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Excessive Antibiotic Utilization in Men with Prostatitis

Brent C. Taylor, PhD, MPH^{1,2}, Siamak Noorbaloochi, PhD^{1,2}, Mary McNaughton-Collins, MD, MPH³, Christopher S. Saigal, MD, MPH^{4,5}, Min-Woong Sohn, PhD^{6,7}, Michel A. Pontari, MD⁸, Mark S. Litwin, MD, MPH^{4,5}, and Timothy J. Wilt, MD, MPH^{1,2} the Urologic Diseases in America Project

1 Center for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, MN

2 Department of Medicine, University of Minnesota, Minneapolis, MN

3 General Medicine Division, Harvard Medical School, Massachusetts General Hospital, Boston, MA

4 David Geffen School of Medicine, University of California, Los Angeles, CA

5 RAND Health, Santa Monica, CA

6 Edward Hines, Jr. VA Hospital, Hines, IL

7 Institute for Healthcare Studies, Northwestern University, Chicago, IL

8 Temple University School of Medicine, Philadelphia, PA

Abstract

Background—Prostatitis accounts for two million outpatient visits annually. The vast majority of prostatitis cases fit the definition of chronic pelvic pain syndrome for which routine antibiotic use is not indicated.

Methods—Inpatient, Outpatient, and Pharmacy Datasets from the Veterans Health Administration were used to quantify the magnitude of antibiotic use attributable to chronic pelvic pain syndrome. Specifically, men with a diagnosis of infectious/acute prostatitis, and/or a urinary tract infection were excluded, and the remaining men with a diagnosis of prostatitis were defined as having chronic pelvic pain syndrome.

Results—Annual prevalence of chronic pelvic pain syndrome was 0.5%. Prescriptions for fluoroquinolone antibiotics were filled in 49% of men with a diagnosis of chronic pelvic pain syndrome compared to five percent in men without chronic pelvic pain syndrome. Men with chronic pelvic pain syndrome were greater than seven times more likely to receive a fluoroquinolone prescription independent of age, race/ethnicity and comorbid conditions. Increased use of other antibiotics was also observed. High utilization was similar in men with either infectious/acute prostatitis or chronic pelvic pain syndrome.

Corresponding author: Brent C. Taylor, Ph.D., M.P.H., Center for Chronic Disease Outcomes Research (111-0), Minneapolis VA Medical Center, 1 Veterans Drive, Minneapolis MN 55417, USA. Tel: 612-467-4941; fax: 612-725-2118. E-mail address: brent.taylor2@med.va.gov.

Reprint requests: Timothy J. Wilt, M.D., M.P.H., Center for Chronic Disease Outcomes Research (111-0), Minneapolis VA Medical Center, 1 Veterans Drive, Minneapolis MN 55417, USA. Tel: 612-467-2681; fax: 612-725-2118. E-mail address: tim.wilt@med.va.gov

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Conclusions—Despite evidence that antibiotics are not effective in the large majority of men with chronic pelvic pain syndrome, they were prescribed in 69% of men with this diagnosis. Some increased use is probably due to uncontrolled confounding by comorbid conditions or inaccurate diagnostic coding. However, a seven-fold higher rate of fluoroquinolone usage suggests strategies to reduce unnecessary antibiotic use in men with prostatitis are warranted.

BACKGROUND

Prostatitis refers to several clinical syndromes and has been categorized in four types: 1) acute bacterial infection, 2) chronic bacterial infection, 3) poorly defined chronic pelvic pain syndrome and 4) asymptomatic prostate inflammation.¹ Acute and chronic bacterial prostatitis account for approximately 5% to 10% of all cases of prostatitis.² Both are clearly associated with bacterial infection (often recurrent) and a urine culture that grows uropathogens. However, most men diagnosed with prostatitis have pelvic pain without evidence of infection.

Because antibiotics are not effective for treatment of abacterial chronic prostatitis, their use should be limited to individuals with confirmed positive cultures on expressed prostatic fluid or associated urinary tract infection.³ Recent efforts have been made to disseminate this information and implement appropriate antibiotic prescribing for several common conditions including prostatitis.

In the USA, chronic pelvic pain syndrome accounts for the vast majority of all prostatitis diagnoses totaling almost two million outpatient visits and 1% of primary care visits annually.⁴ Associated symptoms are common, bothersome, and burdensome in terms of health related quality of life^{5,6} and economic costs.⁷ Because there are no reliable physical or laboratory findings, diagnosis of chronic pelvic pain syndrome is based on exclusion of other causes, particularly infection.

While fluoroquinolones are a Food and Drug Administration approved treatment for prostate infections,⁸ the vast majority of prostatitis cases are not infectious but instead comprise a syndrome of chronic pelvic pain.^{2,4} The etiology of this condition is unclear but a systematic review⁹ and subsequent randomized trials^{10,11} of the efficacy of treatments have demonstrated that routine antibiotics, including fluoroquinolones are not effective. Furthermore, prior research has found that, after excluding men with urinary tract infection, diagnosed cases of chronic pelvic pain syndrome have similar detection rates for uropathogenic and nonuropathogenic bacterial species when compared with asymptomatic controls.¹² Fluoroquinolone use has substantially increased over the past decade driven by the increasing use of newer broader-spectrum fluoroquinolones.^{8,13} They account for nearly one-quarter of all antibiotic prescriptions with family practice and internal medicine providers accounting for more than one-half and urologists ten percent of these. Overuse of antibiotics is a serious public health issue leading to antimicrobial drug resistance, drug related adverse effects and increased costs of medication.¹³

In order to estimate antibiotic utilization, the current study uses data from male veterans receiving care at the Veterans Health Administration (VHA) between 1999 and 2003 to calculate the increased likelihood of antibiotic use, particularly fluoroquinolones, for the treatment of chronic pelvic pain syndrome.

METHODS

Study Population

This study was conducted as part of the Urologic Diseases in America (UDA) project whose aim was to quantify the burden of urologic diseases.^{14–16} The study population consisted of

all male patients aged 18 years and over who used inpatient acute care or outpatient care in the VHA between 1999 and 2003. The Institutional Review Boards of both the Minneapolis and Edward Hines, Jr. VA Hospitals approved the study, including a HIPAA waiver of authorization.

Data Collection

VHA Inpatient and Outpatient datasets and Pharmacy Benefits and Management (PBM) files for October 1, 1998 through September 30, 2003 were merged to assess prostatitis prevalence and antibiotic utilization. International Classification of Diseases, 9th Version, Clinical Modification (ICD-9-CM) diagnostic codes for inpatient and outpatient records were used to detect diagnoses of prostatitis and other potential confounding conditions. The majority of cases of prostatitis are not confirmed as either bacterial or abacterial and there is no specific code for abacterial prostatitis. Therefore, men were defined as either having a diagnosis of “chronic pelvic pain syndrome” or “infectious/acute prostatitis”. “Chronic pelvic pain syndrome” was defined by either the ICD-9 codes for chronic prostatitis (601.1x) or prostatitis, unspecified (601.9x). “Infectious/acute prostatitis” was defined by the ICD-9 codes for ‘acute prostatitis’ (601.0x), ‘abscess of prostate’ (601.2x), ‘prostatocystitis’ (601.3x), ‘prostatitis in diseases classified elsewhere, actinomycosis, blastomycosis, syphilis, tuberculosis’ (601.4x), or ‘other specified inflammatory diseases of prostate, prostatitis: cavitary, diverticular, granulomatous’ (601.8x)]. In order to further identify men with chronic prostatitis unlikely to benefit from antibiotics, men with any diagnosis of urinary tract infection in the same fiscal year were excluded.

Medication data were obtained from the PBM national database Version 3.0. The database for this project contains information from the time frame defined. For the current project, unique patient counts were determined for specific antibiotics frequently used for treatment of bacterial prostatitis or urinary tract infections including: fluoroquinolones, cephalosporins, penicillins, sulfonamides and tetracycline within the fiscal years 1999 through 2003. Patients were only counted once in each year.

Additionally, diagnoses of the following conditions were used as comorbidities that might affect antibiotic utilization: cerebrovascular disease, cardiovascular disease, congestive heart failure, chronic lung disease, dementia, alcohol abuse, diabetes, and hypertension. ICD-9 codes used to define each condition can be obtained from the authors.

Age was categorized into five groups (<50, 50–59, 60–69, 70–79, and 80+). Race/ethnicity data were obtained from the VHA data and, when missing, were supplemented by those in the Medicare Denominator files. Details on the completeness and validity of the self-reported race/ethnicity data have previously been published for these data.¹⁸

Statistical Analysis

Comparisons of differences in age, race/ethnicity, number of comorbid conditions (0, 1, or 2 or more), and prescription of any oral antibiotic or a specific prescription for a fluoroquinolone were calculated for men with and without a diagnosis consistent with chronic pelvic pain syndrome. For all of the primary analyses men with a diagnosis of urinary tract infection were excluded from that year’s analysis. The association between chronic pelvic pain syndrome and fluoroquinolone use was calculated as a prevalence ratio (PR) adjusted for age, race/ethnicity, and number of comorbid conditions, using published log binomial regression methods.¹⁹ Adjusted population attributable risks (PAR) were then calculated from the adjusted prevalence ratio and prevalence of chronic pelvic pain syndrome. The PAR estimates the number of men with fluoroquinolone prescriptions who might be expected to have received prescription(s) due to their chronic pelvic pain syndrome after accounting for age, race/ethnicity and comorbidities.

These methods were repeated to estimate the number of men with an antibiotic prescription, other than fluoroquinolone.

Secondary analyses were conducted to assess the effect of excluding men with infectious/acute prostatitis from the analyses. The primary methods were repeated and the magnitude of effect for infectious/acute prostatitis diagnosis on fluoroquinolone use was compared to that of chronic pelvic pain syndrome.

RESULTS

In the entire cohort of 4,758,039 male users of the VA health care system during 2003, 6,379 (0.13%) men had diagnosis of infectious/acute prostatitis and 126,731 (2.7%) men had a diagnosis of urinary tract infection. The 131,818 men with either a diagnosis of infectious/acute prostatitis or a diagnosis of a urinary tract infection were excluded from all of the other results leaving 4,626,221 men as the denominator. In 2003, 23,037 (0.50%) had a diagnosis consistent with chronic pelvic pain syndrome meaning they had a diagnosis of prostatitis with no corresponding diagnosis of either urinary tract infection or infectious/acute prostatitis (Figure 1). Distributions of diagnoses were similar in each of the four prior years (data not shown).

Chronic pelvic pain syndrome prevalence varied by age, number of comorbidities, and race/ethnicity. Men with chronic pelvic pain syndrome were substantially more likely to be prescribed an antibiotic, particularly a fluoroquinolone, during the same year as their diagnosis than men without chronic pelvic pain syndrome. Among men with a diagnosis of chronic pelvic pain syndrome in 2003, 49% received a prescription for a fluoroquinolone within the same year as compared to only 5% of men without chronic pelvic pain syndrome despite the exclusion of men with infectious/acute prostatitis or urinary tract infection (Table 1). These associations were similar in each of the four prior years (data not shown).

In unadjusted models, men with chronic pelvic pain syndrome had a ten-fold higher prevalence of fluoroquinolone use (PR=10.3; 95% CI 10.1 to 10.4) in 2003. This association was only modestly attenuated by adjustment for age group, race/ethnicity and number of comorbidities (PR=7.9; 95% CI 7.8 to 8.0). From 1999 through 2003, an estimated 32,562 men with a diagnosis of chronic pelvic pain syndrome received a fluoroquinolone, attributable to their chronic pelvic pain syndrome diagnosis, even though they lacked a diagnosis of infectious/acute prostatitis or urinary tract infection during the corresponding year (Table 2). While the adjusted percentage attributable risk for all fluoroquinolone use remained stable over time ranging from 3.54% to 3.30% per year the total number of men who were estimated to have been prescribed a fluoroquinolone to treat their chronic pelvic pain syndrome increased 50% from 5,091 in 1999 to 7,635 in 2003 due to the larger number of men receiving care at VHA and the increased use of fluoroquinolones.

Men with a diagnosis of chronic pelvic pain syndrome were also more likely to have been prescribed other classes of antibiotics (PR=3.57 95% CI; 3.51, 3.63) independent of age, race/ethnicity and number of comorbid conditions (Table 3). Over the five year period, we estimated 14,153 men were prescribed an antibiotic other than a fluoroquinolone to treat their chronic pelvic pain syndrome.

Secondary Analysis Comparing Infectious/Acute Prostatitis to Chronic Pelvic pain Syndrome

When we included all FY2003 male VHA users with a diagnosis of prostatitis (n=34,003), regardless of whether or not it was infectious/acute, we found 28,124 men (0.6% of all VHA users who did not have a diagnosis of urinary tract infection) had at least one diagnosis of

prostatitis during FY2003. Nearly 82% (n=23,037) of these men with prostatitis met our diagnostic criteria for chronic pelvic pain syndrome. The multivariable-adjusted prevalence ratios for fluoroquinolone prescriptions were similar in men with infectious/acute prostatitis and men with chronic pelvic pain syndrome (PR of 8.60 and 8.66, respectively) compared to men with no prostatitis diagnosis. The observation was similar for all of the years (data not shown).

DISCUSSION

The findings from this national clinical care database indicate that the majority of men diagnosed with prostatitis lack an appropriate indication for use of antibiotics. Despite this, most men with a diagnosis of prostatitis received an antibiotic, particularly fluoroquinolones. This high percentage of antibiotic utilization is considerably greater than in men of similar age, race/ethnicity and number of comorbidities who lack a diagnosis of prostatitis. National VA administrative and clinical datasets do not specify the reason for an antibiotic prescription; therefore some individual prescriptions may have been for coexisting conditions. However, it is unlikely that there would be a strong (greater than 7-fold) and consistent association in men without urinary tract infection or infectious/acute prostatitis independent of age, race/ethnicity or comorbidity status. Furthermore, the fact that men with a diagnosis consistent with chronic pelvic pain syndrome had similarly strong associations as men with a diagnosis of infectious/acute prostatitis supports the hypothesis that antibiotic treatment is not restricted to men with prostatitis and a confirmed bacterial infection.

Antibiotic overuse has been identified as one of 20 priority areas for improving health care quality. Increased antibiotic use contributes to the development and spread of antibiotic-resistant bacteria. Once confined to the inpatient setting, resistant bacteria are now common community-acquired infections. The increasing prevalence of antibiotic resistant organisms is associated with morbidity and mortality and has led to more expensive and broad-spectrum empiric antibiotic prescribing. While serious adverse effects are infrequent, nausea, vomiting, diarrhea, headache, dizziness and skin rash are common and reduce quality of life. Therefore, reducing inappropriate use of antibiotics is a critical step in slowing the progression of current levels of resistance, preventing the emergence of new strains of antibiotic-resistant bacteria and improving quality/cost-effective care.

A recent report by the Agency for Healthcare Research and Quality reviewed strategies to improve antibiotic prescribing behavior.²¹ Quality improvement (QI) strategies were found moderately effective at reducing inappropriate antibiotic prescribing. Although no single QI strategy was clearly superior, active clinician education may be more effective in certain settings. Their report focused on acute respiratory tract infections. No previous work has been done on trying to improve antibiotic prescribing behavior in men with chronic pelvic pain syndrome. However, our results highlight the importance of this issue. Particularly, considering that there is no reason to suppose that the level of inappropriate prescribing in the VHA would be any higher than in other health care facilities.

There are limitations for this study relating to the quantification of inappropriate antibiotic use. Some of the difficulties stem from the fact that fluoroquinolones are approved for the treatment of the small minority of men with bacterial prostatitis and a specific diagnostic code to separate these patients from those with Category III prostatitis or pelvic pain syndrome does not exist.² Therefore, while prior research leads us to believe that the vast majority of men defined in our study as having chronic pelvic pain syndrome did not have identified bacterial infections at rates greater than age matched controls,¹² it is likely that some small portion of these men had positive bacterial cultures and were not diagnosed with a urinary tract infection or classified as having infectious/acute prostatitis. Efforts to modify the coding for prostatitis to include

specific reference to whether or not a positive bacterial culture was obtained would improve future quality assurance measurements and possibly prescribing patterns. Our findings of similarly high rates of fluoroquinolone use in either the chronic pelvic pain syndrome group or infectious/acute group suggest that coding issues do not explain the majority of the association, and instead antibiotics are not being restricted to those with confirmed bacterial infections. Additionally, while evidence from a consensus statement^{11;22} and an observational study^{11;23} have suggested that the use of antibiotics, particularly fluoroquinolones, may have some value in men who have never received antibiotic therapy for chronic pelvic pain syndrome, both of these prior articles stated that randomized controlled trials were needed to better address this issue. Two such trials have since been completed and both found no effect beyond that of a placebo.^{10;11} While the lack of benefit could be due to many trial participants having received previous antibiotics, these trials did not provide stratified results in men with no prior antibiotic exposure. It is likely that many men in our study also had received prior antibiotic treatment. It was not possible within our summary dataset to reliably estimate the proportion of men for whom antibiotics were being used the first time to treat their prostatitis. The current study also did not directly connect individual prescriptions to diagnoses at a specific clinical encounter, and instead relied on statistical methods to connect an individual's annual antibiotic utilization with his diagnoses from the same year.

The VHA medical system is the largest fully integrated health care system in the USA,²⁴ and as such offers advantages in terms of size and completeness of medical and pharmacy data. Because of this, we believe that the results of this study are likely valid and generalizable to many other health care systems in the USA. As the current study was part of a broad multiyear project to understand general trends in common urological conditions, we did not attempt to conduct a detailed review of the men diagnosed with prostatitis to determine their history of diagnoses, laboratory findings and detailed medication history. Future research projects could use more of the available medical record information to educate providers as well as evaluate and improve antibiotic prescribing behaviors.

CONCLUSION

Despite evidence that antibiotics are not effective in the majority of men with chronic pelvic pain syndrome, they were prescribed in 69% of men with this diagnosis even after excluding men diagnosed with infectious/acute prostatitis or urinary tract infections. Some increased use is possibly due to uncontrolled confounding by coexisting conditions or misclassification. However, the multivariable-adjusted seven-fold higher rate of fluoroquinolone use is likely due to excessive prescribing in a population unlikely to benefit from treatment. Quality improvement strategies to reduce unnecessary antibiotic use in men with chronic prostatitis are warranted.

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Figure 1. Study Patient Flow Chart for FY2003. A similar process of inclusion and exclusion was conducted for the years 1999, 2000, and 2001 and 2002.

Table 1

Fiscal Year 2003 Cohort Characteristics of Male VA Users Excluding Men with a Diagnosis of Infectious/Acute Prostatitis or Urinary Tract Infection

	Chronic Pelvic Pain Syndrome Diagnosis	
	Yes (n=23,037)	No (n=4,603,184)
Age (%)		
<50	11%	16%
50s	27%	24%
60s	28%	20%
70s	27%	28%
80 and older	7%	12%
Race/Ethnicity (%)		
White	61.8%	58.1%
Black	12.4%	9.4%
Hispanic	2.9%	2.1%
Other	1.0%	0.9%
Not Reported	22.0%	29.4%
Number of Comorbid Conditions (%)		
0	24%	32%
1	35%	31%
2 or more	41%	37%
Fluoroquinolone Prescription (%)	49%	5%
Oral Antibiotic Prescription (%)	69%	14%

Table 2
Association between Chronic Pelvic Pain Syndrome and Fluoroquinolone Use among VA Users Excluding Men with a Diagnosis of Infectious/Acute Prostatitis or Urinary Tract Infection

FY	Prevalence of Chronic Pelvic Pain Syndrome	Adjusted* Prevalence Ratio (95% CI)	Adjusted* PAR	Men with a Prescription(s)	Attributable Men with Prescription(s)
2003	0.50%	7.86 (7.76, 7.95)	3.30%	231,113	7,635
2002	0.51%	7.72 (7.62, 7.82)	3.30%	218,276	7,214
2001	0.55%	7.29 (7.20, 7.39)	3.36%	206,861	6,948
2000	0.54%	7.21 (7.11, 7.32)	3.24%	174,899	5,674
1999	0.56%	7.54 (7.42, 7.66)	3.54%	143,945	5,091
					Total=32,562

* Adjusted for age, race/ethnicity and number of comorbidities

Association between Chronic Pelvic Pain Syndrome and Antibiotic Prescriptions among VA Users Excluding Men with a Diagnosis of Infectious/Acute Prostatitis or Urinary Tract Infection and Excluding Men with a Fluoroquinolone Prescription

Table 3

FY	Prevalence of Chronic Pelvic Pain Syndrome	Adjusted* Prevalence Ratio (95% CI)	Adjusted* PAR	Men with a Prescription(s)	Attributable Men with Prescription(s)
2003	0.27%	3.57 (3.51, 3.63)	0.68%	412,693	2,814
2002	0.28%	3.50 (3.45, 3.56)	0.69%	417,411	2,896
2001	0.31%	3.28 (3.23, 3.33)	0.71%	426,074	3,004
2000	0.31%	3.10 (3.06, 3.14)	0.66%	427,677	2,802
1999	0.34%	2.76 (2.73, 2.79)	0.59%	448,646	2,636
					Total=14,153

* Adjusted for age, race/ethnicity and number of comorbidities