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CLEARANCE OF *MYCOPLASMA GENITALIUM* AND *TRICHOMONAS VAGINALIS* AMONG ADOLESCENTS AND YOUNG ADULTS WITH PELVIC INFLAMMATORY DISEASE: RESULTS FROM THE TECH-N STUDY

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Abstract

Current PID treatment effectively treats *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT). However, coverage may be inadequate for *Mycoplasma genitalium* (MG)/*Trichomonas vaginalis* (TV) infections. We compared the longitudinal MG and TV outcomes with NG/CT outcomes for women enrolled in a longitudinal randomized controlled trial to optimize outcomes after PID. The prevalence of CT and NG were lower at 30 days and 90 days follow-up compared to the prevalence at time of diagnosis. No significant difference was observed for MG (OR 0.95, 0.86–1.04, p=0.265) and TV (OR 0.89, 0.75–1.04, p=0.146) over time for both treatment groups, showing that persistence and or reinfection with MG and TV occur more frequently than with CT or NG following treatment for PID using current national treatment guidelines.

BRIEF SUMMARY

In our study of 286 women with a diagnosis of PID, there was no statistically significant change in *Mycoplasma genitalium* and *Trichomonas vaginalis* prevalence at 30- and 90-day follow-up.

ClinicalTrials.gov Identifier: NCT01640379

Keywords

Pelvic Inflammatory disease (PID); Adolescents; Young Adults; *Mycoplasma genitalium*; *Trichomonas vaginalis*

Introduction

Pelvic inflammatory disease (PID) is a spectrum of upper genital tract infections that include endometritis, salpingitis, pelvic peritonitis and tubo-ovarian abscess.¹ *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are commonly associated with PID. However, PID is a polymicrobial infection^{2,3} and over 70% of PID is caused by organisms other than CT and NG.⁴ In our recent randomized clinical trial of 286 women aged 13–25 years diagnosed with mild to moderate PID, we compared the efficacy of a technology enhanced health nursing (TECH-N) intervention with the standard of care on the 90-day longitudinal prevalence of CT and NG infections. Findings from the study showed a statistically significant decline in CT and NG infections following the 90-day follow-up period (OR 0.54, 95% CI: 0.43,0.67, $p<0.001$)⁵ and corroborates the previously demonstrated effectiveness of current PID treatment guidelines against CT and NG.⁶

Mycoplasma genitalium (MG) is an emerging organism now implicated in many cases of non-gonococcal, non-chlamydial PID.⁷ *Trichomonas vaginalis* (TV) is not discussed in the context of PID in the CDC's STD treatment guidelines, but this infection is disproportionately common in many communities impacted by STIs and PID. MG/TV persistence and or reinfection may increase the risk for recurrent STIs and HIV acquisition.^{8,9}

The efficacy of treatment using the current PID treatment guidelines against MG and TV remains unclear.¹⁰ Doxycycline, a key component of the national treatment regimen for PID, has limited effectiveness against MG¹¹, leading to persistence of MG after CT/NG clearance. Likewise, the optional recommendation for use of metronidazole for PID as stipulated in the guidelines often results in non-adherence and predisposes to continued infection.¹⁰ Given the increased risk for sequelae after recurrent STIs and PID, efforts to optimize vaginal health after PID may be protective. The objective of this study was to evaluate longitudinal MG and TV outcomes compared with CT/NG outcomes over the 90-day follow-up treatment for PID using data from the TECH-N Study.⁵

Methods

The TECH-N study is a 2-arm single-blinded randomized clinical trial (RCT) that includes 286 adolescent and young adult (AYA) women aged 13–25 years with clinically diagnosed mild-moderate PID.¹² Participants were recruited at the time of PID diagnosis from the outpatient clinics and Pediatric and Adult Emergency Departments of an urban hospital in Baltimore, Maryland, USA. Patients were eligible for the study if they were between the ages of 13–25 years, female and had received a diagnosis of mild-moderate PID not requiring inpatient treatment. Exclusion criteria were pregnancy, hindrances to communication due to language, mental, or cognitive difficulties, or a concurrent diagnosis of sexual assault. All eligible patients completed an audio computerized self-interview (ACASI) and provided self-collected vaginal specimens for TV and MG testing. Patients enrolled in the TECH-N intervention group received a full course (14 days) of medications at the recruitment visit per national treatment guidelines, a welcome SMS message, daily medication reminders and a tri-weekly message following the 14-day treatment period up

until 30 days, and home visits by a TECH-N representative at 3–5, 14, and 30 days post PID diagnosis. The control group only received the 14-day course of treatment. Vaginal specimens were collected at the 30-day and 90-day follow-up visits and tested for NG, CT, TV, and MG infections. All participants with positive STI tests were notified of test results and referred for treatment at no cost to the participant. When the TECH-N protocol was initiated, MG was not considered an STI in national guidelines and TV remains an STI for which symptomatic testing and treatment is the only public health control strategy except in HIV positive women where screening is recommended. Human subjects' approval was received from the research center's institutional review board and written informed consent was obtained from all participants at enrollment.

Generalized estimating equations were used to measure the primary outcome of interest; changes in the prevalence of MG and TV compared with CT/NG infection at 0, 30-day and 90-day follow ups in accordance with the timeline for disease clearance and re-infection. Prevalence of MG and CT/NG were modelled jointly conditional on the time of follow-up and allowing for coinfections by specifying individual as the cluster for analysis. Similar models were constructed for the prevalence of TV. Statistical analysis was performed using Stata version 15.0 (StataCorp. 2017. College Station, TX: StataCorp LLC).

Results

Of the 286 enrolled participants, 149 patients (52%) randomized to the intervention group and 137 patients (48%) to the control group were included in this analysis. Selected demographics and baseline STI outcomes for study participants by intervention group and demography is presented in Table 1. The two intervention and control groups were similar in distribution for most baseline characteristics.

Most patients in the study, 268 (94%) were African American with mean age of 18.8 years (SD 2.5), and most (247, 86%) were publicly insured. For most women in the study, sexual debut occurred around the age of 15 years (median 15, IQR 14 – 19) and 186 (57%) had been diagnosed with an STI in the past.

There were 269 (94%) women at the end of the 30-day follow-up period. Of these, 45 (17%) were positive for MG, 25 (9%) for TV, 25 (9%) had either CT or NG, and 17 (6%) and 9 (3%) had CT and NG infections respectively. At the end of the 90-day study period, vaginal specimens were collected from 260 women. A greater number of women were positive for MG, 49 (19%) and TV, 34 (13%). The prevalence of CT and NG were lower at 9 (3%) and 11 (4%), respectively. Infection with either of CT or NG was also low, present in only 19 (7%) of women.

Unlike the previously reported declines in NG/CT infection, no significant difference was observed for MG (OR 0.95, 0.86–1.04, p=0.265). This odds ratio is interpretable as the change in likelihood of infection with MG with an increase in one month of follow-up time. Likewise, TV infections were stable over time (OR 0.89, 0.75–1.04, p=0.146) for both treatment groups even after adjusting for 108 patients prescribed metronidazole (OR 0.89, 0.75–1.04, p=0.148). However, the prevalence of any combination of STIs due to CT, NG or

TV showed statistically significant decline over time (OR 0.69, 0.61–0.80, $P<0.001$). CT, NG or MG prevalence also declined over the study period (OR 0.71, 0.64–0.80, $p<0.001$). These declines may have been driven by both CT and NG.

Overall, the prevalence of infection was lower in the intervention group (% infected) than in the control group (% infected) at the end of the 90-day follow-up. Consistent with these findings, Figure 1 shows the changes in CT/NG, MG, and TV infections over the entire study duration. While CT or NG infections progressively declined in both the intervention and control groups,⁵ infection with MG and TV remained relatively unchanged. The figure also shows the improvement in prevalence of all STIs over time, and this change is not as precipitous as observed with CT or NG infections.

Discussion

This study investigated the clearance of MG and TV infections in women diagnosed with CT and NG STIs over a 90-day follow up period. The results show a clearance of CT and NG but persistence and/or reinfection with MG and TV despite treatment with the standard recommended STI treatment regimen.

While MG and TV are not the focus of recommended PID treatment within the CDC STD treatment guidelines, our work suggests that in communities with high STI prevalence, patients may not have clearance of all STIs at the end of a 14-day treatment course for PID. The persistently high MG infection rates seen at different intervals in our study is consistent with findings of similar studies where more than 50% of MG infected women treated with macrolides were resistant to treatment,¹³ and 16% of treated patients had persistent infection with MG.¹⁴ The proportion of PID attributed to MG in the study (16%) was equally comparable to the 17–19% observed here. Similar findings of multiple studies also corroborate the significant role played by MG in the etiology of PID.¹⁵

Persistent infection with TV despite treatment for PID can easily be ascribed to the non-prescription of an antibiotic to which TV is susceptible. There is a paucity of studies comparing TV infections among persons treated with and without metronidazole. It is arguable that TV persistence may have resulted from a failure to prescribe metronidazole, as this is optional,¹⁰ and other “non-optional” medications in the treatment guideline are ineffective against TV infections. However, the point prevalence of TV remained unchanged after adjusting for metronidazole prescription. Adherence to metronidazole was not ascertained in this study and it is likely that adherence was suboptimal given the long course of treatment (14 days). Metronidazole and other nitroimidazole class antibiotics remain the best treatment option for TV.¹⁶

Our results must be considered in light of several general limitations. This study has limited generalizability as participants were recruited from a single hospital system and city within the United States and findings may not be representative for patient populations outside of these institutions and geographic regions. Although all patients were informed of their interim STI results and offered treatment, only 50% of patients consistently pursued treatment for MG/TV, contributing to persistent infections.¹⁷ This, however, further

highlights the need for close follow-up of patients with PID until point of care testing for these organisms are optimized and universally implemented.

In summary, data from this study indicate that persistence or possibly reinfection with MG and TV occurred more frequently than with CT or NG when using the current national treatment guidelines for PID. While a decline in CT and NG infections was noted, overall clearance of infectious organisms for this polymicrobial disease was less when MG and TV were considered. These findings suggest a need for the revision of the current CDC treatment guidelines to incorporate MG and TV testing and treatment to prevent reinfection and persistence and to avert complications after PID.

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Figure 1:
Prevalence of *C. trachomatis* or *N. gonorrhoea*, *M. genitalium*, *T. vaginalis* and all four infections at 0, 30, and 90-day follow-up.

Table 1.

Selected Demographics and STI Results

Baseline characteristics	Total Population N=286	Intervention Group N=149		Control Group N=137		P-value
Age, years (SD)	286	149	18.7 (2.5)	137	18.9 (2.5)	0.639
Race/Ethnicity (%)	286	149		137		0.640
African American			140 (94%)		128 (93%)	
Hispanic			2 (1%)		4 (3%)	
White			4 (3%)		3 (2%)	
Other			3 (2%)		2 (1%)	
Insurance (%)	286	149		137		0.382
Medicaid			131 (88%)		116 (85%)	
Private			11 (7%)		9 (7%)	
Self-pay			7 (5%)		12 (9%)	
Ever diagnosed with STI (%)	282	148	80 (54%)	134	82 (61%)	0.227
STI at Baseline (%)						
<i>Chlamydia trachomatis</i> (CT)	271	139	45 (32%)	132	25 (19%)	0.017
<i>Neisseria gonorrhoeae</i> (NG)	271	139	11 (8%)	132	16 (32%)	0.341
<i>Chlamydia trachomatis</i> (CT) or <i>Neisseria gonorrhoeae</i> (NG)	273	140	48 (34%)	133	34 (26%)	0.116
<i>Mycoplasma genitalium</i> (MhaaaG)	276	142	34 (24%)	134	29 (22%)	0.650
<i>Trichomonas vaginalis</i> (TV)	276	142	25 (18%)	134	26 (19%)	0.702
CT, NG, MG, or TV	285	148	77 (52%)	137	72 (53%)	0.929