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SHORT REPORT

Persistence after treatment of pharyngeal gonococcal infections in patients of the STI clinic, Amsterdam, the Netherlands, 2012–2015: a retrospective cohort study

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ABSTRACT

Introduction Infection of *Neisseria gonorrhoeae* in the pharynx (pharyngeal Ng) is associated with gonococcal transmission and development of antimicrobial resistance. We assessed proportion of and determinants for persistence after treatment of pharyngeal Ng.

Methods At the STI clinic of Amsterdam, the Netherlands, females-at-risk and men who have sex with men are routinely screened for pharyngeal Ng using an RNA-based nucleic acid amplification test (NAAT; Aptima Combo 2). Patients with pharyngeal Ng were invited for a test-of-cure (TOC) 7 days after treatment with a 500 mg ceftriaxone intramuscularly. We retrospectively examined medical records of patients with pharyngeal Ng (January 2012–August 2015) who returned for a TOC 7–28 days after treatment. Persistence was defined as a positive NAAT at TOC.

Results Out of 2204 pharyngeal Ng cases recorded in the study period, 781 cases (median time between first treatment and TOC of 8 (IQR 7–12) days) were included in the analysis. Persistence after treatment was found in 36 (4.6%) and was less likely among patients who received ceftriaxone in combination with other antibiotics (vs monotherapy) (adjusted OR (aOR) 0.36, 95% CI 0.12 to 1.04) and with longer time from treatment to TOC (aOR 0.74, 95% CI 0.60 to 0.90, per extra day). In those with a TOC 15–28 days after treatment, Ng persisted in only 1.0% (1/105 cases).

Conclusion A small proportion of pharyngeal Ng persists despite appropriate treatment. Combining ceftriaxone with other antibiotics appears to lead to faster clearance. A TOC for pharyngeal Ng 7 days after treatment may be too soon.

pharyngeal Ng.² However, persisting pharyngeal Ng despite appropriate antibiotic treatment has been reported,^{4 5 7 8} and such persistence was associated with antimicrobial resistance against ESCs.⁴

We aimed to assess determinants of persistence after treatment of pharyngeal Ng, which could be useful for appropriate management of pharyngeal Ng in clinical practice.

METHODS

Routine pharyngeal Ng management at the study setting

At the STI clinic, Public Health Service, Amsterdam, the Netherlands, females-at-risk (ie, those who reported receptive oral sex in the preceding 6 months, had been notified of an STI or received money for sex) and all MSM are routinely screened for pharyngeal Ng using an RNA-based nucleic acid amplification test (NAAT), the Aptima Combo 2 Assay (Gen-Probe Diagnostics, San Diego, California, USA). We defined the day when the patients were screened for pharyngeal Ng as ‘the first consultation’.

Patients are requested to return for treatment on a positive NAAT result. However, an immediate treatment might be administered at the first consultation if patient reported genital, anorectal or pharyngeal discharge or pain and had a Gram stained smear of an anogenital sample containing intracellular Gram negative diplococci on light microscopical examination or had been notified for gonorrhoea. The standard treatment for pharyngeal Ng is a single dose of ceftriaxone 500 mg intramuscular. An alternative regimen might be prescribed due to a history of allergy or in case of coinfections requiring additional antibiotics. Depending on the clinical response, some patients might receive several treatment courses for one episode of infection.

Prior to treatment, pharyngeal swabs are also collected for culture and antibiotic susceptibility test (AST) against ceftriaxone, cefixime, cefotaxime, azithromycin, doxycycline and ciprofloxacin, using the Etest method (BioMerieux, Marcy l’Etoile, France), as described (<http://www.biomerieux-usa.com/clinical/etest>).

All patients with pharyngeal Ng were invited for a test-of-cure (TOC) 7 days after treatment.

INTRODUCTION

Pharyngeal infection by *Neisseria gonorrhoeae* (pharyngeal Ng) accounts for up to 16.5% of all gonorrhoea cases, especially in men who have sex with men (MSM).^{1–5} Through various types of sexual contact involving oropharyngeal mucosa and saliva, pharyngeal Ng may generally sustain gonococcal transmission in the society.^{1 2 6}

Extended spectrum cephalosporins (ESCs), for example, ceftriaxone or cefixime, are currently the standard treatment for gonorrhoea, including



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Definitions and inclusion/exclusion criteria

We retrospectively examined a cohort of patients diagnosed with pharyngeal Ng at the STI clinic Amsterdam between 1 January 2012 and 31 August 2015, using electronic medical records data. Demographics and behaviour data were collected using a self-administered questionnaire.

Inclusion criteria for the study were: (1) receiving ceftriaxone as the first treatment (as monotherapy or in combination with antibiotics that are potentially effective to treat pharyngeal Ng, ie, azithromycin, doxycycline, amoxicillin, ciprofloxacin, ofloxacin or benzylpenicillin) and (2) returning for TOC 7–28 days after treatment.

Exclusion criteria were: (1) receiving additional antibiotics between the first treatment and TOC and (2) spontaneous clearance, that is, a negative NAAT result prior to treatment (if cases were not treated immediately).

Persistence was defined as a positive NAAT result at the first TOC visit 7–28 days after treatment (TOC₁). If cases persisted at TOC₁, we followed until 28 days after treatment and reported additional treatments and NAAT results (referred to as TOC₂).

We also examined culture and AST results against ceftriaxone of isolates collected prior to treatment.

Statistical analysis

Statistical analysis was performed in STATA V.13 (StataCorp, College Station, Texas, USA). We compared characteristics of included and excluded patients using χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables. $p < 0.05$ was considered significant.

Bivariable and multivariable analyses for determinants of persistence after treatment were performed using logistic regression; the ORs, their 95% CI and p values were provided. For the multivariable model, in addition to age group as an a priori variable, a more strict approach was applied by only including variables which in bivariable analysis showed $p \leq 0.10$. Using a backward selection approach, the likelihood ratio test assessed the contribution of each variable to the model. We obtained a final model consisting of the a priori variable and all variables with $p < 0.05$.

We reported antibiogram results of cases with a successful pharyngeal Ng culture prior to treatment. Differences in the distribution of minimum inhibitory concentration (MIC) against ceftriaxone between cases that cleared infection and those that persisted were examined using the Wilcoxon rank-sum test.

RESULTS

Between January 2012 and August 2015, pharyngeal Ng was diagnosed in a total of 2204 consultations at the STI clinic Amsterdam: 1984 among MSM and 220 among females-at-risk. We excluded 1423 patients from the analysis because of incomplete treatment information ($n=87$), spontaneous clearance ($n=139$), not receiving ceftriaxone as first treatment ($n=205$) or not returning for TOC 7–28 days after treatment ($n=992$). The remaining 781 patients were included in the analysis.

Compared with excluded patients, included patients were older (median age, IQR] of 32 (25–41) vs 31 (25–39) years), less frequently reported genital, anorectal or pharyngeal symptoms (28.8% vs 41.1%), were less frequently diagnosed with chlamydia or syphilis (18.4% vs 22.5%), were less likely to have HIV (22.5% vs 26.4%), and reported a longer median time from first consultation to treatment (8 (3–11) vs 7 (0–11) days).

However, the two groups did not differ in terms of gender (90.4% male vs 89.8%), median number of sex partners in the preceding 6 months (7 (4–15) vs 8 (4–15)), history of receptive oral sex (100% vs 99.9%), history of sex work (6.0% vs 6.5%), being notified for gonorrhoea (24.0% vs 23.6%) and having *N. gonorrhoeae* coinfections at other anatomical locations (41.6% vs 46.2%).

Median time from treatment to TOC₁ was 8 (7–12) days. Persistence after treatment was observed in 36/781 cases (4.6%). In bivariable analysis, variables that were associated with persistence at $p \leq 0.10$ were history of sex work (OR 2.71, 95% CI 1.00 to 7.35), combination of ceftriaxone and other antibiotics as treatment regimen (vs ceftriaxone as monotherapy, OR 0.29, 95% CI 0.10 to 0.84) and time from treatment to TOC₁ (OR 0.72, 95% CI 0.59 to 0.89, per extra day) (table 1).

In the multivariable model, persistence was less likely in those who were treated with combination of ceftriaxone and other antibiotics (aOR 0.36, 95% CI 0.12 to 1.04) and in those with a longer time from treatment to TOC₁ (aOR 0.74, 95% CI 0.60 to 0.90, per extra day) (table 1).

Among 36 patients with persistence at TOC₁, 15 returned for TOC₂ (among which four received additional ceftriaxone between TOC₁ and TOC₂), whereas 21 were lost to follow-up. At TOC₂, infection was cleared in 14 and had persisted in one case.

Antibiograms of isolates prior to first treatment were available for 149/781 patients. The median and range of MIC against ceftriaxone did not differ between 128 cases that had cleared the infection at TOC₁ (0.004 (0.002–0.125) mg/L) and the 21 cases that persisted (0.004 (0.002–0.047) mg/L). The case that persisted at TOC₂ was susceptible to ceftriaxone (MIC of 0.023 mg/L).

DISCUSSION

We reported pharyngeal gonorrhoea cases that persisted despite appropriate treatment. The proportion of persisted cases was smaller compared with previous studies.^{1 4 5 7 8} Ceftriaxone monotherapy seems to remain effective to treat pharyngeal Ng, as suggested.^{2 7 8} Yet, combining ceftriaxone with another antibiotic appears to lead to faster clearance.

Adequate timing that allows complete clearance with minimum chance for re-exposure is crucial in pharyngeal Ng TOC. The rate of clearance may be influenced by infection site, diagnostic standard and treatment regimen.^{1 4–10} We found that the time to clearance of pharyngeal Ng RNA after appropriate treatment is relatively short.^{4 5 7 8} A time-dependent effect of ceftriaxone might be explained by its pharmacodynamic properties.⁹ The recommended timing for pharyngeal Ng TOC using NAAT varies from 7 to 30 days after treatment,^{4–8} but our study showed that TOC 7 days after treatment may be too soon.

Antimicrobial resistance is an unlikely explanation for persistent pharyngeal Ng in our study: isolates of cleared and persisting cases showed a similar distribution of MIC against ceftriaxone, and none was resistant.

Our study has several limitations. Most culture for pharyngeal samples was not successful and could not be used for confirmation. The use of NAAT to detect actual active infection may not be ideal either. A highly sensitive NAAT could detect genetic materials of non-viable organisms promptly following an exposure or during infection resolution.^{1 6 10} Because samples were only tested at patients' visit, the infection duration could not be precisely estimated. Information on re-exposure between the first and subsequent consultations was unavailable; therefore,

Table 1 Characteristics associated with persistence after treatment of pharyngeal gonococcal infections at the STI clinic, Amsterdam (January 2012–August 2015) based on bivariable and multivariable analysis

Variables	Cases with persistence after treatment			Bivariate analysis		Multivariable analysis*			
	N	N	%†	OR	95%CI	p***	aOR	95%CI	pt††
Total	781	36	4.6	–	–	–	–	–	–
Gender						0.40			
Male	706	31	4.4	1	–				
Female	75	5	6.7	1.56	0.59 to 4.13				
Age group						0.94			0.93
16–24 years	174	8	4.6	1	–		1	–	
25–34 years	290	15	5.2	1.13	0.47 to 2.73		1.01	0.41 to 2.50	
35–44 years	188	8	4.3	0.92	0.34 to 2.51		0.80	0.29 to 2.20	
≥45 years	129	5	3.9	0.84	0.27 to 2.62		0.78	0.25 to 2.49	
Number of sex partner(s) in the preceding 6 months						0.60			
1–5	309	17	5.5	1	–				
6–10	241	9	3.7	0.67	0.29 to 1.52				
≥11	231	10	4.3	0.77	0.35 to 1.73				
History of sex work in the preceding 6 months‡§						0.08			
No	721	31	4.3	1	–				
Yes	46	5	10.9	2.71	1.00 to 7.35				
Being notified about possibility of contracting gonorrhoea¶						0.76			
No	590	28	4.8	1	–				
Yes	190	8	4.2	0.88	0.40 to 1.97				
Reported any STI-related complaint(s) at the first consultation*						0.89			
No	556	26	4.7	1	–				
Yes	225	10	4.4	0.95	0.45 to 2.00				
Diagnosed with any other STIs at the first consultation††						0.14			
No	407	23	5.7	1	–				
Yes	374	13	3.5	0.60	0.30 to 1.20				
Diagnosed with urogenital or anal gonorrhoea coinfection(s) at the first consultation						0.30			
No	456	24	5.3	1	–				
Yes	325	12	3.7	0.69	0.34 to 1.40				
HIV status‡‡						0.72			
Negative	604	28	4.6	1	–				
Positive	175	7	4.0	0.86	0.37 to 2.00				
Time from the first consultation to the first treatment which included ceftriaxone, per extra day	–	–	–	0.99	0.94 to 1.05	0.81			
Antibiotics given for the first treatment						0.008			0.04
Ceftriaxone only	554	32	5.8	1	–		1	–	
Combination of ceftriaxone with other antibiotics§§	227	4	1.8	0.29	0.10 to 0.84		0.36	0.12 to 1.04	
Time from the first treatment which included ceftriaxone to test-of-cure (TOC), per extra day	–	–	–	0.72	0.59 to 0.89	<0.001	0.74	0.60 to 0.90	<0.001
Time from the first treatment which included ceftriaxone to TOC, categorised¶¶	–	–	–	–	–	<0.001	–	–	<0.001

Continued

Table 1 Continued

Variables	Cases with persistence after treatment			Bivariate analysis			Multivariable analysis*		
	N	N	%†	OR	95%CI	p***	aOR	95%CI	pt††
7 days	309	27	8.7	1	–	–	–	–	–
8–14 days	367	8	2.2	0.23	0.10 to 0.52	–	–	–	–
15–28 days	105	1	1.0	0.10	0.01 to 0.75	–	–	–	–

*For 781 records included in the multivariable analysis.

†Row percentage of positive cases among group.

‡For 767 records with available data (14 records had missing data).

§History of sex work in the preceding 6 months was associated with persistence after treatment in bivariable analysis, but not in multivariable analysis

¶For 780 records with available data (one record had missing data).

**Reported following complaints: discharge, pain, ulcers, or lumps in genital, anal or oral region.

††Diagnosed with chlamydia (urogenital, anal or pharyngeal infection), lymphogranuloma venereum or syphilis (acute or chronic).

‡‡For 779 records with available data (two records had missing data).

§§Antibiotics potentially effective to treat gonococcal infections, that is, azithromycin, doxycycline, amoxicillin, ciprofloxacin, ofloxacin or benzylpenicillin.

¶¶Time from the first treatment to TOC in categories was not included in the multivariable analysis.

***p Values obtained by χ^2 test from the logistic regression.

†††p Values calculated by likelihood-ratio test.

aOR, adjusted OR calculated in multivariable analysis using logistic regression.

the possibility that cases of observed persistence may have been reinfections after successful treatment could not be ruled out. Finally, the small number of cases with persistence after treatment limited the power of analysis.

Our study also has several strengths. We analysed a large number of cases that were systematically recorded during a long period. The data were collected from a routine public health STI service in a large city setting.

CONCLUSIONS

A small proportion of pharyngeal Ng persists despite appropriate treatment. Combining ceftriaxone with other antibiotics appears to lead to faster clearance. TOC for pharyngeal Ng 7 days after treatment may be too soon. Prospective studies are needed to produce definite evidence for the most appropriate treatment regimen for pharyngeal Ng and the most appropriate timing for TOC.

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Competing interests HJCDV and MFSVL served on a vaccine advisory board of GSK. Other authors have no conflict of interest to declare.

Patient consent Obtained.

Ethics approval As this was a retrospective cohort study using only routinely obtained data, no ethical clearance or informed consent was required.

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