Editorial

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Is chronic prostatitis/chronic pelvic pain syndrome an infectious disease of the prostate?

For over a hundred years chronic prostatitis was considered an infectious disease of bacterial origin and when antibiotics became available it was believed that it would probably be relegated to the wastebasket of cured diseases [1]. However, despite this promise, antibiotics did not cure most of the patients with prostatitis and with better understanding of microbiology, uropathogenicity and the condition itself, we came to the conclusion that perhaps it was not caused by bacteria or other infectious agents after all. We finally defined the condition of National Institutes of Health (NIH) category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) by the absence of bacterial infection by a recognized uropathogen identified using traditional culture techniques as a cause for the chronic pain and urinary symptoms. This left the door open to further discoveries that infection might play a role in the etiology or pathogenesis of CP/CPPS (using other methods etc). In fact, it has only been several decades when a disease believed to be due to genetics, increased gastric acidity and stress, was discovered to be due to *Helicobacter pylori* and gastritis is now treated with appropriate antimicrobial therapy instead of radical surgery. Could there be a microorganism cause for CP/CPPS, but we just cannot identify it? Clinically we isolate uropathogens from voided urine or expressed prostatic secretion on specific nutritive media and under environmental conditions that do not support growth of many possible bacterial species. Chronic bacterial infections have been shown to be associated with a biofilm mode of growth that is highly recalcitrant to antibiotic therapy and difficult to culture [2]. Or could we be missing an unknown (never discovered) or unrecognized organism (perhaps an organism not recognized as a uropathogen) as the cause. Molecular techniques, that do not rely on bacterial growth *in vitro*, including molecular-phylogenetic approaches based on 16S RNA PCR techniques have resulted in conflicting conclusions regarding the contributions of infectious agents in CP/CPPS [3-10]. We recently reported [11] on the use of next-generation molecular diagnostic Ibis T-5000 Universal Biosensor technology which provides universal and comprehensive identification of all bacterial species present at >1%–3% of the microbiome, to characterize the microbiota of CP/CPPS patients and asymptomatic control subjects recruited within the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Network Epidemiological/Phenotyping Study [12]. The Ibis T-5000 Universal Biosensor technology [13] is able to generate a definitive species-level diagnostic for all known bacterial species. In addition, the system allows for a powerful discovery-based approach that was not subject to restrictions based on a priori assumptions of microbial profiles, including a "most-closely-related match" for unknown organisms.

We noted no differences at the species or genus level between CP/CPPS and control participants for VB2 or VB3 samples (or even VB3 - VB1+2 samples). We believe the clinical significance of minor microbiome differences in VB1 remain unclear. The observed specific microbiome differences for *Burkholderia cenocepacia* (more prevalent in VB1 in CP/CPPS participants compared to controls) and minor differences observed in VB1 for *Propionibacterium acnes* and *Staphylococcus capitis/capare* (both under represented in CP/CPPS participants compared to controls) may or may not be clinically insignificant, but they could also indicate a change in the overall species balance. Others have described *B. cenocepacia* as a pathogen [14], possibly involved in the etiology of CP/CPPS [15,16]. Nevertheless, we did not find a putative organism identified with a significant presence in the segmented specimens to identify an important prostatitis pathogen that could account for this condition.

Although we clearly did not identify, the "smoking gun" pathogen, we cannot necessarily say that microbiome differences are not important in CP/CPPS. We did not

address microbial immunological memory since chronic inflammation and pain may persist after an offending organism has been cleared [17,18]. Various organisms or combinations of organisms, might influence various symptom changes (e.g., flare status) or are associated with select urologic chronic pelvic pain syndrome patients with differing symptom profiles, natural history, and/or underlying biological characteristics. Without biopsy, we may have missed a major impact of biofilm bacteria which in theory may only be detected if there is better mechanical disruption of the biofilm than that obtained by prostate massage. Finally, the microbiome in areas other than the urinary tract, for example in the bowel, may influence the symptoms or clinical phenotypes of men with CP/CPPS [19]. We are addressing some of these issues in the ongoing NIH/National Institute of Diabetes and Digestive and Kidney funded MAPP-2 Clinical Patterns study in which we will be identifying the bacterial, viral and fungal microbiota in the urine and the rectum of CP/CPPS patients and correlating that with symptom patterns, inflammatory biomarkers and even neuroimaging studies over a 2-year period. The story of the role of the microorganism in the men suffering from CP/CPPS is not over yet.

CONFLICTS OF INTEREST

The author has nothing to disclose.

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REFERENCES

1. Nickel JC. Prostatitis: an historical perspective. In: JC Nickel, editor. Textbook of prostatitis. Oxford: ISIS Medical Media; 1999. p. 3-18.
2. Nickel JC, Costerton JW. Bacterial localization in antibiotic-refractory chronic bacterial prostatitis. Prostate 1993;23:107-14.
3. Tanner MA, Shoskes D, Shahed A, Pace NR. Prevalence of corynebacterial 16S rRNA sequences in patients with bacterial and "nonbacterial" prostatitis. J Clin Microbiol 1999;37:1863-70.
4. Shoskes DA, Shahed AR. Detection of bacterial signal by 16S rRNA polymerase chain reaction in expressed prostatic secretions predicts response to antibiotic therapy in men with chronic pelvic pain syndrome. Tech Urol 2000;6:240-2.
5. Krieger JN, Riley DE, Roberts MC, Berger RE. Prokaryotic DNA sequences in patients with chronic idiopathic prostatitis. J Clin Microbiol 1996;34:3120-8.
6. Riley DE, Berger RE, Miner DC, Krieger JN. Diverse and related 16S rRNA-encoding DNA sequences in prostate tissues of men with chronic prostatitis. J Clin Microbiol 1998;36:1646-52.
7. Keay S, Zhang CO, Baldwin BR, Alexander RB. Polymerase chain reaction amplification of bacterial 16s rRNA genes in prostate biopsies from men without chronic prostatitis. Urology 1999;53:487-91.
8. Hochreiter WW, Duncan JL, Schaeffer AJ. Evaluation of the bacterial flora of the prostate using a 16S rRNA gene based polymerase chain reaction. J Urol 2000;163:127-30.
9. Leskinen MJ, Rantakokko-Jalava K, Manninen R, Leppilahti M, Marttila T, Kylmälä T, et al. Negative bacterial polymerase chain reaction (PCR) findings in prostate tissue from patients with symptoms of chronic pelvic pain syndrome (CPPS) and localized prostate cancer. Prostate 2003;55:105-10.
10. Xie H, Huang HC, Yang YR, Wu JB, He QX, Zhu QJ, et al. Detection of 16S ribosomal RNA gene of bacteria in prostate tissues of adults. Zhonghua Yi Xue Za Zhi 2006;86:976-8.
11. Nickel JC, Stephens A, Landis JR, Chen J, Mullins C, van Bokhoven A, et al. Search for microorganisms in men with urologic chronic pelvic pain syndrome: a culture-independent analysis in the MAPP research network. J Urol 2015;194:127-35.
12. Clemens JQ, Mullins C, Kusek JW, Kirkali Z, Mayer EA, Rodríguez LV, et al. The MAPP research network: a novel study of urologic chronic pelvic pain syndromes. BMC Urol 2014;14:57.
13. Ecker DJ, Sampath R, Massire C, Blyn LB, Hall TA, Eshoo MW, et al. Ibis T5000: a universal biosensor approach for microbiology. Nat Rev Microbiol 2008;6:553-8.
14. Schwager S, Agnoli K, Köthe M, Feldmann F, Givskov M, Carlier A, et al. Identification of Burkholderia cenocepacia strain H111 virulence factors using nonmammalian infection hosts. Infect Immun 2013;81:143-53.
15. Arzola JM, Hawley JS, Oakman C, Mora RV. A case of prostatitis due to Burkholderia pseudomallei. Nat Clin Pract Urol 2007;4:111-4.
16. Organ M, Grantmyre J, Hutchinson J. Burkholderia cepacia infection of the prostate caused by inoculation of contaminated ultrasound gel during transrectal biopsy of the prostate. Can Urol Assoc J 2010;4:E58-60.
17. Rudick CN, Berry RE, Johnson JR, Johnston B, Klumpp DJ, Schaeffer AJ, et al. Uropathogenic Escherichia coli induces chronic pelvic pain. Infect Immun 2011;79:628-35.

https://doi.org/10.4111/icu.2017.58.3.149

18. Quick ML, Wong L, Mukherjee S, Done JD, Schaeffer AJ, Thumbikat P. Th1-Th17 cells contribute to the development of uropathogenic Escherichia coli-induced chronic pelvic pain. PLoS One 2013;8:e60987.

19. Shoskes DA, Wang H, Polackwich AS, Tucky B, Altemus J, Eng C. Analysis of gut microbiome reveals significant differences between men with chronic prostatitis/chronic pelvic pain syndrome and controls. J Urol 2016;196:435-41.