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Duration of severe and moderate symptoms in pharyngitis by cause

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KEYWORDS
Pharyngitis;
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Abstract
Objective: This study aimed to assess the cause of acute pharyngitis and determine the duration of severe and moderate symptoms based on the aetiology.
Design: Prospective observational study.
Site: One urban health care centre.
Participants: Patients aged 15 or older with acute pharyngitis were included.
Interventions: Bacterial identification was carried out in the microbiology lab using MALDI-TOF in two throat samples. Patients received a symptom diary to return after one week.
Main measurements: Number of days with severe symptoms, scoring 5 or more in any of the symptoms included in the symptom diary, and moderate symptoms, scoring 3 or more.
Results: Among the 149 patients recruited, beta-haemolytic streptococcus group A (GABHS) was the most common aetiology. Symptoms and signs alone as well as the mean Centor score cannot distinguish between GABHS and other bacterial causes in patients with acute pharyngitis. However, there was a trend indicating that infections caused by *Streptococcus dysgalactiae* and *Streptococcus agalactiae* presented more severe symptoms, whereas infections attributed to the *Streptococcus anginosus* group, *Fusobacterium* spp., and those where oropharyngeal microbiota was isolated tended to have milder symptoms. *S. dysgalactiae* infections showed a trend towards longer severe and moderate symptom duration.

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Conclusion: GABHS was the most prevalent, but group C streptococcus caused more severe and prolonged symptoms.

PALABRAS CLAVE
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Estreptococo;
Fusobacterium;
Antibióticos;
Atención primaria

Duración de los síntomas graves y moderados en la faringitis según la etiología

Resumen
Objetivo: Evaluar la etiología de los episodios de faringitis aguda y determinar la duración de los síntomas graves y moderados según la etiología.
Métodos: Estudio observacional prospectivo.
Emplazamiento: Un centro de salud urbano.
Participantes: Se incluyeron pacientes de 15 años o más con faringitis aguda.
Intervenciones: Se realizó identificación bacteriana en el laboratorio de microbiología utilizando MALDI-TOF en 2 muestras faríngeas. Los pacientes recibieron un diario de síntomas que devolvieron a la semana.
Medidas prinicpales: Número de días con síntomas graves, aquellas puntuaciones de 5 o más en cualquiera de los síntomas del diario de síntomas, y síntomas moderados con puntuaciones de 3 o más.
Resultados: Entre los 149 pacientes incluidos, el estreptococo beta-hemolítico del grupo A (EBHGA) fue la etiología más común. Tanto los síntomas y signos como la puntuación media de la escala de Centor no permiten distinguir la infección de EBHGA de las otras causas bacterianas en pacientes con faringitis aguda. Sin embargo, se observó una tendencia en que las infecciones por *S. dysgalactiae* y *agalactiae* presentaban síntomas más graves, mientras que *S.* grupo *anginosus*, *Fusobacterium* spp. y aquellos con microbiota orofaringea solían presentar síntomas más leves. Las infecciones por *S. dysgalactiae* mostraron una tendencia hacia una mayor duración de síntomas graves y moderados.
Conclusión: El EBHGA es el más prevalente, pero el estreptococo del grupo C causa síntomas más graves y prolongados.

Introduction

Acute pharyngitis is the most frequent infectious disease in primary care,[1] and it is one of the reasons for consultation for which many antimicrobial drugs are commonly prescribed.[2] Group A β-haemolytic *Streptococcus* (GABHS) has been associated with a series of complications, including non-suppurative and suppurative complications. A systematic review on the benefits of antibiotic treatment in pharyngitis demonstrated that it provides benefits in cases of GABHS infection.[3] Therefore, antibiotics are recommended when the infection is caused by GABHS.

In recent years, however, there has been doubt about the need to treat other causes as the incidence of complications in patients with negative results from rapid antigen tests for GABHS is high, mainly due to *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, and anaerobes, such as *Fusobacterium*, because of their involvement in some severe cases and complications.[4] None of the signs and symptoms observed in patients with acute pharyngitis are unique to cases caused by GABHS, making clinical criteria less reliable in distinguishing streptococcal infections from other causes. Nevertheless, certain authors suggest that the duration of severe symptoms might vary depending on the specific microbial cause.[5] The primary aim of the study was to investigate the causes of acute pharyngitis episodes, analyze the average Centor score based on the cause, and assess the duration of severe and moderate symptoms depending on the cause of the acute pharyngitis episode.

Material and methods

This was a prospective observational study conducted at an urban primary care health centre in Catalonia. Patients aged 15 or older with acute pharyngitis who attended the centre starting from January 2019 were consecutively invited to participate. Non-infectious causes of pharyngitis (aphthous ulceration, pharmacological causes), oral candidiasis, patients treated with systemic antibiotics in the two previous weeks, immunocompromised individuals, pregnant women, persons institutionalized in a nursing home, in emergency situations, difficulty in attending the visit, and/or patient or guardian/parent incapacitation to sign the consent were excluded from the study. The inclusion of cases was concluded in March 2020 due to the outbreak of the COVID-19 pandemic.

A data collection sheet was developed, including sociodemographic and clinical data, as well as the Centor criteria.[6]

Table 1 Microorganisms isolated and characteristics of the patients reported in the index visit.[a]

	n (%)	Centor score[b], mean (SD)	Severity of the infection[c], mean (SD)	Treated with antibiotics, *n* (%)	Symptom score[d], mean (SD)
Streptococcus pyogenes	43 (28.9)	2.26 (1.2)	2.02 (0.6)	36 (83.7)	20.37 (7.5)
Streptococcus agalactiae	2 (1.3)	2.50 (0.0)	2.00 (0.0)	1 (50.0)	25.50 (2.1)
Streptococcus dysgalactiae	7 (4.7)	2.43 (1.4)	2.14 (1.3)	5 (71.4)	25.71 (4.5)
Streptococcus anginosus group	8 (5.4)	2.50 (1.3)	1.75 (1.0)	4 (50.0)	14.00 (7.7)
Fusobacterium spp.	6 (4.0)	2.00 (1.4)	1.83 (0.7)	3 (50.0)	20.50 (3.9)
Carriers of *Staphylococcus aureus*	10 (6.7)	2.00 (1.2)	1.50 (0.7)	3 (30.0)	20.11 (2.9)
Commensals	68 (45.6)	1.69 (1.0)	1.68 (0.7)	29 (35.8)	16.44 (6.7)
Total	144 (100)	1.99 (1.2)	1.81 (0.7)	81 (56.3)	18.70 (7.1)

SD, standard deviation.
[a] Insufficient or incorrect sampling in 5 cases.
[b] Addition of the symptoms fever, tonsillar exudates, tender cervical glands and absence of cough.
[c] Based on clinician's judgement, on a scale 1 (mild) to 5 (very severe).
[d] Based on the addition of the following symptoms: febrile sensation, headache, general discomfort, cough, odynophagia, difficulty swallowing (solids or liquids), and difficulty in daily activities. Each was rated from 1 (very mild problem) to 6 (the most serious it can be).

Patients were given a symptom diary, used previously in other studies, to be completed before bedtime, and symptoms were assessed on Likert scales with a 7-point rating (0 = no problem/not affected, 1 = very mild problem, 2 = mild problem, 3 = moderate problem, 4 = significant problem, 5 = serious problem, 6 = the most serious it can be).[7] The following items were recorded in the diary: febrile sensation, headache, general discomfort, cough, odynophagia, difficulty swallowing (solids or liquids), and difficulty in daily activities. The sum of all these symptoms was calculated. The days with severe symptoms, scoring 5 or more in any of these symptoms, and moderate symptomatology, scoring 3 or more, were counted.

In each patient two throat samples were taken by participating doctors and nurses who were trained on how to correctly obtain the samples with vigorous rotation of the swab over the tonsils and posterior pharynx without touching the tongue, teeth, or gums. One swab was sent to the Microbiology Department of the hospital with the eSwab© (Innovation Copan, Brescia, Italy) collection and transport system. The identification of different bacteria was analyzed by MALDI-TOF MS (matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) using a Microflex LT bench top mass spectrometer (BRUKER DALTONICS©, Bremen, Germany), with genus and species identification, paying special attention to the following pathogens: GABHS, *S. dysgalactiae*, *Fusobacterium* species, mainly *F. necrophorum*, and *S. anginosus* group (*anginosus*, *intermedius*, and *constellatus*). Patients were asked to return the symptom diary after one week and were followed for an additional 2 months to assess complications. Descriptive analysis was carried out.

Results

A total of 149 patients with acute pharyngitis were recruited before the COVID-19 pandemic, with an average age of 36.7 years (SD 15.5 years), ranging from 15 to 87 years. Of these, 92 presented with pharyngeal exudate (62.2%), 57 with painful lateral cervical lymph nodes (38.3%), 59 with fever (39.6%), 59 with cough (39.6%), and 20 experienced recurrences (13.4%). Eighty-four patients (56.4%) were treated with antibiotics. A total of 138 patients returned their diaries (92.6%).

Table 1 shows the characteristics of the patients recruited and the microorganisms isolated. The presence of different symptoms was unable to differentiate the cause of various episodes of pharyngitis. However, a trend to a higher Centor score was observed among infections caused by *S. dysgalactiae*, *Streptococcus agalactiae*, and GABHS. No complications were observed in any of the patients recruited. The identification of the causative microorganisms remained undetermined in five cases due to inadequate or erroneous sampling. The most prevalent microorganism was GABHS, accounting for nearly 29% of the cases. Over half of the patients received antibiotic treatment, with a higher percentage observed among those with GABHS infection. The most pronounced symptom scores were documented in infections attributed to *S. agalactiae* and *S. dysgalactiae*, whereas the lowest scores were linked to cases of pharyngitis where no pathogen was identified, as well as infections caused by the *S. anginosus* group and *Fusobacterium* spp.

Table 2 shows the mean duration of severe and moderate symptoms for each of the microorganisms. The duration of severe symptoms was longer for infections caused by *S. dysgalactiae* (group C streptococci), with a mean duration of 2.86 days and the lowest for isolation of commensal flora and infections caused by *S. anginosus* group and *Fusobacterium* spp. There were no differences in the duration of severe or moderate symptoms between those who received antibiotic treatment and those who did not.

Discussion

The key finding of the study is that symptoms and signs alone cannot distinguish between GABHS and other bacterial

Table 2 Duration of severe and moderate symptoms in acute pharyngitis based on the microorganism isolated.

Microorganism	*n*	Duration of severe symptoms, in days		Duration of moderate symptoms, in days	
		Mean	SD	Mean	SD
Streptococcus pyogenes	42	1.78	1.6	3.31	1.8
Streptococcus agalactiae	2	2.00	0.0	3.00	0.0
Streptococcus dysgalactiae	7	2.86	1.5	5.00	1.7
Streptococcus anguinosus group	8	0.75	0.9	2.75	1.6
Fusobacterium spp.	6	1.17	1.0	2.50	0.8
Carriers of *Staphylococcus aureus*	9	1.56	1.5	3.33	1.4
Commensals	63	1.50	2.2	3.66	2.4
Total	138	1.61	1.8	3.47	2.0

SD, standard deviation.

causes in patients with acute pharyngitis. This underscores the necessity of conducting rapid antigen detection tests in clinical practice, particularly when patients present high Centor criteria. This study also suggests that episodes of acute pharyngitis caused by *S. dysgalactiae* show more severe symptoms and a longer duration of severe and moderate symptoms. It was of note that only the intensity of symptoms during the first day was greater in episodes caused by this microorganism compared to others. Interestingly, infections caused by *Fusobacterium* spp. and *S. anginosus* group were slightly milder and comparable to those in which commensals were isolated.

The primary limitation of this study was the low number of infections recruited. The outbreak of the COVID-19 infection disrupted the normal organization of primary care consultations, leading to discontinuation of the study. We made efforts to recover most of the symptom diaries. No complications were observed in our study, and the incidence of infections different from commensals and GABHS was relatively low. Only a study with sufficient power, including a larger number of cases, can clearly elucidate the characteristics of these infections and detect complications. This low sample size is primarily the reason why we did not conduct statistical analysis in our study. Except for GABHS and commensal flora, all other isolates were found in ten or fewer cases. Therefore, conducting any statistical analysis with such a small number of cases would not yield meaningful results. However, we have already observed a trend towards increased symptom intensity with group C streptococcus infections. Another limitation is the administration of antibiotics, primarily for GABHS, which could have potentially shortened the duration of severe symptoms. Doctors had the discretion to utilize rapid antigen detection tests and prescribe treatment based on the results obtained. However, literature suggests that the reduction in symptom duration with antibiotic use is minimal, and this is never the primary reason for administering this therapy when GABHS is identified.[3]

β-Haemolytic streptococci of groups C and G typically present as normal throat flora and rank among the leading causes of pharyngitis in the Western world.[8,9] The necessity of identifying infections caused by these strains remains uncertain for two main reasons. Firstly, some studies have observed that among adolescents and young adults, antimicrobial treatment for pharyngitis caused by this pathogen might be associated with a reduction in symptom duration by up to one day compared to placebo.[10] On the other hand, this pathogen has been associated with a higher number of complications in some studies, although other studies have ruled out this association.[11,12]

Studies exploring a possible causal link between *F. necrophorum* and uncomplicated pharyngitis suggest a potentially underestimated aetiological role.[13] Additionally, *F. necrophorum is* implicated in peritonsillar abscesses, along with *S. anginosus* group infections.[14,15] The understanding of these findings warrants further investigation into optimal treatment strategies for streptococcal pharyngitis. In our study, the combined occurrence of these *S. dysgalactiae*, *Fusobacterium* spp. and *S. anginosus* constituted only about 15% of acute pharyngitis episodes. Among these three micoroorganisms, only *S. dysgalactiae* showed more severe symptoms compared to GABHS infection and a slightly prolonged duration of severe symptoms.

In conclusion, while the presence of symptoms and signs alone does not reliably identify the aetiologic agent in patients with acute pharyngitis, it is recommended to use rapid antigen detection tests for the identification of GABHS infection.[16] The current study has paved the way to better identify these patients, who tend to present more severe symptoms compared to those with acute pharyngitis of other causes.

What is already known

- Acute pharyngitis is the most frequent infectious disease in primary care, and it is one of the reasons for consultation for which many antimicrobial drugs are prescribed.
- The benefit of treating group A β-haemolytic Streptococcus (GABHS) with antibiotics is solid based on the existing evidence.
- There are still doubts regarding whether other bacterial causes of acute pharyngitis, such as group C streptococcus and *Fusobacterium* spp., can be associated with complications and identified solely based on signs, symptoms, and the duration of these symptoms.

What this study adds

- The presence of symptoms and signs alone as well as the mean Centor score cannot distinguish between GABHS and other bacterial causes in patients with acute pharyngitis.
- There was a trend that infections caused by *S. dysgalactiae* (group C streptococcus) presented more severe symptoms, while the *Fusobacterium* spp., and infections with oropharyngeal microbiota isolation had milder symptoms.
- *S. dysgalactiae* infections showed a trend towards longer severe and moderate symptom duration.

Ethical considerations

The study was approved by the Ethics Committee for Primary Care Research IDIAP Jordi Gol, Barcelona (ref. number P15/001).

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Conflicts of interest

The authors declare they have no ocnflicts of interest.

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