Men's Health Journal. 2022; 6(1): e6

ORIGINAL RESEARCH

Prevalence of Atypical Infections in Male Patients with Chronic Pelvic Pain

Elizabeth T. Nagoda[1], Timothy Demus[1], Dhaval Jivanji[2], Giovanni Cragnotti[2], Anthony Bui[1], Alan S. Polackwich[1]*

1. Department of Urology, Mount Sinai Medical Center, Miami Beach, FL, USA.
2. Herbert Wertheim College of Medicine at Florida International University, Miami, FL, USA.

Received: February 2022; Accepted: April 2022; Published online: May 2022

Abstract: **Introduction:** Atypical infections are often considered as a potential etiology for men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). We aimed to describe the prevalence of atypical infections in this patient population to inform clinical management for male patients complaining of pelvic pain. **Methods:**We retrospectively reviewed patients at a single center from January 2016 to January 2019. We included patients with CP/CPPS Type III diagnosed with pelvic or genital pain in the absence of bacterial infection. All patients underwent an atypical infection panel. The primary outcome measure was the presence of any atypical infection. **Results:** In total, 345 patients met the inclusion criteria. Of those, 9/345 (2.6%) had an atypical infection (5 mycoplasma and 4 ureaplasma). The mean age of patients with positive atypical infections was 34 compared to the overall study population (44 years, P=0.01). Two patients with atypical infections were also followed for infertility. Urinalysis was available for 6 of the 9 patients with positive atypical infection: 50% (3 out of 6) were normal and 50% (3 out of 6) had >5 WBC/hpf. Symptoms resolved in 66% (2 out of 3) of the patients with positive atypical infection with available follow-up data. **Conclusions:** Atypical infectious agents were uncommon causes of CP/CPPS. Screening for atypical microbes such as chlamydia, ureaplasma, or mycoplasma may not be necessary for male patients complaining of pelvic or genital pain.

Keywords: Chronic pelvic pain syndrome; Atypical infections; Chronic prostatitis; Pelvic pain; Prostate

Cite this article as: Nagoda E, Demus T, Jivanji D, Cragnotti G, Bui A, Polackwich A. Prevalence of Atypical Infections in Male Patients with Chronic Pelvic Pain. Mens Health J. 2022; 6(1): e6.

1. Introduction

Prostatitis accounts for 8% of all urological visits and 1% of all primary care visits (1). Approximately one in two men will experience some form of prostatitis in their lifetime (2). Prostatitis has been difficult to treat because of its historical mischaracterization and contested etiology. In 1994, the National Institute of Health (NIH) proposed four different subgroups of prostatitis: type I (acute bacterial prostatitis), type II (chronic bacterial prostatitis), type III (chronic prostatitis [CP]/chronic pelvic pain syndrome [CPPS]), and type IV (asymptomatic inflammatory prostatitis) (3). Type III is further subdivided into type IIIA (presence of leukocytes in semen, expressed prostatic secretions [EPS], or urine after prostate massage) and type IIIB (absence of leukocytes) (3). CPPS is characterized by chronic pelvic pain with symptoms of prostate inflammation lasting for at least three months, in the absence of detectable pathogenic bacteria. It can cause a wide variety of symptoms related to pain, urinary function, quality of life, and sexual dysfunction. CPPS is a common condition in urology and is diagnosed in approximately 90% of patients with prostatitis. When classified incorrectly, it can result in the overuse of antibiotics (4, 5).

During a patient evaluation, it is currently recommended that one orders a standard urine culture together with testing for atypical infections such as Chlamydia trachomatis, Neisseria gonorrhea, Trichomonas vaginalis, Mycoplasma genitalium, and Ureaplasma urealyticum (6). This is recommended because of studies establishing an association between women with pelvic pain and infections with atypical bacteria. However, the literature has contradicting results regarding bacterial pathogens as the origin of chronic pelvic pain in men. Studies that utilized the four-glass test and PCR

***Corresponding Author:** Alan Scott Polackwich; Address: Columbia University Division of Urology at Mount Sinai Medical Center, 4302 Alton, RD STE 540, Miami Beach, FL 33140. Email: alan.polackwichjr@msmc.com ; polackwi@gmail.com, hone: (305) 674-2499, Fax: (305)-674-2149 .

techniques to verify the presence of bacterial pathogens in patients with CPPS concluded that the prostate does not harbor normal flora and that a bacterial etiology for CPPS is unlikely (6, 7). On the other hand, similar studies using PCR techniques provided opposing results, but were unable to consistently identify a single organism as a source of etiology (8-12). Lastly, animal model studies have shown the ability to induce pelvic pain by being genetically altered to allow for certain bacteria growth (13, 14).

Despite the lack of concrete evidence demonstrating a bacterial etiology for chronic pelvic pain in men, in conjunction with studies showing that antibacterial monotherapy is not an effective treatment for CPPS, screening for atypical bacteria and the use of antimicrobial treatment as a first-line therapy is still recommended (15, 16).

We aimed to determine the prevalence of atypical infections in male patients with CPPS. Adding evidence to the literature will help guide physicians in clinical practice when managing male patients who present with chronic pelvic pain. We hypothesized a low prevalence of atypical infections in this patient population.

2. Methods

This is a retrospective cohort study of male patients evaluated for pelvic pain from January 2016 to January 2019 at a single institution by a single provider. Institutional IRB approval was obtained for this study. The diagnosis of CPPS was made based on history and physical exam along with appropriate imaging and lab workup. Subjects were evaluated with a urine culture and atypical infection panel. The urine was collected following prostatic massage. Any patient with the presence of bacteria on culture was excluded. The atypical panel was screened for the presence of Chlamydia trachomatis, Neisseria gonorrhea, Trichomonas vaginalis, Mycoplasma genitalium and Ureaplasma urealyticum through Real-Time PCR. Overall, pain in the genital or pelvic region with or without the presence of voiding or sexual dysfunction and no known infection was classified as CPPS. As outlined by the NIH categorization, this would be considered as Type III prostatitis. It was important to elucidate the presence of pain as this distinguishes LUTS from CPPS. All patients received appropriate treatment for their findings.

We retrospectively reviewed medical records of patients who met our inclusion criteria. Subjects with urinary retention, hematuria, kidney stones, positive urine culture, and fever were excluded prior to analysis. Data was collected regarding the progression of their medical conditions and their demographic characteristics for statistical analysis. We compared the characteristics of our study population using Pearson's Chi-square for categorical variables and Student's t test for continuous variables. Statistical analysis was performed using SPSS. All tests were two-sided, and the probability of a type I error was set at 0.05.

3. Results

We included 345 patients in the analysis. In total, 2.6% (9/345) of patients had a positive atypical infection panel. Five were positive for Mycoplasma (1.4%) and four were positive for Ureaplasma (1.1%). No cultures were positive for Gonorrhea or Chlamydia within this cohort. The mean age of patients with a negative panel: was 44 years (SD 14) compared to 34 years in positive cases (SD: 8.1, P=0.01). The mean BMI was 25.5 (SD: 4.3). Most patients were non-smokers (76%) while 18% and 6% were former and current smokers, respectively. Urine Microscopy (UA) was obtained for 6 of the 9 patients as three patients had urinalyses that were conducted at an outside facility. Of the patients with atypical infections and an available UA, 50% (3/6) had a normal urinalysis and 50% (3/6) had a urinalysis with greater than 5 WBC per high power field (P<0.01). Two patients with an atypical infection were seen in the office for infertility (P<0.01) and one had a history of STIs (P<0.01). After antibiotics, 2/9 (22%) patients had symptom resolution, 1/9 (11%) had continued pain, and 6/9 (67%) were lost to follow-up.

4. Discussion

In our single-center study, we found that atypical infections rarely contributed to men with CPPS. Several studies have investigated the possibility of a bacterial etiology for CPPS in male patients and the findings are contradictory. In the literature, a few different studies were able to amplify bacterial DNA from prostate specimens of patients with CPPS (8-12). One of these studies reported the presence of atypical pathogens as a possible etiology for CPPS, which are usually not detected from standard urine cultures. Patients with CPPS were found to have Ureaplasma, Chlamydia, CMV, HPV, and HSV-2 (14). Moreover, Mandar et al. concluded that mycoplasma occurs more frequently in the semen of patients with prostatitis than in healthy controls, drawing an association between atypical infections and prostatitis (15). They also reported that M. urealyticum and M. genitalium DNA were amplified through PCR in 18% of patients with type IIIA prostatitis compared to 0% in their control group (15). However, it is important to point out that these studies had relatively small sample sizes (7). Although these studies show the presence of bacteria in the prostate, randomized controlled trials comparing the use of antibiotics as monotherapy vs. placebo have shown that antibiotics alone are not effective in treating CPPS. One study demonstrated that levofloxacin alone did not improve patient symptoms compared with placebo (16). On the other hand, some studies on animal models showed that bacterial infection might not be the

primary factor contributing to the symptoms of CPPS, but rather the initiator (13, 14). However, this hypothesis does not apply to patients with type IIIB prostatitis as they lack leukocytes in the prostate.

At our institution, the urine specimens were analyzed with SureSwab Real-Time PCR. The test involved the collection of urine and molecular methods to allow for rapid detection of pathogens in the specimen. The prevalence of atypical infections in our study population was 2.6% (9/345). Unfortunately, we could not compare our results with other studies in the literature since, based on our knowledge, this is the only study that has investigated the clinical relevance of atypical infections in male patients with pelvic pain. In our patient cohort, a small number could have been attributed to these atypical infections. Out of these 9 patients, only 2 had symptom resolution after antibiotic treatment. This outcome lends further away from atypical infections causing clinically significant chronic pelvic pain. In our study, 6/9 of patients with positive atypical pathogens received a UA. 50% (3/6) of these patients met the type IIIA categorization while 50% (3/6) met the type IIIB classification. The mean age of patients in our study population was 44 years compared to 33 years for the patients with positive results for atypical pathogens. Sexual activity is an important pathway to the exposure of microorganisms, some of which might result in clinical symptoms, while the rest might result in subclinical infections. Whether sexual activity played a role in our findings is unknown, but further studies should take sexual activity into consideration when looking for prostatic pathogens. Interestingly, those patients who had a known history of infertility or STI were the same individuals with a positive atypical urine infection.

Mycoplasma infections are usually mild chronic infections and their role in prostatitis is yet to be elucidated. In this study, our rates of positivity for atypical infections were much less than those found in the literature. Our findings raise doubts regarding the utility of routine testing for atypical pathogens in men suffering from CPPS. Although the utility of atypical infection testing may be questioned since the rate of positivity is low, testing could be considered in certain patients where clinical suspicion is high for an atypical infection. From the results of our study, younger patients, those with LE on UA, or those with a known history of STI or infertility could be offered further atypical infection testing if presenting with chronic pelvic pain.

There were some limitations in this study. Being a single-center retrospective study could limit generalization to the overall population. Additionally, patients in this study were not validated using a chronic pelvic pain questionnaire like the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) questionnaire (2). This limits the objective assessment of the subjects and the CP/CPPS symptoms they presented with.

5. Conclusion

Atypical infections are not a common cause of chronic pelvic pain in our sample. Patients with a positive culture tended to be younger and more likely to have had a history of infertility or STI. Although our study population was relatively small, our findings support our hypothesis that atypical infections were uncommon in men with pelvic pain. We recognize the limitations of this study; therefore, further research is needed to validate the results. Additional projects focusing on targeted testing based on medical history and the cost-effectiveness of atypical infection screening are also warranted.

6. Appendix

6.1. Acknowledgment

The authors thank the Columbia University Division of Urology at Mount Sinai Medical Center for their help with this work.

6.2. Conflict of interest

No conflict of interest.

6.3. Funding support

None.

6.4. Author's contributions

• EN: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing
• TD: Data collection or management, Data analysis, Manuscript writing/editing
• DJ: Data collection or management, Manuscript writing/editing
• GC: Data collection or management, Manuscript writing/editing
• AB: Protocol/project development, Manuscript writing/editing
• ASP: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

6.5. Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Collins MM, Stafford RS, O'LEARY MP, Barry MJ. How common is prostatitis? A national survey of physician vis-

its. The Journal of urology. 1998;159(4):1224-8.
2. Gonçalves MSM. Prostate Gland Infections and Inflammation: Universidade da Beira Interior (Portugal); 2019.
3. Krieger JN, Nyberg Jr L, Nickel JC. NIH consensus definition and classification of prostatitis. Jama. 1999;282(3):236-7.
4. Litwin MS, McNaughton-Collins M, Fowler FJ, Nickel JC, Calhoun EA, Pontari MA, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. The Journal of urology. 1999;162(2):369-75.
5. Polackwich A, Shoskes D. Chronic prostatitis/chronic pelvic pain syndrome: a review of evaluation and therapy. Prostate Cancer and Prostatic Diseases. 2016;19(2):132-8.
6. Schaeffer EM. Re: Contemporary Management of Chronic Prostatitis/Chronic Pelvic Pain Syndrome. The Journal of urology. 2017;197(5):1275-6.
7. Breser ML, Salazar FC, Rivero VE, Motrich RD. Immunological mechanisms underlying chronic pelvic pain and prostate inflammation in chronic pelvic pain syndrome. Frontiers in Immunology. 2017:898.
8. Nickel JC, Alexander RB, Schaeffer AJ, Landis JR, Knauss JS, Propert KJ, et al. Leukocytes and bacteria in men with chronic prostatitis/chronic pelvic pain syndrome compared to asymptomatic controls. The Journal of urology. 2003;170(3):818-22.
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. The Prostate. 2003;55(2):105-10.
10. Krieger JN, Riley DE, Roberts MC, Berger RE. Prokaryotic DNA sequences in patients with chronic idiopathic prostatitis. Journal of clinical microbiology. 1996;34(12):3120-8.
11. Riley DE, Berger RE, Miner DC, Krieger JN. Diverse and related 16S rRNA-encoding DNA sequences in prostate tissues of men with chronic prostatitis. Journal of Clinical Microbiology. 1998;36(6):1646-52.
12. Tanner MA, Shoskes D, Shahed A, Pace NR. Prevalence of corynebacterial 16S rRNA sequences in patients with bacterial and "nonbacterial" prostatitis. Journal of Clinical Microbiology. 1999;37(6):1863-70.
13. KRIEGER JN, RILEY DE, VESELLA RL, MINER DC, ROSS SO, LANGE PH. Bacterial DNA sequences in prostate tissue from patients with prostate cancer and chronic prostatitis. The Journal of urology. 2000;164(4):1221-8.
14. Xiao J, Ren L, Lv H, Ding Q, Lou S, Zhang W, et al. Atypical microorganisms in expressed prostatic secretion from patients with chronic prostatitis/chronic pelvic pain syndrome: microbiological results from a case-control study. Urologia internationalis. 2013;91(4):410-6.
15. Rudick CN, Berry RE, Johnson JR, Johnston B, Klumpp DJ, Schaeffer AJ, et al. Uropathogenic Escherichia coli induces chronic pelvic pain. Infection and immunity. 2011;79(2):628-35.
16. Murphy SF, Anker JF, Mazur DJ, Hall C, Schaeffer AJ, Thumbikat P. Role of gram-positive bacteria in chronic pelvic pain syndrome (CPPS). The Prostate. 2019;79(2):160-7.

Table 1: Baseline characteristics of sample.

Demographics	Total population	(+) atypical pathogens	p-value
Age (mean, SD) †	44 years (SD 14.0)	34 years (SD 8.1)	0.01
BMI (mean, SD) †	25.5 (SD 4.2)	24.9 (SD 3.5)	0.18
Never smokers (%)‡	76%	89%	0.35
Former smokers (%)‡	18%	11%	
Current Smokers (%)‡	6%	0%	
History of STI‡	1.7%	11%	0.01
History of infertility‡	0%	22%	0.01

†T test; ‡Pearson's chi squared.

Table 2: Prevalence of atypical infections.

Microorganism	Cohort Frequency
Mycoplasma Genitalum	1.4% (5/345)
Ureaplasma urealyticum	1.1% (4/345)
Total atypical pathogens	2.6% (9/345)