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1 **Prostate biopsy related infection: a systematic review of risk factors, prevention**
2 **strategies and management approaches.**

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1 **Abstract**

2 A systematic review to identify risk factors for prostate biopsy-related infection,
3 preventative strategies and optimal management of infectious complications was
4 conducted. Significant risk factors for post biopsy infection include urogenital infection,
5 antibiotic use, international travel, hospital exposure, bacteriuria, previous transrectal
6 biopsy and resistance of faecal flora to antibiotic prophylaxis (especially
7 fluoroquinolones). Patients at risk may benefit from an adjusted biopsy
8 protocol comprising transrectal biopsy under targeted prophylaxis, and/or the use of
9 rectal disinfection techniques or using a transperineal approach. Management of
10 biopsy-related infection should be based on individual risk and local resistance profiles
11 with input from multiple specialties.

12 **Keywords:** biopsy, complications, fluoroquinolone resistance, prostate, sepsis,
13 symptomatic infection

14

15 **1. INTRODUCTION**

16 Transrectal ultrasound-guided (TRUS) biopsy of the prostate (TRUBP) is the most
17 commonly used modality to diagnose prostate cancer, resulting in millions of biopsies
18 performed internationally each year¹. Despite reduced PSA testing and biopsy rates
19 following the U.S. Preventative Services Task Force recommendation in 2012²,
20 widespread use of PSA testing, an ageing population, and increasing implementation of
21 active surveillance protocols for low risk disease requires prostate biopsy to be
22 performed in high numbers worldwide. TRUBP is traditionally considered a safe

1 procedure but infectious complications can occur; including urinary tract infection (UTI;
2 >6%), prostatitis, and sepsis (~1%)^{3, 4} due to particularly Gram-negative
3 Enterobacteriaceae such as *Escherichia coli* resulting in substantial health and
4 economic burden^{1, 5, 6}. TRUBP is considered a 'contaminated' procedure under
5 European Association of Urology (EAU) guidelines, necessitating antibiotic prophylaxis
6 as a standard of care for all cases⁷⁻¹⁰. Fluoroquinolone-based prophylaxis is
7 recommended by many authorities, including the EAU and the American Urological
8 Association, due to their broad coverage against rectal flora and favourable prostatic
9 drug penetration¹¹. Duration of prophylaxis is varied, with no evidence to suggest
10 prolonged duration translates to reduced complications^{8, 12, 13}.

11 Despite antibiotic prophylaxis, observational studies have reported increasing rates of
12 infectious complications over the past two decades and postulate a strong association
13 with changing antimicrobial resistance, especially fluoroquinolone resistance^{5, 14-18}.

14 Teillant and colleagues have reported that, in the USA, 13,120 post-TRUBP infections
15 per year are attributable to fluoroquinolone resistance, which would increase to 64,000
16 infections per year in the event of 100% fluoroquinolone resistance⁵. The management
17 of TRUBP complications causes significant financial burden on health systems, reported
18 to cost more than that due to methicillin-resistant *Staphylococcus aureus* and
19 *Clostridium difficile* in the UK^{19, 20}. The non-financial, unmeasurable burden of disease
20 from TRUBP complications, including the physical suffering and psychological burden of
21 significant illness, hospital admission and anxiety regarding future biopsies, must also
22 be considered²¹. Furthermore, a recent Federal Drug Administration warning of

1 disabling and potentially permanent serious side effects associated with fluoroquinolone
2 therapy warrants consideration²².

3

4 While resources available to urologists, such as the American Urological Association
5 White Paper on the Prevention and Treatment of Common Complications Related to
6 Prostate Biopsy²³, partially outline risk factors and management of post-TRUBP
7 complications, this review sought to critically appraise and summarise available
8 published literature on risk factors, prevention and management of TRUBP-associated
9 infectious complications. The available evidence was reviewed in the context of
10 spreading multi-drug resistance (MDR) to provide recommendations for general use in
11 modern international urology practice.

1 2. MATERIALS AND METHODS

2 A systematic literature search was conducted in January 2016 in accordance with the
3 PRISMA statement and Cochrane Guidelines²⁴. The Cochrane Central Register of
4 Controlled Trials (CENTRAL), PubMed, EMBASE, and LILACS databases were
5 searched for the following key terms: *prostat**, *biopsy*, *infect**, *culture**, *bacter**, *sepsis*,
6 *fever*, *UTI*. Only peer reviewed manuscripts were considered for inclusion.

7 A total of 4,545 citations were identified, including review of reference lists of included
8 manuscripts for applicable studies. After exclusion of duplicates and screening by title
9 and abstract, 737 were considered for full text review with 120 included in the final
10 qualitative review (Supplementary Figure 1).

11 Studies were rated according to the level of evidence (LoE) and the grade of
12 recommendation (GoR) similar to the EAU guidelines (2015) modified from the Oxford
13 Centre for Evidence-based Medicine²⁵. Overall, included studies contained limited
14 randomised data for most scenarios, and consequently the LoE was mostly 2A/2B and
15 GoR B.

1 3. RESULTS

2 3.1 Incidence

3 Complications following TRUBP are reported with great variability and subject to a lack
4 of complication-specific standardised definitions and follow up. Furthermore, the
5 incidence of complications varies per the geographic region in which studies are
6 conducted. Across published reports, a wide-ranging incidence of emergency
7 department presentations (0 – 6%), hospitalisation (up to 4%), and severe sepsis of 0 –
8 1% is observed^{1, 4, 26, 27}. In an attempt to standardise complication estimates across
9 three key measures, hospitalisation, sepsis and acute urinary retention, Bennett and
10 colleagues performed a systematic review and meta-analysis utilising directly
11 standardised prevalence estimates based on cases of new prostate cancer cases
12 according to GLOBOCAN⁶. The reported estimates are presented in Supplementary
13 Table 1.

14
15 Many recent reports highlight an increasing incidence of TRUBP-related complications
16 with time in parallel with a worldwide trend of increasing antimicrobial resistance and
17 subsequent infection with fluoroquinolone resistant micro-organisms^{1, 7, 17, 28-30}. Despite
18 this trend, 30-day mortality estimates remain between 0.1 – 1%^{15-17, 28, 31-33}. As
19 fluoroquinolones are the predominant antimicrobial used for TRUBP prophylaxis,
20 estimates of fluoroquinolone resistance have been included in Supplementary Table 1
21 and graphically represented in Supplementary Figure 2.

22

23

1 **3.2 Risk factors**

2 An appreciation for risk factors predictive of post-TRUBP infection allows the treating
3 urologist to guide prophylaxis, as well as assist in patient selection for alternative
4 sampling methods³⁴. Reported risk factors for post-TRUBP infection are listed in Table
5 1.

7 **3.2.1 Host-related**

8 **3.2.1.1 Antimicrobial resistance**

9 With fluoroquinolone therapy being most commonly used for TRUBP prophylaxis, the
10 risk factor most predictive of post-TRUBP infection is fluoroquinolone resistance in
11 rectal flora^{16, 17, 26, 27, 32, 35-39}. TRUBP causes translocation of rectal bacteria across the
12 rectal mucosa into the prostate and bloodstream. The mechanism of antimicrobial
13 resistance development in rectal flora is presumably either induced by selection
14 pressure following fluoroquinolone use, or acquired by travel to areas of high endemic
15 antimicrobial resistance^{4, 35, 40-43}. Fluoroquinolone resistance in *E. coli* blood stream
16 isolates has been reported to average 12% in the United States and 20% in Europe,
17 with known fluctuation between 10 and 45% secondary to regional differences⁴. The
18 prevalence of fluoroquinolone resistance has been observed to be higher in Asian
19 countries (26.7 – 92%)^{44, 45}.

20 A recent meta-analysis, reporting on nine studies and 2,541 patients, reported that
21 prevalence of fluoroquinolone resistance in rectal flora may be higher (20.4% vs.
22 12.8%) after fluoroquinolone therapy prior to TRUBP. There was a higher incidence of

1 TRUBP-associated infections in patients with fluoroquinolone resistant rectal cultures
2 compared with fluoroquinolone sensitive (7.1% vs. 1.1%), which translated to a 7.4% vs.
3 1.4% risk difference, respectively³⁷. These findings were supported by a collaborative
4 analysis of the original source data, with fluoroquinolone resistance associated with an
5 increased overall risk of infection (OR 3.98, 95% CI 2.37-6.71) and hospitalisation (OR
6 4.77, 95% CI 2.50-9.10), which were highest with fluoroquinolone monotherapy³⁹.

7 8 *3.2.1.2 Prior urogenital infection and/or antibiotic use*

9 Many studies in patients undergoing TRUBP have reported antimicrobial use within the
10 past 3-6 months to be significantly associated with fluoroquinolone resistant carriage in
11 the rectal flora^{17, 34, 38, 40, 46, 47}. These findings have been corroborated using meta-
12 analysis, with history of genitourinary infection (OR 2.56; 95% CI 1.13 – 5.79; n = 1,218)
13 and prior fluoroquinolone use (OR 4.12; 95% CI 2.30 – 7.37; n = 1,356) reported to be
14 significant risk factors for fluoroquinolone-resistance colonisation³⁷. Wagenlehner and
15 colleagues demonstrated on rectal swab culture that single dose prophylaxis was
16 sufficient to select for ciprofloxacin resistant organisms, with a four-fold increase in
17 fluoroquinolone resistance after administration⁴³. This has also been demonstrated in
18 studies investigating empiric antibiotics for elevated PSA, with extended antibiotic
19 administration leading to significantly higher rates of sepsis and resistance following
20 biopsy⁴⁸. Given the high concordance between fluoroquinolone resistance and
21 extended-spectrum beta-lactamase (ESBL) production, it is unsurprising that the use of
22 fluoroquinolone prophylaxis has also been shown to co-select for ESBL-producing *E.*
23 *coli*⁴⁹.

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3.2.1.3 Hospital admission or exposure (healthcare worker)

Hospitalisation in the year preceding biopsy has also been shown to increase carriage of fluoroquinolone resistant organisms and increase biopsy related infection^{11, 17, 38, 50}. Interestingly, this risk has also been observed in physicians⁵¹, as well as relatives of hospital employees⁵².

3.2.1.4 Recent international travel

International travel, particularly involving contact with healthcare facilities, also increases carriage of resistant organisms^{34, 40}. This was particularly true of exposure to healthcare facilities and water sources in the Indian subcontinent and South-East Asia, where resistance rates are known to be high^{6, 42, 53}.

3.2.1.5 Bacteriuria (pre-biopsy urine culture, indwelling catheter in situ)

Asymptomatic bacteriuria is an established risk factor and routine testing is recommended in the EAU guidelines, though poor compliance with this recommendation is reported^{1, 54}. History of urethral catheterisation or prior urogenital infection (urinary tract infection or prostatitis) are also risk factors^{33, 46, 55}.

1 3.2.1.6 Co-morbidities

2 The presence of co-morbidities such as diabetes mellitus, cardiac valve replacement,
3 chronic obstructive pulmonary disease, immunosuppression, or benign prostatic
4 hyperplasia have been variably reported to increase the risk of post-TRUBP
5 complications. Higher comorbidity scores have also been associated with a significantly
6 increased risk of hospitalisation post-biopsy in multiple large retrospective cohorts^{14, 33,}
7 ⁵⁶. Diabetes and the metabolic syndrome have been reported to be associated with both
8 increased risk of infectious complications, and carriage of resistant organisms^{15, 33, 57-59}.
9 However, on meta-analysis of available risk factors, diabetes (OR 1.37; 95% CI 0.77 –
10 2.46; n=1,140) was not significantly associated with fluoroquinolone-resistant
11 colonisation³⁷.

12

13 3.2.1.7 Compliance

14 Non-compliance is difficult to reliably assess but may contribute to complication rates,
15 as high as 43%, in populations with a relatively low baseline prevalence of
16 fluoroquinolone resistance⁶⁰. Of greater concern, the compliance of the treating
17 urologist to best practice guidelines can influence sepsis outcomes, with a large
18 multicenter study by Bruyere and colleagues reporting noncompliance with antibiotic
19 prophylaxis guidelines to be a risk factor for post-TRUBP sepsis (OR 2.3, 95% CI 1.4 -
20 3.9)⁴⁶.

21

22

1 **3.2.2 Surgeon related**

2 *3.2.2.1 Mode of biopsy*

3 Standard TRUBP has many pitfalls which are well known to urologists, thus alternative
4 methods are discussed here. Transperineal biopsy is an alternative method of sampling
5 providing transcutaneous access to the prostate, facilitated by the recent
6 implementation of MRI-fused prostate biopsy methodology^{18, 61}. As prostate cancer
7 detection rates have been reported to be similar, transperineal prostate biopsy has
8 typically been reserved for patients at high risk of sepsis, or for repeat biopsies,
9 especially those with a previous non-diagnostic TRUBP for better detection of anteriorly
10 sited tumours^{3, 18, 62, 63}. Transperineal sampling allows thorough skin preparation in line
11 with typical surgical procedures, and prophylactic antibiotics (eg cephazolin) are
12 targeted to skin flora and common urinary pathogens^{64, 65}. As transperineal biopsies
13 avoid the rectum, this approach has traditionally been thought to have lower rates of
14 infection than the 'transfaecal' route of TRUBP. Transperineal biopsy has been
15 classified as a 'clean-contaminated' procedure in the EAU guidelines, however it could
16 even be argued that it is 'clean' as there is often no breach of urinary tract mucosa
17 using this approach⁶⁶. This benefit is less clear in practice, and studies with direct
18 comparison of morbidity between transrectal and transperineal biopsy are lacking.
19 Recent reports suggest zero or near-zero sepsis rates with the transperineal
20 procedure^{3, 65}, further supported by three large cohort studies totaling 8,093 patients
21 with one case of urosepsis reported and recent meta-analysis estimate of 0.1%^{6, 67-69}.
22 From an antimicrobial stewardship perspective, transperineal biopsy may also avoid
23 selecting for fluoroquinolone- or multi-resistant bacteria, and stem the increasing

1 reliance on an ever-expanding range of antibiotics for biopsy prophylaxis. These clear
2 benefits in decreasing infection related morbidity are at the expense of higher logistical
3 and time considerations, requiring admission to hospital, an operating theatre, and
4 usually general anaesthesia. Transperineal biopsy is also associated with higher rates
5 of post-procedure urinary retention⁶, as shown in Supplementary Table 1.

6 Multi-parametric magnetic resonance imaging (mp-MRI) has emerged in recent years
7 as a valuable tool in the diagnosis and monitoring of prostate cancer⁶¹. Tissue diagnosis
8 with MRI-guided biopsies is generally via the transrectal route, and preliminary
9 experience suggests that complication rates are less than the conventional TRUS
10 approach^{18, 61}. Improved localisation with mp-MRI can reduce unnecessary biopsies, as
11 well as the need for repeat biopsy in patients on active surveillance^{18, 61, 70, 71}. The
12 availability and appropriateness of MRI-guided biopsy remains limited, with
13 approximately 10% of significant lesions deemed 'MRI-invisible', so systematic cores
14 remain necessary^{61, 71}.

16 3.2.2.2 *Number of cores*

17 The extent of sampling has also been a target for risk reduction. An 'extended' biopsy
18 strategy of 12-18 cores is currently recommended to optimise cancer detection, and
19 does not increase complications compared to sextant biopsy^{72, 73}. Biopsies of >18 cores
20 do however have a poor side-effect profile and so called 'saturation' biopsies (>20 cores
21 including transition zone) are rarely indicated^{72, 74}. 18-gauge needles are the most
22 widely used for sampling, and produce similar specimen quality to 16- and 14-gauge

1 needles with low morbidity⁷⁵. Local anaesthetic administration has also not been
2 associated with increased infectious complications⁴⁶.

3

4 3.2.2.3 Previous biopsies

5 Repeat biopsies are indicated for active surveillance of low risk disease, or in men with
6 persistent suspicion of prostate cancer according to elevated PSA, abnormal DRE, or
7 suspicious appearance on imaging⁷⁶. Reports regarding the association between repeat
8 biopsies and an increased risk of infectious complications compared with initial biopsies
9 are mixed^{31, 46, 77}. Any potential risk is concerning in this context, with a retrospective
10 analysis reported increased odds of an infection (OR 1.33, 95%CI 1.01 - 1.74) for every
11 previous biopsy in 591 consecutive men undergoing TRUBP⁷⁷. Repeat biopsy has been
12 reported to be a risk factor for colonisation with resistant *E. coli* strains⁷⁸, with a
13 progressive increase reported for each biopsy undertaken⁷⁹. Post-biopsy complications
14 have been reported to reduce rates of repeat biopsy in men undergoing active
15 surveillance⁸⁰.

16

17 Table 1 presents a risk assessment questionnaire, based on available data, to aide
18 clinicians in assessing the potential for fluoroquinolone resistance and subsequent risk
19 of post-TRUBP complication.

20

21

1 **3.3 Prevention strategies**

2 ***3.3.1 Antimicrobial prophylaxis – Empiric versus Culture-directed (Targeted)***

3 An evolving body of evidence supports either an expanded antibiotic protocol or one
4 targeted to rectal cultures on fluoroquinolone-impregnated MacConkey agar plates⁸¹.

5 Expanded antibiotic protocols can consist of either a broad-spectrum antibiotic or the
6 use of multiple antibiotics, both being a selective force for emergence of multi-resistant
7 pathogens.

8 Targeted prophylaxis aims to lower the risk of post-TRUBP infection due to resistant
9 pathogens and serves to facilitate antimicrobial stewardship, as supported by Liss and
10 colleagues³⁹. Meta-analysis of available data in 2014 comprising 2,541 patients
11 estimated higher infection rates when empirical prophylaxis was used (3.3%, 95% CI
12 2.6-4.2%) than those using targeted methods (0.3%, 95% CI 0-0.9%)³⁷. In contrast,
13 multiple studies, including a large retrospective North American multicenter database
14 from over 5,000 patients, in which up to 34% received targeted prophylaxis, have
15 observed no difference in complications between targeted and empiric prophylaxis
16 groups^{27, 36, 82, 83}. It has been suggested that patients undergoing repeat biopsy require
17 repeat culture prior to each biopsy⁸⁴ and targeted prophylaxis. While potential financial
18 benefits toward antimicrobial stewardship and potentially for infectious complications
19 averted are substantial⁸⁵, further assessment in a randomized controlled trial is
20 required.

21

22

1 **3.3.2 Decontamination**

2 Adjunct strategies of 'decontamination' prior to biopsy including bowel preparation and
3 disinfection of the rectal mucosa are aimed at reducing the bacterial load involved in the
4 inherently 'dirty-to-clean' passage of the TRUBP biopsy needle. Decontamination
5 strategies for TRUBP biopsy are inconsistently practiced and reported less compared to
6 antimicrobial-related studies^{12, 86}.

7 8 **3.3.2.1 Rectal disinfection**

9 Povidone-iodine rectal preparation (PIRP) is simple and affordable, not associated with
10 selection of resistant bacteria, and proven safe for colorectal surgery⁸⁷. From meta-
11 analysis of seven controlled trials (n = 2,049) of rectal disinfection using PIRP prior to
12 TRUBP, significant reductions in fever, bacteruria and bacteraemia (RR 0.31; 95% CI
13 0.21 – 0.45) regardless of prophylaxis used have been reported⁸⁸. Recent retrospective
14 studies further report significant reductions in infectious complications when PIRP was
15 used⁸⁹, as well as in conjunction with targeted prophylaxis⁹⁰. However, a randomised
16 controlled trial of prophylactic povidone-iodine use demonstrated insignificantly reduced
17 complication rates (2.6%) compared with control (4.5%), in a study that is likely to have
18 been underpowered⁹¹. The optimal method of administering PIRP has not been fully
19 elucidated but the use of a suppository or gauze soaked in povidone-iodine has been
20 reported to be superior to a rectal enema^{88, 92}.

21

22

1 3.3.2.2 Rectal cleansing

2 Preparation with a rectal cleansing enema (eg Fleet sodium phosphate) is used by a
3 minority (18 – 30%) of urologists¹³ based on mixed results in currently available
4 evidence^{8, 30, 93-96}.

5 Recommendations for assessment and prevention of prostate biopsy related infection
6 arising from this collaborative systematic review are presented in Table 2.

8 **3.4 Management of prostate biopsy related infection**

9 When considering the optimal treatment for a patient with an infectious complication
10 following prostate biopsy, several factors need to be considered. This includes the
11 severity of the clinical presentation, the likelihood of resistance to empirical antibiotics,
12 the co-morbidities of the host and whether anatomical complications co-exist (such as
13 prostate abscesses or urinary tract obstruction). Choosing appropriate initial therapy is
14 critical as these infections can progress quickly and may result in life-threatening
15 complications. Inadequate or delayed empirical therapy has been associated with
16 excess mortality in Gram-negative sepsis, especially in the setting of a high background
17 prevalence of ESBL-producers⁹⁷⁻⁹⁹. Furthermore, inadequate empirical therapy is not
18 uncommon in the setting of post-TRUBP sepsis, occurring in 36% of patients in one
19 study³⁵.

20

1 **3.4.1 Initial assessment and risk of infection with a multi-drug resistant (MDR)**

2 **organism**

3 Obtaining a detailed history of recent antibiotic use may help assess the risk of
4 resistance and, if fluoroquinolones have been used for prophylaxis, this class of drug
5 should be avoided for empirical therapy. As noted previously, a significant risk factor for
6 the likelihood of infection with a multi-drug resistant pathogen, is recent travel to a
7 country highly endemic for Gram-negative resistance within the preceding 6 months¹⁰⁰.
8 The prevalence of resistance mechanisms such as ESBLs or carbapenemases in
9 Gram-negative uropathogens varies widely across the world, and the situation is
10 dynamic. Carbapenemase-producers tend to also possess numerous other resistance
11 determinants, rendering them multi-drug resistant (MDR), extensively-drug resistant
12 (XDR) or even pan-drug resistant (PDR)^{101, 102}. Clearly this can dramatically reduce
13 treatment options and makes selecting effective empirical therapy extremely
14 problematic should these strains become predominant. In some patients, who are
15 known to be colonised with MDR pathogens, alternatives to TRUBP or avoidance of any
16 interventional procedure may have to be considered given the risks involved¹⁰³.

17 Risk prediction scores for assessing the likelihood of infections with an ESBL-producing
18 organism in the context of Gram-negative sepsis have been developed, but require
19 validation in a local context before they can be reliably implemented^{104, 105}. A simple
20 decision-support algorithm to help identify patients with bacteremia caused ESBL-
21 producers has been recently published, which used 5 clinical variables within a
22 classification tree determined by machine-learning methodology: prior history of
23 colonization/infection with ESBL, chronic indwelling vascular hardware, age ≥ 43 years,

1 recent hospitalization in an ESBL-high burden region and ≥ 6 days of antibiotic exposure
2 in the preceding 6 months¹⁰⁶. In a retrospective cohort of 1,288 patients with
3 bacteremia, this approach demonstrated positive and negative predictive values of
4 90.8% and 91.9% respectively¹⁰⁶. However, this model has only been derived from a
5 single centre in the US and requires validation in other cohorts. Pre-biopsy rectal
6 culture may also facilitate identification of antimicrobial resistance and help guide
7 treatment of biopsy-related sepsis, with one study demonstrating a high concordance
8 between rectal and urine or blood cultures in patients with sepsis¹⁰⁷.

9 10 **3.4.2 Early recognition of infectious complications**

11 It is important for patients undergoing TRUBP to be made aware of the signs and
12 symptoms of infection should they occur post procedure. The early recognition and
13 effective treatment of sepsis is a key factor in improving patient outcomes, and
14 management should broadly follow international guidelines, such as those of the
15 Surviving Sepsis Campaign¹⁰⁸.

16 17 **3.4.3 Empirical therapy for infectious complications**

18 Empirical regimens must have adequate coverage to reflect local patterns of resistance
19 in key uropathogens, especially Gram-negative bacteria such as *E. coli*. Most
20 microbiology laboratories can provide antimicrobial susceptibility data for urinary tract
21 isolates to inform local guidelines, or this information may be available from national
22 surveillance data¹⁰⁹.

1 Given the difficulty in reliably predicting susceptibility to empirical treatment regimens, it
2 is critical that appropriate microbiological specimens are collected for culture, including
3 a mid-stream urine and blood cultures, if the patient is febrile or shows other signs of
4 sepsis. An advantage for the routine use of pre-biopsy rectal screening (close to the
5 date of biopsy) is that positive cultures can guide empirical therapy, given a known
6 concordance between positive rectal and urine or blood cultures in patients with
7 sepsis¹⁰⁷.

8 In general, given the association with fluoroquinolone prophylaxis and MDR-*E. coli*
9 infections, patients presenting with urinary sepsis post-TRUBP will require a broader
10 spectrum of antibiotic coverage than patients with community-onset infections without
11 prior healthcare exposure⁷. Therapy with agents such as 3rd generation cephalosporins
12 (e.g. ceftriaxone or ceftazidime), amoxicillin-clavulanate, fluoroquinolones or gentamicin
13 may have a high likelihood of resistance in this context. Broader-spectrum empirical
14 options need to be considered. This could include piperacillin-tazobactam or
15 carbapenems. Amikacin, usually in combination with a beta-lactam agent, may also be
16 considered given that it frequently retains better *in vitro* activity than gentamicin against
17 *E. coli* isolated from patients with post-TRUBP sepsis³⁵ and has shown an additive
18 benefit in reducing post-TRUBP infections when used as a prophylactic agent³.

19

20 **3.4.4 Directed therapy for MDR Gram negative pathogens**

21 Treatment guidelines for urinary infections often do not adequately address treatment
22 options for MDR pathogens. Consultation with an infectious disease practitioner or

1 medical microbiologist is recommended for these difficult-to-treat organisms. For
2 several reasons, carbapenems have been regarded as the treatment of choice for
3 ESBL-producers^{110, 111}. However, carbapenem resistance has been increasing in many
4 parts of the world¹¹², prompting reconsideration of drugs that were previously
5 considered less effective (such as cefepime, beta-lactam/beta-lactamase inhibitor
6 (BLBLI) drugs, or older agents such as fosfomycin, pivmecillinam, or temocillin).
7 Although published experience with using fosfomycin for treating infections post TRUBP
8 are sparse, it has shown broadly similar efficacy in comparison to carbapenems for
9 patients with lower tract infections caused by ESBL-producers, including for patients
10 with complicating factors¹¹³. It is notable that fosfomycin appears to achieve adequate
11 prostate tissue levels and may be an option for prophylaxis in patients known to be
12 colonised with MDR Gram-negative pathogens^{114, 115}. Mecillinam is another
13 'rediscovered' antibiotic that appears effective in vitro against ESBL-producing *E. coli*¹¹⁶,
14 however there are no published data with respect to pivmecillinam treatment for men
15 with infections post-TRUBP. Temocillin, a derivative of ticarcillin, has received renewed
16 interest in recent years and shows stability to a range of ESBL and AmpC beta-
17 lactamases¹¹⁷. It has been used in addition to ciprofloxacin for routine prophylaxis prior
18 to TRUBP in patients at high risk of colonisation with resistant *E. coli* strains¹¹⁸. Novel
19 beta-lactam/beta-lactamase inhibitor combinations, such as ceftazidime/avibactam and
20 ceftolozane/tazobactam may also prove to be useful against MDR or XDR Gram-
21 negatives where few alternatives exist (although neither drug is effective against all
22 types of beta-lactamases). Both agents have now received FDA approval for the
23 treatment of complicated UTI following two phase 3 studies^{119, 120}.

- 1 A management summary for empiric and definitive therapy, once susceptibility results
- 2 are known, is included as Table 3.

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1 4. CONCLUSIONS

2 Despite heterogeneous reporting, infectious complications following prostate biopsy
3 appear to be increasing due to fluoroquinolone resistance. Preventing TRUBP-related
4 infections therefore requires collaboration between colleagues in the fields of urology
5 and infectious diseases to determine the optimal regimens for prophylaxis and
6 treatment of sepsis, considering local resistance patterns and patient demographics.
7 Nonetheless, it is clear with the decreasing effectiveness of prophylaxis and increasing
8 use of broad spectrum agents that we require a new approach to minimising the harm of
9 post biopsy complications. Effective preventative strategies are available, including
10 targeted prophylaxis, extended antibiotic regimes, and the transperineal approach
11 (Table 2), though the cost effectiveness of these strategies is yet to be elucidated. The
12 findings here are concordant with those described in the American Urological
13 Association White Paper on the Prevention and Treatment of Common Complications
14 Related to Prostate Biopsy²³, which also discusses pre-operative education and
15 institutional-level preventative measures. Randomised evidence is desired to establish
16 these adjunctive tools to improve patient outcomes. Currently, one randomised trial
17 assessing targeted versus empiric antimicrobial prophylaxis is underway
18 (ClinicalTrials.gov identifier NCT01659866), while the efficacy of PIRP is also being
19 assessed in a randomised setting (NCT02245334; WHO ICTRP CTRI/2016/04/006843).
20 While randomised comparisons between complications observed from TRUS and
21 transperineal biopsy approaches are old and sparsely published yet desirable, it is likely
22 that a large study population derived from multiple centres would be required to obtain
23 statistical power. In the meantime, our review supports the specific screening for risk

- 1 factors predictive of post biopsy infection, to aid in the selection of patients for these
- 2 preventative strategies.

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1 **Supplementary Figure 1.** PRISMA flowchart of study selection. From the initial 4545
2 citations, 120 articles were included in the final qualitative review.

3 **Supplementary Figure 2:** Global prevalence of fluoroquinolone resistance in Gram-
4 negative urinary pathogens (adapted from Zowawi et al ¹¹²) – data from published
5 studies or national surveillance databases 2009-2014.

6

7 **Table 1:** Summary of risk factors and proposed TRUBP Risk assessment
8 questionnaire. Risk factors should be considered when determining the optimal biopsy
9 approach and use of adjunctive prevention measures to reduce biopsy-related
10 complication. A risk assessment questionnaire may help identify patients at an
11 increased risk of biopsy-related complication. Adapted from Loeb et al³ and Losco et
12 al⁵¹.

Risk factors	
Host related	Rectal flora antimicrobial resistance (fluoroquinolone most commonly)
	Recent urogenital infection and/or antibiotic use
	Hospital admission or exposure (healthcare worker)
	Recent international travel
	Bacteriuria (pre-biopsy urine culture, indwelling catheter in situ)
	Co-morbidities (Diabetes mellitus, cardiac valve replacement, chronic obstructive pulmonary disease, benign prostatic hyperplasia)
Surgeon related	Approach – transrectal, transperineal, MRI-guided

	Repeat biopsy
	Greater number of biopsy cores
	Contaminated ultrasound gel
Questionnaire	
Rectal flora antimicrobial resistance	Recent or recurrent urogenital infection?
	Antibiotic use (especially fluoroquinolone)?
	Recent hospital admission?
	Occupation as healthcare worker?
	Recent international travel (especially South-east Asia or South America or South-Europe)?
Bacteruria	Pre-biopsy urine culture indicated?
	Indwelling catheter in situ?
Co-morbidities	Diabetes mellitus?
	Cardiac valve disease/replacement?
	Chronic obstructive pulmonary disease?
	Benign prostatic hyperplasia?
	Other immunosuppressive disorder or treatment?
Previous biopsy	Previous biopsy? How many?

1

2

1 **Table 2:** Recommendations for assessment and prevention of prostate biopsy related
 2 infection arising from this collaborative systematic review. Studies were rated according
 3 to the level of evidence (LoE) and the grade of recommendation (GoR) using a system
 4 used in the EAU guidelines (2015) modified from the Oxford Centre for Evidence-based
 5 Medicine²³.

Recommendation	LoE	GoR
1. The proportion of patients undergoing TRUS biopsy harbouring antibiotic-resistant bacteria in their gut flora is not insignificant. Routine quinolone-based prophylaxis may no longer be sufficient for all patients.	1B	A
2. Risk factors should be identified for all patients scheduled for prostate biopsy to determine if an altered prophylaxis regime is to be considered. These include:	2A	B
• Urogenital infection and/or antibiotic use in last 6 months	2A	
• International travel in last 6 months	2A	
• Hospital admission or exposure (healthcare worker) in last 6 months	2A	
• Current bacteriuria/indwelling catheter	2A	
• Previous TRUS biopsy	2A	
• Planned saturation biopsy	2B	
3. Patients <i>without</i> risk factors may proceed to TRUS biopsy using quinolone-based prophylaxis following informed consent of their low risk of sepsis, as well as clear instruction to seek urgent medical attention if they develop symptoms of infection.	1B	A
4. Patients <i>with</i> risk factors should prompt the clinician to consider:		
• a transperineal biopsy, requiring only single dose prophylaxis with IV cephazolin, with risk of sepsis less than 1/1000, OR	2A/3	B
• TRUS biopsy following rectal culture and targeted antibiotic prophylaxis according to culture results, AND/OR	2A	B

- | | | |
|--|----|---|
| • TRUS biopsy with rectal disinfection using Povidone-iodine | 2A | B |
|--|----|---|

1

2 **Table 3:** Management summary for patients presenting with post-TRUBP sepsis.3 Empiric treatment should be region- or hospital-specific and continue until *in vitro*

4 susceptibilities become available. Culture-directed treatment is dependent on the

5 underlying organism and should be implemented when possible.

Indication	IV therapy options	Oral therapy options ¹	Remarks
Empiric management			
Sepsis	Refer to local protocol or antibiogram and seek advice from infectious disease specialist or microbiologist. Consider carbapenems or piperacillin-tazobactam +/- aminoglycoside.		
Culture directed management (if susceptible <i>in vitro</i>)			
Enterobacteriaceae – non-MDR strains	<ul style="list-style-type: none"> • Gentamicin • Ceftriaxone 	<ul style="list-style-type: none"> • Amoxicillin +/- clavulanate • Co-trimoxazole or trimethoprim • Fluoroquinolone 	Use narrowest spectrum according to susceptibility results. Generally gentamicin should only be given for <48h
ESBL-producing Enterobacteriaceae	<ul style="list-style-type: none"> • Carbapenems • Piperacillin-tazobactam² • Aminoglycoside (may be 	<ul style="list-style-type: none"> • Fosfomycin • Temocillin • Pivmecillinam 	If piperacillin-tazobactam is used should

	<p>susceptible to amikacin, but frequently gentamicin resistant)</p> <ul style="list-style-type: none"> • Ceftolozane/tazobactam • Ceftazidime/avibactam 	<ul style="list-style-type: none"> • Amoxicillin-clavulanate² • (Co-trimoxazole or Fluoroquinolone but often resistant) 	<p>be dosed maximally (e.g. 4.5g 6-hourly).</p> <p>Generally aminoglycosides should only be given for</p>
<p>AmpC-producing Enterobacteriaceae (e.g. <i>Enterobacter cloacae/aerogenes</i>, <i>Citrobacter freundii</i>, <i>Serratia marcescens</i>, <i>Morganella morganii</i>)</p>	<ul style="list-style-type: none"> • Carbapenems • Cefepime • Piperacillin-tazobactam (if susceptible, but resistance can develop in complex infections) • Aminoglycosides • Ceftazidime/avibactam 	<ul style="list-style-type: none"> • Co-trimoxazole or trimethoprim • Fluoroquinolone • Fosfomycin • Temocillin 	<p><48h and not used as monotherapy. Cefepime should be dosed at 2g Q8h if normal renal function</p>
<p><i>Pseudomonas aeruginosa</i></p>	<ul style="list-style-type: none"> • Piperacillin-tazobactam • Ceftazidime • Cefepime • (All +/- aminoglycoside) 	<p>Fluoroquinolone (Only oral agent active against <i>Pseudomonas</i> spp.)</p>	
<p>Carbapenem-resistant / XDR organisms</p>	<ul style="list-style-type: none"> • Ceftazidime/avibactam: (for KPC, some OXA-type carbapenemase; not NDM or IMP types) • Ceftolozane/tazobactam: often effective for MDR-<i>Pseudomonas</i> spp. 	<p>Usually very few oral options available</p> <p>Fosfomycin may be effective</p>	<p>Seek specialist advice; carbapenems may still be used if dosed to maximise exposure (e.g. extended</p>

	<ul style="list-style-type: none"> • Combination therapy: e.g. carbapenem + polymixin (or aminoglycoside, e.g. amikacin); dual carbapenems 		infusions) with reference to the MIC, or used in combination
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- 1 ¹ Consider IV to oral switch once patient is afebrile, with resolved clinical signs of
2 sepsis, tolerating oral intake, gastrointestinal absorption is not compromised and source
3 control has been achieved; longer IV duration may be required if positive blood cultures
4 or other complications (e.g. undrained abscess). Total duration is typically 7-14 days
5 ² If susceptible in vitro: use against ESBL-producers is controversial, specialist advice is
6 recommended

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