Infection Related Hospitalizations after Prostate Biopsy in a Statewide Quality Improvement Collaborative

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Purpose: While transrectal prostate biopsy is the cornerstone of prostate cancer diagnosis, serious post-biopsy infectious complications are reported to be increasing. A better understanding of the true prevalence and microbiology of these events is needed to guide quality improvement in this area and ultimately better early detection practices.

Materials and Methods: Using data from the MUSIC registry we identified all men who underwent transrectal prostate biopsy at 21 practices in Michigan from March 2012 to June 2013. Trained data abstractors recorded pertinent data including prophylactic antibiotics and all biopsy related hospitalizations. Claims data and followup telephone calls were used for validation. All men admitted to the hospital for an infectious complication were identified and their culture data were obtained. We then compared the frequency of infection related hospitalization rates across practices and according to antibiotic prophylaxis in concordance with AUA best practice recommendations.

Results: The overall 30-day hospital admission rate after prostate biopsy was 0.97%, ranging from 0% to 4.2% across 21 MUSIC practices. Of these hospital admissions 95% were for infectious complications and the majority of cultures identified fluoroquinolone resistant organisms. AUA concordant antibiotics were administered in 96.3% of biopsies. Patients on noncompliant antibiotic regimens were significantly more likely to be hospitalized for infectious complications (3.8% vs 0.89%, p = 0.0026).

Conclusions: Infection related hospitalizations occur in approximately 1% of men undergoing prostate biopsy in Michigan. Our findings suggest that many of these events could be avoided by implementing new protocols (eg culture specific or augmented antibiotic prophylaxis) that adhere to AUA best practice recommendations and address fluoroquinolone resistance.

Key Words: prostate, biopsy, infection, complications, anti-bacterial agents

Abbreviations and Acronyms

AUA = American Urological Association

FQR = fluoroquinolone resistance

MUSIC = Michigan Urological Surgery Improvement Collaborative

PO = orally

PSA = prostate specific antigen

TMP-SMX = trimethoprim/sulfamethoxazole

TRUS = transrectal ultrasound

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More than 1 million TRUS guided biopsies of the prostate are performed in the United States every year.[1] Generally well tolerated, some of these procedures are nonetheless associated with anxiety, physical discomfort, self-limited bleeding and occasional urinary retention.[1,2] While rates of mild complications have been stable over time, the incidence of serious infectious complications is reported to be increasing, predominantly due to

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antibiotic resistant organisms such as fluoroquinolone resistant Escherichia coli.[1,3,4] These infections often lead to significant morbidity and expensive hospitalizations.[5,6] Likewise, the increasing frequency of such events is cited as additional support for the view that the harms outweigh the potential benefits of routine prostate cancer screening.[2]

Given these emerging concerns, reducing serious infections after transrectal prostate biopsy was identified as an initial priority of the Michigan Urological Surgery Improvement Collaborative. However, as a first step toward quality improvement in this area, there is a need to better understand the true incidence of serious post-biopsy infections. In addition, clinical details regarding the microbiology of such infections are essential to determine whether the frequency of these events might be modified by specific strategies designed to address FQR.

In this context we report and compare baseline rates of infection related hospitalizations after transrectal prostate biopsy among patients treated at MUSIC practices, as well as details from culture data obtained during these hospital admissions. We also examine baseline practice patterns for prophylactic antibiotics, including the association between compliance with best practice recommendations from the AUA and post-biopsy infection related hospitalizations.

METHODS

Michigan Urological Surgery Improvement Collaborative

Aiming to improve the quality and cost efficiency of prostate cancer care in the state of Michigan, MUSIC (www.musicurology.com) was established in 2011 with funding from Blue Cross Blue Shield of Michigan. The collaborative now includes 29 urology practices representing nearly 200 urologists from across the state. Practices participating in MUSIC employ trained clinical data abstractors to extract information from the medical record and enter standardized data elements into a web based clinical registry. Included in the registry are all men seen at participating practices with newly diagnosed prostate cancer and all patients undergoing TRUS guided prostate biopsy. The MUSIC registry contains detailed clinical and demographic information including patient age, primary insurance, PSA before biopsy, prostate size, digital rectal examination findings, number of previous biopsies, receipt of a pre-biopsy enema, and biopsy related complications and hospitalizations. The prophylactic antibiotics used for each biopsy are also recorded in the registry.

We included in this analysis all men who underwent transrectal prostate biopsy at MUSIC practices from March 2012 (start date for the registry) through June 2013 (fig. 1). To enhance the reliability of our estimates we then excluded patients from MUSIC practices that performed fewer than 30 biopsies during the study period. Each practice involved in MUSIC obtained approval for participation from their local institutional review boards. Given its quality improvement focus, participation in the collaborative was deemed exempt from institutional review board oversight in all cases.

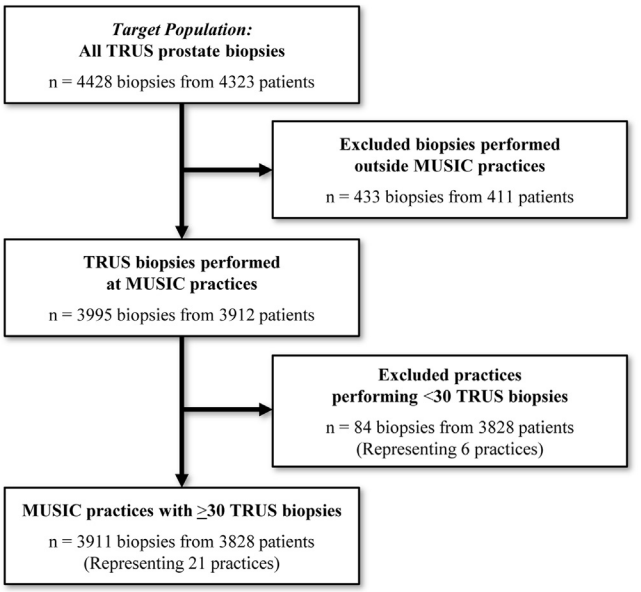

Figure 1. Flow diagram demonstrating inclusion and exclusion criteria for patients who underwent TRUS guided prostate biopsy at MUSIC practices from March 2012 through June 2013.

Primary Outcome

From the MUSIC registry we identified all patients who were hospitalized within 30 days of a prostate biopsy. For this group of patients we worked with local data abstractors to perform a more detailed medical record review to determine the reason(s) for hospitalization. We classified infection related hospitalizations as those with fever, sepsis, urinary tract infection or acute prostatitis as an admitting diagnosis. Additionally, whenever possible, all culture and sensitivity results from urine and/or blood specimens obtained during hospitalization were acquired and reviewed.

Data Validation

As a general quality assurance step for data in the MUSIC registry, members of the Coordinating Center conduct regular on-site audits at each participating practice. The goal of these visits is to ensure the appropriate identification of cases and the integrity of data entered into the registry. In addition, we performed 2 separate validation steps for the hospitalization data available in the registry. 1) We compared registry and claims data for 383 patients with Blue Cross Blue Shield of Michigan as the primary payer who underwent biopsy at MUSIC practices from March through October 2012. For this validation sample all biopsy attributable emergency room visits and hospitalizations identified in the claims data were in complete concordance with data in the clinical registry. 2) Local data abstractors at 3 MUSIC practices completed followup telephone calls to a sample of 127 patients who underwent biopsy between December 2012 and January 2013. Among

the 101 patients (80%) contacted successfully, all patient reported biopsy related emergency room visits and hospitalizations had been reported to the registry.

Statistical Analyses

We first generated descriptive summary statistics for all patients in the analytic sample. We then used appropriate univariate statistical tests to compare the frequency of infection related hospitalization rates across MUSIC practices and according to receipt (or lack thereof) of antibiotic prophylaxis in concordance with best practice recommendations from the AUA.[7] All statistical testing was performed at the 5% significance level (SAS® v9.2).

RESULTS

Table 1 presents characteristics of the 3,812 men undergoing 3,911 transrectal prostate biopsies at 21 MUSIC practices from March 2012 through June 2013. Median age at the time of biopsy was 64 years (range 45 to 83). Median PSA was 5.3 ng/ml and 76% of patients had a PSA greater than 4 ng/ml before prostate biopsy.

From the 3,911 biopsies performed in MUSIC practices the overall 30-day hospital admission rate following prostate biopsy was 0.97% (95% CI ± 0.31%). As illustrated in figure 2 hospitalization rates by practice varied from 0% in 6 practices to 4.2% in a single practice. However, these differences were not statistically significant ($p = 0.16$). Of the hospital admissions 92% (35 of 38) were for infectious complications. We identified no significant associations between our primary outcome (ie post-biopsy infectious hospitalizations) and performance of a pre-biopsy enema ($p = 0.18$), prior prostate biopsy ($p = 0.087$) or prostate size ($p = 0.81$).

Of the 35 patients with infection related hospitalizations culture data were available for 33. Among this group E. coli was identified in the cultures from 30 patients (91%) while Pseudomonas aeruginosa was identified in the remaining 3 (9%). Growth of organisms with FQR was confirmed in 26 patients (79%). While testing for FQR was present in all culture data, there were differences in resistance testing for other antibiotics. For instance, resistance to trimethoprim-sulfamethoxazole and gentamicin was observed in 39% (11 of 28) and 16% (5 of 32) of patients, respectively.

Complete data for antibiotic prophylaxis were available for 92% (3,601 of 3,911) of the biopsies analyzed. A fluoroquinolone, alone or combined with another antibiotic, was prescribed in 96% of cases. Compared with the AUA best practice recommendations, 3.7% of biopsies were identified as being noncompliant (fig. 3). The 3 most commonly prescribed noncompliant antibiotics were gentamicin alone (54 biopsies), TMP-SMX (31) and oral cefuroxime (11). Details of the remaining noncompliant regimens are provided in table 2. Notably the patients on noncompliant regimens were significantly more likely to be hospitalized after prostate biopsy than those whose antibiotics were in compliance with AUA best practice recommendations (3.8% vs 0.89%, $p = 0.0026$).

Table 1. *Patient characteristics*

No. biopsies at MUSIC practices	3,911	
No. unique pts	3,828	
Median pt age (range)	64	(45–83)
No. insurance category (%):*		
Private	1,869	(48.0)
Public	1,403	(36.0)
Uninsured/no insurance/self-pay	41	(1.1)
Other	585	(15.0)
No. ng/ml PSA at biopsy (%):†		
Less than 4	936	(24.0)
4–10	2,421	(62.1)
Greater than 10	541	(13.9)
Median ng/ml PSA at biopsy (range)	5.30	(0.1–1,953)
No. documented abnormal digital rectal examination (%)‡	883	(24.1)
No. cc prostate size (%):§		
Less than 30	875	(22.7)
30–60	2,058	(53.6)
Greater than 60	909	(23.7)
No. previous TRUS guided biopsies (1+)(%)‖	687	(18.0)
No. received pre-biopsy enema (%)¶	2,260	(72.5)
No. prescribed AUA compliant antibiotics (%)**	3,469	(96.3)

* Missing for 13 biopsies.
† Missing for 13 biopsies.
‡ Missing for 249 biopsies.
§ Missing for 69 biopsies.
‖ Missing for 100 biopsies.
¶ Missing for 794 biopsies.
** Missing for 310 biopsies.

DISCUSSION

In a statewide quality improvement collaborative 1% of men who underwent transrectal prostate biopsy from March 2012 through June 2013 were hospitalized within 30 days as a consequence of a procedure related complication. The majority of these hospitalizations were due to infectious causes, with culture data most often confirming the presence of fluoroquinolone resistant organisms. Notably the rates of hospitalization were significantly higher for men who received antibiotic prophylaxis that was not in compliance with best practice recommendations from the AUA.

While we observed some variation in the frequency of post-biopsy hospitalization across MUSIC practices, the aggregate rate in the state of Michigan is not as high as that reported in other recent studies from the United States and Europe.[1,5,8,9] There are several reasons why such discrepancies may exist. There may be differences in patient characteristics including risk factors for infection (eg diabetes, prior antibiotic therapy, medication allergies) among the samples analyzed. In addition, there may be overestimation of hospitalization rates attributable to biopsy from studies based on administrative

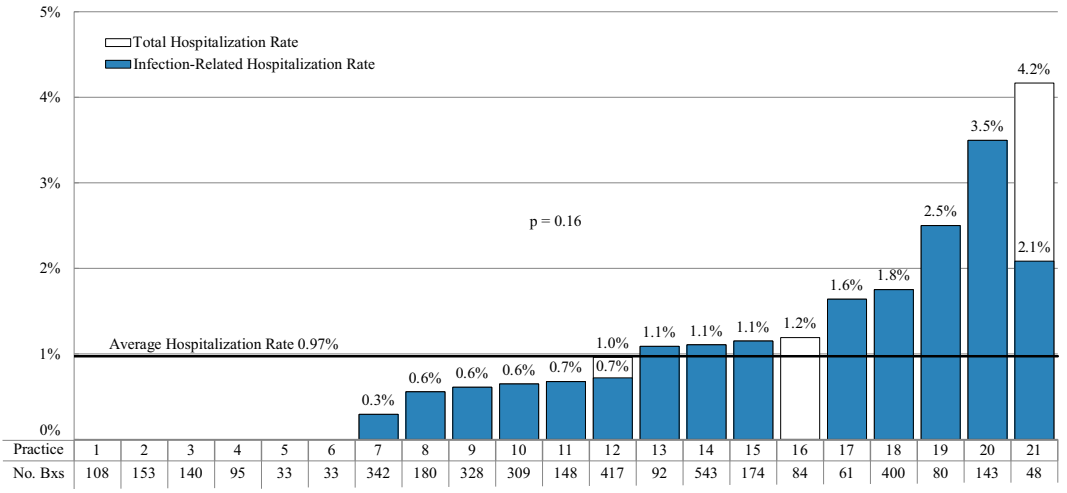

Figure 2. Hospitalization rates within 30 days after transrectal prostate biopsy (*Bx*) across MUSIC practices (March 2012 through June 2013). Blue area represents infection related hospitalizations. Overall biopsy related hospitalization rate for entire study population was 0.97%. Variability among practices was not statistically significant.

or claims data, rather than a clinical registry. These differences notwithstanding, the fact that data in the MUSIC registry are prospectively collected and regularly audited, and that we validated the occurrence of hospitalization for a sample of patients, lead us to believe that the results reported here provide accurate estimates for the risk of infection related hospitalization in the state of Michigan.

This analysis does have several limitations. Although we limited our sample to practices that performed at least 30 biopsies during the interval of interest, the absence of a statistically significant difference in hospitalization rates among practices may still reflect insufficient power. Another limitation is that we did not fit multivariate models to account for potential differences in patient characteristics across MUSIC practices. This decision was based on statistical limitations in the number of covariates that can be included in models with a small number of events for the outcome variable (in this case, hospitalizations). Nonetheless, this concern is mitigated by the fact that we noted no differences among practices in univariate analyses. The planned changes in the AUA best practice recommendations for antibiotic prophylaxis are also a limitation.[10] In early 2014 recommendations from the AUA will be modified to include oral trimethoprim-sulfamethoxazole and parenteral gentamicin monotherapy as acceptable alternatives to fluoroquinolone

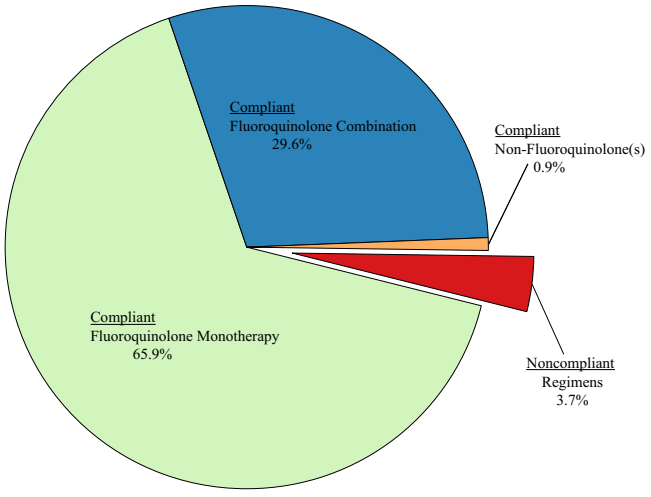

Figure 3. Prophylactic antibiotic use rates across MUSIC practices according to compliance with AUA best practice recommendations. Hospitalization rates for patients who received compliant vs noncompliant antibiotics were 0.89% vs 3.8%, respectively ($p = 0.0026$).

Table 2. *Noncompliant prophylactic antibiotic regimens*

					No. Biopsies
Gentamicin					54
TMP-SMX					31
Cefuroxime PO					11
Cephalexin PO					9
Amoxicillin					4
Ampicillin	+	gentamicin			4
Gentamicin	+	TMP-SMX			3
Amoxicillin	+	ampicillin	+	gentamicin	2
Ampicillin					2
Cefuroxime PO	+	gentamicin			2
Cephalexin PO	+	gentamicin			2
Amoxicillin	+	gentamicin			1
Ampicillin	+	cephalexin PO	+	gentamicin	1
Cefuroxime PO	+	gentamicin	+	TMP-SMX	1
Cefuroxime PO	+	TMP-SMX			1
Clindamycin					1
Gentamicin	+	unknown			1
Nitrofurantoin					1
Piperacillin/tazobactam					1
Total					132

prophylaxis. Even so, reclassification of cases based on these emerging recommendations would have yielded an even greater difference in the likelihood of hospitalization between patients on compliant vs noncompliant prophylactic regimens. While the MUSIC registry includes information about the occurrence and reasons for post-biopsy hospitalization, it does not include data on downstream sequelae of these events such as intensive care unit admission or mortality. A final limitation is that the number of biopsy cores was only available for patients diagnosed with prostate cancer. Accordingly we were unable to examine the correlation between the number of cores sampled and the likelihood of an infectious complication. However, more recently we modified the MUSIC data collection protocol to record this information for patients with biopsies negative for cancer, thereby facilitating future analyses around this important question.

Despite these limitations, our findings have important implications for improving patient outcomes with transrectal prostate biopsy. While it is important to acknowledge that not all biopsy related complications can be avoided, these data from MUSIC underscore the important points that most of the serious complications (ie those resulting in hospitalization) are infectious in etiology and that many of these events are potentially preventable. Along these lines, it appears that strict adherence with the AUA best practice recommendation for antibiotic prophylaxis may be an important first step toward reducing the frequency of these events. However, an important blind spot for the current first line recommendations is the increasing prevalence of FQR. As such, additional strategies are needed to address this concern.

There is increasing evidence supporting the use of screening rectal cultures to identify patients harboring fluoroquinolone resistant organisms before a biopsy, thereby allowing the administration of tailored (ie culture specific) antibiotic prophylaxis that is also in compliance with current best practice recommendations.[7,11] An alternative and perhaps more pragmatic approach would be to augment standard fluoroquinolone prophylaxis with additional agents (eg gentamicin, cefazolin) that are most likely to cover resistant organisms. This approach has also shown promise in reducing hospitalization rates,[12–14] and selection of the additional prophylactic agent may best be determined by review of local antibiograms in conjunction with colleagues in infectious diseases. While our data indicate that fluoroquinolone resistance is a key risk factor for post-biopsy hospitalizations (and, therefore, an important target for immediate quality improvement interventions), evidence of resistance to other agents like TMP-SMX and gentamicin underscores the need to regularly review local antibiotic resistance patterns when selecting optimal augmented prophylaxis regimens.

From a health policy perspective the recent recommendation against routine prostate cancer screening from the U.S. Preventive Services Task Force has generated increased scrutiny, not only of the indications for but also of the safety of prostate biopsy.[2] This study confirms the potential for serious infectious complications after prostate biopsy, but also highlights a pathway forward (ie refined approaches to antibiotic prophylaxis) that could ultimately enhance the safety of prostate cancer screening at a population level. In addition to enhancing patient safety, avoidance of these events could yield substantial cost savings to the health care system as post-biopsy related hospital admissions have been shown to range from $2,400 to more than $12,000 per admission.[12,13]

In response to the data presented here all MUSIC practices are now implementing culture specific or augmented antibiotic prophylaxis (or both) with the goal of achieving optimal adherence with AUA best practices, while also accounting for FQR. Furthermore, we are now collecting data around other established risk factors for biopsy related infections including, among others, diabetes, prior antibiotic treatment, recent international travel and employment in a health care facility. Future studies will assess the degree to which this intervention reduces the frequency of post-biopsy hospital admissions and, in turn, increases the safety and acceptability of transrectal prostate biopsy.

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