

Michigan Urological Surgery Improvement Collaborative (MUSIC)

Prostate Biopsy Toolkit

MUSIC

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Executive Summary

Purpose: With the objective of improving prostate biopsy practice, the Michigan Urological Surgery Improvement Collaborative (MUSIC) assessed if use of a needle disinfectant technique, or alternate prophylactic fluoroquinolone antibiotics reduced sepsis related hospitalization after prostate biopsy. Repeat prostate biopsy practices within MUSIC for patients with pre-malignant pathology were also assessed and compared to recommendations from national guidelines.

Methods: A needle disinfectant technique during prostate biopsy involves the use of either 10% formalin (with or without saline rinse) or 70% alcohol to disinfect the needle tip following each core biopsy. Patients undergoing biopsy in MUSIC from March 2012 to April 2015 were analyzed based on use of augmented antibiotics, rectal swab-culture directed antibiotics, use of ciprofloxacin vs. levofloxacin antibiotic prophylaxis, and needle disinfectant technique (formalin, formalin+saline, or alcohol) for the risk of developing sepsis related hospitalization. Repeat biopsy practice in men after initial biopsy showed multifocal high-grade prostatic intraepithelial neoplasia (HGPIN), or atypical small acinar proliferation (ASAP), were also assessed. The rationale of a bundled approach to reducing sepsis from prostate biopsy is considered, and videos detailing each needle disinfectant technique are provided.

Results: Use of a disinfectant during prostate biopsy (either 10% formalin or 70% alcohol) was associated with a hospitalization rate of 0.54%, compared to 0.92%, when no disinfectant was used ($p=0.019$). In 1,642 patients receiving prophylaxis with levofloxacin the hospitalization rate was 0.26%, compared to 0.81% in 9,916 patients receiving ciprofloxacin prophylaxis ($p=0.004$). MUSIC data has shown that pre and post intervention to the MUSIC biopsy antibiotic pathway has shown lower rates by physicians including a needle disinfectant into their biopsy protocol. Of 364 patients with ASAP or multifocal HGPIN, only 30% of patients underwent a repeat biopsy. On multivariate analysis, the probability of finding cancer on repeat biopsy after multifocal HGPIN was 13.8% (95% CI 10-20%) compared to 35.9% (95% CI 26-47%) for ASAP.

Conclusions: A prostate biopsy infection bundle incorporating updated MUSIC antibiotic pathways incorporating levofloxacin as an alternate fluoroquinolone, the MUSIC biopsy check list, urinalysis prior to biopsy, and use of needle disinfectant technique is recommended to lower risk of sepsis related hospitalization. Further, MUSIC recommends a target rate for repeat biopsy of 70% in patients with ASAP.



Prostate Biopsy Infection Bundle

The Michigan Urological Surgery Improvement Collaborative (MUSIC) identified reducing serious infections after transrectal prostate biopsy as a quality improvement priority. Given the significant human and financial costs associated with prostate biopsy related hospitalizations, MUSIC developed antibiotic guidelines aimed at addressing fluoroquinolone resistance as a risk factor for severe post-biopsy infections. Using clinical pathways that involved either 1) provision of **culture specific antibiotics** based on results from a pre-biopsy rectal swab or 2) use of **augmented antibiotics** (i.e. along with standard fluoroquinolone therapy), most practices throughout the state have seen significant reductions in the hospitalization rate after prostate biopsy.

With the objective of further improving the safety profile of prostate biopsy, MUSIC recently presented collaborative wide data which demonstrated a reduction in infectious complications associated with the use of a needle disinfectant technique during biopsy. In this document we describe a new set of MUSIC measures that will incorporate the Prostate Biopsy Infection Bundle. Our aim is to continue the significant progress already made, and make Michigan the safest place in the world to undergo a transrectal prostate biopsy.

1 What is a bundle?

A bundle is a structured way of improving the processes of patient care and outcomes: a small, straightforward set of methods — generally three to five — that, when performed collectively and reliably, have been proven to improve patient outcomes. Bundles help health care providers reliably deliver the best possible care for patients undergoing particular treatments with inherent risks.

Two bundled interventions which are widely practiced throughout the country include measures to reduce catheter related bloodstream infections (Central Line Bundle) and ventilator-associated pneumonia (Ventilator Bundle). More recently the Michigan Surgical Quality Collaborative (MSQC) demonstrated the value of a bundle for reducing surgical site infections after colectomy.

1.1 MUSIC Prostate Biopsy Infection Bundle

The Prostate Biopsy Infection Bundle are a set of measures that when performed collectively would lower the risk of infectious hospitalization following prostate biopsy. These include:

- **MUSIC antibiotic pathways**
- **Needle disinfectant technique during biopsy**
- **Urinalysis prior to prostate biopsy**

2 MUSIC antibiotic pathways

Contemporary studies have shown that the increase in hospitalization rates after transrectal prostate biopsy have been primarily attributed to infections with fluoroquinolone-resistant bacteria. In MUSIC, of 5,158 prostate biopsies performed in 21 practices up to 12/31/2013, 1.16% of men were hospitalized after a biopsy (**Fig. 1**). Of these, the overwhelming majority of hospitalizations (92%) were due to infection—of which 80% were due to fluoroquinolone resistance.

In order to reduce prostate biopsy-related hospitalizations across the collaborative, MUSIC successfully implemented two antibiotic pathways to deal with the issue of fluoroquinolone resistance.

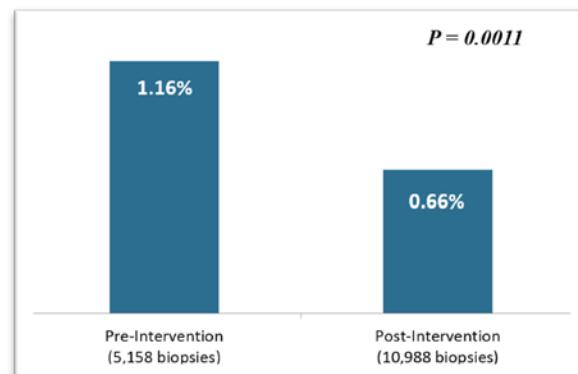


Figure 1: Prostate biopsy infectious hospitalization rates before (pre-intervention) and after (post-intervention) implementing the MUSIC antibiotic pathways.

The first antibiotic pathway uses **culture-specific antibiotics** administered to the patient based on rectal swab cultures taken in advance of prostate biopsy. This method identifies the presence of fluoroquinolone-resistant organisms, and allows tailored antibiotic prophylaxis with culture-directed agents. The alternate method uses additional antimicrobial prophylaxis to standard fluoroquinolone agents: **the augmented pathway**. Both of these pathways have been successful in reducing prostate biopsy-related hospitalizations; in 10,968 men undergoing prostate biopsy, the infectious hospitalization rate after using one of these approaches was 0.66%: a 50% relative reduction in infection related admissions (**Fig. 1**).

2.1 Culture-specific antibiotics

While the adoption of a rectal swab approach is not suitable for every practice in MUSIC, our data demonstrates that **the lowest hospitalization rates (0.33%) are in practices that have adopted a culture specific antibiotic pathway (Fig. 2)**. In those practices implementing an augmented antibiotic approach, the hospitalization rate was 0.67%.

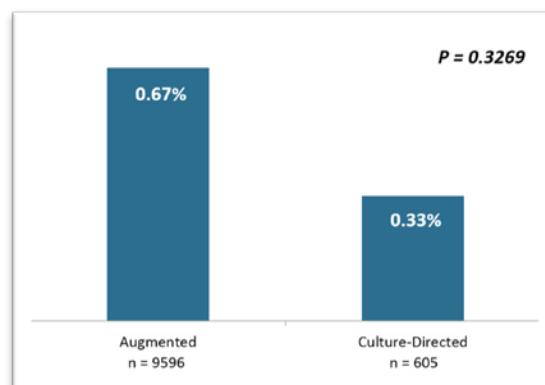


Figure 2: A comparison between the augmented and culture directed antibiotic pathways in reducing infectious hospitalization rates after prostate biopsy.

2.2 Fluoroquinolone prophylaxis: Ciprofloxacin or Levofloxacin

Recent studies have demonstrated reduced rates of severe infection following prostate biopsy when a longer acting oral fluoroquinolone agent, i.e. levofloxacin, is used instead of ciprofloxacin. These findings have also been supported by collaborative wide MUSIC data which also suggests a **lower rate of infection with the use of levofloxacin (Fig. 3)**.

In MUSIC we have found that, with an augmented antibiotic pathway, **1,642 patients receiving peri-procedure levofloxacin had a hospitalization rate of 0.26%**, compared to a rate of 0.81% in 9,916 patients receiving ciprofloxacin prophylaxis ($p=0.004$).

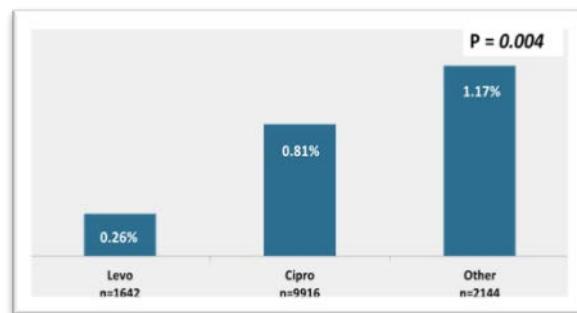


Figure 3: Hospitalization infection rates when using levofloxacin and ciprofloxacin prophylaxis in MUSIC.

MUSIC now recommends levofloxacin as an alternative fluoroquinolone agent for patients undergoing prostate biopsy via the augmented clinical pathway. For patients undergoing a prostate biopsy via the culture specific pathway, levofloxacin may be a suitable agent if culture results demonstrate bacterial sensitivity.

2.3 MUSIC Antibiotic Pathways

Culture-Specific Antibiotics (Rectal Swab Culture) * (See IV for High-Risk patients)		
<i>Culture Sensitive to Ciprofloxacin:</i>	<i>Culture Resistant to Ciprofloxacin but sensitive to TMP/SMX or Cephalosporins:</i>	<i>Culture Resistant to Ciprofloxacin, Cephalosporins, TMP/SMX:</i> <i>(IV antibiotics required for ESBL*)</i>
Ciprofloxacin or Levofloxacin PO	Culture directed antibiotics: (e.g., TMP/SMX PO, Cefazolin IM, Ceftriaxone IM)	Gentamicin IM + / - Clindamycin IM
Augmented Antibiotics (No Culture Available) ** (IM antibiotics should be administered 30 – 60 minutes before the procedure)		
<i>Antimicrobial of Choice:</i>	<i>Alternate Antimicrobials:</i>	<i>Allergic to Penicillins, Fluoroquinolones, and Cephalosporins:</i> <i>(IV antibiotics recommended if infection history*)</i>
Fluoroquinolone (Cipro) PO or (Levofloxacin) + Gentamicin IM**	Fluoroquinolone (Cipro) or (Levo) PO + Cefazolin IM** or Alternative based on local antibiogram (e.g., Cefuroxime, Zosyn)	Gentamicin IM** + / - Clindamycin IM**

Medication Dosing Guidelines:

Ciprofloxacin: (500mg tablet)
 1 tablet PO at least one hour before biopsy and 1 tablet PO on evening after biopsy

Levofloxacin: (750mg tablet)
 1 tablet PO single dose (60 min prior)
 If using multiple doses please consult your local hospital guidelines

TMP/SMX: (Double-strength tablet)
 1 tablet PO at least one hour before biopsy and 1 tablet PO on evening after biopsy

Cefazolin: (1gm vial; dilute in 2.5mL of sterile water = **3mL** solution) WEIGHT BASED PROTOCOL
 (Kefzol) 1gm (3mL) IM for patients < 80kg
 2gm (3mL x2) IM for patients \geq 80kg - **NOTE:** 2 separate injections, 1gm each
Peak serum concentration at 1-2 hours

Ceftriaxone: (1gm vial; dilute in 2.1mL of sterile water or NS = **2.9mL** solution)
 (Rocephin) 1gm (2.9mL) IM, single injection - **NOTE: Peak serum concentrations at 1-2 hours**

Gentamicin: (40mg/mL premixed vial)
 120-160mg (3-4mL) IM, single injection - **NOTE: Peak serum concentrations at 30-60 minutes**

Clindamycin: (150mg/mL premixed vial)
 600mg (4mL) IM, single injection - **NOTE: DO NOT EXCEED 600mg IM**
Peak serum concentrations at 1-3 hours

IM antibiotics should be administered 30-60 minutes before the procedure.

NOTE: It is recommended that the duration of therapy for all prophylaxis regimens be \leq 24 hours.

† - When used alone, oral cephalosporins are not recommended by the AUA or SCIP guidelines due to the lack of research available on the pharmacokinetics and soft-tissue penetration.

* IV Administration for High Risk Patients:

The following patients are classified as High Risk and alternate antibiotic regimen.

NOTE: For IV antibiotics, the prostate biopsy must begin less than 60 min after starting the infusion.

- Extended spectrum beta-lactamase (**ESBL**) bacteria identified on rectal swab.
 History of biopsy-related infection from a resistant organism.
 History of prostatitis (i.e., unresponsive to fluoroquinolones or received multiple courses of fluoroquinolones).

Gentamicin: (Premixed in saline **OR** dilute using 40mg/mL vials[‡]) WEIGHT BASED PROTOCOL
 2mg/kg with maximum dose of 300mg IV
[‡] If using 40mg/mL vials dilute in **50-200mL** of normal saline (conc. 1-1.6 mg/mL)
and infuse over 30-120 min

Fosfomycin: 3Gm PO the night before the procedure

3 Needle disinfectant technique during prostate biopsy

Disinfectants that can be used to inoculate the prostate biopsy needle during prostate biopsy include formalin and alcohol. Recent work from the Atlanta Veterans Affairs Medical Center has shown that the use of formalin disinfection (10% formaldehyde) used to disinfect the needle tip after each biopsy core during prostate biopsy was associated with a significantly lower sepsis rate.

In order to determine the effectiveness of a biopsy needle disinfectant technique in reducing infection following prostate biopsy, MUSIC assessed all practices to determine whether they used disinfectants as part of their routine prostate biopsy process. In a total of 17 MUSIC practices, needle disinfection was used by 40%. Of a total of 66 urologists, 61 were identified as users of a formalin disinfectant technique.

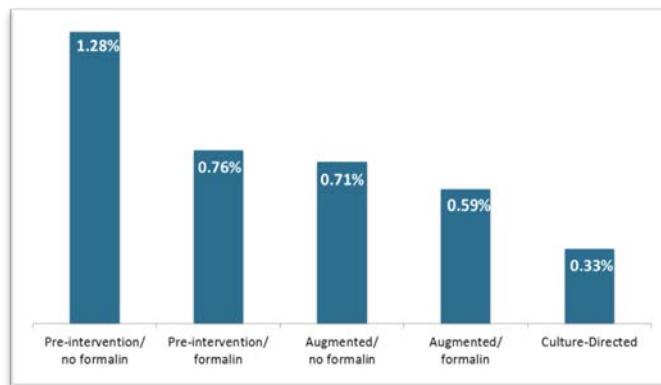


Figure 4: Prostate biopsy infectious hospitalization rates according to utilization of MUSIC antibiotic pathway and needle disinfectant technique.

3.1 Benefit of needle disinfectant

When we analyzed hospitalization rates for infection after prostate biopsy for all patients in the registry (up to April 2015), the highest hospitalization rate was for those patients undergoing a biopsy without needle disinfectant prior to the intervention of the antibiotic MUSIC pathways (1.28%). The lowest hospitalization rates were seen in patients undergoing a culture directed antibiotic pathway (0.33%). Patients undergoing an augmented pathway without formalin had a hospitalization rate of 0.71% while patients undergoing an augmented pathway with the use of a needle disinfectant had a hospitalization rate of 0.59% (Fig. 4).

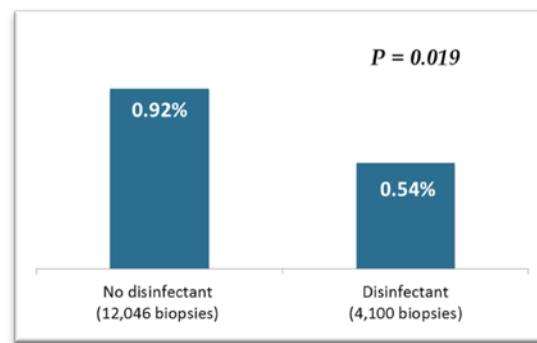


Figure 5: Infection related hospitalization rates for patients undergoing prostate biopsy when using no disinfectant vs needle disinfectant technique.

3.2 Formalin disinfectant

In >16,000 prostate biopsies in MUSIC performed up to April 2015, use of a disinfectant during prostate biopsy (either 10% formalin or 70% alcohol) was associated with a hospitalization rate of 0.54%, compared to 0.92%, when no disinfectant was used (Fig. 5).

When we assessed hospitalization rates before and after the implementation of the MUSIC antibiotic pathways (intervention), the use of formalin as a needle disinfectant was associated with decreases in hospitalization rates – both before and after the intervention phase. **Hospitalization rates for practices using formalin technique before the implementation of the MUSIC antibiotic pathway was 0.76%, while after implementation it was 0.56% (Fig. 6).**

3.3 Alcohol disinfectant

	Formalin disinfectant	Alcohol disinfectant	No-disinfectant
Number of biopsies	3,702	398	12,046
Hospitalization Rate	0.59%	0%	0.92%

Table 1. Biopsy-related infectious hospitalization rates for patients undergoing a formalin or alcohol disinfectant technique.

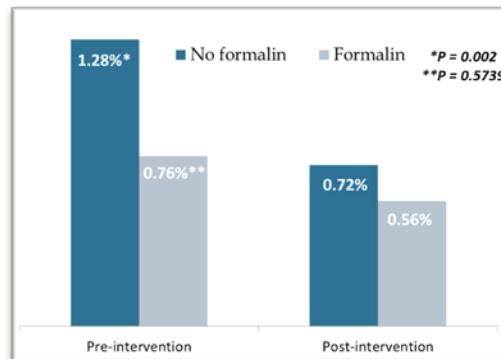


Figure 6: Prostate biopsy infectious hospitalization rates before (pre) and after (post) intervention of MUSIC antibiotic pathways according to use of formalin needle disinfectant technique.

MUSIC data has shown that the use of alcohol (70%) with its rapid bactericidal properties could be similar to formalin in its protective abilities to prevent infectious complications (**Table 1**). A single MUSIC practice with a diverse population has used alcohol routinely with no infectious hospitalizations recorded in the registry after more than 400 biopsies to date. In combination with the MUSIC antibiotic pathway **the use of alcohol as a needle disinfectant can be considered an alternative to formalin.**

3.4 Formalin technique

This technique utilizes formalin to soak the tip of the biopsy needle when removing the prostate core. It is performed by swirling the end of the biopsy needle, with its outer sheath retracted, into 10% formalin (**Fig. 7B**). This dislodges the biopsy core into the specimen bottle while the formalin disinfects the end of the needle. Formalin has bactericidal properties: it destroys bacterial fimbriae and pili and inhibits protein synthesis resulting in bacterial death. It has excellent disinfectant properties against most pathogens including E. Coli. Since the formalin method targets bacteria ex vivo, its use does not promote bacterial resistance.

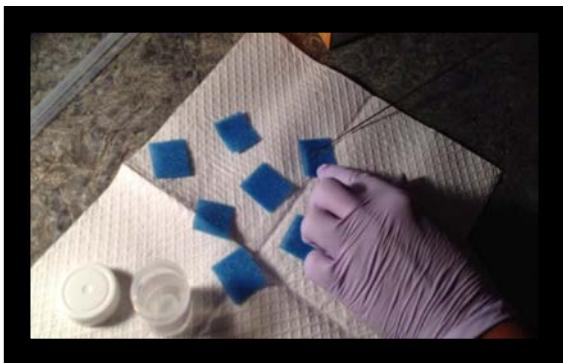


Figure 7A: The prostate biopsy core is removed on a blue sponge.



Figure 7B: The biopsy needle is immersed 3 cm into formalin.



Figure 7C: The prostate biopsy is placed into the pathology specimen kit in its corresponding location.

3.5 Formalin (with saline) rinse technique

Any concern regarding potential harm from using formalin is theoretical. In the study from the VA Atlanta, the volume of formalin on the biopsy needle was measured and found to be less than a third of the safe daily exposure level of formalin. For those concerned with using formalin on the biopsy needle, there is an option to supplement the technique with saline (**Fig. 8**). In this method, once the needle core is removed in the formalin, the biopsy needle is placed in a separate container of normal saline and swirled to remove any excess formalin that may be on the needle. In this technique any excess formalin on the needle is removed before introducing it into the prostate.



Figure 8A: Formalin with saline rinse technique. The needle core is removed in a container filled with formalin solution.



Figure 8 B: The biopsy needle is immediately rinsed in a saline solution before reintroducing the needle to obtain the next core.

3.6 Alcohol technique

An alternative needle disinfectant is to use 70% alcohol. In this method, alcohol solution is used to soak a non-adherent paper where the needle core tissue will be placed. The prostate needle core is removed on to the paper, and the needle tip wiped on the alcohol soaked paper in a manner that removes the core and also expose the needle tip to the alcohol solution (**Fig. 9**).



Figure 9: Alcohol needle disinfectant technique. The non-adherent paper is soaked in 70% alcohol solution (left image), and the biopsy needle tip is wiped on the paper (right image), removing the core tissue and exposing the needle to alcohol.

3.7 Is using formalin carcinogenic?

The maximum exposure to formaldehyde in a transrectal prostate biopsy needle is under the daily level allowed by the Environmental Protection Agency (less than 0.2 mg/kg). In a bench study done by Muta and colleagues, the measured total volume of formaldehyde on the needle tip was 3.9 mg after a 12-core prostate needle biopsy. This amount is less than a third of the safe daily exposure level. The exposure is even lower considering that most of the formalin gets drained off within the needle guide, condom or rectum before the needle enters the prostate. If this exposure is a concern for your practice, using the formalin/saline method is a reasonable alternative as this will further decrease the exposure of formalin. Another option is to use alcohol as a needle disinfectant.

Urinalysis prior to prostate biopsy

The use of urinalysis (urine dipstick) to determine the likelihood of urinary tract infection prior to prostate biopsy is widely practiced. However, little clinical evidence is available that demonstrates the benefit of urinalysis prior to prostate biopsy in reducing infection related complications. One reason for this may be that it could be considered poor quality care to proceed to prostate biopsy in patients with a positive urinalysis.

One prior study by Horcajada et al. (2009) [demonstrated a reduction in bacteremia from 4.4% to 0.9% after implementing a clinical protocol that included the use of urine dipstick prior to prostate biopsy as well a change in the antibiotic prophylaxis. In this study, 17.2% of biopsies were rescheduled due to a positive urine dipstick performed on the day of biopsy.]

Despite the lack evidence, it is reasonable that patients with suspected urinary tract infection should not undergo an invasive procedure such as prostate biopsy. While no current guidelines regarding this scope of practice are currently available, **MUSIC recommends that patients undergoing prostate biopsy should have had a urinalysis performed at least four weeks prior to their prostate biopsy.** Patients with a positive (i.e. nitrite positive) or suspicious urinalysis (i.e. presence of white blood cells) should be screened for symptoms, and considered for a delay in their prostate biopsy until urine cultures determine the presence of bacteruria.



MUSIC Prostate Biopsy Checklist

PATIENT NAME: _____

DOB: ____/____/____ PROSTATE BIOPSY DATE: ____/____/____

	YES	NO	N/A
1. Was a swab performed prior to the prostate biopsy?	<input type="checkbox"/>	<input type="checkbox"/>	
a. <i>If yes</i> , were culture and sensitivity results available at the time of the biopsy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. <i>If yes</i> , will the patient be receiving culture-specific (i.e., tailored) antibiotic prophylaxis?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. <i>If no to any of the above questions</i> , will the patient receive augmented antibiotics?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>NOTE:</i> If the answer to all 3 questions is "No", then STOP, DO NOT PROCEED with biopsy & ALERT the treating physician.			
2. Does the patient have diabetes that <u>requires medication</u> for blood sugar control?	<input type="checkbox"/>	<input type="checkbox"/>	
3. Does the patient or a family member work in a hospital, nursing home or health care facility?	<input type="checkbox"/>	<input type="checkbox"/>	
4. Did the patient receive treatment with antibiotics within 6 months of this biopsy (not including antibiotics prescribed for this biopsy)?	<input type="checkbox"/>	<input type="checkbox"/>	
5. Did the patient travel internationally within 6 months of this biopsy?	<input type="checkbox"/>	<input type="checkbox"/>	
6. Has the patient ever had to have a prostate biopsy prior to the current procedure? a. <i>If yes</i> , did he develop an infection related to the biopsy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Does the patient currently take any blood thinners (e.g., Aspirin, Coumadin, Plavix, etc.)? a. <i>If yes</i> , have they been stopped and/or does the patient have a peri-procedure management plan?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Is the patient currently taking any immunosuppressant medications? (e.g., steroids, methotrexate, organ transplant meds, HIV/AIDS meds, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	
9. What is the indication for today's prostate biopsy (check all that apply):			
a. Elevated PSA	<input type="checkbox"/>		
b. Abnormal PSA velocity	<input type="checkbox"/>		
c. Abnormal % Free PSA	<input type="checkbox"/>		
d. Abnormal DRE	<input type="checkbox"/>		
e. Positive family history	<input type="checkbox"/>		
f. Abnormal biomarker (e.g., PCA3)	<input type="checkbox"/>		
g. Pathology risk factor on prior biopsy (e.g., HG PIN, ASAP)	<input type="checkbox"/>		
h. Active surveillance follow-up	<input type="checkbox"/>		
i. Other	<input type="checkbox"/>		



Prostate Biopsy Bundle Assessment

MUSIC Prostate Biopsy Infection Bundle	
Urinalysis	✓ ✗
MUSIC antibiotic pathway	✓ ✗
Needle disinfectant technique	✓ ✗
MUSIC prostate biopsy checklist	✓ ✗

In summary, MUSIC will be measuring the adherence of practices to the following care measures that constitute the prostate biopsy infection bundle:

- **Urinalysis** performed within two weeks of the prostate biopsy
- **MUSIC antibiotic pathways**, including the option to use *levofloxacin* for fluroroquinolone prophylaxis in patients undergoing augmented approach
- **Formalin, formalin/saline, or alcohol needle disinfectant** during prostate biopsy
- Completion of the **MUSIC biopsy checklist**

FAQ's

1. Does formalin affect the quality of pathology reports?

Expert opinion from two uro-pathologists in Michigan who have been assessing prostate biopsies by urologists that use a formalin needle disinfectant technique, is that they have not noticed any difference in the quality of the core or changes in their ability to report pathology.

2. Is alcohol better than formalin?

At the moment, there is no published literature that shows benefit of using alcohol as a needle disinfectant for reducing the rate of sepsis after prostate biopsy. In contrast, formalin needle disinfection has been shown to significantly reduce sepsis rates following prostate biopsy at the VA Atlanta (Muta et al, 2013). The majority of MUSIC urologists practicing a needle disinfectant technique use formalin, and MUSIC data has shown a significant decrease in the infectious hospitalization rate following prostate biopsy in practices utilizing this method. Alcohol needle disinfectant has also been shown to have very low rates of infectious hospitalization in one MUSIC practice but this has not been validated at any other practices to date. This is something we plan to monitor and assess, in those practices that wish to adopt an alcohol disinfectant technique.

3. Is a disposable needle guide helpful for reducing infection?

We assessed the use of disposable needle guides in MUSIC and their influence on sepsis complications. When we surveyed 61 urologists, we found that 25 used disposable needle guides. We found no differences in infectious hospitalization rates in those urologists using disposable needle guides compared to those using re-usable guides. The AUA recommends both options as reasonable practice for prostate biopsy, but if reusable guides are used, it is important that appropriate sterile cleaning procedures are followed.

4. Is this an easy technique to adopt in my practice?

If using a formalin technique, when dipping the needle in the formalin container, the needle core tissue does not always come out of the needle immediately. It may require some manipulation with the needle against the container to expel the core into the pot. This step might need some practice, but those practices who have adopted this technique have had no difficulties thereafter. An alternative option to the formalin technique is to wipe the needle core on an alcohol soaked paper, and perform the alcohol technique.



Repeat Prostate Biopsy

Repeat Prostate Biopsy

The Michigan Urological Surgery Improvement Collaborative has been analyzing the collaborative use of repeat prostate biopsy in patients where the first biopsy demonstrated premalignant pathology. Premalignant pathology includes multicore high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) or a combination of both.

1. Current guidelines on repeat biopsy

The National Comprehensive Cancer Network (NCCN) recommends that patients with multifocal HGPIN and/or ASAP diagnosed after an initial biopsy undergo a repeat biopsy within 6 months. This repeat biopsy should focus on collecting samples from the area demonstrating the premalignant pathology and the adjacent areas. If no cancer is found after repeat biopsy, the NCCN panel recommends close monitoring with annual digital rectal examination and PSA tests.

2. Repeat biopsy practice in MUSIC

MUSIC analyzed the use of repeat biopsy within from March 2012 to September 2014. This analysis included 29 practices, with 364 patients diagnosed with premalignant pathology (multicore HGPIN and/or ASAP). **Of these 364 patients, only 30% underwent a repeat biopsy (Table 2).**

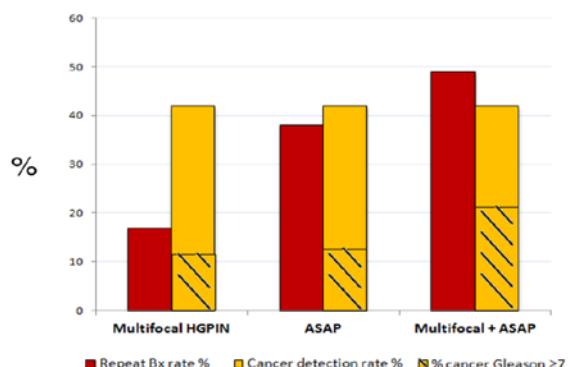
Table 2. MUSIC repeat biopsy practice in patients diagnosed with premalignant pathology after first biopsy.

	Repeat	No repeat
Multiple cores HGPIN	26 (17%)	131 (83%)
ASAP	41 (38%)	73 (62%)
HGPIN + ASAP	42 (49%)	51 (51%)
Total	109	255

3. Repeat Biopsy Cancer Detection Rate in MUSIC

MUSIC analyzed the cancer detection rate in patients who underwent a repeat biopsy after an initial biopsy demonstrated premalignant pathology (multifocal HGPIN, ASAP or multifocal HGPIN and ASAP). We found that approximately 40% of these

Figure 10: Repeat biopsy rate, overall cancer detection rate and detection of Gleason ≥ 7 cancer in patients after initial biopsy showed premalignant pathology.



patients were diagnosed with prostate cancer after repeat biopsy. More importantly, the highest detection rate of Gleason 7 or higher cancer was found in patients with ASAP and multicore HGPIN (**Fig. 10**).

On multivariate analysis, the probability of finding cancer on repeat biopsy after the initial biopsy showed premalignant pathology varied depending on the type of pathology. Multifocal HGPIN had a cancer detection rate of 13.8% (95% CI 10-20%) while the rate of cancer detection with ASAP was much higher at 35.9% (95% CI 26-47%). **Therefore, ASAP has the highest likelihood of prostate cancer detection at the next biopsy.**

4. Why did patients not undergo repeat biopsy?

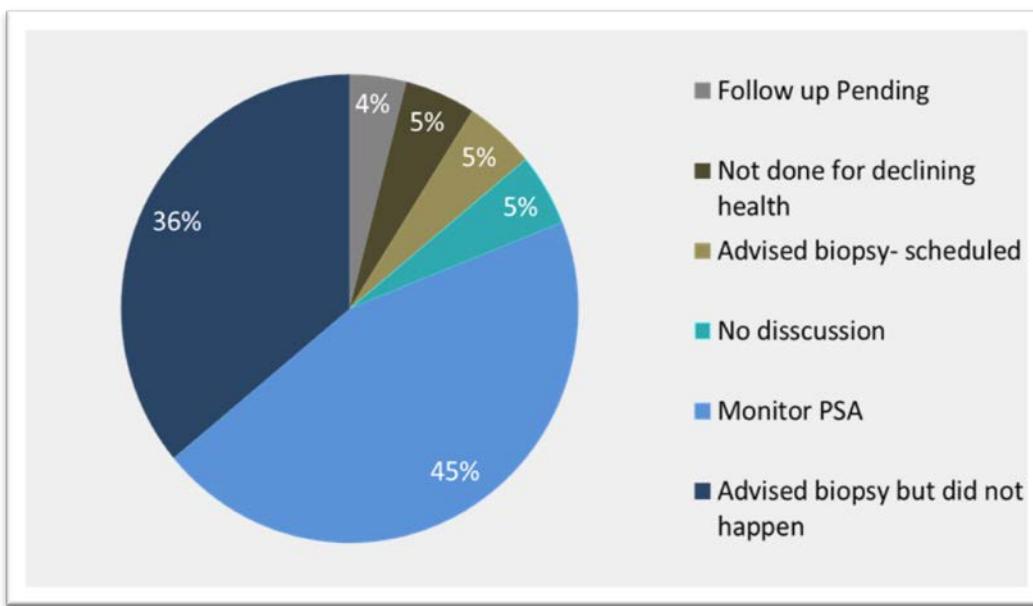


Figure 11: Reasons why repeat biopsy was not performed in patients with premalignant pathology detected at their first biopsy.

Despite NCCN guidelines recommending repeat biopsy for patients with premalignant pathology, we found that a substantial proportion of patients did not undergo repeat biopsy after their first biopsy. Based on a comprehensive chart review of a random subset of patients, we found that 36% had a repeat biopsy advised but the patient did not follow up on this recommendation. A further 45% of care providers chose to monitor PSA over recommending a repeat biopsy (**Fig. 11**). Based on these findings we think a target rate of repeat biopsy at 70% is more realistic than a 100% target rate.

5. MUSIC target rate for repeat biopsy

The current MUSIC rate for repeat biopsy in patients with multicore HGPIN and/or ASAP is 30%.

MUSIC recommends a target rate for repeat biopsy of 70% in patients with ASAP.

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V MUSIC Prostate Biopsy Working Group

This Document was created on 10/21/2015 by members of the MUSIC Coordinating center including: Dr Khurshid Ghani, MD, Mr Andrew Brachulis BS, and Mr Zackery Montgomery.

MUSIC Prostate Biopsy Working Group Members include: Dr Kenneth Lim, DO, Dr Dinesh Telang, MD, Dr Muzammil Ahmed, MD.