scarlet fever. In one study *Chlamydia trachomatis* and *Mycoplasma pneumoniae* were found in respectively 21% and 11% of the patients with a sore throat[54]. Other authors found these organisms in lower percentages[57,62,66]. Little has been reported about the Eppstein Barr virus and the incidence of infectious mononucleosis. The incidence depends on a population's standard of living and its age distribution[26]. Eighty-five percent of mononucleosis patients are between the ages of 15 and 30. In Europe and North America one case per thousand persons per year is seen, which means about two cases per year in an average general practice[26]. There are no data on *Candida albicans* as the cause of sore throat in otherwise healthy patients. The other micro-organisms have not been shown to cause any of the risks the GABHS have shown. Centor states that we cannot at this time correctly ascertain the importance or need for treating patients with these infections[6].

In almost half the cases of sore throat no micro-organism can be identified [14,62,66,67]. Even when a micro-organism is found, it cannot reliably be said to be pathogenetic. Truly infected patients and carriers are difficult to distinguish. The clinical differentiation between the various causes of sore throat is not easy. Because GABHS are considered the most important micro-organism, several studies were carried out to assess the clinical features facilitating the differentiation between GABHS and other causes[5,68,69,70]. A number of clinical features capable to some extent of predicting GABHS-infections were found in one study in children[68]. From this study, a scorecard was developed to predict the chance of GABHS in children with sore throat[7]. Although this scorecard has a number of limitations, it may be useful for situations where further diagnostic testing is not possible. Centor, investigating adults, found a combination of several clinical features more predictive for

the presence of GABHS[69]. When the four clinical features: fever (history), anterior cervical lymphadenopathy, (tonsillar) exudate, and absence of cough were present, 56% of the patients had a throat culture positive for GABHS. When three features were present, 33% of the patients harboured GABHS, and, with two features, 15%[69]. The same clinical features were found to be useful to some extent in other studies[5,10,70,71], although none of these studies led to a higher predictability. The predictive value of the clinical assessment in children is lower than in adults[49]. The diagnostic value of the clinical features has not been assessed in a Dutch population.

2.4 Diagnostic procedures

Since the clinical picture is not completely predictive in adults, and is hardly applicable in children, further diagnostic testing may be helpful.

Throat culture

For decades, in many countries, the throat culture has been the most frequently used diagnostic test, the advice being only to treat with penicillin those patients whose cultures show GABHS[24,72,73,74]. A practical disadvantage of the throat culture is the delay of 24-48 hours when cultures are performed in an office setting. In the Netherlands, as in many other countries, cultures are sent to a laboratory, entailing a further day's delay. Consequently, the throat culture is rarely performed in Dutch general practice. One study reported throat cultures being taken in only 2% of sore throat patients in Dutch general practice[53].

A major shortcoming of the throat culture with respect to GABHS infections is that it is not a gold standard[60]. Information concerning the sensitivity of the throat culture has been collected from studies with duplicate throat swabs[6,75,76]. The sensitivity of one culture compared with two swabs taken and cultured simultaneously was 90% in two studies[75,77] and 74% in another[76]. Imperfect swabbing techniques or a less than optimal method of culturing may be partly responsible for the false negative culture[78].

With the throat culture the organism is detected, but a causal relationship with the complaints cannot be proved[6,78]. The specificity of the throat culture is related to the streptococcal colonisation rate in a population, or, in other words, the percentage of asymptomatic carriers. These carriers are patients who do not have a pharyngitis, but who do have a positive throat culture for GABHS[48]. The false-positive rate plus the

specificity are equal to 100%[6]. The term 'carrier' is also used for patients who have pharyngitis and a positive culture, but who do not develop a serologic response[48]. The term is used in many studies, but the clinical condition referred to is not always clear. This complicates the comparison of the results of several studies. Unless otherwise stated, we indicate with the term 'carriers' the second category. Some authors reported one percent asymptomatic carriers in an adult population[6]. Studies of patients with pharyngitis in different communities have shown a carrier rate of between two and ten percent, with higher rates in children than in adults[26]. Tompkins[36] estimated a carrier rate of 15 to 20% in children with pharyngitis, and of five to ten percent in adults, when culture and antibodies were compared. The difference in specificity between children and adults may be partly explained by the higher percentage of asymptomatic carriers (5-15%) in children[79,80]. About half of the pediatric patients with acute pharyngitis and a culture with GABHS had a significant antibody rise[77,81]. The remaining patients had acute viral sore throat with streptococcal colonization.

These divergent results together with certain practical reasons led one author to conclude that throat cultures contribute little to the management of patients with uncomplicated acute respiratory infections[37]. Recently, the issue of the gold standard has become more complicated, as described in the paragraph on antibody titres.

Rapid antigen detection test

Since the 1980s, several rapid group A streptococcal antigen detection tests have been developed, of varying techniques and quality. First, extraction of the group A carbohydrate antigen from the throat swab is performed. Then, one of the following techniques is used: capillary precipitation, latex agglutination, coagglutination[82,83,84,85,86,87], or an enzyme-linked immunosorbent assay (ELISA). One test incorporates liposomal technology into a membrane-bound immunoassay procedure[88]. If present, the extracted streptococcal antigen is linked to the antibody-coated coloured liposomes on a porous filter, and a visual colour change occurs[88,89,90,91].

Several studies have addressed the diagnostic value of rapid antigen testing[6,92]. Several of these studies are categorized in table 2.1. Sensitivities of a variety of tests were reported between 45%[93] and 96%[97] when compared with the throat culture. Specificities are reported to be high: between 81%[96] and 100%[91,93] when compared with the throat culture (table 2.1). However, one study reported a lower value for an ELISA test: 63%[100]. Predictive values of a positive test result vary from 61%[89,99] to

Table 2.1 Studies of rapid group A streptococcal antigen detection tests compared with a throat culture. Setting, type of test, number of patients studied, diagnostic values and prevalence of GABHS (%).

Pediatric Author	Type	N	Sens	Spec	PV+	PV-	Prevalence
Gerber (1984)[84]	aggl.*	339	83	92	97	93	32
	aggl.*	263	84	99	99	93	32
Lieu (1986)[93]	aggl.	556	45	100	74	100	39
Lieu (1988)[94]	aggl.	225	55	90	68	83	29
Moyer (1990)[91]	lipos.	327	75	100	98	89	32
Outpatient							
McCusker (1984)[85]	aggl.	500	91	91	77	99	23
Redd (1988)[95]	aggl.	286	52	94	85	75	30
Huck (1989)[89]	lipos.	924	65	85	61	87	26
Moyer** (1990)[91]	lipos.	322	60	99	94	97	8
General Practice							
True (1986)[96]	aggl.	538	81	81	72	94	20
Hjortdahl (1987)[97]	aggl.	226	96	91	77	99	23
Hoffmann (1987)[98]	aggl.	468	73	98	96	84	42
Andersen (1992)[52]	aggl.	105	68	97	90	89	27
Burke (1988)[99]	ELISA	250	63	92	63	92	18
Hoffmann (1990)[100]	ELISA	393	79	63	81	86	32
De Meyere (1990)[5]	lipos.	660	73	96	89	90	28

* two different tests studied
** only adults studied

sens = sensitivity
spec = specificity
lipos. = liposome test
aggl. = latex agglutination test
PV+ = predictive value positive test result
PV- = predictive value negative test result
ELISA = enzyme linked immunosorbent assay

99%[84,91,98]. Predictive values of a negative test result vary from 75%[95] to 100%[93,97] in various populations and settings.

In most studies, the diagnostic value of rapid tests have been studied using a throat culture as a reference test[6]. In that situation, two more or less dependent tests are compared, which means that the sensitivity found may be higher than the actual one[101]. To determine their diagnostic value, rapid tests should preferably be compared with a gold standard[79]. Antibody levels have always been used with a view to differentiating between carriers and truly infected persons[79]. However, a serological antibody test has only been performed in a very few studies, including one in a pediatric population[102] and another in a primary care setting[5].

No longer having to wait for the test result in all cases may be advantageous. If the result of the test is positive, treatment is advised; if the test result is negative, a throat culture may - or should be - performed as a back-up, according to the American strategy[34,78,84]. Until recently, in the Netherlands, rapid antigen detection tests have seldom been used, although in many other countries antigen detection tests are used regularly[6,53]. In a European study in 1989-1990 a bacteriologic test was performed in 58% of 4094 patients with acute tonsillitis*. Of these, 85% were throat cultures and 15% rapid tests. Remarkable differences between countries[53] occurred in the use of a bacteriological test. In many countries diagnostic tests were used infrequently; for instance in Austria, former East Germany, Poland, the Netherlands, Portugal and France between 0 and 7% of patients were tested for the presence of GABHS. In contrast, in Rumania, Israel, Yugoslavia, Finland and Greece tests were ordered for more than 75% of patients. The 15% rapid tests were performed in Israel, Italy, Greece and Sweden.

Antibody titres

Serological testing is not helpful for the diagnosis in an individual patient with GABHS because of the necessity of taking two blood samples[103], the second after two weeks or more. These tests may be useful for research objectives, or in the case of a complication[78]. Antibody levels serve as our 'gold standard' against which other tests should be compared[104].

Several antibody tests are available and are being used. The most often performed

* inclusion criteria at least four of the following: sore throat, reddening or swelling of tonsil(s), pus on tonsil(s), enlarged regional lymph nodes, or fever[53].

test is the antistreptolysin O (ASO) test. Another test that measures antibodies against extracellular products of group A streptococci is anti-deoxyribonuclease B (anti-DNase B). In one study, antibodies against cellular products of the group A streptococcus, namely the antistreptococcal group A polysaccharide titres (ASPAT) were reported as especially useful in children[105]. In that study, in 52 GABHS positive children with acute tonsillitis and 52 age- and season-matched controls, the ASPAT showed less overlap between patients and controls than the ASO and anti-DNase B titres. In the majority of diagnostic studies, no antibody tests have been performed[106,107]. In many other studies, an unknown sample was tested[102,108], except for a study by Pichichero[41], in which 95% of 114 pediatric patients were tested. In some studies, high initial titres were found, especially in children and in GABHS positives[5,77]. Patients with low initial titres showed a higher increase of the titre, especially in GABHS positives. De Meyere[5] assessed a significant rise in 33% of GABHS positive patients and in 9% of the GABHS negative patients. In several studies, penicillin appeared to have a restraining influence on the rise of antibody titres[43,109,110,111], which means that antibody titres are unreliable as soon as antimicrobial drugs are being used. A more recent study demonstrated that even antibody levels were not a gold standard[112].

The fact that - apart from the throat culture - antibody titres were not as 'gold' a standard as had been thought made physicians in the USA look for a better definition of a true infection. Nowadays, a GABHS positive patient is often considered as really infected if the complaints improve soon after the administration of penicillin (E.L. Kaplan, 1993; personal communication).

2.5 Clinical course and antimicrobial treatment

The natural course of a GABHS infection is a spontaneous cure within one week[42,44,113,114,115].

Several studies have been carried out to assess the extent to which penicillin V shortens the course of the disease[41,108,112,116,117]. Randolph and colleagues[108] for instance found that an early start with penicillin V made the sore throat and the fever resolve sooner. Other studies have shown a 24 hour reduction in the duration of sore throat in GABHS positive patients[41,112,116]. This effect was especially visible in patients having had complaints for less than 48 hours at the start of the penicillin[116]. Middleton, however, found no difference in signs and symptoms after 24 hours in a

study in which patients were given sufficient amounts of analgesic drugs[117]. The only difference seen was the amount of sore throat after 48 hours in favour of the patients treated with penicillin.

The use of penicillin did not influence the absence of work in a study by De Meyere in 613 patients in a primary care setting: 25% in penicillin group versus 28% in placebo group[5]. No study has ever documented a reduction of absenteeism[118]. The influence of penicillin on the incidence of recurrences has not been established. In two studies, more recurrences were assessed in patients immediately treated with penicillin compared with patients in whom treatment had been postponed for two or three days[41,119]. However, two other studies showed no difference in recurrence rate[120,121].

The bacteriological effect of penicillin is a clear cut advantage. In patients harbouring group A beta-haemolytic streptococci, penicillin eradicates the bacteria within 24 to 48 hours[41,42,43,113,116]. Many authors state that, as a consequence, people treated with penicillin for 24 hours will no longer spread the micro-organism to others. A sooner return to school or work may be the result. However, a reduction of the spread has never been demonstrated in a clinical study[11,41,92].

When looking for the optimal management strategy, the disadvantages of penicillin treatment should also be taken into account. Possible side effects of penicillin include: complaints of nausea, vomiting, and diarrhoea. Tompkins[36] estimated the risk of allergic reactions in patients without a known allergy. The risk of a serious allergic reaction in patients taking oral penicillin, was estimated at 0.025%; the risk of a mild allergic reaction at 0.52%. Other risks may be an enhanced susceptibility to new GABHS infections[122], or the selection of resistant micro-organisms.

In contrast with this rapid eradication, in numerous studies GABHS were cultured after completion of the treatment[116,123]. De Meyere[116] investigated patients treated with a ten day course of either penicillin or placebo ten days after completion of the treatment. GABHS were cultured in 18% of the penicillin group compared with 63% of the placebo group. Another study assessed bacteriologic failures in 25% of the patients[124]. Some of these failures were probably not clinical failures; the patients might have been carriers and non-infectious to others[79]. Possible causes for the failures are: inadequate compliance, the introduction of shorter courses of penicillin, recolonization, absence of protective commensal alpha-haemolytic streptococci[125], or the production of beta-lactamase by co-existent micro-organisms[126]. The influence of a shorter duration of the course was studied by Gerber and colleagues[127]. They found 6% GABHS positive cultures in patients treated for ten

days compared with 18% in patients treated for five days.

In a number of studies, the effect of cephalosporins and macrolides was assessed with the aim of avoiding the possible overgrowth of beta-lactamase resistant micro-organisms[126,128,129,130,131,132,133]. However, no arguments were found for treating uncomplicated cases with these antimicrobial drugs. As for the susceptibility of GABHS for penicillin, no change has been perceived[34]. In Dutch general practice no problems have been encountered with resistance of GABHS. In conclusion, penicillin V is still considered to be the drug of first choice[26,34,48,78].

2.6 Current management

Despite published guidelines for management[53], there are differences between both countries and physicians in the use of diagnostic tools and prescribing habits[134,135,136,137]. In a Dutch study, 74% of the patients with acute tonsillitis were treated with antimicrobial drugs[138]. In a European study, the Dutch prescription rate was lower (68%) than in many other countries (>90%)[53]. In a Danish study of 358 GPs, 63% of the patients with sore throat were treated with antibiotics[139]. Nevertheless, when taking into account the probability of a GABHS infection, this percentage could be much lower. One of the problems is that it is not possible to distinguish with certainty between a GABHS infection and other infections based only upon the clinical features.

Of the prescriptions in the Dutch study above, two-thirds were penicillin V, the remaining mostly amoxicillin[138]. A difference in prescription patterns was visible between the various countries[53]. In Scandinavia, the Netherlands, and the eastern part of Germany oral penicillin was prescribed; in the southern European countries parenteral penicillin was administered, and in Belgium, Rumania and Poland amoxicillin or macrolides were most often prescribed[53]. In a Belgian study, general practitioners participated in a placebo-controlled study, but were also asked to record the prescription they had in mind for patients with a varying chance of GABHS[5]. In 75% no prescription was recorded, in 15% penicillin V, and amoxicillin was recorded as the choice in 5% of the patients. The actual behaviour might have been different.

In a survey among American medical practitioners, a great variation in current diagnosis and treatment was observed. Only 25% of primary care physicians stated that they always obtained cultures for patients with pharyngitis; 23% never used cultures. Most physicians started treatment before culture results were available, and

in 40 to 60% of the patients the treatment was not discontinued in the case of a negative culture result[140,141].

When considering the low incidence of complications in most developed countries, one can question the ubiquitous use of penicillin in patients with sore throat. The resurgences of acute rheumatic fever occurring in several countries in 1985 and 1986 and the serious course in some patients with a 'toxic shock-like syndrome' have made physicians more alert[33]. On the other hand, this vigilance does not necessarily imply penicillin treatment for sore throat cases because of the considerable probability of a non-GABHS throat infection and the disadvantages of penicillin.

Several management strategies have been undertaken in recent years. Centor and colleagues recommend the following: all patients having clinical signs and symptoms predicting a probability of more than 47% of GABHS pharyngitis should be treated without testing[6]. If a clinician has rapid tests available, the use of these tests in most other patients is recommended, and patients with a positive test are treated. If rapid tests are not available, immediate treatment of patients with a pretest probability of higher than 11% is advised[6]. In a Dutch decision analysis in adolescent people a number of factors were taken into account[142,143]: the risk of streptococcal pharyngitis and complications, the carrier rate, and the accuracy of diagnostic tests. Furthermore, the efficacy of antibiotic treatment, allergic reactions, medication compliance, and health outcomes were also taken into consideration. A slightly different strategy was the result. If the prior probability of GABHS is above 85%, oral penicillin is the preferred strategy; if the prior probability of GABHS is below 40%, no antibiotics are indicated; if the probability is between 40 and 85%, a rapid streptococcal antigen detection test is advised and patients with a positive test are treated[142,143]. A large difference is noted between the prior probabilities used in the two strategies.

In conclusion, the issue of sore throat has been studied for decades. Until the 1970s the potential complications were the major arguments for this interest. After that, clinical cure and eradication were considered major items for research. Until now, there has been a great variation both between as well as within countries regarding diagnostic and therapeutic strategies. These differences concern both the management and the management advice. With respect to the Dutch situation there is a lack of data needed for the development of an optimal strategy in general practice.

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Chapter 3

OUTLINE OF THE STUDY

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3.1 Introduction

This chapter provides a short overview of the study procedures and the base-line characteristics of the study population. The three parts of the study, conducted between June 1990 and July 1992, are reported as: the description of the microbiological throat flora, the study of the diagnostic tests, and the therapeutic study. First, the general study procedures are described. Then, data collected for a sub-group of patients are indicated separately. A flow-chart with the numbers of patients included in each part is shown at the end of the chapter (Fig 3.1).

3.2 Study procedures

Before the study started, it had been approved by the Utrecht University Hospital Ethical Committee. The general practitioners (GPs) were recruited by letter or by personal contact with probably interested GPs. Having decided to participate, additional information about the study was given to the physicians and the practice assistants involved. Of the 43 participating practices with 53 GPs, the majority were situated in the central part of the Netherlands. Both rural and more urbanized areas were represented.

General practitioners were asked to enroll patients fulfilling the following inclusion criteria: sore throat with a duration of less than 15 days, and age four to 60. Both written (appendix 1) and verbal information were given to the patient and informed consent was requested. Presence of a language barrier was an exclusion criterion. A selection form was used to register some demographic and clinical data both from participants and non-participants (appendix 2). In the case of non-participation, the reason for this was also registered.

Having given their consent, all patients were included in the microbiological part of the study. This was to establish the current microbiological flora in patients with sore throat in general practice, and to evaluate the diagnostic value of the four clinical features described as predictive for infections with group A beta-haemolytic streptococci (GABHS). The same patients participated in the diagnostic study to assess the diagnostic value of a rapid group A streptococcal antigen detection test.

At the initial visit, a number of base-line characteristics were recorded (see below) and throat swabs were taken for culture and rapid antigen detection testing. Also blood samples were drawn in patients aged 11 and older for the measurement of antibody titres against GABHS. The taking of blood from younger patients was

eliminated soon after the start, because of the high percentage of refusals. At the follow-up visit after fourteen days the patients were seen by the practice assistant. A second blood sample was drawn, and patients were asked about their complaints. If any complaints were present, the GP also saw the patient.

The aim of the therapeutic study was to determine the effectiveness of penicillin V in patients aged four to 60 with sore throat suspected of GABHS. The GPs invited patients to participate in the therapeutic study if they showed three or four of the clinical features described below. Exclusion criteria for the therapeutic study were: (i) an urgent need for antimicrobial treatment* in the opinion of the physician, (ii) the use of antimicrobial drugs during the preceding four weeks, (iii) an allergy to penicillin V, or (iv) earlier participation in the same trial.

Base-line characteristics

The following signs and symptoms were checked from both participants and non-participants: (history of) fever; exudate of tonsils or pharynx, tenderness of anterior cervical lymph-nodes, and absence of cough. Some demographic data were also registered: age, sex and insurance mode (capitation fee versus fee for service). At the initial visit, some of the participants' other symptoms were recorded on a registration form (appendix 3): degree of sore throat (grade 1 to 5), degree of limitation of daily activities (grade 1 to 5)**, the duration of sore throat in days before the initial visit, absence from school or work, and information about previous throat infections and tonsillectomy. In addition to the exudate and tenderness of cervical lymph-nodes, a red throat or a skin rash, if present, were registered. Swabs for a throat culture and for the performance of a rapid group A streptococcal antigen detection test were collected from all patients at the initial visit.

Patients kept a diary while any complaints were present for a maximum of ten days

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* history of acute rheumatic fever/glomerulonephritis;
epidemic streptococcal infections in closed community;
imminent quinsy;
other disorder/ailment prohibiting placebo treatment, such as seriously impaired immune system

** From McGill-Melzack questionnaire:
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.

(appendix 4). For patients participating in the therapeutic study, a short form was used after six months to report on the occurrence of new episodes since participation in the study (appendix 5).

3.3 Study population

A total of 1051 patients were eligible, fulfilling the inclusion criteria (Fig.3.1). Informed consent was given by 640 patients. For some patients relevant data for one of the research questions was not available. As a consequence, the numbers described may vary.

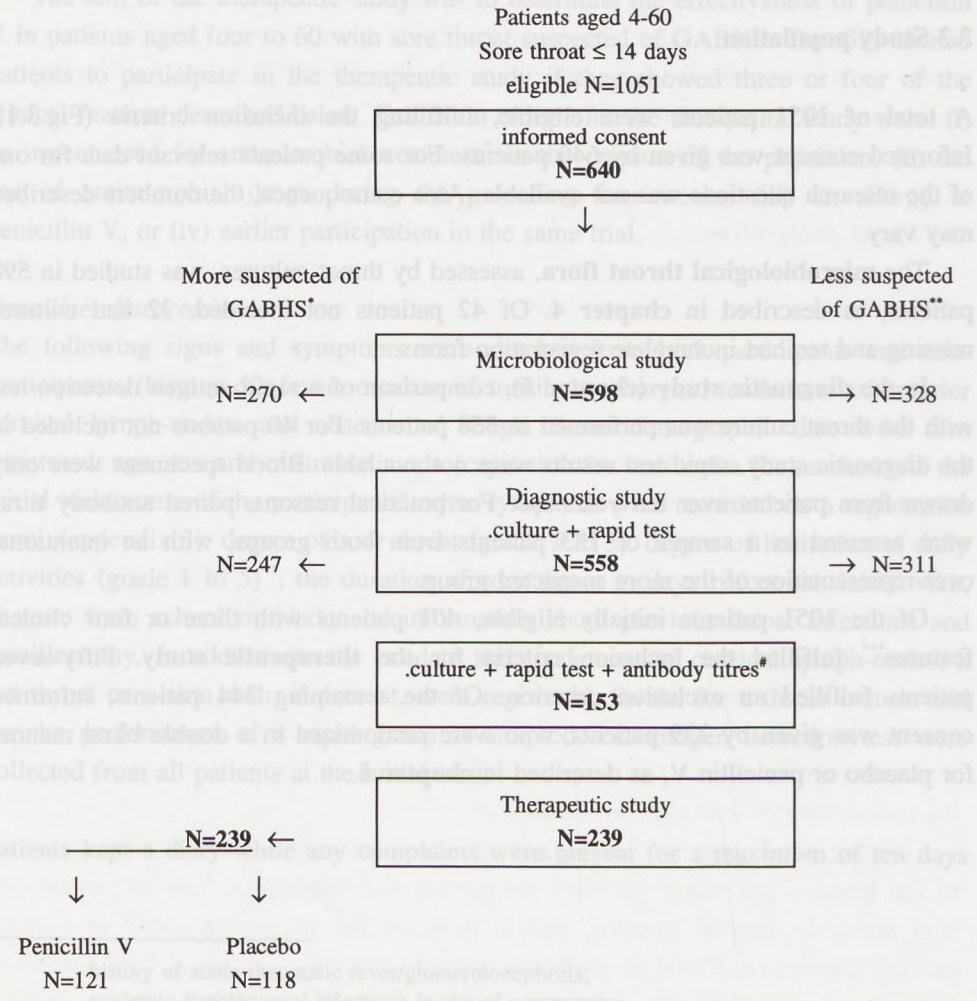
The **microbiological throat flora**, assessed by throat cultures, was studied in **598** patients, as described in **chapter 4**. Of 42 patients not included, 32 had cultures missing and ten had incomplete registration forms.

In the **diagnostic study (chapter 5)**, comparison of a rapid antigen detection test with the throat culture was performed in **558** patients. For 40 patients not included in the diagnostic study, rapid test results were not available. Blood specimens were only drawn from patients over ten years old. For practical reasons, paired antibody titres were assessed in a sample of **153** patients from both groups, with an intentional over-representation of the more suspected group.

Of the 1051 patients initially eligible, 401 patients with three or four clinical features*** fulfilled the inclusion criteria for the **therapeutic study**. Fifty-seven patients fulfilled an exclusion criterion. Of the remaining 344 patients, informed consent was given by **239** patients, who were randomized in a double blind manner for placebo or penicillin V, as described in **chapter 6**.

*** fever (history) $\geq 38.5^{0}$C rectally, (tonsillar) exudate, anterior cervical lymphanopathy, and absence of cough

Fig. 3.1 Flow-chart of sore throat study, and numbers of patients included in various parts of the study



* three or four of the following features: fever (history) ≥38.5°C rectally, (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough

** less than three of the following features: fever (history) ≥38.5°C rectally, (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough

\# antibody titres: antistreptolysin O (ASO), antistreptococcal group A polysaccharide titres (ASPAT), anti-deoxyribonuclease B (antiDNase B)

Chapter 4

BACTERIAL FLORA IN PATIENTS PRESENTING WITH SORE THROAT IN DUTCH GENERAL PRACTICE

'The only typical feature of streptococcal infections is their failure to show a single, consistent, typical feature'.

Feinstein AR (1962).

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Authors: Dagnelie Carien F, FWMM Touw-Otten, MM Kuyvenhoven, M Rozenberg-Arska, RA de Melker.

Fig. 3.1 Flow-chart of sore throat study, and numbers of patients included in

* three or four of the following features: fever (history) ≥38.5°C recently, (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough

** less than three of the following features: fever (history) ≥38.5°C recently, (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough

\# antibody titres against streptolysin O (ASO), deoxyribonuclease B (anti-DNase B), hyaluronidase (anti-HYA), and streptococcal glutamic oxaloacetic transaminase (ASPAT), anti-deoxyribonuclease B (anti-DNase B)

Abstract

The bacterial growth in patients presenting with a sore throat was assayed and four clinical features were tested in order to reliably differentiate between beta-haemolytic streptococci group A (GABHS) and other micro-organisms.

For two years, 53 general practitioners (GPs) in the Netherlands took throat swabs from all patients, aged 4-60, presenting with a sore throat lasting 14 days or less. Four clinical features: fever (history), (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough were registered.

In 70% of the 598 patients one or more micro-organisms were cultured from throat specimens. In 48% of the patients beta-haemolytic streptococci were found (32% group A, 7% group C, 4% group G, 5% others). Enterobacteriaceae were cultured in 5%, *Candida albicans* in 5%, *Staphylococcus aureus* in 4%, various others in 8% of the patients. In 30% of the patients cultures remained negative.

Of the 270 patients with three or four clinical features, 46% (95%CI, 40-52%) harboured GABHS in their throats, while in 328 patients with less than three features 21% (95% CI, 16-25%) were GABHS positive. However, this relationship between presence or absence of clinical features and culture result was not found in the youngest age category (4-14 years old). Culture results were not related to sex, smoking habits or the insurance mode of the patient.

The clinical relevance of several micro-organisms, other than beta-haemolytic streptococci, remains to be determined. The four mentioned signs and symptoms were helpful in predicting the probability of GABHS in patients aged 15 years and older. More negative cultures were seen in the group with less than three clinical features.

4.1 Introduction

A sore throat is a common health problem in general practice. In a Dutch morbidity study the incidence of presented tonsillitis was 54/1000 persons per year. In children, aged 0-14, the annual incidence is 100/1000; in adults over 45 years old 20/1000[1]. Data from Great Britain showed a somewhat lower incidence of tonsillitis: 20-40/1000 persons per year[2]. When experiencing a sore throat, only a minority of people visit their doctor. In Canada people were asked to keep a diary during a 3 month period; 5% mentioned sore throat on at least one day. Of these 5%, only 16% contacted a health professional[3].

In the USA pharyngitis*[4] is responsible for over 40 million visits by adults to health care facilities each year[5].

The term sore throat relates to various possible causes and clinical pictures. In most cases viruses are responsible for throat infections. As for bacteria, for decades group A beta-haemolytic streptococci (GABHS) were considered the most important agent. Until 1986, the virulence of GABHS decreased in the western world. Since 1987 the localized resurgences of acute rheumatic fever and other examples of severe streptococcal infections have made us more alert[6]. Far less is known about other bacteria as a cause of acute throat infections. Recent studies have shown that, apart from streptococci group A, other beta-haemolytic streptococci and other micro-organisms may be present in cultures from patients with throat complaints[7,8,9].Their clinical relevance is still not clear[7,8,9,10,11,12,13,14,15,16,17].

In the Netherlands, the prescription figures for antibiotics are low compared with other countries[18]. In most countries 90% or more of patients with tonsillitis are treated with antimicrobial drugs, while in the Netherlands 72% are treated with antibiotics, mostly penicillin V[19,20].

In many countries cultures are performed on a routine basis[18]. In Dutch primary care throat cultures are taken in less than 0.2% of patients[19], therefore, little is known about the bacterial flora of Dutch patients presenting with a sore throat. The most recent data about the throat flora originate from the early 1960s[21]. Our study aimed to gain insight into the prevalence of GABHS and other micro-organisms, to contribute to the discussion about the management of patients with sore throat. Four clinical features - (recent) fever ≥38.5°C taken rectally, exudate, lymphadenopathy and absence of cough - have been shown to be helpful in distinguishing people with sore throat with a higher chance of GABHS from those with a lower chance in the USA[22].

This study was performed to answer the following questions.

1. How often are GABHS, and non-group A, *Corynebacterium haemolyticum*, and other micro-organisms are cultured from throat specimens of patients visiting their GP with a sore throat?
2. Are the following four clinical features: fever (history) ≥38.5°C rectally, (tonsillar) exudate, anterior cervical lymphadenopathy and absence of cough, predictive for the presence of GABHS?

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* Acute pharyngitis - usually of viral origin (ICPC code R 74.2);
acute tonsillitis - bacterial or viral (ICPC code R 76.1)
In the USA the term pharyngitis is being used for both categories.

4.2 Methods

The study was conducted in the years 1990-1992 in the central region of the Netherlands. Fifty-three GPs participated for certain periods, varying from six to 18 months. Patients meeting the following criteria were included: reason for encounter sore throat, age four to 60, presence of the sore throat for 14 days or less. Patients with either communication problems due to a language barrier, or who had been taking antimicrobial drugs less than four weeks ago, were excluded. The patient was asked about fever (history) and cough; the clinical signs (tonsillar) exudate and anterior cervical lymphadenopathy were registered, as were age, sex, smoking habits and insurance mode (capitation fee versus fee-for-service). The same variables, except the smoking habits, and the reason for exclusion were registered for the sore throat patients who were not enrolled.

After informed consent, patients were categorized into two groups according to their clinical features. The first group consisted of patients having three or four of the four clinical signs and symptoms. The second group had less than three features. All GPs attended a training session to become acquainted with the study procedures and to improve the reliability of the throat swabs.

At the visit cotton swabs were streaked on both tonsils or tonsillar fossae and posterior pharynx wall and transported, mostly by mail, to the Utrecht Laboratory for Primary Care Services (SAL), in modified Stuart medium. Within 48 hours 7% sheep blood agar (Oxoid; Bactim BV) was inoculated and incubated at 37°C in aerobic and anaerobic conditions overnight. CHOC medium was used for *Haemophilus influenzae* and *Neisseria* spp. and incubated under CO_2 atmosphere for 24 and 48 hours. Only colonies with heavy growth on the first isolation were taken into account. Isolated haemolytic streptococci were typed by using a latex agglutination test (Streptex, Murex). For strains that could not be identified other methods were used[23]. The isolated beta-haemolytic bacterial strains were sent to a reference laboratory (National Institute for Public Health and Environmental Hygiene; RIVM) for confirmation and further typing. In cases of disagreement the cultures were re-analysed by the reference laboratory. When more than one micro-organism was isolated from a sample, the most important micro-organism was considered as the potential pathogen, in most cases beta-haemolytic streptococci. Bacteria other than haemolytic streptococci were identified using standard microbiological methods.

The data were analysed with the SPSS X program using chi-square statistics[24]. Results are presented in numbers, percentages and 95% confidence intervals[25].

4.3 Results

One-thousand and fifty-one patients were eligible for the study, of which 411 (41%) were not included for various reasons (table 4.1). Complete data were available for 598 patients. The enrolled patients did not differ from those not included with regard to sex, age, insurance mode or the number of clinical features (table 4.2).

Table 4.1 Patients eligible (n=1051), reasons for not including and evaluating and number of evaluatable patients (n=598)

Eligible Patients n = 1051	Number	Total
Not enrolled		411
Language barrier	69	
Antimicrobial drugs < 4 weeks ago	18	
Patient not cooperative*	184	
Doctor's reasons**	56	
Out of hours/home visits	34	
Various other reasons	50	
Non-evaluatable		42
Incomplete forms	10	
Missing cultures	32	
Evaluatable patients		598

* Follow-up impossible, not interested, no permission for taking blood or culture

** Too busy, follow-up impossible

Table 4.2 Patient characteristics for patients enrolled and not enrolled

	Enrolled n=598	Not enrolled n=411
Age, mean ± SD	27 ± 13	27
Sex (% male)	37	39
% Public Health Plan	67	68
Number clinical features* (%)		
0	8	7
1	25	21
2	25	28
3	22	25
4	21	19

* fever (history); (tonsillar) exudate; anterior cervical lymphadenopathy; absence of cough. Chi-square 4.735, (.20< P <.30).

The confirmation procedure at the reference laboratory resulted in: concordance of results in 82%, discordance in 4% and no conclusion in 14% due to non-typability or lack of growth of the strains.

In 70% of the 598 patients one or more micro-organisms were cultured (table 4.3). Beta-haemolytic streptococci were present in 48% of the patients. One-third of all patients harboured group A. Group C and G were cultured in 7 and 4% of the cases respectively. Various other micro-organisms were cultured in small percentages: streptococcus group B, *Staphylococcus aureus, Haemophilus influenzae,* enterobacteriaceae and *Candida albicans*. Of the enterobacteriaceae cultured, about two-thirds were *Klebsiella* spp. and one-third *Escherichia coli*. Several micro-organisms were rarely cultured. *C. haemolyticum* was not found. In 26% of the patients with a positive culture a combination of micro-organisms was found (table 4.4).

Table 4.3 Results of throat culture in patients with sore throat (n=598), in numbers and percentages

	Number	Per cent
Patients with negative cultures	177	30
Patients with positive cultures	421	70
Gram-positive bacteria		
ß-haemolytic streptococci	287	48
Group A	194	32
Group C	44	7
Group G	22	4
Group B	21	3
Group F	6	1
Staphylococcus aureus	21	4
Streptococcus pneumoniae	6	1
Streptococcus faecalis	5	1
Gram-negative bacteria		
Haemophilus influenzae	11	2
Neisseria species	6	1
Moraxella catarrhalis	3	1
Enterobacteriaceae	36	6
Other micro-organisms		
Candida albicans	25	5
Others	21	4

Table 4.4 Combinations of micro-organisms in patients with sore throat (% of patients with positive cultures; n=421)

	Number	Per cent
Streptococcus group		
A + enterobacteriaceae	16	4
A + *Candida albicans*	9	2
A + *Staphylococcus aureus*	9	2
A + streptococcus group C	1	<1
B + *Candida albicans*	5	>1
C + *Candida albicans*	6	>1
C + *Staphylococcus aureus*	5	>1
G + *Staphylococcus aureus*	4	<1
Other combinations	55	13
Single micro-organisms	311	74

In the group of 270 patients that met three or four of the clinical features, beta-haemolytic streptococci were predominant, especially group A (n=125) and C compared with other micro-organisms (table 4.5). Other micro-organisms and a negative culture result were found significantly more in 328 patients with less than three clinical features. In this group 68 patients (21%) harboured GABHS. The percentages of GABHS decreased with a decreasing number of clinical features from 54 to 0% (Figure 4.1).

Table 4.5 Type of streptococcus in throat culture according to the number of clinical features; percentages

	0-2 features* (n=328)	3-4 features* (n=270)	Difference of percentages 95% CI
Streptococci	**33**	**66**	26 to 41
Group A	21	46	18 to 33
Group C	4	11	3 to 12
Group G	2	6	0.2 to 7
Group B	5	2	-0.2 to -6
Group F	1	1	NC
Other bacteria	**31**	**12**	-13 to -25
Negative	**36**	**22**	-7 to -21

* See legend to table 4.2

NC = not calculated

In patients, aged four to 14 years, no difference was found for the percentages of GABHS found between the group with three or four criteria and the group with less than three criteria; the difference of percentages was 10% (95% CI, -12-32%) (table 4.6). This is in contrast with the older patients, who showed a significant difference (26%; 95% CI, 18-33%) in culture results between the two groups.

No relation was found between smoking, sex or insurance mode and the result of the throat culture.

Fig. 4.1 **GABHS according to the number of clinical features in throat cultures of sore throat patients (n=554); percentages.**

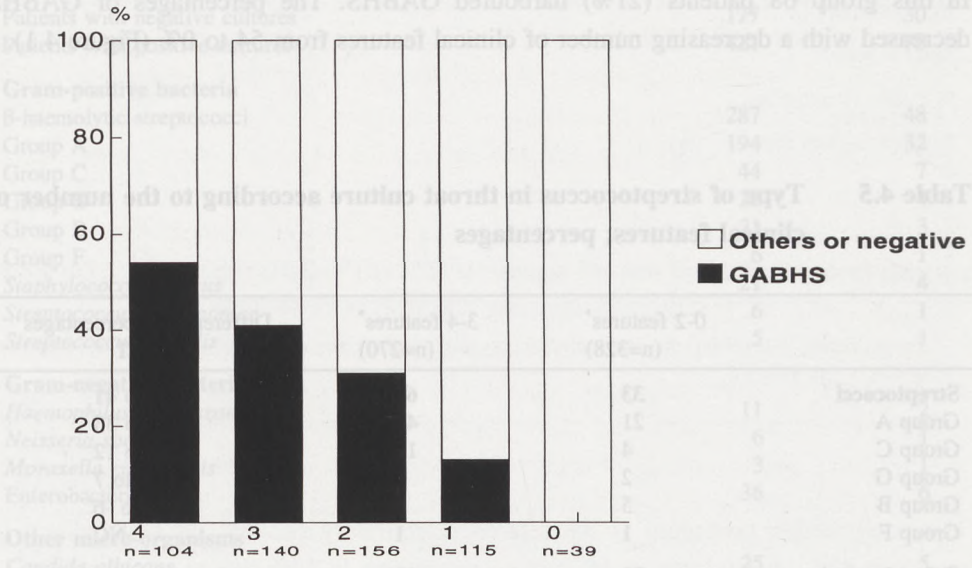


Table 4.6 **Prevalence of GABHS according to the number of clinical features, stratified for age categories 4-14 years and 15-60 years; numbers (percentages)**

	4 - 14 years		15 - 60 years	
	0 - 2	3 - 4	0 - 2	3 - 4
GABHS present	17 (52)	29 (62)	51 (18)	96 (43)
GABHS absent	16 (48)	18 (38)	240 (82)	127 (57)
Total	33 (41)	47 (59)	291 (57)	223 (43)

4.4 Discussion

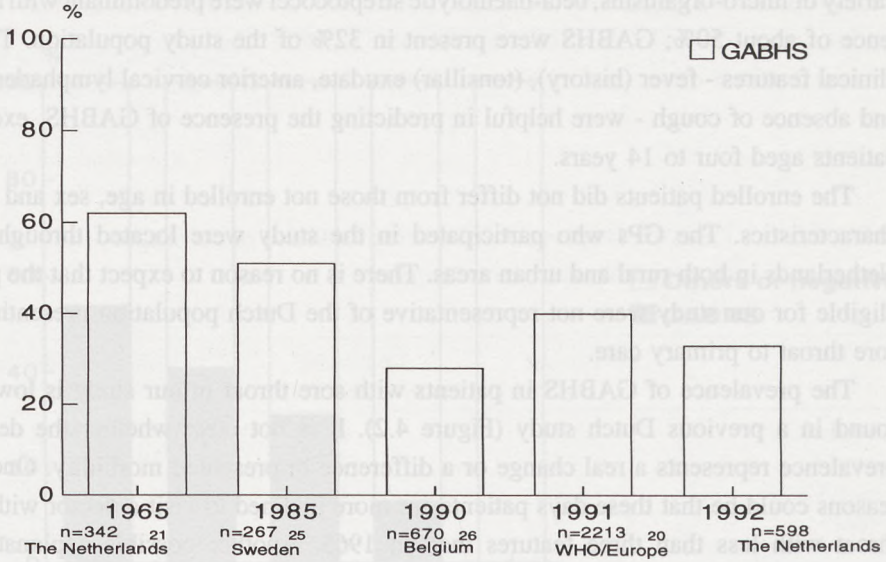
Although the bacterial flora in patients with a sore throat in our study showed a great variety of micro-organisms, beta-haemolytic streptococci were predominant with a prevalence of about 50%; GABHS were present in 32% of the study population. The four clinical features - fever (history), (tonsillar) exudate, anterior cervical lymphadenopathy and absence of cough - were helpful in predicting the presence of GABHS, except for patients aged four to 14 years.

The enrolled patients did not differ from those not enrolled in age, sex and clinical characteristics. The GPs who participated in the study were located throughout the Netherlands in both rural and urban areas. There is no reason to expect that the patients eligible for our study were not representative of the Dutch population presenting with sore throat to primary care.

The prevalence of GABHS in patients with sore throat in our study is lower than found in a previous Dutch study (Figure 4.2). It is not clear whether the decreased prevalence represents a real change or a difference in presented morbidity. One of the reasons could be that these days patients are more inclined to visit a doctor with a sore throat with less than three features than in 1965. Another possible explanation, an overrepresentation of children in the 1965 study[21], has been looked at. However, the percentage of children in that study was comparable with ours. The prevalence found is in accordance with other recent European studies in primary care, in which a prevalence of 30% was found[26,27]. Results of an American study, published in 1975, showed a prevalence of GABHS of 31% for children and 15% for adults[28]. The prevalence of GABHS has decreased in the last few decades. However, in another American study, which included only adults, the prevalence was lower, namely 10%[5].

The relevance of the growth of non-group A beta-haemolytic streptococci is not clear. Our findings are in agreement with several other studies, describing group C streptococcus as a pathogen with a prevalence of 7%[7]. The clinical picture is said to be similar to that of GABHS, but may be less severe[8]. Other authors concluded that group C usually represents only a minor factor in the pathogenesis of pharyngitis[9,10,11]. In our study the prevalence of group C was found significantly higher for the group of patients with three or four clinical features, which is similar to the prevalence of 12% described by Huovinen et al.[9].

Fig. 4.2 Prevalence of group A beta-haemolytic streptococci (GABHS) in patients with a sore throat in several European studies



Less is known of group G streptococci and their relevance is not very clear[9,12,13]. McMillan et al.[14] did not find any difference between patients and controls. On the other hand, a community-wide outbreak of group G streptococcal pharyngitis has been described by Gerber et al.[15]. Group B and F are not known as pathogens in the throat.

There are no data on *C. albicans* as the cause of sore throat in otherwise healthy patients. *S. aureus* was found to be a pathogen by Fujikawa et al.[16]. The clinical picture included a red throat, anorexia, exudate and cough. The role of *H.influenzae* as a pathogen in sore throat was considered by Fujikawa et al.[16], others consider these bacteria as commensal organisms in most cases[17,29]. *H.influenzae* was associated with such symptoms as fever, anorexia, tonsillar exudate and cough[16]. In our study *H.influenzae* was found in only 19 cases, in eight cases combined with beta-haemolytic streptococci, which is why we do not know whether these bacteria were responsible for the clinical picture.

The high percentage of enterobacteriaceae cultured is rather striking. A similar percentage has been described before in specific populations, but not in a primary care

setting[30]. In contrast to the results of Banck and Nyman[31] and Miller et al.[32] no *C. haemolyticum* were found in our study. We concluded that there is no need to consider *C. haemolyticum* as a potential problem in Dutch primary care.

The four clinical features correlated positively with the chance of GABHS and helped us to divide the patients into a group with a higher and a lower possibility of GABHS, except for the age category 4-14 years. This is especially important in countries where no routine throat cultures are performed, or in situations where a physician does not want to wait for the result of the culture before deciding on a treatment policy.

The presence of GABHS is still considered to necessitate antibiotic treatment in patients with signs of infection. The following reasons for treating with antibiotics are mentioned: (i) possible reduction of the incidence of rheumatic fever; (ii) prevention of suppurative complications; (iii) shortening the course of the disease; and (iv) prevention of transmission to other persons[33]. In recent years strategies have been developed to reduce unnecessary culturing, and reducing excessive antibiotic treatment by using algorithms with clinical criteria[5,34,35]. Several medical decision analyses have also been performed on the management of patients with a sore throat[36,37,38]. In these analyses clinical features were used that were comparable with the features we used. For patients with a lower chance of GABHS the advantages of treatment are lower and the risks of treatment are relatively higher[36]. However, this does not apply to the youngest age category (4-14 years old), whose clinical features were not discriminating for GABHS and who had a high chance of GABHS. This is in accordance with the findings of Forsyth[28], who concluded that clinical criteria similar to ours are only moderately accurate predictors of a negative culture. The number of children in our study was too small to enable us to draw a conclusion. The probability of GABHS in this group is much higher, 40% in an USA study[14], 58% in our study.

The high percentage of GABHS in the youngest age category might partly be explained by a proportion of carriers. In several studies a considerable percentage of carriers (±10%) was found in children[28,10,39].

4.5 Conclusion

The prevalence of GABHS in sore throat patients has decreased since the 1960s, but is still 32% in a Dutch general practice setting.

For GPs the four clinical features may be helpful in estimating the chance of GABHS in patients 15 years and older and deciding on the treatment policy. For

younger patients these clinical criteria may not be helpful in this respect, but further study is needed.

A considerable number of other micro-organisms was present, but not much is known about their relevance. More studies are needed to decide whether the presence of those bacteria should lead to causal treatment.

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Chapter 5

DIAGNOSTIC VALUE OF A GROUP A STREPTOCOCCAL ANTIGEN DETECTION TEST IN GENERAL PRACTICE

To be submitted in a shorter version to an international journal

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5.1 Introduction

Acute sore throat belongs to the ten most frequently presented complaints in Dutch general practice; either viruses or bacteria may be causative[1]. In the USA, sore throat is the third most common reason for office visits: 27 million per year[2]. The incidence of acute tonsillitis- a major cause of sore throat -was reported by the Dutch National Survey of Morbidity and Interventions as 25/1000 persons per year[3]. The most important micro-organism involved in acute pharyngotonsillitis is the group A beta-haemolytic streptococcus (GABHS) because of its possible, although infrequent, risk of suppurative or non-suppurative sequelae. After the resurgences of acute rheumatic fever in several countries in the mid eighties[4], the incidence has decreased again. More recently, quite a few cases of a 'toxic shock-like syndrome' due to GABHS have occurred in many countries[5,6,7]. Thus, continued vigilance is advised[7,8].

To decide whether a patient is harbouring GABHS, the following diagnostic possibilities are available: judgement based on clinical picture, a throat culture, or a rapid diagnostic test. The clinical features of a GABHS infection are not completely distinctive, but some signs and symptoms are helpful in differentiating between a higher and a lower chance of GABHS[9,10]. Then, further testing may be performed with a throat culture or a rapid antigen detection test.

Throat culture

In many countries, for decades, the throat culture has been the most frequently used diagnostic test, the advice being only to treat with penicillin patients whose cultures show GABHS[11,12,13,14]. A major disadvantage of the throat culture is the delay of 24 to 48 hours when cultures are performed in an office setting. In the Netherlands, as in many other countries, cultures have to be sent to a laboratory, entailing a delay of one day or more. Consequently, in Dutch general practice throat cultures are performed in less than two percent of the patients with acute tonsillitis[15]. Another shortcoming of the throat culture is the fact that it is not a gold standard[16]. Information regarding the sensitivity of the throat culture has been gathered from studies with duplicate throat swabs[17,18,19,20]. The sensitivity of one culture compared with two cultures from two swabs taken simultaneously was 90% in two studies[18,19] and 74% in another[20]. An imperfect swabbing technique or a less than optimal method of culturing may be partly responsible for false negative cultures[21].

The specificity of the throat culture is related to the streptococcal colonization

rate, or percentage of asymptomatic carriers in a population. These carriers are patients who do not have pharyngitis, but do have a positive throat culture for GABHS[22]. The false-positive rate plus the specificity equal 100%[17]. The term 'carrier' is also used for patients who have pharyngitis and a positive culture, but who do not develop a serologic response[22]. With the term 'carriers' we indicate the latter category, unless otherwise stated. In many studies the condition referred to is not clear. This complicates comparison of the results of several studies. Some authors reported one percent asymptomatic carriers in an adult population[17]. Studies in patients with pharyngitis in different communities have shown a carrier rate of between two and ten percent, with higher rates in children than in adults[23]. When comparing cultures and antibodies, Tompkins[24] estimated a carrier rate of 15 to 20% in children with pharyngitis, and five to ten percent in adults. This difference in specificity of the throat culture between children and adults may be partly explained by the higher percentage of asymptomatic carriers (5-15%) in children[25,26]. About half the pediatric patients with acute pharyngitis and a culture with GABHS had a significant antibody rise[18,27]. The remaining patients had acute viral sore throat with streptococcal colonisation.

In conclusion, with the throat culture, the organism is detected, but a causal relationship with the complaints cannot be proved[17,21]. Based on these divergent results as well as for practical reasons, one author concluded that throat cultures contributed little to the management of patients with uncomplicated acute respiratory infections[28].

Rapid group A streptococcal antigen detection test

To avoid the delay entailed by the throat culture, several group A streptococcal antigen detection tests have been developed with varying techniques and quality[29,30]. First, extraction of the group A carbohydrate antigen from the throat swab is performed. Then, one of the following techniques is used: capillary precipitation, latex agglutination, coagglutination[31,32,33,34,35,36], or an enzyme-linked immunosorbent assay (ELISA). One test incorporates liposomal technology into a membrane-bound immunoassay procedure[37]; if present, the extracted streptococcal antigen is linked to the antibody-coated coloured liposomes on a porous filter, and a visual colour change occurs[37,38,39,40].

Several studies have addressed the diagnostic value of rapid antigen testing, using a throat culture as a reference test[17]. They report sensitivities lying between 45%[41] and 96%[42] with the throat culture as a reference test for each. Relatively high speci-

ficities are reported: they lie between 81%[43] and 100%[40,41]. Predictive values of a positive test result vary from 61%[38] to 99%[33]. Predictive values of a negative test result vary from 75%[44] to 100%[41] with the throat culture as a reference test.

To determine diagnostic value, rapid tests should preferably be compared with a gold standard. Antibody titres have always been used to differentiate between carriers and truly infected persons[18]. A serological antibody test has only been performed in a very few studies - one in a pediatric population[45], another in primary care[46]. But, apart from the problem with the 'gold' standard, the question remained whether these diagnostic tests performed equally well in primary care, especially in terms of sensitivity[47,48]. To evaluate the diagnostic accuracy of a new test, it should be investigated in the setting where it is to be used[48], because of differences in population studied, experience of personnel and other unknown local factors. Once the rapid streptococcal antigen detection tests have demonstrated their diagnostic value, they might play a role in the management of sore throat.

Antibody titres

The measuring of antibody titres does not facilitate the management of individual patients because of the delay before the result is known. Antibody titres have been used for research objectives in particular, and have served as our 'gold standard' against which other tests should be compared[49]. As mentioned in chapter 2, recently the 'goldness' of the antibody response as a standard has been called in question. A significant antibody response requires a rise of at least two dilution increments between the acute and convalescent sera[21,50]. Several antibody tests are available and are being used. The most often performed test is the antistreptolysine O (ASO). Another test measuring antibodies against extracellular products of group A streptococci is anti-deoxyribonuclease B (anti-DNase B). In one study, antibodies against cellular products of the group A streptococcus, namely the antistreptococcal group A polysaccharide titres (ASPAT), were demonstrated with the use of human sensitized erythrocytes[51]. In that study, in 52 children with tonsillitis and a GABHS-positive culture, and 52 age- and season-matched controls, the absolute levels of the ASPAT were compared between the two groups. The level of the ASPAT appeared to have less overlap between patients and controls than the ASO and anti-DNase B titres. The authors asserted that the ASPAT was especially useful in children.

Research questions

This study has been performed in order to answer the following questions.

What is the diagnostic value of a rapid group A streptococcal antigen detection test in general practice:

a. with a throat culture as a reference test, in patients aged four to 60, and

b. with an antibody titre as a reference test in patients aged 11-60 presenting with sore throat?

5.2 Methods

Patients

Patients were recruited by 53 general practitioners during the years 1990 to 1992. Inclusion criteria were: sore throat for no longer than 14 days and age four to 60. Patients with a language barrier were excluded. Patients' age, sex, and insurance mode (capitation fee versus fee for service) were registered. The presence of four clinical features was registered, two from the patient's history: fever (history) and absence of cough; and two signs: (tonsillar) exudate and anterior cervical lymphadenopathy. Both written and verbal information were given to the patient, and informed consent was requested.

Patients were categorized into two groups according to the presence of three or four, or less than three of the specified clinical features[9,10]. The patients with three or four clinical features received either penicillin V or placebo as part of the therapeutic study described elsewhere (see chapter 6). The group with less than three features received no, or a symptomatic, treatment.

Bacteriological assessments

At the initial visit two throat samples were taken, one for culturing and one to perform a rapid test. A test using liposomal technology was selected because of its ease of performance and at least average quality (Directigen 1,2,3 Strep A; Becton Dickinson BV)[37]. The physicians involved participated in a training session to improve the reliability of the throat swabs. The throat culture was performed with cotton swabs, streaked on both tonsils or tonsillary fossae and the posterior pharyngeal wall. No instructions were given regarding the order for taking the two swabs.

The rapid test was performed according to the manufacturer's instructions, during

the visit or immediately afterwards, mostly by practice assistants trained by the coordinator for this purpose. Throat cultures were transported by mail to the Utrecht Laboratory for Primary Care Services in modified Stuart medium. Within 48 hours of collection, 7% sheep blood agar (Oxoid) was inoculated and incubated at 37°C in aerobic and anaerobic conditions overnight. Only colonies with heavy growth on the first isolation were taken into account and re-analysed after 48 hours. Isolated haemolytic streptococci were typed using a latex agglutination test (Streptex, Murex). For strains that could not be identified, other methods were used[52]. The isolated beta-haemolytic bacterial strains were sent to a reference laboratory - National Institute for Public Health and Environmental Hygiene - for confirmation. In cases of disagreement cultures were re-analysed by the reference laboratory whose final result was considered definitive.

At the initial visit, blood specimens were drawn from patients aged 11 and older. At a follow-up visit after 14 days, convalescent blood specimens were drawn. All sera were stored at -70°C, and were analysed by the Department of Clinical Microbiology of Rotterdam University at the end of the study. The following antibody-titres were measured: antistreptolysin-O (ASO), antistreptococcal group A polysaccharide titres (ASPAT), and anti-deoxyribonuclease B (anti-DNase B). Antistreptolysin (ASO) titres were estimated according to Rantz and Randall[53]. DNase B was prepared according to the method of Marker and Gray[54], and anti-DNase B titres were measured as described by Klein and colleagues[55]. Antibodies to group A streptococcal polysaccharide (ASPAT) were determined as described by Goedvolk and colleagues[51].

Statistical analysis

For practical reasons, only a selection of the sera of all patients aged 11 years and older were analysed. For patients with three or four clinical features a non-selective sample was taken. Of the less suspected group, patients of GPs who had included 15 or more patients were selected. The reason for this was to have this small number of sera compared with throat cultures and rapid tests which were as reliable as possible. A significant antibody response is defined as a rise in titre of two dilution increments (=fourfold) or more between the first and second sample. In the case of very low titres of the ASPAT, a three dilution increment was said to be significant, because pairs were not always analysed simultaneously.

The data were analysed using the SPSS X and SPSS-PC program[56]. Results are presented in numbers, percentages and 95% confidence intervals[57]. The diagnostic

value of the tests are expressed in sensitivity, specificity, predictive value of a positive and a negative test result[58], and in positive and negative likelihood ratio.

Table 5.1 Definition of sensitivity and specificity of a diagnostic test and of the predictive value of a positive and negative test result. Likelihood ratios of a positive and negative test.

- The sensitivity of a test is the proportion of truly diseased persons in the screened population who are identified as diseased by the test.
- The specificity of a test is the proportion of truly non-diseased persons who are so identified by the test.
- The predictive value of a positive test result is the probability that a person with a positive test result actually has the disease.
- The predictive value of a negative test result is the probability that a person with a negative test result does not have the disease[58].

$$\text{Likelihood ratio positive test} = LR^{+} = \frac{sensitivity}{1 - specificity}$$

$$\text{Likelihood ratio negative test} = LR^{-} = \frac{1 - sensitivity}{specificity}$$

For the comparison of the results of the rapid test and throat culture, the influence of the number of clinical features (three or four and less than three, respectively), and the influence of age category (four to 14 years, and 15 and older) is assessed by stratified analysis. The result of the throat culture is compared with the three antibody titres, and the percentage of carriers assessed. The diagnostic value of the antibody titres is then assessed by calculating the positive and negative likelihood ratios compared with the throat culture (see table 5.1). From the comparison of the antibody titres with the throat culture, the antibody titre with the best diagnostic value is selected. The diagnostic value of the rapid antigen test is assessed in comparison with that antibody titre and compared with the throat culture.

The influence of the duration of sore throat before enrolment on the initial levels of the antibody titres is calculated using the chi-square statistical test. The influence of antimicrobial treatment and age category (11-14 or 15 and older) on the presence or absence of a significant antibody increase is assessed.

5.3 Results

Six hundred and forty patients were included in the study for the comparison of rapid test and throat culture. For 10 patients, their registration forms were missing and for 32 patients, their throat cultures were missing (as described in chapter 4). For a further 40 patients, the results of their rapid tests were inconclusive (10) or missing (30). These patients did not differ from the patients evaluated with respect to clinical picture, mean age or positive culture-rate. As a result, clinical data, throat cultures and antigen test results were available for 558 patients.

For 171 selected patients the sera were analysed for antibody titres. For 18 patients only one serum sample was available, so paired blood samples were analysed in 153 patients, aged 11 years and older. Eighty-eight patients had three or four clinical features (46% GABHS), and 65 patients had less than three (32% GABHS). The mean age of patients in the sample did not differ from the remaining patients (both 29 years).

GABHS were present in the throat cultures of 183 patients (33%). Rapid tests were positive in 135 patients (24%). The results of the rapid test compared with the throat culture in the two clinical groups of patients are shown in table 5.2.
For all patients, the sensitivity of the rapid test compared with the throat culture was 65% and the specificity 96%. In our population, the predictive value was 88% for a positive test result and 85% for a negative test. For patients with three or four clinical features, the sensitivity was considerably higher (75%) than for patients with less than three features, but the specificity was lower for patients with three or four features. The predictive values showed no significant difference between the two clinical groups. The probability of a positive rapid test differed considerably: 12% (less than 3 features) versus 40% (3 or 4 features). The size of the confidence intervals varies considerably because of the varying numbers of patients. The prevalence differed considerably between the two groups.

Table 5.2 Throat culture and rapid antigen detection test compared in patients with 0 to 2 (n=311), and 3 or 4 clinical features* (n=247); numbers. Sensitivity, specificity, and predictive values of rapid test compared with throat culture, and prevalence in two clinical groups; percentages; differences of proportion and 95% confidence intervals (CI) of differences.

Features:		0-2		3-4		Total	
Culture:		GABHS+	GABHS-	GABHS+	GABHS-	GABHS+	GABHS-
Rapid test	+	32	4	87	12	119	16
	-	35	240	29	119	64	359
Total		67	244	116	131	183	375

	0-2	3-4	all	diff.	95% CI
Sensitivity	48	75	65	27	13 to 42
Specificity	98	91	96	7.5	2 to 13
Predictive value +	89	88	88	NC	
Predictive value -	87	80	85	7	-1 to 14
Prevalence	22	47	33	25	18 to 33

* fever (history), anterior cervical lymphadenopathy, (tonsillar) exudate, and absence of cough
NC = not calculated

The results for the two age categories four to 14 and 15 and older, are shown in table 5.3. The sensitivity of the rapid test was slightly higher in the younger patients, but the difference was not significant. The specificity of the rapid test was slightly higher in the younger patients, but the relevance of this difference is limited. The positive predictive value was higher than for the older patients and the negative predictive value was lower, probably because of the significantly higher prevalence of GABHS in the younger age group (58 versus 29%). The probability of a positive test result also differed between the younger and the older age category (43% versus 21%).

Table 5.3: Throat culture and rapid antigen detection test compared, in patients aged 4-14 (n=79) and 15 years and older (n=479); numbers. Sensitivity, specificity, and predictive values of rapid test compared with throat culture, and prevalence in two age groups; percentages; differences of proportion and 95% confidence intervals (CI) of differences.

Age Category:		4-14		15 and older		Total	
Culture:		GABHS+	GABHS-	GABHS+	GABHS-	GABHS+	GABHS-
Rapid test	+	34	0	85	16	119	16
	-	12	33	52	326	64	359
Total		46	33	137	342	183	375

	4-14	15 and older	difference	95% CI
Sensitivity	74	62	12	-3 to 27
Specificity	100	95	5	2 to 27
Predictive value +	100	84	16	9 to 23
Predictive value -	73	86	13	0.5 to 26
Prevalence	58	29	30	18 to 41

In patients aged 15 and older having three or four clinical features, the prior probability of GABHS was 43% (table 4.6). In 37% of these patients, the result of the rapid test was positive, increasing the posterior probability of GABHS to 88%. In patients with a negative rapid test result, the probability decreased to 19%. In patients aged 15 and older with less than three features, the probability of GABHS was 18% (table 4.6). With a positive rapid test result, the posterior probability of GABHS in these patients increased to 85%, but a positive test result was seen in only 9% of the patients. With a negative rapid test result, the posterior probability decreased to 11%.

The results of the ASO, ASPAT and antiDNase B titres in the paired sera of 153 patients, and the results of the throat culture are shown in table 5.4.

Of all patients, 8% showed a significant increase of the level of the ASO, 9% of

the ASPAT, and 14% of the antiDNase B. At least one significantly increased titre was seen in 27% of the patients, of whom 5% had two significantly increased titres. No patients had three significantly increased titres. Of the GABHS-positive patients, 13% showed a significant increase of the levels of the ASO, 15% of the ASPAT, and 25% of the antiDNase B. In 46% of the GABHS-positive patients, at least one significantly increased titre was seen, of whom 7% had two increased titres. The percentage of 'carriers' was high when individual titres were considered: 87% for the ASO, 85% for the ASPAT and 75% for the antiDNase B. Considering all three titres, 46% of the patients had no increased titres, so 54% may be considered to be carriers. In GABHS-negative patients a significant increase of one or two titres was seen in 10% of the patients.

Table 5.4 **Presence or absence of GABHS in throat culture of patients without or with two dilution increments (fourfold) or higher increase of anti-streptolysin-O (ASO), ASPAT, and antiDNase B titres; numbers (n=153). Sensitivities and specificities of throat culture with titres as reference tests, and of titres with throat culture as reference tests; percentages and 95% confidence intervals of values (95%CI).**

Throat culture	**ASO**	≥ 2x	-	Total
GABHS+		9	62	71
GABHS-		3	79	82
Total		12	141	153

	95% CI
Sensitivity of throat culture, compared with ASO: 75	43 to 95%
Specificity of throat culture, compared with ASO: 56	48 to 64
Sensitivity of ASO, compared with throat culture: 13	6 to 23
Specificity of ASO, compared with throat culture: 96	90 to 99

	ASPAT	≥ 2x	-	Total
GABHS+		11	60	71
GABHS-		3	79	82
Total		14	139	153

	95% CI
Sensitivity of throat culture, compared with ASPAT: 79	49 to 95%
Specificity of throat culture, compared with ASPAT: 57	49 to 65
Sensitivity of ASPAT, compared with throat culture: 16	8 to 26
Specificity of ASPAT, compared with throat culture: 96	90 to 99

	anti-DNase	≥ 2x	-	Total
GABHS+		18	53	71
GABHS-		4	78	82
Total		22	131	153

	95% CI
Sensitivity of throat culture, compared with anti-DNase B: 82	60 to 95%
Specificity of throat culture, compared with anti-DNase B: 60	51 to 68
Sensitivity of anti-DNase B, compared with throat culture: 25	16 to 37
Specificity of anti-DNase B, compared with throat culture: 95	88 to 99

Of the three antibody titres, the antiDNase B showed the highest positive likelihood ratio combined with the lowest negative likelihood ratio, with the throat culture as a reference test (table 5.5).

Table 5.5 Positive and negative likelihood ratios of two dilution or higher increment of antibody titres with the throat culture as a reference test (n=153).

	LR+	LR-
ASO-titre compared with throat culture:	3.25	0.91
ASPAT-titre compared with throat culture:	3.75	0.89
antiDNase B-titre compared with throat culture:	5.0	0.79

For the comparison of the rapid test with the antibody titres, data for 139 patients were available. Because the selection of sera had been made before the rapid test data were available, test results were missing for ten patients and inconclusive for four. The result of the comparison of rapid test and antiDNase B titre and the throat culture in the 139 patients is shown in table 5.6.

Table 5.6 **Result of rapid test and throat culture with antiDNase B titres as a reference test; presence of absence of two dilution increments (fourfold) or higher increase; numbers (n=139*). Sensitivities and specificities of rapid test compared with antiDNase B titre; percentages and 95% confidence intervals (95% CI). Likelihood ratios of a positive and a negative result of rapid test and throat culture compared with antiDNase B.**

		AntiDNase B titre		Total
		≥ 2x	-	
Rapid test	+	12	35	47
	-	8	84	92
Total		20	119	139
Throat culture	+	16	49	65
	-	4	70	74
Total		20	119	139

	Rapid test	95% CI	Throat culture	95% CI
Sensitivity	60	36 to 81	80	56 to 94
Specificity	71	62 to 79	59	50 to 68
Predictive value +	26	14 to 40	25	15 to 37
Predictive value -	91	84 to 96	95	87 to 99

	LR+	LR-
Rapid test	2.07	0.56
Throat culture	1.95	0.34

* of 14 patients test results inconclusive, or missing

The sensitivity of the rapid test compared with the antiDNase B titre was 60%, the specificity 71%. The positive and negative likelihood ratios of the rapid test and the

throat culture were comparable. The rapid test performed slightly better regarding the positive likelihood ratio and the throat culture with respect to the negative likelihood ratio.

The level of the initial titres was not influenced by the duration of sore throat before enrolment (chi-square 1.36, 0.01 and 0.06 for ASO, ASPAT and antiDNase B respectively). However, patients with a high initial ASO and antiDNase B titre showed significantly fewer increased titres (chi-square 6.69, and 4.82 respectively). As for the ASPAT titre no association was seen between the initial titre and the presence of a significant increase.

Controlling for treatment in GABHS-positive patients showed the following: 10% of 21 patients treated with penicillin and 14% of 50 patients not treated had a significant rise of the ASO titre; 14% versus 16% of the ASPAT titre, and 24 versus 26% of the antiDNase B titre. Of the 153 patients 13 (9%) were aged between 11 and 14. Of these, 11 patients were GABHS-positive. Four of them showed a significant increase of one or more titres.

5.4 Discussion

In this descriptive study of 558 patients with sore throat, the rapid antigen detection test appeared to be of limited value when compared with the throat culture. A sensitivity of 65% is rather low, but it is comparable to other studies[38,44,59,60,61,62]. When stratifying for the number of clinical features, a differentiation occurred: the sensitivity was lower in the group with less than three features, but was 75% in the group with three or four features. An important difference between the two clinical groups was the prevalence of GABHS (22 versus 47%). This means that the antigen detection test is more suitable for patients selected for their clinical picture, with a higher probability of GABHS. The predictive value of the presence of three or four clinical features in our study was 46%. If no test had been performed, about half of the patients with three or four clinical features would have been unjustifiably treated with penicillin. If however, a rapid test had been performed, 40% of these patients would have had a positive test result; 88% of these results would be correctly positive. For the remaining patients a reduction of treatment is possible.

Table 5.7 Studies of rapid group A streptococcal antigen detection tests compared with a throat culture. Setting, type of test, number of patients studied, diagnostic values and prevalence of GABHS (%).

Pediatric Author	Type	N	Sens	Spec	PV+	PV-	Prevalence
Gerber (1984)[33]	aggl.*	339	83	92	97	93	32
	aggl.*	263	84	99	99	93	32
Lieu (1986)[41]	aggl.	556	45	100	74	100	39
Lieu (1988)[59]	aggl.	225	55	90	68	83	29
Moyer (1990)[40]	lipos.	327	75	100	98	89	32
Outpatient							
McCusker (1984)[34]	aggl.	500	91	91	77	99	23
Redd (1988)[44]	aggl.	286	52	94	85	75	30
Huck (1989)[38]	lipos.	924	65	85	61	87	26
Moyer** (1990)[40]	lipos.	322	60	99	94	97	8
General Practice							
True (1986)[43]	aggl.	538	81	81	72	94	20
Hjortdahl (1987)[42]	aggl.	226	96	91	77	99	23
Hoffmann (1987)[62]	aggl.	468	73	98	96	84	42
Andersen (1992)[60]	aggl.	105	68	97	90	89	27
Burke (1988)[61]	ELISA	250	63	92	63	92	18
Hoffmann (1990)[63]	ELISA	393	79	63	81	86	32
De Meyere (1990)[46]	lipos.	660	73	96	89	90	28
Dagnelie (1994)	lipos.	558	65	96	88	85	33

* two different tests studied
** only adults studied

sens = sensitivity
spec = specificity
lipos. = liposome test
aggl. = latex agglutination test
PV+ = predictive value positive test result
PV- = predictive value negative test result
ELISA = enzyme linked immunosorbent assay

Our results are in concordance with three studies investigating the same rapid test[38,40,46]. They are summarized in table 5.7 together with a number of other studies. The sensitivity found in

the age category four to 14 is the same as that assessed by Moyer in a pediatric population[40]. The sensitivity in patients aged 15 and older was low, but comparable to the figure in an adult population in the same study, with a prevalence of 8% GABHS[40]. De Meyere and Huck found sensitivities of about 70%[38,46]. The above mentioned sensitivities are much lower than those reported in some other studies[33]. McCusker and his colleagues reported a sensitivity of 91% in a mixed population of children and adults[34]. When subdividing according to age, the sensitivity was 89% for children and 97% for adults. Surprisingly, the difference they found between the age groups is opposite to the results of Moyer and of our study.

The specificity we found was high, and in agreement with other studies[44,46,60,61,62]. The three studies investigating the same test as that studied here showed specificities of 85%[38], 96%[46] and 100%[40] respectively (table 5.7). One study comparing five different tests reported a lower value for the specificity of an ELISA test: 63%[47, 63]. Predictive values vary considerably for the different studies[34,43,62]. The varying prevalences of GABHS in the populations studied are probably responsible for some of the differences encountered (table 5.7). The prevalence of 33% GABHS in our study is higher than in some other studies in a primary care setting[42,43,61], but lower than in Hoffmann's study[62]. In two of the three studies investigating the same test as that we studied, predictive values were also in the range we found[40,46]. Huck however reported a lower positive predictive value[38].

It should be appreciated that, in studies assessing the diagnostic value of a rapid test using a throat culture as a reference test, two more or less dependent tests are being compared[64]. The difference between observed and true sensitivity is small for values of prevalence of 30% and below. The error in the specificity is negligible[64]. Consequently, the actual sensitivity may even be slightly lower than the value assessed in our study.

Considering the antibody titres, the majority of GABHS-positive patients did not show a significant antibody rise. If one titre were taken into consideration, very high percentages of carriers would be assessed. With the analysis of three titres, the supposed carrier rate was comparable to other studies[18,27,45]. The false-negative culture rate (negative culture combined with increased titre) was in concordance with the 10% false-negatives usually mentioned[17]. For the high percentage of carriers, the following explanations were found in the literature:

(i) The presence of high initial titres has been reported as reducing the increase of the antibody titres[18]. Our results were in concordance with this.

(ii) Antimicrobial therapy may decrease the percentage of patients showing a signifi-

cant rise in antibody titre[65,66,67]. Other studies have failed to demonstrate this effect[18,27]. In our study the majority of patients were not treated with penicillin. Moreover, no significant difference was seen between the two groups.
(iii) The time lapse between the first and second sample has been reported to play a role[50,66,68]. The second specimen should be taken at least two weeks, but preferably longer, after the first sample[18]. An increase in the rate of 'definite' infection occurred when the time interval before measuring the second titre was extended[66]. Bisno stated that an interval of three weeks was necessary[68]. In conclusion, the taking of the second blood sample after 14 days in our study may have been rather early.
(iv) The virulence of the GABHS has decreased, and a hypothesis may be that the formation of antibodies is restricted to patients with serious infections only.

A study by Gerber and colleagues[69] demonstrated that antibody levels were not a gold standard. Since then, the role of antibody titres as a gold standard for a true infection has been called in question. As a result, nowadays, in many countries such as the USA, the clinical picture of a patient together with the result of a diagnostic test and a prompt response to penicillin treatment is considered sufficient evidence for differentiation between a carrier and a truly infected person (E.L.Kaplan, personal communication 1993).

The performance of more than one antibody test in our study resulted in an increase of the percentage of patients with serologic proof of infection from 25%, when only the best performing test was considered to 46% when the results of three titres were taken into account. This has been described by Kaplan, who stated that, by increasing the number of different types of antibodies for which one tests, the percentage of patients with 'definite' infection increases[18]. In one study, the ASPAT titre appeared to be especially useful for children[51]. However, in our study the results of the ASPAT titre were no better in patients aged 11 to 14; but since the number of children was small, a reliable conclusion cannot be drawn.

A comparison of a rapid test with antibody titres was found in only two other studies[45,46]. Gerber and colleagues[45] compared a latex agglutination test with the throat culture, ASO and antiDNase B titres. In our study, almost half the patients with negative rapid test results and a positive culture showed an antibody rise[45]. De Meyere found a non-significant association between the ASO-titre and the same rapid test that we studied[46]. In our study, the negative predictive value of the rapid test was high in comparison with the antiDNase B titres.

Limitations

The possible limitations of our study are the following. The reliability of the throat cultures was increased by taking two measures. First, the participating GPs were trained in the sampling of throat swabs. Second, all beta-haemolytic micro-organisms were re-analysed by a reference laboratory. Although no further quality control of the sampling of the swabs was performed, the results of the throat cultures did not differ substantially from studies in other countries.

A non-random selection was chosen for the sample of antibody titres. The aim of this selection was to increase the number of GABHS-positive patients, those most important in daily practice. We are aware of the possibility of bias. However, the difference in prevalence of GABHS between the total population and the patients whose antibody titres were analysed, differed only slightly (33% versus 40%; 95% CI of difference -2 to 16). The mean age of the selected group and the other patients was the same.

Conclusion

The impact of rapid tests on the management of sore throat has been studied by several authors[41,43,44,61]. The treatment rate for cases detected by the rapid test was markedly higher (84%) than the rate (44%) for cases only detected by culture[41]. On the other hand, a reduction in blind antibiotic prescribing should reduce unnecessary cost and antibiotic exposure[43]. However, some authors reported a tendency towards the prescribing of antibiotics in patients with negative tests[44,61,70]. As Redd stated[44]: 'Physicians were more concerned about overlooking cases of strep pharyngitis than they were about reducing the treatment of patients with non-strep pharyngitis. A more sensitive test with a higher negative predictive value would be necessary to prevent treatment of persons with non-strep pharyngitis'.

Because of the delay entailed by the throat culture result, the chance is high that, once a treatment with penicillin has been started, it is not discontinued when the result of the throat culture is negative[71,72,73]. Two studies reported continuation of penicillin in 40 to 60% of the patients with a negative throat culture[71,72]. Mäkela reported a discontinuation rate as low as one to three percent[73]. Her assertion should be borne in mind. These methods need to be evaluated according to their impact on treatment decisions considering all sore throat patients. If negative test results do not lead to the withholding of an antibiotic treatment, the combined cost of tests and prescriptions may become very high[73].

Perhaps the best way to reach a reduction in the number of unnecessary prescriptions would be the application of a model developed by Centor and colleagues[9,17]. This model makes use of several clinical signs and symptoms and of the prevalence of group A streptococcal pharyngitis in a population in order to assess the pre-test probability of streptococcal pharyngitis in patients. In our study, the same clinical features appeared to be useful in patients aged 15 and older, when making a preselection of patients with a higher probability of GABHS. In addition to this clinical picture, the rapid test has a sufficiently positive predictive value and a sufficient percentage of positive test results. The present Dutch level of antibiotic prescribing would be considerably reduced if the current guidelines were followed. The advantage of the use of a rapid test may be that, in the case of a negative test, the physician feels safer when telling a patient during a consultation that an antimicrobial drug is not needed[23]. This could signify an important way of reducing unnecessary antibiotic prescribing.

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Chapter 6

DO PATIENTS WITH SORE THROAT BENEFIT FROM PENICILLIN?

A randomized double blind placebo controlled clinical trial with penicillin V in family practice.

Zelfs indien zij hun ziekte als ernstig beschouwen, herkrijgen vele patienten hun gezondheid eenvoudigweg door de voldoening over een begrijpende dokter. (Hippocrates)

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Abstract

Background

The efficacy of penicillin V in the resolution of sore throat and fever and the return to usual daily activities was assessed in patients aged 4 to 60 years with sore throat. In countries in which the use of rapid antigen detection tests is not daily practice, the presence of group A beta-haemolytic streptococci (GABHS) can only be estimated; as a result there are arguments both for and against the blind prescription of antibiotics. Performance of a throat culture does not resolve the dilemma experienced in many countries, the more so since the decreased incidence of rheumatic fever since the 1950s.

Methods

Patients visiting 37 family practices in the Netherlands with an acute sore throat characterized by three of four relevant clinical features - fever, (tonsillar) exudate, anterior cervical lymphadenopathy and absence of cough - were included in a randomized placebo controlled trial. The randomized patients received either penicillin V or placebo for ten days in a double blind way. The outcome parameters were: degree of sore throat, presence or absence of fever, limitation of daily activities, the result of a throat culture after two days of therapy; short term complications, and new episodes within six months. Data were analysed according to the intention-to-treat principle.

Results

Of the 239 patients participating in the study, 121 received penicillin V and 118 received a placebo. Evaluation after two days showed a difference in resolution of sore throat with an odds ratio of 2.1 (95% CI 1.3-3.6) in favour of those treated with penicillin compared with the placebo. On subdividing into GABHS-positive (46%) and GABHS-negative patients, it was found that the faster resolution of sore throat was only present in the GABHS-positives (adjusted odds ratio 5.3; 95% CI 1.9-15.1). A significant difference was seen in the course of fever in GABHS-positive patients (adjusted OR 5.3; 95% CI 1.0-27.7). No difference was found in the limitation of daily activities between the two treatment groups. After one week, any clinical difference between the two groups had disappeared. A complication occurred in two patients (1 GABHS, 1 streptococcus group G) treated with placebo. In 111 patients harbouring GABHS, 4% of the patients treated with penicillin harboured GABHS at

the first follow-up visit, compared with 75% of the placebo treated patients. A new episode of sore throat or other upper respiratory tract infection occurred within six months in 11% of the placebo-group and 18% of the penicillin-group (NS).

Conclusions

Treating a patient with a sore throat with penicillin V is controversial. The disappearance of sore throat and fever in the first few days was a factor in favour of penicillin. However, there was no difference between both groups of patients in the limitation of their daily activities The difference in bacteriological cure rate for GABHS-positives was evident; the clinical relevance of this is limited though. When the purpose is the removal of the streptococci, testing is necessary in order to treat all GABHS-positive patients. As far as the clinical course is concerned treatment may be beneficial, but not necessary. The policy may differ according to the aim of the physician and the patient.

6.1 Introduction

Sore throat is a complaint frequently presented in family practice. A minority of the patients with sore throat have acute tonsillitis[1]. Dutch morbidity studies show an incidence of presented cases of acute tonsillitis of 20[2] to 25/1000[3] persons per year. In patients aged 15-24 the incidence is highest[1]. Sore throats occur even more often, as apart from tonsillitis common colds are included in morbidity studies. In the USA pharyngitis*[4] is responsible for over 40 million visits by adults to health care facilities each year[5].

Patients with a sore throat do not always have a bacterial infection[6,7]. In a recent study, nearly 50% of the patients with a sore throat, visiting their family physician were harbouring beta-hemolytic streptococci, 32% group A beta-hemolytic streptococci (GABHS)[6]. So one third of all patients complaining of a sore throat harboured GABHS, including carriers. If all patients with sore throat were treated, the majority of patients would be at risk of being treated unjustifiably.

There are several arguments in favour of antibiotic treatment. For example, shortening the clinical course of the disease is often postulated as a possible effect of

* In the USA the term pharyngitis is used for both acute pharyngitis and acute tonsillitis (ICPC codes R74.2 and R76.1), the former being of viral origin and the latter viral or bacterial[4].

penicillin, as is the reduction of complications such as acute rheumatic fever[8]. Several aspects need to be weighed against each other. On the one hand, in GABHS cases, there is the clinical improvement, the possible reduction of the risk of complications and the spread of the infection[9]. On the other hand, the negative aspects of antibiotic treatment include allergic reactions, other side effects, selection of resistant micro-organisms, increased susceptibility to new GABHS-infections[10], increase in medicalization and costs. Apart from this, the influence of antibiotics on recurrences of infection is unknown[11,12,13]. Few double blind placebo controlled studies have been performed[11,14,15,16,17,18,19] and only four of these were in family practice[15,16,18,19]. The quality and results of the latter were divergent.

The lack of scientific knowledge and cultural differences in the judgement of contrary arguments lead countries to operate widely different policies[20]. In the USA physicians are advised to perform a rapid streptococcal antigen detection test, and, if it is positive, to treat the patient[21]. If it is negative, the physician is advised to take a throat culture and choose between immediate treatment or waiting for the result of the culture. In the Netherlands, until now rapid tests and throat cultures have seldom been used (<2%)[20], because of no reimbursement of the cost of the rapid tests and the delay of three days or more for culture results. Diagnostic tests are used infrequently in many countries[20]. For instance in Austria, former East Germany, Poland, the Netherlands, Portugal and France between 0 and 7% of patients were tested for the presence of GABHS. In contrast, in Rumania, Israel, Yugoslavia, Finland and Greece tests were ordered for more than 75% of patients.

Instead, use is made of four clinical features originally described by Centor and colleagues[22] to differentiate between GABHS-positive and -negative patients. When four of the features - fever (history), anterior cervical lymphadenopathy, (tonsillar) exudate, and absence of cough - were present, the chance of a positive throat culture for GABHS in adults has been shown to be more than 50%; with three features the chance was 33%. In this study these features were used to make a pre-selection of patients at risk for a GABHS-infection[6].

This study was performed to assess the effectiveness of penicillin V compared with a placebo in patients with sore throat suspected of a GABHS-infection, in: (i) the clinical improvement of the patient: course of sore throat, ability to perform daily activities, fever, anterior cervical lymphadenopathy, and exudate; (ii) reducing the number of suppurative complications; (iii) eradicating the GABHS, and (iv) reducing the occurrence of new episodes of upper respiratory tract infections in the first six months after the treatment.

6.2 Methods

Eligible patients

Patients were recruited from 37 family practices during the years 1990 to 1992. The 43 family doctors in these practices participated for at least six months and no more than 18 months. The practices participating were located throughout the central part of the Netherlands, in both rural and more urbanized areas. In the Dutch health care system family physicians act as a gatekeeper to specialist secondary care[23], so they see every patient who visits a doctor with a sore throat. Patients were eligible for the study if they fulfilled the following criteria: acute sore throat, aged four to sixty years, and having three or four of the following clinical features[22]: fever (history), anterior cervical lymphadenopathy, (tonsillar) exudate and absence of cough. Excluded were patients who, in the opinion of their doctors, needed antimicrobial drugs because of imminent quinsy, a concomitant disease demanding antibiotic treatment or seriously impaired resistance. Other reasons for exclusion were: sore throat for more than 14 days, allergy to penicillin V, the use of antimicrobial drugs during the preceding four 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.

Base-line characteristics

At the initial visit of the participating patients the following clinical symptoms were recorded: degree of sore throat (grade 1 to 5), (reported) fever or not, degree of limitation of daily activities (grade 1 to 5**), and cough[24,25]. Patients were divided in two age categories, one group aged 4 to 14, and one group with patients of 15 years and older. Recorded from each patient's history were: duration of sore throat in days, absence from school or work, and number of consultations for a sore throat in the preceding year. The following symptoms were checked both from participants and non-participants through a physical examination: exudate of tonsils or pharynx and tenderness of anterior cervical lymph-nodes. Furthermore, age, sex, system of health

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** From McGill-Melzack questionnaire[24,25]:
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.

insurance (fee for service or sick fund capitation fee), and, where applicable, the reason for not participating were recorded.

Bacteriology

The family physician, who had been trained for this, took throat samples for culturing at the initial visit and again at the first follow-up visit after two days. The throat cultures were obtained with cotton swabs, streaked on both the tonsils or tonsillar fossae and the posterior pharyngeal wall, and then transported by mail in a modified Stuart medium. Within 48 hours 7% sheep blood agar (Oxoid) was inoculated and incubated at 37°C in aerobic and anaerobic condition overnight. Only colonies with heavy growth on the first isolation were taken into account. Isolated hemolytic streptococci were typed by using a latex agglutination test (Streptex,Murex). Other methods were used for strains which could not be identified[26]. All isolated beta-hemolytic bacterial strains were sent for confirmation to a reference laboratory (National Institute of Public Health and Environmental Protection). In cases of disagreement the cultures were re-analysed by the reference laboratory.

Follow-up

At the first follow-up visit after two days the patients were re-evaluated by the physician, without knowing the treatment or the result of the throat culture. The degree of sore throat and the degree of limitation of activities were recorded and the exudate and anterior cervical lymphadenopathy were re-assessed. The temperature was taken orally with a digital thermometer. A fever was defined as an oral temperature of 37.5°C or higher[27]. Again, a throat swab was taken for culturing.

Patients kept a diary for as long as the sore throat was present, up to ten days. In the diary the degree of throat complaints was recorded every night. Compliance with the trial medication was recorded daily for ten days. In case the trial medicine was not taken the reason for this was recorded.

At a second follow-up visit fourteen days after the initial visit, the patients were seen by the practice assistant and were asked about their complaints. If any complaints were present, the physician also saw the patient.

After six months a short questionnaire was sent to the participating practices for every patient included in the trial. Questions were asked regarding any encounters of sore throat or related conditions. A complication was defined as a return visit occurring within four weeks after the start of therapy with either a lymphadenitis, sinusitis, otitis media, quinsy, acute rheumatic fever or acute glomerulonephritis.

Treatment

Random and blind allocation was performed for either feneticillin (250 mg for four to nine years old, 500 mg for 10 years and older) or placebo (tablets or capsules, identical in shape and taste), three times a day, for ten days. Randomization on a one-to-one basis was performed for the age categories four to nine and 10-60 years separately. Every practice received numbered bottles with medication, ten per category, and bottles were given in a prescribed order.

Tablets of paracetamol (120 mg age four to six, 250 mg age seven to 12, and 500 mg age 13 years and older) were provided for two days and patients were instructed to take them, if they felt a need for them, up to a maximum of four times a day. At the first and second follow-up visit the remaining trial medication tablets were counted; paracetamol tablets were only counted on the first follow-up visit. Patients were asked not to take any other analgesic agents. If, however, they used other analgesics, or any other medicine, they were asked to record their use. A patient taking three or more analgesic tablets in two days was considered a "user". If a patient or a family physician felt the need for it, the code of the treatment could be broken by making a telephone call to the coordinator. The reason for breaking the code was recorded.

All adverse effects of the trial medication were recorded as reported by patients to their family doctors, or recorded in their diary. Complaints of nausea, vomiting, abdominal pain, diarrhea, rash and dizziness were considered to be adverse effects.

Outcome measurements

Primary outcome measurements were the resolution of sore throat, the disappearance of fever, and the resolution of limitation in daily activities. The percentage of negative cultures after two days was assessed. Failure was defined as a need for breaking the code during the first two weeks.

The occurrence of any suppurative or non-suppurative complications within four weeks, or the occurrence of new episodes of sore throat or other related upper respiratory tract infections within six months after the start of the therapy, were compared between the treatment and the control group.

Statistical analysis

The reliability of the coding of the data and the computerization was high: a concordance between two raters of more than 98% was reached. The primary data analysis was based on the intention-to-treat principle[28]: whether trial medication was taken or

not, the patients were analyzed according to their originally assigned treatment until after the follow-up at six months.

The data were analysed using the SPSS X program with the application of Chi-square statistics and unpaired T-tests[29]. The results are presented in numbers, percentages and 95% confidence intervals[30]. The EGRET statistical package was used for the calculation of odds ratios and adjusted odds ratios with a logistic regression[31].

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 ratios may be interpreted as a relative risk. The following factors were considered: (i) the result of the initial throat culture, (ii) the duration of throat complaints before the initial visit, (iii) the number of clinical features at onset, (iv) the age-category (4-14 years or 15 years and older), (v) the time between the initial and first follow-up visit ($\leq$ 60 hours or $>$ 60 hours), and (vi) the use of analgesic medication.

The course of the sore throat from day to day is presented graphically by means of a Kaplan-Meier curve[32]. End-points were defined as the moments at which a sore throat had disappeared. If a sore throat was present at day 2 and had disappeared by day 3, the interval would have been 2.5 days, etc. As for the intensity of the soreness of the throat, only patients with at least discomforting complaints were included in this part of the analysis. Patients were censored if follow-up stopped before the complaints had disappeared. The difference between the two curves is expressed in terms of the hazard ratio - that is to say, 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 and were adjusted for base-line incomparability[31,33]. The precision of the hazard ratio estimates was described by means of 95% confidence intervals obtained from the Cox model[31]. Controls for confounding and effect modification were performed on the same factors as in the logistic regression.

6.3 Results

A total of 401 patients fulfilled the inclusion criteria for the study. Fifty-seven patients (15%) fulfilled an exclusion criterion*. For 105 patients, informed consent was not received for reasons mentioned in table 6.1.

Table 6.1 Patients not participating: reasons for non-inclusion

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

Informed consent was given by 239 patients participating in the study. No difference with respect to age, sex, and system of health insurance was observed between participants, patients excluded for medical reasons, and other non-participants (table 6.2). However, a significant difference in the number of clinical features present between participants and excluded patients was observed.

* (1) use of antimicrobial drugs < four weeks ago: 18
(2) no penicillin allowed (presumed allergy?): 6
(3) need of penicillin according to the physician: 36
(4) earlier participation in trial: 2.
5 patients fulfilled both (1) and (3)

Table 6.2 Characteristics of participants, patients excluded for medical reasons, and other non-participants (n=401)

	participants (n=239)	patients excluded (n=57)	other non-participants (n=105)
age, mean (SD)	26 (12.0)	28 (13.5)	24 (12.4)
sex (%male)	39	32	41
presence 3 clinical features*(%)	61**	43**	57
insurance (% Public Health Plan)	69**	55***	67

* fever (history), anterior cervical lymphadenopath, (tonsillar) exudate, and absence of cough
** difference of proportion 18%; 95% CI of difference 4 to 33%
*** difference of proportion 13%; 95% CI of difference -1 to 28%

The participants' characteristics are summarized in table 6.3. One hundred and twenty one patients were randomized for penicillin and 118 for placebo. More children were included in the placebo-group, but the mean age of the penicillin treated patients did not differ from the mean age in the placebo-group (table 6.3). No difference was found in either the initial clinical presentation, or the percentage of visits for sore throat in the previous year. The results of the throat culture did not differ between the children in the two groups. Exudate was equally present in 75% of patients, and anterior cervical lymphadenopathy in 96%.

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

Table 6.3 Base-line characteristics of patients treated with penicillin V versus placebo (n=239)

	penicillin V n = 121		placebo n = 118	
demographic:				
mean age (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	
presenting symptoms:				
fever (history) at visit (% yes)	83		85	
degree sore throat** (median)	4		4	
presence of 3 clinical features (%)***	64		58	
number of days stayed at home, mean (SD)	0.92	(1.2)	0.88	(1.0)
duration of sore throat, in days, mean (SD)	4.1	(2.2)	4.0	(2.3)
limitation daily activities**** (median)	3		3	
culture result:				
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; 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; 5=totally incapacitated

Follow-up

At the first follow-up visit after two days, fewer of the patients treated with penicillin (36 of 117) than with placebo (57 of 117) still had a sore throat (OR 2.1) (table 6.4). For the group of GABHS-positive patients, a significant difference in the resolution of sore throat was seen between the two treatment groups (OR 3.8). There was no difference in the GABHS-negative patients. Adjustment for age category, the time lapse between the initial and first follow-up visit, and the use of analgesics made the effect of penicillin on the resolution of sore throat even more pronounced (adjusted OR 5.3). Adjustment for either the prior duration of sore throat or the number of clinical features at onset did not influence the result.

Table 6.4 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 (CI)

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

* and ** legend see table 6.3

\# adjustment for age, moment of return and use of analgesics

\#\# adjustment for age, prior duration of sore throat and use of analgesics

In the group as a whole, there was no difference in the presence of fever after two days between the penicillin-treated (14 of 94) and the placebo-treated patients (24 of 95) patients (table 6.4). In the GABHS-positive patients, however, for the patients treated with penicillin a significant difference in their favour was visible which remained after adjusting for age category, for the prior duration of sore throat and for

the use of analgesics (adjusted OR 5.3). Adjustment for the time lapse between the two visits, and for the number of clinical features at onset did not influence the result.

As for the presence of limitation of activities, neither in the whole group (penicillin: 37 of 117, placebo: 51 of 117), nor in patients with GABHS was a difference visible, even after adjusting for age category, for the prior duration of sore throat and for the use of analgesics (adjusted OR 1.7) (table 6.4). Adjustment for either the time lapse between the two visits, or for 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.

While a considerable decrease of exudate occurred within two days, no difference was visible in this respect between the two treatment groups (both 28%). The palpability or tenderness of anterior cervical lymph nodes barely decreased: 89% of the placebo patients and 86% of those on penicillin still showed these signs after two days.

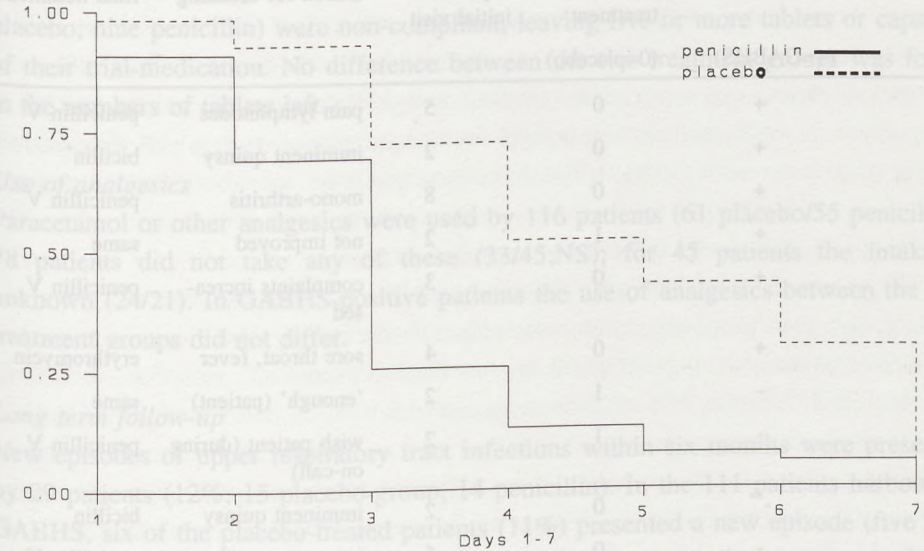
Bacteriological results

The difference in bacteriological results between the GABHS-positive patients treated with penicillin and the placebo-treated patients was evident: 4% of the penicillin group compared with 75% of the placebo group still harboured GABHS at the first follow-up visit (95%CI of difference 59 to 84).

Clinical course according to diary

Analysis of the diary registration of complaints was limited to the first six days, because nearly all patients had recovered by then. The crude hazard ratio for penicillin compared with placebo was 0.7 (95% CI 0.5 to 0.9). The course of the sore throat in GABHS positive patients in the first week is shown in fig. 6.1. Because twelve (four placebo, eight penicillin) patients had grade two sore throats the curve commences with less than 100% of the patients. In GABHS-positive patients, the crude hazard ratio was 0.4 (95% CI 0.3 to 0.7). When the factor of age was controlled for, the hazard ratio for treatment was 0.5 (95% CI 0.3 to 0.8). Other factors had no influence. The difference in the GABHS-positive patients was significant (p=0.003). The hazard ratio in the GABHS-negative group was 1.0 (95% CI 0.7 to 1.4).

Fig. 6.1 Proportion of GABHS-positive patients, still complaining of sore throat in penicillin group and placebo group according to diary registration (n=103)



Breaking code and adverse effects of treatment

The code of the treatment was broken for 12 patients (5.4%), usually three days after the initial visit, because there was no improvement or even an increase in clinical symptoms (table 6.5). Six placebo treated patients (A,B,C,E,F,I) (5% of the patients taking placebo) may be considered to be treatment failures. At the moment of deciding to break the code, the result of the initial throat culture was not known. One placebo treated patient (C) with GABHS recovered at first, but developed an arthritis of the elbow after eight days. Relevant findings were an elevated ESR (31 in one hour), and a slightly elevated ASO (338; normal ≤ 200). The patient received oral penicillin V and recovered within two weeks. One patient (B) with GABHS developed an imminent quinsy and was treated with benzathine-procaine penicillin i.m. The next day, spontaneous perforation of the abscess occurred and the patient recovered soon afterwards. Another patient (E) with GABHS felt worse after three days and showed lymphadenopathy and fever. The physician decided to shift the treatment to oral penicillin V and recovery followed.

Table 6.5 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 lymphnodes	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	increase 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

One placebo-treated patient (I) whose throat culture showed a group G streptococcus developed an imminent quinsy after two days. He received benzathine-procaine penicillin i.m., followed by oral penicillin. Patients A and F had their treatment shifted for less important reasons. No other suppurative complications were observed.

Adverse effects of the trial medication were seen in 10 patients (8%) in the penicillin-group: there were five cases of nausea and abdominal complaints, three of diarrhea, and two with other complaints. Of these, seven patients decided not to continue the trial medication, mostly between one and four days after the start of the treatment. One child could not swallow the tablets (placebo). Two patients treated with placebo and one treated with penicillin were withdrawn from the study after

three to five days because of infectious mononucleosis. No rashes were seen.

Compliance

Apart from the six (placebo) patients with a broken trial code, 14 patients (five placebo, nine penicillin) were non-compliant, leaving five or more tablets or capsules of their trial-medication. No difference between the two treatment groups was found in the numbers of tablets left.

Use of analgesics

Paracetamol or other analgesics were used by 116 patients (61 placebo/55 penicillin), 78 patients did not take any of these (33/45;NS); for 45 patients the intake is unknown (24/21). In GABHS-positive patients the use of analgesics between the two treatment groups did not differ.

Long term follow-up

New episodes of upper respiratory tract infections within six months were presented by 29 patients (12%; 15 placebo-group, 14 penicillin). In the 111 patients harbouring GABHS, six of the placebo-treated patients (11%) presented a new episode (five sore throat, one sinusitis) and 10 patients (18%) treated with penicillin (nine sore throat, one otitis media). No patients presented more than one episode. This means that no difference was observed between the two groups (95%CI of difference -6 to 21). A time lapse between the initial consultation and the moment of a new episode did not differ either.

Patients excluded

Of the 57 patients excluded, a significantly lower percentage had three clinical features (table 6.2). Of the 36 patients excluded because they needed antimicrobial drugs, 21 patients had four clinical features. In 13 of these 21 patients no follow-up is available, but the eight remaining patients were all treated with an antimicrobial drug, mostly penicillin V. Of these eight patients, five (three GABHS+) were excluded because of a peritonsillar infiltration or imminent quinsy. The remaining patients were treated for reasons not directly related to the sore throat.

6.4 Discussion

In this randomized double blind placebo controlled trial, the administration of penicillin V in patients with an acute sore throat and three or four relevant clinical features reduced the duration of sore throat by one to two days in patients with a throat culture positive for GABHS in comparison with placebo. This difference disappeared within one week. After 14 days, a sore throat was still present in 10% of the patients in each treatment group. If fever was present, it resolved significantly sooner in patients with GABHS. No difference was seen for other outcome parameters, such as limitations of activity, exudate or cervical lymphadenopathy. The treatment effect we found did not vary between practices.

The effect of the treatment on the results of the throat culture after two days was evident, but less pronounced than the effect described by Randolph and his colleagues in a pediatric population: 3 versus 100% difference[14]. However, that study only included children, 80% of whom were seen within 24 hours, and only GABHS-positive patients were evaluated. They found a larger clinical effect than in our study, where only 6% of the patients were seen within 24 hours, and 80% after 48 or more hours. An earlier resolution of the sore throat was also found in two other randomized double blind and placebo-controlled studies of sufficient size[15,16]. In one of these studies this effect was seen in both GABHS-positive and GABHS-negative patients[16]. In another study in a family practice setting, the effect of penicillin and placebo for three days, both with additional anti-inflammatory therapy, were compared in patients from 4 to 29 years old[18]. Evaluation after 24 hours showed no difference. The only significant difference was the amount of sore throat after 48 hours, in favour of the patients taking penicillin. The resulting management advice was to wait for the result of the throat culture, and to treat symptomatically in the meantime. Several other placebo-controlled clinical trials had major limitations: the treatment was not blind[34,35,36,37], the study size was small[17,34], or the setting incomparable, that is to say, in military camps[36,37]. In one study[19] baseline characteristics were missing, as were the results of the cultures in the majority of patients. Other clinical trials dealt with the comparison of penicillin V with another drug such as erythromycin or cephalosporins, either single or double blinded[38,39,40,41,42,43].

The duration of fever in our study was influenced to a lesser extent than in the study of Randolph and colleagues[14]. No difference was found in the reduction of cervical lymphadenitis. An earlier return to school or work is often given as the reason for treating patients with penicillin. This could not be confirmed by our

results.

In one GABHS-positive patient (B) treated with placebo, a complication was observed (table 6.5). The patient with the mono-arthritis (C) could not be considered as a case of rheumatic fever, because she only fulfilled two minor Jones criteria: arthralgia and elevated ESR[44]. The patient with the group G streptococcus (I) could have benefited from penicillin[45]. The other patients, whose treatment was shifted to penicillin, may also be called treatment failures, although in most cases the reasons for the shift did not seem very urgent. As expected in a study of this size, no non-suppurative complications were seen. The risk for acute rheumatic fever (ARF) cannot be neglected[46], although the chance is low: 1 in 30,000[47]. Nevertheless, in most cases prevention is impossible, because at least one third of the cases follow streptococcal infections that were asymptomatic[48,49], or were not presented. In only one - not a blind - study the occurrence of ARF was reduced by treating patients with penicillin i.m.[8]. The attack rate in patients with GABHS treated with penicillin i.m. was estimated at 10% of the risk without treatment[50]. A reduction of ARF after oral penicillin has never been demonstrated[51]. The reports of severe group A streptococcal infections, leading to a 'toxic shock-like syndrome' in many countries, including the Netherlands, has raised new discussions[52,53,54]. In 10% of 20 patients described by Stevens and his colleagues, GABHS were cultured from the pharynx[53]. At present the average patient with sore throat should not be considered to be at risk for this serious complication.

As in this study, the number of patients in most studies is too small for evaluation of the risk of very rare complications. Prevention of acute glomerulonephritis by treating patients with penicillin has never been shown[13]. The two cases of imminent quinsy, although not negligible, were too few to show a significant difference between the two treatment groups. No suppurative complications were found in two studies[11,15], one of which took place in primary care[15]. Until now, no studies have demonstrated opposite results.

The bacteriological effect of penicillin may be an advantage. In patients harboring group A beta-hemolytic streptococci, penicillin eradicates the bacteria within 24 to 48 hours[11,16,37,55]. Many authors state that, as a consequence, people treated with penicillin for 24 hours will no longer spread the micro-organism to others. A more rapid return to school or work would be the result. However, a reduction of the spread has never been demonstrated in a clinical study[11,56,57]. One can imagine that the effect of treating one patient is too small. As soon as patients return to school, they are colonized with new streptococci.

No significant difference between the treatment and the control group was observed regarding new episodes of upper respiratory tract infections. This means that the persistence of GABHS in untreated patients was not related to more frequent infections afterwards. Further, a possible reduction in antibody response in patients treated with penicillin did not lead to more frequent infections. Several researchers have studied the effect of a 48-hour delay in the initiation of penicillin therapy on the recurrence rate[11,58,59,60]. Gerber and colleagues[60] found no difference in recurrence rate, just as Rosenstein and colleagues[58] had found earlier. In contrast, however, two studies indicated fewer recurrences when treatment was delayed[11,59]. In Pichichero's study patients were seen within 24 hours, so, in contrast with our study, very little time had passed for antibody formation. Pichichero asserted that 'the reduction or elimination of natural antibody response to the infection may predispose patients to relapse or recurrence'[11].

The clinical relevance of our results vary according to the situation in which the physician is working. In everyday family practice, physicians have to deal with the whole spectre of sore throat patients, and clinical differentiation between GABHS-positive and other patients is only possible to a limited extent[6]. Should a diagnostic test be performed and the patient turns out to be GABHS-positive, a treatment with penicillin would result in an earlier resolution of the sore throat, of fever and in a bacteriological effect. But, in the case of overall penicillin-treatment, the majority of patients would be treated unjustifiably. For most developed countries, where complications of a GABHS-infection are rarely seen, we can conclude that the advantage of treatment with penicillin is limited.

In the Netherlands, prescription of antibiotics is less frequent (74% of tonsillitis cases)[61] than in most other countries, where prescribing an antimicrobial drug for a possible GABHS-tonsillitis is more common[20]. As we have shown, a lower prescription rate of antimicrobial agents is totally justified. The reasons for treating with antibiotics could benefit from reconsideration in countries with a higher prescription rate.

In many studies, except for that by Middleton[18], symptomatic treatment was not considered a possible contribution to well-being and recovery. We measured the use of analgesics as well, thereby increasing the external validity of our study because the use of analgesics occurs in everyday practice[51].

As possible limitations of our study, the following reservations need to be put forward. We measured compliance by counting medication and by having people record their daily intake in a diary. This method may be considered to be less

objective than the testing of urine, but counting gives more information about the number of doses omitted[62]. When considering the intention-to-treat principle, the original assignment is important. In this way, our conclusions apply to normal family practice.

By registering non-participants, we conclude that our data are capable of generalization to all Dutch patients, 4 to 60 years old, visiting their family doctor with a sore throat and having three or four of the specified clinical features and none of the exclusion criteria we used. Of the patients excluded for medical reasons, 18 patients had medical reasons which were more relevant. In five patients a complication was imminent. These five patients plus the 13 for whom no further information was available, represent a small but important group (4% of eligible patients) to which our results cannot be generalized. Fifteen other patients with three clinical features but without follow-up are considered a less important group.

Because of the exclusion of house-calls - for practical reasons - it is possible that a number of serious cases were not investigated. In a Dutch morbidity study, 22% of the visits for acute tonsillitis were house-calls[61]. However, the percentages of antimicrobial drugs prescribed in that study did not differ between house-calls and office visits: they were 72% and 78% respectively. This suggests that the degree of illness probably hardly differs. Moreover, the GPs participating in our study were asked to record house-calls on a selection form (appendix 2). According to this registration - which may be incomplete - only 5% of the eligible patients were seen at house-calls.

In patients with new episodes of upper respiratory tract infections no bacteriological investigations were performed, so nothing is known about the cause of the recurrence. However, because the incidence of new episodes did not differ between the two groups, this lack of information does not influence our conclusions.

Depending on the local situation, a management advice could be as follows. If the aim is to 'sterilize' the throat, one should use a rapid test, or wait for the result of the throat culture, and only treat GABHS-positive patients. A few days' delay in treatment is acceptable in most patients, because prevention of rheumatic fever later on is still possible[17,63]. In the meantime, the use of analgesics may add to the clinical well-being of the patient[18]. Besides, this procedure saves costs, less allergy is caused and a better antibody response is facilitated[17]. Even when the culture is positive, in many cases no serological evidence of infection is found. This is partly due to carriers, who do not need penicillin[64].

As for the clinical course, penicillin treatment is only necessary, in cases of

imminent complications. In patients with a higher probability of GABHS, that is to say, three or four clinical features, penicillin is beneficial, but it is not necessary for improving the resolution of sore throat and fever.

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GENERAL DISCUSSION AND CONCLUSIONS

De moeder van Hatice heeft pijn in haar hoofd en in haar keel. Daarom zit ze nu bij de dokter. Die gaat haar beter maken. Hatice is meegegaan. Dat vindt ze wel leuk. Bij de dokter is zoveel te zien. ... De dokter pakt een spatel uit de doos. 'Doet u uw mond even wijd open,' vraagt hij aan de moeder van Hatice, 'dan kan ik even naar uw keel kijken.' ... 'Wanneer ik klaar ben, mag jij ook even in de mond van mama kijken,' zegt de dokter, 'en straks mag jij ook een spatel in je mooie tasje stoppen.' ... Hatice is weer thuis. Ze pakt uit haar tasje de spatel, die de dokter haar heeft gegeven. 'Mama,' roept ze, 'heb je nog pijn?' 'Ja,'zegt mama tegen Hatice,' 'ik heb nog steeds keelpijn.' 'Doe je mond dan maar eens helemaal open; dan ga ik kijken of ik jou beter kan maken.'

Hatice's mother had a headache and a sore throat. That's why she was at the doctor's. He was going to make her better again. Hatice has come too. She likes that. There's so much to see at the doctor's. The doctor took a spatula out of the box. 'Open wide,' he said to Hatice's mother. 'Then I can look at your throat.'...' When I've finished, you can look at Mummy's throat too,' said the doctor, ' and then you can have a spatula to put in your nice little bag.'

When Hatice got home she took the spatula the doctor had given her out of her bag. 'Mama,' she called, 'do you still have pain?' 'Yes,' Mummy replied 'I've still got a sore throat.' 'Open your mouth wide then I can see if I can make you better.'

From: Ignace Schretlen, Eet jouw dokter ook patat?

GENERAL DISCUSSION AND CONCLUSIONS

7.1 Introduction

Although upper respiratory tract infections (URTIs) are common illnesses in general practice, many aspects regarding diagnosis and treatment are unknown. Physicians vary considerably in their management of patients with URTIs[1]. A general practitioner should take two important issues into consideration; whether to test patients with sore throat at all, and if so, whether to treat them with an antimicrobial drug. One issue is the assessment of the cause of the sore throat. Another issue is the weighing of the advantage of an antimicrobial treatment on the one hand, against the possible risk of that treatment on the other.

For decades, penicillin V has been considered a useful treatment in GABHS tonsillitis, with the aim of preventing complications[2]. With the decreased incidence of suppurative and non-suppurative complications, other factors have become more important. Recently, the influence of penicillin on the eradication of the GABHS as well as on the clinical course of a GABHS infection has been studied [3,4,5,6,7,8,9].

In this chapter, a summary is given of the aims of the study and the most important results. The aims of the study were:

1a. To obtain knowledge about the current microbiological flora in patients presenting with sore throat in general practice. The prevalence of GABHS and other micro-organisms in patients presenting with sore throat in Dutch general practice was assessed.

1b. To assess whether the four clinical features: fever (history) ≥38.5°C taken rectally, (tonsillar) exudate, anterior cervical lymphadenopathy and absence of cough, described by Centor and colleagues[10], were predictive of the presence of GABHS.

2. To assess the diagnostic value of a rapid group A streptococcal antigen detection test in general practice, with a throat culture as a reference test, and with antibody titres as a reference test.

3. To determine the effectiveness of penicillin V compared with placebo in patients aged 4-60 presenting with a sore throat, and clinically suspected of a GABHS infection. The following aspects were studied: (i) the clinical improvement of the patient; (ii) the occurrence of suppurative complications, (iii) the eradication of GABHS, and (iv) the occurrence of new episodes of upper respiratory tract infections in the first six months after the treatment.

In the section on etiology (7.2) the results of the study of the microbiological throat

flora (chapter 4) are summarized and discussed. In section 7.3 the results of the study of the diagnostic tests (chapter 5) are summarized. The question as to whether performing a rapid test contributes usefully to the management of sore throat in general practice is discussed. The results of the therapeutic study (chapter 6) are reviewed in section 7.4. The limitations of our study and the extent to which the findings can be generalized are discussed in section 7.5. In the final section (7.6) some general conclusions are drawn and guidelines are formulated for the management of sore throat in general practice. Some recommendations are given for future research.

7.2 Etiology

A great variety of micro-organisms was assessed in patients with sore throat[11] (chapter 4). The beta-haemolytic streptococci were predominant, with a prevalence of about 50%. GABHS were present in 32% of the study population, comparable to other recent studies in primary care[12,13]. This implies a decrease since the early 1960s, when 60% GABHS were found in patients with sore throat[14].

A variety of non-group A beta-haemolytic streptococci were cultured in our study, the relevance of which is not clear. Group C streptococcus has been described as a pathogen in other studies[15,16]. From our study we conclude that, at this moment, group C streptococcus (found in 7% of the patients) is not a pathogen to be treated in sore throat in Dutch general practice. Other beta-haemolytic streptococci were found in smaller percentages: group G in 4%, group B in 3%, group F in 1%, and other streptococci in 2%. Based on the clinical picture and course, we confirm other studies reporting their significance as limited[17,18,19,20].

Moraxella catarrhalis was found in 1% of the study population, but it is not considered a pathogen in sore throat[21]. The role as pathogens of the other micro-organisms found, such as *Candida albicans* (5%), *Staphylococcus aureus* (4%)[22], *Haemophilus influenzae* (2%)[22,23,24] and enterobacteriaceae (6%), is questionable. Until more is known about the clinical relevance of these organisms, a causal treatment is not advised. No micro-organisms were cultured in 30% of the patients, slightly fewer than the 40% reported by McMillan[20]. Some patients might have had a viral infection, since we did not perform virological diagnostic testing.

Since the four clinical features had not been developed or tested in a Dutch general practice setting, their diagnostic value required evaluation. This is particularly

true because Dutch GPs are used to relying on the clinical picture rather than cultures or rapid tests. The four clinical features - fever (history), (tonsillar) exudate, anterior cervical lymphadenopathy and absence of cough - were helpful in predicting the presence of GABHS. Forty-six percent of the patients with three or four clinical features harboured GABHS, compared with 21% of the patients with less than three features (95% CI of difference 18 to 33%). After stratification for age, the difference was only found in patients aged 15 and older: 43% and 18% respectively. No relationship between the clinical picture and the presence of GABHS was found in the youngest age category (4-14 years old).

Our results differ from those of several other authors[25,26,27]. Poses asserted that a clinical judgement is of little value, because physicians overestimate the probability of streptococcal pharyngitis[25]. In contrast, the negative predictive value of the clinical judgement was 88% in a study Stillström and colleagues performed in general practice[28]. They concluded that exclusion of GABHS aetiology on clinical grounds would more often be right than wrong. In our study, the negative predictive value of the clinical picture (that is, less than three features) was 79% in all patients, and 83% in patients aged 15 and older.

7.3 Diagnosis

In addition to the clinical picture, two diagnostic procedures for detecting GABHS for the management of patients with sore throat are available. One is the throat culture, seldom performed in Dutch general practice, because of the delay before the results are known. The second is the rapid group A streptococcal antigen detection test, also rarely used. When the rapid test was compared with the throat culture as a reference test, a sensitivity of 65% was found and a specificity of 96%. The predictive value of a positive rapid test result was 88%, and the predictive value of a negative test result was 85% in the population we studied (chapter 5). These results are comparable with other studies in primary care in which the rapid test has been related to the throat culture[29,30,31,32].

After stratification into the group of patients with three of four clinical features versus less than three features, the rapid test showed a better sensitivity (75%) in the first group of 247 patients. The four clinical features were especially useful for patients aged 15 and older; having three or four clinical features, their prior probability of GABHS was 43% (table 4.6). In 37% of these patients, the result of the rapid

test was positive, increasing the posterior probability of GABHS to 88%. In patients with a negative rapid test result, the probability decreased to 19%. In patients aged 15 and older with less than three features, the probability of GABHS was 18% (table 4.6). With a positive rapid test result, the posterior probability of GABHS in these patients increased to 85%, but a positive test result was seen in only 9% of the patients. With a negative rapid test result, the posterior probability decreased to 11%. In conclusion, rapid testing provided relevant additional information in patients aged 15 and older with three or four clinical features. In patients with less than three features, the additional value of testing was limited. No testing is advised in these patients, unless a physician wishes to treat all GABHS positive patients. In that case, 88% of the patients will be tested to no purpose.

In the age category four to 14 years old, the clinical features were not predictive: 62% of the patients with three or four clinical features harboured GABHS as opposed to 52% of the patients with less than three features (difference NS; see chapter 4). Altogether, the prior probability of GABHS in the youngest age category was 58%, irrespective of the clinical picture. When the result of the rapid test was positive, which occurred in 43% of these patients, the posterior probability of GABHS increased to 100% (table 5.3). In patients with a negative rapid test result, the probability decreased to 27%. In conclusion, testing provided important additional information in patients aged four to 14. False-positive test results may occur, however, because of the higher percentage of carriers found in children.

On comparing the throat culture with three antibody titres as a reference test, 46% of the GABHS positive patients showed a significant increase of one or more titres. This would imply a carrier rate of 54%. A significant increase of the titres was seen in 10% of the GABHS negative patients; they probably had false-negative cultures. Of the three antibody titres, the antiDNase B showed the best test results in terms of sensitivity and specificity when compared with the throat culture.

Recently, some authors have questioned the role of antibody titres as a gold standard of a true infection[6]. Currently, in many countries, such as the USA, the clinical picture of a patient together with the result of a diagnostic test and a prompt response to treatment with penicillin is considered sufficient for the differentiation between a carrier and a truly infected person (E.L. Kaplan, 1993; personal communication).

In conclusion, the diagnostic value of the rapid streptococcal antigen detection test investigated was moderate. This finding is in concordance with other studies in primary care. The test may be considered useful in patients aged 15 and older with a

more suspected clinical picture. In patients younger than the age of 15, testing is always considered useful, irrespective of the clinical picture.

7.4 Treatment

In the therapeutic study, patients presenting with sore throat, and having three or four clinical features were randomized in a double blind manner for a ten-day course of either penicillin V or placebo. The therapeutic study had the following results. In patients with a throat culture positive for GABHS treated with penicillin V, a resolution of the sore throat was seen between one and two days earlier than in GABHS positive patients treated with placebo. The duration of fever was reduced in the GABHS positive patients having a fever. No differences were seen between the two groups regarding other clinical parameters: ability to perform daily activities, anterior cervical lymphadenopathy, and exudate. Absence from work or school was not influenced by the treatment.

No suppurative complications were seen in patients treated with penicillin V. Two patients taking placebo - one GABHS positive and one harbouring group G streptococci - developed an imminent quinsy. The size of our study was too small to assess a significant difference. A larger study population is needed for definitive conclusions to be drawn.

The adverse effects of penicillin were mild, but they were nevertheless a reason for discontinuing the medication in 6% of the patients. As expected, the most striking effect of penicillin was the eradication of GABHS. Of the GABHS positive patients, only 4% harboured GABHS after two to four days of penicillin treatment, in contrast with 75% of the patients taking placebo. The presence of sore throat after one week or more, and the occurrence of new episodes of upper respiratory tract infections in the first six months after the treatment were the same, despite the persistent presence of the GABHS. Our finding is in contrast with the results of Pichichero and colleagues[7] who showed significantly more subsequent GABHS infections in patients treated at the initial office visit compared with patients whose treatment was delayed for 48 hours. Other authors[6,33] have reported results in accordance with ours.

The bacteriological effect of penicillin V is evident. In patients harbouring GABHS, penicillin eradicates the bacteria within 24 to 48 hours[7,14,34,35]. Many authors state that, as a consequence, people treated with penicillin for 24 hours no longer spread the organism to others[36]. In countries where this is considered to be

an important aspect, patients are allowed an earlier return to school or work. However, no clinical study has ever proven a reduction of the spread of the infection[7,37]. The effect of treating one patient would be small, especially a child who, on returning to school, would be colonized with new streptococci. In conclusion, the clinical significance of the eradication of GABHS is restricted.

In short, the treatment with penicillin resulted in earlier clinical resolution of sore throat and fever and rapid eradication of GABHS. The side effects and other elements not studied, such as induction of resistance, medicalization and cost, put the results in a different perspective. These aspects may be interpreted as in favour of or against penicillin, according to the value attached to such aspects.

7.5 Limitations of the study and extent to which it can be generalized

Some remarks concerning the reliability and validity of our data are needed to permit assessment of the value of our conclusions. Our study only included patients aged four to 60, so no conclusions may be drawn for patients below the age of four or above the age of 60. However, the incidence of acute tonsillitis in the age categories below four and above 60 is low[38].

The GPs who participated in the study were located throughout the Netherlands in both rural and urban areas. There is no reason to expect the patients eligible for the three parts of the study not to have been representative of the Dutch population presenting with sore throat to primary care. The patients participating in the study did not differ from the non-participants regarding demographic and clinical characteristics. We therefore conclude that our data are capable of being generalized to all Dutch patients aged four to 60, to whom none of the exclusion criteria are applicable, presenting with sore throat to primary care.

The throat culture played a central role in the three parts of our study. To increase the reliability of the throat cultures, two measures were taken. First, the participating GPs were trained in the sampling of throat swabs. Second, all beta-haemolytic micro-organisms were re-analysed by a reference laboratory (National Institute for Public Health and Environmental Hygiene).

For the sample of antibody titres analysed in the diagnostic study, a non-random selection was chosen. An intentional over-representation of the more suspected patients was selected so as to investigate more GABHS positive patients. The mean age of these patients and the non-selected patients did not differ.

For the therapeutic study, certain limitations require attention.
(i) We cannot generalize the results to patients who have been excluded for taking antimicrobial drugs less than four weeks previously.
(ii) Because - for practical reasons - house-calls were excluded, some serious cases may possibly not have been investigated. According to the registration of the participating GPs on a selection form (appendix 2), which may be incomplete, only 5% of the eligible patients were seen at house-calls.
(iii) Of the patients excluded, 34 needed antimicrobial drugs. Our results cannot be generalized to the five patients with an imminent quinsy.
(iv) The measuring of the use of analgesics improves the external validity of our study, because analgesics are taken regularly in daily life[39].
(v) The control of compliance by counting medication and by making patients record their daily intake gives more information about the number of omitted doses[40]. In this way our conclusions are closer to everyday general practice.
(vi) The applicability of our study in other countries and cultures depends on the difference encountered regarding several aspects. The Dutch general practice setting may imply a different behaviour of GPs, and different patient expectations. In our study, the duration of complaints before the initial visit was much longer than in some studies in other countries[5]. As a result, patients would be cured within a few days in any case. Another difference is the lower prescription rate of antimicrobial drugs in the Netherlands[1]. Patients possibly visit less frequently because they are not used to a routinely prescribed antimicrobial treatment.

7.6 Proposed management

'The optimal strategy depends on the physician's main objective.'

'Every treatment strategy is a compromise'
DeNeef P.

In this section, some important considerations for the management of patients with sore throat are reviewed and a management strategy for Dutch general practice and comparable settings in countries such as the UK and Scandinavia with the same risks of GABHS and the same views on the issues of testing and treating GABHS is outlined.

As indicated in section 7.1 two important issues should be taken into consideration; the question whether or not to test patients with sore throat, and whether or not to treat them with an antimicrobial drug. When considering the actual situation, the answer of whether or not to treat, may differ according to the purpose of the physician.

(i) If, in patients clinically suspected of GABHS, the physician wishes to shorten the duration of sore throat and maybe fever, rapid testing is advised, followed by treatment of patients whose test is positive.

(ii) If the purpose is eradication of GABHS, a rapid test is advised with treatment of patients with a positive test result. If in this situation the rapid test is negative, a back-up culture may be advised in order not to miss patients with false-negative test results.

(iii) If the aim is a supposed reduction of suppurative or non-suppurative complications, the decision depends on the incidence of these complications in the population. In the majority of developed countries complications are rarely seen, and the advantages and disadvantages of penicillin are more or less in balance. Then, the prevention of iatrogenic harm should be a major goal for practising physicians.

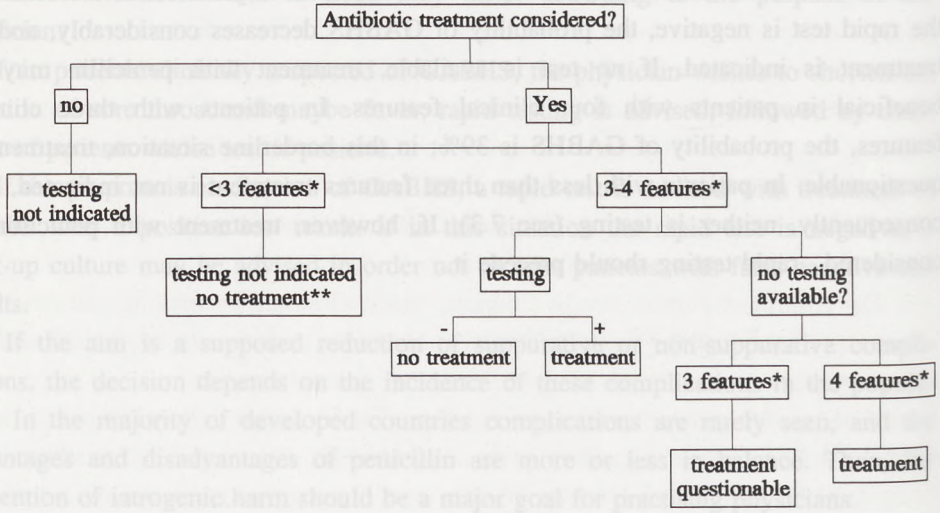
(iv) As far as a sooner return to school or work is intended, cultural differences play an important role. In many countries, as for instance the USA, the infectivity of patients is a reason for keeping them at home.

The advantages and disadvantages of various strategies were balanced against each other in a Dutch decision analysis for the management of sore throat. The results were: treat a patient with an antimicrobial drug without testing when the prior probability of GABHS is higher than 88%; do not treat a patient with a prior probability of below 40%; test the remaining patients[41]. In daily practice the first situation never occurs, which means that testing is advised in patients with a prior probability of 40% and higher. In patients with a positive diagnostic test, treatment with penicillin is advised; in patients with a negative test, no treatment is given.

In section 7.3 an outline was presented of the diagnostic value of the four clinical features, followed by testing with the rapid group A streptococcal antigen detection test. If eradication of GABHS is the main objective, a rapid test should be performed in all patients and patients with positive test results should be treated. Considering the moderate sensitivity, a back-up culture is advised if a physician wishes to treat all GABHS positive patients. If, instead, a more selective approach is preferred - which is the case in Dutch general practice - the following strategy is advised (fig. 7.1 and 7.2).

In patients aged 15 and older, the presence of three or four clinical features has a positive predictive value of 43%. If treatment with penicillin is considered, rapid testing provides additional information. If the result is positive, the probability of GABHS increases considerably, and penicillin treatment is justified. If the result of the rapid test is negative, the probability of GABHS decreases considerably, and no treatment is indicated. If no test is available, treatment with penicillin may be beneficial in patients with four clinical features. In patients with three clinical features, the probability of GABHS is 39%; in this borderline situation, treatment is questionable. In patients with less than three features treatment is not indicated, and consequently, neither is testing (see 7.3). If, however, treatment with penicillin is considered, rapid testing should precede it.

Figure 7.1: Optimal strategy for the management of sore throat in general practice. Patients aged 15 and older.

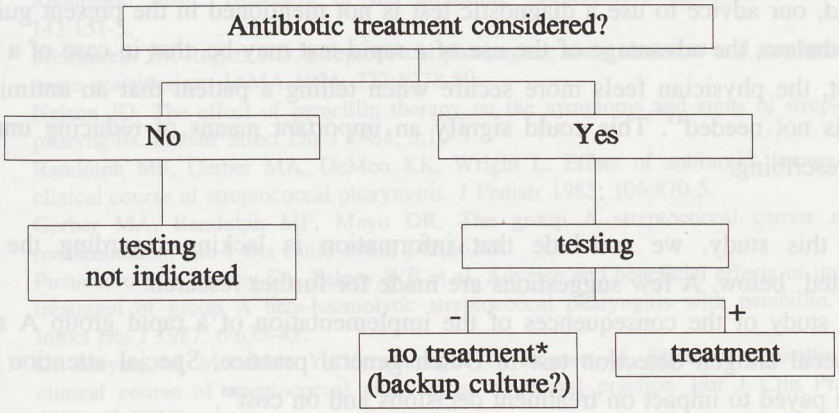


* clinical features: fever (history) ≥38.5°C taken rectally, (tonsillar) exudate, anterior cervical lymphadenopathy and absence of cough

** exceptions described below

In patients aged four to 14 years the prior probability of GABHS is higher, and the clinical features appear not to be predictive. Consequently, testing is advised in all situations where treatment with penicillin is considered (fig.7.2). It must, however, be borne in mind that patients with a positive test may well represent carriers whose recognition is impossible. Treatment of carriers with penicillin is not necessary. Consequently, in children who are not very ill, not testing and not treating is an acceptable alternative.

Figure 7.2: Optimal strategy for the management of sore throat in general practice. Patients aged 4-14.



* exceptions described below

The above mentioned strategy represents a maximum treatment policy. Our study has demonstrated that the long term advantage of treating a patient with penicillin V is limited. Patients with a GABHS infection who are not treated with penicillin improve just as well, but take a little longer. This means that not even all cases of proven GABHS infections, such as scarlet fever, should be treated with penicillin. If the patient is not very ill, neither testing nor treating a patient is justified.

As long as the risks in the Netherlands of GABHS infections do not increase through increased virulence of GABHS or an increased complication rate, a symptomatic treatment instead of an antibiotic treatment is quite adequate. There are, however, a few exceptions to this statement. High risk patients, such as patients with a history of acute rheumatic fever, an imminent suppurative complication, or a seriously impaired immune system, should be treated more readily. The choice of the

treatment in uncomplicated cases of GABHS tonsillitis is penicillin V, unless an allergy for penicillin V is present.

The strategy described is in general agreement with the Dutch practice guideline 'Acute sore throat'[42] of the Dutch College of General Practitioners, but with two exceptions. First, the patients aged four to 14 are not mentioned as a special group. Second, our advice to use a diagnostic test is not mentioned in the present guideline. Nevertheless, the advantage of the use of a rapid test may be, that in case of a negative test, the physician feels more secure when telling a patient that an antimicrobial drug is not needed[43]. This could signify an important means of reducing unnecessary prescribing.

From this study, we conclude that information is lacking regarding the topics indicated below. A few suggestions are made for further research.

- A study of the consequences of the implementation of a rapid group A streptococcal antigen detection test in Dutch general practice. Special attention should be payed to impact on treatment decisions and on cost[44].
- The performance of a cost-effectiveness analysis of the management of sore throat.
- A study of the clinical features predictive of GABHS in children.
- A study of a shorter duration of penicillin treatment, and its influence on the clinical course (is planned).
- A study of the spread of GABHS infection to those sharing house, school or work place, and the influence of penicillin V on the limitation of the spread
- A meta-analysis of studies regarding sore throat, with special attention for the occurrence of suppurative complications

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SUMMARY

Summary

The study described was conducted in the years 1990-1992 by 53 general practitioners (GPs) in 43 practices in the central region of the Netherlands. Patients presenting with sore throat were invited to participate in a study of the microbial throat flora and diagnostic tests. Patients fulfilling a specified clinical picture were also asked to participate in a therapeutic study.

In 1986, a decision analysis regarding sore throat was performed by the Utrecht Department of General Practice with the aim of developing a guideline for the management of sore throat in general practice. Several epidemiological aspects of sore throat in general practice were available. Nevertheless, a lack of data was encountered regarding the microbial throat flora and preferred diagnostic procedures. Moreover, dilemmas were encountered regarding treatment of sore throat, in view of the possible complications of group A beta-haemolytic streptococci (GABHS) and of the treatment.

Inclusion criteria for the study were: sore throat with a duration of less than 15 days, and age four up to and including 60. Presence of a language barrier was an exclusion criterion.

This study had the following aims:

1. To obtain knowledge regarding the current microbiological flora in patients presenting with sore throat in Dutch general practice.
2. To assess the diagnostic value of a rapid group A streptococcal antigen detection test in a primary care population.
3. To determine the effectiveness of penicillin V regarding clinical course, occurrence of complications, eradication of GABHS, and subsequent episodes of upper respiratory tract infections in patients aged 4-60 with sore throat, suspected of GABHS in general practice.

An important aspect of the study was the assessment of the diagnostic value of four clinical features described as predictive of infections with GABHS. In addition to the clinical picture, other diagnostic procedures are available. The throat culture has a number of limitations, the major disadvantages being the time lapse - between the taking of the swab and the result - and its limited diagnostic value. Rapid tests for the detection of GABHS represent a new technology without a time lapse. Diagnostic

values of these tests were reported as limited, but results of studies differ considerably.

The effect of an antimicrobial treatment on the clinical course has been investigated by many authors who have often reported an improved clinical recovery. Apart from this, penicillin V has been reported to have a major bacteriological effect, the significance of which is to be discussed. Since the suppurative and non-suppurative sequelae of GABHS infections have decreased, the importance of penicillin V regarding the management of sore throat is called in question.

The main results of the study are:

The bacterial growth assessed in patients with sore throat showed a great variety of micro-organisms. In 70% of the 598 patients, one or more micro-organisms were cultured from throat specimens. GABHS were found in 32% of these patients; other beta-haemolytic streptococci in 16%; and various other micro-organisms, such as Enterobacteriaceae, *Candida albicans* and *Staphylococcus aureus* in 22%. In 30% of the patients cultures remained negative. The clinical relevance of several micro-organisms, other than beta-haemolytic streptococci, remains to be determined.

Four clinical features - fever (history) ≥38.5°C rectally, (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough - were evaluated regarding the presence of GABHS. Of the 270 patients with three or four clinical features, 46% harboured GABHS in the throat, while in 328 patients with less than three features only 21% were GABHS positive. However, this relationship between presence or absence of clinical features and culture result was not found in the youngest age category (4-14 years old). More negative cultures were seen in the group with less than three clinical features. The four signs and symptoms described appeared to be helpful in predicting the probability of GABHS in patients aged fifteen years and older.

The diagnostic value of the rapid group A streptococcal antigen detection test was assessed in comparison with the throat culture and with an antibody titre. The rapid test performed moderately in an unselected population of 568 patients: the sensitivity was 65% with the throat culture as a reference test, the specificity 96%, the positive predictive value 88% and the negative predictive value 85%. After stratification into

the group of patients with three of four clinical features versus less than three features, the rapid test showed a better sensitivity (75%) in the first group of 247 patients. In addition to this clinical picture, the rapid test had a sufficient positive predictive value and a sufficient percentage of positive test results.

As for the antibody titres, the majority of GABHS-positive patients did not show a significant antibody rise. When one titre was taken into consideration, very high percentages of carriers were assessed. At the analysis of three antibody titres, 54% of the GABHS positive patients did not show a significant increase in any of the three titres. The resulting carrier rate of 54% is comparable with other studies.

The rapid group A streptococcal antigen detection test may provide additional information in patients with three or four clinical features, with a higher probability of GABHS. The advantage of the use of the rapid test may be that, in the case of a negative test, the physician feels safer in telling the patient during the consultation that an antimicrobial drug is not needed. This could signify an important means of reducing unnecessary antibiotic prescribing.

Nevertheless, these tests still need to be evaluated according to their impact on treatment decisions considering all sore throat patients. In some studies the discontinuation of the penicillin already started was assessed as low as one to three percent in patients whose throat culture appeared negative. If negative test results do not lead to withholding an antibiotic treatment, the combined cost of tests and prescriptions may become very high.

The therapeutic study was performed in 239 patients clinically suspected to be more likely of having a GABHS infection. Patients presenting with sore throat, characterized by three or four relevant clinical features, were included - after informed consent - in a randomized double blind placebo controlled trial comparing the effectiveness of penicillin V with placebo. Outcome parameters were the degree of sore throat, presence or absence of fever, the degree of limitation of daily activities, and the result of the throat culture after two days of therapy. Other parameters were short term complications, and new episodes of upper respiratory tract infection within six months. Of the 239 patients participating, 121 received penicillin V and 118 received placebo. Evaluation after two days showed a difference in resolution of sore throat in GABHS positive patients in favour of those treated with penicillin compared with placebo (adjusted odds ratio 5.3). A significant difference was seen in the resolution

of fever in GABHS-positive patients (adjusted OR 5.3). No difference was observed in the degree of limitation of daily activities between the treatment and the control group. After one week, any clinical difference between the treatment and the control group had disappeared.

In the GABHS negative patients no difference in clinical cure between the two groups was seen. A complication occurred in two patients - one harbouring GABHS, one streptococcus group G - treated with placebo. The number of patients studied was too small to be able to assess a significant difference in the complication rate between the two groups.

In 111 patients harbouring GABHS, 4% of the patients treated with penicillin harboured GABHS at the first follow-up visit after two days, compared with 75% of the placebo treated patients. Nevertheless, a new episode of sore throat or other upper respiratory tract infection occurred in 11% of the placebo group and 18% of the penicillin group within six months (difference NS).

Treating a patient with a sore throat with penicillin V is controversial. When the purpose is the removal of the streptococci, testing is necessary in order to treat all GABHS positive patients. As far as the clinical course is concerned treatment may be beneficial, but not necessary. The policy may differ according to the aim of the physician and the patient.

A general conclusion is formulated using the results of the three parts of the study described above.

- The use of the four clinical features (see above) in patients aged 15 and older is considered useful for the differentiation between a higher and a lower probability of GABHS.
- The rapid test has additional value in patients aged 15 and older having three or four clinical features.
- In patients aged 4 to 14, the clinical features appeared not to be helpful for the differentiation between GABHS and other causes. In these patients a rapid test may have additional value irrespective of the clinical picture.
- A treatment with penicillin is only considered necessary in case of an imminent complication. At the same time, treatment is beneficial in patients with a probability of GABHS above 40%, with the aim of an earlier clinical cure.

The management strategy of sore throat in general practice proposed is:

- If for patients aged 4 to 14, presenting with sore throat antimicrobial treatment is considered, test all patients, followed by treatment with penicillin V of patients with a positive test result.
- If for patients aged 15 and older, presenting with sore throat antimicrobial treatment is considered, a clinical preselection is advised, followed by a rapid test in patients with three or four clinical features. If the test is positive, treatment with penicillin V should follow. If the test is negative, no treatment is advised.

In **Chapter 1** some epidemiological aspects of sore throat in general practice are described. The lack of data regarding the microbial throat flora and diagnostic procedures are indicated. Dilemmas regarding treatment are summarized. The development of a guideline and a decision analysis regarding sore throat are described.

In **Chapter 2** the current knowledge about the epidemiology of sore throat is reviewed. The incidence of sore throat and acute tonsillitis is presented and discussed, as well as of the possible complications of the group A beta-haemolytic streptococci (GABHS). The etiology of sore throat, and the pathogenicity of other micro-organisms cultured are reviewed. The relevance of four clinical features for the prediction of GABHS is described. The limitations of the throat culture are reviewed and rapid tests for the detection of GABHS described. The natural course of GABHS infections in the throat is described, as well as the effect of an antimicrobial treatment on the clinical course.
Current management and possible management strategies are reviewed.

Chapter 3 provides an outline of the study procedures, and of the base-line characteristics registered. The populations in the different parts of the study, as well as the non-participants are described, and shown in a flow-chart.

In **Chapter 4** the bacterial growth of the patients studied is described. The four clinical features - fever (history) ≥38.5°C rectally, (tonsillar) exudate, anterior cervical lymphadenopathy, and absence of cough - were evaluated for the presence of GABHS.

Chapter 5 describes the diagnostic value of the rapid group A streptococcal antigen detection test, compared with the throat culture and with an antibody titre. The rapid

test performed moderately in an unselected population of 568 patients, but a higher sensitivity in the group of 247 patients with three or four clinical features. The rapid test may provide additional information in patients aged 15 and older with three or four clinical features. In younger patients, the rapid test has additional value irrespective of the clinical picture.

In **Chapter 6** the therapeutic study in 239 patients presenting with sore throat and suspected of a GABHS infection is described. The effectiveness of penicillin V compared with placebo is assessed in 121 patients receiving penicillin V and 118 receiving placebo. Evaluation after two days showed a difference in resolution of sore throat and of fever in GABHS positive patients in favour of those treated with penicillin, compared with placebo. After one week any clinical difference between the treatment and the control group had disappeared. A significant difference was found in the eradication of GABHS in the patients originally harbouring GABHS. A new episode of sore throat or other upper respiratory tract infection within six months occurred equally in both groups.

In **Chapter 7** the aims of the study are reviewed in the light of the results obtained. The extent to which the study can be generalized and the limitations of the study are described. A management strategy of sore throat in general practice is proposed. Last but not least, from our study several suggestions for future research have emerged.

Samenvatting

Het onderzoek waarvan in dit proefschrift verslag wordt gedaan, is uitgevoerd in de jaren 1990 tot 1992. Medewerking is verleend door 53 huisartsen in 43 huisartspraktijken, merendeels in Midden-Nederland, met uitlopers in Noord-Brabant en Twente. De duur van de deelname per praktijk liep uiteen van zes tot 18 maanden. Aan alle patiënten die met keelpijn bij hun huisarts kwamen, is gevraagd of ze wilden deelnemen aan een onderzoek naar de bacteriele flora in de keel, en naar de waarde van een diagnostische test voor het aantonen van beta-haemolytische streptococcen van groep A. Patiënten die voldeden aan een omschreven klinisch beeld werden bovendien uitgenodigd mee te doen aan een therapeutisch onderzoek.

Het onderwerp bovenste luchtweginfecties is sinds het midden van de jaren tachtig onderwerp van onderzoek bij de Utrechtse Vakgroep Huisartsgeneeskunde. Zo is ondermeer in 1986 een besliskundige analyse uitgevoerd betreffende acute keelpijn. Doel was een richtlijn te ontwikkelen voor het beleid bij keelpijn in de huisartspraktijk. Over de epidemiologie van keelpijn was een aanzienlijke hoeveelheid gegevens voorhanden. Toch ontbraken er gegevens, onder andere aangaande de huidige microbiele flora in de keel en mogelijke diagnostische procedures. Tevens bestond er een dilemma met betrekking tot het behandelen van keelpijn, met het oog op mogelijke complicaties van de beta-haemolytische streptococcen van groep A (-GABHS) enerzijds en van de therapie anderzijds.

Insluitingscriteria voor het onderzoek waren: keelpijn gedurende maximaal 14 dagen, en leeftijd vier tot en met 60 jaar. Aanwezigheid van een taalbarriere vormde een uitsluitingscriterium.

Het onderzoek had de volgende doelstellingen:

1. Het verwerven van kennis betreffende de huidige microbiele keelflora in Nederland bij patiënten die met keelpijn hun huisarts bezoeken.
2. Vaststellen van de diagnostische waarde van een snelle antigeen test voor het aantonen van beta-haemolytische streptococcen van groep A in een eerstelijnspopulatie.
3. Het vaststellen van de effectiviteit van penicilline V met het oog op het klinisch beloop, het optreden van complicaties, het uitroeien van de GABHS, en het optreden van nieuwe episoden van bovenste luchtweginfecties, bij patiënten van vier

tot en met 60 jaar met keelpijn in de huisartspraktijk, die worden verdacht van een infectie met GABHS.

Een belangrijk onderdeel van het onderzoek was het vaststellen van de diagnostische waarde van een viertal klinische kenmerken, die eerder in de literatuur beschreven zijn als voorspellend voor infecties met GABHS. Naast het klinisch beeld zijn andere diagnostische mogelijkheden aanwezig. De keelkweek heeft een aantal beperkingen, met name het tijdsverloop tussen het afnemen van de kweek en de uitslag, en de beperkte diagnostische waarde. Snelle tests voor het vaststellen van GABHS vormen een nieuwere techniek, waarbij geen tijdverlies optreedt. De diagnostische waarde van deze tests blijkt tot nu toe matig, maar de resultaten van onderzoek lopen sterk uiteen.

Vele auteurs hebben de invloed van een behandeling met antibiotica op het klinisch beloop nagegaan; veelal werd een bespoediging van het herstel gerapporteerd. Tevens is een belangrijk bacteriologisch effect van penicilline beschreven, waarvan de betekenis ter discussie staat. Sinds de purulente en niet-purulente complicaties van GABHS-infecties in aantal zijn afgenomen, wordt het belang van penicilline bij de behandeling van keelpijn ter discussie gesteld.

De belangrijkste resultaten van het onderzoek zijn:

De microbiele flora, aangetroffen bij patiënten met keelpijn, liet een groot aantal verschillende micro-organismen zien. Bij 70% van de 598 patiënten zijn een of meer micro-organismen gekweekt uit de keel. Van de 598 patiënten had 32% GABHS in de keelkweek en 16% andere beta-haemolytische streptococcen. Bij 22% van de patiënten zijn diverse andere micro-organismen gevonden, zoals Enterobacteriaceae, Candida albicans en Staphylococcus aureus. Bij 30% van de patiënten bleef de kweek negatief. Het klinische belang van verschillende micro-organismen, anders dan de beta-haemolytische streptococcen van groep A, dient nog te worden vastgesteld.

Een viertal klinische kenmerken - (recente) koorts $\geq$ 38.5°C rectaal, (tonsillair) exsudaat, gezwollen voorste cervicale lymfklieren en afwezigheid van hoest - zijn onderzocht met het oog op aanwezigheid van GABHS. Van 270 patiënten met drie of vier van deze klinische kenmerken had 46% GABHS in de keelkweek, terwijl van 328 patiënten met twee of minder kenmerken slechts 21% GABHS in de keel had.

Deze samenhang tussen aanwezigheid of afwezigheid van klinische kenmerken en kweekresultaat was echter niet aanwezig bij de jongste leeftijdsgroep van vier- tot 14-jarigen. Meer negatieve kweken werden gezien in de groep met twee of minder klinische kenmerken. Bij patiënten van 15 jaar en ouder bleken de vier bovengenoemde symptomen zinvol voor het voorspellen van de kans op GABHS.

De diagnostische waarde van de snelle groep A streptococcen antigeen test is nagegaan in vergelijking met de keelkweek en met een antilichaam titer, te weten de anti-DNase B titer (zie onder). De snelle test gaf een matig resultaat te zien bij een ongeselecteerde populatie van 568 patiënten: de sensitiviteit was 65% met de keelkweek als referentietest, de specificiteit 96%, de voorspellende waarde van een positieve test 88% en de voorspellende waarde van een negatieve test 85%. Na splitsing in de groep patiënten met respectievelijk drie of vier klinische kenmerken versus twee of minder kenmerken, liet de snelle test een betere sensitiviteit (75%) zien in de eerste groep van 247 patiënten. Toegevoegd aan dit klinische beeld had de snelle test een voldoende positief voorspellende waarde en een voldoende percentage positieve test resultaten.

De meerderheid van de GABHS-positieve patiënten liet geen significante antilichaamtiterstijging zien. Indien een van de drie titers: antistreptolysine titer (AST), antistreptococcen groep A polysaccharide titer (ASPAT) en antideoxyribonuclease B (anti-DNase B) afzonderlijk werd bekeken, was een laag percentage significante titerstijgingen, ofwel een hoog percentage dragers te zien. Indien de drie titers tegelijk werden bekeken en een significante stijging van één titer als positief werd beschouwd, had 54% van de GABHS-positieve patiënten geen enkele significante stijging. Dit percentage dragers (54%) is vergelijkbaar met andere studies.

De snelle groep A streptococcen antigeen test kan aanvullende informatie verschaffen bij patiënten met drie of vier klinische kenmerken, die een hogere kans hebben op GABHS. Het voordeel van het gebruik van de snelle test kan zijn, dat een arts bij een negatieve uitslag met een gerust hart kan zeggen dat een antibioticum niet nodig is. De test zou een belangrijk hulpmiddel kunnen zijn bij het terugdringen van het onnodig voorschrijven van antibiotica.

Niettemin zullen deze tests nog moeten worden geevalueerd met betrekking tot hun invloed op het al dan niet voorschrijven van antibiotica bij alle keelpijn patiënten. In sommige studies bleek een onderbreking van een eenmaal gestarte penicilline kuur bij slechts een tot drie procent van de patiënten wiens keelkweek negatief

was, plaats te vinden. Als een negatief test resultaat de beslissing tot het voorschrijven van antibiotica niet beinvloedt, worden de totale kosten van tests en recepten erg hoog.

Het interventie-onderzoek vond plaats bij 239 patiënten die op klinische gronden meer verdacht werden van een GABHS-infectie. Patiënten die met keelpijn bij hun huisarts kwamen en die drie of vier relevante klinische kenmerken hadden, werden na toestemming ingesloten in een gerandomiseerde dubbelblinde en placebo-gecontroleerde studie, waarin de effectiviteit van penicilline is vergeleken met placebo. Effect parameters waren de aanwezigheid van keelpijn na twee dagen, aan- of afwezigheid van koorts, de beperking van dagelijkse activiteiten en het resultaat van de keelkweek na twee dagen behandeling. Andere parameters waren complicaties op korte termijn en nieuwe episoden van bovenste luchtweginfecties in de eerste zes maanden na de studie. Van de 239 deelnemende patiënten kregen er 121 feneticilline en 118 placebo. Evaluatie na twee dagen liet een verschil zien in het verminderen van de keelpijn bij GABHS-positieve patiënten in het voordeel van de met penicilline behandelde patiënten vergeleken met placebo (adjusted odds ratio 5.3). Een significant verschil werd ook gezien wat betreft het verdwijnen van de koorts bij GABHS-positieve patiënten (adjusted odds ratio 5.3). Er was geen verschil te zien in het verloop van de beperking van dagelijkse activiteiten tussen de behandelgroep en de controle groep. Na een week waren de verschillen tussen de beide groepen verdwenen.

Bij de GABHS-negatieve patiënten werd geen verschil in klinisch herstel gezien tussen de twee groepen. Een complicatie werd gezien bij twee met placebo behandelde patiënten, een met GABHS in de keelkweek, een met streptococcus groep G. Beide patienten herstelden voorspoedig na gerichte behandeling. Het aantal patiënten in dit onderzoek was te klein om een significant verschil in aantal complicaties tussen de twee groepen te kunnen vaststellen.

Bij 111 GABHS-positieve patiënten, had 4% van de met penicilline behandelde patiënten nog een GABHS in de kweek bij het tweede consult na twee dagen, vergeleken met 75% van de met placebo behandelden. Desondanks werd een nieuwe episode van keelpijn of een andere bovenste luchtwegaandoening in de volgende zes maanden gezien bij 11% van de placebo groep en 18% van de penicilline groep (verschil NS).

Het behandelen van een keelpijn-patient met penicilline is controversieel. Als verwijdering van de streptococcen het doel is, is testen noodzakelijk om alle GABHS-positieve patiënten te kunnen behandelen. Met het oog op het klinisch beloop kan behandeling een gunstig effect hebben, maar noodzakelijk is deze niet. Het beleid kan uiteenlopen al naar gelang het doel van de arts en de patient.

Een algehele conclusie op grond van de drie delen van het onderzoek is als volgt:

- Het gebruik van de vier klinische kenmerken (zie boven) bij patiënten van 15 jaar en ouder is zinvol voor het onderscheid tussen een hogere en een lagere kans op GABHS.
- De snelle streptococcen test heeft aanvullende waarde bij patiënten van 15 jaar en ouder met drie of vier klinische criteria.
- Bij patiënten van vier tot 14 jaar bleken de klinische criteria niet zinvol voor het differentieren tussen GABHS en andere oorzaken. Bij deze patiënten heeft een snelle test aanvullende waarde ongeacht het klinisch beeld.
- Behandeling met penicilline wordt alleen noodzakelijk geacht bij een dreigende complicatie. Tegelijkertijd kan behandeling een gunstig effect hebben bij patiënten met een kans op GABHS boven de 40%, met het oog op een sneller klinisch herstel.

Het voorgestelde beleid bij keelpijn in de huisartspraktijk is als volgt:

- Als bij patiënten van vier tot 14 jaar met keelpijn een behandeling met antibiotica wordt overwogen door de huisarts, wordt toepassing van een snelle test bij alle patiënten geadviseerd, gevolgd door behandeling met smalspectrum penicilline van patiënten met een positief test resultaat.
- Als bij patiënten van 15 jaar en ouder met keelpijn een behandeling met antibiotica wordt overwogen door de huisarts, wordt een selectie vooraf op klinische gronden geadviseerd, gevolgd door een snelle test bij patiënten met drie of vier klinische criteria. Als de test positief is, volgt behandeling met smalspectrum penicilline. Als de test negatief is, wordt geen behandeling geadviseerd.

In **Hoofdstuk 1** worden enkele epidemiologische aspecten van keelpijn in de huisartspraktijk beschreven. Een gebrek aan gegevens betreffende de microbiele keelflora en diagnostische procedures wordt vastgesteld. De dilemma's betreffende de behandeling worden samengevat. De ontwikkeling van een richtlijn en een beslis-kundige analyse betreffende keelpijn worden beschreven.

In **Hoofdstuk 2** wordt een overzicht gegeven van de huidige kennis over de epidemiologie van keelpijn. De incidentie van keelpijn en acute tonsillitis worden weergegeven en besproken, evenals het voorkomen van mogelijke complicaties van de GABHS. De etiologie van keelpijn en het al dan niet pathogeen zijn van andere gekweekte micro-organismen wordt weergegeven. Het belang van vier klinische kenmerken voor de voorspelling van GABHS wordt beschreven. De beperkingen van de keelkweek worden genoemd, en snelle tests voor het vaststellen van GABHS besproken. Het natuurlijk beloop van GABHS-infecties in de keel wordt beschreven, evenals het effect van een behandeling met antibiotica op het klinisch beloop. Het huidige beleid en mogelijke behandelingsstrategieën worden weergegeven.

Hoofdstuk 3 geeft een overzicht van de in het onderzoek gebruikte procedures en van de basis kenmerken die zijn vastgelegd. De populaties in de verschillende delen van het onderzoek worden beschreven en weergegeven in een stroomdiagram. De niet-deelnemers worden eveneens beschreven.

In **Hoofdstuk 4** wordt de bacteriele groei bij de onderzochte patiënten beschreven. De vier klinische kenmerken - (recente) koorts $\geq$ 38.5°C rectaal, (tonsillair) exsudaat, gezwollen voorste cervicale lymfklieren en afwezigheid van hoest - zijn geëvalueerd met betrekking tot de aanwezigheid van GABHS.

Hoofdstuk 5 beschrijft de diagnostische waarde van de snelle groep A streptococcen antigeen test, in vergelijking met de keelkweek en met een antilichaam titer. De snelle test geeft aanvullende informatie bij patiënten van 15 jaar en ouder met drie of vier klinische kenmerken. Bij jongere patiënten heeft de snelle test aanvullende waarde ongeacht het klinisch beeld.

In **Hoofdstuk 6** wordt het behandelings-onderzoek beschreven uitgevoerd bij 239 patiënten die met keelpijn de huisarts bezochten en verdacht werden van een GABHS-infectie. De effectiviteit van smalspectrum penicilline bij 121 patiënten is vergeleken met placebo bij 118 patiënten. Evaluatie na twee dagen liet een verschil zien in het verdwijnen van de keelpijn en de koorts bij GABHS-positieve patiënten ten gunste van de met penicilline behandelden. Na een week was elk klinisch verschil tussen de behandelgroep en de controle groep verdwenen. Een significant verschil is gevonden voor het verwijderen van de GABHS bij de aanvankelijk GABHS-positieve patiënten. Een nieuwe episode van keelpijn of andere bovenste luchtweginfecties binnen zes

maanden trad evenveel op in beide groepen.

In **Hoofdstuk 7** worden de doelstellingen van het onderzoek besproken in het licht van de gevonden resultaten. De mate waarin het onderzoek kan worden gegeneraliseerd en de beperkingen van de studie worden beschreven. Een voorstel wordt gedaan voor het beleid bij keelpijn in de huisartspraktijk. Tot slot komen uit dit onderzoek enkele suggesties naar voren voor toekomstig onderzoek.

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Appendix 1

Patient information for therapeutic study

This practice is currently participating in a study of the cause and treatment of sore throat. Your physician has just asked you to participate in this study. You will find some information about the study in this letter. If after reading it you still have some questions, you can put them to your physician or the practice assistant.

Why is this study being performed?
Sore throat has many causes. Most of the causes are quite innocent and treatment with antimicrobial drugs is unnecessary. The complaints resolve spontaneously. However, in some cases specific bacteria cause a tonsillitis. In those cases penicillin or an analgesic drug may be given. Even if no treatment is given, the patient recovers within one week. Antimicrobial drugs are often unnecessary. In this study we wish to gain knowledge regarding sore throat's causes and the preferred treatment.

The study will be carried out by your general practitioner (GP), in collaboration with the Utrecht University Department of General Practice. Children aged 4 years and older, and adults up to and including the age of 60 who have had a sore throat for no more than 14 days are being studied. The examination your GP has just performed has revealed the possibility of a streptococcal throat infection. Your GP will explain to you what this means. However, it is not yet certain which treatment is preferable in these cases, so it is very important to study this question. That is why your GP is asking you to participate in the therapeutic study.

If you would like more information you may ask for it, and should you not wish to participate, you may say so. During the study it is important to follow the instructions carefully.

This is what is required of patients participating in the study:
- at the usual visit your GP will ask a few more questions and perform a physical examination;
- the taking of two throat swabs;
- an extra visit to your GP on the third day, during which two more throat swabs will be taken;

- the drawing of two blood specimens, one at the first visit and one after 14 days;
- the keeping of a diary of complaints for ten days. This diary is handed over to the practice assistant at the second follow-up visit after 14 days.

After you have given your consent, your GP will ask you a few more questions and perform a physical examination. Then your GP or the practice assistant will take two throat swabs. You will receive some more information from the practice assistant regarding the medication in the therapeutic study. You will receive a box containing medicines, either penicillin or a placebo (having no working substance). Neither you, nor your GP knows which you receive. The GP may however ask for this information should it seem necessary. Apart from this, you will receive analgesics for two days. You are asked not to take any other medicaments against sore throat (or throat lozenges), because they could disturb the study.

Medicines: take 1 capsule or tablet three times a day for 10 days (finish them)
If needed, take paracetamol three to five times a day for the first two days.

The practice assistant will draw a blood sample. You will then be given a diary for you to register your complaints and body temperature. The practice assistant will explain the diary to you, and will make an appointment for you to visit the GP in two days' time.

Visit, Day 3

You return for follow-up on day 3, bringing your diary and the trial medicines with you. Your GP will ask you a few questions and examine your throat. Again, a throat swab will be taken. A shift of treatment may be decided on, if this appears (is?) necessary. The practice assistant will check the registration of your diary, will count the medicines, and will make an appointment for you with the assistant after 12 days.

Would you please fill in the diary daily, and use the medication according to the advice?

Should you have any questions, you can get in touch with your GP or the practice assistant. You should certainly do so if your complaints seem to be getting worse. As

soon as your temperature has remained below 37.5 C for one complete day you may stop taking and recording your temperature.

Visit after 14 days

You will visit the practice assistant according to the appointment schedule, bringing your diary and the medicine box with you. The assistant will check the diary and the medicine box and draw another blood sample. The diary and the GPs registration form will be sent to the coordinator of the study, who will anonymize them. That for you is the end of the study. If you would like to receive a short report of the study, fill in and return the postcard included in your diary. This report will arrive no earlier than two or three years from now.

Even after you have started your participation in the study, it is possible to stop. Your GP will then treat you as usual. Your GP can provide more information. Please ask for it if anything is unclear.

Thank you for your cooperation, it is appreciated.

Appendix 1

Patiënteninformatie voor behandelings-onderzoek

In deze praktijk vindt momenteel een onderzoek plaats naar de oorzaak van keelpijnklachten en de behandeling ervan. Uw arts heeft u gevraagd of u (of uw kind) mee wilt doen aan het keelpijnonderzoek. In deze folder vindt u nadere informatie over dit onderzoek. Als u na het lezen ervan nog vragen hebt, kunt u deze stellen aan uw huisarts of aan de assistente.

Waarom dit onderzoek?

Er zijn veel oorzaken voor keelpijn. De meeste zijn van onschuldige aard en behandeling met antibiotica is dan niet nodig. De klachten gaan vaak vanzelf over. Soms is er sprake van een keelontsteking ten gevolge van bepaalde bacteriën. Dan kan behandeling met penicilline plaatsvinden en/of met een pijnstillend middel. Ook als geen behandeling wordt gegeven, zijn de klachten meestal binnen een week over. Antibiotica zijn lang niet altijd nodig.

Met dit onderzoek hopen wij te weten te komen:

1. waardoor de keelpijn wordt veroorzaakt;
2. welke behandeling de beste is.

Uitvoerenden

Het onderzoek zal worden uitgevoerd door uw huisarts, in samenwerking met het Utrechtse Universitair Huisartseninstituut.

Doelgroep

Het onderzoek vindt plaats bij kinderen vanaf 4 jaar en volwassenen tot en met 60 jaar, die hoogstens 14 dagen keelpijn hebben.

Uit het onderzoek van uw huisarts blijkt dat u mogelijk bepaalde bacteriën (streptococcen) in uw keel hebt. De huisarts zal u uitleggen wat dit betekent. Het is echter niet zeker, welke behandeling daarvoor de beste is. Het is van het grootste belang dat dit verder wordt uitgezocht. Daarom zal de huisarts u vragen mee te doen aan het behandelingsonderzoek.

U kunt nadere informatie vragen en als u niet voor dit onderzoek voelt, kunt u dit zeggen. Het is belangrijk dat u tijdens het onderzoek de instructies goed opvolgt. Van patiënten die meedoen aan het onderzoek, wordt het volgende gevraagd:

- het gebruikelijke bezoek aan uw huisarts, waarbij wat uitgebreidere vragen worden gesteld en lichamelijk onderzoek wordt gedaan:
- afname van twee keeluitstrijkjes;
- een extra bezoekje aan de huisarts op de derde dag, waarbij weer twee keeluitstrijkjes worden afgenomen.
- afname van een buisje bloed op de eerste en ± veertiende dag;
- een dagboek bijhouden van uw klachten gedurende 10 dagen;
  dit dagboek levert u de veertiende dag in als u bij de assistente terugkomt.

Na uw toestemming zal de huisarts nog een aantal vragen stellen en verder lichamelijk onderzoek doen. Vervolgens neemt de huisarts of de assistente een keeluitstrijkje af. Daarna krijgt u van de assistente nog wat uitleg over het behandelingsonderzoek. Dit houdt het volgende in: u krijgt een potje met medicijnen die of een bepaald soort penicilline of een placebo (een middel zonder werkzame stof) bevatten. Wat u krijgt, weet u niet en uw huisarts evenmin. Deze kan dit echter wel navragen bij de onderzoeker als het nodig zou zijn dit te weten.
Ook krijgt u pijnstillers mee voor de eerste twee dagen. Gebruik zelf liever geen middelen (ook geen zuigtabletten) tegen de keelpijn, deze kunnen het onderzoek verstoren.

Medicijnen: neem 3x daags 1 capsule of tablet uit het potje gedurende 10 dagen (kuur afmaken!).
Neem naar behoefte 3 tot 5x daags volgens voorschrift paracetamol uit de envelop met pijnstillers gedurende 2 dagen.

De assistente zal een buisje bloed bij u afnemen. Verder krijgt u een klachtendagboek mee, waarin u enkele dingen noteert, onder andere de temperatuur. Zij zal u uitleggen hoe dit moet. De assistente zal een afspraak met u maken voor een bezoek aan de huisarts over 2 dagen.

Consult dag 3

U komt op dag 3 terug bij de huisarts. U brengt dan het dagboek, het medicijn-potje en de envelop mee. De huisarts zal nog enige vragen stellen en in de keel kijken.

Ook zal een tweede keeluitstrijkje worden gemaakt. Als het nodig is, kan worden besloten de behandeling te veranderen. De assistente loopt samen met u het dagboek door, telt de medicijnen en geeft u een afspraak mee voor over 12 dagen bij haar.
Wilt u dagelijks het dagboek invullen en de medicijnen volgens voorschrift gebruiken?
Als u vragen heeft, kunt u contact opnemen met uw huisarts of de assistente. Doet u dit in elk geval als de klachten verergeren. Als u een dag lang geen temperatuursverhoging boven 37,5°C meer hebt, kunt u stoppen met het opnemen van de temperatuur.

Consult na 14 dagen
U komt volgens afspraak terug bij de assistente met het dagboek en het medicijnpotje. De assistente zal het dagboek samen met u doorlopen en een tweede buisje bloed afnemen, of u hiervoor verwijzen naar het prikpunt van het artsenlaboratorium. Het dagboek en het formulier van de huisarts gaan dan naar de onderzoeker, die het anoniem zal verwerken.
Daarmee is voor u het onderzoek afgesloten.

Mocht u als patiënt een rekening ontvangen van het laboratorium, dan kunt u deze doorsturen naar de vakgroep huisartsgeneeskunde. Dit geldt niet voor ander onderzoek dat op initiatief van uw huisarts zelf is aangevraagd.
Als u na afloop van het onderzoek een kort verslag wilt ontvangen, kunt u het betreffende kaartje bij uw dagboek invullen en opsturen (dit verslag komt over 2 of 3 jaar).

Ook als u eenmaal meedoet met het onderzoek, is het mogelijk uw medewerking te beëindigen. Dan zal uw huisarts u verder net als anders behandelen. Verdere informatie zult u van uw huisarts krijgen. Vraagt u er bij eventuele onduidelijkheid gerust naar!

Wij danken u voor uw medewerking.

Appendix 2

Selection form

date: .. - .. - 19..

Inclusion criteria: Patient: ☐ has had sore throat ≤ 14 days
☐ is aged 4-60

Demographic data:
year of birth 19..
sex ☐ m ☐ f
health insurance ☐ health insurance association ☐ fee for service

Check the following clinical features:

	yes	no
cough absent	☐	☐
fever (history) ≥ 38.0 °C (axillary/orally) 38.5 °C (rectally)	☐	☐
exudate pharynx or tonsils	☐	☐
enlarged anterior cervical lymph nodes	☐	☐

3 or 4 times yes: therapeutic study ☐
other patients : diagnostic study ☐

Exclusion criterion: ☐ considerable language barrier
-> stop filling this form; give form to practice assistant; follow your own policy

Exclusion criteria for therapeutic study:

Patient: ☐ has been using antibiotics ≤ 4 weeks ago
☐ needs antibiotics*
☐ is not allowed to take penicillin (e.g. allergy)
☐ has already participated in this therapeutic study

If at least one criterion present: participation diagnostic study

* reason:
- history of acute rheumatic fever/ glomerulonephritis,
- GABHS-epidemic in closed community (military camp, large family living in restricted accommodation),
- imminent peritonsillar infiltration/quinsy, or
- ailment excluding placebo treatment

Now the patient is asked to read the information letter in the waiting room. After reading it, the patient returns to the GP. Ask whether there is any hindrance to participation by the patient. Ask whether the patient is willing to participate.

Reason for non-participation: ☐ the patient does not want to participate, because ...
-> stop filling this form; give form to practice assistant; follow your own policy

Reason for non-participation in trial: ☐ the patient does (not) want penicillin
-> participation diagnostic study

patient wishes to participate; therapeutic and diagnostic study ☐
diagnostic study ☐

Appendix 3

Consult dag 1 **Groep I en II** **Datum** ... - ... -19... Tijd ..... uur

ANAMNESE

1. Hoe lang heeft u keelpijn: ... uren/ ..... dagen

2. Hoeveel keelpijn heeft u:
- ☐ weinig
- ☐ matig
- ☐ veel
- ☐ zeer veel

3. Bent u van uw werk of school thuisgebleven vanwege uw (keel)klachten? n.v.t. ☐ ja ☐ nee ☐
zo ja, ... dag(en)

4. Wordt u beperkt in uw normale bezigheden door uw (keel)klachten? ja ☐ nee ☐
zo ja,
- ☐ enigszins beperkt
- ☐ matig beperkt
- ☐ ernstig beperkt
- ☐ tot niets in staat

5. Heeft u huiduitslag (gehad de afgelopen 2 weken)? ja ☐ nee ☐
zo ja, ... dagen

6. Bent u neusverkouden? ja ☐ nee ☐

7. Heeft u minder dan 8 uur geleden zuigtabletten gebruikt? ja ☐ nee ☐

8. Rookt u? ☐ ☐

zo ja, ☐ 1-9 sig./dag
☐ 10-19
☐ ≥ 20

9. Heeft u andere klachten? ☐ ☐

zo ja, te weten _____

10. Bent u misschien al betrokken bij het contactonderzoek? ☐ ☐

VOORGESCHIEDENIS

11. Is de patiënt de laatste twee maanden nog op het spreekuur geweest met keelpijn? ☐ ☐

12. Heeft de patiënt tonsillectomie ondergaan? ☐ ☐

13. Heeft patiënt gedocumenteerde recidiverende keelinfecties? ☐ ☐

zo ja, ...(aantal) het laatste jaar

14. Ruimte voor opmerkingen betreffende voorgeschiedenis:

_____

LICHAMELIJK ONDERZOEK

15. Algemene indruk ☐ ziek
☐ hangerig/niet lekker
☐ gezond

		ja	**nee**
16. Aspect keel:	rood	☐	☐

17. Aspect keel: "stippen" of exsudaat ☐ ☐

(a) zo ja, ☐ tonsillair

☐ niet-tonsillair

(b) zo ja, ☐ aanzienlijk exsudaat of veel stippen

☐ enkele stip

18. Tonsillen aanwezig? ☐ ☐

zo ja, ☐ normaal

☐ afwijkend, te weten _____

Eventueel nu al afname keeluitstrijk (2x) voor kweek en streptest.
Streptest in reageerbuis zetten; spoedig naar assistente brengen.

19. Cervicale lymfklieren:

voorste: palpabel ☐ ☐

gevoelig bij palpatie ☐ ☐

achterste: palpabel ☐ ☐

gevoelig bij palpatie ☐ ☐

20. Exantheem ☐ ☐

zo ja jeuk? ☐ ☐

localisatie _____

aspect _____

Verdacht roodvonk ☐ ☐

Overig lichamelijk onderzoek, **indien verricht:**

21. Otoscopie normaal? ☐ ☐

indien nee, _____

(in geval van moeheid en cervicale lymfklierzwelling):

22. 1 of meer lymfklieren elders

axillair:	palpabel	☐	☐
	gevoelig bij palpatie	☐	☐
lies:	duidelijk vergroot	☐	☐
	gevoelig bij palpatie	☐	☐

23. Lever	palpabel	☐	☐
zo ja,	vergroot	☐	☐
	gevoelig	☐	☐
Milt	palpabel	☐	☐

24. Aanvullend lichamelijk onderzoek _____

Uitslag streptest: ☐ positief
☐ negatief

Appendix 4

Patient diary, day 1 to 10

1. Fever at night .. C

measured orally/ axillary/ rectally (encircle)

2. Sore throat today?	**3.** Improvement today?	**4.** Activities today?
☐ none	☐ much better	☐ normal level
☐ mild	☐ slightly better	☐ some reduction
☐ discomforting	☐ the same	☐ moderate reduction
☐ distressing	☐ slightly worse	☐ large reduction
☐ horrible or excruciating	☐ much worse	☐ totally incapacitated

5. Other complaints related to your throat: ☐ yes ☐ no

if yes, which _____

6. Housemates with sore throat? ☐ yes, how many? ☐ no

7. For patients participating in therapeutic study:
Did you take the medication given
according to the prescription? ☐ yes ☐ no

If not, the reason for this was _____

8. Other remarks _____

_____

Appendix 4

Patienten dagboek, dag 1-10

1. Temperatuur s'avonds .. °C
oraal/in oksel/anaal (omcirkelen)

2. Keelpijn vandaag?

- ☐ geen
- ☐ weinig
- ☐ matig
- ☐ veel
- ☐ zeer veel

3. Algemene verbetering vandaag?

- ☐ veel beter
- ☐ iets beter
- ☐ hetzelfde
- ☐ iets erger
- ☐ veel erger

4. Aktiviteiten vandaag?

- ☐ normaal
- ☐ enigszins beperkt
- ☐ matig beperkt
- ☐ ernstig beperkt
- ☐ tot niets in staat

5. Andere klachten in verband met de keel:

- ☐ ja
- ☐ nee

zo ja, welke _____

6. Huisgenoten met keelpijn?

- ☐ ja, hoe veel?
- ☐ nee

7. Alleen voor groep I:
Heeft u de meegegeven medicijnen volgens voorschrift ingenomen?

- ☐ ja
- ☐ nee

Indien nee, reden: _____

8. Ruimte voor opmerkingen: _____

_____

Appendix 5

Navraagformulier
Gegevens van patienten 1/2 jaar na deelname aan het keelpijnonderzoek

Naam patient ..... geb.dat. .. .. 19..
Adres ..... woonpl. .....

patientnr. .. .. T ...
Datum dag 1 .. .. 19 ..

Heeft sindsdien consult plaatsgevonden? ja / nee
zo ja, in verband met:

		datum		
* sinusitis	+ / -	. . 19..	= .. dagen/	.. weken na dag 1
* OMA	+ / -	. . 19..	= .. dagen/	.. weken na dag 1
* lymfadenitis	+ / -	. . 19..	= .. dagen/	.. weken na dag 1
* keelpijn	+ / -	. . 19..	= .. dagen/	.. weken na dag 1

* andere niet-purulente complicaties

acuut reuma	+ / -	datum .. .. 19 ..	= .. weken
acute glom.nefritis	+ / -	datum .. .. 19 ..	= .. weken

Andere patienten (groep II of rest) met:

acuut reuma	+ / -	bijzonderheden .....
acute glom.nefritis	+ / -	bijzonderheden .....

NAWOORD

Dit proefschrift kwam tot stand dankzij de daadwerkelijke hulp en morele steun van heel veel mensen. De woorden op schrift, waarmee ik de dank voor deze hulp en steun heb willen uitdrukken, schieten tekort, maar zijn welgemeend.

Toen ik in 1986 bij de Utrechtse Vakgroep Huisartsgeneeskunde begon met het protocollen project, kon ik niet vermoeden waartoe dit zou leiden. In de loop van het project troffen we veel lacunes aan in de kennis omtrent keelpijn. Mijn nieuwsgierigheid werd gewekt en een 'eigen onderzoek' bleek ineens voor het grijpen te liggen. Hoewel begonnen als 'baan', bleek al snel dat het zelf onderzoek doen een uitdaging was. Bij deze omslag hebben mijn begeleiders Fransje, Marijke en Ruut, maar ook Arnout en Luc een centrale rol gespeeld. Hiervoor wil ik hen in het bijzonder bedanken.

Lieve Ruut, je vraag: 'Vind je het nog leuk?', heb ik vooral dankzij jou steeds bevestigend kunnen beantwoorden. Je was steeds betrokken, soms zelfs grenzeloos; maar het evenwicht bleef bewaard dankzij de vraag: 'Hoe is het met Carien?'. Je huisarts-zijn heb je in al die jaren niet verloochend. Je ziek-zijn in '93 heeft daaraan gelukkig weinig kunnen veranderen. Je pragmatisme, je oog voor de grote lijn en steeds voelbare steun waren erg belangrijk voor me. Je warme uitstraling - die we node misten in '93 - is een voorbeeld voor me.

Lieve Fransje, ook jij hebt me veel bijgebracht, op je eigen, heldere en ook geduldige wijze. Met name je snelheid in het omgaan met statistische begrippen en principes waren voor mij wel eens frustrerend. Tegelijkertijd heb ik ervan geleerd. Je vermogen om wat onhelder was in een schema weer te geven, bleek vaak verhelderend. Ineens doorzag ook ik dan het probleem. Je ziek-zijn in '93 betekende een schok en een gemis. Dat je op dat moment nog in staat was zaken te regelen en Yolanda te vragen, trof mij zeer.

Lieve Yolanda, aanvankelijk begeleider op afstand, later als co-promotor, was je verfrissend in je helderheid en directheid. Het is een kunst heldere vragen te stellen, en die kunst versta je, ook in het persoonlijke vlak. Twaalf dagen voor de datum van inleveren vroeg je me of ik (nog) geen slapeloze nachten had. Mijn ontkennende antwoord verbaasde je; diezelfde nacht begonnen ze... Je kennis van moderne analyse-technieken bleek een belangrijke aanvulling. Je neiging tot vereenvoudiging was vaak verhelderend naast mijn neiging tot uitvoerigheid. Je vraag: 'Wat vind jezelf?' verraste mij met regelmaat.

Lieve Marijke, in de fase van het voorbereiden van het onderzoek en tijdens de

uitvoering heb je me nauwgezet en deskundig begeleid. De grootste valkuilen met betrekking tot de analyse-fase zijn daarmee vermeden. Ook daarna bleef je, ondanks alle drukte, meer op de achtergrond bereid tot commentaar en hulp o.a. bij het vinden van literatuur. Je warme belangstelling bleef steeds voelbaar.

Lieve Carla, paranymf 'pur sang', betrokken in wel en wee van het onderzoek en van de promovendus. Je nauwgezetheid bij de analyses heeft me - hopelijk - iets geleerd. Je doorzettingsvermogen als er weer iets in het gegevens-bestand niet klopte, was bewonderenswaardig en stimulerend. Mij zonk dan wel eens de moed in de schoenen... Het 'kwek'-bestand zal ik niet snel vergeten. Helaas is het overbuur zijn nu voorbij, maar de rest blijft.

Luc en Arnout, als ervaren huisartsen raakten jullie betrokken bij het 'groot KPO'. Aanvankelijk leverden jullie beiden veel opbouwend commentaar en welkome suggesties. Luc, naderhand kwamen je prioriteiten elders te liggen, maar je interesse was er nog steeds, net als in mijn opleidingstijd. Arnout, door de muziek leerde ik je beter kennen, wat belangrijk bleek bij het naar waarde schatten van je commentaar. Veel dank.

Vele hulpen, co-assistent en basisarts, zijn ingeschakeld in de loop der jaren. Hen allen wil ik graag bedanken voor hun enthousiaste inzet. Met name wil ik noemen Saskia Boidin, Mirjam Harfterkamp, Corry de Koning, Erik Mees, Astrid Scholten, Renee van Snippenburg, Leo Weusten en Esther Wijnheijmer, die zich nuttig maakten met literatuur zoeken of met codeerwerkzaamheden. De meesten van jullie hebben nu betere vooruitzichten dan toen: veel dank en veel succes! Ook Jannemieke Knijn maakte zich onmisbaar bij het contact-onderzoek. Inmiddels ben je collega-onderzoeker; kennelijk beviel het je.

De data-unit, thans informatica-centrum, ben ik dankbaar: Marino, je deed met invoeren monnikenwerk, tot het bittere eind. Fré was slechts kort 'ingeschakeld'; ook Yola, je verving Carla zo nodig en al had je je handen vol, het KPO kon er nog wel bij.

Dan de vele secretaresses die ik heb gehad, te beginnen met Carla Versluis. Carla, je was zorgvuldig in je werk, dacht creatief mee bij het ontwerpen van de boekjes en gezellig tijdens de dagen praktijkbezoek. Na jou kwamen er velen: Ingrid, je was weliswaar niet 'representatief', maar daar ben ik aan gewend geraakt. Voor het overige leerde je snel wat een 'echte' secretaresse geacht wordt te doen. Met je vertrek van het WO-secretariaat kwam een eind aan peuken, oorbellen en veel gelach. Gaby, je was er niet lang, en niet alles ging goed; maar aan je inzet heeft het niet gelegen. Met je hoofd in Australië kun je ook niet op alles letten... Berry, volgens Renée ben je een schatje, maar dat laat ik aan haar over. Mij heb je in ruim zes weken enorm geholpen, met je onvermoeibare inzet. De opmaak van een proefschrift is meer werk dan ik gedacht had.

Je kennis van PC's was daarbij uiterst nuttig, al haat je WP... Wie weet, kom je zelf nog eens in deze fase? Marianne, de laatste maand werd jij mijn rechterhand en dat deed je met grote nauwkeurigheid. De vele foutjes en oneffenheden die je uit de tekst haalde, verbaasden me elke keer. Ik had ze niet gezien. Je geduld vond ik bewonderenswaardig. Jammer dat je er bij het (heel even bittere) eind niet bij kon zijn. Renée, op de achtergrond van alles was jij en had alles in de gaten. Je deskundigheid bij proefschriften is van grote waarde voor steeds weer nieuwe en onervaren promovendi. Je steun, open oog, ook in voor jullie hectische tijden zijn heel belangrijk geweest. De laatste dag bleek dit opnieuw bewezen te moeten worden. Heleen, sorry, dat je hierdoor je moeder alweer moest missen, en sterkte met je knie. Alle anderen: Monique, Gonny, Diana, Joyce, als het nodig was sprongen jullie even in, een voorbeeld van collegialiteit!

Maya Rozenberg, ik dank je voor je deskundige adviezen op microbiologisch terrein. Je was altijd bereid me even te woord te staan, en gaf grondig commentaar op mijn stukken.

Aan de SAL ben ik dank verschuldigd voor de hulp bij het voorbereiden en uitvoeren van de lab-bepalingen. Het 'KPO' werd bij jullie al snel een begrip. De samenwerking was steeds vlot en plezierig. Ook Tjaco Ossewaarde en Kees Elzenaar van het RIVM waren steeds bereikbaar en verzorgden op deskundige wijze de aanvullende bepalingen.

Mrs. Anne Hawkins, u verzorgde de Engelse correcties van de tekst tot in de puntjes. Ons overleg heeft ook mijn gebruik van het Nederlands beïnvloed. Rein, de door jou ontworpen omslag was een verrassing voor me: bij het schrijven hiervan had ik hem nog niet gezien, maar ik verwacht er veel van! Martin Bass, thank you very much for your comments and encouraging help. I greatly appreciated it.

Hans, mijn 'oude' leermeester, van jou leerde ik snel lopen, eten en huisarts zijn. Ik denk er met plezier aan terug. Frank Almekinders, je gaf me alle ruimte om mijn proefschrift af te ronden, wat ik erg gewaardeerd heb. De andere 'beroeps'mensen hebben hiervoor ook begrip opgebracht en waren steeds belangstellend. Dank hiervoor. Andere instituutsgenoten droegen op hun eigen wijze bij: commentaar van Marcel en Niek, belangstelling van veel anderen. Mijn oude kamergenoten, Niek en Frank, vaak heb ik genoten van onze gesprekken, over hoe het allemaal anders moest. En over wat huisartsgeneeskundig onderzoek is; we zijn er nog niet uit. Wie weet als we alle drie post-doc zijn?

Graag wil ik ook de huisartsen en assistentes die hebben meegewerkt aan het onderzoek van harte bedanken voor hun inzet. Zonder hen was er niets tot stand gekomen. Eén naam wil ik noemen: Harry Buitenhuis, je werd topscorer, met ruim 10% van de ingesloten patienten op je naam. Hopelijk heeft je enthousiasme je niet teveel gekost.

Engelien, je was en bent collegiaal in vele betekenissen. Je mee- en vooruit denken bleken zeer waardevol. Je persoonlijke steun heb ik als bemoedigend ervaren. Hopelijk kunnen de extra taken nu wat meer verdeeld worden.
Lieve mamma en pappa, voor jullie gevoel droegen jullie niet zoveel bij. Gelukkig dat er vijf dagen voor het inleveren toch nog een klusje was! Voor mijn gevoel deden jullie echter heel veel: jullie steun op de achtergrond was van groot belang.
Lieve Machiel, terwijl je zelf nog een aardig gevuld bordje voor je had staan, 'kreeg' je mij erbij, eerst worstelend met de computer, later met het denk- en schrijfwerk. Je was er steeds, ook als ik je naar mijn idee niet direct nodig had. Vaak was dat een vergissing van mij...
Lieve Ria, naast je zorg voor Renske en Sanne, nam (en neem) je ons veel uit handen. Heel veel dank hiervoor.
Lieve Renske en Sanne, in het begin was het nog spel, even kijken als ik aan het werk was. Al snel speelde het zich af buiten jullie blikveld. Het begrip 'boek schrijven' was bekend, maar dat dat zò lang duurt...

CURRICULUM VITAE

Carien Dagnelie werd geboren in Rotterdam op 25 juni 1955. Na in 1973 het eindexamen beta aan het Erasmiaans Gymnasium te Rotterdam te hebben behaald, studeerde zij een jaar in Wageningen aan de toenmalige Landbouw Hogeschool (N-propaedeuse). In 1974 begon zij in Utrecht de geneeskunde-studie, die zij voltooide in 1981. Naast haar studie hield zij zich o.a. bezig met roeien en muziek maken.
In 1982 en 1983 vervulde zij arts-assistentschappen cardiologie en gynaecologie-verloskunde-chirurgie. In 1984 begon zij met de opleiding tot huisarts bij de Vakgroep Huisartsgeneeskunde in Utrecht en in het gezondheidscentrum in Rhenen. Vanaf 1985 was zij part-time huisarts in IJsselstein. Daarbij werd voorjaar 1986 een start gemaakt met haar wetenschappelijke activiteiten: het opstellen op basis van de literatuur van protocollen voor het handelen van huisartsen bij bovenste luchtwegaandoeningen. Dit gebeurde in een 0,5 aanstelling bij de Utrechtse Vakgroep Huisartsgeneeskunde. Medio 1988 kreeg dit een vervolg in een aanstelling bij de Nederlandse Organisatie voor Wetenschappelijk Onderzoek in het kader van het Stimuleringsprogramma Huisartsgeneeskunde. In deze periode heeft zij, gedetacheerd bij de Utrechtse vakgroep gewerkt aan het onderzoeksproject waarvan in dit proefschrift verslag wordt gedaan.
Sedert 1991 is zij naast het onderzoek in deeltijd werkzaam in een huisartspraktijk in Nieuwerkerk aan den IJssel.
Naast haar opleiding en werk is zij actief (geweest) in de Vereniging van Nederlandse Vrouwelijke Artsen (VNVA) en in de commissie vrouwelijke huisartsen van de Landelijke Huisartsen Vereniging. Sinds 1988 is zij lid van het Algemeen Bestuur van het Nederlands Huisartsen Genootschap. Zij is getrouwd en heeft twee kinderen.