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Moderate and severe pharyngitis in young adult inhabitants of Poznan, western Poland

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A – Study Design, B – Data Collection, C – Statistical Analysis, D – Data Interpretation, E – Manuscript Preparation, F – Literature Search, G - Funds Collection

Summary Background. Acute pharyngitis is a frequent clinical problem.

Objectives. To assess: the frequency of streptococcal etiology (β-HS) in moderate to severe pharyngitis among young adult patients, the accuracy of the Centor score (CS) in predicting the likelihood of the β-HS etiology and the usefulness of the rapid antigen detection test (RADT) in the appropriate selection of patients that ought to be treated with antibiotics.

Material and methods. 202 individuals (101 patients and a sex- and age-matched control group) aged 18-44 participated in the study. Two throat swabs were performed: the first one to carry out RADT for group A streptococci (GAS), and the second one to grow a conventional culture. Data on the antibiotic therapy were recorded as well.

Results. β-HS were responsible for one-third of the studied cases of pharyngitis (GAS – 22.8%, 23/101; high non-GAS colony count -9.9%, 10/101). The frequency of the isolation of β -HS depending upon the CS was as follows: CS2 -13.2% (5/36), CS3 -40.5% (15/36), CS4-61.5% (16/36). RADT's effectiveness in identifying GAS was significantly higher than that of CS alone (p < 0.001). Antibiotics were prescribed in 59 cases, including 45% of RADT-negative patients (35/77). The primary choice was penicillin (37.3%, 22/59).

Conclusions. In young adult pharyngitis patients with CS2-4, β-HS are responsible for a minority of cases. Among these bacteria, almost one third are non-GAS. Centor criteria, as the only diagnostic tool in predicting the streptococcal etiology of the disease, are of moderate usefulness. The use of RADT significantly increases the diagnostic accuracy of GAS-related pharyngitis.

Key words: streptococci, pharyngitis, GAS, RADT, non-GAS, Centor score.

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Background

Acute pharyngitis can be defined as the co-existence of sore throat, fever, pharyngotonsillar erythema and edema. It constitutes an important problem in the daily practice of general practitioners and is also a frequent cause of consultations in the case of adult patients [1]. In countries with temperate climate (e.g. Poland), the majority of cases occur in winter and early spring, contributing to an increased incidence of respiratory tract infections during this period of the year. Pharyngitis can be caused by a variety of microorganisms, with viruses being the most common. Nevertheless, bacteria are also an important etiologic agent of this clinical syndrome. The role of group A β-hemolytic streptococci (GAS) in this context is well defined. Due to these facts, pharyngitis is one of the principal causes of the overuse of antibiotics, including broad-spectrum ones as well [2, 3].

In spite of the existence of modern national recommendations for the management of pharyngitis [4], real-life practice shows that they are frequently not adhered to. Briefly, a throat culture or a rapid antigen detection test (RADT) should be performed in patients with a Centor score (CS, or Centor criteria) of 2 or 3, and those in whom group A streptococci (GAS) were detected should be treated with antibiotics. In individuals with 4 Centor criteria, it is recommended to begin empiric therapy, pending the results of microbiological testing. The preferred drug for treating GAS pharyngitis is phenoxymethylpenicillin (penicillin V). The role of β-hemolytic streptococci belonging to serological groups other than A (non-GAS) in causing pharyngitis and the management of such cases is a controversial issue. To the best of our knowledge, data for adults from Poland are not available.

Objectives

This study had the following objectives:

- to assess the frequency of streptococcal etiology in moderate or severe pharyngitis (corresponding to at least CS2) in the case of young adult patients aged 18-44, taking under particular consideration non-GAS,
- to assess the adequacy of CS in determining the likelihood of the streptococcal etiology of this clinical syndrome,
- to assess the usefulness of RADT in the appropriate selection of patients that ought to be treated with antibiotics, in accordance with the current national recommendations for the management of acute pharyngitis.

Material and methods

This prospective case-control study included 101 adult patients aged 18-44 who, in the period from March 1, 2014, to February 28, 2015, went to general practitioners in several

districts of Poznan (one of the largest cities in Poland, situated in the west of the country), because of sore throat lasting no longer than 7 days (median: 3 days; range: 1–7 days). Those individuals who had been treated with antibiotics in the period of 4 weeks preceding their recruitment were excluded from this analysis. All patients were assessed for the presence of the so-called Centor criteria, i.e. lack of cough, fever at a level of at least 38°C, the presence of anterior cervical lymphadenopathy and an exudate on the surface of tonsils. Only patients with at least 2 of these criteria and who agreed to participate in the study were qualified as participants.

Volunteers from the control group, being the inhabitants of the same area, were age- (± 2 years; range: 18–44 years) and sex-matched to patients. All of them were healthy and had not received any antibiotics in the period of 4 weeks prior to being recruited.

Two throat swabs were taken from each study participant. The first sample was delivered (transport medium: Amies) to a microbiological laboratory (Laboratory of Microbiology of Jozef Strus Multidisciplinary Municipal Hospital in Poznan) within 24 hours from sampling, and the second was immediately used in the office to perform RADT for the qualitative ascertaining of the presence of group A streptococcal antigen (OSOM Strep A Test; Sekisui Diagnostics, LLC, San Diego, California, USA) in accordance with the manufacturer's recommendations. Throat swabbing and the microbiological test for β-hemolytic streptococci (β-HS) were conducted in accordance with the instructions contained in the generally available national guidelines [1]. The growth of the colony of β-HS was assessed semi-quantitatively in accordance with the following rules: low bacterial growth within the first quadrant of the plate (+), moderate count – within the second quadrant (++), and abundant growth – within the third or third and fourth quadrant (+++ or ++++). Serotyping according to the Lancefield classification (A, B, C, D, F and G) was performed with the use of SLIDEX® Strepto Plus (bioMérieux® SA, Marcy-L'Étoile, France) latex agglutination tests.

All the physicians recruiting patients were trained in correct throat swabbing and performing RADT in accordance with the manufacturer's recommendations. Moreover, they were provided with information regarding the current national recommendations on the treatment of pharyngitis. The final decision on how to proceed and what antibiotic therapy to choose was made in each case by the general practitioner treating the patient and was not influenced by the research team; nevertheless, we recorded all cases when anti-microbial medication was prescribed.

The economic analysis of the costs of diagnosing and treating pharyngitis within this study was conducted upon the basis of the following presumptions:

- the cost of symptomatic treatment is identical for each case, regardless of CS or the result of microbiological diagnostics,
- the cost of a single RADT used in this study amounted to 6 PLN (1.39 EUR),
- the cost of a single culture with serogroup identification in the case of ascertaining the presence of β-HS amounted to 25 PLN (5.80 EUR),
- the cost of the antibiotic therapy matches 100% of the price of the antibiotic in the Drug Index of Medycyna Praktyczna (Practical Medicine) (available at www. mp.pl, accessed June 25, 2015), whereas the treatment of choice consists in the daily administration of 3 million units of penicillin V in two divided doses over 10 days,
- the cost of the anti-microbial medications prescribed by the physicians treating the study participants matches 100% of their prices in the same source, whereas the actual regimen of the antibiotic therapy (dosing and time of treatment) with the use of the cheapest preparation of a given medication was applied, also if it differed from the one suggested in the recommendations.

Statistical analysis

Numerical data were presented as median and range. Compatibility of data with normal distribution was checked by the Shapiro–Wilks test. Since the data did not follow normal distribution, the comparison between patients and the control group was performed by the Mann–Whitney test. Categorical data were presented as numbers and percentages. The comparison was done by the test for proportions and the chi-square test of independence. Statistical analysis was performed with Statistica 12 (Statsoft, Inc.) software. All tests were considered significant at p < 0.05.

Ethical approval

The study was approved by the Bioethics Committee of Poznan University of Medical Sciences (reference number 988/13). A written informed consent was obtained from all study participants.

Results

The characteristics of all study participants are presented in Table 1. The results of tonsillopharyngeal swab cultures and RADT for the patients and the control group are summarized in Table 2.

Table 1. Characteristics of study participants (patients and controls) ($n = 202$)					
Variable	Patients (n = 101)	Controls (n = 101)	<i>p</i> -value		
Median age (range)	26 (18–44) years	26 (19–44) years	0.739		
Male gender (%)	40 (39.6%)	40 (39.6%)	1.000		
No. of individuals in the household (days)	3.1 ± 1.2 (1–6)	3.1 ± 1.3 (1–6)	0.689		
More than 3 individuals in the household	32 (31.7%)	43 (42.6%)	0.109		
Child/children in the household	42 (41.6%)	39 (38.6%)	0.666		
Mean no. of children	0.6 ± 0.9 (0-3)	0.6 ± 0.9 (0-3)	0.916		
More than 1 child in the household	18 (17.8%)	21 (20.7%)	0.592		
More than 2 children in the household	8 (7.9%)	3 (2.9%)	0.121		
Contact with a case of pharyngitis in the last week	41 (40.6%)	32 (31.7%)	0.187		

Table 2. Tonsillopharyngeal swab culture results, RADT results and its performance in study participants (n = 202)

Result of culture/ RADT	Controls (n = 101)	Patients (n = 101)	<i>p</i> -value
Positive culture	14 (13.9%)	36 (35.6%)	< 0.001
GAS	1 (1%)	23 (22.8%)	< 0.001
Non-GAS (any growth)	13 (12.9%)	13 (12.9%)	1.000
Non-GAS (abundant	4 (3.9%)	10 (9.9%)	0.096
growth)	(n = 100*) 4 (4%)	(n = 78*) 10 (12.8%)	0.030
RADT(+) GAS(+) (true positive RADT)	0	22	N/A
RADT(+) GAS(-) (false positive RADT)	4	2	N/A

Table 2. Tonsillopharyngeal swab culture results, RADT results and its performance in study participants (n = 202)

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Result of culture/ RADT	Controls (n = 101)	Patients (<i>n</i> = 101)	<i>p</i> -value		
RADT(-) GAS(-) (true negative RADT)	96	76	N/A		
RADT(-) GAS(+) (false negative RADT)	1	1	N/A		
Sensitivity of RADT	0%	95.7%	< 0.001		
Specificity of RADT	96%	97.4%	0.577		
PPV of RADT	0%	91.7%	< 0.001		
NPV of RADT	99%	98.7%	0.841		
Accuracy of RADT	95.0%	97.0%	0.468		

^{*23} patients and one individual from the control group with *S. pyogenes* positive culture results were excluded from this analysis. Abbreviations: GAS, group A β -hemolytic streptococci (*S. pyogenes*); non-GAS, other (non-A) groups of β -hemolytic streptococci; PPV, positive predictive value; NPV, negative predictive value; N/A, not assessed;

RADT, rapid antigen detection test.

In the case of all 24 individuals who were culture-positive for GAS (23 patients and 1 individual from the control group), abundant bacterial growth was observed. In the case of patients with identified non-GAS streptococci (n = 13), the following representatives were cultured: C group (GCS) - 7 cases (with abundant growth in 6 of them), G group (GGS) - 4 cases (abundant growth in 3 patients), B group (GBS) - 1 case (abundant growth) and D and F groups (GDS and GFS, respectively) - both in the case of the same patient. In the control group, GCS and GFS were observed respectively in 9 (including an abundant growth in 4 individuals) and 4 cases.

The results of the swab culture from the throat in combination with the number of Centor criteria in patients with pharyngitis are shown in Table 3.

It is worth noticing that the accuracies of the appropriate diagnosis of the GAS status based upon clinical assessment with the application of CS, amounting to, respectively, 70.3% (71/101) for the sub-group of patients whose score was 4 and 63.4% (64/101) for those whose scores were 3 or 4, were significantly lower in comparison with the situation in which, after an initial qualification (at least CS2), RADT was performed. Here, the accuracy amounted to 97% (whereas for both of the comparisons p was < 0.001).

Anti-microbial treatment was prescribed in the case of 59 patients. All RADT-positive individuals received the treatment, including 2 patients that were culture-negative (false positive RADT). Nearly half of 77 RADT-negative cases (45.5%, n = 35)

received an antibiotic, and this group included: 1 patient who was culture-positive for GAS (false-negative RADT result), 10 patients who were culture-positive for non-GAS (with an abundant growth in 8 cases) and 24 patients who were culture-negative (i.e. 40.7% of individuals who were prescribed an antibiotic).

Table 3. Clinical features and culture results in patients with pharyngitis (n = 101) Result of the culture criteria β-HS Negative Non-GAS (n = 65)(n = 23)(n = 36)Tender an-18 (78%) 11 (85%) 29 (81%) 42 (65%) terior LA Exudate 12 (92%)b 21 (91%)^a 33 (92%)^c 39 (60%)a, b, c 14 (61%) 10 (77%) 24 (67%) 38 (58%) Fever 22 (96%) 10 (77%) 32 (89%) 53 (82%) No cough 2 of the 3 (7.9%) 33 (86.8%) 2 (5.3%)^d 5 (13.2%)^d abovementioned 3 of the 10 (27%) 22 (59.5%) 5 (13.5%)d 15 (40.5%)d abovementioned All of the 10 (38.4%) 10 (38.5%) 6 (23.1%)^d 16 (61.5%)^d above

 a – p = 0.005, b – p = 0.025, c – p < 0.001, d – in each of these groups, a low growth of non-GAS was observed in one patient. Abbreviations: β-HS, β-hemolytic streptococci; GAS, group A β-hemolytic

Abbreviations: β -HS, β -hemolytic streptococci; GAS, group A β -hemolytic streptococci (*S.pyogenes*); LA, lymphadenopathy; non-GAS, other (non-A) groups of β -hemolytic streptococci.

Penicillin V was prescribed to 22 out of 59 patients (37.3%). In the remaining cases, the following anti-microbial treatment was implemented: cefadroxil – 11 patients (18.6%), amoxicillin with clavulanic acid – 8 patients (13.6%), amoxicillin – 7 patients (11.9%), macrolides – 6 patients (10.2%), cefuroxime axetil – 4 patients (6.8%), fluconazole, ciprofloxacin and metronidazole – 1 patient each (1.7%); 2 individuals received 2 antibiotics (combinations: cefadroxil + clarithromycin and penicillin V + metronidazole).

The economic analysis of various scenarios for the management of patients with pharyngitis and with at least CS2 (objective: treating cases caused by GAS) is summarized in Table 4.

The analysis of the structure of the antibiotic therapy used in patients based upon the CS and the adopted criterion of the adequacy of treatment (GAS or abundant growth of any potentially pathogenic β -HS) is presented in Table 5.

Table 4. Economic analysis of various procedures of treating GAS in patients with pharyngitis					
	Treatment recommended/ prescribed in the current study	Treat only RADT positive cases	Treat only GAS(+) (culture-positive) cases	Treat patients with CS3-4 (NICE)	CS2-3: RADT CS4: atb
Unnecessary atb prescription	36	2	0	43	17
No application of atb in cases of GAS(+) = atb underuse	0	1	0	3	1
Appropriate treatment*	62	98	101	55	83
Correct atb use	23	22	23	20	22
Total no. of atb prescriptions	59	24	23	63	39
Cost per patient with ap- propriate (GAS-oriented) treatment	19.93 PLN (4.62 EUR)	12.46 PLN (2.89 EUR)	29.87 PLN (6.93 EUR)	29.37 PLN (6.81 EUR)	17.46 PLN (4.05 EUR)

^{*} atb in the case of GAS(+) patients or symptomatic treatment in the case of GAS(-) patients.

Abbreviations: atb, antibiotic; CS, Centor score; GAS, group A β-hemolytic streptococci (*S. pyogenes*); NICE, the National Institute for Health and Care Excellence; RADT, rapid antigen detection test.

Table 5. Antibiotic therapy depending on the adopted treatment indication						
Centor score	Atb use in this	Criterion				
(CS)	study	Treat only cases with GAS(+) culture result	Treat only RADT(+) cases	Unjustified atb use in this study	Treat only cases with abundant growth of β-HS	
CS2 (n = 38)	11 (28.9%) ^a	3 (7.9%)	2 (5.3%)	8 (21.0%)	4 (10.5%)	
CS3 (n = 37)	23 (62.2%)	10 (27%)	11 (29.7%)	13 (35.1%) ^b	14 (37.8%)	
CS4 (n = 26)	25 (96.1%)	10 (38.5%)	11 (42.3%)	15 (57.7%) ^b	15 (57.7%)	
Total (n = 101)	59 (58.4%)	23 (22.8%)	24 (23.8%)	36 (35.6%)	33 (32.7%)	

^a – an antibiotic was also prescribed to one patient with a negative RADT result; *S. pyogenes* was grown from this patient's throat swab culture. ^b – unjustified prescription of an antibiotic to one patient might have resulted from a false-positive RADT result.

Abbreviations: atb, antibiotic; β-HS, beta-hemolytic streptococci GAS; group A β-hemolytic streptococci (S. pyogenes); RADT, rapid antigen detection test.

Discussion

This study gives rise to the conclusion that among young adult patients with moderate and severe pharyngitis (characterized by at least 2 Centor criteria), the etiology of the disease was most frequently non-streptococcal. Most likely, the majority of those cases were related to viral infections. This remark has important practical consequences, as those individuals did not require any antibiotic therapy.

Nevertheless, in slightly over one-third of those study participants, β -HS were found in the throat swab culture; in the majority of them (91.7%, n=33), abundant bacterial growth was observed. In accordance with expectations [5–7], the dominant group (69.7%) was that of GAS, while in the case of the remaining patients – the representatives of other serological groups (non-GAS) were discovered.

GAS constitute the most important cause of pharyngitis justifying antibiotic therapy [4, 8, 9]. Our analysis shows that the basic limitations of the gold standard of the microbiological diagnostics of this clinical syndrome, the objective of which is to identify GAS (time of waiting for result and costs), may be circumvented by the use of RADT. The sensitivity and specificity of this test in the study being discussed here exceeded the values provided by Stewart et al. in the meta-analysis relevant to 1216 adults with pharyngitis [10]. It is worth adding that a Polish study, which provides similar observations on the adequacy of RADT in the case of children, has been published recently [11]. What is significant is that the application of RADT in making therapeutic decisions not only makes it possible to use antibiotics justifiably (epidemiological aspect, limiting side effects), but is also cost-effective. Similar conclusions were formulated by other researchers as well [7]. In connection with the above, we think that there is an urgent need to popularize the application of these tests by general practitioners in Poland.

This requires a comment that, despite the use of RADT in our study, the frequency of prescribing antibiotic treatment to patients with negative RADT results was surprisingly high (45%). A similar phenomenon was observed in some analyses from different countries (Spain, Sweden and USA), although this frequency was slightly lower (30-40% of cases) [12-14]. This was probably due to the lack of experience in the application of RADT on the part of physicians, as well as insufficient knowledge of its diagnostic accuracy [14]. Moreover, they might have suspected that other significant bacteria, e.g. the streptococci from groups different than A (non-GAS) or Fusobacterium necrophorum, were the cause of infection, while their presence was impossible to be detected with the use of this test. It is also possible that other factors, like inappropriate habits of physicians and misconceptions about patients' expectations, could play an important role when deciding about antibiotic therapy despite the negative results of RADT.

The growth of non-GAS in the throat swab culture in the case of some patients justified the prescription of antibiotics. The points in favor of finding the less frequent serological

groups of β -HS to be the causal factor of pharyngitis in the case of these persons are: a more frequently ascertained abundant bacterial growth in patients with non-GAS-positive culture (versus the control group), as well as the fact that the CS of the majority of them (9/10) was 3 or 4.

Although the role of non-GAS as etiological factors of pharyngitis was confirmed in a few earlier reports [5, 6, 15, 16], the procedure in such cases has not been conclusively determined, and numerous recommendations (including the Polish ones as well) put the emphasis on diagnosing and treating cases connected with GAS [4, 8, 9].

This results from several premises. First, it is not possible to definitely determine the actual connection between the presence of β -HS (in this age group, non-GAS much more often than GAS are responsible for the carrier state in patients) and its role in causing the symptoms of pharyngitis in the case of a particular patient or viral superinfection as the source of the condition in the case of the carrier of these bacteria [17]. Second, cases of pharyngitis with non-GAS etiology are usually self-limited, and complications – although possible – are infrequent in the descriptions of the disease [8]. Third, an additional difficulty in confirming the participation of these bacteria in causing the symptoms is connected with the necessity of performing a throat swab culture.

Nevertheless, because non-GAS may be the cause of pharyngitis with the same clinical course as those caused by GAS [6, 16], and performing microbiological diagnostics taking under consideration this etiology is not cost-effective, as it is suggested by observations from this study (data not shown), antibiotic therapy will continue to be prescribed in excess by physicians, in particular in more severe cases (Table 5). In this context, it is also worth emphasizing that the presence of one additional Centor criterion increased more than three-fold the likelihood of isolating both GAS (from 7.9% to 27%) and any other potentially significant β -HS (from 13.2% to 40.5%), and if the patient's CS was 4, this likelihood was over four times higher (38.5% and 61.5%, respectively) than for persons with CS2.

The results of our analysis, considered in the light of the available Polish data, indicate that the physicians treating the study participants first and foremost changed the profile of the prescribed antibiotics, most frequently using penicillin V. What is of importance is that the application of amoxicillin, amoxicillin with clavulanate and macrolides together matched the frequency of prescribing a first-choice narrow-spectrum drug. Panasiuk et al. reported that in 424 cases of pharyngitis (Lublin Region, eastern Poland), antibiotics were prescribed in 87.5% of them, preferring amoxicillin (35.6%), amoxicillin with clavulanate (13.2%), as well as macrolides (10.4%); penicillin V was prescribed only once (0.2%) [2]. According to the Polish results of the international Happy Audit 2 (in which family medicine educational centers from 10 cities, including Poznan, participated), based on the analysis of 5137 visits by patients with respiratory system infections, antibiotics were prescribed in 37% of the cases, with amoxicillin, amoxicillin with clavulanate and macrolides used in, 28.9%, 24.4% and 22.4%, respectively, of patients undergoing anti-bacterial treatment and penicillin V in 6.7% of patients [18].

Summarizing the considerations above, we propose that, in Poland, the prescription of antibiotics in RADT-negative cases of more severe pharyngitis (3 or 4 Centor criteria) should be permitted, intensively promoting a delayed prescription of the drug in these cases (e.g. by issuing a prescription that may be filled 24–48 hours after the visit) – this exclusively concerns penicillin V. In our opinion, the application of this strategy may result in a more reasonable prescription of anti-microbial treatment in real-life setting [19] than is the case nowadays. In the case of patients with severe hypersensitivity reactions to penicillin in the past, it would be necessary to conduct microbiological diagnostics.

This study has certain limitations. The most important ones are: a comparatively small number of participants and the lack of the possibility to assess the outcome of patients with pharyngitis. Third, we were unable to conduct diagnostics for infections caused by *Fusobacterium necrophorum*. This is a microorganism frequently reported as an important cause of pharyngitis in youth and young adults, sometimes complicated by Lemierre's syndrome [20, 21]. Moreover, it needs to be remembered that the diagnostic efficacy of the gold standard in diagnosing the

bacterial etiology of pharyngitis, namely, the throat swab culture, is not perfect, and false positive results (e.g. in the case of carriers), as well as false negative ones, are possible [4]. Finally, there was no control group in our study including patients with moderate to severe pharyngitis for whom therapeutic decisions would be made exclusively upon the basis of the clinical history, without access to RADT.

Despite these limitations, facing an acute lack of Polish studies in this field and, at the same time, given the fact that the results obtained by us and the conclusions from larger analyses conducted by other researchers working on the problem being discussed here coincide, we believe that this report will prove to be useful in the daily practice of physicians in Poland.

Conclusions

In young adult pharyngitis patients with CS2-4, β -HS are responsible for a minority of cases.

Among these bacteria, one third are non-GAS. Centor criteria, as the only diagnostic tool in predicting the streptococcal etiology of the disease, are of moderate usefulness. The use of RADT significantly increases the diagnostic accuracy of GAS-related pharyngitis.

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Conflict of interest: The authors declare no conflict of interests.

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