

# Evaluation of a needle disinfectant technique to reduce infection-related hospitalisation after transrectal prostate biopsy

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## Objectives

To determine whether a needle disinfectant step during transrectal ultrasonography (TRUS)-guided prostate biopsy is associated with lower rates of infection-related hospitalisation.

## Patients and Methods

We conducted a retrospective analysis of all TRUS-guided prostate biopsies taken across the Michigan Urological Surgery Improvement Collaborative (MUSIC) from January 2012 to March 2015. Natural variation in technique allowed us to evaluate for differences in infection-related hospitalisations based on whether or not a needle disinfectant technique was used. The disinfectant technique was an intra-procedural step to cleanse the biopsy needle with antibacterial solution after each core was sampled (i.e., 10% formalin or 70% isopropyl alcohol). After grouping biopsies according to whether or not the procedure included a needle disinfectant step, we compared the rate of infection-related hospitalisations within 30 days of biopsy. Generalised estimating equation models were fit to adjust for potential confounders.

## Results

During the evaluated period, 17 954 TRUS-guided prostate biopsies were taken with 5 321 (29.6%) including

a disinfectant step. The observed rate of infection-related hospitalisation was lower when a disinfectant technique was used during biopsy (0.60% vs 0.90%;  $P = 0.04$ ). After accounting for differences between groups the adjusted hospitalisation rate in the disinfectant group was 0.85% vs 1.12% in the no disinfectant group (adjusted odds ratio 0.76, 95% confidence interval 0.50–1.15;  $P = 0.19$ ).

## Conclusions

In this observational analysis, hospitalisations for infectious complications were less common when the TRUS-guided prostate biopsy included a needle disinfection step. However, after adjusting for potential confounders the effect of needle disinfection was not statistically significant. Prospective evaluation is warranted to determine if this step provides a scalable and effective method to minimise infectious complications.

## Keywords

prostate cancer, prostate biopsy, infection, quality improvement

## Introduction

Infectious complications from transrectal prostate biopsies are estimated to occur after 5–7% of biopsies and can lead to significant morbidity and substantial cost [1]. Although less common, more severe infections requiring hospitalisation occur after 1–3% of biopsies and are associated with even greater human and financial costs [1]. Fluoroquinolone resistance has been shown to be a contributing factor to these infections and modifications to prophylactic pathways

including rectal culture-directed antibiotics and addition of non-fluoroquinolone augmented prophylactic regimens have led to decreases in infectious complications [2–4]. These strategies represent important quality initiatives that have improved patient care. However, implementation challenges, risks of further resistance, and antibiotic side-effects may leave room for even greater improvement [1].

An ideal quality improvement strategy to reduce prostate biopsy related infections would be effective, inexpensive, easy

to implement, and safe, whilst not augmenting antibiotic resistance. Non-antibiotic strategies of varied effectiveness, such as rectal preparation and transperineal biopsy, have previously been investigated but have not been widely adopted [5,6]. More recently, the role of intra-procedural needle disinfection using 10% formalin during prostate biopsy was evaluated as a means to potentially reduce intra-prostatic bacterial inoculation and thus diminish the risks of UTI and/or sepsis after biopsy [7]. That single-centre study did not show a statistically significant benefit to needle disinfection; however, the simplicity of this intervention is compelling and warrants further investigation.

In this context, we evaluated the impact of an intra-procedural needle disinfectant step on the rate of infection-related hospitalisation within 30 days of TRUS-guided prostate biopsy for patients managed in the diverse academic and community practices comprising the Michigan Urological Surgery Improvement Collaborative (MUSIC). Understanding whether addition of intra-procedural needle disinfection to TRUS-guided prostate biopsy reduces infection-related complications will help urologists working to optimise the safety of prostate biopsy.

## Patients and Methods

### Data Source

MUSIC was established in 2011 in partnership with Blue Cross Blue Shield of Michigan. The quality improvement collaborative currently comprises 43 urology practices with >240 urologists, which represents nearly 90% of the urologists in the State. For all prostate biopsies taken across the collaborative, trained data abstractors review all clinical documentation related to a prostate biopsy and follow-up, and prospectively enter into a web-based clinical registry a standardised set of demographic and clinicopathological data pertaining to biopsy findings and complications occurring within 30 days. Prior reports have described the MUSIC's data quality control activities, including annual data audits at each practice and validation analyses based on insurance claims [4,8]. Each MUSIC practice obtained an exemption or approval for collaborative participation from a local Institutional Review Board.

### Patients and Comparison Groups

The cohort for this analysis included all TRUS-guided prostate biopsies taken in participating MUSIC practices from January 2012 to March 2015. During the period evaluated, natural variation across providers and practices determined whether a disinfectant step was used or not during a given procedure. After the MUSIC Coordinating Centre verified each urologist's technique, biopsies were grouped according to whether or not a disinfectant technique was used.

## Needle Disinfectant Techniques

Urologists that used a needle disinfectant technique used one of two strategies for needle disinfection referred to hereafter as the 'formalin technique' or the 'alcohol technique'. In the formalin technique, after each core is taken, with a standard spring-loaded biopsy needle, the external sheath is withdrawn to expose the core. The needle is then submerged in a sterile specimen cup containing 10% formalin and swirled to dislodge the core and bathe the needle in the disinfectant solution (Fig. 1). Some urologists rinsed the needle in a cup of sterile saline before using it to obtain the next specimen. The alcohol technique involves 70% isopropyl alcohol as the disinfectant solution, which is used to soak a Telfa® sponge (American Surgical Company, Salem, MA, USA). After each core is obtained the external sheath is drawn back to expose the core, the needle is wiped on the alcohol soaked sponge to dislodge the core and also disinfect the needle tip (Fig. 2).

## Outcome

The primary outcome measure compared across groups was the rate of hospital admission within 30 days of biopsy for a primary diagnosis of UTI, fever, or sepsis.

## Statistical Analyses

We performed univariate comparisons of demographic and baseline clinical information for the disinfectant vs no disinfectant groups. Student's *t*-tests were used to compare continuous measures, whilst chi-squared tests were used for categorical outcomes. After comparing the rate of hospitalisation across groups, we used common statistical methods [9,10] to fit a generalised estimating equation (GEE) model with logit link to assess the independent association

Fig. 1 Demonstration of the formalin disinfectant technique.



between use of a disinfectant technique and post-biopsy infection-related hospitalisation. The model adjusted for patient age, presence of diabetes, history of prior biopsy, and whether a biopsy occurred before or after our State-wide intervention aimed at addressing fluoroquinolone resistance with either culture-directed or augmented antibiotic prophylaxis [4]. The model accounted for within-patient correlation for patients with more than one biopsy in the dataset.

Two sub-group analyses were performed. In the first sub-group analysis, we fitted a separate GEE model to a sub-cohort of biopsies where more information about other infectious risk factors was available. At the time of these procedures, a questionnaire was completed detailing whether

**Fig. 2** Demonstration of the alcohol disinfectant technique. Needle is wiped against a Telfa sponge soaked in 70% isopropyl alcohol to dislodge sampled prostate core.



a patient received antibiotics in the 6 months before biopsy, had travelled internationally in the past 6 months, or was taking immunosuppressive medications. Each of these factors was added as a dichotomous co-variate in a GEE model that also included all co-variables for the base model used in the primary analysis, and we again evaluated for an independent relationship between the disinfectant technique and infection-related hospitalisation after adjusting for these other factors. In a second sub-group analysis, the observed rate of infection-related hospitalisation was compared across study groups for the subsets of biopsies taken before and after the aforementioned State-wide antibiotic intervention that has significantly reduced infection rates across the MUSIC [4]. All statistical testing was performed using commercially available software [Statistical Analysis System (SAS) version 9.4; SAS Institute, Cary, NC, USA] at the 5% significance level.

## Results

Across 41 practices and 233 urologists, 16 920 patients underwent 17 954 TRUS-guided biopsies during the study period. Most of the biopsies were taken without a disinfectant technique (12 633, 70.4%). Amongst the biopsies taken with a disinfectant technique, the formalin technique was used in 4 870/5 321 (91.5%), with the alcohol technique used in the remaining 451 (8.5%) biopsies.

Demographic information for the study groups is reported in Table 1. The mean age was similar, at 64.1 vs 64.4 years ( $P = 0.08$ ), in the no disinfectant and disinfectant groups, respectively. Men in the needle disinfectant group were less likely to have received a prior biopsy (Table 1). Relative to biopsies taken without a disinfectant technique, a greater proportion of the biopsies using a disinfectant technique were taken after the collaborative-wide effort to reduce biopsy-related infections with use of either culture-directed or augmented antibiotic prophylaxis (87.6% vs 63.3%;  $P < 0.001$ ).

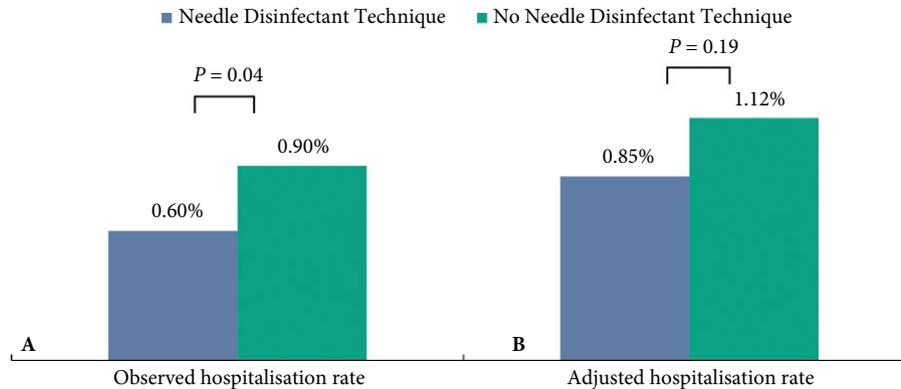
Infection-related hospitalisations were less common after biopsies that included a needle disinfectant technique, with 32 admissions (0.60%) vs 114 admissions (0.90%) for biopsies no disinfectant step [odds ratio (OR) 0.67;  $P = 0.040$ ] (Fig. 3a). There were no admissions reported for the 451 biopsies taken

**Table 1** The characteristics of patients undergoing TRUS-guided prostate biopsy with or without a needle disinfectant technique.

Variable	No disinfectant	Disinfectant	$P^*$
Number of patients	12 633	5 321	–
Age, years, mean (SD)	64.1 (8.4)	64.4 (8.3)	0.08
Patients with diabetes, $n$ (%)	1 794 (14.2)	771 (14.5)	0.99
History of prior biopsy, $n$ (%)	3 240 (25.9)	1 261 (23.9)	0.004
Number of cores sampled, mean (SD)	12.4 (3.3)	12.4 (3.8)	0.23
Biopsy occurrence after the MUSIC antibiotic intervention, $n$ (%)	7 995 (63.3)	4 660 (87.6)	<0.001

\*Student's  $t$ -test used to compare continuous measures and chi-squared test for categorical measures.

**Fig. 3** Comparison of the rate of infection-related hospitalisation after prostate biopsy: (A) observed rate (B) risk adjusted\* rate (\*adjusted for age, presence of diabetes, history of prior biopsy, and timing of biopsy related to collaborative-wide antibiotic initiative). Chi-squared test used to compare differences across groups.



using 70% isopropyl alcohol as a disinfectant. There were no deaths in either group, or any reported adverse events related to the use of needle disinfectant.

Table 2 reports findings from our multivariable analyses. Men with diabetes and those undergoing biopsy prior to the MUSIC's antibiotic intervention were more likely to be hospitalised for an infection after biopsy. After adjusting for the covariates in Table 2, there was no longer a statistically significant difference in hospitalisation rates across study groups (adjusted OR 0.76, 95% CI: 0.50–1.15;  $P = 0.19$ ; Fig. 3B).

In the first sub-group analysis there were 8 382 biopsies included. After adjusting for the factors included in the primary analysis, as well as for use of antibiotics during the 6 months before biopsy, recent international travel, and whether a patient was taking immunosuppressants at the time of biopsy, there was not a statistically significant difference in hospitalisation rates attributable to use of a needle disinfectant technique (adjusted OR 0.86, 95% CI: 0.47–1.58;  $P = 0.64$ , reference = no use of disinfectant). None of the

added risk factors was a significant predictor of hospitalisation in this sub-cohort, with the following adjusted ORs for hospitalisation: (i) using antibiotics in 6 months before biopsy (adjusted OR 1.20, 95% CI: 0.67–2.17;  $P = 0.54$ ), (ii) recent international travel (adjusted OR 1.72, 95% CI: 0.81–3.67;  $P = 0.16$ ), and (iii) use of immunosuppressants at time of biopsy (adjusted OR 1.77, 95% CI: 0.55–5.71;  $P = 0.33$ ).

A second sub-group analysis of the 5 299 biopsies taken before the MUSIC antibiotic intervention showed no significant difference in hospitalisation rates when 661 disinfectant biopsies (five hospitalisations, rate 0.76%) were compared to 4 638 taken without disinfectant (56 hospitalisations, rate 1.21%;  $P = 0.31$ ; Fig. 4). Similarly, there was no difference in rate of infection-related hospitalisation when comparing 4 660 disinfectant biopsies (27 hospitalisations, rate 0.58%) to 7 995 biopsies taken without disinfectant (58 hospitalisations, rate 0.73%;  $P = 0.33$ ) after the collaborative-wide antibiotic intervention (Fig. 4).

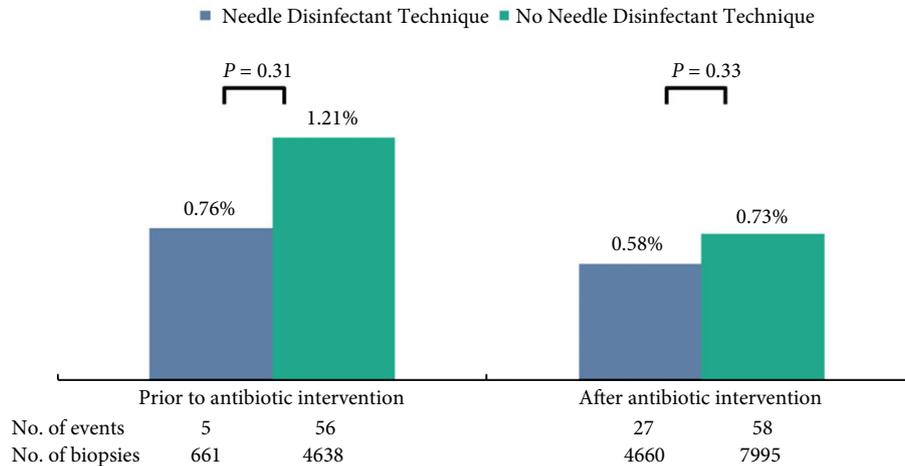
## Discussion

In our present evaluation of nearly 18 000 TRUS-guided prostate biopsies taken in Michigan, ~30% of TRUS-guided prostate biopsies used a needle disinfectant step. Amongst this large sample of patients from academic and community urology practices, the rate of infection-related hospitalisation within 30 days of biopsy was lower amongst biopsies where a disinfectant technique was used. However, after accounting for potential confounders, adjusted hospitalisation rates no longer differed across study groups. A sub-group analysis of the biopsies taken before implementation of a State-wide antibiotic intervention showed that there was no significant difference in hospitalisation rates during that period. Similarly, when examining biopsies taken after the antibiotic intervention, hospitalisation rates did not differ significantly.

**Table 2** Results of multivariable regression analysis to predict probability of hospitalisation after prostate biopsy.

Variable	Adjusted OR (95% CI)	P
Disinfectant technique used		
No	Reference	
Yes	0.76 (0.50–1.15)	0.19
Age (per year)	0.99 (0.96–1.01)	0.18
Diabetes present		
No	Reference	
Yes	1.87 (1.25–2.78)	0.002
History of prior biopsy		
No	Reference	
Yes	0.94 (0.63–1.39)	0.75
Study period		
Prior to antibiotic intervention	Reference	
After antibiotic intervention	0.61 (0.43–0.87)	0.006

**Fig. 4** Comparison of the observed rate of infection-related hospitalisation for biopsies performed before and after the collaborative-wide antibiotic intervention. Chi-squared test used to compare differences across groups.



Our present findings build on a single-centre investigation that introduced the concept of the formalin disinfectant technique [7]. Issa et al. [7] reported a 0.30% rate of urinary infection or sepsis in 1 642 prostate biopsies taken with a 10% formalin needle disinfection step. Despite a very low rate of infection, the authors did not find a statistically significant reduction in infections when disinfectant biopsies were compared to a cohort of 990 biopsies taken in the same centre without needle disinfection (infection rate 0.80%;  $P = 0.13$ ). To further evaluate a mechanistic explanation for a protective effect of formalin, *in vitro* experimentation has also been used to show that treating MacConkey agar dishes with 10% formalin for 10 s prevents growth of fluoroquinolone resistant *E. Coli* in the culture media and further, that needle-tips from transrectal biopsies where a needle disinfectant technique is used do not demonstrate bacterial growth [7]. In the present analysis, we found a lower rate of hospitalisation when the biopsy protocol included a disinfectant step (0.60% vs 0.90%;  $P = 0.04$ ); however, given the observational nature of our investigation it was necessary to evaluate for alternative explanations for our findings. As noted, the MUSIC led a State-wide antibiotic initiative associated with notable reductions in infection rates during the period evaluated in the present analysis [4]. Given the impact of the antibiotic initiative on the outcome of interest, it was important to account for this and other important co-variables in evaluating the disinfectant technique. After accounting for these factors, there was not a statistically significant difference in hospitalisation attributable to the use of a disinfectant technique.

The included sub-analyses were performed to provide more detail on the impact of needle disinfection whilst accounting for the collaborative-wide antibiotic intervention in a different way. In looking at only the biopsies taken before the changes

to antibiotic prophylaxis, the absolute difference in hospitalisation rates was larger than when looking at the entire cohort (1.21% for biopsies that did not use disinfectant vs 0.76% for those that did). Statistical significance may have been precluded due to the small number of events in both groups and the relatively limited number of biopsies (661) taken with disinfectant before the antibiotic intervention. After our antibiotic intervention, we found the rate of infection-related hospitalisation dropped to 0.73% amongst biopsies taken without a disinfectant technique. Despite a larger cohort of disinfectant biopsies in this period, the rate of hospitalisation (0.58%) was not significantly lower when compared to biopsies taken without disinfectant. We hypothesise that the impact of disinfectant may be masked in the period after the antibiotic intervention given the substantially lower rate of infection in the no disinfectant group. Disinfectant techniques may have protective effects; however, we are not able to show this in a statistically significant manner given the relative rarity of events and the confounding influence of our antibiotic State-wide guideline intervention.

Before considering increased adoption or further investigation, potential safety concerns of needle disinfection should be considered. Formalin is an aqueous solution of formaldehyde, recognised by the WHO and Environmental Protection Agency (EPA) as a chemical irritant and possible carcinogen [11,12]. The average formaldehyde exposure from a standard 12-core biopsy using a disinfectant technique has been estimated at 3.9 mg [7]. This is significantly lower than the maximum exposure threshold set by the EPA at 0.2 mg/kg/day (i.e. for a 70 kg person maximum daily exposure threshold = 14 mg) [11]. Formaldehyde exposure is common in normal human living environments, and the exposure from a single prostate biopsy is in range with the degree of

exposure humans experience from common sources on a daily basis (Table S1 [7,11,12]). Although, our present investigation did not directly evaluate exposure or safety, the published data suggests the potential for harmful effects from a formalin disinfectant step would be remote. Incorporating a saline rinse after formalin disinfection may further reduce the load inoculated to the prostate, and is used as an adjunct by some urologists in the MUSIC. Similarly, it is unlikely that isopropyl alcohol is of substantial concern for patient safety. Isopropyl alcohol is a common over-the-counter disinfectant with a proven safety record when used in small volumes, and according to the Centers for Disease Control it is not a human carcinogen [13]. Across our collaborative there have been no reports of biopsy complications or unintended events, such as granulomatous prostatitis or impaired pathological assessment, which could be linked to the use of a disinfectant technique.

Our present findings should be considered in the setting of several limitations. First, this is an observational analysis where the disinfectant technique was not strictly standardised (e.g., dwell time in disinfectant solutions was per clinician routine and may vary across providers) and, as detailed, an antibiotic-based quality improvement initiative was implemented during the period evaluated. Further, it is possible other co-variables (e.g., antibiotic type) that we are not able to account for may influence the outcome as well. Although, a randomised controlled trial would be beneficial for establishing whether the disinfectant technique is protective, it would need to be a large trial given the rarity of infection-related hospitalisations after prostate biopsy (e.g., assuming a hospitalisation rate of 1.2% in the control group, and the disinfectant technique could reduce the event rate by 0.5%, it would require nearly 6 000 patients in each group to detect the effect of disinfectant with a power of 0.8). In the context of limited resources, we felt an observational analysis would be an important first-step in determining whether further consideration of disinfectant techniques is warranted. Second, physician self-report for disinfectant utilisation was used to group biopsies into the study groups. The MUSIC Coordinating Centre verified behaviour for each urologist. Although there is possibility of mis-grouping of some of the biopsies, we anticipate the impact of mis-grouping would be small.

These limitations notwithstanding and in the context of concerns about both rising antibiotic resistance and the safety of extended fluoroquinolone therapy [14] there are important implications to this work. Avoiding infectious hospitalisation, the associated morbidity, and costs via a simple, low-risk modification to biopsy procedures represents a potential for improvement with minimal disadvantages. Furthermore, as needle disinfection does not increase antibiotic utilisation; it may represent an important adjunct or alternative to the antibiotic-based quality improvement strategies that continue

to carry the potential for worsening antibiotic resistance despite laudable reductions in post-biopsy infections shown within our collaborative [4] and elsewhere [3]. This, to our knowledge, represents the largest evaluation of the needle disinfectant technique to date. In the absence of a statistically significant difference in adjusted hospitalisation rates, we cannot state that needle disinfection should be a new standard, but feel it may remain prudent to incorporate needle disinfection into biopsy regimens given the potential for benefit with little to no risk. Further, we feel this investigation provides evidence regarding the necessity of a prospective study of this technique in order to limit confounding and more definitively determine if there is a benefit to needle disinfection.

Moving forward, we have planned further prospective investigation of this technique within the MUSIC, where several pilot sites have changed practice to adopt a disinfectant technique. Analysis of outcomes before and after this change within pilot sites will afford us further information on the impact of needle disinfection. We are also interested in the sub-population of biopsies being taken with isopropyl alcohol as a disinfectant. Given patients in this group had no infectious hospitalisations during the study; we continue to monitor the impact of this method to determine if it is possibly superior to the formalin technique.

In conclusion, men undergoing TRUS-guided prostate biopsy within the MUSIC were less commonly hospitalised for infectious complications within 30 days of biopsy when their procedure included a needle disinfectant technique using either 10% formalin or 70% isopropyl alcohol. Despite differences in hospitalisation rates, multivariable analyses revealed no significant difference in hospitalisation rates attributable to the use of a needle disinfectant after accounting for potential confounders. Despite these findings, needle disinfection may remain a scalable, low-risk intervention to reduce infectious complications after prostate biopsy that warrants further investigation.

## Acknowledgements

The authors acknowledge the significant contributions of the clinical champions, urologists, administrators and data abstractors in each participating MUSIC practice (details around specific participating urologists and practices can be found at [www.musicurology.com](http://www.musicurology.com)), as well as members of the MUSIC Coordinating Center at the University of Michigan. In addition, we would like to acknowledge the support provided by David Share, MD, MPH; Tom Leyden, MBA; Rozanne Darland, BSBA; David Bye II, MBA; and the Value Partnerships programme at the Blue Cross and Blue Shield of Michigan (BCBSM).

## Funding/Support

Support for the MUSIC is provided by BCBSM as part of the BCBSM Value Partnerships programme. This work was also funded by grant 1T32-CA180984 (GBA) from the National Cancer Institute.

## Role of the Funder/Sponsor

Neither BCBSM nor the National Cancer Institute had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Conflict of Interest

None.

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**Abbreviations:** EPA, Environmental Protection Agency; GEE, generalised estimating equation; MUSIC, Michigan Urological Surgery Improvement Collaborative; OR, odds ratio.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1** Quantity of human formaldehyde exposure from common environmental sources.