ROLE OF POINT-OF-CARE TESTS IN ADULTS WITH ACUTE HARYNGITIS IN PRIMARY CARE.

Olga Calviño Domínguez

Dipòsit Legal: T 1415-2015

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Doctoral thesis

Olga Calviño Domínguez

Departament de Medicina i Cirurgia. Facultat de Medicina i Ciències de la Salut. Universitat Rovira i Virgili

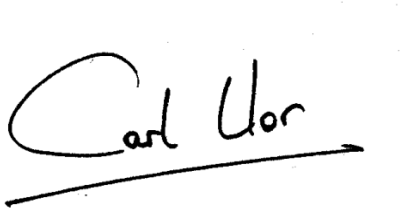
Departament de Medicina i Cirurgia
Facultat de Medicina i Ciències de la Salut

Sant Llorenç, 21
43201 Reus
Tel. 977 759345

FAIG CONSTAR que aquest treball, titulat "Role of point-of-care tests in adults with acute pharyngitis in primary care", que presenta Olga Calviño Domínguez per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Medicina i Cirurgia d'aquesta Universitat i que acompleix els requeriments per poder-se presentar davant el tribunal corresponent.

Tarragona, 10 d'abril de 2015

Els directors de la tesi doctoral



Dra. Silvia Hernández Anadón

Dr. Carles Llor Vilà

A Jose, mi marido

A nuestros hijos, Carlos y Guillermo

Por vuestro cariño, por vuestra paciencia, por haberos robado tantas horas de mi dedicación para poder elaborar el presente trabajo.

ACKNOWLEDGMENTS

A mis directores de Tesis, los Dres. Carles LLor y Silvia Hernández por su generosidad, entusiasmo y paciencia con la que han dirigido esta Tesis Doctoral. Su estimulo me ha iniciado en la labor de la investigación, enseñándome que sola la curiosidad, el tesón y, sobretodo la rigurosidad nos permite adentrarnos en el extenso campo del conocimiento. La compresión y la amistad que me han brindado han hecho, si cabe, mucho más agradable el aprendizaje.

A mis padres, por su cariño, su ejemplo y su estímulo. Han sido un referente para mí en todos los ámbitos de mi vida, de tal forma que gran parte de lo que soy se lo debo a ellos.

A mi hermana Mª José, a Enrique y a mis sobrinos Álvaro, Alejandro y Diego, por quererme y apoyarme en todo momento a pesar de la distancia física que nos separa.

A todos mis compañeros del CAP Jaume I por su desinteresada ayuda en la inclusión de pacientes para el estudio, a los profesionales del Departamento de Microbiología del Hospital Joan XXIII; a mi ex-director, el Dr. Jordi Bladé, por haberme facilitado la realización de esta tesis.

A Silvia, mi mejor amiga, nuevamente muchas gracias.

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SUMMARY

Background. Pharyngitis is one of the most common reasons for a consultation in primary care. It is also one of the most common reasons for prescribing antibiotics in our country, with an estimated prescription rate of more than 60%. However, this process is usually viral in origin, since only 15-25% of pharyngeal infections in adults are of bacterial origin, and the benefits of antibiotic treatment are marginal.

Aim. To evaluate the validity of two immunochromotographic rapid antigen detection tests (RADT) in patients highly suspected of presenting pharyngitis by group A β-haemolytic streptococci (GABHS). In addition, the repetition of the RADT in patients with a previously negative test was also evaluated, and the association of C-reactive protein (CRP) levels with aetiology of pharyngitis was also determined.

Design. Four prospective observational substudies carried out from January 2007 to May 2012.

Study setting: One urban primary care centre in Tarragona.

Subjects. Patients aged 14 or older with acute pharyngitis and at least two Centor criteria (tonsillar exudates, presence or history of high temperature, tender laterocervical nodes and/or absence of cough) were consecutively recruited. The validity of the Analyz-Strep A was evaluated in patients aged 18 or more with at least three criteria and the association of CRP levels with the infection aetiology was carried out in adults with the four criteria.

Measurements and interventions. All the patients underwent at least a pharyngotonsillar swab for microbiological culture, which was sent in Amies medium to the Department of Microbiology of the Hospital Joan XXIII. The samples were taken by previously trained family doctors by swabbing the tonsils and/or posterior wall of the pharynx, without touching the tongue, teeth or gums. In the validation studies another swab was taken for the RADT, following the manufacturer's instructions. Two different devices were used in the different substudies: OSOM® Strep A (Genzyme lab) and the Analyz-Strep A Rapid® test. The CRP rapid test used was the QuickRead/Go device from Orion Diagnostica. All these rapid tests were provided by the different manufacturers free of charge for these studies. For the statistical analysis, the χ^2 test was used for the analysis of the qualitative variables and the Student-Fisher t test was applied for comparing the means. The sensitivity, specificity, the positive predictive value, and the negative

predictive value were calculated to assess the validity of the different RADTs. Only P-values <0.05 were considered to be statistically significant.

Results. A total of 686 patients were studied. The prevalence of GABHS ranged from 22% to 24.8% among patients with two or more Centor criteria, with the highest percentage observed among patients with the four criteria, ranging from 38.9% to 49.1%, followed by those with three and two criteria. The prevalence of group C streptococcus ranged from 8.8% to 15.8% in the different studies performed. The sensitivity of the OSOM Strep A test among patients with at least two Centor criteria was 95%, with a specificity of 93%, a positive predictive value of 79.2%, and a negative predictive value of 98.5%. These results were 96.4%, 91.6%, 79.1% and 98.7%, respectively, with the repetition of the RADT in patients with a first negative RADT result. These results were 93.6%, 93%, 88%, and 96.4% with the use of Analyz-Strep A Rapid test among patients with three or four criteria. In the substudy in which the CRP levels were compared with the aetiology of the pharyngeal infection, the highest concentrations were observed among patients with group C streptococcal infection with a mean value of 56.3 mg/l, while those with GAHBS had a mean concentration of 34.4 mg/l.

Conclusions. The studies considered in this thesis had the limitation that the microbiological analysis did not consider the study of anaerobes, and therefore, some of the patients in whom no bacteria were identified may have been infected by these germs. However, the microbiological procedure did take into account the identification of streptococci other than GABHS, and this may explain the high incidence of group C streptococcal infection identified. One of the strengths of the study was the fact that only a few general practitioners were involved in this study and all had been previously trained on how to obtain a valid pharyngeal sample before the inception of the studies. The main result of these studies shows the usefulness of a single immunochromotographic RADT determination for the diagnosis of GABHS infection with the repetition of RADT in those with a previous negative result being unnecessary. This study also shows that CRP is not useful for distinguishing patients with GABHS infection.

Key words: Acute pharyngitis; Point-of-care tests; Validation; C-Reactive Protein; Anti-Bacterial Agents.

RESUMEN

Fundamento. La faringitis es una de las razones más frecuentes de visita en atención primaria. También es una de las razones por las que se prescriben más antibióticos en nuestro país, observada en más del 60% de las ocasiones. Sin embargo, este proceso suele ser de origen viral, ya que sólo 15-25% de las infecciones faríngeas en adultos son de origen bacteriano y los beneficios del tratamiento antibiótico son marginales.

Objetivo. Evaluar la validez de dos tests antigénicos rápidos (TAR) inmunocromatográficos en pacientes con alta sospecha de presentar faringitis por estreptococo β-hemolítico del grupo A (EBHGA). Además, se evaluó la repetición del TAR en pacientes con una prueba previamente negativa y se determinó también la asociación de los niveles de proteína C reactiva (PCR) con la etiología de la faringitis.

Diseño. Cuatro subestudios observacionales prospectivos realizados entre enero de 2007 hasta mayo de 2012.

Emplazamiento. Un centro de salud urbano de Tarragona.

Sujetos. Se incluyeron consecutivamente a pacientes de 14 años o más con clínica de faringitis aguda y al menos dos criterios de Centor (exudado faringoamigdalar, presencia o historia de fiebre, adenopatías laterocervicales dolorosas y/o ausencia de tos). Se evaluaron, por una parte, la validez del Analyz-Strep A en pacientes de 18 años o más con al menos tres criterios y, por otra, la asociación de los niveles de PCR con la etiología de la infección faríngea en adultos con los cuatro criterios.

Medidas e intervenciones. Todos los pacientes fueron sometidos al menos un frotis faringoamigdalar para cultivo microbiológico, que fue enviado al Departamento de Microbiología del Hospital Joan XXIII con un medio Amies. Las muestras fueron obtenidas por los médicos de familia participantes, que fueron previamente entrenados para tomar un frotis de las amígdalas y/o pared posterior de la faringe, sin tocar lengua, dientes ni encías. En los estudios de validación se tomó otro frotis faríngeo para el estudio de TAR, siguiendo las instrucciones de los fabricantes. Se utilizaron dos dispositivos en los distintos subestudios: OSOM® Strep A (laboratorio Genzyme) y la prueba Analyz-Strep A Rapid®. La PCR usada fue el dispositivo QuickRead/Go de Orion Diagnostica. Todas estas pruebas rápidas se proporcionaron de forma gratuita por los fabricantes para estos estudios. Para el análisis estadístico, se utilizó la prueba de χ^2 para el análisis de las variables cualitativas y la prueba de la t de Student-Fisher para

comparar las medias. Se analizaron la sensibilidad, la especificidad, el valor predictivo positivo y el valor predictivo negativo para la evaluación de la validez de los diferentes TAR. Se consideraron significativas las diferencias con una $p < 0,05$.

Resultados. Se estudiaron un total de 686 pacientes. La prevalencia de EBHGA varió entre el 22% y el 24,8% entre los pacientes con dos o más criterios de Centor, observándose el mayor porcentaje entre los que tenían cuatro criterios, que osciló entre el 38,9% y el 49,1%, seguidos de los pacientes con tres y dos criterios. La prevalencia de estreptococo del grupo C varió entre el 8,8% y el 15,8% en los diferentes estudios realizados. La sensibilidad de la prueba de OSOM Strep A entre los pacientes con al menos dos criterios de Centor fue del 95%, con una especificidad del 93%, un valor predictivo positivo del 79,2% y un valor predictivo negativo del 98,5%. Estos resultados fueron 96,4%, 91,6%, 79,1% y 98,7%, respectivamente, con la repetición del TAR en aquellos pacientes con un primer resultado negativo. Los resultados con el uso de Analyz-Strep A entre los pacientes con tres o cuatro criterios fueron 93,6%, 93%, 88%, y 96,4%. En el subestudio en que se compararon los niveles de PCR con la etiología de la faringitis, se observó que las concentraciones más altas correspondían a los pacientes que presentaban infección por el estreptococo del grupo C con un valor medio de 56,3 mg/l, mientras que aquellos con EBHGA presentaban un valor medio de 34,4 mg/l.

Conclusiones. Los estudios considerados en esta tesis tiene la limitación de que no se efectuó una identificación de anaerobios en el análisis microbiológico y, por tanto, algunos de los pacientes con cultivo negativo podrían haber presentado infección por estos gérmenes. Sin embargo, el procedimiento microbiológico sí tuvo en cuenta la identificación de estreptococos distintos del EBHGA, lo que explicaría la alta incidencia de infección por estreptococo del grupo C. Una fortaleza del estudio fue el hecho de que sólo se involucraron pocos médicos y todos ellos fueron entrenados previamente sobre cómo obtener una muestra faríngea valida antes del inicio de los estudios. Los principales resultados de estos estudios muestran la utilidad de una determinación única de un TAR inmunocromatográfico para el diagnóstico de la infección por EBHGA, sin que sea necesario repetir otro TAR en los resultados negativos. Este estudio también muestra que la PCR no es útil para distinguir los pacientes con infección por EBHGA.

Palabras clave: Faringitis aguda; Pruebas de diagnóstico rápido; Validación; Proteína C reactiva; Agentes antibacterianos.

RESUM

Fonament. La faringitis és una de les raons més freqüents de visita en atenció primària. També és una de les raons per les quals es prescriuen més antibiòtics al nostre país, observada en més del 60% de les ocasions. No obstant això, aquest procés sol ser d'origen viral, ja que només 15-25% de les infeccions faríngies en adults són d'origen bacterià i els beneficis del tractament antibiòtic són marginals.

Objectiu. Avaluar la validesa de dos tests antigènics ràpids (TAR) immunocromatogràfics en pacients amb alta sospita de presentar faringitis per estreptococ β-hemolític del grup A (EBHGA). A més, s'avaluà la repetició del TAR en pacients amb una prova prèviament negativa i es determinà també l'associació dels nivells de proteïna C reactiva (PCR) amb l'etiologia de la faringitis.

Disseny. Quatre subestudis observacionals prospectius duts a terme entre gener de 2007 fins al maig de 2012.

Emplaçament. Un centre de salut urbà de Tarragona.

Subjectes. S'inclogueren consecutivament pacients de 14 anys o més amb clínica de faringitis aguda i almenys dos criteris de Centor (exsudat faringoamigdalar, presència o història de febre, adenopaties laterocervicals doloroses i/o absència de tos). S'avaluaren, d'una banda, la validesa de l'Analyz-Strep A en pacients de 18 anys o més amb almenys tres criteris i, d'una altra, l'associació dels nivells de PCR amb l'etiologia de la infecció faríngia en adults amb els quatre criteris.

Mesuraments i intervencions. Tots els pacients van ser sotmesos almenys a un frotis faringoamigdalar per a cultiu microbiològic, que va ser enviat al Departament de Microbiologia de l'Hospital Joan XXIII amb un medi Amies. Les mostres van ser obtingudes pels metges de família participants, que foren prèviament ensinistrats per agafar un frotis de les amígdales i/o paret posterior de la faringe, sense tocar llengua, dents ni genives. En els estudis de validació es va agafar un altre frotis faringi per a l'estudi de TAR, seguint les instruccions dels fabricants. S'empraren dos dispositius en els diferents subestudis: OSOM® Strep A (laboratori Genzyme) i la prova Analyz-Strep A Rapid®. La PCR emprada va ser el dispositiu QuickRead/Go d'Orion Diagnostica. Totes aquestes proves ràpides vans er proporcionades de forma gratuïta pels fabricants per aquests estudis. Per a l'anàlisi estadística es va utilitzar la prova de χ^2 per a l'anàlisi de les variables qualitatives i la prova de la t d'Student-Fisher per comparar les

mitjanes. S'analitzaren la sensibilitat, l'especificitat, el valor predictiu positiu i el valor predictiu negatiu per a l'avaluació de la validesa dels diferents TAR. Es consideraren significatives les diferències amb una $p < 0,05$.

Resultats. S'analitzaren un total de 686 pacients. La prevalença de EBHGA varià entre el 22% i el 24,8% entre els pacients amb dos o més criteris de Centor, observant-se el percentatge més elevat entre els que tenien quatre criteris, que oscil·là entre el 38,9% i el 49,1%, seguits dels pacients amb tres i dos criteris. La prevalença d'estreptococ del grup C varià entre el 8,8% i el 15,8% en els diferents estudis realitzats. La sensibilitat de la prova de OSOM Strep A entre els pacients amb almenys dos criteris de Centor va ser del 95%, amb una especificitat del 93%, un valor predictiu positiu del 79,2% i un valor predictiu negatiu del 98,5%. Aquests resultats foren 96,4%, 91,6%, 79,1% i 98,7%, respectivament, amb la repetició del TAR en aquells pacients amb un primer resultat negatiu. Els resultats obtinguts amb l'ús de l'Analyz-Strep A entre els pacients amb tres o quatre criteris foren 93,6%, 93%, 88%, i 96,4%. En el subestudi en què es compararen els nivells de PCR amb l'etiologia de la faringitis, s'observà que les concentracions més altes corresponien als pacients que presentaven infecció per l'estreptococ del grup C amb un valor mig de 56,3 mg/l, mentre que aquells amb EBHGA presentaven un valor mig de 34,4 mg/l.

Conclusions. Els estudis considerats en aquesta tesi tenen la limitació de què no es va fer una identificació d'anaerobis en l'anàlisi microbiològica i, per tant, alguns dels pacients amb cultiu negatiu podrien haver presentat infecció per aquests gèrmens. Tanmateix, el procediment microbiològic sí que va tenir en compte la identificació d'estreptococs distints de l'EBHGA, fet que explicaria l'alta incidència d'infecció per estreptococ del grup C. Una fortalesa de l'estudi va ser el fet de què només s'involucraren pocs metges i tots aquells foren ensinistrats prèviament sobre com obtenir una mostra faríngia vàlida abans del començament dels estudis. Els principals resultats d'aquests estudis mostren la utilitat d'una determinació única d'un TAR immunocromatogràfic per al diagnòstic de la infecció per EBHGA, sense que sigui necessari repetir un altre TAR quan el resultat inicials és negatiu. Aquest estudi també mostra que la PCR no resulta útil per distingir els pacients amb infecció per EBHGA.

Paraules clau: Faringitis aguda; Proves de diagnòstic ràpid; Validació; Proteïna C reactiva; Agents antibacterians.

ABBREVIATIONS

CI	Confidence interval
CRP	C-reactive protein
GABHS	Group A β-haemolytic streptococcus
GP	General Practitioner
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
NNT	Number needed to treat
NS	Not significative
NSAID	Non-steroidal anti-inflammatory drug
RADT	Rapid antigen detection test

INTRODUCTION

EPIDEMIOLOGY

Pharyngitis, also known as sore throat, pharyngotonsillitis or tonsillitis, is an extremely common presenting symptom/diagnosis and one of the most frequent reasons why patients see their general practitioners (GP) [*Bisno AL, 2001; Cenjor J et al, 2003*]. In a prospective family study, 16% of adults and 41% of children reported an illness with sore throat over a 1-year time frame [*Danchin MH et al, 2006*]. The US National Ambulatory Medical Care Survey have documented between 6.2 and 9.7 million visits to GPs, clinics, and emergency departments each year for children with pharyngitis, and more than five million visits per year for adults [*Linder JA et al, 2005; Nash DR et al, 2002; Steinman MA et al, 2003*]. Pharyngitis accounts for 1.3% of outpatient visits to health care providers in the United States, and it accounted for an estimated 15 million patient visits in 2006 [*Hing E et al, 2008*]. We see this symptom so often that our vocabulary even includes the phrase "just a sore throat" [*Centor RM et al, 2011*]. The economic burden of streptococcal pharyngitis among children in the United States has been estimated at $224 million to $539 million per year, with a substantial fraction of the associated costs attributable to parents' lost time from work [*Pfoh E et al, 2008*].

In an observational prospective study conducted in two Spanish primary care practices, including all persons with infectious diseases older than 14 years of age, sore throat was the most common infection observed and accounted for approximately 15% of all the infections [*Llor C et al, 2010a*]. Four factors affect the epidemiology of pharyngitis reported in the literature. These include:

- Age of the population studied
- Laboratory methods used to identify the causative organisms
- Season of the year, and
- The clinical severity of the illness

Despite these caveats, the highest burden of disease from sore throat is consistently found in children and young adults, with approximately 50% of cases diagnosed in patients between 5 and 24 years of age [*André M et al, 2002*]. School-aged children of 5 to 18 years of age usually account for the greatest overall number of cases with pharyngitis [*Danchin MH et al, 2006*]. In temperate climates, most cases of pharyngitis occur in the winter and early spring, corresponding to peak times of respiratory virus activity. This is also true for streptococcal

pharyngitis, in which as many as half of the cases in children may be due to this etiologic agent during these peak months [*Glezen WP et al, 1967; Martin JM et al, 2004*].

AETIOLOGY

The spectrum of agents that cause pharyngitis is broad and includes numerous viruses and both typical and atypical bacteria (**Table 1**) as well as non-infectious causes [*Bisno AL, 2001; Shulman ST et al, 2012*].

Table 1. Infectious causes of acute sore throat

Type of organisms	Organism	Clinical manifestations
Viruses	Adenovirus	Pharyngoconjunctival fever. The most frequent
	Rhinovirus	Common cold
	Coronavirus	Common cold
	Influenza virus	Influenza
	Parainfluenza virus	Cold, croup
	Coxsackievirus	Herpangina, hand-foot-mouth disease
	Herpes simplex virus	Gingivostomatitis (primary infection)
	Epstein-Barr virus	Infectious mononucleosis
	Cytomegalovirus	Mononucleosis-like syndrome
	Human immunodeficiency virus	Acute primary infection syndrome
Bacteria	Group A β-haemolytic streptococcus	Pharyngitis, scarlet fever
	Groups C and G β-haemolytic streptococci	Pharyngitis

	Mixed anaerobes	Vincent's angina (necrotizing gingivostomatitis)
	Fusobacterium necrophorum	Lemierre's syndrome (septic thrombophlebitis of the internal jugular vein)
	Arcanobacterium haemolyticum	Pharyngitis, scarlatiniform rash
	Neisseria gonorrhoeae	Pharyngitis
	Treponema pallidum	Secondary syphilis
	Francisella tularensis	Pharyngeal tularemia
	Corynebacterium diphteriae	Diphtheria
	Yersinia enterocolitica	Pharyngitis, enterocolitis
	Yersinia pestis	Plague
Atypical bacteria	*Mycoplasma pneumoniae*	Bronchitis, pneumonia
	Chlamydophila pneumoniae	Bronchitis, pneumonia
	Chamydophila psittaci	Psittacosis

Non-infectious pharyngitis

Although most cases of sore throat result from infection, many non-infectious processes can lead to pharyngeal irritation. These causes are usually identified by a careful history and physical examination. A thorough social history may identify cigarette smoking and poorly humidified air in the home or workplace [*Kociolek LK et al, 2012]*. Pharyngeal and laryngeal trauma may result from inhalation or ingestion of caustic substances, such as chemicals or smoke, or from direct penetrating trauma, and these patients may be quite ill-appearing with the additional findings of pneumonitis or airway compromise. Dysphagia and foreign body sensation should prompt consideration of an oesophageal or oropharyngeal foreign body, particularly in young children. Gastro-oesophageal reflux, vocal strain, and allergic rhinitis,

either from direct effects of the allergen or secondary to postnasal drip, can also cause sore throat.

Viral pharyngitis

Respiratory viruses account for most cases of pharyngitis and account for 25% to 45% of all cases, often occurring with other signs or symptoms of upper respiratory tract infection [*Bastien N et al, 2005; Huovinen P et al, 1989; Putto A, 1987*]. Essentially all viruses known to cause upper respiratory tract infections have been described in both adults and children with pharyngitis. Although the symptomatology often overlaps among patients infected with these viruses, some may have additional characteristic signs and symptoms, particularly Epstein-Barr (generalized lymphadenopathy and splenomegaly), adenovirus (conjunctivitis and preauricular lymphadenopathy), and herpes simplex (gingivostomatitis).

Although the methodology between different studies is highly variable, adenovirus is frequently identified as the most prevalent viral cause of pharyngitis [*Bastien N et al, 2005; Esposito S et al, 2004; Huovinen P et al, 1989*]. Respiratory infections with adenovirus are well described in children and young adults, occur year round, and cause both upper and lower tract disease. Examining sore throat or pharyngitis specifically, adenovirus is identified as the etiological agent in 25% of cases in children and 3% of ambulatory adults [*Chi H et al, 2003; Esposito S et al, 2004, Huovinen P et al, 1989; Hustedt JW et al, 2010*]. Retrospective reviews have demonstrated than pharyngitis or tonsillitis is reported in 40% to 88% of children with adenovirus infections [*Chang SY et al, 2008; Domínguez O et al, 2005*]. Exudates are noted in approximately half of the cases and are often described as thick and white with marked throat pain. In addition, almost three fourths of children with adenovirus infections have fever higher than 39ºC that persists for a mean of 6 days [*Lin CH et al, 2007*]. Among military recruits followed prospectively, approximately 35% of those with culture-confirmed adenovirus infection had sore throat and 29% were febrile [*McNamara MJ et al, 1962*]. Bilateral cervical lymphadenopathy (32%), conjunctivitis (17%) and rash (12%) have also been described in patients with adenovirus respiratory tract infections [*Domínguez O et al, 2005*]. Pharyngoconjunctival fever is a specific syndrome caused by adenovirus infections often occurring in outbreaks and associated with swimming or bathing [*McMillan JA et al, 1992*]. Patients typically present with fever, conjunctivitis, pharyngitis, and cough but may also report headache, myalgia, and malaise. Lymphadenopathy is found on examination in

approximately half of the patients, whereas one fourth also has coryza [*Nakayama MC et al, 1992*]. This disorder is highly contagious with an attack rate of approximately 50%, and it spreads via direct inoculation into the conjunctiva. Although the conjunctivitis may be quite intense and last for 1 to 2 weeks, there is invariably complete resolution of all symptoms with no sequelae [*Nakayama MC et al, 1992*].

Primary infection with herpes simplex virus commonly causes gingivostomatitis in young children whereas pharyngitis is noted among adolescents and young adults. In a series of 35 college students with herpes simplex pharyngitis, infections occurred year round, with the majority of patients presenting with fever, pharyngeal erythema, exudates, and enlarged, tender cervical adenopathy [*McMillan JA et al, 1993*]. Approximately one third also had symptoms more characteristic of herpes simplex virus, including ulcerations of the mouth, lips, or pharynx or swollen, tender, erythematous gingiva.

Enteroviruses classically cause an undifferentiated febrile illness but are also recognised as a cause of pharyngitis and upper respiratory tract infections with most disease occurring in summer and autumn. Non-polio enteroviruses have been identified in 8% to 29% of cases of pharyngitis in children using reverse transcriptase polymerase chain reaction [*Hosoya M et al, 2002: Sharland M et al, 1996*]. Fever is common, but the throat examination is notable for only mild erythema without exudates or significant adenopathy. Two specific pharyngeal syndromes typically associated with enterovirus infections are herpangina and hand-foot-and-mouth disease. Among children with fever and clinical signs of pharyngeal or tonsillar infection, Hosoya et al identified 24 children with herpangina, of whom 75% had an enterovirus detected in their throat swabs [*Hosoya M et al, 2002*]. The majority of cases of herpangina are due to group A coxsackieviruses; however, group B coxsackieviruses, echoviruses, enterovirus 71, adenovirus and herpes simplex virus have also been detected [*Nakayama T et al, 1989; Tsai HP et al, 2001*]. Both endemic and epidemic herpangina are well described, with young children affected more commonly that newborns and adults. The clinical manifestations include hyperemia if the pharynx with discrete 1- to 4-mm erythematous-based vesicles or ulcerations sparsely distributed on the tonsillar pillars, uvula, soft palate, or posterior pharynx [*Rotbart HA et al, 2000*]. Sore throat and fever are invariably present, but symptoms typically resolve spontaneously in approximately one week. Similar to herpangina, hand-foot-and-mouth disease is characterised by the presence of erythematous-based vesicles and ulcerations in the pharynx of a patient with significant sore throat. In

contrast to herpangina, vesicles are also noted on the hands, feet, and buttocks in patients with hand-foot-and-mouth disease and the fever tends to be less prominent [*Rotbart HA et al, 2000*]. Although most cases are self-limited, severe multisystem disease accompanying hand-foot-and-mouth disease and herpangina have also been described during outbreaks associated with enterovirus 71 [*Chen KT et al, 2007*].

Infectious mononucleosis is a multisystem disorder caused by primary infection with Epstein-Barr virus and defined by the triad of fever, pharyngitis, and adenopathy [*Hurt C et al, 2007*]. Among 150 young adults with serologically confirmed acute Epstein-Barr virus infection, three fourths reported sore throat and fatigue, with approximately half noting fever, painful cervical adenopathy, and headache at their initial visit [*Rea TD et al, 2001*]. Other symptoms included cough, myalgia, arthralgia, and nausea. Rash is uncommon and is typically described as a diffuse maculopapular eruption in patients given ampicillin or related compounds. On examination, pharyngitis with mildly painful anterior and posterior cervical lymphadenopathy is detected in 75% of patients, whereas splenomegaly and hepatomegaly are uncommon despite minimally elevated transaminase levels in more than half of the cases [*Rea TD et al, 2001*]. The pharyngitis that accompanies infectious mononucleosis is subacute in onset and may be accompanied by mild to moderate enlargement of the tonsils as well as exudates and palatal petechiae [*Hurt C et al, 2007*]. Symptoms substantially improve over the first month of illness and after 6 months are almost completely resolved [*Rea TD et al, 2001*]. Although infectious mononucleosis has been traditionally described in adolescents and young adults, children also commonly develop fever, exudative pharyngitis, and painful cervical adenopathy during primary infection with Epstein-Barr virus [*Sumaya CV et al, 1985*]. In addition, rash and splenomegaly are more common in young children with primary Epstein-Barr virus infection than in adolescents or adults [*Sumaya CV et al, 1985*]. Periorbital or eyelid oedema as a symptom or primary Epstein-Barr virus infection seems to be unique to children [*Sumaya CV et al, 1985*]. A mononucleosis-like illness has also been described due to primary infection with cytomegalovirus, human herpesvirus 6, herpes simplex virus type 1 and human immunodeficiency virus 1.

Whereas some patients with primary human immunodeficiency virus infection may not have clinical signs or symptoms before seroconversion, most develop an acute retroviral syndrome [*Schaker T et al, 1996*]. Symptoms usually begin 1–5 weeks after the virus is contracted and persist for 2 weeks on average, although they may continue for 8 weeks or more. Fever and

fatigue are the most common symptoms; each is reported in up to 90% of patients, and pharyngitis is reported in over 70% of patients. The acute retroviral syndrome may be confused with infectious mononucleosis, although the former is more likely to be associated with non-exudative pharyngitis, less pronounced tonsillar hypertrophy, mucocutaneous ulceration, and a maculopapular rash [*Bisno AL, 2001*]. Maintaining a high index of suspicion for human immunodeficiency virus, especially in patients with such risk factors as high-risk sexual activity or intravenous drug use, is particularly important during the acute phase because seroconversion may not have occurred. Thus, human immunodeficiency virus antibodies may be negative in the acute phase, in which case the diagnosis can be made only by detecting human immunodeficiency virus RNA or p24 antigen in the blood. Initiation of antiretroviral therapy during the acute phase may improve the response to therapy and secondary prevention of human immunodeficiency virus transmission [*Cohen MS et al, 2011*].

Other respiratory viruses that cause pharyngitis include rhinoviruses, influenzas A and B, parainfluenza viruses, respiratory syncytial virus, coronaviruses, human metapneumovirus and human bocavirus [*Bastien N et al, 2005; Choi JH et al, 2008; Døllner H et al, 2004; Esposito S et al, 2004; Huovinen P et al, 1989; Louie JK et al, 2005*].

Group A β-haemolytic streptococcus

The role of group A β-haemolytic streptococcus (GABHS) or *Streptococcus pyogenes* as a bacterial pathogen in sore throat is evident and is not questioned. Reviews and guidelines considering the diagnosis of sore throat have therefore been focused mainly or exclusively on group A streptococci and related symptomatic presentation. GABHS is responsible for 5 to 15% of cases of pharyngitis in adults and 20 to 30% of cases in children [*Bisno AL, 1996; Ebell MH et al, 2000; Hoffmann S, 1992; Komaroff AL et al, 1986; McIsaac WJ et al, 2000*]. Streptococcal pharyngitis occurs most commonly among children between 5 and 15 years of age. In temperate climates, the incidence is highest in winter and early spring.

Pharyngitis attributable to GABHS is sudden in onset in older children and adults. Sore throat associated with GABHS may result in difficulty swallowing. Fever, headache, and gastrointestinal symptoms, such as nausea, vomiting and abdominal pain, are also associated with strep throat but are not always present. Physical examination generally reveals

pharyngeal erythema, tonsillar enlargement, and a grey-white exudate covering the posterior pharynx and tonsillar pillars. Petechiae are sometimes observed on the soft palate with erythema and oedema of the uvula. Anterior cervical lymphadenopathy, often at an angle of the jaw, is typical of GABHS, and nodes may be quite large and tender. Patients may also present with a characteristic scarlatiniform rash that typically begins on the trunk, spreads to the extremities, and spares the palms and soles. The rash is usually described as confluent with a sandpaper-like quality. Scarlet fever is caused by one or more of the pyrogenic exotoxins produced by pharyngeal strains of GABHS pharyngitis are tonsillar or pharyngeal exudates, tender anterior cervical nodes, fever of history of fever, and absence of cough. GABHS has been associated with a number of complications, including non-suppurative conditions, mainly acute rheumatic fever and post-streptococcal glomerulonephritis, and suppurative complications, such as quinsy, cervical lymphadenitis, sinusitis, otitis media and mastoiditis [*Bessen D et al, 1989; Mandell GL et al, 1995; Stollerman GH, 1997*].

Asymptomatic carriage of β-haemolytic streptococci is frequent, especially in children. According to Tanz et al [*Tanz RR et al, 2007*], over 20% of asymptomatic school children may be carriers of GABHS infection during the winter and spring. Several European investigations examined the carriage rates in children and adults. The highest rate was found in subjects aged 14 years or less (10.9%), whereas rates were 2.3% in patients aged 15–44 years and 0.6% in those aged 45 years or older [*Hoffmann S, 1985*]. Similar results emerged in a Swedish study [*Stromberg A et al, 1988*], reporting carriage rates of 11.3% in 4-year–old children, 5.9% in school children and 0.8% in adults. In a study from Croatia [*Begovac J et al, 1993*], carriage rate of group A streptococci was 8.3% overall, with highest rates being reported for subjects aged 6–14 years. Higher rates were found in a prospective study conducted in Turkey on 351 asymptomatic primary school children; as about 26% of them were GABHS infection carriers [*Ozturk CE et al, 2004*]. In general, when it comes to adults studies suggest that GABHS colonisation of the pharynx in unusual in adults. Two prospective studies involving >400 adults found a carriage rate of only 0-2%, without seasonal variation [*Danchin MH et al, 2007; Fang FC et al, 2015; Woods WA et al, 1999*].

Non-group A β-haemolytic streptococci

A number of studies are available on the symptomatic presentation of β-haemolytic streptococci other than group A streptococci. Group C and G streptococci are commonly

found as normal flora in the human pharynx; however they have also become increasingly recognized as potential causes of pharyngitis [*Cimolai N et al, 1988; Turner JC et al, 1997*]. Two observational studies (one cohort study, one case–control study) supported a milder clinical presentation of group C or group G streptococcal pharyngitis than pharyngitis caused by GABHS. On the other hand, five observational studies (three cohort, two case–control) and one case series investigation reported a similar clinical picture [*Corson AP et al, 1989; Dagnelie CF et al, 1993; Dunn N et al, 2007; Fretzayas A et al, 2009; Gerber MA et al, 1991; Meier FA et al, 1990; Lindbæk M et al, 2005; Turner JC et al, 1993; Zwart S et al, 2000a*]. At least 12 original studies, mostly case series and case reports, described severe symptoms or complications following acute sore throat associated with group C and group G streptococci [*Almroth G et al, 2005; Corson AP et al, 1989; Dudley JP et al, 1991; Fulginiti VA et al, 1980; Gettler JF et al, 1993; Jansen TL et al, 1998; Morgan MC et al, 1989; Natoli S et al, 1996; Shah M et al, 2007; Turner JC et al, 1990; Turner JC et al, 1997; Young L et al, 1992*]. A case–control study of college students found that patients with group C streptococci had exudative tonsillitis and anterior cervical adenopathy more frequently than subjects negative for this infection [*Turner JC et al, 1990*]. In a prospective study carried out in Norway group C β-haemolytic streptococcus accounted for roughly 15% of the cases among patients with sore throat [*Lindbæk M et al, 2005*]. *Streptococcus dysgalactiae* subsp. *equisimilis* (group C) is the most commonly non-GABHS associated with sore throat [*Turner JC et al, 1997*] and recently *S. equi* subsp. *zooepidemicus* has emerged as a potentially important human pathogen [*Balter S et al, 2000*].

On the other hand, there is little evidence to address the issue of whether there is an association between group G streptococci and severe or recurrent pharyngitis. Group C streptococci can cause severe or recurrent pharyngitis and is known to cause epidemic pharyngitis after ingestion of contaminated food including salads (especially those with eggs) and milk products, but there is insufficient evidence for a role of group C streptococci in other adverse outcomes. Signs and symptoms from pharyngitis due to group C and G streptococci may be indistinguishable from GABHS infection.

Uncommon bacterial causes of pharyngitis

Although pharyngitis can be caused by a broad variety of pathogens, many are either difficult to diagnose, do not require treatment, or are self-limited without significant sequelae.

Therefore, many causes do not require additional laboratory testing or empirical treatment. However, certain agents, such as *Neisseria gonorrhoeae* or *Corynebacterium diphtheriae* must be considered in specific patients with particular risk factors. Among patients with tonsillitis due to *N. gonorrhoeae*, a whitish-yellow exudate was observed in 20% [*Balmelli C et al, 2003*]. Because the clinical manifestation of pharyngitis caused by *N. gonorrhoeae* is nonspecific and symptoms may be mild, a thorough history including risk factors for sexually transmitted infections should be obtained in adolescents and young adults with pharyngitis to make this diagnosis. Diphtheria is a potentially life-threatening communicable disease caused by *C. diphtheriae* but is now rare in the Western world because of universal vaccination. A diphtheria-like illness secondary to *C. ulcerans* has been reported in several developed nations, although it is considered a zoonotic infection with low likelihood of human-to-human transmission [*Centers for Disease Control, 2010*]. The hallmark of diphtheria is a thick, grey pharyngeal exudate. This pseudo-membrane may be limited to the tonsils, or if severe, may extend widely into the pharynx, larynx, and trachea, resulting in severe neck swelling and airway obstruction [*Bisno AL, 2001*]. Immunity to *C. diphtheriae* decreases with age—more than 90% of school-aged children have immunity compared with 30% of adults aged 60–69 years [*Kretsinger K et al, 2006*]. Adherence to the recommendations of the Advisory Committee on Immunization Practices for administration of Td vaccine to adults will reduce the proportion of susceptible adults. Diphtheria should be suspected based on clinical grounds, especially if the patient has epidemiologic risk factors, such as incomplete vaccination and travel to, or exposure to individuals from, an endemic region. Another cause, although uncommon, is the pharyngitis due to *Treponema pallidum*, causing a chancre with lymphadenopathy [*Gedela K et al, 2012*]. *Yersinia enterocolitica* has also been associated with pharyngitis in Spain [*García-Callejo FJ et al, 2011*].

Throat findings in patients with *Arcanobacterium haemolyticum* infection include pharyngeal erythema and exudate, fever, and cervical lymphadenopathy, similar to GABHS pharyngitis. The distinguishing clinical feature of pharyngitis due to *A. haemolyticum* is the rash that may occur in as many as one half of infected individuals. The rash is scarlatiniform, macular, or maculopapular and is most frequently seen in adolescents and young adults [*Mackenzie A et al, 1995; Nyman M et al, 1997*]. The rash begins on the distal extremities, typically involving the extensor surfaces but sparing the palms and soles, followed by centripetal spread [*Miller RA et al, 1986*]. Rarely, *A. haemolyticum* may cause more severe infection, such as

pneumonia and pyomyositis, but in these cases is most often a co-infecting agent [*Therriault BL et al, 2008*].

Fusobacterium necrophorum is the most common causative pathogen of Lemierre disease, an infection of the parapharyngeal space that leads to septic thrombophlebitis of the internal jugular vein with bacteraemia and metastatic pulmonary nodules [*Riordan T, 2007*]. Lemierre disease may be complicated by septicaemia; suppurative intracranial complications; and erosion of the carotid artery, which may be life-threatening. Lemierre disease is often suspected based on clinical grounds in a toxic-appearing patient; however, several recent European reports also suggest a possible causative role of *F. necrophorum* in uncomplicated pharyngitis [*Amess JA et al, 2007; Batty A et al, 2005; Jensen A et al, 2007*]. *F. necrophorum* has been identified from throat swabs of adolescents and young adults with non-streptococcal pharyngitis by both throat culture and molecular methods, namely polymerase chain reaction [*Amess JA et al, 2007; Batty A et al, 2005*]. Some clinical scientists also suggest a role for *F. necrophorum* in cases of recurrent or persistent pharyngitis and peritonsillar abscess [*Klug TE et al, 2011a*], although because the organism is part of normal pharyngeal flora [*Klug TE et al, 2011b*], these studies are difficult to interpret. This germ has also been associated with sinusitis, appendicitis, abscesses, and endocarditis [*Kuppalli K et al, 2012*]. In a recent study, Centor et al reported a cross-sectional comparison of 312 patients aged 15 to 30 at a university health clinic presenting with a sore throat and 180 healthy students-likely mostly medical students without sore throat. The investigators assessed the Centor score, collected throat swabs, and performed polymerase chain reaction testing to detect *F. necrophorum*, GABHS, groups C and G streptococcus, and *Mycoplasma pneumoniae*. In patients with an acute sore throat, the rate of detection of *F. necrophorum* was 21%, GABHS was 10%, groups C and G streptococcus was 9%, and *M. pneumoniae* was 2%. The respective rates in asymptomatic students were 9%, 1%, 4% and 0% [*Centor RM et al, 2015*]. Despite this study, and with the exception of Lemierre disease, a causative role of *F. necrophorum* as a primary pathogen in pharyngitis and its complications remains unproven at this time [*Hagelskjaer Kristensen L et al, 2008*]. Additional investigation is required to determine its role, as well as the necessity for and effectiveness of therapy. Lemierre disease can also be caused by community-associated methicillin-resistant *Staphylococcus aureus*); recent reports document emergence of this organism as an occasional cause of Lemierre disease [*Chanin JM et al, 2011*]. Because first-line therapy for *F. necrophorum* (i.e., ampicillin-sulbactam)

does not treat methicillin-resistant *S. aureus* infection, additional empirical antibiotic therapy for this germ should be considered for a patient who may be at high risk for infection with this organism. *Fusobacterium* is usually missed by standard tests and further research with appropriate methods with anaerobic incubation is needed [*Baron EJ et al, 2013*].

Atypical germs

Both *M. pneumoniae* and *Chamydophila pneumoniae* have been identified as a cause of pharyngitis in all age groups with a higher prevalence generally noted for *M. pneumoniae* and more limited to paediatrics [*Esposito S et al, 2004; Esposito S et al, 2006; Klar A et al, 1985; Levy M et al, 1991; Volter C et al, 2004*]. Disease occurs year round, but seasonal peaks and community outbreaks occurring every few years have also been described [*Layani-Milon MP et al, 1999*]. Most adult cases seem to present as an undifferentiated acute respiratory infection or an influenza-like illness; however, isolated pharyngitis has also been noted [*Thom D et al, 1994*]. In an outbreak of respiratory disease due to *M. pneumoniae* in a military unit, sore throat was reported in 35% to 70% of patients, with fatigue, headache, and cough noted more commonly. The only risk factor for symptomatic disease identified after the outbreak was cigarette smoking [*Klement E et al, 2006*]. Esposito et al described several case series of children with pharyngitis caused by *M. pneumoniae* or *C. pneumoniae* and identified dysphagia in 25% to 36%, tonsillar hypertrophy in 76% to 83%, cervical adenopathy in approximately 50% and pharyngitis due to atypical bacterial infection compared with common viral causes of sore throat, children with infection due to *M. pneumoniae* or *C. pneumoniae* were significantly more likely to have a history of recurrent pharyngitis [*Esposito S et al, 2002*]. In addition, children with pharyngitis due to atypical bacterial infections treated with azithromycin had lower rates of subsequent respiratory infections including lower tract disease, compared with children given symptomatic treatment alone [*Esposito S et al, 2006*]. Case reports and case series found a possible association between *M. pneumoniae* infection and Bell's palsy or Stevens–Johnson syndrome.

CLINICAL MANIFESTATIONS

Patients with pharyngitis primarily present with a sore throat. Additional clinical features, signs, and symptoms may be present depending on the underlying cause. The onset of

symptoms in patients with streptococcal pharyngitis is often abrupt. In addition to throat pain, symptoms may include fever, chills, malaise, headache, and particularly in younger children abdominal pain, nausea, and vomiting [*Wannamaker LW, 1972*]. Occasionally, streptococcal pharyngitis is accompanied by scarlet fever, which is manifested as a finely papular erythematous rash that spares the face, may be accentuated in skin folds, and may desquamate during convalescence.

Cough, coryza, and conjunctivitis are not typical symptoms of streptococcal pharyngitis, and, if present, they suggest an alternative cause such as a viral infection. Throat pain may be severe, and it is often worse on one side. However, severe unilateral pain or an inability to swallow should raise concern about a local suppurative complication such as peritonsillar or retropharyngeal abscess, particularly if these symptoms arise or progress several days into the illness. Among children younger than 3 years of age, exudative pharyngitis due to streptococcal infection is rare. In this age group, streptococcal infection may be manifested as coryza, excoriated nares, and generalized adenopathy [*Wannamaker LW, 1972*]. In most persons, fever resolves within 3 to 5 days, and throat pain resolves within 1 week, even without specific treatment [*Brink FW et al, 1951; Denny FW et al, 1953*].

Many symptoms overlap among infectious causes, whereas others are unique to a particular pathogen. Therefore, the diagnosis of streptococcal pharyngitis on clinical grounds is notoriously unreliable [*Centor RM et al, 1981; Poses RM et al, 1985*]. Because certain infections are self-limited and do not require additional evaluation or treatment, particularly respiratory viral pathogens, their features should be recognized. GABHS, the most common bacterial cause of pharyngitis, requires additional evaluation and treatment, so the clinician should be aware of features unique to infection with this pathogen. The clinician should also be aware of signs and symptoms that may indicate a particularly serious pathogen, such as diphtheria or human immunodeficiency virus, or sequelae, such as airway compromise, that require additional evaluation and treatment. Symptoms and signs are variable, and the severity of illness ranges from mild throat discomfort alone to classic exudative pharyngitis with high fever and prostration.

The diagnosis is further complicated by the fact that infection due to many other agents, such as those caused by groups C and G β-haemolytic streptococci and maybe fusobacterial pharyngitis, may be indistinguishable clinically from pharyngitis caused by group A streptococcus (**Table 2**).

Table 2. Epidemiologic and clinical features suggestive of GABHS and viral pharyngitis

Features	Viral	Streptococcal
Age	< 4 years and > 45 years	5-15 years
Season	Variable	Winter and early spring presentation
Onset	Gradual onset	Sudden onset
Symptoms	Mild fever. Mild odinophagia	Fever. Severe odinophagia
Other symptoms	Cough, conjunctivitis, coryza, hoarseness, myalgias, diarrhoea, viral exanthema, discrete ulcerative stomatitis	Headache, nausea, vomiting, abdominal pain, scarlatiniform rash
Pharynx	Erythematous. Exudate (65%)	Tonsillopharyngeal inflammation. Exudate (70%). Palatal petechiae
Cervical nodes	Multiples and small or absent	Tender. Enlarged

A systematic review of studies in children and adults found that the sign that most frequently increase the likelihood of GABHS pharyngitis is the presence of tonsillar exudates, with a positive likelihood ratio (LR+) of 3.4, followed by pharyngeal exudates (LR+: 2.1), and exposure to someone with a case of pharyngitis caused by GABHS in the previous two weeks (LR+: 1.9). Conversely, the absence of enlarged tonsils and the absence of tender cervical adenopathy were not associated with pharyngitis caused by GABHS, reporting a negative likelihood ratio (LR–) for GABHS pharyngitis of 0.6, and the absence of exudate also decreased the likelihood of a streptococcal infection, presenting a LR– of 0.7 [*Ebell MH et al, 2000*].

In children, scarlatiniform rash (LR+: 3.9), palatine petechiae (LR+: 2.7), pharyngeal exudates (LR+: 1.9), vomiting (LR+: 1.8), and tender cervical adenopathy (LR+: 1.7) are all associated with GABHS pharyngitis [*Shaikh N et al, 2012*].

ROLE OF CLINICAL SCORING IN THE DIAGNOSIS OF STREPTOCOCCAL INFECTIONS

Because individual signs and symptoms have limited value, a number of clinical decision rules have been developed to diagnose GABHS pharyngitis [*Joachim L et al, 2010; McIsaac WJ et al, 2000; Steinhoff MC et al, 2005*].

The Centor score for the diagnosis of GABHS throat infections was proposed in 1981 [*Centor RM et al, 1981*]. This constituted the first clinical rule published in acute pharyngitis and it was based on the study of 286 adult patients with sore throat who presented to the Emergency Department at the University College of Virginia. Centor et al identified four signs and symptoms to estimate the probability of acute GABHS pharyngitis in adults with sore throat. The four signs and symptoms were tonsillar exudate, swollen tender anterior cervical nodes, the lack of cough and fever. According to the Centor score [*Centor RM et al, 1981*], the risk of GABHS infection depended on the number of signs and symptoms, with a risk of 56% among patients with the four criteria in Centor's study, 32% among those with three criteria, 15% among those with two, 6.5% among patients with only one criterion and 2.5% in those with none of these criteria [*Centor RM et al, 1981*]. This clinical decision rule was validated only in adults and not in children.

The Centor score was later modified by adding age, and was validated in about 600 adults and children (3–15 years old) in a Canadian study [*McIsaac WJ et al, 1998*]. The modified Centor score was based on a total sore throat score that determines the likelihood of GABHS pharyngitis. To determine the patient's total sore throat score it is necessary to assign points, allocating one point for each criterion.

The risk of GABHS infection also depends on the total sore throat score [*McIsaac WJ et al, 1998*], being higher among patients with all the criteria and lower among those without these criteria. The modified Centor score was further adapted in 2004 [*McIsaac WJ et al, 2004*] and the adapted version has been validated in both adults and children [*Ebell MH et al, 2000; Fine AM et al, 2012*]. Although the criteria remained the same, the estimated risk of GABHS infection was updated as shown in **table 3**, in which, a range based on the different papers published were taken into account. It is of note that only one half of the patients with a Centor score of 4 actually have GABHS pharyngitis.

Table 3. Risk of GABHS infection with the use of the streptococcal clinical scoring rules

Centor total score[1]	Risk of streptococcal infection %	McIsaac total score[2]	Risk of streptococcal infection %
4	38-63	≥4	51-53
3	25-35	3	28-35
2	10-17	2	11-17
1	4-6	1	5-20
0	2-3	≤0	1-2.5

A more recent study, conducted by researchers from Southampton University, proposed the FeverPAIN (fever, purulence, attend rapidly, inflamed tonsils, no cough or coryza) score, which has been shown to reduce use of antibiotics by 30% without worsening other outcomes, reduce costs, and reduce antibiotic resistance. The FeverPAIN score was validated for detection of Lancefield groups A, C, and G streptococcus, resulting in somewhat higher percentages of those with strep throat in each risk group [*Little P et al, 2013a; Little P et al, 2013b; Little P et al, 2014a*].

The World Health Organization has proposed a simple heuristic for use in under resourced settings: treat for GABHS pharyngitis in all children with pharyngeal exudate plus enlarged, tender cervical lymph nodes. Although this approach is highly specific (more than 90%), the sensitivity is very low (less than 15%), and it cannot be recommended [*Rimoin AW et al, 2005*]. However, two recent studies have identified more sensitive scores with adequate specificity that can be used for children with sore throat in under resourced settings. One suggests that GABHS pharyngitis be empirically treated in any child with sore throat and at least two of the following: no rhinitis, no rash, or enlarged cervical nodes [*Steinhoff MC et al, 2005*]. Another score is somewhat more complex, taking into account age, symptoms suggesting GABHS pharyngitis, and symptoms suggesting viral pharyngitis [*Joachim L et al, 2010*]. A very recent Turkish paper has described another score called Mistik Score, that has been observed to be useful to diagnose viral sore throat, with the predictive model for positive viral analysis including the following variables: absence of headache, stuffy nose,

sneezing, temperature of ≥37.5C on physical examination, and the absence of tonsillar exudates and/or swelling [*Mistik S et al, 2015*]. The probability of a positive viral analysis for a score of 5 was 82.1%. Despite being this figure high, this score has not been validated. **Table 4** describes the most frequently clinical rules used in adults with pharyngitis..

Table 4. Streptococcal clinical scoring rules available

	Centor[1]	McIsaac[2]	FeverPAIN[3]	FeverP(A)IN[3]
Temperature >38.5C in the past 24h	+1			
Temperature >38C in the past 24h		+1	+1	+1
Tonsillar exudate	+1		+1	+1
Tonsillar exudate or swelling		+1		
Severe inflammation			+1	+1
Tender anterior cervical nodes	+1	+1		
No cough	+1	+1	+1	+1
Age 3-14 years		+1		
Age 15-44 years		0		
Age >44 years		-1		
Rapid attendance (illness ≤3 days)			+1	

[[1]*Centor RM et al, 1981;* [2]*McIsaac WJ et al, 1998;* [3]*Little P et al, 2013a*]

RATIONALE FOR ANTIBIOTIC TREATMENT

GABHS pharyngitis is a self-limited illness; without treatment, fever and symptoms commonly resolve within a few days. Prescribing antibiotics for patients with a sore throat is a common practice and more than half of the patients with sore throat are treated with antibiotics in the Western countries, with percentages of antibiotic prescribing ranging from

49% to 57% among children and from 52% to 98% among adults with acute pharyngitis [*Cooper RJ et al, 2001; Demelker RA et al, 1991; Gonzales R et al, 1997; Linder JA et al, 2001; Linder JA et al, 2005; Llor C et al, 2010b; McCaig LF et al, 2002; Nash DR et al, 2002; Neumark T et al, 2010; Neuner JM et al, 2003; Nyquist AC et al, 1998; Patterson CA et al, 2003; Steinman MA et al, 2003*]. Prescribing style is an important source of variation in prescription of antibiotics for sore throat within and across countries, even after adjusting for patient and GP characteristics [*Cordoba G et al, 2015*]. However, as mentioned before in this thesis, GABHS is the cause of only 5% to 30% of the cases of pharyngitis [*Bisno AL, 1996; Cooper RJ et al, 2001; Komaroff Al et al; 1986; Linder JA et al, 2001*].

Excessive utilisation of antibiotics is associated with the presence of side effects and the spread of individual and community resistances [*Costelloe C et al, 2010; Pichichero ME, 1995*]. In addition, unnecessary use of antibiotics leads to a medicalisation of an otherwise self-limiting condition which is associated with a more frequent reattendance on future occasions [*Little P et al, 1997a*]. GPs usually suspect that patients want antibiotics and in case of doubt they are more prone to prescribe an antibiotic [*Butler CC et al, 2001*]. Other risks associated with antibiotic overprescription are summarised in **table 5**.

Table 5. Risks that have been shown to be associated with overuse of antibiotics

Risks associated with overuse of antibiotics
Increase of antimicrobial resistance
Increase of more severe diseases
Increase of the length of disease
Increase of the risk of complications
Increase of the mortality rate
Increase of healthcare costs
Increase of the risk of adverse effects, some being life-threatening
Increase of re-attendance due to infectious diseases
Increased medicalisation of self-limiting infectious conditions, such as acute pharyngitis

Recent surveys demonstrated a significant increase in the use of broad-spectrum antibiotics for the treatment of pharyngitis, a practice that is thought to contribute to the growing problem of antibiotic resistance and the medicalization of a generally benign illness [*Steinman MA et al, 2003*].

A systematic review of the use of antibiotics for sore throat that included 27 trials with 12,835 patients found that antibiotics have some benefits in patients with GABHS infection (**Table 6**) [*Spinks A et al, 2013*]. Although these data are compelling, the dates of the studies included in the review should be considered. Most were conducted before 1975, when there were much higher rates of secondary complications, making the benefits of antibiotics seem more dramatic. As an example, the review found that the incidence of acute otitis media as a secondary complication of sore throat was 3% before 1975, compared with 0.7% in 2013. This difference increases the number needed to treat (NNT) from 50 to nearly 200 to prevent a single case of acute otitis media.

Without treatment, streptococcal pharyngitis is associated with persistence of positive throat cultures for up to 6 weeks in 50% of patients [*Catanzaro FJ et al, 1954*]. In contrast, treatment with an active antibiotic results in negative throat cultures within 24 hours in more than 80% of patients [*Krober MS et al, 1985; Randolph MF et al, 1985*]. It is recommended that patients receive treatment for streptococcal pharyngitis for 24 hours before they return to school or work because shorter intervals are associated with a higher rate of positive cultures [*Snellman LW et al, 1993*]. Antibiotic therapy also reduces the duration of streptococcal symptoms [*Brink WR et al, 1951; Denny FW et al, 1953; Krober MS et al, 1985; Randolph MF et al, 1985*]. When patients are prescribed an appropriate antibiotic for GABHS pharyngitis, for instance penicillin, they improve substantially about 18–24 hours more rapidly than without therapy [*Shulman ST et al, 2012*]. Antibiotics may be less effective in ameliorating symptoms if treatment is delayed [*Brink WR et al, 1951*].

Another evaluation used a national database of more than one million cases of sore throat and found that although there was a decrease in the incidence of quinsy after the use of antibiotics, the NNT was 4,300, suggesting that the small decrease in risk of an uncommon complication did not warrant the widespread use of antibiotics for a self-limited disease [*Petersen I et al, 2007*].

Table 6. Benefits of treating with antibiotics the sore throat due to GABHS

Benefit	Observations
Decreases symptom duration	Mean 16-hour reduction in sore throat symptoms treated with antibiotics. In adults, penicillin decreases symptom duration by approximately two days in patients with Centor scores of 3 or 4 [*Zwart S et al, 2000a*]. A similar study in children showed no benefit [*Zwart S et al, 2003*]. Throat soreness and fever were reduced by about half by using antibiotics [*Spinks A et al, 2013*]. The NNT to benefit to prevent one sore throat at day three is less than 6; at week one it is 21
Decreases contagion	Therefore, antibiotic therapy has a public health benefit. In approximately one fourth of individuals of the household is expected to be infected when there is a case [*James WE et al, 1960; Lindbæk M et al, 2004a*]
Decreases suppurative complications	Antibiotics mainly decrease quinsy (peritonsillar abscess) within two months (risk ratio: 0.15; 95% CI: 0.05 to 0.47) compared to those taking placebo; however, the incidence of rheumatic fever is very low nowadays [*Marijon E et al, 2012*]. Antibiotics also reduce the incidence of acute otitis media within 14 days (risk ratio: 0.30; 95% CI: 0.15 to 0.58) and acute sinusitis within 14 days (risk ratio 0.48; 95% CI: 0.08 to 2.76) [*Spinks A et al, 2013*]
Decreases non-suppurative complications	Mainly decreases the incidence of acute rheumatic fever by more than two-thirds within one month (risk ratio: 0.27; 95% CI: 0.12 to 0.60), even though the incidence of this condition has dramatically dropped in the Western countries. The trend of protecting against acute glomerulonephritis exists but there are too few cases to be sure [*Spinks A et al, 2013*]
Decreases streptococcal shock syndrome	Although rarely, untreated streptococcal pharyngitis can cause death, primarily from the streptococcal shock syndrome [*Centor RM, 2013*]

When a patient's symptoms persist, there are several possible explanations: The patient may have developed a suppurative complication limiting response to antibiotic therapy, such as a peritonsillar or retropharyngeal abscess or suppurative adenitis, and may require surgical intervention; alternatively, he or she may have viral pharyngitis and also be a chronic carrier of GABHS. Symptoms of viral pharyngitis usually resolve within 3–7 days [*Lindbæk M et al, 2006*].

Complications of sore throat

Complications of GABHS pharyngitis are generally rare in both children and adults [*Abdel-Haq et al, 2006; Almorth G et al, 2005; Galioto NJ, 2008; Gerber MA, 2005; Gerber MA et al, 2009; Hanna BC et al, 2006; Little P et al, 2013c; Martin JM et al, 2006; Talmon Y et al, 2008*]. Potential adverse outcomes include both suppurative (i.e. quinsy, acute otitis media, cervical lymphadenitis, mastoiditis, acute sinusitis) and non-suppurative (i.e. acute rheumatic fever, acute glomerulonephritis) complications (**Table 7**).

Table 7. Complications of group A β-haemolytic streptococcal pharyngitis

Suppurative complications	Non-suppurative complications
Quinsy (peritonsillar abscess)	Acute rheumatic fever
Retropharyngeal abscess	Acute poststreptococcal glomerulonephritis
Cervical lymphadenitis	Poststreptococcal reactive arthritis
Sinusitis	
Otitis media	
Mastoiditis	

Quinsy, also known as peritonsillar abscess, is a complication that occurs mainly in young adults, is a polymicrobial infection but GABHS is the main organism associated with the disease [*Dunn N et al, 2007; Galioto NJ, 2008; Gerber MA et al, 2009; Martin JM et al,*

2006; Mazur E et al, 2015; Steer AC et al, 2007; Talmon Y et al, 2008; Tanz RR et al, 2007; Watson N et al, 2000].

Acute rheumatic fever has been widely investigated during the last decades, but its incidence is now very low in Europe and in most developed countries, but it remains very prevalent in poor areas [*Carapetis JR et al, 2005*]. Acute rheumatic fever is diagnosed based on the Jones criteria (**Table 8**), and it manifests an average of 2–3 weeks after onset of GABHS pharyngitis [*Guidelines for the diagnosis of rheumatic fever, 1992*].

Table 8. Revised Jones criteria for acute rheumatic fever

Major criteria	Minor criteria
Carditis	Fever
Migratory polyarthritis	Arthralgia
Sydenham chorea	Elevated erythrocyte sedimentation rate or C-reactive protein
Erythema marginatum	Prolonged P–R interval on electrocardiogram
Subcutaneous nodules	Evidence of preceding streptococcal infection (any one of the following): - Elevated or rising antistreptolysin O or anti-DNAse B titer - Positive throat culture for group A β-haemolytic streptococci

A diagnosis of acute rheumatic fever requires 2 major or 1 major and 2 minor criteria, in addition to evidence of a recent streptococcal infection.

Both acute rheumatic fever and rheumatic heart disease affect nearly 20 million people worldwide. Each year, approximately 233,000 people die of complications from acute rheumatic fever, primarily rheumatic heart disease, and it is the leading cause of cardiac-related deaths worldwide in patients younger than 50 years. The World Health Organization

estimates that 500,000 people each year acquire rheumatic fever, and 60% of these people develop rheumatic heart disease [*Carapetis JR et al, 2005; Gerber MA et al, 2009; Morbidity and Mortality Weekly Report, 1988*].

Many guidelines recommend prescribing antibiotics to prevent acute rheumatic fever if streptococcal pharyngitis is suspected. This recommendation is most likely based on the findings of the Fort Warren studies in the United States in the 1950s [*Catanzaro FJ et al, 1958; Little P et al, 1997b; Siegel AC et al, 1961; Spink W et al, 1946; Wannamaker L et al, 1951; Weinstein L et al, 1971*]. They found a 0.3% to 3% reduction of the incidence of acute rheumatic fever if streptococcal angina was treated with parenteral penicillin. These findings, however, have never been confirmed in other trials with penicillin [*Goslings WR et al, 1963; Haverkorn MJ et al, 1971; Saslaw M et al, 1956*] nor have they been confirmed in consecutive prospective studies [*Gordis L, 1985; Land MA et al, 1983; Valkenburg HA et al, 1971*]. Almost a half-century ago, an editorial claimed that the statement that 3% of such streptococcal infections will be followed by acute rheumatic fever rests mainly on the extensive work at Fort Warren, and it is not at all certain that conditions reflect these in general practice. There can therefore be no hard and fast rule that 3% of streptococcal infections are followed by acute rheumatic fever [*Congeni B et al, 1987*]. By the 1980s acute rheumatic fever was considered a vanishing disease that had disappeared in the Western world [*Bonora G et al, 1989; Howie JG et al, 1985*]. Some local revivals of acute rheumatic fever were registered in the United States (n=164) and in Italy (n=21), but closer analysis suggested that antibiotics did not play an important role [*Glover JA, 1943; Spinks A et al, 2013*]. The morbidity and mortality rates for acute rheumatic fever in Western countries had clearly been declining before the use of antibiotics in the 1950s, and an effect of antibiotic use could not be shown [*Pichichero ME et al, 1987; Randolph M et al, 1985*]. That some guidelines rely on the results of the Fort Warren studies, whereas others do not, may explain the observed differences. Likewise, regional variation of the incidence of acute rheumatic fever could contribute. Notwithstanding, where some guidelines recommend penicillin to prevent acute rheumatic fever, other guidelines consider acute sore throat, even a streptococcal infection, as a self-limiting disease and state that antibiotics have only a limited effect on shortening the clinical evolution [*Chamovitz R et al, 1954; De Meyere M et al, 1992; Denny FW et al, 1950; Denny FW et al, 1953; Houser HB et al, 1953; Linder JA et al,*

2006; Pichichero ME et al, 1987; Randolph M et al, 1985; Robertson KA et al, 2005; Ross JS et al, 2006; Wannamaker LW et al, 1951].

Acute glomerulonephritis is another rare consequence of sore throat, following GABHS pharyngitis, usually occurs 10–14 days after infection, and is characterized by haematuria, proteinuria, azotemia, and hypertension. Unlike acute rheumatic fever, glomerulonephritis can occur after both GABHS pharyngitis and skin infections and is not preventable with appropriate antibiotic treatment.

Uncommon complications of pharyngitis caused by group C or G streptococci that have been reported include reactive arthritis, subdural empyema and acute glomerulonephritis, but a causal relationship was not clearly established [*Cimolai N et al, 1988; Gerber MA et al, 1991; Scoggins L et al, 2010*]. In 1997, Efstratiou reported consistent results of group C and G septicaemia over a 10-year period [*Efstratiou A, 1997*]. While sore throat caused by GABHS is known to be rarely associated with acute rheumatic fever in developed countries, this has not been reported as a complication following group C or group G streptococcal infection [*Gerber MA et al, 2004*]. There are, however, studies and expert opinions indicating that group C and group G streptococci might contribute to acute rheumatic fever pathogenesis in high-incidence settings [*Chandnani HK et al, 2015; Haidan A et al, 2000; McDonald M et al, 2004*]. Some clinical scientists have also attempted to associate GABHS infections with waxing and waning tic disorders and obsessive–compulsive behaviours in prepubertal children, although this is highly controversial and remains unproven [*Shulman ST et al, 2009*].

Little et al recently conducted the Decision rule for severe Symptoms and Complications of Acute Red Throat in Everyday practice (DESCARTE) study in general practices throughout the United Kingdom in which fewer than 50% of patients with tonsillitis were prescribed antibiotics [*Little P et al, 2013c*]. The researchers enrolled 14,610 adults presenting with acute sore throat as the main symptom, with an abnormal examination result of the pharynx but without complications at the time of presentation. Overall, 56% of patients were prescribed antibiotics. Complications were assessed in patients who sought additional care within one month with new or unresolved symptoms. The entire cohort was analysed together (regardless of antibiotic use), with the researchers assuming that antibiotic treatment would attenuate the severity of, but not completely prevent, complications.

Complications— quinsy, otitis media, sinusitis, impetigo, or cellulitis—occurred in approximately 1% of patients, regardless of whether they received immediate or delayed antibiotics or were not given antibiotics. In multivariate analysis, severe tonsillar inflammation and severe earache were predictive of complications, but not strongly so, and 70% of complications occurred when neither was present. Similarly, a Centor score of at least 4 had a positive predictive value for complications of only 1.7% and the FeverPAIN score was similarly not helpful (positive predictive value: 2.1%) [*Little P et al, 2013c*]. Most complications occurred in patients who had low scores on both predictors or who had bacterial complications. Testing for GABHS infection was not performed in most patients. However, systemic complications, such as glomerulonephritis and rheumatic heart disease, were not reported [*Little P et al, 2013c*].

In summary, there is no doubt that antibiotic therapy reduces the risk of complications in patients with GABHS sore throat. The DESCARTE study showed a lower risk of suppurative complications in patients prescribed immediate or delayed antibiotics compared to those prescribed no antibiotics, once the analysis controlled for significant baseline differences between the treatment and control groups [*Little P et al, 2014b*]. This, along with earlier studies, clearly suggests that antibiotics do in fact reduce the risk of suppurative complications including peritonsillar abscesses [*Dagnelie CF et al, 1996; Spinks A et al, 2013; Zwart S et al, 2000*]. Moreover, the DESCARTE study included patients with sore throat from any cause, the vast majority of whom did not harbour GABHS, so the potential benefit of antibiotic treatment in patients with streptococcal infection may have been underestimated. In addition, multiple studies have shown that the clinical benefit of antibiotic therapy is not dependent on the duration of symptoms [*Dagnelie CF et al, 1996; Zwart S et al, 2000*]. Moreover, even when delayed up to 9 days, treatment can also reduce the likelihood of rheumatic fever [*Catanzaro FJ et al, 1954*].

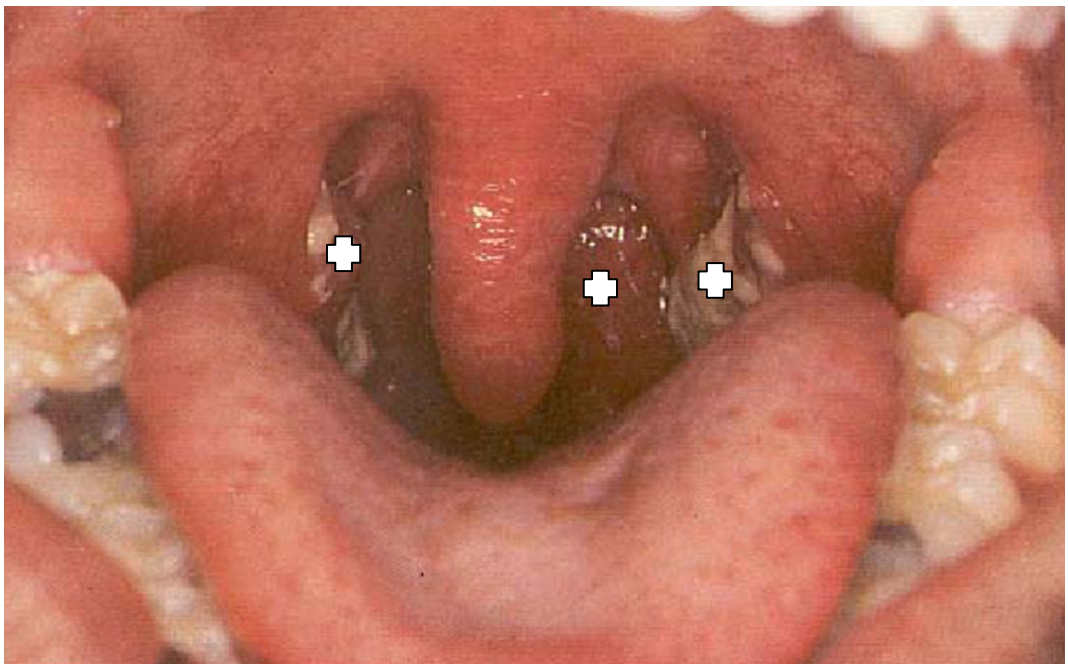
LABORATORY TESTS IN PHARYNGITIS

Throat culture

Even though paired acute and convalescent serologies should be the gold standard for the detection of GABHS in the pharynx, most studies consider that throat culture is enough for detecting the presence of group A streptococci in the upper respiratory tract and confirming

acute GABHS pharyngitis in patients with symptoms of sore throat [*Snow V et al, 2001*]. Throat culture yield is improved when collected appropriately, with the specimen obtained from the surface of either tonsil (or tonsillar fossae) and the posterior pharyngeal wall (**Figure 1**).

Figure 1. Areas were the pharyngeal swab must be collected



A child who cannot cooperate often requires immobilization of the neck to improve collection technique. Diagnostic accuracy is reduced when the specimen is collected from other areas of the mouth and oropharynx or if the patient has received an antibiotic shortly before the throat swab is obtained.

The duration of incubation of the culture also affects diagnostic accuracy [*Kellogg JA, 1990, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica, 1993*]. Cultures should first be examined 18–24 hours after incubation and re-examined after 48 hours for a final reading. When these practices are followed, sensitivity of a single throat culture is 90%–95% and specificity is >95%. The major disadvantage of throat culture in clinical practice is the delay in obtaining the results. The mean turnaround in obtaining the result of a throat culture is 48 hours [*Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica, 1993*]. In addition to this 48-hour delay, there is debate as to whether negative

cultures should be re-examined after an additional day to increase the sensitivity of the test [*Kocoglu E et al, 2006; Shulman ST, 2003*]. Most of the reviews and guidelines considered do not support throat culture as a necessary clinical instrument for routine diagnosis of GABHS [*Chapin KC et al, 2002; Forward KR et al, 2006; Gerber MA et al, 2004; Gieseker KE et al, 2002; Lindbæk M et al, 2004b; Shulman ST, 2003*].

Rapid antigen detection tests for GABHS

A wide variety of rapid antigen detection tests (RADT) are available for diagnosing GABHS pharyngitis, with different diagnostic properties [*Gerber MA et al, 2004; Tanz RR et al, 2009*]. The RADTs for the diagnosis of the streptococcal pharyngitis are based on acid extraction of cell-wall carbohydrate antigen and detection of the antigen with the use of a specific antibody. An alternative approach has been the rapid identification of *S. pyogenes*-specific DNA sequences by means of hybridisation with a DNA probe or by means of a real-time polymerase-chain-reaction assay. A wide range of sensitivity has been reported for currently available RADTs and the measured sensitivity has been shown to depend on the clinical likelihood of streptococcal infection in the test population [*Edmonson MB et al, 2005; Tanz RR et al, 2009*]. Swabbing the posterior pharynx and tonsils and not the tongue, lips, or buccal mucosa increases the sensitivity of these tests [*Fox JW et al, 2006a*].

The great majority of RADTs have a high specificity compared with culturing a throat swab on a sheep blood agar plate culture [*Gerber MA et al, 2004*], and thus a positive result can be considered to be definitive and to obviate the need for culture. The negative predictive values of the RADTs are high, generally being around 95% [*Chapin KC et al, 2002; Forward KR et al, 2006: Humair JP et al, 2006*]. Two systematic reviews aimed at evaluating the validity of RADTs. The first one was published in in Spanish [*Ruiz-Aragón J et al, 2010*], but failed to examine potential sources of heterogeneity. The more recent meta-analysis explores the variability of sensitivity and specificity using a systematic approach; the goal of this systematic review was to identify accurate, unbiased estimates of RADT characteristics for children, adults, and RADT variety [*Stewart EH et al, 2014*]. The authors included 59 studies that examined 55,766 patients [*Abu-Sabaah AH et al, 2006; Al-Najjar FY et al, 2008; Andersen JB et al, 2003; Araujo Filho BC et al, Armengol CE et al, 2004; Atlas SJ et al, 2005; Ayanruoh S et al, 2009; Buchbinder N et al, 2007; Camurdan AD et al, 2008; Chapin KC et al, 2002; Chiadmi F et al, 2004; Cohen R et al, 2004; Cohen JF et al, 2012;*

Contessotto Spadetto C et al, 2000; dos Santos AG et al, 2005; Dimatteo LA et al, 2001; Edmonson MB et al, 2005; Enright K et al, 2011; Ezike EN et al, 2005; Flores Mateo G et al, 2010; Fontes MJ et al, 2007; Forward KR et al, 2006; Fourati S et al, 2009; Fox JW et al, 2006a; Gieseker KE et al, 2003; Gurol Y et al, 2010; Hall MC et al, 2004; Hinfey P et al, 2010; Humair JP et al, 2006; Johansson L et al, 2003; Kawakami S et al, 2003; Keahey L et al, 2002; Kim S, 2009; Lindbæk M et al, 2004b; Paper 1; Paper 2; Llor C et al, 2011; Maltezou HC et al, 2008; Mayes T et al, 2001; McIsaac WJ et al, 2004; Mezghani Maalej S et al, 2010; Mirza A et al, 2007; Nerbrand C et al, 2002; Parviainen M et al, 2011; Regueras de Lorenzo G et al, 2012; Rimoin AW et al, 2010; Rogo T et al, 2011; Roosevelt GE et al, 2001; Rosenberg P et al, 2002; Santos O et al, 2003; Sarikaya S et al, 2010; Schmuziger N et al, 2003; Sheeler RD et al, 2002; Tanz RR et al, 2009; Uhl JR et al, 2003; van Limbergen J et al, 2006; Wong MC et al, 2002]. Forty three studies (18,464 patients) fulfilled the higher quality definition (at least 50 patients, prospective data collection, and no significant biases) and 16 (35,634 patients) did not. For the higher quality immunochromatographic methods in children (10,325 patients), heterogeneity was high for sensitivity and specificity. For enzyme immunoassay in children (342 patients), the pooled sensitivity was 86% (95% CI: 79–92%) and the pooled specificity was 92% (95% CI: 88–95%). For the higher quality immunochromatographic methods in the adult population (1,216 patients), the pooled sensitivity was 91% (95% CI: 87–94%) and the pooled specificity was 93% (95% CI: 92–95%). For enzyme immunoassay in the adult population (333 patients), the pooled sensitivity was 86% (95% CI: 81–91%) and the pooled specificity was 97% (95% CI: 96–99%).

In this systematic review of RADTs, the number of patients included in studies that met high methodological quality criteria was significantly smaller than the number of patients included in lower quality studies (18,464 vs. 35,634, respectively). However, the authors did not identify important sources of the high heterogeneity of sensitivity and specificity estimates among higher quality studies using immunochromatographic methods in children (10,325 patients). In children, immunochromatographic and enzyme immunoassay methods outperform optical immunoassay methods.

However, the performance of RADTs for GABHS is influenced by the skill, experience and expertise of the individual obtaining the throat swab and performing the RADT. The performance is also a function of the clinical characteristics of the illness of the patients selected for testing. As a result of this bias, often called spectrum bias, the performance of

RADT is not an absolute feature of a given test [*Bisno AL et al, 2002; Gerber MA et al, 2004*]. To improve the accuracy of RADT, the test should be performed by trained staff [*Fox JW et al, 2006b*] and performed in the posterior pharyngeal wall and both tonsils as mentioned before [*Fox JW et al, 2006a; Shulman ST, 2003; van der Veen EL et al, 2006*].

In conclusion, in both children and adults, all the observational studies and the guidelines considered support a high accuracy of immunochromotographic RADTs when these were performed in patients with a high probability of strep throat [*Atlas SJ et al, 2005; Edmonson MB et al, 2005; Hall MC et al, 2004; Humair JP et al, 2006; Maltezou HC et al, 2008; Tanz RR et al, 2009*], with the accuracy of RADTs being greater among patients with clinical criteria for GABHS, in both children and adults.

Role for additional tests in the assessment of severity of acute sore throat

Blood investigations are commonly carried out in patients presenting with tonsillitis. The significance of raised inflammatory markers in those with tonsillitis is debatable, but there is some evidence that their increase is linked to a higher likelihood of acute GABHS sore throat requiring antibiotics [*Holm A et al, 2007; Koo CY et al, 2011; van der Meer V et al, 2005*].

Regarding the diagnosis of Epstein-Barr pharyngitis Monospot testing is routinely undertaken mainly in hospital practice for the diagnosis of infectious mononucleosis, but results can be misleading, with current commercially available. Monospot tests quoted to be 70–92% sensitive and 96–100% specific [*Elgh F et al, 1996*]. The gold standard investigation is Epstein–Barr virus serology, since the presence of specific immunoglobulin M antibodies confirms infection, but the test is more costly and results take longer than the heterophile antibody test and is probably unnecessary in the majority of cases [*Bird JH et al, 2014; Womack J et al, 2015*]. Evidence within the literature suggests that the lymphocyte count alone or when used in combination with the total white cell count could be used as a quick screening test prior to monospot or serological testing, since infectious mononucleosis is unlikely if the lymphocyte count is less than 4,000 mm^3 [*Biggs TC, 2013*]. However, it is reported that in the paediatric population or those with strong clinical signs of infectious mononucleosis, these methods may be more unreliable. Moreover, these tests are not recommended in the primary care setting, since the prevalence of infectious mononucleosis is very low and a negative result does not rule out the existence of this disease. Measurement of

serum antibodies to streptolysin O or DNase B, although useful for retrospective diagnosis of streptococcal infection to provide support for the diagnosis of acute rheumatic fever or poststreptococcal glomerulonephritis, is not helpful in the management of pharyngitis, since titres do not begin to increase until 7 to 14 days after the onset of infection, reaching a peak in 3 to 4 weeks. Because serial tests are needed, they cannot be recommended for routine diagnosis in sore throat [*Matthys J et al, 2007*].

One review, focused on complications of GABHS pharyngitis, concluded that laboratory testing (e.g. erythrocyte sedimentation rate) might be indicated for suspected poststreptococcal adverse outcomes [*Hahn RG et al, 2005*]. Further, no evidence of whether clinical information combined with biomarker data provides better prognostic information for sore throat. On the basis of the results of this systematic review, it is not necessary to routinely use biomarkers in the assessment of acute sore throat. However, more research on the use of other biomarkers, particularly the use of C-reactive protein (CRP) or the utilisation of other biomarkers to better predict those cases of sore throat that need antibiotic therapy is clearly needed.

Use of RADTs is associated with an improvement of antibiotic usage

Many papers about the benefit of RADTs on antibiotic utilisation have been published, most of them since 2002 (**Table 9**). Some of these studies were carried out with children [*Maltezou HC et al, 2008; McIsaac WJ et al, 2004*] and others with adults [*Atlas SJ et al, 2005; Humair JP et al, 2006; Linder JA et al, 2006; McIsaac WJ et al, 2004; Worrall G et al, 2007: Llor C et al, 2011*]. Other studies included patients of all ages [*Johansson L et al, 2003; Little P et al, 2013a; McIsaac WJ et al, 2002; Rosenberg P et al, 2002*]. Findings in children and adults were similar. Overall, five studies indicated that the use of RADTs (alone) could reduce antibiotic use, whereas three other studies indicated that a strategy involving a combination of clinical score and RADT use could reduce antibiotic use.

Regarding studies performed with adults, clinicians using RADTs decreased the number of antibiotics. Worrall et al observed a percentage of antibiotics prescribed of 58% among clinicians who did not used the RADT compared to the 27% observed among those who did use the RADT [*Worrall G et al, 2007*]. In another study carried out in primary care, the use

of RADT significantly decreased the antibiotic prescribing from 60% to 37% in Switzerland [*Humair JP et al, 2006*].

Table 9. Papers considering the effect of use of RADTs on antibiotic use

Author	Type of study	Observations
McIsaac WJ et al, 2002	Randomised clinical trial	Control group: clinical check list. Intervention group: chart stickers that prompted them to calculate a score based on clinical findings and provided management recommendations linked to score totals
Rosenberg P et al, 2002	Prospective cohort study	Outcome: use of antibiotics according to results of tests
Johansson L et al, 2003	Prospective cohort study	The physicians estimated probability of infection with GABHS; they also noted management that would have been used before receiving any test results
McIsaac WJ et al, 2004	Prospective cohort study	Comparison of recommendations of two guidelines with RADT alone, clinical rules, and treatment for culture positive: A. culture all, B. two North American guidelines, C. one guideline, D. the other guideline, E. modified Centor score and culture approach, F. RADT approach. Outcome: Total and unnecessary antibiotics.
Atlas SJ et al, 2005	Prospective cohort study	For each patient with symptoms of acute pharyngitis was performed a RADT and culture. Antibiotic prescriptions at the clinical encounter were compared among patients with positive or negative RADT
Humair JP et al, 2006	Prospective cohort study	Five strategies: A. symptomatic treatment, B. systematic RADY, C. selective RADT, D. empirical antibiotic usage, E. systematic culture. Outcome: appropriate antibiotic use
Linder JA et	Retrospective	A retrospective analysis to determine if clinicians in practice

al, 2006	cohort study	use clinical criteria or microbiological testing to reduce antibiotic prescribing
Worrall G et al, 2007	Randomised clinical trial	Four arms: A. usual practice, B. decision rules only, C. RADT only, D. decision rules + RADT. Outcome: prescribing rates and type of antibiotic prescribed
Maltezou HC et al, 2008	Randomised clinical trial	Comparison of 3 groups: A private-public paediatrician, clinical diagnosis, B. private-public paediatrician, diagnosis by RADT and culture, C. hospital paediatrician, diagnosis by RADT and culture
Llor C et al, 2011	Randomised clinical trial	Two strategies: A. clinical score, B. RADT. Outcome: number of antibiotics prescribed and inappropriateness of antibiotic prescribing
Little P et al, 2013a	Pragmatic clinical trial	An internet programme randomised patients to targeted antibiotic use according to A. Delayed prescribing of antibiotics, B. clinical score, C. RADT

In a Spanish clinical trial, clinicians without access to RADT were more likely to prescribe antibiotics compared with those who performed rapid tests (64.1% versus 43.8%) and the more Centor criteria the patients presented, the greater the number of antibiotics prescribed, regardless of whether RADT was available. However, antibiotics were prescribed in 30.7% of the cases with negative RADT in this results study [*Llor C et al, 2011*].

However, a recent pragmatic clinical trial carried out in the UK, Little et al failed to observed a protective effect with the use of RADTs compared to use of only clinical criteria and another group assigned to delayed antibiotic prescribing [*Little P et al, 2013a*].

In conclusion, there is inconsistent evidence on which diagnostic strategy is best to reduce (unnecessary) antibiotic use [*Little P et al, 2014a*]. A strategy based on the use of clinical scores alone may be associated with higher antibiotic use as compared with either a combination of clinical score and RADT use or use of RADTs alone. Clinical scoring systems and rapid tests can be helpful in targeting antibiotic use [*Bjerrum L et al, 2013*].

RECOMMENDED THERAPY IN PATIENTS WITH PHARYNGITIS

Antibiotic therapy

The recommended treatment for streptococcal pharyngitis is penicillin V. The highest levels of evidence in terms of type of antibiotics comes from a Cochrane review conducted in 2013 examining the role of antibiotics in the presence of GABHS [*van Driel ML et al, 2013*]. The review included seventeen trials in its analysis (5,352 total participants); 16 compared penicillin with other antibiotic agents (six with cephalosporins, six with macrolides, three with carbacephem and one with sulphonamides), with the final one comparing clindamycin with ampicillin. Study conclusions revealed no strong evidence to show any meaningful differences across types of antibiotic studied.

As penicillin is cheap, reliable (no significant resistance to GABHS seen yet), safe for use in those with infectious mononucleosis and is well tolerated, it is an appropriate first-line treatment in those with suspected bacterial infection. Despite >70 years of penicillin use, clinical isolates of penicillin-resistant GABHS have not been described. This is apparently because the organisms are intolerant to mutations that reduce the affinity of penicillin-binding proteins [*Horn DL et al, 1998*].

The authors of this review could find no evidence within the literature comparing the efficacy of intravenous antibiotics therapy compared with oral therapy in the management of tonsillitis within the secondary care setting, mainly in patients with mild and moderate pharyngitis –the commonest scenario in primary care –. Anecdotally, it is presumed that intravenous therapy is preferable to oral administration. Many patients presenting to hospital will be unable to take oral therapy initially, making intravenous therapy more appropriate. Another study used to validate the treatment algorithm presented in this article revealed that a trial of intravenous antibiotic therapy (used in combination with fluid rehydration and steroid therapy) was associated with a significantly reduced rate of hospital admission and length of stay [*Bird JH et al, 2013*]. Although teasing out the exact effect of using the combination of an intravenous antibiotic with steroid is difficult, what is clear is in the population of patients presenting with inability to swallow with systemic features, the use of an intravenous antibiotic initially and then converting to oral therapy later is likely to be sound clinical practice.

In conclusion, oral penicillin V should be considered as first-line antibiotic in case of streptococcal infection.

Non-antibiotic therapy

The use of probiotics along with antibiotics makes little difference in terms of cure and, therefore, they are not recommended [*Gilbey P et al, 2015*].

Paracetamol is known to be effective and superior to placebo at reducing fever, headache and throat pain for up to 6 hours [*Bachert C et al, 2005*]. Non-steroidal anti-inflammatory drugs (NSAID), namely diclofenac and ibuprofen, are also highly effective when compared to placebo [*Boureau F et al, 1999; Gehanno P et al, 2003; Shy BD et al, 2014*]. NSAIDs should be used with caution in the presence of dehydration due to nephrotoxic effects, and rehydration therapy should be commenced in conjunction. No studies were found contraindicating the use of codeine, tramadol or other opioid metabolites. Caution must be taken when using opiates in those whom airway compromise is already a concern, due to the addition of opioid-associated respiratory depression. With regard to topical therapy, treatment with flurbiprofen 8.75 mg lozenge has shown to relieve sore throat pain, swollen throat and difficulty swallowing immediately after the intake [*Russo M et al, 2013; Shephard A et al, 2015*]. Ambroxol is also slightly more effective in relieving pain in acute sore throat than mint flavoured lozenges and placebo in the first hour after their intake [*Chenot JF et al, 2014*]. However, the additional benefits of both NSAID and ambroxol lozenges beyond three hours after their intake remain unclear. Moreover, some authors have reported an association of some complications of pharyngitis such as quinsy with a history of previous NSAIDs [*Demeslay J et al, 2014*]. In children, there have been no randomised control trials examining the efficacy of pain relief in sore throat regarding paracetamol, ibuprofen and diclofenac; either alone or in comparison with each other. Recent medicines and healthcare products regulatory agency guidance has suggested caution over the use of codeine within the paediatric population, especially in those with potential respiratory depression [*Robb PJ, 2013*].

In terms of topical mouthwash, a multicentre, prospective, randomised, double-blinded, placebo-controlled study enrolled 147 patients comparing chlorhexidine, gluconate and benzydamine hydrochloride with placebo on the systemic effects of streptococcal pharyngitis [*Cingi C et al, 2011*]. The study concluded that when combined with oral antibiotics, topical analgesic sprays decreased the intensity of clinical signs in patients with streptococcal pharyngitis. Similar findings have also been documented regarding the use of topical analgesic sprays versus placebo in viral pharyngitis in a study including 164 patients. Both

pain and quality of life were improved at day 3 and day 7 using mouth sprays versus placebo, with no measurable side-effects [*Cingi C et al, 2010*]. Evidence would suggest that the use of topical mouth sprays in acute tonsillitis, bacterial or viral, is well tolerated with few side-effects and may result in improvements in symptoms.

Regarding the efficacy of corticosteroids, the only relevant evidence within this area comes from the primary care setting. A Cochrane systematic review and meta-analysis reviewing eight trials in the ambulatory setting (369 children, 374 adults) examined patients given a short course of corticosteroid or placebo (in addition, all patients also received an antibiotic) [*Hayward G et al, 2012*]. Results revealed an increased likelihood of complete resolution of pain at 24 and 48 h regardless of GABHS status, and a reduction in the meantime to onset of pain relief by more than 6 hours. Interestingly, another Cochrane review only including patients diagnosed with infectious mononucleosis revealed an improvement in symptoms at 12 hours (versus placebo), but these benefits were not maintained following this time period [*Candy B et al, 2006*]. The algorithm highlighted within this latter review suggests that in the absence of complications, a single dose of corticosteroid should be considered. This is likely to work effectively as a pain reliever but also, it is hoped, aid early oral intake which should expedite oral therapy and hospital discharge. In terms of administration route, a few studies have examined the most appropriate delivery method of corticosteroids in tonsillitis, and to date, there appears to be no conclusive evidence. The highest level of evidence (randomised, double-blind, placebo-controlled trial) comes from a study conducted by Márvez-Valls et al examining oral versus intramuscular delivery of steroids in exudative pharyngitis in 70 patients [*Márvez-Valls EG et al, 2002*]. They concluded no significant difference between the two groups, when assessing visual analogue pain scores at 24 and 48 hours. This would suggest that if tolerated, oral steroids would be an appropriate delivery method. Of course in the acute setting, patients with severe tonsillitis might not be able to swallow medication or fluids, meaning a parenteral route would have to be considered.

VARIABILITY OF MANAGEMENT RECOMMENDATIONS

Differences among guidelines are not merely academic; they have important consequences for daily practice [*Linder JA et al, 2006*]. A patient consulting a GP for acute sore throat will be managed differently according to the country. One of the major points of disagreement

between international guidelines on the management of acute pharyngitis is related to indications of the use of RADTs [*Matthys J et al, 2007*].

In particular, from the available guidelines, it is still not clear whether a clinical decision alone, the use of RADTs, or a combination of clinical score with RADTs, should drive the decision on the use of antibiotics in patients presenting in the primary-care setting with acute pharyngitis. Hence, GPs in the USA, France, Finland or Spain will generally adopt a diagnostic test to decide on treatment, while in the UK and the Netherlands the decision will be driven by the severity of the disease [*Matthys J et al, 2007*]. In the UK and the Netherlands no diagnostic tests are used at all. These approaches are based on scientific evidence. The differences seem to be related to selection or interpretation of the available studies (**Table 10**).

Table 10. Summary information from guidelines evaluating the use of point-of-care tests in the diagnosis of GABHS pharyngitis

Guideline	Country	Conclusions
European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [*Pelucchi C et al, 2012*]	Europe	Testing and inflammatory markers not recommended. Antibiotic treatment recommended for patients with at least three criteria
Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) [*AFSSAPS, 2003*]	France	Testing only patients with at least two clinical criteria by using a RADT. Inflammatory markers testing not recommended
Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA) [*Cars O et al, 2012*]	Sweden	Testing only patients with at least two clinical criteria by using a RADT. If a RADT is negative and suspicious remain that the aetiology is streptococcal, a throat swab should be taken for culture. Inflammatory markers testing not recommended

Finnish Medical Society Duodecim [*Duodecim, 2007*]	Finland	Testing only patients with at least two clinical criteria by using a RADT. If a RADT is negative and suspicious remain that the aetiology is streptococcal, a throat swab should be taken for culture. Inflammatory markers testing not recommended
National Institute for Health and Clinical Excellence (NICE) [*NICE, 2008*]	UK	Testing and inflammatory markers not recommended. Antibiotic treatment recommended for patients with at least three criteria and consider delayed prescribing for those with two criteria
Scottish Intercollegiate Guidelines Network (SIGN) [*SIGN, 2010*]	Scotland	Testing and inflammatory markers not recommended. Antibiotic treatment recommended for patients with at least three criteria
Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM) [*Wächtler H et al, 2011*]	Germany	Testing and inflammatory markers not recommended. However, RADT can be used in patients with at least three criteria and its result should guide therapy
Nederlands Huisartsen Genootschap [*Starreveld JS et al, 2008*]	Holland	Testing and inflammatory markers not recommended. Antibiotic treatment recommended for patients with at least three criteria
Sociedad Española de Medicina Familiar y Comunitaria (semFYC) [*Molero JM et al, 2010*]	Spain	Testing only patients with at least two clinical criteria by using a RADT. Inflammatory markers testing not recommended
Societat Catalana de Medicina de Família [*Cots JM et al, 2005*]	Spain	Testing only patients with at least two clinical criteria by using a RADT and its result should guide therapy. Inflammatory markers testing not recommended
Italian Panel on the Management of Pharyngitis	Italy	Testing only patients with at least two clinical criteria by using a RADT. Inflammatory markers

in Children [*Chiappini E et al, 2012*]		testing not recommended
Infectious Diseases Society of America (IDSA) [*Shulman ST et al, 2012*]	USA	Testing only patients with at least two clinical criteria by using a RADT. Inflammatory markers testing not recommended
American College of Physicians (ACP); American Academy of Family Physicians (AAFP) [*Snow V et al, 2001*]	USA	Treat patients who have four criteria and test patients with two and three criteria or test no one and treat patients who meet three or four criteria. Inflammatory markers not recommended
Centers for Disease and Prevention (CDC) [*Cooper RJ et al, 2001*]	USA	Recommends for patients with two or more criteria the following strategies: (a) Test patients with two, three, or four criteria by using a rapid antigen test, and limit antibiotic therapy to patients with positive test results; (b) test patients with two or three criteria by using a rapid antigen test, and limit antibiotic therapy to patients with positive test results or patients with four criteria; or (c) do not use any diagnostic tests, and limit antibiotic therapy to patients with three or four criteria

Areas of uncertainty

Fine et al reported a major validation of clinical prediction rules for predicting GABHS pharyngitis [*Fine AM et al, 2012*]. They examined the prediction model that first reported in 1981 [*Centor RM et al, 1981*] and the modification (incorporating age into the decision rule) that McIsaac et al reported in 1998 [*McIsaac WJ et al, 1998*]. This validation confirms a recent meta-analysis that arrived at the same finding [*Aalbers J et al, 2011*]. These models provide a probability of a positive GABHS culture based on a prevalence estimate and 4-point scoring system. The 4-point system appears to work well for preadolescent pharyngitis, where ultimately the clinician must make a dichotomous decision— GABHS infection or a

viral infection. However, as patients enter adolescence and continue growing into young adulthood, the model becomes more controversial; indeed, the 2 US guidelines differ in their approach to adult pharyngitis [*Centor RM et al, 2007*]. To understand why there is less certainty in the diagnosis of pharyngitis in adolescents and older persons, several important differences between this population and young children are noted [*Mitchell MS et al, 2011*]:

- Adolescents and young adults respond to penicillin treatment of GABHS with a 2-day decrease in symptoms, while preadolescents do not appear to show this effect [*Zwart S et al, 2000a: Zwart S et al, 2003*];
- Group C (and other non–group A) β-haemolytic streptococcal pharyngitis occurs more frequently in adolescents and young adults than in preadolescents. In adolescents and young adults, treatment of group C streptococcal pharyngitis results in a 1-day shorter duration of symptoms [*Zwart S et al, 2000b*];
- While both age groups develop Epstein-Barr infections, only the adolescents and young adults develop the infectious mononucleosis syndrome; and
- *F. necrophorum* pharyngitis occurs much more frequently in adolescents and young adults, as does the Lemierre syndrome

Given these differences, we could ask ourselves if we should empirically treat adolescents and young adults with antibiotics if they have a Centor score of 3 or 4. To answer this question we should make explicit the potential benefits and risk of antibiotic therapy. If a pharyngitis has a bacterial cause (at least with GABHS and group C streptococcal pharyngitis), then treatment with appropriate antibiotics will decrease symptom duration for adolescents and young adults [*Spinks A et al, 2013*]. We cannot be certain that antibiotics can decrease the duration of fusobacterial pharyngitis. Given this information, some authors back up the treatment of GABHS, group C streptococci, group G streptococci, and fusobacterial pharyngitis.

All experts and guidelines agree not to test or treat patients with scores of 0 or 1 with antibiotics. Scores of 2 are indeterminate, and currently, most guidelines suggest rapid streptococcal testing. In other countries such as the United Kingdom, a strategy of delayed prescribing of antibiotics, is highly recommended among Centor score 2 [*National Institute for Health and Clinical Excellence, 2008*]. Overall, patients with scores of 3 or 4 represent approximately 30% of all adolescent and adult patients with pharyngitis. Some authors

recommend patients with scores of 3 and/or four to be treated empirically without further testing but others do recommend the use of RADT.

In this context, several decision analyses have compared the cost-effectiveness of various strategies for diagnosis and treatment (**Table 11**). One analysis of four strategies for the management of pharyngitis in children (treatment of all patients with symptoms, RADT alone, culture alone, or RADT plus culture) concluded that a RADT plus culture was most cost-effective when the costs of managing complications of streptococcal infection and treatment were included [*Lieu TA et al, 1990*]. Another study involving children, which included these four strategies plus a "treat none" strategy and used a sensitivity of 80% for the RADT, showed that the RADT alone was the most cost-effective approach [*Ehrlich JE et al, 2002*].

Table 11. Strategies of antibiotic therapy in pharyngitis

Strategies of antibiotic therapy in pharyngitis
No treatment
Treatment of all patients with symptoms
Treatment based on an algorithm of signs and symptoms alone
Antibiotic treatment based on the results of a throat culture
Treatment based on the results of a RADT alone
Treatment based on the results of a RADT plus culture in patients with a negative RADT
Treatment based on an algorithm of signs and symptoms in combination with the selective use of culture
Treatment based on an algorithm of signs and symptoms in combination with the selective use of RADT (most recommended)

Some clinical guidelines are now advocating an increasingly nihilistic approach to acute pharyngitis, in which diagnostic testing is not performed and antibiotic treatment is not provided [*Gaines C et al, 2015*]. However, many GPs remain uncomfortable with this

nihilistic approach, and surveys indicate that antibiotic prescribing to adults presenting with sore throats continues to vastly exceed the prevalence of GABHS in this population [*van Brusselen D et al, 2014*]. A similar study involving adults concluded that empirical treatment of all symptomatic patients was the least cost-effective strategy and that the other four strategies had similar cost-effectiveness. The strategy of treating only patients with a positive culture was the least expensive. However, a RADT plus culture would be the most cost-effective strategy if the prevalence of streptococcal pharyngitis were greater than 20% [*Neuner JM et al, 2003*]. A similar result was observed in a relatively recent meta-analysis carried out in our country in paediatric population [*Giráldez-García C et al, 2011*]. A consistent finding is that empirical antibiotic treatment on the basis of symptoms alone results in overuse of antibiotics, increased costs, and an increased rate of side effects from antibiotics, as compared with other strategies.

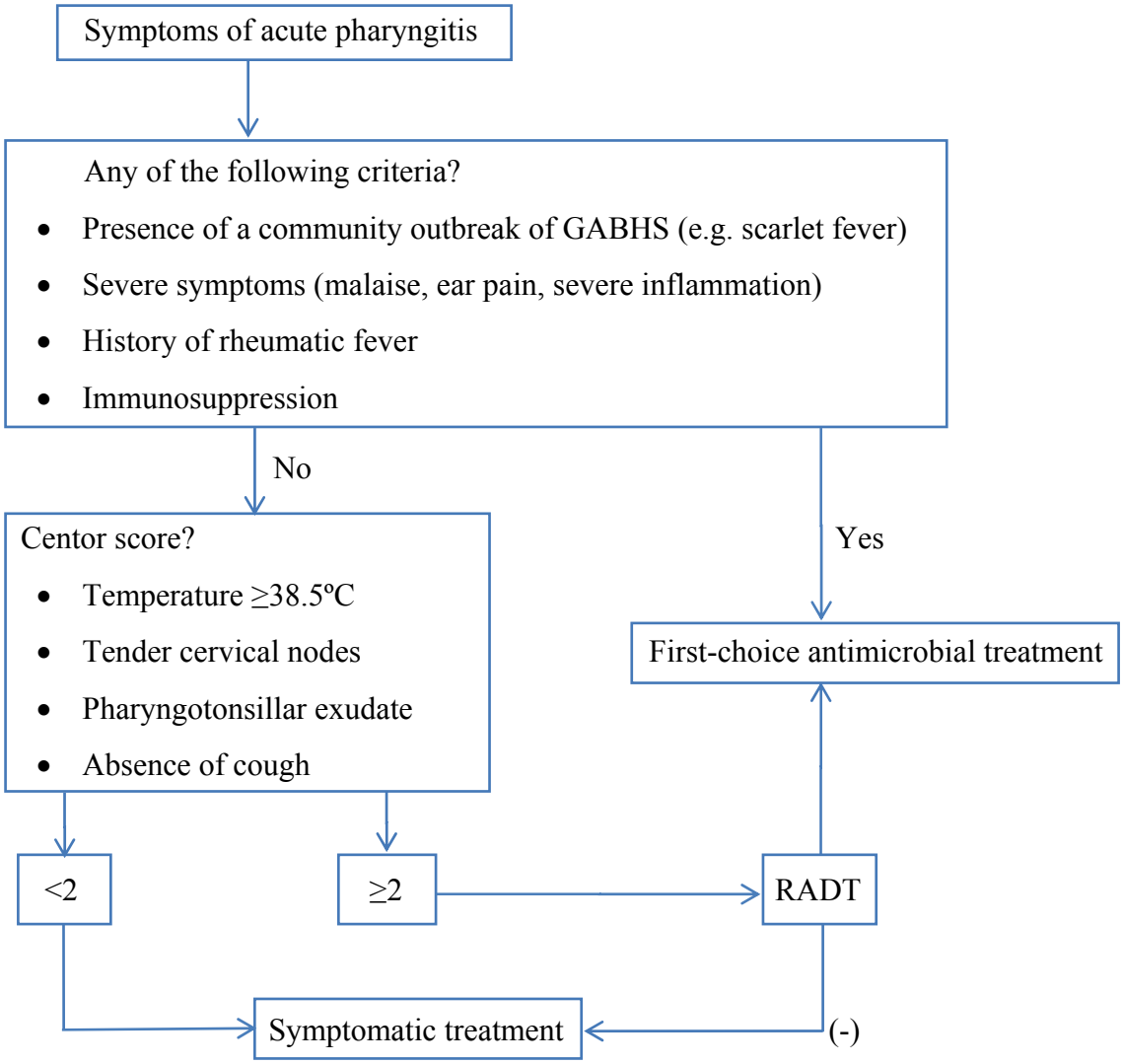
Table 12 describes when a RADT should be recommended by the Spanish Society of Family Medicine (semFYC) depending on the age of the patients and describes the situations in which these RADTs should not be used in clinical practice [*Molero JM et al, 2010*].

Table 12. When use of RADT should and should not be recommended in the practice (semFYC guidelines)

Clinical condition	Observations
Patients aged 4 or more with pharyngitis and two or more Centor criteria	Fever or history of fever, tonsillar exudate or tonsil inflammation, tender anterior cervical glands, absence of cough
Patients younger than 4 years, only if there is any of these conditions	Community outbreak of GABHS infection, paronychia, impetigo, scarlatiniform rash, strawberry tongue
RADT should not be carried out with the presence of any of these conditions	Suspected viral infection (age younger than 4 years and patients with Centor score less than two), immunocompromised patient, previous taking of antibiotics, history of rheumatic fever, chronic pharyngitis, severe symptoms, or outbreak of GABHS infection in the community

What is clear-cut is that patients with a Centor score of 0 or 1 are unlikely to have GABHS infection, and, therefore, further testing should not be recommended. As recently mentioned by Linder, although management of adults with a sore throat is simple, clinicians often overcomplicate it [*Linder JA, 2015*]. Approximately one half of adults who seek care for a sore throat will have a Centor score of 0 or 1, but many clinics indiscriminately test all patients who present with pharyngitis [*Fine AM et al, 2012; Linder JA et al, 2006*].

Figure 2. Management of acute pharyngitis (semFYC recommendations, 2015)



Indiscriminant testing may improve patient flow, but it exposes patients to inconvenience, discomfort, expense, false-positive test results, and unnecessary antibiotics. Better triage

before visits. Whether by online symptom checkers, phone, video, or asynchronous e-visits, could reduce unnecessary visits for a self-limited illness [*Fine AM et al, 2013*].

These recommendations have also endorsed by other primary care Spanish scientific societies, such as *Sociedad Española de Médicos de Atención Primaria* (SEMERGEN), *Sociedad Española de Médicos Generales y de Familia* (SEMG) and *Sociedad Española de Pediatría Extrahospitalaria y de Atención Primaria* (SEPEAP). However, since some key papers have been published over the last five years, an algorithm has recently been published by the Spanish Society of Family Medicine [*Llor C et al, 2015*].

Figure 2 updates these recommendations with the inclusion of the latest papers published on acute pharyngitis. It constitutes the guidelines to be followed by GPs and paediatricians in Spain. This clear-cut algorithm clearly describes the situations in which antibiotic therapy should not be administered, since viral infections are not considered in this flowchart. However, this algorithm might not possibly reflects the truth about when antibiotic therapy should be warranted, since there is no sufficient evidence about the need of antibiotic therapy in streptococcal causes other than GABHS and fusobacterial pharyngitis, but on the basis of the current evidence, constitutes the least worst guideline available at the time being [*Cots JM, et al, 2015*], and it is mainly based on a paradigm: In primary health care, never prescribe antibiotics to patients suspected of having an uncomplicated sore throat caused by GABHS without first confirming the presence of this bacterium [*Gunnarsson MS et al, 2012*].

OBJECTIVES

Main objective

To evaluate the validity of two immunochromotographic RADT in patients with a high suspicion of presenting pharyngitis by GABHS.

Secondary objectives

1. To assess the validity of the RADT OSOM® Strep A (Genzyme lab) for diagnosing GABHS pharyngitis in patients aged 14 or older with acute sore throat and at least two Centor criteria.
2. To assess the validity of the Analyz-Strep A Rapid® test (Orion Diagnostica) for diagnosing GABHS pharyngitis in adults with acute sore throat and at least three Centor criteria.
3. To evaluate if the repetition of the RADT OSOM® Strep A (Genzyme lab) in patients aged 14 or more with acute sore throat and at least two Centor criteria with a previously negative RADT improves the validity of the RADT.
4. To evaluate the association between CRP concentrations with the aetiology of pharyngitis in adults with acute sore throat and four Centor criteria.

METHODS

Common methods used in the four substudies

Samples for gold standard were taken by the GPs, who had previously been trained to perform the technique correctly with vigorous rotation of the tonsils and the posterior pharynx without touching the tongue, teeth or gums. They were sent to the Department of Microbiology of the Hospital Joan XXIII of Tarragona with AMIES (Copan Innovation, Brescia, Italy) as medium. Samples were seeded in a plate of blood agar and were incubated at 37ºC in an atmosphere of CO_2 at 5% during 48 h. A culture was considered positive for GABHS, with a growth of any number of β-haemolytic colonies, Gram staining with streptococcal morphology and a catalase negative test with posterior identification, with an automated panel for WIDER Gram-positive cocci (Soria Melguizo, Madrid, Spain). Results were confirmed with posterior serogrouping with the Streptococcal Grouping Kit (Oxford, UK). The culture was considered negative after 48 hours of incubation, with the absence of β-haemolytic colonies. In patients, with a negative RADT, the determination was repeated.

Data analysis

Clinical characteristics were compared using t-test for continuous variables and chi-squared analysis for categorical variables. The sensitivity, specificity and positive and negative predictive values of the RADTs were determined by a two-way contingency table, using culture results as the gold standard. Statistical significance was accepted at $p<0.05$.

Paper 1

Validation of a rapid antigenic test in the diagnosis of pharyngitis caused by GABHS (Aten Primaria 2008;40:489–94.)

- GPs participating: Prospective study was carried out in six surgeries at the primary care centre Jaume I (Tarragona, Spain).
- Time span: From January 2007 to March 2008.
- Patients: Adults aged 14 years or more with acute pharyngitis and ≥2 Centor criteria – history of fever, presence of tonsillar or pharyngeal exudates, presence of tender cervical glands and/or absence of cough– recruited consecutively. Subjects who had received

systemic antibiotics within the previous 2 weeks and if a swab could not be collected were excluded.

- Sample size: It was calculated to be 170 subjects for a precision of 6% and expected proportion of 20%, with a 95% confidence interval.
- RADT used: OSOM® StrepA (Genzyme Diagnostics, Cambridge, MA, USA).

Paper 2

Repetition of the rapid antigen test in initially negative supposed streptococcal pharyngitis is not necessary in adults (Int J Clin Pract 2009;63:1340–4.)

- GPs participating: Prospective study was carried out in six surgeries at the primary care centre Jaume I (Tarragona, Spain).
- Time span: From January 2007 to October 2008.
- Patients: Adults aged 14 years or more with acute pharyngitis and ≥2 Centor criteria – history of fever, presence of tonsillar or pharyngeal exudates, presence of tender cervical glands and⁄or absence of cough– recruited consecutively. Subjects who had received systemic antibiotics within the previous 2 weeks were excluded.
- RADT used: OSOM® StrepA (Genzyme Diagnostics, Cambridge, MA, USA).
- In patients, with a negative RADT, the determination was repeated.

Paper 3

Validation of Analyz-Strep A Rapid test in the diagnosis of acute pharyngitis (Aten Primaria 2015;47:69–70.)

- GPs participating: Prospective study was carried out in six surgeries at the primary care centre Jaume I (Tarragona, Spain).
- Time span: From January 2011 to December 2011.
- Patients: Adults aged 18 years or more with acute pharyngitis and ≥3 Centor criteria – history of fever, presence of tonsillar or pharyngeal exudates, presence of tender cervical glands and⁄or absence of cough– recruited consecutively.

- RADT used: Analyz-Strep A Rapid® test (Orion Diagnostica, Espoo, Finland).

Paper 4

Association between C-reactive protein rapid test and group A streptococcus infection in acute pharyngitis. J Am Board Fam Med 2014;27:424–6.

- GPs participating: Prospective study was carried out in six surgeries at the primary care centre Jaume I (Tarragona, Spain).
- Time span: from January 2010 to May 2012.
- Patients: Adults aged 18 years or more with acute pharyngitis and 4 Centor criteria – history of fever, presence of tonsillar or pharyngeal exudates, presence of tender cervical glands and absence of cough– recruited consecutively.
- RADT used: Patients underwent a CRP rapid test during the consultation by means of two devices: QuikRead® and QuikRead Go® (Orion Diagnostica, Espoo, Finland).

RESULTS

PAPERS DESCRIBING THE ROLE OF RADT IN SORE THROAT IN ADULTS

PAPER 1.

Llor C, Hernández Anadón S, Gómez Bertomeu FF, Santamaria Puig JM, Calviño Domínguez O, Fernández Pagés Y. Validation of a rapid antigenic test in the diagnosis of pharyngitis caused by group a beta-haemolytic Streptococcus. Aten Primaria 2008;40:489–94.

PAPER 2.

Llor C, Calviño O, Hernández S, Crispi S, Pérez-Bauer M, Fernández Y, et al. Repetition of the rapid antigen test in initially negative supposed streptococcal pharyngitis is not necessary in adults. Int J Clin Pract 2009;63:1340–4.

PAPER 3.

Calviño Domínguez O, Hernández Anadón S, Teresa Martínez Blesa M, Hernández Anadón M. Validación Analyz-Strep A Rapid test en el diagnóstico de la faringitis aguda. Aten Primaria 2015;47:69–70.

PAPER 1

Llor C, Hernández Anadón S, Gómez Bertomeu FF, Santamaria Puig JM, Calviño Domínguez O, Fernández Pagés Y. Validation of a rapid antigenic test in the diagnosis of pharyngitis caused by group a beta-haemolytic Streptococcus. Aten Primaria 2008;40:489–94.

Includes:

Author's reply: Clarifications on the StrepA validity study. Aten Primaria 2009;41:469–70.

Localizador web
Artículo 250.467

Validación de una técnica antigénica rápida en el diagnóstico de la faringitis por estreptococo β-hemolítico del grupo A

Carles Llor[a], Silvia Hernández Anadón[a], Frederic Francesc Gómez Bertomeu[b], Josep Maria Santamaria Puig[b], Olga Calviño Domínguez[a] e Yvonne Fernández Pagés[a]

Objetivo. Determinamos la validez de la técnica antigénica rápida (TAR) OSOM StrepA Genzyme en el diagnóstico de la faringitis aguda causada por estreptococo β-hemolítico del grupo A (EBHGA).
Diseño. Estudio de pruebas diagnósticas.
Emplazamiento. Equipo urbano de atención primaria.
Participantes. Todos los pacientes mayores de 14 años atendidos en 6 consultas con síntomas de odinofagia y 2 o más de los criterios de Centor (exudado faringomigdalar, adenopatías laterocervicales dolorosas, ausencia de tos y/o historia o presencia de fiebre).
Mediciones principales. A todos los pacientes se les tomó una muestra faringoamigdalar con 2 hisopos, uno para TAR y otro que fue remitido servicio de microbiología para realizar cultivo.
Resultados. Fueron evaluables 182 sujetos, con una edad media de 30,6 ± 12,1 años, 116 mujeres (63,7%). Presentaron 2, 3 y 4 criterios de Centor 63, 83 y 36 sujetos, respectivamente. El cultivo fue positivo en 102 casos (56%), observándose infección por EBHGA en 40 pacientes (22%; intervalo de confianza [IC] del 95%, 21,2-22,8); en 26 casos se aisló estreptococo del grupo C (14,3%). La infección por EBHGA presentó una mayor prevalencia entre los pacientes con 4 criterios (un 38,9% frente a un 25,3% observado con 3 criterios y frente al 7,9% con 2 criterios; p < 0,001). La TAR tuvo una sensibilidad del 95%, una especificidad del 93%, un valor predictivo positivo del 79,2% y un valor predictivo negativo del 98,5%.
Conclusiones. Estos resultados demuestran la utilidad de la TAR para el diagnóstico de la faringitis estreptocócica. Su uso debería extenderse a todas las consultas de atención primaria.

Palabras clave: Faringitis. *Streptococcus pyogenes*. Técnica antigénica rápida. Estreptococo β-hemolítico del grupo A.

VALIDATION OF A RAPID ANTIGENIC TEST FOR THE DIAGNOSIS OF ACUTE PHARYNGITIS CAUSED BY GROUP A β-HAEMOLYTIC *STREPTOCOCCUS*

Objective. To determine the validity of the rapid antigen test (RAT) OSOM StrepA Genzyme for the diagnosis of acute pharyngitis caused by group A β-haemolytic strep (GABHS).
Design. Diagnostic techniques survey.
Setting. Urban primary care centre, Spain.
Participants. All patients over 14 years old seen in 6 surgeries with sore throat and 2 or more Centor criteria: pharyngotonsillar exudate, tender laterocervical nodes, absence of coughing, and/or history or presence of fever.
Principal measurements. Pharyngeal swabs were taken from all the patients, one for RAT and another to send for culture in the microbiology department.
Results. A total of 182 patients were evaluable, with a mean age of 30.6 (12.1) years of which 116 were women (63.7%); 63 patients had 2 Centor criteria; 83 had 3 and 36, the 4 criteria. The culture was positive in 102 patients (56%), with GABHS showing infection in forty (22%; 95% confidence interval [CI], 21.2-22.8). Group C *streptococcus* was isolated in 26 patients (14.3%). GABHS was higher among patients with four Centor criteria (38.9% vs 25.3% observed among those with 3 criteria and 7.9% with 2 criteria; P<.001). Sensitivity of RAT was 95%, with a specificity of 93%, a positive predictive value of 79.2% and a negative predictive value of 98.5%.
Conclusions. These results show the usefulness of RAT for diagnosing streptococcal pharyngitis. Its use should be spread to all primary care practices.

Key words: Pharyngitis. *Streptococcus pyogenes*. Rapid antigen test. Group A β-haemolytic *streptococcus*.

English version available at
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A este artículo sigue un comentario editorial (pág. 495)

[a]Medicina de Familia. Centro de Salud Jaume I. Tarragona. España.
[b]Servicio de Microbiología. Hospital Joan XXIII. Tarragona. España.

Financiación: Hemos dispuesto de forma gratuita de tiras OSOM StrepA de Genzyme, que han sido facilitadas por el Laboratorio Leti. No hemos recibido ninguna cuantía económica directa o indirecta de dicho laboratorio para la realización de este estudio.

Correspondencia: C. Llor.
Foixarda, 95.
43008 Tarragona. España.
Correo electrónico:
carles.llor@urv.cat

Manuscrito recibido el 26-3-2008.
Manuscrito aceptado para su publicación el 28-4-2008.

Introducción

La faringitis es, junto con la rinitis, el motivo asistencial más frecuente de consulta al médico de atención primaria en España[1]. Es también una de las razones más frecuentes por las que se prescribe un antibiótico en nuestro país, con una tasa aproximada de prescripción del 80%[1-3]; a pesar de ello, sólo el 50% de las faringitis en niños y el 15-25% de las de los adultos tienen una etiología bacteriana[2-4]. No debe tratarse de forma sistemática con antibióticos ya que, según los metaanálisis efectuados, la mayor parte de las faringitis se curan aunque no se administren antibióticos[5]. Sólo la infección causada por *Streptococcus pyogenes* o estreptococo β-hemolítico del grupo A (EBHGA) requiere la utilización de un antibiótico, ya que corta la transmisión y diseminación de *S. pyogenes* en la comunidad, reduce la sintomatología respecto el grupo no tratado en una media de 16 h y porque previene las complicaciones supurativas; según la revisión Cochrane, por cada 100 pacientes tratados con antibióticos respecto el grupo asignado a placebo se produce un caso menos de fiebre reumática, 2 casos menos de otitis media aguda y 3 casos menos de abscesos periamigdalinos[5,6]. Sin embargo, la mayor parte de estudios incluidos en esta revisión se llevaron a cabo en la década de 1950 y 1960, y la incidencia de complicaciones en las dos últimas décadas es mucho menor que en la época en la que se llevaron a cabo estos ensayos clínicos[7]. Recientemente se ha publicado un trabajo en el Reino Unido en el que se confirma que la disminución en la prescripción de antibióticos para tratar la faringitis en los últimos años no se acompaña de un mayor número de casos de fiebre reumática o de abscesos periamigdalinos[8].

La faringitis aguda plantea problemas al médico de atención primaria, ya que es difícil diferenciar clínicamente la etiología por EBHGA de la no estreptocócica. El patrón oro para su diagnóstico sigue siendo el cultivo faríngeo, pero presenta algunas limitaciones importantes, como la demora en la consecución de los resultados y, además, no permite distinguir entre infección aguda y estado de portador. Habitualmente, en la práctica, se utilizan los criterios clínicos para llegar a identificar a aquellos pacientes que deben seguir un tratamiento antimicrobiano. En este sentido, los más conocidos son los 4 criterios propuestos por Centor[9]: historia o presencia de fiebre, exudado faringoamigdalar, adenopatías laterocervicales dolorosas y ausencia de tos. Más tarde, McIsaac incluyó también la edad, de forma que se consideraba otro criterio la edad inferior a 15 años[10]. En los últimos años se han desarrollado nuevas técnicas antigénicas rápidas (TAR) para el diagnóstico de las faringoamigdalitis agudas producidas por EBHGA, con una mejor sensibilidad y especificidad que las que existían en la década de 1990.

En este estudio pretendemos evaluar la validez del OSOM Genzyme StrepA en pacientes con 2 o más criterios de Centor.

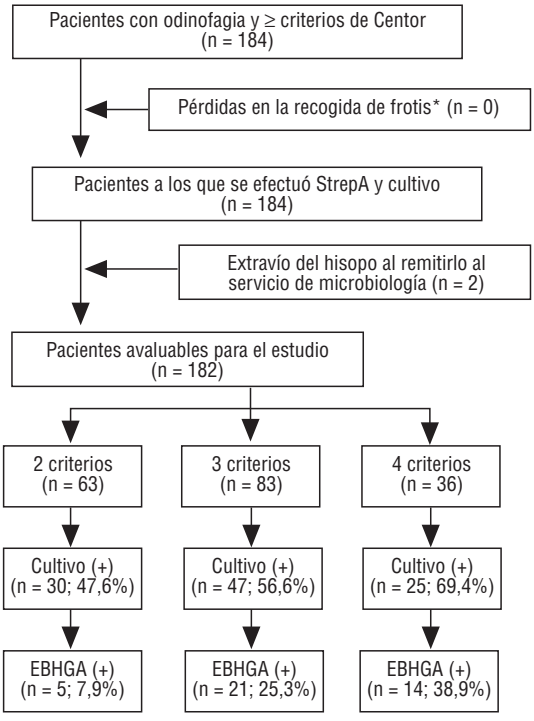
Métodos

Se trata de un estudio observacional prospectivo efectuado entre enero de 2007 y marzo de 2008. Se incluyeron consecutivamente en 6 consultas de nuestro centro de salud pacientes mayores de 14 años con clínica de odinofagia y 2 o más de los criterios de Centor: exudado faringomigdalar, adenopatías laterocervicales dolorosas, ausencia de tos y/o historia o presencia o historia de fiebre (> 38 ºC). Se excluyeron los pacientes que habían recibido tratamiento antimicrobiano en las 2 semanas previas y si no se habían podido recoger frotis. El tamaño de la muestra se calculó en 170 individuos para una precisión del 6% y una proporción esperada del 20%, con un intervalo de de confianza (IC) del 95%. Se confeccionó una hoja de recogida de datos en la que constaban edad, sexo, presencia de estos 4 criterios y si la infección era recurrente (menos de 2 meses desde el último episodio) o no recurrente. Para este estudio se tomaron 2 muestras a cada paciente, friccionando sobre las amígdalas y/o pared posterior de la faringe, sin tocar ni la lengua ni los dientes ni las encías, con una torunda con algodón para cultivo. La toma de muestras fue realizada por los 6 médicos de familia, que previamente habían sido entrenados para efectuar la técnica de forma correcta. Con una de las muestras se realizó el OSOM StrepA (Laboratorio Genzyme), siguiendo las instrucciones del fabricante. El otro hisopo, con medio de transporte tipo AMIES (Copan Innovation Italy), se envió al Servicio de Microbiología del Hospital Joan XXIII de Tarragona. Se procedió a la siembra en una placa de agar sangre y se incubaba a una temperatura de 37 ºC en atmósfera de CO_2 al 5% durante 48 h. Se consideró cultivo positivo para *S. pyogenes* el crecimiento de cualquier número de colonias β-hemolíticas, tinción de Gram positiva con morfología de estreptococo y test de catalasa negativo, con posterior identificación mediante el panel automatizado para cocos grampositivos WIDER (Fco. Soria Melguizo). Los resultados se confirmaron con el posterior serogrupado mediante el *Streptococcal Grouping Kit* (Oxford, Reino Unido). El cultivo se consideró negativo tras 48 h de incubación con ausencia de colonias β-hemolíticas.

Para el análisis estadístico se utilizaron las pruebas de la χ^2 para el análisis de variables cualitativas y de la t de Student-Fisher para comparación de medias. Se calcularon la sensibilidad, la especificidad, el valor predictivo positivo y el valor predictivo negativo para los distintos criterios de Centor y para la TAR. Se consideraron diferencias estadísticamente significativas valores de $p < 0,05$.

Resultados

Se incluyeron en el estudio de forma consecutiva 184 pacientes con síntomas de faringitis y, al menos, 2 criterios de Centor, aunque 2 hisopos se extraviaron en el transporte al servicio de microbiología, por lo que resultaron evaluables 182 casos (véase esquema general del estudio). La edad media fue de 30,6 ± 12,1 años, con 116 mujeres (63,7%). Un total de 63 pacientes presentaban 2 criterios de Centor, 83 presentaban 3 criterios y 36 pacientes, 4 criterios. El criterio de Centor que más frecuentemente presentaban



Esquema general del estudio

Un paciente presentó náuseas con el procedimiento, aunque se pudieron recoger los dos frotis.
EBHGA: estreptococo β-hemolítico del grupo A.

los pacientes fue el exudado faringoamigdalar (158 casos; 86,8%), seguido de la historia de fiebre (140 casos; 76,9%), mientras que el menos frecuente fue la presencia de adenopatías laterocervicales dolorosas (89 casos; 48,9%). El cultivo fue positivo para algún microorganismo en 102 casos (56%), siendo más frecuente entre los que presentaban 4 criterios (25 casos; 69,4%), sin que se observaran diferencias estadísticamente significativas con los otros dos grupos de pacientes. En la tabla 1 se describe la etiología observada según el número de criterios de Centor y en la figura 1 se exponen los distintos agentes etiológicos aislados en el cultivo. No se observaron diferencias estadísticamente significativas entre ambos sexos y la incidencia de faringoamigdalitis estreptocócica. La edad media entre los cultivos positivos para EBHGA fue ligeramente inferior a los que presentaron cultivo negativo, incluso sin hallar diferencias estadísticamente significativas (29,7 ± 11 frente a 30,9 ± 12,3 años). La incidencia de infección por EBHGA fue significativamente más alta entre los que presentaban 4 criterios de Centor, seguida de los pacientes con 3 criterios y de los que tenían sólo 2 criterios.

Los criterios de Centor asociados con una mayor frecuencia de infección por EBHGA fueron la ausencia de tos y la presencia de adenopatías laterocervicales dolorosas. Así, se aisló EBHGA en el 27,6% de los pacientes que no presentaban tos, porcentaje significativamente mayor al observado entre los sujetos que sí tosían (9,1%; $p < 0,01$). La infección por EBHGA se observó más frecuentemente entre los pacientes que presentaban adenopatías laterocervicales dolorosas (el 29,2 frente al 15,1% en aquellos casos que no las tenían; $p < 0,05$). La infección por EBHGA también fue algo más frecuente entre los que tenían historia o presencia de fiebre (el 23,6 frente al 16,7%) y entre aquellos casos con exudado faringoamigdalar (el 22,8 frente al 16,7%); sin embargo, en estos 2 casos no se observaron diferencias estadísticamente significativas (fig. 2). En la tabla 2 se describe la validez de los criterios de Centor en el diagnóstico de la faringitis por EBHGA.

La TAR fue positiva en 48 casos y negativa en las restantes 134 determinaciones (tabla 3). La sensibilidad observada con esta técnica fue del 0,95% y la especificidad, del 0,93%. Se observaron 10 falsos positivos y 2 falsos negativos. El valor predictivo positivo fue del 0,79 y el valor predictivo negativo, del 0,98.

TABLA 1 **Etiología observada según número de criterios de Centor**

Germen	Dos	Tres	Cuatro	Total
EBHGA	5 (7,9%)	21 (25,3%)	14 (38,9%)	40 (22,0%)
Estreptococo del grupo B	3 (4,8%)	4 (4,8%)	1 (2,8%)	8 (4,4%)
Estreptococo del grupo C	11 (17,5%)	10 (12,0%)	5 (13,8%)	26 (14,3%)
Estreptococo del grupo F	3 (4,8%)	2 (2,4%)	1 (2,8%)	6 (3,3%)
Estreptococo del grupo G	0	2 (2,4%)	0	2 (1,1%)
Otros estreptococos	4 (6,3%)	1 (1,2%)	0	5 (2,7%)
Otras bacterias distintas de estreptococos	4 (6,3%)	7 (8,4%)	4 (11,1%)	15 (8,2%)
Cultivo negativo	33 (52,4%)	36 (43,4%)	11 (30,6%)	80 (44,0%)
Total	63 (100%)	83 (100%)	36 (100%)	182 (100%)

EBHGA: estreptococo β-hemolítico del grupo A.

Discusión

La sensibilidad y la especificidad alcanzadas con la TAR utilizada, superiores al 90%, junto con el elevado valor predictivo negativo, en nuestro estudio del 98,5%, hacen de esta prueba una herramienta diagnóstica de gran ayuda para el médico de familia. Antes de discutir los resultados tenemos que destacar los puntos diferenciales de nuestro estudio comparado con otros. Hemos incluido a pacientes con clínica de faringitis con sospecha de etiología estreptocócica; es decir, a aquellos casos con 2 o más de los criterios de Centor. Aun así, la incidencia observada de EBHGA fue del 22%. En otros

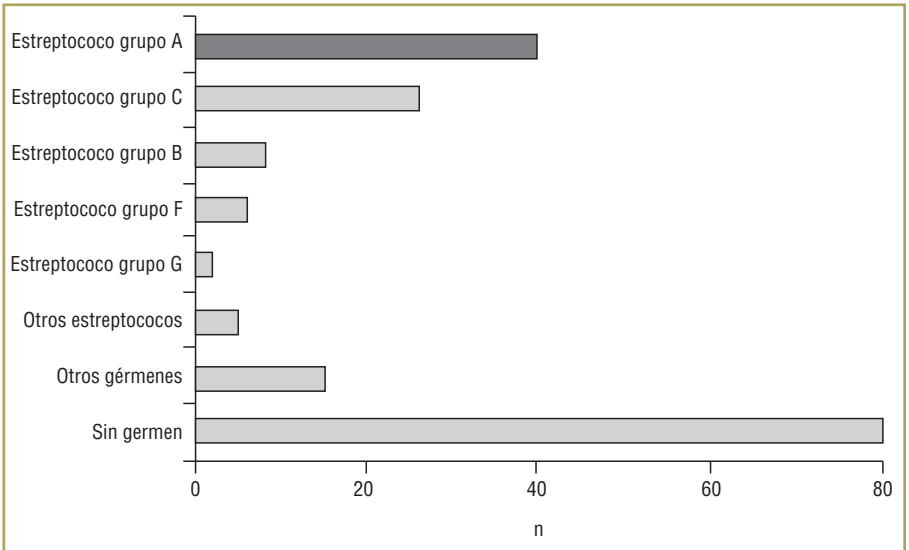


FIGURA 1 Etiología observada en los cultivos faríngeos.

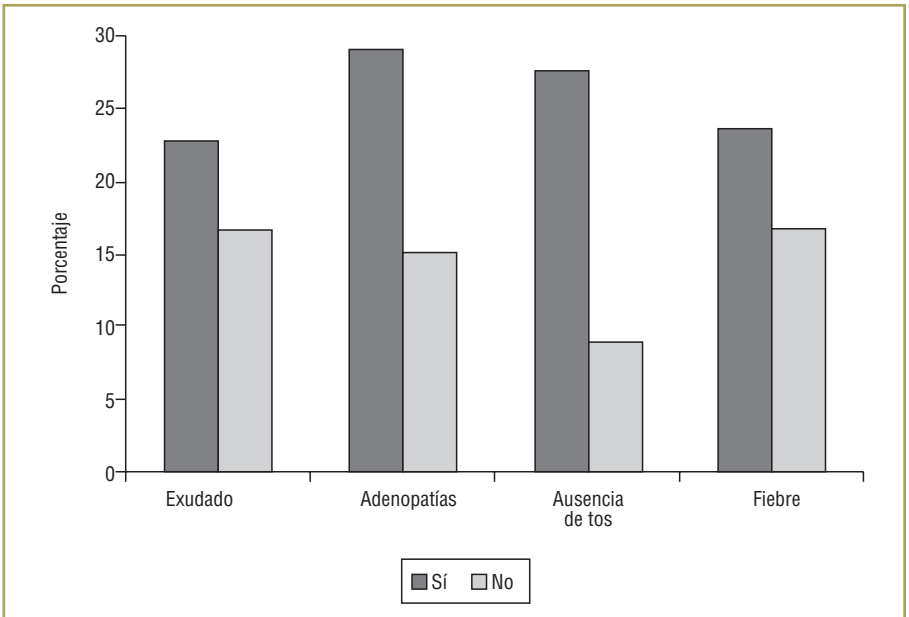


FIGURA 2 Infección confirmada por estreptococo β-hemolítico del grupo A según presencia o ausencia de criterios de Centor.

TABLA 2 **Sensibilidad, especificidad, valor predictivo positivo y valor predictivo negativo de los criterios de Centor en el diagnóstico de la faringitis por estreptococo β-hemolítico del grupo A**

	Sensibilidad	Especificidad	Valor predictivo positivo	Valor predictivo negativo
Fiebre > 38 ºC	82,5%	24,6%	23,6%	83,3%
Exudado faringoamigdalar	90,0%	14,1%	22,8%	83,3%
Ausencia de tos	87,5%	35,2%	27,6%	90,9%
Adenopatías dolorosas	65,0%	55,6%	29,2%	84,9%

estudios publicados en esta misma revista, los criterios de inclusión eran más laxos y éste es, sin duda, uno de los motivos para haber hallado unos resultados más favorables en nuestro trabajo[11-13]. Sólo el trabajo de Díaz-Berenguer observó unos valores de validez similares a los nuestros, aunque el valor predictivo positivo de la TAR era algo menor en aquél, lo que estuvo motivado por la menor prevalencia de EBHGA[12]. Es erróneo comparar los resultados de las TAR actuales con los obtenidos a principios de la década de 1990, ya que los aparatos de TAR actuales son más sensibles. Tampoco se puede comparar el estudio microbiológico ya que, por ejemplo, en el estudio de Díaz-Berenguer se utilizaban discos de bacitracina, cuando en la actualidad esta metodología ya no se usa porque comportaba una elevada tasa de falsos negativos[12].

Otra de las conclusiones de nuestro trabajo, ya documentada en otros estudios, es la poca fiabilidad de los criterios clínicos para diagnosticar la faringitis estreptocócica. Incluso entre pacientes con todos los criterios de Centor, la probabilidad de que presentaran una infección estreptocócica era inferior al 40%. En nuestro trabajo, la presencia de cualquiera de estos criterios hacía más probable la etiología estreptocócica, al igual que se ha observado en otros trabajos, y de estos criterios los fundamentales son la presencia de adenopatías laterocervicales dolorosas y la ausencia de tos[11,12,14]. Sólo estos criterios eran significativamente más prevalentes entre los pacientes con infección por EBHGA. En cambio, no se han observado diferencias estadísticamente significativas con la presencia de exudado ni con la presencia de fiebre. Estos mismos datos se han observado en otros estudios; incluso, en

TABLA 3 Relación entre el resultado de la técnica antigénica rápida y el cultivo faríngeo

	Cultivo positivo	Cultivo negativo	Total
OSOM StrepA +	38	10	48
OSOM Strep A –	2	132	134
Total	40	142	182

Sensibilidad: 38/40 = 0,95
Especificidad: 132/142 = 0,93
Valor predictivo positivo: 38/48 = 0,79
Valor predictivo negativo: 132/134 = 0,98

el trabajo de Lindæk et al el EBHGA presentaba una prevalencia superior entre los pacientes de los que no se había obtenido exudado[14]. En el estudio de Marín et al[13], recientemente publicado en esta revista, se comenta que el sistema de puntuación clínica alcanza un alto valor predictivo negativo y una especificidad que permiten diagnosticar con bastante certeza las faringitis no estreptocócicas. Sin embargo, en nuestro trabajo la probabilidad de infección por un germen distinto del EBHGA era superior al 60% entre los pacientes que presentaban 4 criterios y superior al 70% entre los que presentaban 3 criterios. La utilización de criterios clínicos para descartar la faringitis estreptocócica puede ser útil en países en vías de desarrollo, pero en estos casos se ha visto que es más útil la combinación de otros criterios, además de los de Centor[15]. En España, no obstante, con una utilización muy importante de antibióticos para tratar esta afección, es imprescindible realizar un cambio de hábitos y utilizar las TAR. Sólo de esta forma se conseguiría reducir la prescripción de antibióticos de la misma forma que se observó en un ensayo clínico efectuado en Canadá[16].

Un aspecto que preocupa mucho al médico que atiende a un paciente con faringitis supuestamente estreptocócica es la fiabilidad del resultado negativo. En nuestro estudio, los médicos eran libres de utilizar tratamiento antibiótico independientemente del resultado de la TAR. Las guías sugieren que si se hallan resultados negativos, sobre todo en las faringitis con todos los criterios de Centor, se necesita confirmación mediante un cultivo[6]. Sin embargo, esta práctica no suele implementarse, ya que su resultado tarda entre 24 y 48 h. En nuestro estudio, sólo 2 pacientes con resultado negativo (los 2 casos con 3 criterios de Centor) presentaban, en realidad, una infección por EBHGA. Además, en otro estudio efectuado en España, se ha comprobado también la utilidad de las TAR hasta el punto de considerar innecesario el cultivo en los casos negativos[17]. Mostov, en una revisión reciente[18], tampoco lo recomienda en los adultos. Una línea de investigación que puede plantearse en un futuro es la elevada incidencia observada de infección por estreptococo β-hemolítico del grupo C, del 14,3% en nuestro medio, aproximadamente el doble de lo observado en Noruega[14]. Se discute en la actualidad el papel patógeno de este germen, ya que Zwart et al observaron que la penicilina podía reducir, aunque marginalmente, la duración de los síntomas de faringitis por estreptococo β-hemolítico del grupo C[19]. Presenta factores de virulencia similares a los de *S. pyogenes* y pueden causar el mismo tipo de infecciones. Se ha asociado con brotes de faringitis con un cuadro clínico similar al producido por EBHGA, pero las secuelas no supurativas son mucho menos frecuentes.

Como conclusión, creemos que debería dotarse a todos los centros de atención primaria de TAR para el diagnóstico de la infección por EBHGA. La TAR es fácil de realizar, no precisa ningún soporte técnico ni personal especializado y es rápida. Una determinación de TAR cuesta entre 2 y 3 € según los distintos fabricantes, precio que se compensa con lo que cuesta una caja de amoxicilina, de penicilina V o de amoxicilina-ácido clavulánico. De todas formas, no se trata tanto de un problema económico como de calidad asistencial.

Lo conocido sobre el tema

- **El estreptococo β-hemolítico es la causa de un 15-25% de las faringoamigdalitis agudas en los adultos y su incidencia aumenta cuantos más criterios de Centor presenta un paciente: exudado amigdalar, historia o presencia de fiebre, ausencia de tos y/o presencia de adenopatías laterocervicales dolorosas.**
- **El uso de criterios clínicos para llevar a cabo el diagnóstico de faringitis estreptocócica no es útil. Incluso, en pacientes con todos los criterios de Centor, la incidencia de faringitis estreptocócica es inferior al 50%.**

Qué aporta este estudio

- **La técnica antigénica rápida constituye un método ideal para diagnosticar la faringitis por *S. pyogenes* en la comunidad, ya que su determinación es fácil y rápida, y presenta una sensibilidad y una especificidad superiores al 90%.**
- **El elevado valor predictivo negativo de la técnica antigénica rápida (ante un resultado negativo se descarta la etiología por EBHGA) descarta la necesidad de realizar un cultivo posterior.**
- **La utilización de estas técnicas antigénicas rápidas debería tenerse en cuenta principalmente en los pacientes con más de 2 criterios de Centor.**
- **La incidencia de faringitis causada por estreptococo β-hemolítico del grupo C, cercana al 15% en nuestra población, abre una línea de investigación interesante, ya que no existe en la actualidad un consenso claro sobre su tratamiento.**

Agradecimiento

Queremos agradecer al Laboratorio Leti su generosidad por facilitarnos tiras de OSOM StrepA de Genzyme de forma gratuita, siempre que lo hemos requerido para la buena marcha de este trabajo.

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COMENTARIO EDITORIAL

Debemos utilizar las técnicas antigénicas rápidas para tratar las enfermedades infecciosas en la consulta de atención primaria

Josep Maria Cots Yago

Medicina de Familia. Centro de Salud La Marina. Barcelona. Grupo de Infecciosas de la Sociedad Española de Medicina Familiar y Comunitaria. Departamento de Medicina. Facultad de Medicina. Universidad de Barcelona. Barcelona. España.

La faringitis es uno de los motivos más frecuentes de asistencia sanitaria en atención primaria. La mayoría de las veces se trata de un proceso de etiología viral que se autolimita en menos de una semana; sólo en un pequeño porcentaje de casos su origen es bacteriano (10-15%) y es la que se conoce como faringoamigdalitis o amigdalitis aguda. Se han descrito distintos agentes bacterianos como causantes de este infección pero es, sin duda, la originada por *Streptococcus pyogenes* la que requiere un tratamiento antibiótico apropiado, ya que se ha demostrado que éste reduce la sintomatología de la infección, corta la transmisión de la infección estreptocócica y disminuye la aparición de complicaciones supuradas y no supuradas. En la práctica habitual el diagnóstico es clínico y, por tanto, el tratamiento se hace de forma empírica. Sin embargo, numerosos estudios alertan sobre la prescripción antibiótica inadecuada que se hace en esta afección, principalmente en cuanto al sobretratamiento, sometiendo a los pacientes a los problemas provenientes de un tratamiento antibiótico excesivo, como efectos secundarios y expansión de las resistencias en la comunidad. En este número de la revista se publica un trabajo sobre la validez de una prueba diagnóstica rápida en el diagnóstico de la faringitis estreptocócica, concretamente, de una técnica antigénica rápida[1]. No es la primera vez que se publica un estudio de estas características en esta revista y, como exponen los autores, se han publicado otros trabajos similares, algunos de ellos ya hace más de 15 años. Los resultados de todos estos estudios aconsejan la utilización de estas técnicas en la consulta de atención primaria. Entonces, podríamos preguntarnos porque su uso no se ha generalizado, ni tan siquiera en las consultas pediátricas, en las que la incidencia de infección estreptocócica es más alta que entre la población mayor de 14 años. Ciertamente, estas técnicas son ahora más sensibles y específicas que hace 15 años y muestra de ello son los mejores resultados observados en el estudio reciente de Llor et al[1]. Otro aspecto positivo, y que señalan los propios autores, es el elevado valor predictivo negativo hallado para el diagnóstico de la faringitis estreptocócica, aspecto muy valorado por el médico, ya que ante un resultado negativo puede descartarse con casi total seguridad la infección por *S. pyogenes*. Este aspecto es fundamental si se tiene en cuenta que en los países en los que se aplican estas técnicas se prescriben antibióticos con resultados negativos. En un estudio efectuado en los EE.UU. se comprobó que hasta a un 30% de pacientes con resultados negativos los médicos de familia les prescriben antibióticos[2]. Otro aspecto a destacar del trabajo de Llor et al es la limitada validez de los datos clínicos para diagnosticar una faringitis estreptocócica. Aunque es un tema ya conocido, vale la pena destacar que estos criterios tan utilizados, como la presencia de exudado faringoamigdalar o la fiebre, son sólo un poco más predictores de etiología estreptocócica que su ausencia y, curiosamente, en este estudio no se observaron diferencias estadísticamente significativas. Estos 2 criterios, junto con la presencia de adenopatías cervicales dolorosas y la ausencia de tos, conforman los 4 criterios para recibir tratamiento antibiótico, descritos por vez primera por Centor et al en 1981[3] (de ahí que a estos criterios se les conozca también con el nombre de este autor). Numerosas guías de práctica clínica, entre las que se encuentra la de la Sociedad Norteamericana de Enfermedades Infecciosas,

Puntos clave

- En las amigdalitis bacterianas, *Streptococcus pyogenes* es la bacteria más frecuente, con unas resistencias a la penicilina del 0%.
- Los criterios clínicos poseen una sensibilidad del 50%, incluso con 4 criterios de Centor.
- El tratamiento basado sólo en los síntomas clínicos produce una sobreutilización de los antibióticos.
- Las técnicas de diagnóstico rápido para detectar *S. pyogenes* son fiables y útiles, tienen un valor predictivo negativo del 98,5% y una gran facilidad para su utilización en la consulta de atención primaria.

recomiendan tener en cuenta estos criterios y en aquellos que presentan dos o más, asegurar la etiología estreptocócica con la utilización de las técnicas antigénicas rápidas[4], ya que incluso en aquellos pacientes que presentan todos los criterios de Centor, la incidencia de faringitis estreptocócica no llega a la mitad de los casos. Sólo en los casos positivos debería administrarse tratamiento antibiótico, el cual, en pacientes no alérgicos a la penicilina, debería ser la penicilina V, que puede administrarse cada 12 h la dosis de 1.200.000 U. Es una pena que, ante la ausencia de resistencias de *S. pyogenes* frente a este antibiótico, se sustituta por otros antibióticos de mayor espectro antibacteriano y, por tanto, con mayor tendencia a generar resistencias. En cambio, sí que se han publicado un 30% de resistencias frente a los macrólidos, con un mecanismo de resistencia inducido, de manera que en un porcentaje elevado de casos se producen resistencias frente a macrólidos de 14 y 15 átomos y no frente a los de 16 átomos; por esta razón, se recomienda administrar estos últimos o las lincosamidas como tratamiento de elección en los pacientes con posible alergia a los β-lactámicos en España (fig. 1)[5].

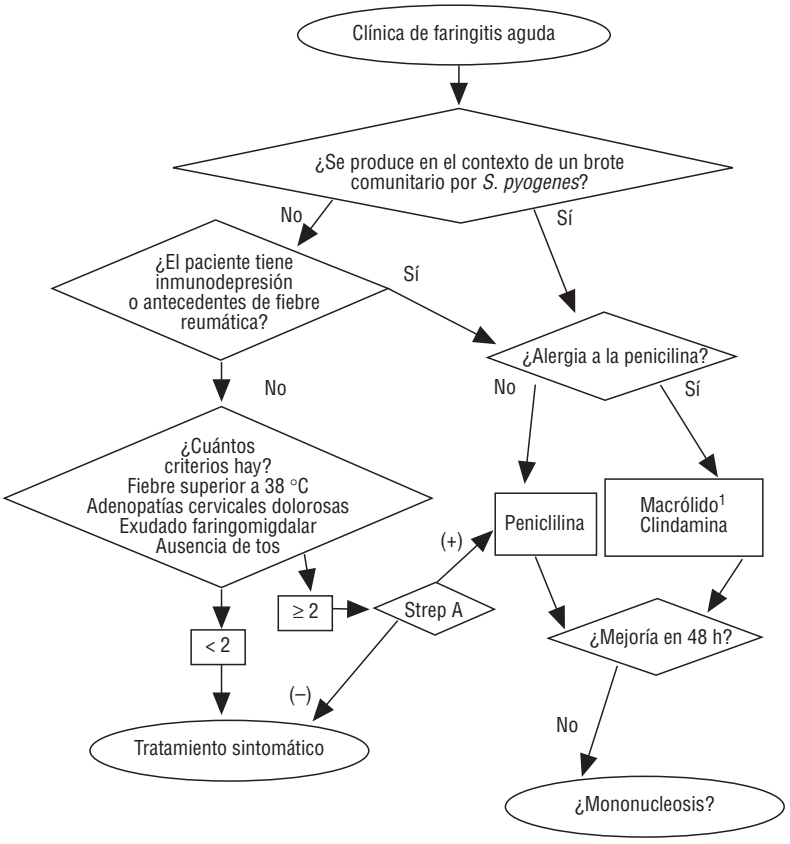

FIGURA 1

Abordaje y tratamiento en la faringitis aguda.

[1]Se prefiere un macrólido de 16 átomos, como josamicina o midecamicina.
Si se trata de una faringoamigdalitis de repetición debe administrarse la asociación de amoxicilina y ácido clavulánico.

El uso de estas técnicas antigénicas rápidas no es más complicado que el uso de tiras reactivas de orina y no consume un tiempo excesivo. Incluso, en casos positivos, se puede llegar al diagnóstico en no más de 2 minutos desde que se inicia su determinación. En la mayoría de los países europeos, así como en Estados Unidos y Canadá, su uso se ha generalizado[6]. La publicación de este estudio debería significar un punto de inflexión y, junto con otros proyectos actuales, como el Happy Audit, que busca la introducción de métodos diagnósticos rápidos en la consulta, debería significar una toma de conciencia y un cambio de hábitos por parte de los médicos de familia y los pediatras. Por supuesto, estos resultados deberían ser asumidos por la administración, quien debería dotar a nuestros centros de salud de estas pruebas diagnósticas. Una determinación cuesta aproximadamente 3 €, algo menos de lo que cuesta una envase de penicilina. Este factor, junto con la consideración de una menor exposición a la población a los antibióticos cuando éstos no están indicados, resuelve un problema de salud pública, tanto para el paciente que no deberá tomar un antibiótico innecesario, evitando así los posibles efectos secundarios, como para el ámbito comunitario, controlando el incremento de las resistencias. Por tanto, ¿a qué esperamos?

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Respuesta del autor: aclaraciones sobre el estudio de validez del StrepA

Author's reply: Clarifications on the StrepA validity study

Sr. Director:

Quisiéramos iniciar la carta preguntándoles a los autores qué abordaje seguirían ante una paciente con clínica clara de infección urinaria con tira reactiva negativa, tomando como referencia el estudio de Litlle et al, que hallaron que la presencia de nitritos más leucocituria o sangre presentaba una sensibilidad del 77%, una especificidad del 70%, un valor predictivo positivo del 73% y un valor predictivo negativo del 92%[1].

Nuestro trabajo fue un estudio de validación (con resultados mucho mejores que en la tira reactiva de orina) y no se revisaron algunos de los aspectos que describen en su carta[2]. Tampoco creemos que todos estos aspectos deban analizarse, ya que, o se ha hecho en estudios previos o no son relevantes para llevar a cabo estudios de investigación. Está demostrado que la utilización de pruebas rápidas, incluyendo StrepA, comporta una mayor satisfacción de profesionales y pacientes[3]. También está claro que su uso se asocia a un menor uso de antibióticos, válido también en países mediterráneos[4]. Menor uso de antibióticos significa menos efectos adversos y un aspecto que se echa de menos en su carta y sin duda el más importante: menor generación de resistencias bacterianas.

Ustedes comentan que la incidencia de infección por *Streptococcus pyogenes* fue más alta que en otros estudios y es lógico, ya que incluimos pacientes con 2 o más criterios de Centor. Este aspecto está ampliamente explicado en la discusión del artículo así como también se comenta la baja prevalencia de *S. pyogenes* observada en nuestro estudio, no sólo entre pacientes con 2 criterios, sino también en aquéllos con 3 y 4. Probablemente, la mayor incidencia de infección por estreptococo C en España podría, en parte, explicar este fenómeno. En cuanto a la edad de los pacientes, sólo 4 pacientes tenían 14 o 15 años y sólo uno de ellos presentaba infección por *S. pyogenes*. Aunque McIsaac et al consideraron la edad inferior a 15 años como otro criterio de tratamiento antibiótico, los criterios de Centor no lo contemplan[5,6]. Por otra parte, es difícil que se pueda producir un sesgo de información, ya que los médicos no conocíamos el resultado del cultivo en el momento de interpretar el StrepA (el cultivo tarda aproximadamente 48 h). Su impresión de que el uso del StrepA podría conllevar medicalización no se confirma, ya que nuestra experiencia de utilizarlo durante 3 años indica precisamente lo contrario. Cada vez tratamos menos las odinofagias infecciosas con antibióticos. Es cierto que en algunos casos los pacientes acuden a nuestras consultas para hacerse la «prueba», pero sólo la indicamos cuando pensamos que pueda tener una causa estreptocócica. Es obvio que la positividad del StrepA no distingue infección de estado de portador pero tampoco lo hace el cultivo; en todo caso, es un mal menor aunque algunos casos se tratarán innecesariamente con antibióticos.

En nuestro estudio, la probabilidad de hallar un resultado de StrepA positivo en un paciente con faringitis estreptocócica fue 13,6 veces más frecuente que en un individuo sano (tabla 1) y la probabilidad de encontrar un StrepA negativo en un paciente sano fue un 18,6% más frecuente que en un paciente con infección. Las razones de probabilidad positivas superiores a 10 y negativas inferiores a 0,1 deberían proporcionar cambios importantes y concluyentes en el uso de pruebas diagnósticas (también para individuos con 2 criterios, tabla 1). La ventaja que tiene esta técnica (sobre la tira reactiva de orina, por ejemplo) es que el resultado de la prueba es diagnóstico, es decir, si es positivo debe tratarse con antibióticos, aun sabiendo que hay algunos falsos positivos, pero cuando el resultado es negativo, no hay que tratar. Entonces, ¿por qué no la empezamos a usar?

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Tabla 1 Parámetros de validez del estudio de validación según el número de criterios de Centor y total

	Dos (n = 63)	Tres (n = 83)	Cuatro (n = 36)	Total (n = 182)
S	5/5 = 1	19/21 = 0,905	14/14 = 1	38/40 = 0,95
E	56/58 = 0,966	58/62 = 0,935	18/22 = 0,818	132/142 = 0,93
VPP	5/7 = 0,714	19/23 = 0,826	14/18 = 0,778	38/48 = 0,792
VPN	56/56 = 1	58/60 = 0,967	18/18 = 1	132/134 = 0,985
RPP	1/(1–0,966) = 29,4	0,905/(1–0,935) = 13,9	1/(1–0,818) = 5,5	0,95/(1–0,93) = 13,6
RPN	(1–1)/0,966 = 0	(1–0,905)/0,935 = 0,05	(1–1)/0,818 = 0	(1–0,95)/0,93 = 0,05

E: especificidad; RPN: razón de probabilidad negativa; RPP: razón de probabilidad positiva; S: sensibilidad; VPN: valor predictivo negativo; VPP: valor predictivo positivo.

PAPER 2

Llor C, Calviño O, Hernández S, Crispi S, Pérez-Bauer M, Fernández Y, et al. Repetition of the rapid antigen test in initially negative supposed streptococcal pharyngitis is not necessary in adults. Int J Clin Pract 2009;63:1340–4.

ORIGINAL PAPER

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Repetition of the rapid antigen test in initially negative supposed streptococcal pharyngitis is not necessary in adults

C. Llor,[1] O. Calviño,[2] S. Hernández,[2] S. Crispi,[2] M. Pérez-Bauer,[2] Y. Fernández,[2] T. Martínez,[2] F. F. Gómez,[3] J. M. Cots[4]

[1]Primary Care Centre Jaume I, University Rovira i Virgili, Tarragona, Spain
[2]Primary Care Centre Jaume I, Tarragona, Spain
[3]Department of Microbiology, Hospital Joan XXIII, Tarragona, Spain
[4]University of Barcelona, Barcelona, Spain

Correspondence to:
Carl Llor,
c. Foixarda, 95. 43008
Tarragona, Spain
Tel.: + 34 671085857
Fax: + 34 977248459
Email: carles.llor@urv.cat

Disclosure
None.

SUMMARY

Aims: To determine whether the repetition of the rapid antigen detection test (RADT) in patients, with a high suspicion of presenting pharyngitis by group A β-haemolytic streptococci (GABHS), with a previously negative test improves the validity of the test. **Methods:** Two hundred and twenty-two patients aged 14 years or more with acute pharyngitis and two or more Centor criteria – tonsillar exudates, fever, tenderness in the lymph glands and/or absence of cough – were consecutively recruited. In all patients, a pharyngotonsillar sample was obtained with two swabs, one for the RADT (OSOM® Strep A Genzyme test, Genzyme Diagnostics, Cambridge, MA, USA) and the other was sent to the Department of Microbiology for culture. In patients with a negative RADT, the determination was repeated. The sensitivity, specificity and predictive values were determined. **Results:** Cultures were positive for GABHS in 55 patients (24.8%). Three false-negatives and 14 false-positives were observed by comparing the rapid test with throat culture, achieving a sensitivity of 94.5% and a specificity of 91.6%. Positive and negative predictive values were 78.8% and 98.1% respectively. Taking the second determination in the negative cases into account, the results were 96.4%, 91.6%, 79.1% and 98.7% respectively. **Conclusions:** The negative predictive value achieved with the RADT determination was very high. Repetition of the test only slightly improved this percentage, making repetition of this test unnecessary.

What's known
- Some physicians are concerned about not treating patients with clinical manifestations, suggestive of streptococcal pharyngitis with antibiotics.
- In countries with a long tradition of empiric treatment in pharyngitis and a high level of antibiotic prescription, reliable diagnostic tests, which minimise the number of false-negatives are required.

What's new
- The negative predictive value achieved with the RADT determination was very high with the first swab.
- Repetition of the test only marginally improved the validity of the first procedure, thereby making the repetition of the antigen determination, in daily clinical practice in patients, with suspicion of streptococcal infection and a negative antigenic test result unnecessary.

Introduction

Acute pharyngitis is one of the most common illnesses attended by general practitioners and is one of the infections for which more antibiotics are prescribed (1). However, group A β-haemolytic streptococcus (GABHS) is isolated from the throat of approximately 20–30% of subjects with acute pharyngitis (2). Laboratory confirmation of GABHS is recommended in patients with acute pharyngitis, because it is difficult to differentiate clinically between viral and GABHS pharyngitis (3,4). The two methods for diagnosing GABHS pharyngitis are the throat culture and the rapid antigen detection test (RADT).

Throat culture is not performed as 48 h are required to achieve results, and it is not efficient. Until a few years ago, the use of RADT was marginal and the use of these tests in some healthcare centres only began recently. In addition, modern RADT is simple to perform in office settings, and the results are available at the point of care in < 5 min. Even though the specificity of the modern RADTs has generally been regarded as very high (95–99%), some physicians are concerned about not treating patients with clinical manifestations suggestive of streptococcal pharyngitis with antibiotics (5–8). Indeed, some studies have reported that among patients with a high suspicion of presenting streptococcal pharyngitis up to 25% of the patients are prescribed antibiotic treatment even with negative RADT results because of lack of trust of the professionals towards the results of the test (9,10). This phenomenon is based on the concern that false-negative RADT results may lead to misdiagnosis of GABHS pharyngitis, which could result in suppurative and non-suppurative complications and in the increased risk of transmitting the germ to others.

doi: 10.1111/j.1742-1241.2009.02048.x

Using two swabs instead of one could theoretically increase the inoculum size and improve the performance of the RADT. This may help clinical practitioners reach a prompt and accurate diagnosis and initiate an appropriate therapy in a larger number of patients at the point of care. We therefore performed the study to assess whether a backup RADT for all negative RADT results improves the validity of the test.

Methods

Study design

A prospective study was carried out in six surgeries at the primary care centre Jaume I (Tarragona, Spain) from January 2007 to October 2008. The details of this study were published in a local journal (11), but briefly adults aged 14 years or more with acute pharyngitis and two or more Centor criteria (12) – history of fever, presence of tonsillar or pharyngeal exudates, presence of tender cervical glands and/or absence of cough – were consecutively recruited. Subjects who had received systemic antibiotics within the previous 2 weeks were excluded. A data collection sheet was elaborated including the age, gender, presence of these four criteria and whether the infection was recurrent (< 2 months since the last episode) or not. Samples were taken by the family physicians, who had previously been trained to perform the technique correctly with vigorous rotation of the tonsils and the posterior pharynx without touching the tongue, teeth or gums. RADT was undertaken with all the samples with the OSOM StrepA (Genzyme Diagnostics, Cambridge, MA, USA) following the manufacturer's instructions. The other sample was sent to the Department of Microbiology of the Hospital Joan XXIII of Tarragona with AMIES (Copan Innovation, Brescia, Italy) as medium. Samples were seeded in a plate of blood agar and were incubated at 37 °C in an atmosphere of CO_2 at 5% during 48 h. A culture was considered positive for GABHS, with a growth of any number of β-haemolytic colonies, Gram staining with streptococcal morphology and a catalase negative test with posterior identification, with an automated panel for WIDER Gram-positive cocci (Soria Melguizo, Madrid, Spain). Results were confirmed with posterior serogrouping with the Streptococcal Grouping Kit (Oxford, UK). The culture was considered negative after 48 h of incubation, with the absence of β-haemolytic colonies. In patients, with a negative RADT, the determination was repeated.

Data analysis

Clinical characteristics were compared using *t*-test for continuous variables and chi-squared analysis for categorical variables. The sensitivity, specificity and positive and negative predictive values of the RADTs were determined by a two-way contingency table, using culture results as the gold standard. Statistical significance was accepted at $p \leq 0.05$.

Results

Two hundred and twenty-two patients with clinical manifestations of pharyngitis and at least two Centor criteria, with a mean age of 30.6 ± 11.7 years, of which 136 of who were women (61.3%) were consecutively recruited. A total of 71 individuals presented two Centor criteria (32%), 97 presented three criteria (43.7%) and 54 patients had four criteria (24.3%). The most frequent Centor criterion presented was the tonsillar or pharyngeal exudate (194 patients; 87.4%), followed by a history of fever (174 patients; 78.4%), while the least frequent was the presence of tender cervical glands (114 patients; 51.4%).

Table 1 shows the aetiology observed according to the number of Centor criteria. The culture demonstrated GABHS infection in 55 patients (24.8%).

Table 1 Aetiology of the pharyngeal infection according to the Centor score

Germ	Two	Three	Four	Total
GABHS	8 (11.3%)	25 (25.8%)	22 (40.7%)	55 (24.8%)
Group B streptococcus	4 (5.6%)	4 (4.1%)	1 (1.9%)	9 (4.0%)
Group C streptococcus	13 (18.3%)	13 (13.4%)	9 (16.6%)	35 (15.8%)
Group F streptococcus	3 (4.2%)	2 (2.1%)	1 (1.9%)	6 (2.7%)
Group G streptococcus	0	2 (2.1%)	1 (1.9%)	3 (1.4%)
Other streptococci	4 (5.6%)	4 (4.1%)	1 (1.9%)	9 (4.0%)
Other bacteria but streptococci	5 (7.1%)	7 (7.2%)	4 (7.4%)	16 (7.2%)
Negative culture	34 (47.9%)	40 (41.2%)	15 (27.7%)	89 (40.1%)
Total	71 (100%)	97 (100%)	54 (100%)	222 (100%)

GABHS, group A β-haemolytic streptococcus.

Table 2 Streptococcal aetiology according to the presence or absence of the Centor criteria

	Present		Absent		
Criterion	**GABHS, *n* (%)**	**Total**	**GABHS, *n* (%)**	**Total**	**p-value**
Pharyngotonsillar exudate	48 (24.7%)	194	7 (25.0%)	28	ns
Tender cervical glands	38 (33.3%)	114	17 (15.7%)	108	< 0.005
Absence of cough	47 (28.8%)	163	8 (13.6%)	59	< 0.05
History of fever	47 (27.0%)	174	8 (16.7%)	48	ns

GABHS, group A β-haemolytic streptococcus.

Group C streptococci were observed in 35 patients (15.8%) and other streptococci bacteria in 27 (12.2%). No statistically significant differences were observed between the two genders and the incidence of streptococcal pharyngotonsillitis. The mean age among the GABHS positive cultures was slightly lower to that of those presenting negative cultures, although the differences were not statistically significant (30.5 ± 10.7 year vs. 30.6 ± 12.1 year). The incidence of GABHS infection was higher among the patients presenting four Centor criteria (22 patients; 40.7%), followed by those with three criteria (total of 25; 25.8%) and patients with only two criteria (eight patients; 11.3%; $p < 0.001$). Table 2 describes the incidence of GABHS infection depending on the presence or absence of the different Centor criteria. The criteria most associated with streptococcal infection were the presence of tender laterocervical glands and the absence of cough, while pharyngotonsillar exudates and the history or presence of fever were not associated with streptococcal infection.

Table 3 Validity of the rapid antigenic test before and after repetition of the test in initially negative cases

	Positive culture	Negative culture	Total
First swab*			
OSOM StrepA+	52	14	66
OSOM Strep A–	3	153	156
Total	55	167	222
A second swab performed in case of a first negative result†			
OSOM StrepA+	53	14	67
OSOM Strep A–	2	153	155
Total	55	167	222

*Sensitivity: 52/55: 94.5%; Specificity: 153/167: 91.6%; Positive predictive value: 52/66: 78.8%; Negative predictive value: 153/156: 98.1%. †Sensitivity: 53/55: 96.4%; Specificity: 153/167: 91.6%; Positive predictive value: 53/67: 79.1%; Negative predictive value: 153/155: 98.7%.

The RADT was positive in 66 patients (29.7%) and negative in the remaining 156 determinations (Table 3). Three false-negatives and 14 false-positives were reported on comparison with the culture result. The sensitivity observed with a single determination was of 94.5%, with a specificity of 91.6%. The positive predictive value was 78.8%, and the negative predictive value was 98.1%. On repetition of the RADT in 156 patients with a negative result in the first test, one test was weakly positive, being positive at follow-up throat culture. The sensitivity achieved with the repetition of the test was somewhat better than when only the first result was considered (96.4%). Likewise, both the positive and the negative predictive values increased slightly (79.1% and 98.7% respectively).

Discussion

The sensitivity and specificity of > 90% achieved with the RADT, together with the high negative predictive value of > 98%, in this study make this test a diagnostic tool of great aid for family physicians. Moreover, repetition of the test only marginally improved this percentage, thereby making the repetition of the antigen determination, in daily clinical practice, in patients with suspicion of streptococcal infection and a negative antigenic test result unnecessary.

Before discussing the results, we should indicate the limitations and points which differentiate this study from others. First, as only one rapid antigen test was evaluated, the results of this study should not be generalised to other commercially available rapid antigen tests. Second, six family physicians collected the samples. Although they were previously trained in sample collection, this procedure carries possible variability. Our study included patients with clinical manifestations of pharyngitis with suspicion of streptococcal aetiology, that is, patients with two or more Centor criteria. Nonetheless, the incidence of GABHS observed was of 24.8%. In other studies,

the inclusion criteria were less rigorous, which probably explains the high percentage of pharyngitis caused by GABHS observed in this study. Third, we know that a single throat culture is not the gold standard, and size of the inoculum is of major influence on the sensitivity of any test, rapid test or culture. Although asymptomatic carrier rates are reported to be between 2% and 9% in adults depending on age, the finding of a positive throat culture, in the presence of clinical findings, is accepted to be sufficient to establish the diagnosis of streptococcal pharyngitis (13). It is also erroneous to compare the results of the current tests with studies carried out previously, as the present equipment is more sensitive.

Rapid streptococcal carbohydrate antigen tests are widely used in the clinical setting because the results are available during a patient's visit. The main drawback of carbohydrate detection systems is the modest sensitivity and that is the reason why many guidelines recommend backup throat cultures for negative RADTs (14). In our study, the sensitivity of the first RADT compared with single throat culture was 94.5%. This is much greater than the sensitivity reported by office-based reports of RADT sensitivity (5–9). One of the reasons for variation in the sensitivity of the RADT for GABHS is the number of bacteria or the inoculum size present in a throat swab (15). Therefore, proper collection of samples from pharynx and tonsils, sufficient quantity of sample and ability to perform and interpret the RADT correctly are fundamental. Furthermore, studies have found that the sensitivity or RADTs improves as the clinical likelihood of streptococcal pharyngitis increases. We only considered those patients with two or more Centor criteria, which probably explain the high sensitivity found in our study.

One aspect which is particularly worrisome to a physician attending a patient with a supposed streptococcal pharyngitis is the reliability of a negative result. In our study, the clinicians were free to use antibiotic treatment regardless of the result of the test. The negative predictive value observed in our study was > 98%. Therefore, we suggest that negative results in pharyngitis with two or more Centor criteria do not require confirmation with throat culture. In another study, the use of two RADTs obtained simultaneously did not improve the sensitivity of the test when compared with one swab in children aged 5–18 years (16). Furthermore, culture is almost never used in our surgeries except in some cases of recurrent pharyngitis. In a recent review, Mostov did not recommend the use of culture in adult patients (17).

A subject of concern in our study is the high incidence of group C β-haemolytic streptococcal infection observed in 15.8% of the patients, being approximately double that observed by Lindbæk et al. in Norway (18). The pathogenic role of this germ is currently under debate as Zwart et al. (19) observed that penicillin may reduce, albeit only marginally, the duration of the symptoms of pharyngitis by group C β-haemolytic streptococci. The virulence factors are similar to those of GABHS and may cause the same type of infections. It has been associated with outbreaks of pharyngitis with a clinical picture similar to that produced by GABHS but with fewer suppurative sequelae. Interestingly, pharyngitis caused by group C streptococci was more frequent among the patients with only two Centor criteria and was much less frequent among those with three criteria.

In conclusion, in a country such as Spain, in which the diagnosis is based on strictly clinical criteria and the physicians are used to treating most of the cases of pharyngitis with antibiotics, the use of a rapid diagnostic test aids in a quite reliable differentiation of GABHS infection. Although a high number of false-positive may be observed with the test, the number of patients requiring antibiotic treatment is always lower than when the decision is based on strictly clinical criteria. Moreover, the sensitivity of the test is high and does not significantly differ when the test is repeated in cases of negative results, thereby simplifying the consultation of a patient with a supposed streptococcal pharyngitis.

Funding

To perform this study, all the participating primary care physicians were provided with OSOM StrepA Genzyme strips by the Leti Laboratory. None of the physicians received any direct or indirect economic support from the Leti Laboratory for undertaking this study.

Ethical approval

The study completely fulfilled all the regulations referring to observational studies. The Spanish healthcare authorities were informed and approved the implementation of this study and its characteristics. All the data included in the database were encoded to ensure confidentiality. Consent from patients or parents or legal guardians was obtained prior to their participation in the study.

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Paper received January 2009, accepted February 2009

PAPER 3

Calviño Domínguez O, Hernández Anadón S, Teresa Martínez Blesa M, Hernández Anadón M. Validación Analyz-Strep A Rapid test en el diagnóstico de la faringitis aguda. Aten Primaria 2015;47:69–70.

«La tesis doctoral puede presentarse como un compendio de publicaciones del doctorando sobre una misma línea de investigación. De estas publicaciones, como mínimo 3 artículos o capítulos habrán sido publicados o aceptados para su publicación con posterioridad al inicio de sus estudios de doctorado, en un medio incluido en el *Science Citation Index* (o equivalente según la CNEAI)»[3]. Vuelta a revisar la información a principios de 2014, podemos decir que la situación no ha variado sustancialmente.

Consideramos que esta metodología de trabajo supone múltiples beneficios tanto para el doctorando como para los directores de tesis. Por ejemplo, favorece el aprendizaje integrado del proceso de investigación y de publicación para el doctorando[1], y el nacimiento/desarrollo/maduración de una línea de investigación conjunta entre el doctorando y los directores. También, permite a los directores rentabilizar el tiempo invertido, gracias a su participación como coautores en las publicaciones realizadas. De esta manera, el proceso de tesis doctoral supone una etapa de producción científica compartida y un valor añadido, al dejar de ser considerada literatura gris con difusión y acceso limitado[1].

La E-dirección de tesis doctoral

Las tecnologías de la información y la comunicación propician un contexto idóneo para el desarrollo de competencias como la iniciativa, la autonomía, la responsabilidad, el pensamiento crítico o el trabajo colaborativo[4]. Sin duda, programas y aplicaciones como: Dropbox, Skype, WhatsApp y Google Docs, Sites, Calendar... están revolucionando los nuevos estilos de dirección de tesis. Cuando la incompatibilidad de horarios y/o la distancia física es evidente, el uso de estos recursos elimina las barreras geográficas y temporales, surgiendo un nuevo estilo basado en el *blended learning* o enseñanza flexible[1].

En nuestra experiencia la *E-doctoranda* evalúa positivamente la puesta en marcha de estas estrategias en el proceso de *E-dirección*, que se ha caracterizado por: 1) más del 70% de comunicación virtual; y 2) entre una a dos tutorías presenciales (jornadas tutoriales) por año durante el proceso de elaboración de tesis. En su opinión, el estilo directivo le ha estimulado hacia un proceso autónomo, activo y motivacional en el aprendizaje de la metodología para la investigación y la publicación de artículos.

No quisiéramos finalizar esta reflexión compartida sin mencionar las ventajas que, en nuestra opinión, supone la *E-codirección* de tesis por compendio de publicaciones: favorece el trabajo colaborativo y en equipo y propicia el intercambio de roles, dinamizador, evaluador, crítico... De esta forma, el doctorando (y consecuentemente el producto final, la tesis doctoral) se beneficia gracias a la suma de las aptitudes de los directores.

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Sofía Berlanga Fernández[a,*], Rosa María Pérez Cañaveras[b] y María Flores Vizcaya Moreno[b]

[a] *Área Básica de Salud (ABS) Sta. Eulalia Sur, Institut Català de la Salut, Hospitalet del Llobregat, Barcelona, España*
[b] *Departamento de Enfermería, Facultad de Ciencias de la Salud, Universidad de Alicante, Alicante, España*

* Autor para correspondencia.
Correo electrónico: Sbf10@hotmail.es
(S. Berlanga Fernández).

http://dx.doi.org/10.1016/j.aprim.2014.03.015

Validación del Analyz-Strep A Rapid Test en el diagnóstico de la faringitis aguda

Validation Analyz-Strep A Rapid Test in the diagnosis of acute pharyngitis

Sr. Director:

La faringitis es, junto con la rinitis, el motivo asistencial más frecuente de consulta al médico de atención primaria en España[1]. La Sociedad Española de Medicina de Familia en su última revisión[2] y la Sociedad Europea de Enfermedades Infecciosas y Microbiología Clínica[3] aconsejan en pacientes con probable infección por estreptococo β-hemolítico del grupo A (EBHGA) efectuar una prueba de detección antigénica rápida para la confirmación diagnóstica, ya que solo la infección causada por EBHGA debe tratarse con tratamiento antibiótico. El objetivo del estudio es evaluar la validez de una prueba de detección antigénica rápida Analyz-StrepA Rapid Test en un centro de salud urbano, en 6 consultas tanto de medicina de familia como de enfermería durante el año 2011.

Se reclutó consecutivamente a todos los pacientes mayores de 18 años atendidos con odinofagia y 3 o 4 criterios de Centor (exudado faringomigdalar, adenopatías laterocervicales dolorosas, ausencia de tos y/o historia o presencia de fiebre)[4]. A todos se les tomó una muestra faringoamigdalar con 2 hisopos, uno para la prueba de detección antigénica rápida y otro que se envió al servicio de microbiología para cultivo, mediante siembra en una placa de agar sangre,

Tabla 1 Validez del Analyz-Strep A Rapid Test

	3 criterios	4 criterios	Total
Número	80	53	133
% EBHGA	26,3	49,1	35,3
Sensibilidad	90,5	96,2	93,6
Especificidad	96,6	85,2	93,0
Valor predictivo positivo	90,5	86,2	88,0
Valor predictivo negativo	96,6	95,8	96,4

EBHGA: estreptococo β-hemolítico del grupo A.

que se incubaba a una temperatura de 37 °c en atmósfera de CO_2 al 5% durante 48 h. Se consideró cultivo positivo para EBHGA el crecimiento de cualquier número de colonias β-hemolíticas, tinción de Gram positiva con morfología de estreptococo y test de catalasa negativo, con posterior identificación mediante el panel automatizado para cocos grampositivos WIDER (F. Soria Melguizo). Los resultados se confirmaron con el posterior serogrupado mediante el Streptococcal Grouping Kit (Oxford, Reino Unido).

Fueron evaluables 133 sujetos, con una edad media ± desviación estándar de 31,4 ± 11,6 años, con 78 mujeres (58,6%). Presentaron 3 y 4 criterios de Centor 80 y 53 sujetos, respectivamente. El cultivo mostró infección por EBHGA en 47 casos (35,3%) y en 17 casos se aisló estreptococo C (12,8%). La infección por EBHGA fue más prevalente entre los que presentaban 4 criterios (49,1%, comparado con el 26,3% observado con 3 criterios; $p < 0,001$). La prueba de detección antigénica rápida mostró una sensibilidad del 93,6%, una especificidad del 93%, un valor predictivo positivo del 88% y un valor predictivo negativo del 96,4%. La sensibilidad de la prueba fue mayor entre los pacientes con los 4 criterios de Centor que entre los que presentaban 3 criterios (tabla 1).

Estos resultados indican que la prueba de detección antigénica utilizada en este estudio presenta una validez ligeramente inferior a la observada con otra marca comercial (OSOM StrepA)[5], aunque el valor predictivo negativo de la prueba, superior al 95%, puede considerarse óptimo para poder ser utilizado en atención primaria. Se observó un sesgo de espectro, ya que la sensibilidad fue más elevada entre los pacientes con los 4 criterios de Centor, hecho que también se ha detectado en otros estudios[6]. El coste de la prueba es 1,9 € por determinación, lo que puede considerarse una relación coste-efectividad favorable, teniendo en cuenta la elevada prescripción de antibióticos en esta patología infecciosa. Su utilización comportaría una prescripción más racional de antibióticos en aquellos pacientes que presentan una infección por EBHGA.

Financiación

Para la realización de este estudio, todos los profesionales participantes dispusimos de forma gratuita de pruebas de detección antigénica rápida, facilitada por el laboratorio NIRCO. No hemos recibido ninguna cuantía económica directa o indirecta del laboratorio NIRCO para la realización de este estudio.

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Olga Calviño Domínguez[a,*], Silvia Hernández Anadón[a], M. Teresa Martínez Blesa[a] y Marta Hernández Anadón[b]

[a] *Centro de Salud Jaume I, Tarragona, España*
[b] *Centro de Salud Salou, Salou, Tarragona, España*

* Autor para correspondencia.
Correo electrónico: olgacd@comt.es
(O. Calviño Domínguez).

http://dx.doi.org/10.1016/j.aprim.2014.04.011

PAPERS DESCRIBING THE ROLE OF CRP IN SORE THROAT IN ADULTS

PAPER 4.

Calviño O, Llor C, Gómez F, González E, Sarvisé C, Hernández S. Association between C-reactive protein rapid test and group A streptococcus infection in acute pharyngitis. J Am Board Fam Med 2014;27:424–6.

PAPER 4

Calviño O, Llor C, Gómez F, González E, Sarvisé C, Hernández S. Association between C-reactive protein rapid test and group A streptococcus infection in acute pharyngitis. J Am Board Fam Med 2014;27:424–6.

BRIEF REPORT

Association between C-Reactive Protein Rapid Test and Group A Streptococcus Infection in Acute Pharyngitis

Olga Calviño, MD, Carl Llor, PhD, Frederic Gómez, PhD, Eva González, MD, Carolina Sarvisé, MD, and Silvia Hernández, PhD

Introduction: **The diagnosis of streptococcal infection is usually made with the use of Centor criteria, but some family doctors also rely on the determination of C-reactive protein (CRP) to guide antibiotic therapy.**

Methods: **This was an observational study conducted in a health center. Adults with acute pharyngitis and the presence of the 4 Centor criteria (tonsillar exudates, tender cervical glands, history of fever, and absence of cough) were recruited. The patients underwent a pharyngotonsillar swab for microbiologic study and a CRP rapid test during the consultation.**

Results: **A total of 149 patients were enrolled. The most frequent etiology was group A streptococcus, present in 83 cases (55.7%). The highest CRP concentration was observed among patients with group C streptococcus infection, with a mean of 56.3 mg/L (95% confidence interval, 25.7–86.5 mg/L). For patients with group A streptococcus infection, the mean CRP value was 34.4 (95% confidence interval, 25.6–43.3 mg/L).**

Conclusion: **CRP concentrations are not associated with group A streptococcus infection in patients with acute pharyngitis. The use of this point of care test is therefore not useful for distinguishing patients who require antibiotic therapy. (J Am Board Fam Med 2014;27:424–426.)**

Keywords: **Antibiotics, C-Reactive Protein, Infectious Diseases, Pharyngitis, Streptococcus Group A**

Point-of -care testing for C-reactive protein (CRP) was introduced into community clinical practice in the early 1990s and is widely used in Scandinavian countries.[1] This test provides results in about 3 minutes and guides decisions regarding antibiotic treatment. Several randomized clinical trials and observational studies have found that CRP rapid testing significantly reduces the prescription of antibiotics to patients with lower respiratory tract infections[2]; several studies have shown that elevated CRP concentrations are associated with bacterial etiology.[3] Among patients with acute pharyngitis, only those infections caused by group A streptococcus (GAS) should be treated with antibiotics.[4] However, some series have shown a high prevalence of non-GAS infection, and complications after infections caused by groups C and G streptococci have been reported.[5] In some countries, this diagnosis is conducted with the aid of rapid antigen detection tests, but because of the uncertainty of infections caused by streptococci other than GAS, some physicians also rely on CRP to guide antibiotic treatment, despite the use of this test not being recommended in such situations.[1] We conducted a study aimed at understanding the relationship between the etiology of sore throat and CRP concentrations in patients with suspected streptococcal infection.

This article was externally peer reviewed.
Submitted 10 December 2013; revised 9 February 2014; accepted 11 February 2014.
From the Institute of Primary Care and Public Health, Cardiff University School of Medicine, Cardiff, UK (CL); Primary Care Center Jaume I, Tarragona, Spain (OC, SH); and the Department of Laboratory and Microbiology, Hospital Joan XXIII, Tarragona, Spain (FG, EG, CS).
Funding: none.
Conflict of interest: CL reports having a grant from the Fundació Jordi Gol i Gurina for a research stage at the University of Cardiff. He also reports receiving research grants from the European Commission (Sixth and Seventh Programme Frameworks), Catalan Society of Family Medicine, and Instituto de Salud Carlos III (Spanish Ministry of Health). The other authors have nothing to declare.
Corresponding author: Carl Llor, PhD, Institute of Primary Care and Public Health, Cardiff University School of Medicine, 5th Floor, Neuadd Meirionnydd Heath Park, Cardiff CF14 4XN, UK (E-mail: LlorC@cardiff.ac.uk).

Table 1. C-Reactive Protein (CRP) Concentrations Based on the Bacteria Causing Pharyngitis in Patients with 4 Centor Criteria

Organism	Patients, n (%)	CRP Concentrations (mg/L)	
		Mean (95% CI)	Median (IQR)
GAS	83 (56.1)	34.4 (25.6–43.3)	12.0 (4.0–62.0)
Non-GAS infection*	65 (43.9)	29.9 (19.7–40.2)	8.0 (4.0–46.0)
No bacteria	29 (19.6%)	27.9 (11.0–44.9)	4.0 (4.0–37.5)
Group B streptococcus	8 (5.4%)	19.1 (0–41.0)	4.0 (4.0–36.7)
Group C streptococcus	13 (8.8)	56.3 (25.7–86.9)	61.0 (4.0–94.5)
Group G streptococcus	5 (3.4)	31.6 (0–65.3)	38.0 (4.0–56.0)
Other streptococci	10 (6.7)	9.2 (4.4–14.0)	8.0 (4.0–11.2)

CI, confidence interval; GAS, group A streptococcus; IQR, interquartile range.
*One patient had infection from a bacteria not included here.

Methods

An observational study was undertaken in an urban health center from January 2010 to May 2012. Adults ≥18 years old with acute pharyngitis and the presence of the 4 Centor criteria[6]—history of fever, presence of tonsillar exudates or hypertrophy, presence of tender cervical glands, and absence of cough—were consecutively recruited. All patients underwent a pharyngotonsillar swab for microbiologic culture, which was sent to the Department of Microbiology, Joan XXIII University Hospital (Tarragona, Spain) in Amies medium (Copan Innovation, Brescia, Italy). Samples were seeded on a plate of blood agar and were incubated at 37°C in an 5% carbon dioxide atmosphere for 48 h. A culture was considered positive for GAS with a growth of any number of β-hemolytic colonies, gram-positive staining with streptococcal morphology, and a catalase negative test with posterior identification with an automated panel for gram-positive cocci using the Wider System (F. Soria Melguizo, Madrid, Spain). Results were confirmed with posterior serogrouping with the Streptococcal Grouping Kit (Thermo Scientific, Oxford, UK). The culture was considered negative with the absence of β-hemolytic colonies after 48 hours of incubation. Patients underwent a CRP rapid test during the consultation by means of QuikRead/Go devices (Orion Diagnostica, Espoo, Finland).

Results

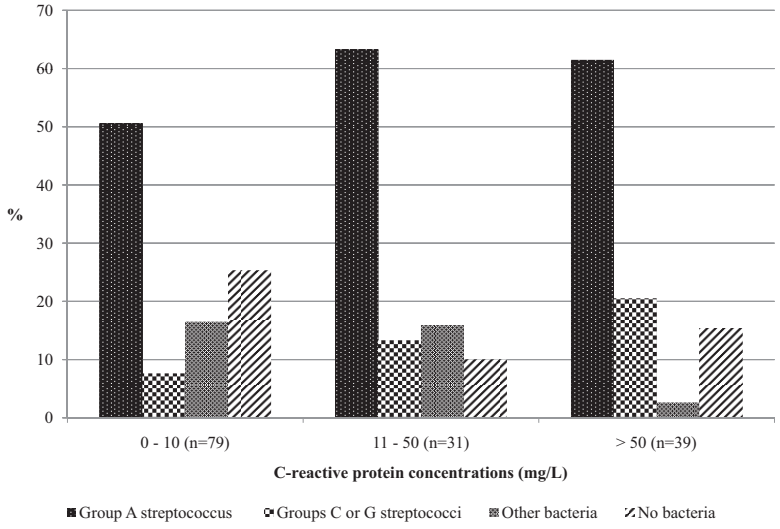
A total of 149 patients were enrolled. The most frequent etiology was GAS, present in 83 cases (55.7%). No bacteria were identified in 29 patients (19.5%). The age of the patients ranged from 18 to 51 years, with a mean of 28.5 years. GAS infection presented a higher CRP concentration compared with other etiologies (34.4 vs 29.9 mg/L, respectively), with no statistically significant differences (Table 1). The highest CRP concentration was observed among patients with group C streptococcus infection. Infection with groups C and G β-hemolytic streptococci was associated with slightly higher concentrations of CRP (49.9 mg/L) compared with those with infection by GAS, other causes, or no infection (Figure 1). The highest CRP concentration (182 mg/L) was observed in a patient presenting with a peritonsillar abscess and no bacterium identified during the consultation.

Discussion

This study has several limitations. Only patients with the 4 Centor criteria were recruited, which explains why more than half of the patients actually had a GAS infection. Outcomes were not collected, nor was the evolution of symptoms measured, but we do not consider these limitations to be important since our goal was to identify the association of CRP concentrations with the etiology of the pharyngitis. The microbiologic study did not take into account the study of anaerobes, and some of the patients in whom no bacteria were identified may have been infected by these organisms. In our study the CRP rapid test used a finger prick blood sample; however, studies comparing these rapid tests with the routine CRP laboratory test have shown a very good correlation, thereby demonstrating its reliability.

Some studies have shown high CRP concentrations with GAS infection. Hjortdahl and Melbye[7] observed a mean CRP concentration of 50.4 mg/L

Figure 1. Association between C-reactive protein concentrations and the cause of infection among patients with sore throat and 4 Centor criteria.



among patients with GAS infection, and Melbye et al[8] observed an even higher mean value of 100.3 mg/L; however, they recruited only 11 patients with GAS. On the other hand, other studies have shown no relationship between CRP concentrations and GAS infection. In a Swedish study, the mean CRP value was 37.6 mg/L for the group with rapid antigen detection tests showing GAS and 37.4 mg/L for those with a test not showing GAS.[9] Lindbæk et al[10] observed mean CRP values of 43 mg/L, with the highest concentrations being found in infections caused by groups C and G streptococci, which is similar to our results.

Conclusion

Some studies suggest that CRP testing is overused.[1,9] Our results show that CRP is not useful for differentiating GAS infection from other etiologies that do not require antibiotic therapy.

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DISCUSSION

MAIN FINDINGS

The results of the four studies of this thesis clearly find, on the one hand, that clinical criteria are not reliable for diagnosing streptococcal pharyngitis, and the other hand, the immunochromotographic RADTs are sufficiently valid to be routinely used in primary care if a patient with sore throat is suspected to have a streptococcal infection. Furthermore, when the result is negative there is no need to repeat it or send a new pharyngeal swab for culture and other tests, such as CRP, are not recommended. The sensitivity and specificity achieved (greater than 90%) with the immunochromotographic RADT used, along with the high negative predictive value observed in the studies of this thesis, make this test a very helpful diagnostic tool for the primary care physician.

WEAKNESSES OF THE STUDIES

As already known, a single throat culture is not the best gold standard. In fact, detection of an organism by even culture is not definitive evidence of infection. Although not clinically useful, the gold standard for pharyngeal infection, even for GABHS, is paired acute and convalescent serologies [*Linder JA, 2015*]. In addition, our microbiological lab, the Microbiology Unit of Hospital Joan XXIII, was unable to detect some important bacterial aetiologies, such as *Fusobacterium* species or atypical germs. Nonetheless, microbiological procedures did reliably detect streptococcal infection, including GABHS and other β-haemolytic streptococci. Although asymptomatic carrier rates are reported to be up to 2% in adults depending on age, the finding of a positive throat culture, in the presence of clinical findings, is accepted to be sufficient to establish the diagnosis of streptococcal pharyngitis [*Gunnarsson RK et al, 1997*].

Another weakness is the training of the GPs who performed the pharyngeal tests. Fox et al showed that RADT sensitivity was consistently greater when the test was performed by laboratory profesionals than when it was performed by non-laboratory personnel [*Fox JW et al, 2006*]. In the studies of this thesis, a maximum of 6 GPs collected the samples. Although they were previously trained in sample collection, this procedure carries possible variability. However, rather than a limitation this constitutes a strength of the present thesis, since most studies involve a higher number of clinicians, leading to a higher heterogeneity.

Our studies included patients with clinical manifestations of pharyngitis with suspicion of streptococcal aetiology, that is, patients with two or more Centor criteria. Nonetheless, the incidence of GABHS observed was greater than 20%. In other studies, the inclusion criteria were less rigorous, which probably explains the high percentage of pharyngitis caused by GABHS observed in this study.

COMPARISON WITH OTHER STUDIES

As only two rapid immunochromotographic antigen tests were evaluated, the results of this thesis should not be generalised to other commercially available RADTs. It would be wrong to compare the results of current RADT with those obtained at the beginning of the 1990's, since the current RADT kits which use an immunocromatographic system, are more sensitive than the enzyme immunoassay systems, used for instance by other Spanish researchers, such as Bladé or Díaz-Berenguer [*Bladé J et al, 1991; Díaz-Berenguer JA et al, 1992*]. Neither can the microbiology study be compared, as, for example, in the study by Díaz-Berenguer, bacitracin disks were used; and also because this method is not used nowadays, as it produced a high rate of false negatives [*Díaz-Berenguer JA et al, 1992*].

Three different RADTs have been launched in the market:

- Optical immunoassay devices
- Enzyme immunoassay devices
- Immunocromatographic devices

In the recent meta-analysis about validity of RADTs for diagnosing GABHS infection in patients with sore throat, only 43 studies fulfilled the higher quality definition; i.e., at least 50 patients, prospective data collection, and no significant biases; with the inclusion of 18,464 patients [*Stewart EH et al, 2014*]. For the higher quality studies in the adult population, the pooled sensitivity for the immunochromatographic methods in the adult population (1,216 patients) was 91% (95% CI: 87–94%) and the pooled specificity was 93% (95% CI: 92–95%). For enzyme immunoassay (333 patients), the pooled sensitivity was 86% (95% CI: 81–91%) and the pooled specificity was 97% (95% CI: 96–99%). However, this meta-analysis did not include three studies [*Bladé J et al, 1991; Díaz-Berenguer JA et al, 1992; Madurell J*

et al, 2011], and therefore I carried out the study again with the inclusion of these three studies performed in Spain, with similar results, as shown in **Figure 3** and **Figure 4**.

Figure 3. Forest plots for sensitivity of immunochromatographic, enzyme immunoassay and optical immunoassay methods to diagnose GABHS pharyngitis with the use of the higher study methodological quality in adults

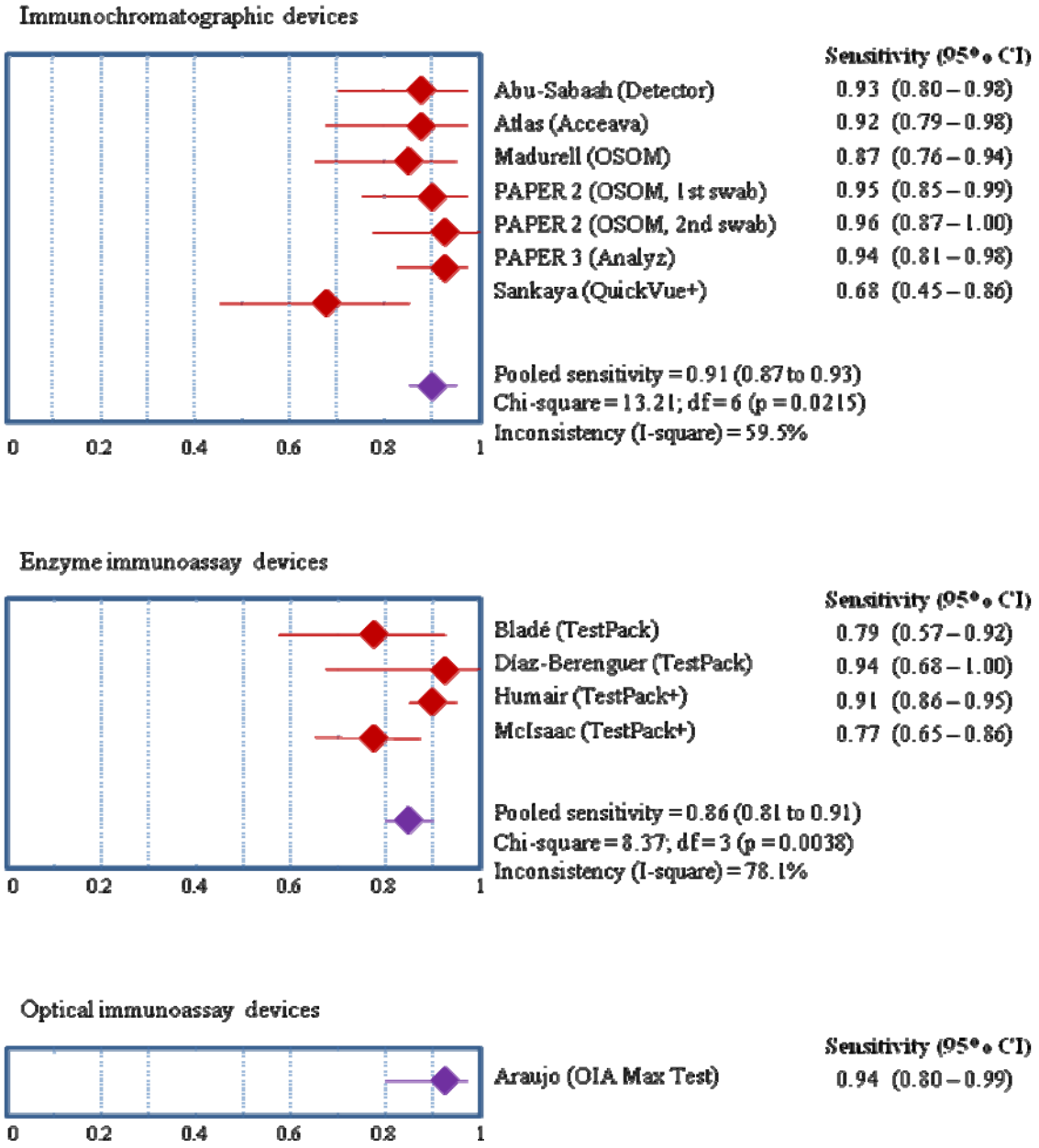
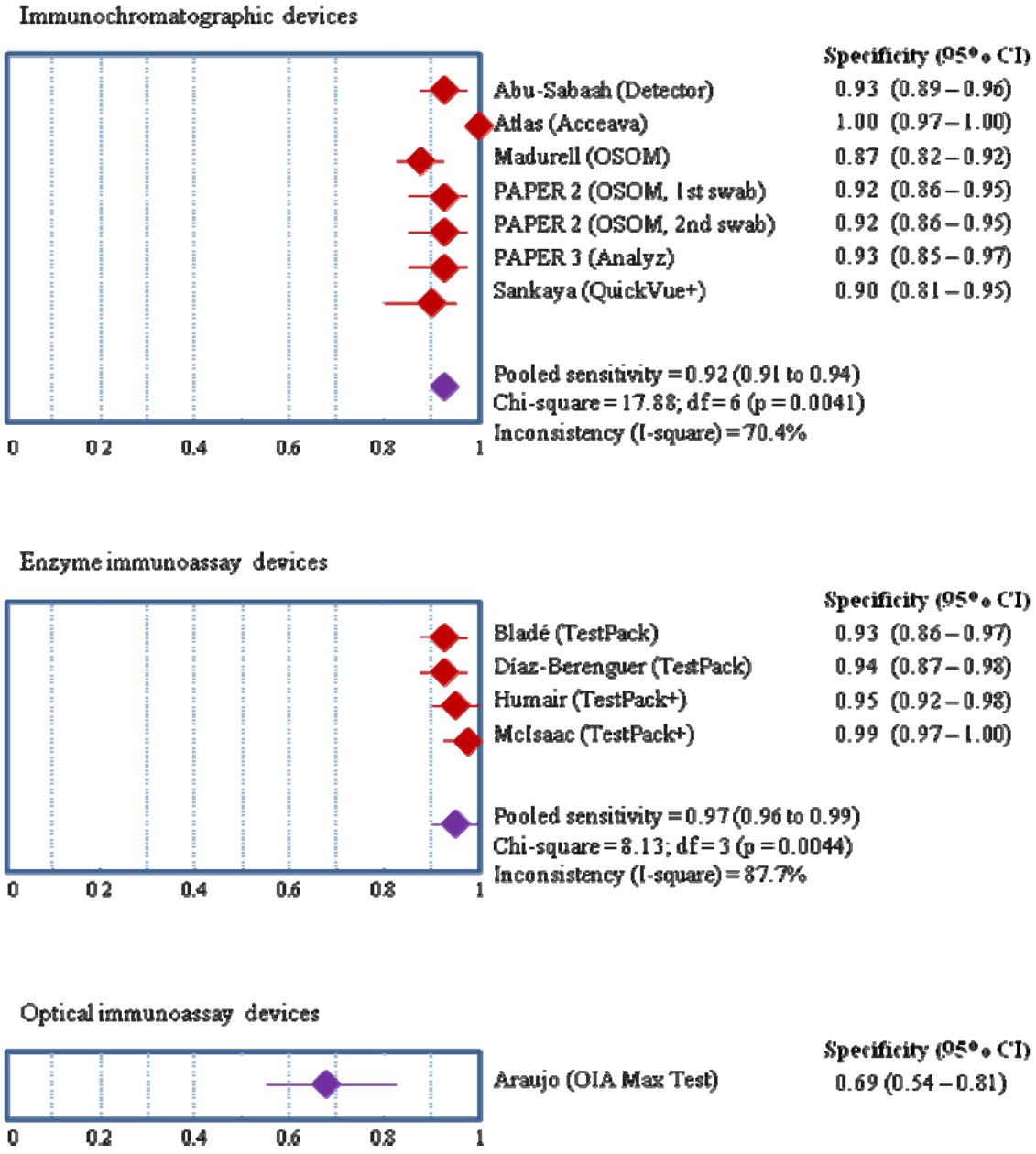


Figure 4. Forest plots for specificity of immunochromatographic, enzyme immunoassay and optical immunoassay methods to diagnose GABHS pharyngitis with the use of the higher study methodological quality in adults



These figures clearly state that the immunochromotographic kits are the most sensitive of all and the enzyme immunoassay devices are more specific than the former but they are only a little more specific. Therefore, there is no doubt that the immunochromotographic devices should be recommended in the clinical practice.

On the basis of these results, the comparison of validity of RADTs among the different devices available is unfair [*Gerber MA et al, 2004*]. It is also erroneous to compare the results of the current tests with studies carried out previously, as the present equipment is more sensitive and the present studies included patients with at least Centor scores of 2. Different studies have found that the sensitivity of rapid streptococcal antigen tests improves as the clinical likelihood of streptococcal pharyngitis increases, phenomenon known as spectrum bias [*DiMatteo LA et al, 2001; Edmonson MB et al, 2005; Hall MC et al, 2004*]. This bias, also called spectrum effect by some authors [*Mulherin SA et al, 2002*], results in biased results when pooled sensitivities are calculated. The paper number 3 clearly demonstrates this spectrum effect, with a sensitivity of Analyz-Strep A of 96.2% among patients with the four Centor criteria and 90.5% when patients with Centor 3 were included. Heterogeneity can be addressed with relatively simple stratification procedures, with the use of stratified sensitivity and specificity estimates, likelihood ratios, and receiver-operating characteristic curves.

A number of factors have the potential to further lower the sensitivity of RADT performed. These factors include improper collection of samples from sites other than the pharynx or tonsils, insufficient quantity of sample, and inability to perform and interpret the test correctly. The size of the inoculum is also of major influence on the sensitivity of any test, rapid test or culture. In a prospective study evaluating the sensitivities of four RADT kits to detect clinical and reference strains of GABHS at different dilutions, the investigators observed that all kits were only faintly positive or negative at low colony counts and, obviously, the faint appearance of a positive test at low colony counts contributes to inter-observer variability [*Upton A et al, 2014*]. When the Strep A procedure was repeated when a prior RADT was negative (paper 2), only one case turned out to be a faint positive result. As already asserted for the first generation of RADT [*Dagnelie CF et al, 1998*], the new generation of RADTs, such as immunocromatographic tests, may have an additional value for the management of sore throat. In children, eight observational studies (five prospective cohort, three retrospective cohort) and two guidelines supported the need for confirmation by a throat culture after a negative RADT. One clinical trial, two observational studies (both were prospective cohorts) and one guideline did not consider confirmation by a throat culture necessary [*Armengol CE et al, 2004; Camurdan AD et al, 2008; Choby BA, 2009; Cohen R et al, 2004; Edmonson MB et al, 2005; Forward KR et al, 2006; Gieseker KE et al, 2002; Hall MC et al, 2004; Maltezou HC et al, 2008; McIsaac WJ et al, 2004; Nerbrand C et al, 2002,*

van Limbergen J et al, 2006]. In adults, except for one prospective study, the observational study and two guidelines did not support the need to perform a throat culture after a negative RADT. The negative predictive value observed in our studies was > 96%. Therefore, we suggest that negative results in pharyngitis with two or more Centor criteria do not require confirmation with throat culture. In another study, the use of two RADTs obtained simultaneously did not improve the sensitivity of the test when compared with one swab in children aged 5–18 years [*Ezike EN et al, 2005*]. Furthermore, culture is almost never used in our surgeries except in some cases of recurrent pharyngitis. Different studies do not recommend the use of culture in adult patients [*Mostov PD, 2007; Nakhoul GN et al, 2013*].

Another factor that can modify the validity of the RADT is the competing interests of the authors of the studies. In this thesis, all the kits were provided free by the manufacturers. As reported in several diagnostic accuracy studies on a specific RADT, the RADTs are less sensitive than declared by the manufacturer [*Forward KR et al, 2006; Nerbrand C et al, 2002; Tanz RR et al, 2009*] (**Table 13**). The FaringoCat study and the validation study, both carried out in Spain, showed similar results, but lower than those provided by the manufacturer. The positive predictive values of the RADT ranged between 77% [*Forward KR et al, 2006*] and 97% [*Camurdan AD et al, 2008*], generally being around 90% [*Johansson L et al, 2003*].

Table 13. Validation characteristics of OSOM Strep A (Genzyme, UK) observed in two studies and the data provided by the manufacturer

	n	GABHS	Se	Sp	PPV	NPV	PLR	NLR
FaringoCat	273	49 (17.8)	89.8	93.8	75.9	97.7	14.5	0.11
Validation study	222	55 (24.8)	94.5	91.6	79.1	98.7	11.2	0.06
Data provided by the manufacturer	639	175 (27.4)	96.0	97.8	94.4	98.5	44.5	0.04

Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio

A subject of concern in our studies is the high incidence of group C β-haemolytic streptococcal infection, being in one study approximately double that observed by Lindbæk et al in Norway [*Lindbæk M et al, 2005*]. As already mentioned in the Introduction section of this thesis, the pathogenic role of this germ is currently under debate as Zwart et al observed that penicillin may reduce, albeit only marginally, the duration of the symptoms of pharyngitis by group C β-haemolytic streptococci [*Zwart S et al, 2000*]. The virulence factors are similar to those of GABHS and may cause the same type of infections. It has been associated with outbreaks of pharyngitis with a clinical picture similar to that produced by GABHS but with fewer suppurative sequelae. Interestingly, pharyngitis caused by group C streptococci was more frequent among the patients with only two Centor criteria and was much less frequent among those with three criteria. More studies evaluating the aetiology of pharyngitis in adults are therefore needed.

Another message of this thesis is the low sensitivity of CRP for the diagnosis of GAHBS sore throat. Few studies have evaluated the validity of this biomarker. In a recent study aimed at investigating the benefit of having CRP, white blood cell count, and absolute neutrophil count measured in these patients, the researchers failed to demonstrate an increase of the diagnostic accuracy when added to the Centor score and RADT [*Christensen AM et al, 2014*]. In a Norwegian study CRP (sensitivity 73% and specificity 67%) and white blood cells count (sensitivity 71% and specificity 77%) measurements were more reliable as compared to clinical criteria (sensitivity 64% and specificity 71%) in the distinction between acute pharyngitis caused by GABHS and that caused by other pathogens. However, the authors noted that the RADT had a higher specificity (93%) and similar sensitivity (71%) compared to CRP and white blood cells count [*Hjortdahl P et al, 1994*]. Gulich et al found that the addition of CRP to the clinical assessment increased the sensitivity, from 61% to 78% and the specificity, from 73% to 82% in the diagnosis of bacterial pharyngitis. However, they did not find any improvement with the addition of white blood cell count and clinical features [*Gulich MS et al, 1999*]. These moderately good results for CRP in the previous studies might be explained by the fact that none of them identified other streptococcal causes such as groups C and G β-haemolytic streptococcus, as we did perform in our study.

Procalcitonin has also been claimed as a purported biomarker that could differentiate GABHS from other causes in patients with sore throat. However, Christensen et al failed to observe any difference in mean procalcitonin levels between GABHS and non-GABHS acute

tonsillitis patients [*Christensen AM et al, 2014*]. The sensitivity (72%) and specificity (58%) were accordingly low. In a previous study of procalcitonin levels in acute pharyngitis patients, significantly higher mean procalcitonin levels were found in children with a bacterial growth compared to children without a bacterial aetiology [*Elsammak M et al, 2006*]. Using optimal cut-off levels, the specificity was higher for procalcitonin (87%) than CRP (73%), but the sensitivity was lower (procalcitonin 73%, CRP 80%). An explanation for the highest procalcitonin reliability may have been the fact that Elsammak et al distinguished between bacterial and non-bacterial acute tonsillitis rather than between GABHS and non-GABHS. Neither Elsammak et al did identify streptococcal aetiologies different from GABHS [*Elsammak M et al, 2006*].

Table 14. Criteria for selection of point-of-care equipment for primary care

The test should be valid and reliable (from studies performed by independent bodies)
The test result should have direct consequences for the GP's decision-making
The long-term quality control must be assured
The sample should be tested immediately, once this has been obtained
The turnaround time of diagnostic testing should be available quickly enough
Testing should avoid the re-consultation of the patient for obtaining the result
The test should be self-contained and user-friendly instrumentation
Testing should eliminate the need to fill out forms and transport of specimens
The test should be used frequently enough
There should be enough information available for a correct interpretation of test results
The indication for using the test should be clear
The test should predict clinical outcome in patients with the relevant indication
A good connectivity between the testing devices and computed records is recommended
The use of the test should be associated with GP satisfaction and patient acceptability
The routine use of point-of-care test should be cost-effective

A recent Cochrane Library review suggests that antibiotic use in patients with acute respiratory tract infections could be reduced by carrying out the CRP rapid test in addition to routine examinations [*Aabenhus R et al, 2014*], confirming a previous meta-analysis [*Huang et al, 2013*]. However, the researchers of this review only included studies involving upper and lower respiratory tract infections and sore throats were not considered. As shown in paper 4 of this thesis, this rapid test failed to identify GABHS infection in adults with pharyngitis. Cals put forward different criteria that a point-of-care test should meet [*Cals J et al, 2013*]. Table 14 summarises and modifies all these criteria (**Table 14**).

According to the studies of this thesis, in adults with sore throat RADT should be carried out in those with a Centor score of at least 2 and CRP should not be recommended.

CONCLUSIONS

1. The reliability of the clinical criteria for the diagnosis of pharyngitis caused by GABHS is very low.
2. The sensitivity and specificity observed with the utilisation of the two immunochromotographic RADTs for the diagnosis of GABHS infection is greater than 90% and is therefore recommended to be used in primary care for adolescents and adults with sore throat and at least two Centor criteria.
3. The high negative predictive value of these RADTs, greater than 96% in the studies included in this thesis, permits discarding the presence of GABHS when the RADT result is negative.
4. The high negative predictive value of the RADT means that there is no need to carry out a subsequent culture.
5. Repetition of the RADT only marginally improved the validity of the first procedure, thereby making the repetition of the RADT in daily clinical practice in patients with sore throat with at least two Centor criteria and a negative antigenic test result unnecessary.
6. The sensitivity of the RADTs evaluated increased with a higher number of Centor criteria, revealing a spectrum effect.
7. The CRP is not useful for distinguishing the patients with GABHS infection and therefore its determination is not recommended.
8. Despite being the presence of GABHS highest among patients with four Centor criteria, the percentage ranged from 38.9% to 49.1% in the different studies.
9. The prevalence of group C streptococcal infection ranged from 8.8% to 15.8% in the different studies, with the greatest percentages of infection among patients with two Centor criteria and was associated with the highest CRP concentrations.

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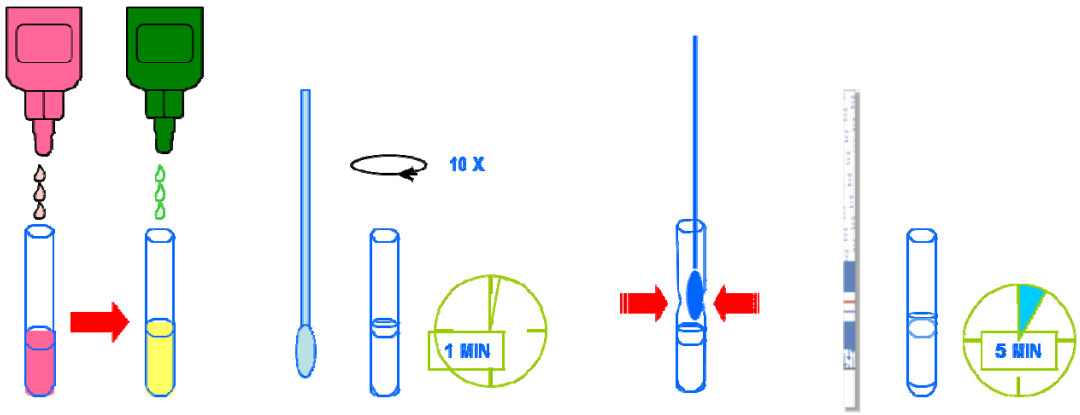
APPENDICES

APPENDIX 1. OSOM® Strep A, Genzyme

Parts of the device:

Instruction manual delivered to the GPs participating in the study:



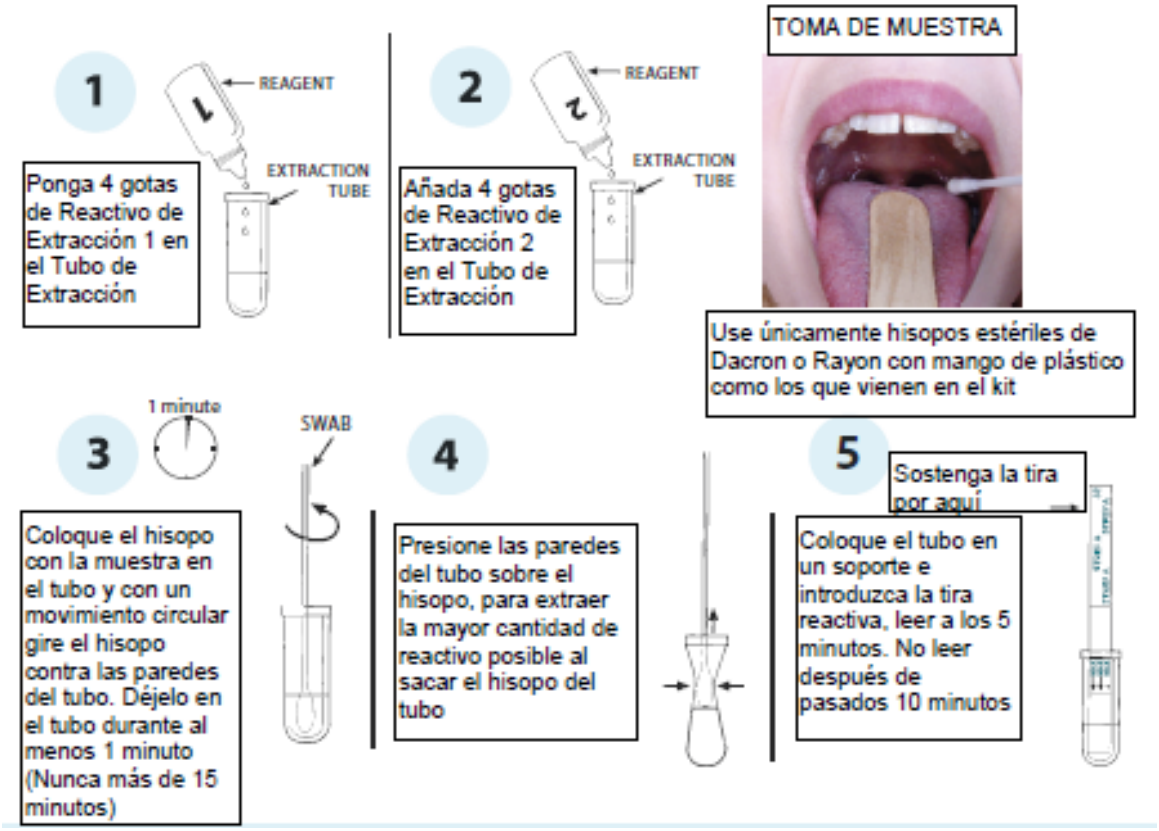
1. Añadir 3 GOTAS de reactivo 1 (rosa) + 3 GOTAS de reactivo 2 en un tubo. La solución se vuelve amarillento claro
2. Introducir el hisopo con la muestra. Mezclar la solución girando el hisopo 10 veces. Dejar reposar durante 1 minuto
3. Extraer el hisopo, exprimiendo con los dedos, para sacar la mayor cantidad de líquido posible
4. Introducir una TIRA de prueba en el tubo, con las flechas hacia abajo. Leer resultados a los 5 minutos

How to interpret the results of the dipstick:

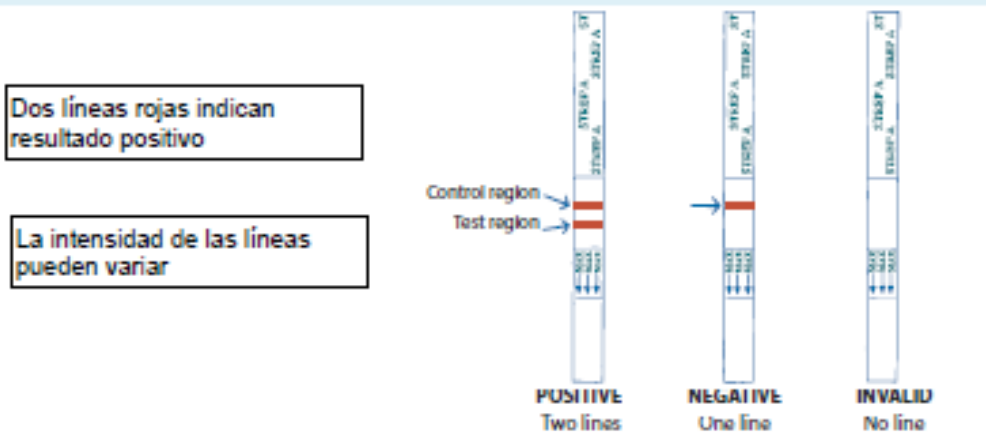
On the left hand a positive dipstick, with two lines, corresponds to GABHS pharyngitis whereas the dipstick on the right, with only one line, depicts a negative result.

APPENDIX 2. Analyz-Strep A Rapid® test

Instruction manual delivered to the GPs participating in the study:



How to interpret the results of the dipstick:



APPENDIX 3. Updated recommendations on management of acute pharyngitis

Based on the review paper published in the *Butlletí de la Societat Catalana de Medicina Familiari Comunitària*

Calviño O, Llor C, Hernández S, Cots JM. Actualización en las recomendaciones en el manejo diagnóstico y terapéutico de la faringitis aguda. Butlletí 2015;33:2. Available at: http://pub.bsalut.net/butlleti/vol33/iss1/2

ACTUALIZACIÓN EN LAS RECOMENDACIONES EN EL MANEJO DIAGNÓSTICO Y TERAPÉUTICO DE LA FARINGITIS AGUDA

Autores: Olga Calviño[1], Carles Llor[1], Silvia Hernández[1], Josep Maria Cots[2]

[1]Médico de atención primaria. Centre de Salut Jaume I, Tarragona

[2] Médico de atención primaria. Centre de Salut La Marina, Barcelona

Correspondencia: olgacd@comt.es

Revisores: Ernest Vinyoles y Sebastià Juncosa

Publicado: *enero 2015*
Olga Calviño, Carles Llor, Silvia Hernández, Josep Maria Cots (2015)

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RESUMEN

En el artículo se realiza una revisión actualizada del manejo de la faringitis aguda en atención primaria. Varios estudios se han publicado en los últimos tres años sobre cuál sería el mejor manejo de esta patología, tanto en lo que se refiere a su diagnóstico como por otras estrategias que deberíamos que poner en marcha des de nuestras consultas. En cuanto al tratamiento, no hay novedades ya que la penicilina sigue siendo el mejor tratamiento para esta infección. No obstante, sería necesario impulsar un abordaje más racional, lo que implicaría identificar aquellos pacientes que se pueden beneficiar del tratamiento antibiótico y evitar la sobreprescripción que se hace hoy día. Además, estudios realizados en el Reino Unido ponen de manifiesto que las complicaciones supurativas para dejar de tratar episodios bacterianos son muy raros en la actualidad.

MANEJO DIAGNÓSTICO Y TERAPÉUTICO DE LA FARINGITIS AGUDA

Es fundamental en atención primaria identificar las faringitis causadas por estreptococo del grupo A (EGA), ya que los pacientes que la presentan se pueden beneficiar del tratamiento antimicrobiano. Este ha demostrado ser eficaz en la reducción, aunque de manera muy marginal, de la duración de los síntomas, concretamente en 16 horas[1]. No obstante, esta diferencia es mayor en adolescentes y adultos jóvenes, ya que el tratamiento antimicrobiano puede reducir los síntomas de estos pacientes en aproximadamente dos días. En cambio, no parece que los niños se beneficien tanto de la terapia antibiótica[2,3]. Además, el tratamiento antibiótico en la faringitis causada por EGA ha demostrado que reduce el número de complicaciones y también la incidencia de complicaciones no supurativas, como la fiebre reumática. Sin embargo, es necesario saber que el número de complicaciones por una faringitis no tratada es actualmente muy bajo en Europa[4].

En los últimos años se están publicando artículos sobre los posibles beneficios del tratamiento antibiótico en otras causas de faringitis aguda[5]. Hay discusión sobre la necesidad de tratar la infección causada por otros estreptococos β-hemolíticos, principalmente la causada por los grupos C y G. El tratamiento antibiótico de la faringitis estreptocócica por estreptococo del grupo C podría estar asociado a una duración ligeramente más corta de los síntomas, aunque esta diferencia es muy marginal[2]. También se debe comprobar que el estreptococo β-hemolítico del grupo C puede causar glomerulonephritis e incluso provocar algunos casos de fiebre reumática aguda. Hay más dudas sobre el beneficio del tratamiento antibiótico en las faringitis causadas por estreptococo del grupo G[6]. Otra causa que ha merecido mucha atención en los últimos años es la infección ocasionada por *Fusobacterium necrophorum*. Asimismo, no hay certeza de que el tratamiento antibiótico pueda reducir la

duración de los síntomas de la faringitis causada por este anaerobio[5].

Con la evidencia disponible actualmente, el médico de atención primaria debe identificar la infección por EGA ya que estos casos deben ser tratados con antibióticos. El diagnóstico es generalmente clínico en nuestro país. Los hallazgos clínicos que a menudo acompañan a la faringitis aguda causada por EGA son dolor de garganta, muy frecuentemente de aparición abrupta, fiebre, dolor de cabeza, náuseas, dolor abdominal, vómitos, inflamación y/o presencia de exudado faringoamigdalar, adenopatías latero-cervicales dolorosas y ausencia de tos. No obstante, ninguno de estos factores es específico de la faringitis causada por EGA, ya que los criterios clínicos presentan poca validez a la hora de distinguir la causa estreptocócica de otras causas. Varios estudios han evaluado escalas de predicción clínica que aumentan la posibilidad de infección causada por EGA. La más conocida es la de Centor, que utiliza cuatro criterios: fiebre, exudado faringoamigdalar, adenopatías latero-cervicales dolorosas y ausencia de fiebre, en que se suma un punto por cada uno de estos criterios, oscilando la puntuación global de 0 a 4[7]. Otra clasificación es la de McIsaac, en que se añade la edad a la escala anterior (añadiendo otro punto si la edad es de menos de 15 años)[8]. Recientemente, investigadores británicos han ideado otra escala, el denominado FeverPAIN (fiebre en las últimas 24 horas, purulencia, consulta al médico antes de los 3 primeros días de los síntomas (attendance), inflamación de las amígdalas y no tos o coriza)[9]. No obstante, esta escala se debe validar antes de poder utilizarse, y por tanto, se recomienda continuar utilizando la escala de Centor.

La evidencia es muy clara en el sentido de que los pacientes con ningún o sólo uno de estos criterios tienen un riesgo muy bajo de infección por la EBA y, por tanto, no requieren de ningún abordaje diagnóstico o terapéutico[7,10]. Las guías de práctica clínica más influyentes como son la de la Infectious Diseases Society of America, la de la American College of Physicians o la del National Institute for Health and Clinical Excellence o NICE británico así lo recomiendan[11-13]. Algunos autores recomiendan la prescripción diferida de antibióticos para los pacientes con un riesgo intermedio, como por ejemplo, aquellos con dos criterios (con un 10% de probabilidades de infección por EGA)[9,14]. Además, el uso de esta estrategia se asocia con una menor probabilidad de complicaciones supurativas, comparable a lo que se obtiene cuando se prescribe tratamiento antibiótico inmediato[15].

La mayoría de los expertos son de la opinión de que no se pueden utilizar estas escalas de puntuación clínica sin una evaluación adicional para el diagnóstico de faringitis por EGA porque los médicos estamos acostumbrados a sobreestimar la probabilidad de infección por esta causa causa[11,12]. Esto se apoya en dos estudios de buena calidad donde se mostraba que los pacientes con cuatro criterios presentaban entre un 39 y un 57% de probabilidad de presentar un cultivo faríngeo positivo por EGA[7,16]. Los porcentajes más altos se encuentran en estudios realizados en niños de 5 a 14 años y los más bajos, en aquellos de más de 15 años. Por tanto, el uso de estas escalas no es suficiente para saber con exactitud si un paciente tiene una faringitis causada por EGA o no. Un estudio reciente muestra que el uso sólo de criterios clínicos no se acompaña de unas razones de verosimilitud óptimas, ya que

en cualquier caso no son ni superiores a 5 ni a 0,2[17]. De hecho, la sensibilidad del juicio clínico varia entre el 49 y el 74% y la especificidad entre el 58 y el 76%[18]. Incluso, los médicos más experimentados son capaces de diagnosticar la faringitis EGA en no más del 75% de las ocasiones, basándose únicamente en criterios clínicos[19]. Además, los médicos de atención primaria evaluamos los diferentes criterios de Centor de manera distinta. Así, en España, los médicos son 28 más proclives a indicar tratamiento antibiótico con la presencia de exudado faringoamigdalar en una faringitis aguda que cuando este criterio no está presente en un paciente[20]. Es importante señalar que hasta un 30% de las causas virales cursan con exudado amigdalar y en un 65% de los casos de etiología bacteriana, el exudado no hi está presente.

El cultivo faríngeo es la prueba de oro para conocer la etiología de la infección. Su principal inconveniente es el tiempo que se necesita para obtener resultados. En la década de los ochenta se empezaron a desarrollar pruebas de detección antigénica rápida de EGA, también denominada Strep A, en muestras faríngeas tomadas con escobillón. Estas técnicas tienen la ventaja de la disponibilidad del resultado en el momento de la consulta. Estas pruebas se basan en la extracción del ácido nitroso del antígeno de carbohidratos del EGA a partir de los microorganismos obtenidos de la garganta. Es de aplicación sencilla en la consulta médica, habiéndose de recoger la muestra con la ayuda de un depresor, inmovilizando la lengua, haciéndose la toma de la área amigdalar y de la pared posterior de faringe, así como de cualquier zona inflamada o ulcerada. Es imprescindible evitar que la torunda no toque úvula, mucosa bucal, labio o lengua, tanto antes como después de la[21] (Fig. 1). Los hisopos se depositan en cubetas o cubiletes y se añade un reactivo que contiene anticuerpos antiestreptocócicos. Las pruebas de detección antigénica rápida utilizados para el diagnóstico etiológico de la faringitis aguda tienen el inconveniente de que sólo detecta la presencia de la EGA pero no descarta otras etiologías, como aquellos producidos por estreptococos β-hemolíticos de los grupos C y G, las manifestaciones clínicas de las que pueden ser similares a la producida por la EGA. Estas pruebas ofrecen la ventaja de diagnosticar la faringitis estreptocócica en unos pocos minutos, con una especificidad asociada mayor del 95% cuando se utilizan en pacientes con dos o más criterios de Centor[19,22]. Dado que el número de falsos positivos es muy bajo, estas pruebas rápidas permiten tomar decisiones terapéuticas bastante fiables. No obstante, su sensibilidad oscila entre el 60% y el 96%, utilizando el cultivo faríngeo como gold standard[19,22,23].

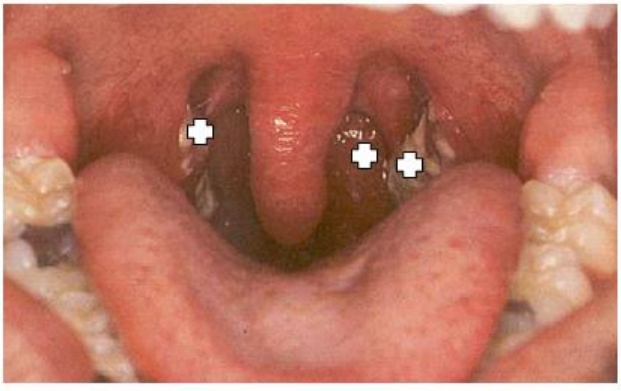
La validez del Strep A depende de la técnica de recogida de la muestra (pudiendo haber resultados falsos negativos cuando se obtiene poco material), área donde se recoge (la que ofrece mejor rendimiento es cuando se recoge en amígdalas y/o pared posterior de la faringe), procedimiento y condiciones del cultivo, probabilidad de infección estreptocócica (algunos autores han comprobado un sesgo de espectro, de forma que la sensibilidad del Strep A aumenta cuanto mayor es el número de criterios de Centor que presenta un paciente[24], presencia de otros gérmenes en la faringe (pudiendo presentarse resultados falsos positivos si la garganta de un paciente presenta un crecimiento importante de Staphylococcus aureus), uso de pruebas más allá de la fecha de

caducidad y marca comercial del Strep A[25]. Otro aspecto que hay que considerar es que la positividad del Strep A no distingue infección aguda de estado de portador pero tampoco no lo hace el cultivo. Los porcentajes de portadores asintomáticos pueden llegar a ser del 30% y su prevalencia es más alta en los niños de 5 a 14 años pero en adultos no llega al 5%[1].

Se ha observado que los médicos que utilizan pruebas de detección antigénica rápida prescriben menos antibióticos en las faringitis que aquellos que no hacen[26,27]. A pesar del elevado valor predictivo negativo de la prueba, los médicos españoles prescriben antibióticos en poco más del 30% de los casos con Strep A negativo, tal como se observó en un ensayo clínico realizado recientemente[27]. Probablemente es debido a que estamos acostumbrados a recetar sistemáticamente antibióticos en pacientes con al menos dos criterios de Centor. Este alto porcentaje de prescripción de antibiótica también se ha observado en otros estudios y en otros lugares, Así, por ejemplo, en un estudio retrospectivo de 6 años realizado en Suecia, se prescribieron también antibióticos en aproximadamente el 40% de los casos con resultados negativos del Strep A[28].

Aunque las infecciones por EGA pueden presentarse también en niños de menos de 4 años, la prevalencia de la infección por EGA en este grupo etario es francamente muy baja[29]. Es importante destacar que las complicaciones no supurativas, como la fiebre reumática, son muy raras en este grupo de edad y el único beneficio del tratamiento es el de reducir la transmisión de persona a persona[12]. Por eso, las sociedades científicas no recomiendan realizar un Strep A en este grupo de edad, excepto en le caso que se presenten factores de riesgo como contactos en casa con una historia de fiebre reumática[11,12]. (Tabla 1).

Figura 1. Puntos en los que hay que recoger el frotis faringoamigdalar



Hay que frotar alguna o algunas de las zonas de la figura. Si el paciente presenta exudado, hipertrofia o hiperemia amigdalar, es suficiente con sólo frotar una amígdala. En caso de un paciente amigdalectomizado hay que recoger muestra en la pared posterior de la faringe

Tabla 1. **¿Cuándo es necesario recomendar la utilización de pruebas de detección antigénica rápida en la consulta?**

Pacientes de 4 años o más con faringitis y ≥ 2 criterios de Centor
Fiebre o historia de fiebre
Exudado o hipertrofia amigdalar
Adenopatías laterocervicales dolorosas
Ausencia de tos
Pacientes < 4 años con faringitis y ≥ 2 criterios de Centor, sólo si
Presencia de brote comunitario per EGA
Paroniquia
Impétigo
Lengua en fresón
Rash escarlatiniforme

EGA: estreptococo del grupo A

Tabla 2. **Tratamiento específico de la faringitis aguda por EGA**

Antibiótico	Dosis	Duración
Primera elección		
Penicilina V (fenoximetilpenicilina)	500-800mg/12 h o 250 mg/8 h	7-10 días
Alternativas		
Penicilina G	1,2 millones de UI im	1 dosis
Amoxicilina	500 mg/12 h	7-10 días
Alérgicos a β-lactámicos		
Josamicina	1 g/12 h	10 días
Diacetilmidecamicina	600 mg/12 h	10 días
Antibióticos en recurrencias		
Amoxicilina y ácido clavulánico	500-125 mg/8 h	10 días
Clindamicina	300 mg/8 h	10 días

EGA: estreptococo del grupo A

RECOMENDACIONES

Matthys et al señalaron que el manejo de la faringitis aguda suponía uno de los puntos más importantes de desencuentro en las guías internacionales, principalmente en cuanto a la utilización de técnicas de detección antigénica rápida[30]. Así, por ejemplo, un médico que trabaja en Reino Unido o en Holanda suele guiar su decisión , terapéutica sólo en base a criterios clínicos mientras que un médicos en Dinamarca o Francia lo hace con una combinación de criterios clínicos y pruebas de detección antigénica rápida a la hora de prescribir antibióticos en la faringitis aguda. La recomendación más racional es que estas pruebas se utilicen sólo en casos de probable infección estreptocócica. Todos los expertos y guías de práctica clínica están de acuerdo en que no es necesario testar y por tanto, tampoco no tratar con antibióticos aquellas faringitis sin ningún o un solo criterio de Centor. La presencia de dos criterios es indeterminada y en la actualidad, las directrices disponibles sugieren realizar el test rápido del Strep A, aunque la guía NICE considera que no se debe testar ni tampoco no tratar con antibióticos estas faringitis[13], aunque si que recomiendan en este grupo realizar una prescripción diferida de antibióticos[31]. En un estudio publicado recientemente, Little et al vieron que los pacientes asignados a la prescripción diferida de antibióticos consumieron menos de la mitad de antibióticos que aquellos que fueron tratados de forma inmediata y re frecuentaron un 40% menos que aquellos que fueron tratados inmediatamente con antibióticos[15]. La mejor recomendación en los pacientes con dos criterios de Centor es hacer el Strep A. En Reino Unido, el NICE aboga porque los clínicos consideren el tratamiento inmediato con antibióticos entre los pacientes que presentan tres o más criterios de Centor[13]. No obstante, en estos casos habría que recomendar el uso del Strep A. Las recomendaciones de la Sociedad Española de Medicina de Familia en su última revisión aconseja en pacientes con dos o más criterios realizar una prueba de detección antigénica rápida[32], de la misma forma que lo aconseja la Sociedad Europea de Enfermedades Infecciosas y Microbiología Clínica[33]. Además, se ha visto que al estrategia que ha demostrado presentar un cociente coste-efectividad más atractivo es el de realizar pruebas de detección antigénica rápida a los pacientes con mayor probabilidad de infección por EGA y tratar los casos positivos[34].

En cambio, no hay que testar cuando se piensa que la infección es viral ni en las faringitis recurrentes, ya que en estos casos, la validez del test rápido es menor[35].

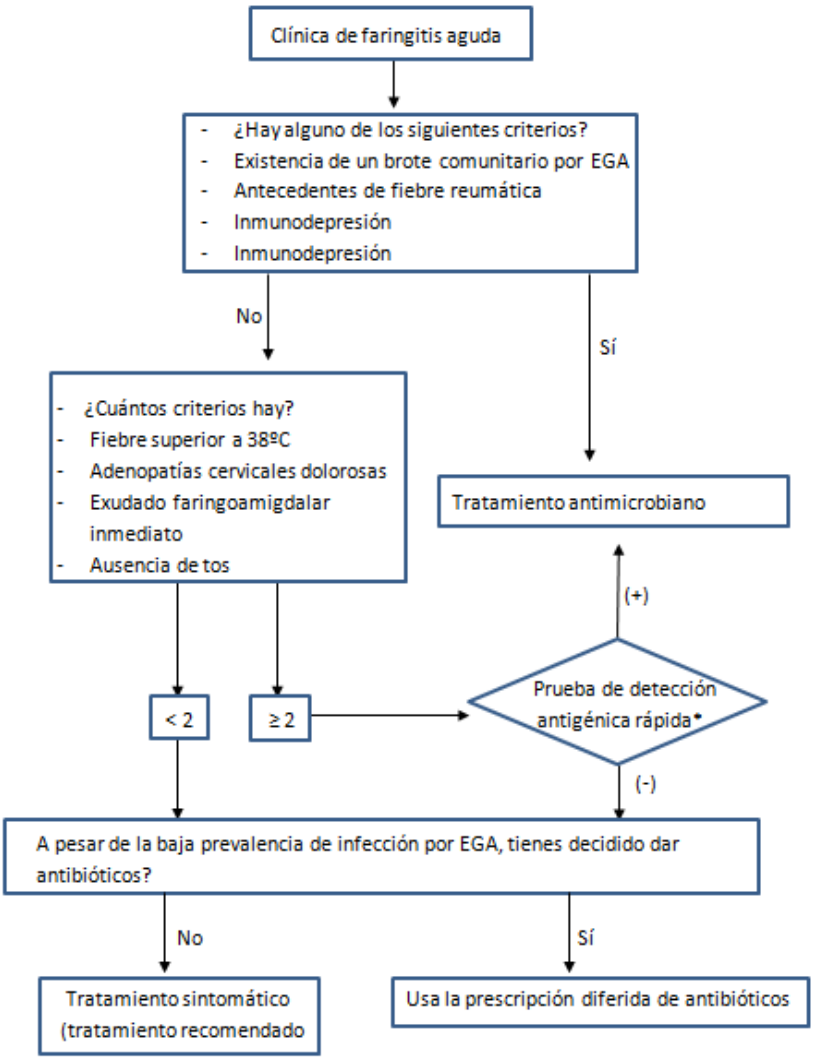
Hay dos reglas de oro que los médicos de familia deben conocer:

- Si decidimos tratar con antibióticos una faringitis aguda, entonces sería necesario que hiciéramos una prueba de detección antigénica rápida para EGA. Sólo así nos daremos cuenta de que en la mayoría de los casos su resultado es negativo.
- Si el resultado del test es positivo es necesario que prescribamos un antibiótico; si el resultado es negativo, no. Aunque si el clínico quiere dar antibióticos en estos casos (porqué el paciente se encuentra mal, considera que el paciente demanda este tratamiento, porque no se cree el resultado de la prueba, etc.), la mejor recomendación que se puede hacer es

utilizar la prescripción diferida de antibióticos (Fig. 2).

El tratamiento antibiótico recomendado debe ser la penicilina V o fenoximetilpenicilina, ya que la EGA ha sido y sigue siendo sensible a este antibiótico en todo el mundo[36]. En el caso de alergia a los β-lactámicos hay que considerar la prescripción de un macrólido. Aunque las resistencias de la EGA a los macrólidos se han reducido mucho en los últimos años en España, hay que seguir considerando un macrólido de 16 átomos, ya que los porcentajes de resistencia siguen siendo inferiores para estos últimos[37] (Tabla 2).

Figura 2. Abordaje recomendado en la faringitis aguda en pacientes de 4 años o más



*En caso de no disponer de técnicas antigénicas rápidas tratar sólo con antibióticos a los pacientes con al menos 3 criterios (guía NICE)

EGA: estreptococo del grupo A

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APPENDIX 4. Abstracts in conferences from studies of this thesis

II CONGRESO DE LAS SOCIEDADES VALENCIANA, BALEAR Y CATALANA DE MEDICINA FAMILIAR Y COMUNITARIA

II CONGRÉS DE LES SOCIETATS VALENCIANA, BALEAR I CATALANA DE MEDICINA FAMILIAR I COMUNITÀRIA

La Dra. Eugenia Carandell Jäger, Presidenta del Comitè Científic del II Congrés de les Societats Valenciana, Balear i Catalana de Medicina Familiar i Comunitària

CERTIFICA:

que els Drs. YVONNE FERNANDEZ PAGES, SILVIA HERNANDEZ ANADON, CARLES LLOR VILA, OLGA CALVIÑO DOMINGUEZ, GURUTZE AGUIRRE ALAVA i JOSEP MARIA SANTAMARIA PUIG han presentat, la Comunicació-Poster següent:

PRUEBA ANTIGENICA RAPIDA PARA FARINGOAMIGDALITIS POR ESTREPTOCOCO ß DEL GRUPO A¿ ES COSTE EFECTIVA?

I, perquè així consti, signo aquest certificat a la ciutat de Castelló, a 23 de maig de 2008

Dra. Eugenia Carandell Jäger
Presidenta del Comitè
Científic

Societat Valenciana de Medicina Familiar i Comunitària
SBMFC Societat Balear de Medicina de Família i Comunitària
camfic societat catalana de medicina familiar i comunitària

II CONGRESO DE LAS SOCIEDADES VALENCIANA, BALEAR Y CATALANA DE MEDICINA FAMILIAR Y COMUNITARIA

II CONGRÉS DE LES SOCIETATS VALENCIANA, BALEAR I CATALANA DE MEDICINA FAMILIAR I COMUNITÀRIA

La Dra. Eugenia Carandell Jäger, Presidenta del Comitè Científic del II Congrés de les Societats Valenciana, Balear i Catalana de Medicina Familiar i Comunitària

CERTIFICA:

que els Drs. SILVIA HERNÁNDEZ ANADÓN, CARLES LLOR VILÀ, OLGA Mª CALVIÑO DOMINGUEZ, YVONNE FERNÁNDEZ PAGÉS, MANEL PÉREZ BAUER i SILVIA CRISPI CIFUENTES han presentat, la Comunicació-Poster següent:

Validación de las técnicas antigénicas rápidas en el diagnóstico de la faringitis por estreptococo beta-hemolítico del grupo A

I, perquè així consti, signo aquest certificat a la ciutat de Castelló, a 23 de maig de 2008

Dra. Eugenia Carandell Jäger
Presidenta del Comitè Científic

II CONGRESO DE LAS SOCIEDADES VALENCIANA, BALEAR Y CATALANA DE MEDICINA FAMILIAR Y COMUNITARIA

II CONGRÉS DE LES SOCIETATS VALENCIANA, BALEAR I CATALANA DE MEDICINA FAMILIAR I COMUNITÀRIA

La Dra. Eugenia Carandell Jäger, Presidenta del Comitè Científic del II Congrés de les societats Valenciana, Balear i Catalana de Medicina Familiar i Comunitària

CERTIFICA:

que els Drs. OLGA CALVIÑO DOMÍNGUEZ, CARLES LLOR VILÀ, SILVIA HERNÁNDEZ ANADÓN, YVONNE FERNÁNDEZ PAGÉS, MANUEL PÉREZ BAUER i FREDERIC F. GÓMEZ BERTOMEU han presentat, la Comunicació-Poster següent:

CARACTERÍSTICAS DE LA FLORA FARÍNGEA EN EL ADULTO SANO: STREPTOCOCCUS TIPO C ¿ENDÉMICO O CASUAL?

I, perquè així consti, signo aquest certificat a la ciutat de Castellón, a 23 de maig de 2008

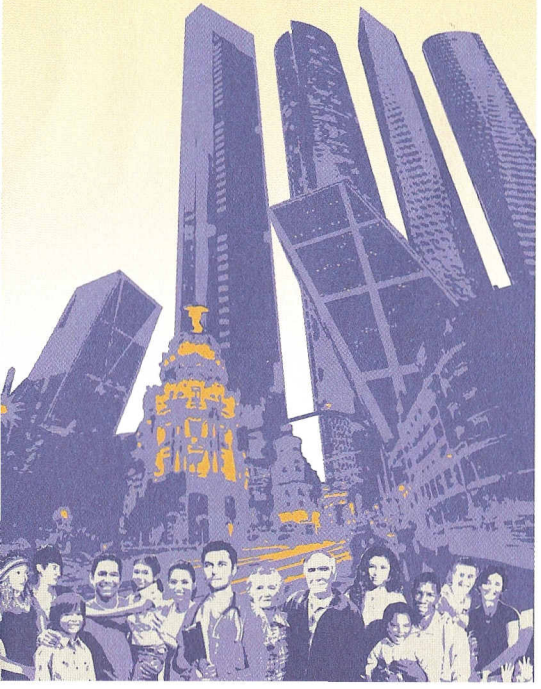
E. Carandell

Dra. Eugenia Carandell Jäger
Presidenta del Comitè Científic

Societat Valenciana de Medicina Familiar i Comunitària · SMFC Societat Balear de Medicina de Família i Comunitària · camfic societat catalana de medicina familiar i comunitària

Madrid'08
Del 19 al 22 de noviembre de 2008
Siempre con las personas

Certificado de Comunicación



XXVIII Congreso de la Sociedad Española de Medicina de Familia y Comunitaria

El Comité Científico y el Comité Organizador del XXVIII Congreso de la Sociedad Española de Medicina de Familia y Comunitaria certifican que la comunicación titulada:

Repetición de la toma faringoamigdalar en la utilización de una técnica antigénica rápida para el diagnóstico de la faringitis por estreptococo betahemolítico del grupo A: ¿es necesaria?

Hernández S, *Calviño O, Fernández Y, Francesc Gómez F, Aguirre G, Llor C*

ha sido presentada en este Congreso.

Madrid, 22 de noviembre de 2008

Araceli Garrido
Presidenta del Comité Científico

Carmen Moliner
Presidenta del Comité Organizador

semFYC
Sociedad Española de Medicina de Familia y Comunitaria

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Siempre con las personas

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XXVIII Congreso de la Sociedad Española de Medicina de Familia y Comunitaria

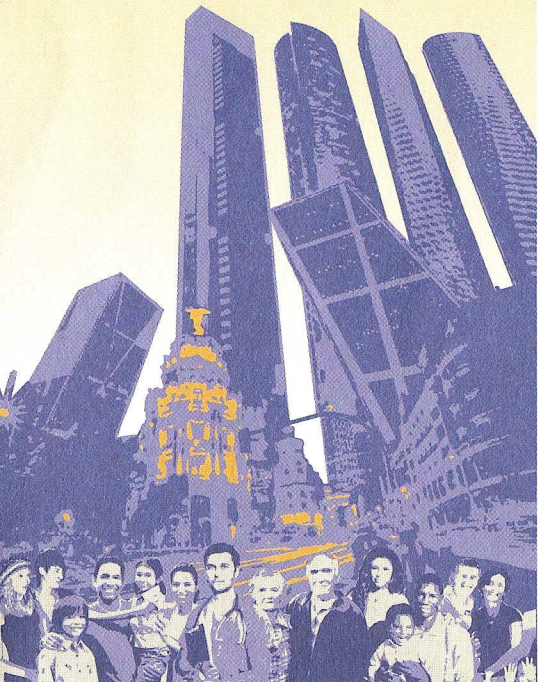
Certificamos que:

La Comunicación titulada:

REPETICIÓN DE LA TOMA FARINGOAMIGDALAR EN LA UTILIZACIÓN DE UNA TÉCNICA ANTIGÉNICA RÁPIDA PARA EL DIAGNÓSTICO DE LA FARINGITIS POR ESTREPTOCOCO BETAHEMOLÍTICO DEL GRUPO A: ¿ES NECESARIA? (ID 334)

S. Hernández, O. Calviño, Y. Fernández, F. Gómez, G. Aguirre, C. Llor Vilà

ha sido presentada en la sesión de las **Mejores Comunicaciones Orales** del congreso.



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Carmen Moliner
Presidenta del Comité Organizador

Araceli Garrido
Presidenta del Comité Científico

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Sociedad Española de Medicina de Familia y Comunitaria

16th WONCA EUROPE CONFERENCE

Malaga - Spain
6-9 October 2010

Certificate of Presentation

The Scientific Committee and the Organizing Committee of ***the 16th WONCA Europe Conference****, held in Malaga from Wednesday, 6 October to Saturday, 9 October 2010, certify that the presentation titled:*

Signs and symptoms assciated with a positive strepa test and negativeculture in patients with acute pharyngotonsilitis and 4 centror criteria

Calviño Domínguez O, *Llor C, Hernández Anadón S, Crispi Cifuentes S, Bladécreixenti J, Martínez Blesa T*

was presented during the Conference.

M. Gálvez

Manuel Gálvez-Ibáñez, M.D., Ph.D., M.Sc.
Chair of the Scientific Committee
16th WONCA Europe Conference 2010

Luis Gálvez-Alcaraz, MD, PhD
Chair of the Organizing Committee
16th WONCA Europe Conference 2010

Conference secretariat:
semFYC congresos
C/ del Pi, 11, 2ª Pl., Of. 13 • 08002 Barcelona
Tel. 93 317 71 29 • Fax 93 318 69 02
e-mail: congresos@semfyc.es

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CERTIFICADO DE PRESENTACIÓN DE COMUNICACIÓN

019

Título: ASOCIACIÓN EXISTENTE ENTRE PCR Y ESTREPTOCOCO DEL GRUPO A

Autores: Olga Calviño Domínguez
Carles Llor Vilà
Silvia Hernández Anadón
Teresa Martínez Blesa
Ana Moragas Moreno
Vanesa Revuelta Garrido

La Comunicación arriba reseñada ha sido presentada en el marco del XIX Congreso Nacional y XIII Internacional de la Medicina General y de Familia, celebrado en Santander durante los días 23, 24, 25 y 26 de Mayo de 2012.

Dr.Antonio Torres Villamor
Presidente del Comité Científico

www.semfyc.es/bilbao2012

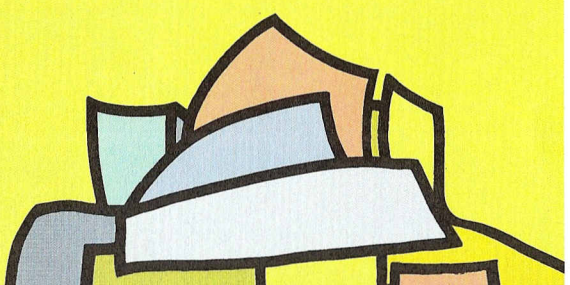
XXXII CONGRESO DE LA SOCIEDAD ESPAÑOLA DE MEDICINA DE FAMILIA Y COMUNITARIA

¡Súbete!

13, 14 y 15 de junio de 2012

Euskalduna Jauregia
Palacio de Congresos
y de la Música

CERTIFICADO DE COMUNICACIÓN



BILBAO'12

El Comité Científico y el Comité Organizador del XXXII Congreso de la Sociedad Española de Medicina de Familia y Comunitaria certifican que la comunicación titulada:

La determinación de la proteína C reactiva no es útil en la farinagoamigdalitis *(Comunicación oral)*

Llor C, *Calviño Domínguez O, Hernández Anadón S, Moragas Moreno A, Fernández Pagés Y, Baldé Creixenti J*

ha sido presentada en este congreso.

Bilbao, 15 de junio de 2012

Susana Martín Benavides
Presidenta del Comité Organizador

Rafael Rotaeche del Campo
Presidente del Comité Científico

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Sociedad Española de Medicina de Familia y Comunitaria

35º Congreso Nacional SEMERGEN

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SEMERGEN Sociedad Española de Médicos de Atención Primaria AP

Barcelona, 23-26 de octubre **2013**

Sede: Fira de Barcelona - Gran Vía - Palacio 8
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El Comité Científico certifica que la comunicación titulada

80/62 - El uso de pruebas rápidas disminuye la presión de los pacientes para que el médico prescriba antibióticos en las infecciones del tracto respiratorio

del/de los autor/es

(1) Silvia Hernández Anadón, (2) Carles LLor Vilà, (3) Lars Bjerrum, (4) Josep Mº Cots Yago, (5) Marta Hernández Anadón, (6) Olga Calviño Domíguez, (7) Vanesa Revuelta, (8) Irene Pascual Palacios, (9) Laura Palacios Llamazares, (10) INVESTIGADORES GRUPO HAPPY AUDIT

ha sido presentada en el **35º Congreso Nacional SEMERGEN**, *celebrado en Barcelona del 23 al 26 de octubre de 2013.*

Barcelona, 26 de octubre de 2013

Dra. Dª. Elena Martínez Prats
Presidenta del Comité Científico

35º Congreso Nacional SEMERGEN

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Sede: Fira de Barcelona - Gran Vía - Palacio 8
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El Comité Científico certifica que la comunicación titulada

80/58 - Validez del Analyz-Strep A Rapid Test en el diagnóstico de la faringitis

del/de los autor/es

(1) Olga Calviño Domíguez, (2) Carles LLor Vilà, (3) Silvia Hernández Anadón, (4) Laura Palacios Llamazares, (5) Teresa Martinez Blesa, (6) Vanesa Revuelta, (7) Marta Hernández Anadón, (8) Irene Pascual Palacios, (9) Josep Mª Cots Yago

ha sido presentada en el **35º Congreso Nacional SEMERGEN**, *celebrado en Barcelona del 23 al 26 de octubre de 2013.*

Barcelona, 26 de octubre de 2013

Dra. Dª. Elena Martínez Prats
Presidenta del Comité Científico

CONGRESO NACIONAL DE MEDICINA GENERAL Y DE FAMILIA

Ciencia, arte y luz

Sevilla
PALACIO DE CONGRESOS
29-31 MAYO 2014

Certificado de comunicación

Título: **ASOCIACIÓN ENTRE LA PRUEBA RÁPIDA DE PROTEÍNA C-REACTIVA (PCR) Y ETIOLOGÍA DE ODINOFAGIA EN PACIENTES CON SOSPECHA DE INFECCIÓN POR STREPTOCOCCUS GRUPO UN ß-HEMOLÍTICO GRUPO A.**

Nº: **580**

Autores:

OLGA CALVIÑO DOMÍNGUEZ
CARL LLOR VILÀ
SILVIA HERNÁNDEZ ANADÓN
FREDERIC GÓMEZ BERTOMEU
MARTA HERNÁNDEZ ANADÓN
TERESA MARTINEZ BLESA

La comunicación arriba reseñada ha sido presentada en el marco del **XXI CONGRESO NACIONAL DE MEDICINA GENERAL Y DE FAMILIA**, celebrado en Sevilla durante los días 29, 30 y 31 de Mayo de 2014

Dr. Higinio Flores Tirado
Presidente del Comité Científico

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Salud para todos, todos por la salud *Osasuna guztion alde, guztiok osasunaren alde*

Certificado de Comunicación

El Comité Científico certifica que la comunicación titulada

63/44 - Asociación entre el test de Proteína C reactiva rápido en sangre capilar y la infección por Streptoccccus del grupo A en la faringitis aguda

del/de los autor/es

(1) Olga Calviño Dominguez, (2) Carles Llor Vilà, (3) Silvia Hernández Anadón, (4) Frederic Gómez Bertmeu, (5) Eva González, (6) Carolina Sarviase, (7) Marta Hernández Anadón, (8) Silvia Crispi Cifuentes, (9) Teresa Martínez Blesa

ha sido presentada en el **36º Congreso Nacional SEMERGEN**, *celebrado en el Palacio Euskalduna Jauregia de Bilbao del 8 al 11 de octubre de 2014*

Bilbao, 11 de octubre de 2014

Dr. D. Gregorio Mediavilla Tris

Presidente del Comité Científico