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The efficacy of Azithromycin and Doxycycline Treatment for Rectal Chlamydial Infection: A Retrospective Cohort Study in South Australia

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Abstract

OBJECTIVE. To investigate treatment efficacy of two treatments for rectal chlamydial infection.

METHODS. We performed a retrospective analysis of all patients diagnosed with rectal chlamydial infection between 2009 and 2015 in Adelaide, Australia. Patients were treated with either azithromycin (1 g single dose) or doxycycline (100 mg twice a day for 10 days) and returned for repeat testing 14 to 180 days after treatment commenced. Log binomial models were used to estimate the relative risk (RR) of recurrent rectal chlamydia associated with the treatment with azithromycin versus doxycycline.

RESULTS. In men, rectal chlamydia prevalence was 6.7% and in women this was 8.1%. Of the 526 patients diagnosed with rectal chlamydial infections, 419 (79.7%), 93 (17.7%) and 14 (2.6%) patients were treated with doxycycline, azithromycin or other medication respectively. Of these patients, 173 (41.3%) of 419 doxycycline-treated patients and 31 (33.3%) of 93 azithromycin-treated patients were retested between 14 and 180 days after treatment commenced (*P*=0.16). Among these patients, the repeat rectal chlamydia test was less commonly positive in those treated with doxycycline (5.8%; 95% Confidence Interval (CI) 0.03-0.10) compared with those treated with azithromycin (19.4%; 95% CI 0.09-0.36) and (p=0.01). In the multivariate analysis, azithromycin-treated patients had a significant higher risk of a positive test in the 14 and 180 days after treatment commenced (adjusted relative risk (aRR) 2.96, 95% CI 1.16-7.57).

CONCLUSION. The findings suggest that doxycycline may be more effective than azithromycin in treating rectal chlamydial infection.

Keywords: Chlamydia trachomatis, rectal, azithromycin, doxycycline, treatment

Introduction

Rectal chlamydia diagnoses have increased considerably among MSM in recent years and it is now more common than urethral infection.[1, 2] There are also increasing reports of rectal chlamydia among women coinciding with studies showing that anal sex among heterosexuals is more common.[3] Prevalence of rectal chlamydia has been reported to be as high as 24.4% among MSM and 17.5% among women.[4] It is possible that further increases in rectal chlamydial infection will occur due to the widespread uptake of biomedical prevention such as pre-exposure prophylaxis (PrEP) for HIV. [5] There are ongoing concerns about rectal chlamydia treatment failure with a systematic review and meta-analysis finding that the efficacy of single-dose azithromycin treatment may be considerably lower than 1 week of doxycycline for treating rectal chlamydial infection (82.9% versus 99.6%). [6-8]

As rectal chlamydial infection is associated with increased risk of HIV seroconversion,[9-11] screening patients who reported receptive anal intercourse and effective treatment for rectal chlamydial infection are critical for HIV prevention. Current STI treatment guidelines recommend azithromycin (1 g single dose) or doxycycline (100 mg twice a day for 7 days) for the treatment of rectal chlamydial infection.[12-15] To date there is only one double-blinded

randomised controlled trial planned comparing antibiotic therapy for rectal chlamydial infection.[16]

In this study, we aim to review the efficacy of 1 g of azithromycin as a single dose compared with 100 mg of doxycycline twice daily for 10 days following our clinic guidelines in the treatment of rectal chlamydial infection in men and women attending the sexual health clinic in Adelaide, Australia.

Methods

Study design and population

Using the data extracted from Adelaide STI clinic, a retrospective cohort of all men and women who were positive for rectal chlamydial infection diagnosed by nuclear acid amplification test (NAAT) at the STI clinic in Adelaide, Australia, between 2009 and 2015 was defined for analysis. Rectal specimens from women who reported receptive anal intercourse have been routinely collected since September 2012.

Data collection

All data were collected as part of routine sexual health services at Adelaide STI clinic. Demographic, clinical and epidemiological data were entered into a computerised database and retrieved for the purpose of this study. Since September 2012, the recommended treatment for rectal chlamydial infection at Adelaide STI clinic has been changed from azithromycin to doxycycline, which allowed us to assess the efficacy of Azithromycin and Doxycycline Treatment for Rectal Chlamydial Infection.

Throughout the study period, the clinic protocol was to obtain rectal specimens from all male patients who reported receptive anal intercourse. Prior to September 2012, we did not ask women other than sex workers about anal sex and therefore we did not offer rectal sampling, however rectal specimens from all women who reported receptive anal intercourse have been collected since then. At Adelaide STI Clinic, all rectal specimens were tested using nucleic acid amplification testing (NAAT) (APTIMA combo 2, GenProbe Diagnostics, San Diego, California) by SA Pathology.

We defined repeat testing of rectal chlamydial infection as having a positive result on the first repeat test for rectal chlamydial infection obtained in the 14 and 180 days after the date of treatment commenced. We excluded tests occurring less than 14 days after treatment to decrease the risk of false positive results from NAAT testing. We limited the analysis to all

patients who were re-tested within 180 days of diagnosis to minimize the effect of spontaneous resolution of infection. We have excluded those patients if they were treated with medication other than a doxycycline or azithromycin.

Statistical analysis

We used two sample *t tests* to compare the mean time between treatment and testing and Fisher exact's test to analyse statistically significant differences in the proportion for categorical variables. Log binomial models were used to estimate the unadjusted and adjusted relative risk (RR) and 95% confidence interval (CI) of recurrent infection associated with treatment with azithromycin versus doxycycline. The multivariate model included demographic (e.g., age, race and gender), clinical indicators (e.g., HIV status, previous STI, anorectal symptoms) and behavioral (e.g., number of sex partners and IDU) factors. Log binomial models were undertaken to estimate the association between each characteristic and recurrent infection, and a backward, stepwise elimination ($P<0.10$) to identify factors associated with recurrent infection were implemented.

All analyses were performed using Stata statistical software, version 14.1 (StataCorp, College Station, TX).

Ethics

The study was approved by South Australia Department of Health Human Research Ethics Committee (approval number HREC/12/SAH/87).

Results

Rectal chlamydia prevalence was 6.7% and 8.1% respectively in men and women who presented to the clinic with a rectal swab over the study period. A total of 526 patients were diagnosed with rectal chlamydial infection between 2009 and 2015, seventy-three percent (n=384) were men, 379 (99%) were MSM and 27% (n=142) were women. The patient age range was 16-79 years old (median age 28 years) and 4% (22/526) of patients had HIV-infection. The majority of the rectal chlamydial infection was asymptomatic (330/526, 63%). Of these 526 patients, 419 (79.7%), 93 (17.7%) and 14 (2.6%) patients were treated with doxycycline, azithromycin or other medication respectively.

Except for year of diagnosis, there were no statistically significant differences in demographic or behavioural characteristics between patients who returned for a repeat test and patients who did not return for a repeat test and there were no statistically significant differences in

demographic or behavioural characteristics for those patients who were treated with azithromycin and doxycycline (Table 1).

Of the 204 patients who returned for a repeat test within 180 days after treatment commenced, the majority of them (173, 84.8%) were treated with doxycycline and only 31 (15.2%) were treated with azithromycin. There was no significant difference in the interval between treatment and repeat test between azithromycin (mean=97 days) and doxycycline (mean=84 days) groups (*P*=0.07) (Table 2).

Repeat rectal chlamydial infection was more commonly positive in females (12.8%) compared to males (6.4%) but this was not statistically significant (*P*=0.155). Treatment with azithromycin was significantly associated with 3-fold higher risk (RR 3.35; 95% CI 1.31-8.55) of repeat rectal chlamydial infection 14-180 days after treatment commenced. The significant association of treatment regimen with repeat rectal chlamydial infection remained after adjusting for other factors (Table 2).

Discussion

In this clinic sample of patients diagnosed with rectal chlamydial infections between 2009 and 2015, we found that patients treated with azithromycin had a significantly higher risk of repeat NAAT positivity in the rectal specimens compared with patients treated with doxycycline. The data suggest that a 10-day course of doxycycline may be more effective than a single dose of 1-g of azithromycin in the treatment of rectal chlamydial infection. However, the proportion of repeat positivity in rectal chlamydial infection treated with doxycycline was much higher (5.8%) than that in the meta-analysis (0.4%),[6] which is possibly due to the nature of our study where we were generally unable to exclude repeat infections.

There are a number of limitations that must be considered when interpreting our data. Firstly, our data are from a retrospective observational study and as such are dependent of the quality of recorded data. Also because the study was observational and not randomized there could be confounding factors which may have influenced the results. We did adjust for potential confounding factors in the multivariate analysis, and this adjustment for confounders did not change the significant association of azithromycin with repeat positivity in rectal chlamydial infection. However there may be unmeasured confounding factors operating (e.g., number of receptive anal sex partners, sex with anonymous partners). Secondly, only female sex workers were tested at the rectal site before 2012, but as only one female sex worker among the 204 participants this could not materially influenced the results. Thirdly, because there were

relatively few cases treated with azithromycin in our study, this limited the statistical power to look at subgroups in the study. Fourthly, we had re-testing data on only a third of participants. Although we have shown that there was no difference in variables between patients who returned for a repeat test and patients who did not return for a repeat test, it may be that there was a difference in failure rates between those who did and did not return. If there was a systematic bias between treatment arms in those who returned for testing compared to those who did not, then this could have influenced our results. Fifthly, for some patients there was a considerable duration of follow up time of up to 180 days. Longer follow-up means that repeat infection becomes more likely although we did have equal follow up in both treatment groups. Sixthly we did not have sexual behavior data on the individuals between their initial and follow up test and so we cannot determine whether there was a systematic bias between the two groups. Finally, we cannot differentiate between persistent infection and reinfection in the absence of genotyping, thus, it is possible that at least some of the infections are the result of reinfection. We could also not assess if any patients had lymphogranuloma venereum (LGV) as our clinic does not routinely test for LGV. Undiagnosed cases of LGV may have been included, which may contribute to a lower azithromycin efficacy.

Regardless of these limitations, our findings are consistent with published observational data that suggests that doxycycline may be up to 20% more effective than azithromycin for rectal

chlamydia. [17] It is also biologically plausible that azithromycin may not be as effective for rectal chlamydia as urogenital infections for several reasons including the possibility that the immune response to infection is different in the rectal mucosa which may impact on azithromycin being delivered to the site of infection; this doesn't apply to doxycycline.[18] However, doxycycline has its own disadvantage as adherence to a 7-day or 10-day course of doxycycline may lead to an increased risk of treatment failure. [19]

In conclusion, our paper suggests that azithromycin was associated with repeat rectal chlamydial infection, comparing to doxycycline. These findings add to the growing body of evidence suggesting that doxycycline may be more effective than azithromycin for the treatment of rectal chlamydia in men and women. A randomised control trial is needed to evaluate the treatment regimens for rectal chlamydial infection.

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Table 1: Characteristics of patients diagnosed with rectal chlamydia by completion of repeat test and treatment received (n=438)

Characteristics*	Patients without a repeat test (n=234)		Patients with a repeat test 14-180 days after treatment					
			Total (n=204)		Azithromycin (n=31)		Doxycycline (n=173)	
	n	%	n	%	n	%	n	%
Age								
mean		31.5		31.5		32.2		31.4
IQR		23.0-37.6		22.6-37.9		21.5-43.0		22.9-36.2
Race								
Indigenous	2	0.9	2	1.0	1	3.3	1	0.6
Asian	19	8.2	30	14.7	3	9.7	27	15.6
Caucasian	203	87.1	163	79.9	26	83.9	137	79.2
African/other	9	3.9	9	4.4	1	3.2	8	4.6
HIV status								
Negative	220	94.0	196	96.1	29	93.6	167	96.5
Positive	14	6.0	8	3.9	2	6.5	6	3.5
No. sex partners in past 3 mths								
0-1	58	24.8	45	22.1	6	19.4	39	22.5
2-4	116	49.6	85	41.7	12	38.7	73	42.2
≥5	60	25.6	74	36.3	13	41.9	61	35.3
Previous STI	53	22.7	46	22.6	7	22.6	39	22.5
Year of diagnosis†								
2009	0	0	1	0.5	1	3.2	0	0
2010	0	0	0	0	0	0	0	0
2011	1	0.4	2	1.0	1	3.2	1	0.6
2012	24	10.3	38	18.6	22	71.0	16	9.3
2013	41	17.5	56	27.5	2	6.5	54	31.2
2014	68	29.1	63	30.9	4	12.9	59	34.1
2015	100	42.7	44	21.6	1	3.2	43	24.9
Concurrent urethral/cervical chlamydia	85	38.0	57	29.5	7	24.1	50	30.5
Concurrent gonorrhea	41	17.5	25	12.3	5	16.1	20	11.6
Any symptom	97	41.5	64	31.4	11	33.5	53	30.6
Interval between treatment and repeat test, day								
14-30			4	2.0	1	3.2	3	1.7

31-60	63	30.9	5	16.1	58	33.5
61-90	54	26.5	8	25.8	46	26.6
91-180	83	40.7	17	54.8	66	38.2

*due to missing values, not all variables sum to column total

† *P*<0.05, statistically significant difference in characteristic between patients who returned for a repeat test and who did not return for a repeat test

Table 2: Demographic, Clinical and Behavioural factors at the time of initial diagnosis associated with repeat positivity in rectal chlamydial infection among patients re-tested 14 to 180 days after treatment commenced (N=204)

Factors	Repeat positive Rectal chlamydia (n*)	Total Number (N**)	Repeat positive Rectal chlamydia (%)	Unadjusted		Adjusted	
				RR	95% CI	RR	95% CI
Treatment							
Azithromycin	6	31	19.4	3.35	1.31-8.55	2.96	1.16-7.57
Doxycycline	10	173	5.8	Reference		Reference	
Gender							
Male	10	157	6.4	Reference			
Female	6	47	12.8	2.00	0.77-5.23		
Age							
<20	2	20	10.0	Reference			
20-24	6	55	10.9	1.09	0.24-4.97		
25-29	4	40	10.0	1.0	0.20-5.00		
30-49	2	71	2.8	0.28	0.42-1.88		
≥50	2	18	11.1	1.11	0.17-7.09		
Race							
others	2	41	4.9	Reference			
Caucasian	14	163	8.6	1.76	0.42-7.44		
HIV status							
Negative	16	199	8.0	-			
Positive	0	5	0.0	-			
No. partners in past 3 mths							
0-1	6	78	7.7	Reference			
2-4	6	76	7.9	1.03	0.35-3.04		
≥5	4	50	8.0	1.04	0.31-3.50		
IDU†							

Yes	1	14	7.1	0.93	0.13-6.56		
No	14	182	7.7	Reference			
Previous STI‡							
Yes	4	46	8.7	1.13	0.38-3.34		
No	12	156	7.7	Reference			
Symptoms^							
Yes	8	58	13.8	2.52	0.99-6.39	2.20	0.87-5.58
No	8	146	5.5	Reference		Reference	

*n=number of positive tests **N=Total number of repeat test †IDU =injecting drug use (ever)

‡Previous STI (GC, Syphilis, Chlamydia, Herpes, Warts and HBV) ^Symptoms refer to any symptom for clinic visit