Novel causes of urethritis in men

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Background: Nongonococcal urethritis (NGU) is the commonest male genital tract syndrome. Up to 50% of NGU cases are idiopathic, i.e. no aetiological agent is identified. This poses significant challenges for clinicians in the diagnosis and treatment of NGU, and often results in antibiotic misuse and overuse. To identify potential infectious causes of urethritis, inform clinical management, and promote antimicrobial stewardship, we characterised and compared the urethral microbiota of men with and without idiopathic urethritis.

Methods: Participants were derived from a case-control study conducted at the Melbourne Sexual Health Centre between 2004-2005 that examined viral and bacterial pathogens and sexual practices associated with NGU. Men with NGU who tested negative for established causes of NGU (*Chlamydia trachomatis*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, adenoviruses, HSV) were classified as idiopathic urethritis cases (n=96), and controls (n=103) were men reporting no current urethral symptoms. All men provided a first pass urine sample that was used to characterize the urethral microbiota using 16S-rRNA gene sequencing. Analysis of compositions of microbiomes with bias correction (ANCOM-BC) was used to identify bacterial taxa associated with idiopathic urethritis.

Results: When stratified by sex of sexual partner, the abundance of *Haemophilus influenzae* was increased in men-who-have-sex-with-men with idiopathic urethritis (ANCOM-BC-Coefficient=3.39, false discovery rate [FDR]-*P*=0.004), and the abundance of *Corynebacterium* was increased in men-who-have-sex-with-women with idiopathic urethritis (ANCOM-BC-Coefficient=1.05, FDR-*P*=0.055). Other taxa including *Ureaplasma*, *Staphylococcus haemolyticus, Streptococcus pyogenes, Escherichia*, and *Staphylococcus pneumoniae*, were found to dominate the urethral microbiota of cases but not controls, suggesting that these organisms may also contribute to urethritis.

Conclusion: Our findings suggest that a range of bacteria are likely to be causing idiopathic urethritis and that these bacteria may be influenced by sexual practices and sex of partners. The bacteria that we identified represent biologically plausible aetiologic agents of urethritis that should be investigated further in larger studies.

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