Clinical Infectious Diseases
MAJOR ARTICLE

Associations Between Findings of *Fusobacterium necrophorum* or β-Hemolytic Streptococci and Complications in Pharyngotonsillitis—A Registry-Based Study in Southern Sweden

David Nygren,[1,2] Lisa Wasserstrom,[3] Karin Holm,[1,2] and Gustav Torisson[2,4]

[1]Division of Infection Medicine, Lund University, Lund, Sweden; [2]Department of Infectious Diseases, Skåne University Hospital, Lund/Malmö, Sweden; [3]Department of Clinical Microbiology, Infection Control and Prevention, Skåne University Hospital, Lund, Sweden; and [4]Clinical Infection Medicine, Department of Translational Medicine, Lund University, Malmö, Sweden

Background. Most pharyngotonsillitis guidelines focus on the identification of group A streptococci (GAS), guided by clinical scores determining whom to test with a rapid antigen detection test. Nevertheless, many patients testing negative with this test are evaluated for group C/G streptococci (GCS/GGS) and *Fusobacterium necrophorum*, yet their importance remains debated. Our primary aim was to evaluate associations between complications and findings of *F. necrophorum*, GAS, or GCS/GGS in pharyngotonsillitis.

Methods. This was a retrospective, registry-based study of pharyngotonsillitis cases tested for *F. necrophorum* (polymerase chain reaction) and β-hemolytic streptococci (culture) in the Skåne Region, Sweden, in 2013–2020. Patients with prior complications or antibiotics (within 30 days) were excluded. Data were retrieved from registries and electronic charts. Logistic regression analyses were performed with a dichotomous composite outcome of complications as primary outcome, based on *International Classification of Diseases, Tenth Revision*, codes. Cases with negative results (polymerase chain reaction and culture) were set as reference category. Complications within 30 days were defined as peritonsillar or pharyngeal abscess, otitis, sinusitis, sepsis or septic complications, recurrence of pharyngotonsillitis (after 15–30 days) or hospitalization.

Results. Of 3700 registered cases, 28% had *F. necrophorum*, 13% had GCS/GGS, 10% had GAS, and 54% had negative results. The 30-day complication rates were high (20%). *F. necrophorum* (odds ratio, 1.8; 95% confidence interval, 1.5–2.1) and GAS (1.9; 1.5–2.5) were positively associated with complications, whereas GCS/GGS were negatively associated (0.7; 0.4–0.98).

Conclusions. Our results indicate that *F. necrophorum* is a relevant pathogen in pharyngotonsillitis, whereas the relevance of testing for GCS/GGS is questioned. However, which patient to test and treat for *F. necrophorum* remains to be defined.

Keywords. pharyngotonsillitis; sore throat; *Fusobacterium necrophorum*; group A streptococci; group C/G streptococci.

Pharyngotonsillitis is among the most frequent complaints in primary care, accounting for 11% of antibiotic prescriptions in Sweden [1]. Most guidelines recommend treatment of *Streptococcus pyogenes* (group A streptococci [GAS]) pharyngotonsillitis after identification by a rapid antigen detection test (RADT), preceded by either the Centor criteria [2], modified Centor criteria [3], or FeverPAIN score [4–6]. The rationale for antibiotic therapy includes reduction of purulent (eg, peritonsillar abscess) and nonpurulent (eg, rheumatic fever) complications [7].

To our knowledge, no guidelines suggest the routine diagnostics of *Fusobacterium necrophorum* [6], which may also cause pharyngotonsillitis [8, 9]. In patients with nonstreptococcal pharyngotonsillitis, the test positivity rates for *F. necrophorum* by polymerase chain reaction (PCR) have been as high as 48% in selected age groups (18–32 years) [10]. High tonsillar carriage rates (up to 21%) have also been described in asymptomatic adolescents and young adults [9–11]. While *F. necrophorum* has been more commonly found in cases compared with controls, there is insufficient knowledge on the extent of the association between complications and findings of *F. necrophorum*, as well as group C/G streptococci (GCS/GGS) [5, 12, 13] in pharyngotonsillitis cases.

Several studies have found an increasing incidence of invasive *F. necrophorum* infections [14–17]. In a previous study, Nygren and Holm [18] found that 59% of patients presenting with Lemierre syndrome had sought healthcare before the subsequent septic presentation, yet only 6% had received antibiotic

Received 14 July 2022; editorial decision 31 August 2022; published online 7 September 2022

Correspondence: D. Nygren, Division of Infection Medicine, Department of Clinical Sciences, BMC, B14, Sölvegatan 19, 22362 Lund, Sweden (david.nygren@med.lu.se).

Clinical Infectious Diseases® 2023;76(3):e1428–e35

https://doi.org/10.1093/cid/ciac736

treatment. Whether early antibiotic treatment could prevent complications is unknown because no randomized controlled trials have evaluated the efficacy of antibiotic therapy in *F. necrophorum* pharyngotonsillitis.

In Sweden, pharyngotonsillitis guidelines were updated in 2012. The use of throat culture for GAS and GCS/GGS and diagnostics for *F. necrophorum* were mentioned as an option in patients with negative RADT results yet persistent symptoms after 3 days or on deterioration after the index visit [19].

In the current study, the primary aim was to evaluate the association between complication rates and findings of *F. necrophorum,* GAS, or GCS/GGS in patients presenting with pharyngotonsillitis who had been investigated for both *F. necrophorum* and β-hemolytic streptococci. The secondary aim was to describe complications in patients empirically or nonempirically treated with antibiotics awaiting microbiology results.

METHODS

Study Setting and Design

The study was carried out in the Skåne Region, Sweden, with a population of approximately 1.4 million (2020). Owing to data availability, inclusion occurred from 1 June 2013 to 31 December 2020. This was a retrospective, registry-based study including all patients with pharyngotonsillitis in whom both a throat culture for β-hemolytic streptococci and PCR for *F. necrophorum* were performed at a primary healthcare center (n = 100) or hospital (n = 9) during emergency department or outpatient visits. The unique personal identification number was used to link information about healthcare-related contacts with information about microbiological, clinical, laboratory, hospitalization, and drug prescription data from regional databases.

Case Definition and Exclusion Criteria

A case was defined as an episode of pharyngotonsillitis (codes J02–J03 from *International Classification of Diseases, Tenth Revision* [*ICD-10*]) in a patient for whom simultaneous throat culture for β-hemolytic streptococci and *F. necrophorum* PCR were performed. Cases were categorized according to the presence of pathogens; results included *F. necrophorum*, GAS (defined as either culture or RADT positive), GCS/GGS (grouped together), or negative (in both PCR and culture). Excluded were patients with a previous (within 30 days) diagnosis of chronic tonsillitis, peritonsillar or other pharyngeal abscess, sinusitis, otitis, sepsis or septic complications, including complications registered on the day of the index visit, or with previous (within 30 days antibiotic) therapy (defined as a β-lactam antibiotic, clindamycin, or metronidazole). The Supplementary Appendix 1 lists *ICD-10* codes (including KSH-7 codes, a simplified coding system based on the *International Classification of Diseases* and used in Swedish primary healthcare centers) used to define pharyngotonsillitis, exclusion criteria and complications.

Microbiological Diagnostics

According to clinical and laboratory routine, tonsillar swab samples were obtained using the ESwab test containing Liquid Amies medium and a regular flocked swab (Copan). For throat cultures, 30 µL of the sample was plated on Columbia agar plates containing sheep blood in the top layer, where the substrate was prepared using Columbia II agar (BD2997596). The plates were incubated anaerobically in an Electrotek anaerobic workstation (Electrotek Scientific) for a minimum of 16 hours. Typical β-hemolytic colonies were Lancefield classified using a Streptex Latex Agglutination Test, according to the manufacturer's instruction (Remel; Thermo Scientific R30950501) as GAS, GCS, or GGS. Further species identification of GCS/GGS (eg, *Streptococcus dysgalactiae* supsp. *equisimilis* and *dysgalactiae*, *Streptococcus equi,* and *Streptococcus canis*) with matrix-assisted laser desorption/ionization–time of flight mass spectrometry in throat cultures was not routinely performed.

The real-time PCR used for *F. necrophorum* was modified from the methods presented by Jensen et al [10] and Aliyu et al [20] and performed as described by Nygren et al [11]. All samples were analyzed at the Department of Clinical Microbiology at the Skåne University Hospital, Lund, Sweden.

Outcomes

The primary outcome was defined as a dichotomous (1/0) composite outcome on day 1–30 from the index visit using *ICD-10* codes for the following complications: peritonsillar abscess, other pharyngeal abscess, otitis, sinusitis, recurrence of pharyngotonsillitis (day 15–30), sepsis or septic complications, and hospitalization. Hospitalizations with an orthopedic, psychiatric, or surgical (eg, trauma) primary diagnosis were excluded (see Supplementary Appendix 1 for primary diagnoses associated with hospitalization). Recurrence of pharyngotonsillitis was defined as a new diagnosis of acute pharyngotonsillitis after 15–30 days. Data on outcomes were ascertained from regional databases covering registered diagnoses for healthcare-related contacts.

Baseline Data

Baseline data on age, sex, and comorbid conditions included in the Charlson comorbidity index [21] were ascertained using registry data from the preceding year. Data on C-reactive protein (CRP), fever (temperature ≥38.0°C), RADT, coinfections ±1 day from the index visit, and antibiotic therapy were acquired from regional databases. Initiation of antibiotic therapy was defined as either the day antibiotics were given in the hospital or the day the prescription was collected at the pharmacy.

Effective antibiotic therapy was defined as a β-lactam antibiotic or clindamycin but including metronidazole in patients who tested positive for *F. necrophorum*. In descriptive statistics, cases with 2 identified pathogens were presented as separate cases in each pathogen group. In regression analyses and in Kaplan-Meier curves, cases with coinfection were defined as *F. necrophorum* if present and as GAS if other β-hemolytic streptococci were also present.

Statistical Calculation, Bias, and Sensitivity Analyses

No formal power calculation was done, and the number of cases during the study period determined the sample size. In the primary analysis, logistic regression analyses were performed with the primary (composite) outcome as dependent variable. Crude odds ratios (ORs) were estimated for patients with *F. necrophorum*, GAS, or GCS/GGS versus those with negative PCR and culture results. These were subsequently adjusted for sex, age category (0–12 [reference category], 13–30, or >30 years), index test location (primary healthcare center or hospital), and any of the comorbid conditions of the Charlson comorbidity index (no/yes) [21]. Owing to the registry-based design, variables with missing or unavailable data (CRP levels, fever, and anamnestic and clinical information) were not used in regression analyses.

Antibiotic therapy was considered an effect modifier with suspected indication bias (ie, patients with more severe presentations were more likely to receive treatment). Therefore, it was not included in the regression analyses. Instead, in a secondary analysis we stratified data into 2 groups based on empiric antibiotic therapy (no/yes) within 1 day of the index visit and investigated associations between bacterial findings and the primary outcome separately in each group.

A subgroup analysis was performed in patients with negative RADT results, excluding those with unknown RADT status (not registered or not determined) or positive RADT results, investigating associations between culture and PCR findings and complications in this subset of RADT-negative patients. Subgroup analyses were also performed for patients aged 0–12, 13–30, or >30 years, investigating associations between microbiological findings and complications in each age category.

Several sensitivity analyses were performed. For coinfections, because cases with *F. necrophorum* were defined as *F. necrophorum* regardless of coinfections in regression analyses, the separate associations between all possible combinations of pathogens with outcomes were evaluated. All patients with a prior diagnosis of pharyngotonsillitis within 30 days (who did not meet other exclusion criteria) were excluded. The period of inclusion (2013–2016 vs 2017–2020) was used as an independent variable to evaluate the impact of increased testing or other chronological bias.

Statistical analyses were performed using Stata Statistical Software (release 13; StataCorp,) and illustrations were created using GraphPad Prism 9 (GraphPad Software). This study was approved by the local ethical review board in Lund, Sweden (no. 2017/971).

RESULTS

A total of 3700 case patients were included, of whom 1034 (28%) tested positive for *F. necrophorum*, 481 (13%) for GCS/GGS, and 371 (10%) for GAS (culture or RADT) and 2016 (54%) had negative results (Figure 1). Among cases defined as GAS, 233 of 371 (63%) had an RADT performed and registered; 122 of 233 RADT results (52%) were positive. Accordingly, the GAS group included 122 RADT-positive cases and 249 cases included by culture. Of GAS cases, 91% had growth in cultures, leaving 9% that had only RADT positivity yet were still defined as GAS. All patients were followed up for 30 days after the index visit.

Baseline Characteristics

When age was categorized into predefined groups of 0–12, 13–30 and >30 years, a large majority of patients with *F. necrophorum* infection were 13–30 years old. A similar age distribution was seen in those with GCS/GGS, while patients with GAS and negative results had less distinct age distributions. No distinct sex overrepresentation for any bacterial finding was found. Patients with GAS had a higher proportion of index tests performed at a hospital. Comorbid conditions were rare (Table 1).

In total, 1286 of 3700 patients (35%) had unknown RADT status. No patients were reported to have coinfections with 2 different β-hemolytic streptococci. Among patients with *F. necrophorum*, 48 of 1034 (5%) were coinfected with GAS (RADT or culture) and 154 of 1034 (15%) with GCS/GGS. Data on fever at index visit were available in 612 of 3700 cases (17%), which is why no comparisons could be made. CRP levels were available in 2282 of 3700 cases (62%). CRP levels were higher among test-positive cases, with similar levels for different pathogens (Table 1).

Outcomes

The primary outcome of any complication within 30 days was found in 742 of 3700 patients (20%) (Table 2). The 3 most common complications of the composite score were hospitalization, with 338 events (9%), recurrence of pharyngotonsillitis (day 15–30), with 320 events (9%), and peritonsillar abscess, with 172 events (5%). The other complications of the composite score were rare. The highest complication rates were seen when GAS was identified (28%), followed by *F. necrophorum* (26%), negative results (17%), and GCS/GGS (16%) (Table 2). For GCS/GGS and GAS, these rates included coinfections with *F. necrophorum*. In patients with GCS/GGS as the sole finding, the complication rate was lower, 40 of 327 (12%).

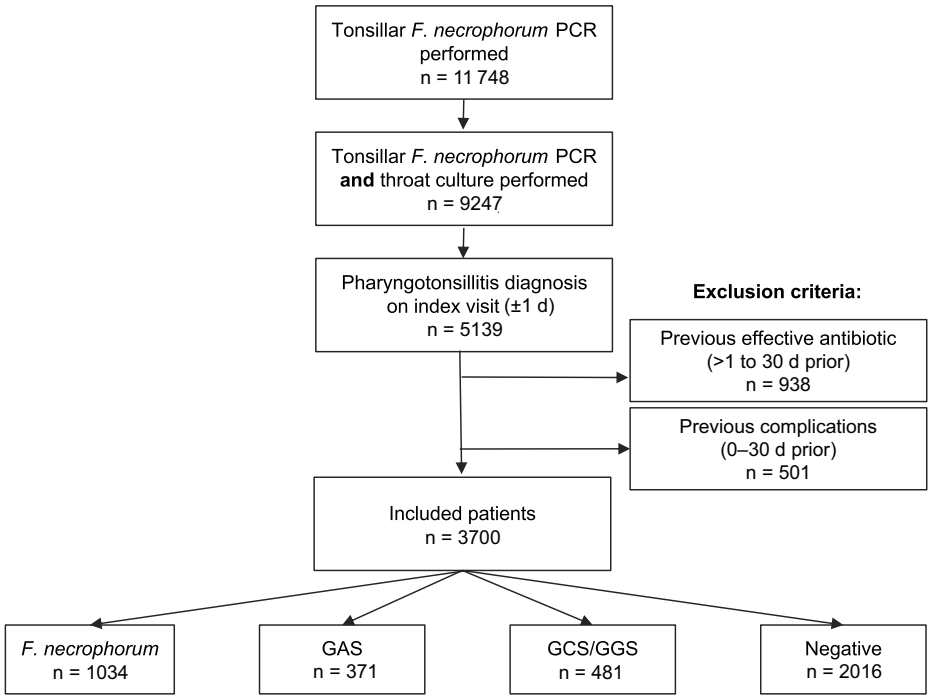

Figure 1. Flowchart of the steps for inclusion in the study, case definitions and exclusion criteria with numbers of identified cases by pathogen detected. Owing to coinfections, each case can be represented in >1 box describing microbiological findings. The numbers of coinfections can be found in the Supplementary Appendix 2; Supplementary Table 5. Previous complications were defined as chronic tonsillitis, peritonsillar or other pharyngeal abscess, otitis, sinusitis, and sepsis or septic complications. Abbreviations: *F. necrophorum, Fusobacterium necrophorum*; GAS, group A streptococci; GCS/GGS, group C/G streptococci; PCR, polymerase chain reaction.

In logistic regression analyses, findings of GAS or *F. necrophorum* were associated with increased complication rates, whereas findings of GCS/GGS were associated with decreased complication rates (Table 3). Timing of events by bacterial finding was visualized in Kaplan-Meier curves for any complication (Figure 2) and separately for peritonsillar abscess, which highlights an association with *F. necrophorum* (Figure 3). Recurrence of pharyngotonsillitis (day 15–30) was most commonly seen in patients with *F. necrophorum*, highlighted by a continuous increase in complications illustrated in the Kaplan-Meier curves after day 15 (Figure 2).

Antibiotic Therapy

When patients with negative findings were stratified by empiric antibiotic therapy within the first day of the index visit, complication rates were higher in treated than in nontreated patients (24% [n = 1013] vs 9% [n = 1003]), highlighting probable indication bias. Similarly, CRP levels were higher in treated than in nontreated patients (median [interquartile range], 81 [35–145] vs 13 [3–42] mg/L, respectively). Patients with *F. necrophorum* infection who were treated within the first day after the index visit also had higher complication rates than nontreated patients (31% [n = 682] vs 17% [n = 352], respectively). Because we could not adequately adjust for this bias, we stratified patients into 2 cohorts according to whether or not they received antibiotic therapy within the first day after the index visit, and we compared patients within each cohort.

Among patients not empirically treated with antibiotics (n = 1552), only *F. necrophorum* was associated with increased complication rates (OR, 2.0; 95% confidence interval [CI], 1.4–2.9). Neither patients with GAS nor those with GCS/GGS had higher rates of complications than patients with negative results. Of these 1552 nontreated patients, 68 (4%) were defined as having GAS. Not surprisingly, RADT positivity was rare in this cohort because treatment is then recommended (10 of 1058 RADT-tested patients in this cohort [1%]) (Supplementary Appendix 2; Supplementary Tables 1 and 2).

Subgroup and Sensitivity Analyses

In a subgroup analysis of RADT-negative patients with pharyngotonsillitis (n = 2292), only *F. necrophorum* was associated with increased complication rates (OR, 2.0; 95% CI, 1.5–2.5). In this cohort, findings defined as GAS (4% [n = 97]), were not associated with increased complication rates (OR, 1.5 (95% CI, 0.8–2.5), yet a type 2 error cannot be ruled out (Supplementary Appendix 2; Supplementary Table 3). In the subgroup analyses investigating associations stratified by age, *F. necrophorum* was associated with complications among patients 13–30 or >30 years old (Supplementary Appendix 2; Supplementary Table 4). Finally, none of the sensitivity

Table 1. Baseline Characteristics and Antibiotic Therapy by Bacterial Findings

	Patients, No. (%)[a]				
	Fusobacterium necrophorum (n = 1034)	GAS (n = 371)	GCS/GGS (n = 481)	Negative (n = 2016)	All (N = 3700)
Age, median (IQR)	21 (18–27)	30 (19–40)	21 (18–27)	25 (18–37)	23 (18–34)
Age group					
0–12 y	11 (1)	50 (13)	23 (5)	239 (12)	321 (9)
13–30 y	840 (81)	150 (40)	361 (75)	1021 (51)	2209 (60)
>30 y	183 (18)	171 (46)	97 (20)	756 (38)	1170 (32)
Female sex	597 (58)	203 (55)	311 (65)	1178 (58)	2174 (59)
Any comorbid condition	15 (1)	15 (4)	8 (2)	114 (6)	150 (4)
Index visit in primary care	828 (80)	267 (72)	397 (83)	1685 (84)	3021 (82)
Fever (≥38°C)	85/187 (45)	56/104 (54)	49/72 (68)	140/293 (48)	307/612 (50)
CRP, median (IQR), mg/L	76 (25–156)	87 (35–163)	72 (33–134)	34 (6–86)	52 (13–115)
Antibiotic within 1 d					
Any effective antibiotic[b]	682 (66)	291 (78)	301 (63)	1013 (50)	2148 (58)
β-Lactam	404 (39)	214 (58)	180 (37)	665 (33)	1382 (37)
Clindamycin	270 (26)	77 (21)	121 (25)	348 (17)	758 (20)
Metronidazole[c]	36 (3)	…	…	…	…
Antibiotic within 3 d					
Any effective antibiotic[b]	792 (77)	314 (85)	355 (74)	1058 (52)	2354 (64)
β-Lactam	455 (44)	235 (63)	226 (47)	717 (36)	1534 (41)
Clindamycin	414 (40)	105 (28)	146 (30)	394 (20)	976 (26)
Metronidazole[c]	62 (6)	…	…	…	…

Abbreviations: CRP, C-reactive protein; GAS, group A streptococci; GCS/GGS, group C/G streptococci; IQR, interquartile range.

[a]Data represent no. (%) of patients unless otherwise specified. Cases with coinfections are presented in multiple columns.

[b]Effective antibiotic therapy was defined as a β-lactam antibiotic or clindamycin, with the addition of metronidazole in cases positive for *F. necrophorum*.

[c]Metronidazole was reported only for *F. necrophorum* owing to its lack of efficacy against β-hemolytic streptococci.

analyses had a notable impact on associations between microbiological findings and complications, including when the impact of coinfections was examined (Supplementary Appendix 2; Supplementary Tables 5–7).

DISCUSSION

This study aimed to describe associations between microbiological findings and complications in patients with pharyngotonsillitis tested with *F. necrophorum* PCR and throat culture for β-hemolytic streptococci. We found higher complication rates when GAS or *F. necrophorum* were identified, whereas GCS/GGS were negatively associated with complications. In a subgroup analysis of RADT-negative patients, only *F. necrophorum* had a positive association with complication rates. Among patients who had not received empiric antibiotics within 1 day of the index visit, only *F. necrophorum* was associated with increased complication rates.

Hospitalization, recurrence of pharyngotonsillitis (after 15–30 days), and peritonsillar abscess constituted the 3 major

Table 2. Complication Rates Within 30 Days by Bacterial Findings[a]

	Patients, No (%)				
Complication	*F. necrophorum* (n = 1034)	GAS (n = 371)	GCS/GGS (n = 481)	Negative (n = 2016)	All (N = 3700)
Any complication (composite outcome)	273 (26)	104 (28)	76 (16)	338 (17)	742 (20)
Specific complications					
Hospitalization	110 (11)	66 (18)	31 (6)	151 (7)	338 (9)
Recurrence of pharyngotonsillitis (d 15–30)	133 (13)	31 (8)	41 (9)	138 (7)	320 (9)
Peritonsillar abscess	82 (8)	21 (6)	11 (2)	70 (3)	172 (5)
Other pharyngeal abscess	8 (0.8)	5 (1)	4 (0.8)	13 (0.6)	27 (0.7)
Otitis	0 (0)	3 (0.8)	0 (0)	11 (0.5)	14 (0.4)
Sinusitis	1 (0.1)	1 (0.3)	0 (0)	11 (0.5)	13 (0.4)
Sepsis or septic complications	5 (0.5)	1 (0.3)	2 (0.4)	1 (0.05)	8 (0.2)

Abbreviations: *F. necrophorum, Fusobacterium necrophorum*; GAS, group A streptococci; GCS/GGS, group C/G streptococci.

[a]Cases with coinfections are presented in multiple columns. One patient may have several specific complications (eg, sepsis and hospitalization).

Table 3. Crude and Adjusted Associations Between Bacterial Findings and Any Complication Within 30 Days (Composite Outcome)

Bacterial Findings and Adjustment Variables	Crude OR (95% CI)	Adjusted OR (95% CI)
Bacterial findings[a]		
Negative (n = 2016)	Reference	Reference
F. necrophorum (n = 1034)	1.8 (1.5–2.1)[b]	1.8 (1.5–2.2)[b]
GAS (n = 323)	1.9 (1.5–2.5)[b]	1.7 (1.3–2.3)[b]
GCS/GGS (n = 327)	0.7 (.5–.98)[b]	0.7 (.5–1.03)
Adjustment variables		
Age group		
0–12 y	Reference	Reference
13–30 y	1.1 (0.8–1.5)	1.2 (0.9–1.6)
>30 y	1.1 (0.8–1.5)	1.3 (0.9–1.8)
Female sex	0.9 (0.7–1.01)	0.9 (0.7–1.04)
Any comorbid condition	1.5 (1.1–2.2)[b]	1.8 (1.2–2.7)[b]
Index visit at the hospital	3.4 (2.9–4.1)[b]	3.4 (2.8–4.1)[b]

Abbreviations: CI, confidence interval; *F. necrophorum, Fusobacterium necrophorum*; GAS, group A streptococci; GCS/GGS, group C/G streptococci; OR, odds ratio.

[a]Cases with coinfection were defined as *F. necrophorum* if present and as GAS if other β-hemolytic streptococci were present.

[b]Significant at $P < .05$.

complications. Hospitalization was most commonly seen in patients with GAS infection, while those with *F. necrophorum* had the highest rates of recurrence of pharyngotonsillitis (15–30 days) (Table 2) and peritonsillar abscess (Figure 3). It can be difficult to interpret a finding of *F. necrophorum* in pharyngotonsillitis because most cases occur in the same age group where tonsillar carriage is seen [11, 22]. We found a test positivity rate of *F. necrophorum* of 28%, and higher (38%) among patients aged 13–30 years, in line with previous studies [8–10, 23]. However, our findings suggest that *F. necrophorum* is both frequently found in patients with pharyngotonsillitis and associated with a high degree of complications, primarily among patients aged 13–30 years, but also in those >30 years of age. Interestingly, our findings question the relevance of GCS/GGS in pharyngotonsillitis, with complication rates lower than in test-negative patients [8, 12, 24]. Furthermore, while power could be an issue in the subgroup analysis of RADT-negative patients, GAS was not associated with higher complication rates, raising questions about the role of throat culture for β-hemolytic streptococci in general.

While an association between *F. necrophorum* and increased complication rates is highlighted, conclusions are harder to draw on the impact of antibiotics. When patients were compared based on empiric antibiotic therapy, treated patients had higher complication rates and CRP levels. We believe this is related to confounding by indication; ie, patients with severe presentations have higher baseline risk of complications, and clinicians are more prone to treat them. When the cohort of patients who were not empirically treated was analyzed, only *F. necrophorum* remained associated with increased complication rates, further suggesting that antibiotic therapy should be considered in cases with *F. necrophorum* pharyngotonsillitis. Here, RADT-positive patients were naturally uncommon since guidelines recommend treatment of these patients, but RADT-negative/culture-positive GAS cases constituted 4% (n = 97). These cases were not associated with complication rates, but a type 2 error cannot be excluded.

The main limitation of the current study is its retrospective design, leading to lack of data on clinical signs and symptoms,

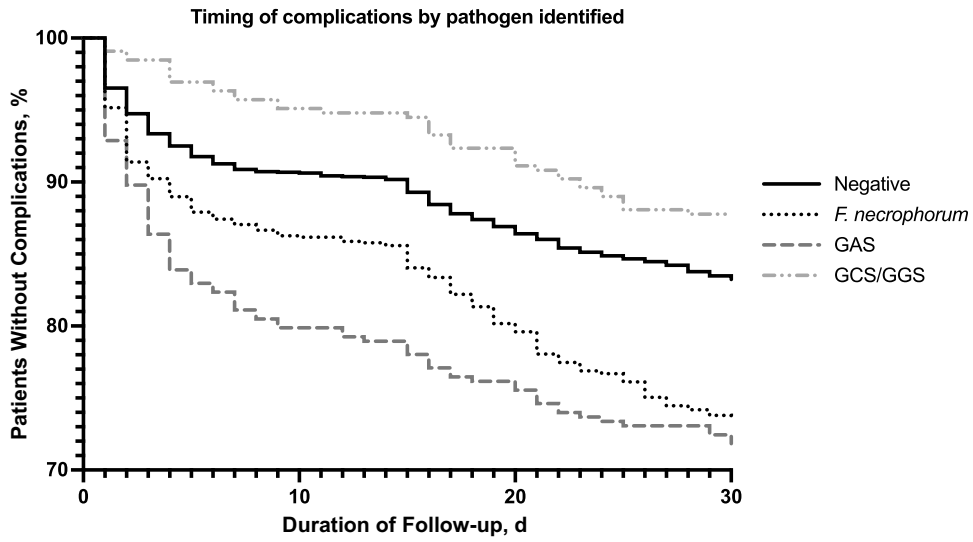

Figure 2. Kaplan-Meier curve highlighting timing of complications in patients with pharyngotonsillitis by pathogen. Cases with coinfection were defined as *Fusobacterium necrophorum* if present and as group A streptococcus (GAS) if other β-hemolytic streptococci were present. Complications were defined as a composite score (0/1) for days 1–30 of peritonsillar abscess, other pharyngeal abscess, otitis, sinusitis, recurrence of pharyngotonsillitis (days 15–30), sepsis or septic complications, and hospitalization. Abbreviation: GCS/GGS, group C/G streptococci.

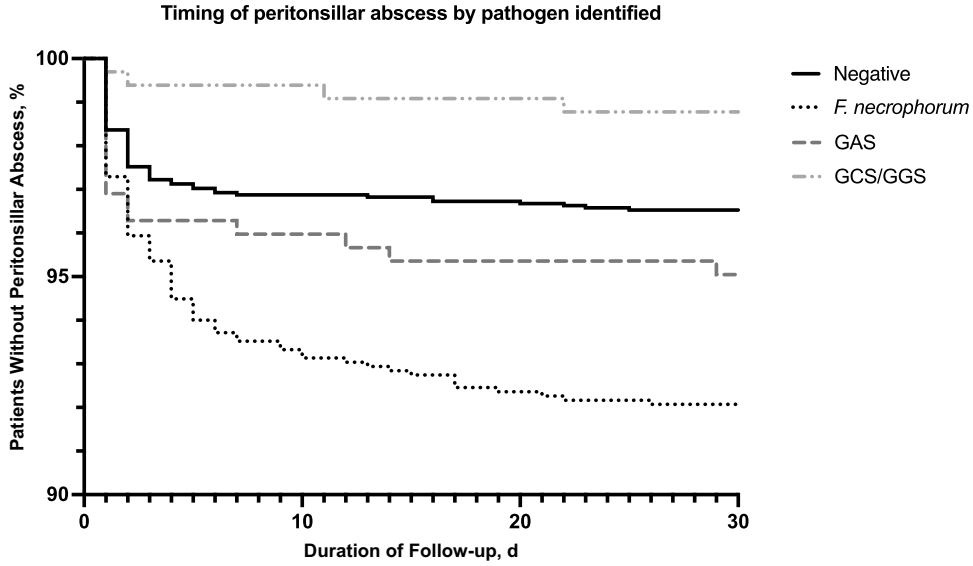

Figure 3. Kaplan-Meier curve highlighting timing of peritonsillar abscess in patients with pharyngotonsillitis by pathogen. Cases with coinfection were defined as *Fusobacterium necrophorum* if present and as group A streptococcus (GAS) if other β-hemolytic streptococci were present. Abbreviation: GCS/GGS, group C/G streptococci.

as well as probable indication bias, which has already been mentioned. Furthermore, we acknowledge probable selection bias, owing to a narrow definition of pharyngotonsillitis restricting cases to J02–J03 (*ICD-10*) and the requirement of diagnostic workup for inclusion. This has most likely led to the selection of more severely ill patients, leading to higher test positivity rates, as well as higher complication rates than normally expected [1, 7, 19]. This could explain the high percentage of empirical antibiotics reported or indicate that current guidelines are not followed. Consequentially, the generalizability of findings is limited to patients with severe symptoms of pharyngotonsillitis with a high suspicion of a bacterial cause.

Our findings of an association between *F. necrophorum* and increased complication rates strongly indicate its relevance as a significant pathogen in pharyngotonsillitis [14–16, 18, 25, 26]. Furthermore, our findings suggest against performing throat cultures to identify β-hemolytic streptococci in patients with negative RADT results. In RADT-negative patients with pharyngotonsillitis, current guidelines fail to instruct, and voices for improved guidance have already been raised [27]. However, our findings do not define which patients to test for *F. necrophorum,* and we cannot conclude whether antibiotic therapy can prevent complications in *F. necrophorum* pharyngotonsillitis. Because the rate of asymptomatic tonsillar carriage can be as high as 1 in 5 in adolescents and young adults [10, 11], testing all RADT-negative patients with sore throat in this age group and treating all positive cases could risk overtreatment. However, our results show that many complications, especially peritonsillar abscess, occur early after the index visit (Figures 2 and 3). Thus, the current guideline of testing RADT-negative patients after 3 days of persistent symptoms may be inappropriate [19]. Therefore, future studies should focus on how to identify patients with *F. necrophorum* pharyngotonsillitis at risk of complications and evaluate antibiotic therapy in these patients to guide policy makers.

In conclusion, we present observational evidence that *F. necrophorum* is a relevant pathogen in pharyngotonsillitis with high complication rates. Our findings suggest that throat cultures to identify β-hemolytic streptococci may not be needed in RADT-negative patients with pharyngotonsillitis, but which patient to test and treat for *F. necrophorum* remains to be defined.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgements. The authors are grateful to Ann-Cathrine Petersson for the introduction of the *Fusobacterium necrophorum* polymerase chain reaction regionally and to Lena Hyllebusk for assistance in data retrieval, both at the Department of Clinical Microbiology, Infection Control and Prevention, Skåne University Hospital, Lund, to Katarina Hedin and Jon Pallon at the Department of Clinical Sciences, Family Medicine, Lund University, for valuable input and discussions during study design, and to Forum Söder, Region Skåne, for assistance in registry data retrieval.

Financial support. This work was supported by the Swedish Government Funds for Clinical Research (ALF) and Region Skåne.

Potential conflicts of interest. K. H. reports grants or contracts, unrelated to this work, from the Royal Physiographic Society of Lund. All other authors report no potential conflicts. All authors have submitted the

ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Skoog Ståhlgren G, Tyrstrup M, Edlund C, et al. Penicillin V four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study. BMJ **2019**; 367:l5337.
2. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. Med Decis Mak **1981**; 1:239–46.
3. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low D. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA **2004**; 291:1587–95.
4. Little P, Moore M, Hobbs FDR, et al. PRImary care Streptococcal Management (PRISM) study: identifying clinical variables associated with Lancefield group A β-haemolytic streptococci and Lancefield non-group A streptococcal throat infections from two cohorts of patients presenting with an ACU. BMJ Open **2013**; 3: e003943.
5. ESCMID Sore Throat Guideline Group, Pelucchi C, Grigoryan L, et al. Guideline for the management of acute sore throat. Clin Microbiol Infect **2012**; 18:1–27.
6. Coutinho G, Duerden M, Sessa A, Caretta-Barradas S, Altiner A. Worldwide comparison of treatment guidelines for sore throat. Int J Clin Pract **2021**; 75:e13879.
7. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for treatment of sore throat in children and adults. Cochrane Database System Rev **2021**; 12:CD000023.
8. Centor RM, Atkinson TP, Ratliff AE, et al. The clinical presentation of *Fusobacterium*-positive and streptococcal-positive pharyngitis in a university health clinic: a cross-sectional study. Ann Intern Med **2015**; 162:241–7.
9. Holm K, Bank S, Nielsen H, Kristensen LH, Prag J, Jensen A. The role of *Fusobacterium necrophorum* in pharyngotonsillitis—a review. Anaerobe **2016**; 42:89–97.
10. Jensen A, Kristensen LH, Prag J. Detection of *Fusobacterium necrophorum* subsp. *funduliforme* in tonsillitis in young adults by real-time PCR. Clin Microbiol Infect **2007**; 13:695–701.
11. Nygren D, Brorson E, Musonda M, Wasserstrom L, Johansson Å, Holm K. Geographical differences in tonsillar carriage rates of *Fusobacterium necrophorum*—a cross-sectional study in Sweden and Zambia. Anaerobe **2021**; 69:102360.
12. Gunnarsson RK, Manchal N. Group C beta hemolytic streptococci as a potential pathogen in patients presenting with an uncomplicated acute sore throat—a systematic literature review and meta-analysis. Scand J Primary Health Care **2020**; 38:226–37.
13. Gerber MA, Randolph MF, Martin NJ, et al. Community-wide outbreak of group G streptococcal pharyngitis. Pediatrics **1991**; 87:598–603.
14. Bank S, Jensen A, Nielsen HM, Kristensen LH, Voldstedlund M, Prag J. *Fusobacterium necrophorum* findings in Denmark from 2010 to 2014 using data from the Danish microbiology database. APMIS **2016**; 124:1087–92.
15. Kristensen L H, Prag J, Malczynski J, Kristensen JH. Incidence and clinical epidemiology of necrobacillosis, including Lemierre's syndrome, in Denmark 1990–1995. Eur J Clin Microbiol Infect Dis **1998**; 17:561–5.
16. Hagelskjær Kristensen L, Prag J. Lemierre's syndrome and other disseminated *Fusobacterium necrophorum* infections in Denmark: a prospective epidemiological and clinical survey. Eur J Clin Microbiol Infect Dis **2008**; 27:779–89.
17. Brazier JS, Hall V, Yusuf E, Duerden BI. *Fusobacterium necrophorum* infections in England and Wales 1990–2000. J Med Microbiol **2002**; 51:269–72.
18. Nygren D, Holm K. Invasive infections with *Fusobacterium necrophorum* including Lemierre's syndrome: an 8-year Swedish nationwide retrospective study. Clin Microbiol Infect **2020**; 26:1089.e7–12.
19. Aronsson B, Claesson K. New treatment recommendations: management of pharyngo-tonsillitis in ambulatory care. Lakartidningen **2012**; 109:2367.
20. Aliyu SH, Marriott RK, Curran MD, et al. Real-time PCR investigation into the importance of *Fusobacterium necrophorum* as a cause of acute pharyngitis in general practice. J Med Microbiol **2004**; 53:1029–35.
21. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
22. Agerhäll M, Henrikson M, Johansson Söderberg J, et al. High prevalence of pharyngeal bacterial pathogens among healthy adolescents and young adults. APMIS **2021**; 129:711–6.
23. Hedin K, Bieber L, Lindh M, Sundqvist M. The aetiology of pharyngotonsillitis in adolescents and adults—*Fusobacterium necrophorum* is commonly found. Clin Microbiol Infect **2015**; 21:263.e1–7.
24. Cimolai N, Morrison BJ, Macculloch L, Smith DF, Hlady J. Beta-haemolytic non-group A streptococci and pharyngitis: a case–control study. Eur J Pediatr **1991**; 150:776–9.
25. Nygren D, Elf J, Torisson G, Holm K. Jugular vein thrombosis and anticoagulation therapy in Lemierre's syndrome—a post-hoc observational and population-based study of 82 patients. Open Forum Infect Dis **2021**; 8:1–7.
26. Riordan T. Human infection with *Fusobacterium necrophorum* (necrobacillosis), with a focus on Lemierre's syndrome. Clin Microbiol Rev **2007**; 20:622–59.
27. Centor RM, Atkinson TP, Xiao L. *Fusobacterium necrophorum* oral infections—a need for guidance. Anaerobe **2022**; 75:102532.