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Selective transperineal prostate biopsy for fluoroquinolone-resistance patients reduces sepsis and cost

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Abstract

Background: Urosepsis is a recognized complication of transrectal ultrasound-guided prostate biopsy (TRUS-Bx). Pre-biopsy rectal swabs have been used to identify patients with microorganisms in the rectal flora resistant to the conventionally used empirical prophylaxis. The transperineal route of biopsy (TP-Bx) has a lower complication risk but comes at an increased cost.

Materials and methods: Retrospective cohort study including patients undergoing prostate biopsies between October/2015 and April/2018. The intervention cohort, a rectal swab was performed, the result of which dictated the biopsy route; TRUS-Bx against TP-Bx. TP-Bx for patients with fluoroquinolone resistance or extended-spectrum β-lactamase. The control cohort underwent TRUS without a rectal swab receiving empirical antibiotics—oral ciprofloxacin and intravenous gentamicin.

Results: Total 1000 patients were included in which 500 underwent a swab, 14 (2.8%) developed post-TRUS biopsy infective complications with 3 having positive bacteremia (0.6%); 500 had no swab, 47 (9.4%) developed post-TRUS biopsy infective complications with 22 (4.4%, $p < 0.05$) having positive bacteremia. Three patients (0.6%) of patients who underwent swab developed urinary tract infection symptoms whilst 12 (2.4%) had urinary tract infection in the control group. In those patients that underwent a swab, 14 required hospitalization with mean length of stay of 2.5 days versus 43 patients of the control with 3.6 days. Cost analysis concluded savings of this strategy was £18,711.

Conclusions: We have demonstrated a protocol that reserves template biopsies for higher risk patients and can significantly reduce sepsis and other infectious complication rates whilst also proving to be a cost-efficient strategy. We recommend that units not utilizing rectal swabs to uncover the fluoroquinolone resistance rate by introducing them. We advocate units that already utilize rectal swabs, to introduce transperineal biopsy for their higher risk patients.

Keywords: Prostate cancer; Rectal swab; Sepsis; Targeted antibiotic prophylaxis; Transperineal biopsy; Transrectal ultrasound-guided biopsy

1. Introduction

1.1. Problem description

Prostate cancer is the most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012.[1] In the United Kingdom, there are 47,700 cases diagnosed each year making it the most commonly diagnosed cancer in males and accounting for the second most common cause of cancer mortality.[2] Due to its high prevalence, the diagnosis and treatment of prostate cancer provides a significant burden for healthcare systems.

Despite the advances in imaging, particularly multi-parametric MRI, to aid detection of prostate cancer, tissue diagnosis remains necessary prior to treatment.[3] Transrectal ultrasound-guided biopsy (TRUS-Bx) of the prostate is the most common technique used to obtain tissue diagnosis of prostatic carcinoma. Complications of this approach include hematuria, hematospermia, acute urinary retention, and infectious complications ranging from urinary tract infection (UTI) through to severe sepsis.

1.2. Knowledge available

There is a significant proportion of patients with resistant rectal vault flora to the conventionally used fluoroquinolone to cover TRUS-Bx; these patients are having higher odds of developing infectious complications.[4] A number of studies are demonstrating rise of fluoroquinolone-resistant (FQ-R) over the recent years.

Although, the transperineal biopsy of prostate (TP-Bx) is associated with a lower risk of febrile complications and a negligible rate of sepsis, universal adoption of TP-Bx for all patients being investigated for suspected prostate cancer could lead to increased set-up costs as TP-Bx is often performed under general anesthesia.

Pre-biopsy rectal swabs can help to identify patients with microorganisms in the rectal flora resistant to the conventionally used empirical prophylaxis with fluoroquinolone and/or aminoglycoside. As this group of patients with FQ-R rectal vaults flora,

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is likely to experience infectious complications even with targeted prophylaxis following TRUS-Bx; our interest was sparked in studying the use of TP-Bx for this group of patients.[4]

The aim of this study is to:

1. Provide a protocol that utilizes rectal swabs to identify high-risk patients that should undergo transperineal route to reduce the rate of sepsis.
2. Demonstrate that this protocol is cost efficient for the healthcare providers.

2. Methods

2.1. Context

This is a retrospective cohort study comparing two different protocols used to obtain prostate biopsy for the investigation of prostate cancer. This research includes all patients underwent prostate biopsies for suspected cancer between October 2015 and April 2018. Patient who had repeat biopsies as part of an active surveillance protocol were excluded from analysis.

2.2. Intervention

In the intervention cohort of patients, a rectal swab was performed and the result of this dictated the route of the biopsy for the patient; TRUS-Bx against TP-Bx. Patients that were found to be colonized with bacteria resistant to the standard prophylaxis had a TP-Bx procedure and patients with susceptible bacteria underwent TRUS-Bx.

This was compared to control cohort of patients from October 2015 to September 2016 that underwent TRUS-Bx without rectal swabs whilst receiving our department's standard empirical antibiotics prophylaxis consisting of oral ciprofloxacin 500 mg given approximately an hour prior to TRUS-Bx and intravenous administration of gentamicin 160 mg.

2.3. Study of intervention

Rectal swabs were cultured on BioMerieux chromID^{TM} extended-spectrum β-lactamase (ESBL) agar, chromID^{TM} CARBA agar and a Mueller Hinton agar with a ciprofloxacin and gentamicin disc; plates are incubated overnight to establish carriage of antimicrobial resistant Enterobacterales.

Any resulting positive growth from the ESBL and CARBA agars is identified using MALDI-TOF and a full susceptibility profile is established. The zones of inhibition for ciprofloxacin and gentamicin are read and reported as per European Committee on Antimicrobial Susceptibility Testing standards.[5]

Table 1 demonstrates the protocol for prostate biopsy route (transrectal or transperineal) depending on rectal swab result. Patients having TRUS-Bx had systematic 10-cores biopsy regardless the pre-biopsy imaging (patients with positive pre-operative MRI had 8 random cores and 2 targeted while patients with negative MRI or no MRI had 10 random cores). TP-Bx were performed under general anesthesia, in a day-case setting, using a recognized template mapping protocol with approximately 18 cores obtained in total.[3]

2.4. Measures

Our primary outcomes were post-TRUS biopsy infective complications (PTBIC), which were divided into 3 categories:

1. Sepsis: defined as bacteremia proved with blood culture along with febrile illness and elements of systemic compromise as categorized by quick sequential organ failure assessment, requiring hospital admission.[6]
2. UTIs: defined as UTI proved on urine culture with or without febrile illness.
3. Non-severe PTBICs: febrile illness with negative urine and blood culture.

Table 1

Rectal swab result format, suggested antibiotic results and route of biopsy.

Agents screened	Result	Risk	Route of biopsy
Ciprofloxacin	Sensitive	Low	TRUS-Bx
Gentamicin	Sensitive		
ESBL and CPE negative			
Ciprofloxacin	Sensitive	Low	TRUS-Bx
Gentamicin	Resistant		
ESBL and CPE negative			
Ciprofloxacin	Resistant	High	TP-Bx
Gentamicin	Sensitive		
ESBL and CPE negative			
Ciprofloxacin	Resistant	High	TP-Bx
Gentamicin	Resistant		
ESBL and CPE negative			
ESBL or CPE positive	Detected	High	TP-Bx

CPE = carbapenemase-producing Enterobacteriaceae; ESBL = extended-spectrum β-lactamase; TRUS-Bx = transrectal ultrasound-guided prostate biopsy; TP-Bx = transperineal route of biopsy.

Our secondary outcomes include the length of stay for the hospital admissions with PTBICs from both cohorts, along with costs of each strategy.

2.5. Analysis

This study is a retrospective analysis with clear quantitative focus with the above outlined outcomes. The statistical analysis was performed with the use of contingency chi-square calculator to assess statistical significance. We used the modified Clavien-Dindo classification to categorize complications.[7] The cost of stay along and the cost of each intervention were defined by the hospital ICD-10 coding system.

2.6. Ethical consideration

We gained approval from the research and development unit in Castle Hill Hospital, Hull, United Kingdom. Moreover, as our study is assessing quality improvement to improve patient safety, no NHS ethical approval was required as per NHS health research authority and the medical research council.

3. Results

3.1. PTBICs

From a total of 1000 patients included in this study with 500 patients each in both control and intervention groups. The result of PTBIC between control and intervention groups are shown in Table 2.

In the control group of 500 patient having TRUS-Bx without a rectal swab, 47 (9.4%) developed PTBIC. Of those 43 (8.6%) require hospital admission with a mean length of stay of 3.6 days. Sepsis with positive blood cultures was identified in 22 (4.4%) with one patient requiring intensive care unit admission for ionotropic support (Clavien-Dindo grade 4A complication). Twelve (2.4%) developed microbiologically proven UTI with 8 requiring hospital admission. The remaining 13 patients (2.6%) were admitted with a diagnosis of non-severe PTBIC.

Table 2

Comparison between the pre-intervention cohort and the intervention cohort.

	No swab pre-intervention	Swab post-intervention	*p*
Number of patients	500	500	
Total number of PTBIC	47 (9.4%)	14 (2.8%)	<0.05
Sepsis	22 (4.4%)	3 (0.6%)	<0.05
UTI	12 (2.4%)	3 (0.6%)	<0.05
Nonsevere PTBIC	13 (2.6%)	8 (1.6%)	>0.05
Hospital admissions	43/47	14/14	
Mean length of stay, days	3.6	2.5	

PTBIC = post-TRUS biopsy infective complications; UTI = urinary tract infection.

A rectal swab was obtained prior to biopsy in 500 patients forming the intervention group. Fourteen (2.8%) patients from this cohort developed PTBIC, all requiring hospital admission with a mean length of stay of 2.5 days. Sepsis with bacteremia was only seen in 3 (0.6%). This is a statistically significant reduction in the number of septic patients ($p=0.0003$, χ^2 with Yates correction). Three patients had microbiologically proven UTI, which is a statistically significant reduction ($p<0.05$, χ^2 with Yates correction). Eight patients had non-severe PTBIC. No infectious complications were recorded after TP-Bx.

3.2. Rectal swab results

Total 500 patients had rectal swabs examined for the presence of ESBL production and carbapenemase-producing Enterobacteriaceae as well as ciprofloxacin and gentamicin resistance, the results of which are shown in Table 3 along with subsequent PTBIC rates.

Of 459 (91.8%) patients were identified with no significant resistance and/or gentamicin resistance. These were categorized as low risk to develop PTBIC and 453 of them underwent TRUS-Bx as our protocol suggests whilst the remaining 6 underwent TP-Bx due to patient preference. Eleven of the 453 developed PTBIC (2.4%).

Fourteen (2.8%) patients had ciprofloxacin resistance; only 8 of them had TP-Bx whilst the remaining 6 had TRUS-Bx and hence, were investigated against the desired protocol. Two out of the 6 (33%) developed PTBIC. Multi-drug resistance, CPE and/or ESBL were identified in 27 patients (5.4%) in whom 20 of them had TP-Bx as per protocol whilst 7 had TRUS-Bx (investigated against the desired protocol). one of these 7 (14%) of these patients had PTBIC. There was no difference between the FQ-R in the rectal flora identified between 2017 and 2018 (8 and 7 patients, respectively).

3.3. Cost analysis

Forty-three patients in the no swab cohort required hospital admission with a total cost of £81,384 with an average cost of each individual admission at £1893. Whilst the cost of the 14 patients admitted who underwent a rectal swab came to £ 23,434 with an average of £1674. In this cost, we have included the medical and support staff, the clinical equipment used, the pathology cost for blood and microbiology specimens process, the cost medications, as well the cost of the hospital beds admission.

The cost of each rectal swab is £2.59, and this includes the pathology process only. There was no added clinical encounter as the swab was taken in the clinic by the clinician who booked the biopsy.

The cost of a standard systematic TRUS-Bx is £576. The cost of a TP-Bx as a day case procedure under general anesthetic is £1692. This includes the cost of medical staff and support staff, equipment and medication, theatre operative time and recovery time.

As outlined in Table 4 the overall cost savings of applying this strategy was £18,711. Our intervention cohort had added costs of the rectal swabs and TP-Bx albeit, this was counteracted by the lower number of overall admissions and lower cost of each individual admission when compared to the control group.

Table 4

Overall cost breakdown between the pre-intervention cohort and the intervention cohort.

	No swab pre-intervention	Swab post-intervention
Total number of patients	500	500
Number of hospitalized patients	43	14
Total cost of admission	£81,384	£23,434
Total cost of rectal swab		£1,295
Number of TRUS-Bx	500	466
Total cost of TRUS-Bx	£288,000	£268,416
Number of TP-Bx	0	34
Total cost of TP-Bx		£57,528
Total cost	£369,384	£350,673

TRUS-Bx = transrectal ultrasound-guided prostate biopsy; TP-Bx = transperineal route of biopsy.

4. Discussion

The protocol we used has reduced significantly the PTBIC rate from 9.4% to 2.8% including an important significant reduction in patients with bacteremia and sepsis from 4.4% to 0.6%. This study has also demonstrated that the reduction in PTBIC does not come at increased cost. In fact, the implementation of the protocol led to a small cost-saving of £18,711 during the study period. In this cost, however, no additional patient-driven cost included such as missed days off work due to sepsis which potential will lead to a greater economic benefit (less sepsis rate and less inpatient days admission by rectal swab implementation).

Table 3

Results of the rectal swabs, corresponding route of biopsy, and swab result specific PTBIC rates.

Swab result	Total number	TP	PTBICs post-TP	TRUS	PTBICs post-TRUS
Ciprofloxacin and gentamicin sensitive	439	0	0	439	10/439 (2.3%)
Ciprofloxacin sensitive gentamicin resistant	20	6	0	14	1/14 (7.1%)
Ciprofloxacin resistant and gentamicin sensitive	14	8	0	6	2/6 (33.3%)
Ciprofloxacin and gentamicin resistant	6	4	0	2	0
ESBL/CPE positive	21	16	0	5	1 (20%)

CPE = carbapenemase-producing enterobacteriaceae; ESBL = extended-spectrum β-lactamase; TP = transperineal; PTBIC = post-TRUS biopsy infective complications; TRUS = transrectal ultrasound.

Our true sepsis rate reduction was 4.4%–0.6% ($p < 0.05$) by avoiding TRUS-Bx and performing TP-Bx for the higher risk patient. Another strategy to reduce post biopsy sepsis is by applying targeted antibiotics prophylaxis before TRUS-Bx. This strategy involves tailoring the antibiotics prophylaxis based on the prebiopsy rectal swabs. In a systematic review of a tailored antibiotic prophylaxis biopsy protocol by Cussans et al.[8] a similar reduction was demonstrated in the overall PTBIC and sepsis rates with the use of target prophylaxis before TRUS-Bx of 0.72%. Although, tailored prophylaxis is an interesting alternative for centers without TP-Bx facilities Cussans et al.[8] concludes that 27 men would need to receive targeted antimicrobial prophylaxis to prevent one PTBIC; while, in our study, only 15 men need to be screened with a rectal swab to prevent one PTBIC. Another, important benefit by our recommended protocol in these high-risk patients, is potential side effects from extended antibiotics cover (such as increase sensitivity rates or *clostridium difficile* colitis) are avoided completely.

In recent studies, literature has identified, FQ-R and ESBL prevalence rates between 12.7% and 50.9% with an overall prevalence of 22.8%.[8–10] In our study, FQ-R and ESBL was identified in 41 patients (8.2%). The varying rates of prevalence of FQ-R geographically could be related to geographic and healthcare antimicrobial use. Rectal swabs can only detect this significant prevalence and hence units with a high number of PTBIC after TRUS biopsy should consider introduction of recta.

Stefanova et al.[11] recommended that despite the extensive screening of patients with rectal swabs the reduction of sepsis by the targeted biopsies and the postbiopsy hospital admission is cost saving strategy. Transperineal prostate biopsies can be performed under local anesthetic in a clinic setting, also with image-guidance. This would likely lead to further reduction in costs.

Reducing hospital admissions was the main driver in cost reduction however; a significant reduction in the length of stay between the 2 cohorts was also identified (3.6 days for preswab to 2.5 days for patients with swab). Treating PTBIC empirically prior to blood and urine culture results can be aided by the result of the swab as also highlighted by Gottesman et al.[12]

The main limitation of this study is that it is a retrospective study; however, when designing the intervention protocol, primary outcomes such as sepsis and infectious complications rate were in mind.

During the initial stages of the protocol implementation, lack of adherence for higher risk patients was noted leading to patients with FQ-R and ESBL to undergo TRUS-Bx. The rates of PTBIC in patients with FQ-R and ESBL that underwent TRUS-Bx were 33.3% and 20%, respectively. This further support our hypothesis that targeted prophylaxis should be augmented with the use of TP-Bx for higher risk patients.

The cost analysis did not include the set-up cost and maintenance the TP-Bx equipment as this was done outside the timeframe of the study.

5. Conclusion

We have demonstrated a protocol that reserves template biopsies for higher risk patients and can significantly reduce sepsis and other infectious complication rates whilst also proving to be a cost-efficient strategy. We recommend that units not utilizing rectal swabs to uncover the fluoroquinolone resistance rate by introducing them. We advocate units that already utilize rectal swabs, to introduce transperineal biopsy for their higher risk patients.

Acknowledgments

None.

Statement of ethics

As our study is assessing quality improvement to improve patient safety, no NHS ethical approval was required as per NHS health research authority and the medical research council.

Conflict of interest statement

No conflict of interest has been declared by the author.

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Author contributions

None.

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