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Concordance of Rectal and Cervical Chlamydia trachomatis OmpA Genotypes Infecting Women in Birmingham, Alabama

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Chlamydia trachomatis strains can be differentiated by their major outer membrane protein (OmpA) composition, with at least 20 OmpA types and variants having been identified.^{1–4} Limited studies evaluating non-LGV *C. trachomatis* OmpA types causing rectal chlamydial infection have reported OmpA distributions that somewhat differ from those causing genital infection;^{5–8} in particular, OmpA type G is one of the most prevalent OmpA types in rectal chlamydial infections in men who have sex with men (MSM) but is uncommon in genital chlamydial infections in men. One possible explanation is that specific OmpA types may have greater tropism for the rectal versus genital mucosal environment. For patients with *C. trachomatis* detected at both genital and rectal sites, one may presume these are identical isolates, however if there are differences in tropism of a specific OmpA type for the genital versus rectal mucosa, then perhaps different OmpA types could be isolated from the genital versus rectal mucosa in the same patient.

In a previous surveillance project of *C. trachomatis* OmpA genotypes causing rectal chlamydial infection in subjects attending an STD clinic in Birmingham, AL, genital specimens were also collected from these subjects, tested for *C. trachomatis* by culture, and then stored at -70° C. We previously published our findings of the *C. trachomatis* OmpA genotypes causing rectal infections in these subjects.⁸ The primary objective of our current study was to assess for concordance of *C. trachomatis* OmpA genotypes in strains isolated from the genital tract versus rectum from subjects in this prior surveillance project. Further, we wanted to evaluate for any differences in patient characteristics in those with concordance versus discordance of OmpA types isolated from the genital tract versus rectum.

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We retrospectively reviewed demographical data, clinical data, and results of genital chlamydia testing in subjects diagnosed with rectal chlamydial infection in the prior surveillance project. Because genital chlamydial infection was very rare in men with rectal chlamydial infection, only females were evaluated in this current OmpA concordance study. In female subjects with *C. trachomatis* detected in their cervical specimens, OmpA genotyping of the cervical *C. trachomatis* strains was performed by methodology previously described.⁹ Briefly, genomic DNA was extracted and purified, and nested amplification was performed with primer pairs amplifying a DNA fragment containing the entire *ompA* gene from all *C. trachomatis* OmpA types. PCR products were purified and sequenced on ABI Automated Capillary DNA Sequencing System (Applied Biosystems, Foster City, CA). Sequences were assembled and edited with DNA Sequencer version 4.6 (Genecodes, Ann Arbor, MI) and compared to Chlamydia GenBank sequences for identification of the OmpA genotypes for the cervical and rectal isolates. To further assess for OmpA concordance of cervical and rectal isolates, the completed cervical and rectal sequence chromatograms were aligned in Sequencher. For two patients, mixed sequences were detected in the variable domains of the rectal isolate. The dominant OmpA type was determined based on the most prominent sequence peaks displayed in the chromatogram. Portions of the variable domain sequences of the second genotype present were deduced using the secondary peak display function in Sequencher. These were then aligned in Genbank to get the most probable *ompA* type; a similar method has been used for distinguishing HIV strain mutants.^{10,11} Sequences of mixed infections at one mucosal site (rectal or cervical) were aligned with sequence(s) at the other mucosal site to assess for OmpA concordance. Statistical analyses using the Fisher's exact test or the Wilcoxon rank-sum test were conducted on Stata (Stata Corp. Release 8.0, College Station, TX).

Of 31 females (median age 22, 94% African American) for whom rectal OmpA genotypes were previously determined, 25 (81%) had cervical specimens that tested CT-positive versus 6 (19%) that tested negative; subjects with cervical chlamydial infection were younger (median age 22 vs 24) and more often HIV-positive (9 of 25 [36%] vs. 1 of 6 [17%]), though these findings did not reach statistical significance ($P > 0.1$). Cervical *C. trachomatis* OmpA genotypes were determined from 22 of the 25 subjects with cervical chlamydial infection; there was no available residual cervical specimen for OmpA genotyping in one subject and OmpA genotyping was unsuccessful in two subjects (due to unsuccessful amplification of *ompA*). Of the 22 subjects with cervical isolates successfully OmpA genotyped, 20 (91%) were African American, the median age was 22 (range 16-37), and 9 (41%) were HIV-positive. One subject had cervicitis and one subject had pelvic inflammatory disease noted on examination. No subjects reported rectal symptoms.

Twenty of 22 (91%) subjects had a single *C. trachomatis* OmpA genotype infection at both the rectal and cervical sites. Sixteen of the 20 (80%) subjects with a single *C. trachomatis* OmpA infection at each site had concordant OmpA genotypes with the following numbers of each genotype: B (1), D (2), E (7), F (1), G (1), Ia (1), Ja (1), and K (2). Most had identical *ompA* sequences between cervical and rectal strains. The median age was 23 (range 17-37) and 7 (44%) were HIV-positive. Four of the 20 (20%) subjects with a single *C. trachomatis* OmpA infection at each site had discordant OmpA genotypes isolated from the cervical versus rectal specimens with the following OmpA type differences in the four subjects as follows: J vs. D, E vs. F, Ia vs. Ja, and Ia vs. E. The median age of these subjects was 19 (range 16-22) and one subject was HIV positive.

Two of 22 (9%) subjects had a mixed *C. trachomatis* OmpA genotype infection at the rectal site but only a single OmpA genotype at the cervical site; in both subjects, the cervical OmpA genotype was the same as one of the rectal OmpA genotypes. The cervical versus rectal OmpA genotypes from these two subjects were: Subject 1, D vs. D and F and Subject 2, E vs. E and Ja. Of note, the 6 female subjects who had a negative cervical chlamydia culture did not have

cervical specimens available for attempting to amplify *ompA*; the rectal *OmpA* types from these subjects were D (1), E (3), F (1), and Ja (1), which resembles the rectal distribution from subjects who had a positive chlamydia culture.

The finding of discordance of *OmpA* types at the genital versus rectal sites is novel. Possible explanations for the *OmpA* discordance include: 1) a mixed infection at one of the mucosal sites that might not have been detected (perhaps due to a small number of *ompA* copies), 2) differences in the tropism of a specific *OmpA* type for the rectal versus cervical mucosa, and 3) differential exposure of subjects to infection (in a patient with multiple chlamydia-infected partners, different sites were exposed or the sites were exposed at different times). Tropism of a specific *C. trachomatis* strain relates to the ability of the organism to establish infection or to persist within specific host tissue, and is likely influenced both by biological properties of the organism (such as *OmpA* composition) and immunogenetic characteristics of the host. The cell lining of the endocervix and rectum are both simple columnar epithelium, while the cell lining of the ectocervix and anus are stratified squamous epithelium. Tropism has been one of the possible explanations as to why *OmpA* type G is so highly prevalent in rectal but not genital infections in MSM. However, in a recent study of rectal *OmpA* types in MSM and women in Birmingham, AL, we found *OmpA* type G was not highly prevalent in rectal chlamydial infections in women (as it was in MSM in that study) and that the *OmpA* distribution of rectal isolates in women resembled that reported for genital *OmpA* distributions in other studies (with *OmpA* type E being highly prevalent).⁸ It may be possible that behavioral and epidemiological factors (sexual practices within a core group of subjects with high risk for STDs) have a greater influence on *OmpA* distributions than does tissue tropism.

Our study had limitations. The small sample size limited our power to detect associations of patient characteristics (such as age and HIV status) with *OmpA* concordance. Clinical data and anogenital specimens for *OmpA* typing were not available from the sexual partners, which would have been helpful in further understanding the discordance in *OmpA* types. For the mixed rectal *OmpA* genotype infections, while we could determine that one of the rectal isolates was the same *OmpA* genotype as the cervical isolate, we could not state with certainty that the *ompA* sequences of this rectal isolate and the cervical isolate were identical. Sequences were based on the amplification product and separate clones were not isolated for sequencing, only partial sequences of the variable domains were compared to deduce the mixed sequences. Finally, our study only evaluated differences in the *OmpA* type of the *C. trachomatis* strains, and it is possible that the chlamydial strains may have differed in composition of other surface proteins that could have potentially influenced tissue tropism.

In conclusion, we found that the majority of female subjects with rectal chlamydial infection had concomitant cervical chlamydial infection, and discordance in rectal versus cervical *C. trachomatis* *OmpA* types was not uncommon. Factors contributing to discordance of *OmpA* types at different mucosal sites remain to be elucidated.

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