Accepted Manuscript

Title: Prostate Biopsy Related Infection: a Systematic Review of Risk Factors, Prevention Strategies and Management Approaches.

Author: Matthew J. Roberts, Harrison Y. Bennett, Patrick N. Harris, Michael Holmes, Jeremy Grummet, Kurt Naber, Florian M.E. Wagenlehner

PII: S0090-4295(16)30953-0
DOI: http://dx.doi.org/doi: 10.1016/j.urology.2016.12.011
Reference: URL 20190

To appear in: *Urology*

Received date: 1-11-2016
Accepted date: 12-12-2016

Please cite this article as: Matthew J. Roberts, Harrison Y. Bennett, Patrick N. Harris, Michael Holmes, Jeremy Grummet, Kurt Naber, Florian M.E. Wagenlehner, Prostate Biopsy Related Infection: a Systematic Review of Risk Factors, Prevention Strategies and Management Approaches., *Urology* (2016), http://dx.doi.org/doi: 10.1016/j.urology.2016.12.011.

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

Matthew J. Roberts[1,2,3], Harrison Y. Bennett[1], Patrick N. Harris[1,2,4], Michael Holmes[5], Jeremy Grummet[6,7], Kurt Naber[8], Florian M. E. Wagenlehner[9]

1 – School of Medicine, The University of Queensland, Brisbane, Queensland, Australia

2 –Centre for Clinical Research, The University of Queensland, Brisbane, Queensland, Australia

3 –Department of Urology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

4 –Pathology Queensland, Department of Microbiology, Central Laboratory, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

5 –Urology Department, Waikato Hospital, Hamilton, New Zealand.

6 –Department of Urology, Alfred Health, Melbourne, Victoria, Australia.

7 –Department of Surgery, Monash University, Melbourne, Victoria, Australia.

8 –Department of Urology, Technical University of Munich, Munich, Germany.

9 –Clinic for Urology, Pediatric Urology and Andrology, Justus Liebig University Giessen, Germany

Corresponding author: Dr Matthew Roberts

Level 6, UQ Centre for Clinical Research, Building 71/918, Royal Brisbane and Women's Hospital Campus, Herston, QLD 4029, Australia

Tel: +61 422 378 975, Fax: +61 7 3346 5509,

m.roberts2@uq.edu.au

Total word count: 4,000 **Abstract word count:** 98

Conflicts of interest: Matthew Roberts: none. Harrison Bennett: none. Patrick Harris: none. Michael Holmes: none. Jeremy Grummet: sponsored to attend UAA 2016 by Biobot. Kurt Naber: paid consultant to Bionorica, DaiichiSankyo, Enteris Biopharma, Leo Pharma, MerLion, OM Pharma, Paratek, Rosen Pharma, Zambon. Florian Wagenlehner: paid consultant Achaogen, Actelion, AstraZeneca, MSD, Janssen.

Acknowledgements: M.J.R. is supported by a Doctor in Training Research Scholarship from Avant Mutual Group Ltd., a Cancer Council Queensland PhD Scholarship and Professor William Burnett Research Fellowship from the Discipline of Surgery, School of Medicine, The University of Queensland, Australia. PH is supported by an Australian Postgraduate Award from the University of Queensland.

This manuscript represents a shortened version of a chapter submitted for publication in the living textbook, Urogenital Infections (GMS GmbH).

Abstract

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

Keywords: biopsy, complications, fluoroquinolone resistance, prostate, sepsis, symptomatic infection

1. INTRODUCTION

Transrectal ultrasound-guided (TRUS) biopsy of the prostate (TRUBP) is the most commonly used modality to diagnose prostate cancer, resulting in millions of biopsies performed internationally each year[1]. Despite reduced PSA testing and biopsy rates following the U.S. Preventative Services Task Force recommendation in 2012[2], widespread use of PSA testing, an ageing population, and increasing implementation of active surveillance protocols for low risk disease requires prostate biopsy to be performed in high numbers worldwide. TRUBP is traditionally considered a safe

procedure but infectious complications can occur; including urinary tract infection (UTI; >6%), prostatitis, and sepsis (~1%)[3, 4] due to particularly Gram-negative Enterobacteriaceae such as *Escherichia coli* resulting in substantial health and economic burden[1, 5, 6]. TRUBP is considered a 'contaminated' procedure under European Association of Urology (EAU) guidelines, necessitating antibiotic prophylaxis as a standard of care for all cases[7-10]. Fluoroquinolone-based prophylaxis is recommended by many authorities, including the EAU and the American Urological Association, due to their broad coverage against rectal flora and favourable prostatic drug penetration[11]. Duration of prophylaxis is varied, with no evidence to suggest prolonged duration translates to reduced complications[8, 12, 13].

Despite antibiotic prophylaxis, observational studies have reported increasing rates of infectious complications over the past two decades and postulate a strong association with changing antimicrobial resistance, especially fluoroquinolone resistance[5, 14-18]. Teillant and colleagues have reported that, in the USA, 13,120 post-TRUBP infections per year are attributable to fluoroquinolone resistance, which would increase to 64,000 infections per year in the event of 100% fluoroquinolone resistance[5]. The management of TRUBP complications causes significant financial burden on health systems, reported to cost more than that due to methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile* in the UK[19, 20]. The non-financial, unmeasurable burden of disease from TRUBP complications, including the physical suffering and psychological burden of significant illness, hospital admission and anxiety regarding future biopsies, must also be considered[21]. Furthermore, a recent Federal Drug Administration warning of

disabling and potentially permanent serious side effects associated with fluoroquinolone therapy warrants consideration[22].

While resources available to urologists, such as the American Urological Association White Paper on the Prevention and Treatment of Common Complications Related to Prostate Biopsy[23], partially outline risk factors and management of post-TRUBP complications, this review sought to critically appraise and summarise available published literature on risk factors, prevention and management of TRUBP-associated infectious complications. The available evidence was reviewed in the context of spreading multi-drug resistance (MDR) to provide recommendations for general use in modern international urology practice.

2. MATERIALS AND METHODS

A systematic literature search was conducted in January 2016 in accordance with the PRISMA statement and Cochrane Guidelines[24]. The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, and LILACS databases were searched for the following key terms: *prostat**, *biopsy*, *infect*, culture*, bacter*, sepsis, fever, UTI*. Only peer reviewed manuscripts were considered for inclusion.

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

Studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) similar to the EAU guidelines (2015) modified from the Oxford Centre for Evidence-based Medicine[25]. Overall, included studies contained limited randomised data for most scenarios, and consequently the LoE was mostly 2A/2B and GoR B.

3. RESULTS

3.1 Incidence

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

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

3.2 Risk factors

An appreciation for risk factors predictive of post-TRUBP infection allows the treating urologist to guide prophylaxis, as well as assist in patient selection for alternative sampling methods[34]. Reported risk factors for post-TRUBP infection are listed in Table 1.

3.2.1 Host-related

3.2.1.1 Antimicrobial resistance

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

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

TRUBP-associated infections in patients with fluoroquinolone resistant rectal cultures compared with fluoroquinolone sensitive (7.1% vs. 1.1%), which translated to a 7.4% vs. 1.4% risk difference, respectively[37]. These findings were supported by a collaborative analysis of the original source data, with fluoroquinolone resistance associated with an increased overall risk of infection (OR 3.98, 95% CI 2.37-6.71) and hospitalisation (OR 4.77, 95% CI 2.50-9.10), which were highest with fluoroquinolone monotherapy[39].

3.2.1.2 Prior urogenital infection and/or antibiotic use

Many studies in patients undergoing TRUBP have reported antimicrobial use within the past 3-6 months to be significantly associated with fluoroquinolone resistant carriage in the rectal flora[17, 34, 38, 40, 46, 47]. These findings have been corroborated using meta-analysis, with history of genitourinary infection (OR 2.56; 95% CI 1.13 – 5.79; n = 1,218) and prior fluoroquinolone use (OR 4.12; 95% CI 2.30 – 7.37; n = 1,356) reported to be significant risk factors for fluoroquinolone-resistance colonisation[37]. Wagenlehner and colleagues demonstrated on rectal swab culture that single dose prophylaxis was sufficient to select for ciprofloxacin resistant organisms, with a four-fold increase in fluoroquinolone resistance after administration[43]. This has also been demonstrated in studies investigating empiric antibiotics for elevated PSA, with extended antibiotic administration leading to significantly higher rates of sepsis and resistance following biopsy[48]. Given the high concordance between fluoroquinolone resistance and extended-spectrum beta-lactamase (ESBL) production, it is unsurprising that the use of fluoroquinolone prophylaxis has also been shown to co-select for ESBL-producing *E. coli*[49].

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 physicians[51], as well as relatives of hospital employees[52].

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].

3.2.1.6 Co-morbidities

The presence of co-morbidities such as diabetes mellitus, cardiac valve replacement, chronic obstructive pulmonary disease, immunosuppression, or benign prostatic hyperplasia have been variably reported to increase the risk of post-TRUBP complications. Higher comorbidity scores have also been associated with a significantly increased risk of hospitalisation post-biopsy in multiple large retrospective cohorts[14, 33, 56]. Diabetes and the metabolic syndrome have been reported to be associated with both increased risk of infectious complications, and carriage of resistant organisms[15, 33, 57-59]. However, on meta-analysis of available risk factors, diabetes (OR 1.37; 95% CI 0.77 – 2.46; n=1,140) was not significantly associated with fluoroquinolone-resistant colonisation[37].

3.2.1.7 Compliance

Non-compliance is difficult to reliably assess but may contribute to complication rates, as high as 43%, in populations with a relatively low baseline prevalence of fluoroquinolone resistance[60]. Of greater concern, the compliance of the treating urologist to best practice guidelines can influence sepsis outcomes, with a large multicenter study by Bruyere and colleagues reporting noncompliance with antibiotic prophylaxis guidelines to be a risk factor for post-TRUBP sepsis (OR 2.3, 95% CI 1.4 - 3.9)[46].

3.2.2 Surgeon related

3.2.2.1 Mode of biopsy

Standard TRUBP has many pitfalls which are well known to urologists, thus alternative methods are discussed here. Transperineal biopsy is an alternative method of sampling providing transcutaneous access to the prostate, facilitated by the recent implementation of MRI-fused prostate biopsy methodology[18, 61]. As prostate cancer detection rates have been reported to be similar, transperineal prostate biopsy has typically been reserved for patients at high risk of sepsis, or for repeat biopsies, especially those with a previous non-diagnostic TRUBP for better detection of anteriorly sited tumours[3, 18, 62, 63]. Transperineal sampling allows thorough skin preparation in line with typical surgical procedures, and prophylactic antibiotics (*eg* cephazolin) are targeted to skin flora and common urinary pathogens[64, 65]. As transperineal biopsies avoid the rectum, this approach has traditionally been thought to have lower rates of infection than the 'transfaecal' route of TRUBP. Transperineal biopsy has been classified as a 'clean-contaminated' procedure in the EAU guidelines, however it could even be argued that it is 'clean' as there is often no breach of urinary tract mucosa using this approach[66]. This benefit is less clear in practice, and studies with direct comparison of morbidity between transrectal and transperineal biopsy are lacking. Recent reports suggest zero or near-zero sepsis rates with the transperineal procedure[3, 65], further supported by three large cohort studies totaling 8,093 patients with one case of urosepsis reported and recent meta-analysis estimate of 0.1%[6, 67-69]. From an antimicrobial stewardship perspective, transperineal biopsy may also avoid selecting for fluoroquinolone- or multi-resistant bacteria, and stem the increasing

reliance on an ever-expanding range of antibiotics for biopsy prophylaxis. These clear benefits in decreasing infection related morbidity are at the expense of higher logistical and time considerations, requiring admission to hospital, an operating theatre, and usually general anaesthesia. Transperineal biopsy is also associated with higher rates of post-procedure urinary retention[6], as shown in Supplementary Table 1.

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

3.2.2.2 Number of cores

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

needles with low morbidity[75]. Local anaesthetic administration has also not been associated with increased infectious complications[46].

3.2.2.3 Previous biopsies

Repeat biopsies are indicated for active surveillance of low risk disease, or in men with persistent suspicion of prostate cancer according to elevated PSA, abnormal DRE, or suspicious appearance on imaging[76]. Reports regarding the association between repeat biopsies and an increased risk of infectious complications compared with initial biopsies are mixed[31, 46, 77]. Any potential risk is concerning in this context, with a retrospective analysis reported increased odds of an infection (OR 1.33, 95%CI 1.01 - 1.74) for every previous biopsy in 591 consecutive men undergoing TRUBP[77]. Repeat biopsy has been reported to be a risk factor for colonisation with resistant *E. coli* strains[78], with a progressive increase reported for each biopsy undertaken[79]. Post-biopsy complications have been reported to reduce rates of repeat biopsy in men undergoing active surveillance[80].

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

3.3 Prevention strategies

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

An evolving body of evidence supports either an expanded antibiotic protocol or one targeted to rectal cultures on fluoroquinolone-impregnated MacConkey agar plates[81]. Expanded antibiotic protocols can consist of either a broad-spectrum antibiotic or the use of multiple antibiotics, both being a selective force for emergence of multi-resistant pathogens.

Targeted prophylaxis aims to lower the risk of post-TRUBP infection due to resistant pathogens and serves to facilitate antimicrobial stewardship, as supported by Liss and colleagues[39]. Meta-analysis of available data in 2014 comprising 2,541 patients estimated higher infection rates when empirical prophylaxis was used (3.3%, 95% CI 2.6-4.2%) than those using targeted methods (0.3%, 95% CI 0-0.9%)[37]. In contrast, multiple studies, including a large retrospective North American multicenter database from over 5,000 patients, in which up to 34% received targeted prophylaxis, have observed no difference in complications between targeted and empiric prophylaxis groups[27, 36, 82, 83]. It has been suggested that patients undergoing repeat biopsy require repeat culture prior to each biopsy[84] and targeted prophylaxis. While potential financial benefits toward antimicrobial stewardship and potentially for infectious complications averted are substantial[85], further assessment in a randomized controlled trial is required.

3.3.2 Decontamination

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

3.3.2.1 Rectal disinfection

Povidone-iodine rectal preparation (PIRP) is simple and affordable, not associated with selection of resistant bacteria, and proven safe for colorectal surgery[87]. From meta-analysis of seven controlled trials (n = 2,049) of rectal disinfection using PIRP prior to TRUBP, significant reductions in fever, bacteruria and bacteraemia (RR 0.31; 95% CI 0.21 – 0.45) regardless of prophylaxis used have been reported[88]. Recent retrospective studies further report significant reductions in infectious complications when PIRP was used[89], as well as in conjunction with targeted prophylaxis[90]. However, a randomised controlled trial of prophylactic povidone-iodine use demonstrated insignificantly reduced complication rates (2.6%) compared with control (4.5%), in a study that is likely to have been underpowered[91]. The optimal method of administering PIRP has not been fully elucidated but the use of a suppository or gauze soaked in povidone-iodine has been reported to be superior to a rectal enema[88, 92].

3.3.2.2 Rectal cleansing

Preparation with a rectal cleansing enema (*eg* Fleet sodium phosphate) is used by a minority (18 – 30%) of urologists[13] based on mixed results in currently available evidence[8, 30, 93-96].

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

3.4 Management of prostate biopsy related infection

When considering the optimal treatment for a patient with an infectious complication following prostate biopsy, several factors need to be considered. This includes the severity of the clinical presentation, the likelihood of resistance to empirical antibiotics, the co-morbidities of the host and whether anatomical complications co-exist (such as prostate abscesses or urinary tract obstruction). Choosing appropriate initial therapy is critical as these infections can progress quickly and may result in life-threatening complications. Inadequate or delayed empirical therapy has been associated with excess mortality in Gram-negative sepsis, especially in the setting of a high background prevalence of ESBL-producers[97-99]. Furthermore, inadequate empirical therapy is not uncommon in the setting of post-TRUBP sepsis, occurring in 36% of patients in one study[35].

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

Obtaining a detailed history of recent antibiotic use may help assess the risk of resistance and, if fluoroquinolones have been used for prophylaxis, this class of drug should be avoided for empirical therapy. As noted previously, a significant risk factor for the likelihood of infection with a multi-drug resistant pathogen, is recent travel to a country highly endemic for Gram-negative resistance within the preceding 6 months[100]. The prevalence of resistance mechanisms such as ESBLs or carbapenemases in Gram-negative uropathogens varies widely across the world, and the situation is dynamic. Carbapenemase-producers tend to also possess numerous other resistance determinants, rendering them multi-drug resistant (MDR), extensively-drug resistant (XDR) or even pan-drug resistant (PDR)[101, 102]. Clearly this can dramatically reduce treatment options and makes selecting effective empirical therapy extremely problematic should these strains become predominant. In some patients, who are known to be colonised with MDR pathogens, alternatives to TRUBP or avoidance of any interventional procedure may have to be considered given the risks involved[103].

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

recent hospitalization in an ESBL-high burden region and ≥6 days of antibiotic exposure in the preceding 6 months[106]. In a retrospective cohort of 1,288 patients with bacteremia, this approach demonstrated positive and negative predictive values of 90.8% and 91.9% respectively[106]. However, this model has only been derived from a single centre in the US and requires validation in other cohorts. Pre-biopsy rectal culture may also facilitate identification of antimicrobial resistance and help guide treatment of biopsy-related sepsis, with one study demonstrating a high concordance between rectal and urine or blood cultures in patients with sepsis[107].

3.4.2 Early recognition of infectious complications

It is important for patients undergoing TRUBP to be made aware of the signs and symptoms of infection should they occur post procedure. The early recognition and effective treatment of sepsis is a key factor in improving patient outcomes, and management should broadly follow international guidelines, such as those of the Surviving Sepsis Campaign[108].

3.4.3 Empirical therapy for infectious complications

Empirical regimens must have adequate coverage to reflect local patterns of resistance in key uropathogens, especially Gram-negative bacteria such as *E. coli*. Most microbiology laboratories can provide antimicrobial susceptibility data for urinary tract isolates to inform local guidelines, or this information may be available from national surveillance data[109].

Given the difficulty in reliably predicting susceptibility to empirical treatment regimens, it is critical that appropriate microbiological specimens are collected for culture, including a mid-stream urine and blood cultures, if the patient is febrile or shows other signs of sepsis. An advantage for the routine use of pre-biopsy rectal screening (close to the date of biopsy) is that positive cultures can guide empirical therapy, given a known concordance between positive rectal and urine or blood cultures in patients with sepsis[107].

In general, given the association with fluoroquinolone prophylaxis and MDR-*E. coli* infections, patients presenting with urinary sepsis post-TRUBP will require a broader spectrum of antibiotic coverage than patients with community-onset infections without prior healthcare exposure[7]. Therapy with agents such as 3rd generation cephalosporins (e.g. ceftriaxone or ceftazidime), amoxicillin-clavulanate, fluoroquinolones or gentamicin may have a high likelihood of resistance in this context. Broader-spectrum empirical options need to be considered. This could include piperacillin-tazobactam or carbapenems. Amikacin, usually in combination with a beta-lactam agent, may also be considered given that it frequently retains better *in vitro* activity than gentamicin against *E. coli* isolated from patients with post-TRUBP sepsis[35]and has shown an additive benefit in reducing post-TRUBP infections when used as a prophylactic agent[3].

3.4.4 Directed therapy for MDR Gram negative pathogens

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

medical microbiologist is recommended for these difficult-to-treat organisms. For several reasons, carbapenems have been regarded as the treatment of choice for ESBL-producers[110, 111]. However, carbapenem resistance has been increasing in many parts of the world[112], prompting reconsideration of drugs that were previously considered less effective (such as cefepime, beta-lactam/beta-lactamase inhibitor (BLBLI) drugs, or older agents such as fosfomycin, pivmecillinam, or temocillin). Although published experience with using fosfomycin for treating infections post TRUBP are sparse, it has shown broadly similar efficacy in comparison to carbapenems for patients with lower tract infections caused by ESBL-producers, including for patients with complicating factors[113]. It is notable that fosfomycin appears to achieve adequate prostate tissue levels and may be an option for prophylaxis in patients known to be colonised with MDR Gram-negative pathogens[114, 115]. Mecillinam is another 'rediscovered' antibiotic that appears effective in vitro against ESBL-producing *E. coli*[116], however there are no published data with respect to pivmecillinam treatment for men with infections post-TRUBP. Temocillin, a derivative of ticarcillin, has received renewed interest in recent years and shows stability to a range of ESBL and AmpC beta-lactamases[117]. It has been used in addition to ciprofloxacin for routine prophylaxis prior to TRUBP in patients at high risk of colonisation with resistant *E. coli* strains[118]. Novel beta-lactam/beta-lactamase inhibitor combinations, such as ceftazidime/avibactam and ceftolozane/tazobactam may also prove to be useful against MDR or XDR Gram-negatives where few alternatives exist (although neither drug is effective against all types of beta-lactamases). Both agents have now received FDA approval for the treatment of complicated UTI following two phase 3 studies[119, 120].

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

4. CONCLUSIONS

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

REFERENCES

1. Wagenlehner FM, van Oostrum E, Tenke P, et al. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. *Eur Urol.* 2013;63:521-527.
2. Banerji JS, Wolff EM, Massman JD, 3rd, Odem-Davis K, Porter CR, Corman JM. Prostate Needle Biopsy Outcomes in the Era of the U.S. Preventive Services Task Force Recommendation against Prostate Specific Antigen Based Screening. *J Urol.* 2016;195:66-73.
3. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. *Eur Urol.* 2013;64:876-892.
4. Wagenlehner FM, Pilatz A, Waliszewski P, Weidner W, Johansen TE. Reducing infection rates after prostate biopsy. *Nat Rev Urol.* 2014;11:80-86.
5. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *Lancet Infect Dis.* 2015;15:1429-1437.
6. Bennett HY, Roberts MJ, Doi SA, Gardiner RA. The global burden of major infectious complications following prostate biopsy. *Epidemiol Infect.* 2016;144:1784-1791.
7. Williamson DA, Barrett LK, Rogers BA, Freeman JT, Hadway P, Paterson DL. Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant Escherichia coli. *Clin Infec Dis.* 2013;57:267-274.
8. Zani Emerson L, Clark Otavio Augusto C, Rodrigues Netto Jr N. Antibiotic prophylaxis for transrectal prostate biopsy. *Cochrane Database Syst Rev.*: John Wiley & Sons, Ltd; 2011.
9. Wolf JS, Jr., Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol.* 2008;179:1379-1390.
10. Grabe M, Bjerklund-Johansen TE, Botto H, et al. Perioperative antibacterial prophylaxis in urology. *Guidelines on urological infections.* Vol 2013. Arnhem, The Netherlands.: European Association of Urology (EAU); 2011.
11. Kandemir O, Bozlu M, Efesoy O, Guntekin O, Tek M, Akbay E. The incidence and risk factors of resistant E. coli infections after prostate biopsy under fluoroquinolone prophylaxis: a single-centre experience with 2215 patients. *J Chemother.* 2016;28:284-288.
12. Shandera KC, Thibault GP, Deshon GE. Variability in patient preparation for prostate biopsy among American urologists. *Urology.* 1998;52:644-646.
13. Davis P, Paul E, Grummet J. Current practice of prostate biopsy in Australia and New Zealand: A survey. *Urol Ann.* 2015;7:315-319.
14. Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications after prostate biopsy: data from SEER-Medicare. *J Urol.* 2011;186:1830-1834.
15. Loeb S, van den Heuvel S, Zhu X, Bangma CH, Schroder FH, Roobol MJ. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. *Eur Urol.* 2012;61:1110-1114.

16. Nam RK, Saskin R, Lee Y, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol.* 2010;183:963-968.

17. Carignan A, Roussy JF, Lapointe V, Valiquette L, Sabbagh R, Pepin J. Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? *Eur Urol.* 2012;62:453-459.

18. Borghesi M, Ahmed H, Nam R, et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy. *Eur Urol.* 2016.

19. Batura D, Gopal Rao G. The national burden of infections after prostate biopsy in England and Wales: a wake-up call for better prevention. *J Antimicrob Chemother.* 2013;68:247-249.

20. Batura D, Gopal Rao G. The national burden of infections after prostate biopsy in England and Wales: a wake-up call for better prevention--authors' response. *J Antimicrob Chemother.* 2013;68:2419-2420.

21. Roberts MJ, Parambi A, Barrett L, et al. Multifocal abscesses due to multiresistant Escherichia coli after transrectal ultrasound-guided prostate biopsy. *Med J Aust.* 2013;198:282-284.

22. US Food and Drug Administration. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm

23. Liss MA, Ehdaie B, Loeb S, et al. AUA White Paper on The Prevention and Treatment of the More Common Complications Related to Prostate Biopsy Update. . Vol 2016: American Urological Association (AUA), Education and Research, Inc.; 2016.

24. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.

25. *Guidelines. Methodology section.* 2015 ed.

26. Gopal Rao G, Batura D. Emergency hospital admissions attributable to infective complications of prostate biopsy despite appropriate prophylaxis: need for additional infection prevention strategies? *Int Urol Nephrol.* 2014;46:309-315.

27. Womble PR, Dixon MW, Linsell SM, et al. Infection related hospitalizations after prostate biopsy in a statewide quality improvement collaborative. *J Urol.* 2014;191:1787-1792.

28. Carmignani L, Picozzi S, Spinelli M, et al. Bacterial sepsis following prostatic biopsy. *Int Urol Nephrol.* 2012;44:1055-1063.

29. Liss MA, Chang A, Santos R, et al. Prevalence and significance of fluoroquinolone resistant Escherichia coli in patients undergoing transrectal ultrasound guided prostate needle biopsy. *J Urol.* 2011;185:1283-1288.

30. Zaytoun OM, Vargo EH, Rajan R, Berglund R, Gordon S, Jones JS. Emergence of fluoroquinolone-resistant Escherichia coli as cause of postprostate biopsy infection: implications for prophylaxis and treatment. *Urology.* 2011;77:1035-1041.

31. Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Is repeat prostate biopsy associated with a greater risk of hospitalization? Data from SEER-Medicare. *J Urol.* 2013;189:867-870.

32. Campeggi A, Ouzaid I, Xylinas E, et al. Acute bacterial prostatitis after transrectal ultrasound-guided prostate biopsy: epidemiological, bacteria and treatment patterns from a 4-year prospective study. *Int J Urol.* 2014;21:152-155.

33. Lundstrom KJ, Drevin L, Carlsson S, et al. Nationwide population based study of infections after transrectal ultrasound guided prostate biopsy. *J Urol.* 2014;192:1116-1122.

34. Anderson E, Leahy O, Cheng AC, Grummet J. Risk factors for infection following prostate biopsy - a case control study. *BMC Infec Dis.* 2015;15:580.

35. Williamson DA, Roberts SA, Paterson DL, et al. Escherichia coli bloodstream infection after transrectal ultrasound-guided prostate biopsy: implications of fluoroquinolone-resistant sequence type 131 as a major causative pathogen. *Clin Infec Dis.* 2012;54:1406-1412.

36. Liss MA, Johnson JR, Porter SB, et al. Clinical and microbiological determinants of infection after transrectal prostate biopsy. *Clin Infec Dis.* 2015;60:979-987.

37. Roberts MJ, Williamson DA, Hadway P, Doi SA, Gardiner RA, Paterson DL. Baseline prevalence of antimicrobial resistance and subsequent infection following prostate biopsy using empirical or altered prophylaxis: A bias-adjusted meta-analysis. *Int J Antimicrob Agents.* 2014;43:301-309.

38. Steensels D, Slabbaert K, De Wever L, Vermeersch P, Van Poppel H, Verhaegen J. Fluoroquinolone-resistant E. coli in intestinal flora of patients undergoing transrectal ultrasound-guided prostate biopsy--should we reassess our practices for antibiotic prophylaxis? *Clin Microbiol Infect.* 2012;18:575-581.

39. Liss MA, Taylor SA, Batura D, et al. Fluoroquinolone resistant rectal colonization predicts risk of infectious complications after transrectal prostate biopsy. *J Urol.* 2014;192:1673-1678.

40. Patel U, Dasgupta P, Amoroso P, Challacombe B, Pilcher J, Kirby R. Infection after transrectal ultrasonography-guided prostate biopsy: increased relative risks after recent international travel or antibiotic use. *BJU Int.* 2012;109:1781-1785.

41. Rogers BA, Aminzadeh Z, Hayashi Y, Paterson DL. Country-to-country transfer of patients and the risk of multi-resistant bacterial infection. *Clin Infec Dis.* 2011;53:49-56.

42. Williamson DA, Masters J, Freeman J, Roberts S. Travel-associated extended-spectrum beta-lactamase-producing Escherichia coli bloodstream infection following transrectal ultrasound-guided prostate biopsy. *BJU Int.* 2012;109:E21-22.

43. Wagenlehner F, Stower-Hoffmann J, Schneider-Brachert W, Naber KG, Lehn N. Influence of a prophylactic single dose of ciprofloxacin on the level of resistance of Escherichia coli to fluoroquinolones in urology. *Int J Antimicrob Agents.* 2000;15:207-211.

44. Lee JW, Park SC, Kim MK, Cheon MW, Kim GY, Cho JH. Prevalence of antimicrobial resistance in normal rectal flora of patients undergoing transrectal ultrasonography-guided prostate biopsy in Korea. *Int J Urol.* 2014;21:811-814.

45. Siriboon S, Tiengrim S, Taweemongkongsup T, Thamlikitkul V, Chayakulkeeree M. Prevalence of antibiotic resistance in fecal flora of patients undergoing transrectal ultrasound-guided prostate biopsy in Thailand. *Urol Int.* 2012;88:187-193.

46. Bruyere F, Malavaud S, Bertrand P, et al. Prosbiotate: a multicenter, prospective analysis of infectious complications after prostate biopsy. *J Urol.* 2015;193:145-150.

47. Taylor S, Margolick J, Abughosh Z, et al. Ciprofloxacin resistance in the faecal carriage of patients undergoing transrectal ultrasound guided prostate biopsy. *BJU Int.* 2013;111:946-953.

48. Akduman B, Akduman D, Tokgoz H, et al. Long-term fluoroquinolone use before the prostate biopsy may increase the risk of sepsis caused by resistant microorganisms. *Urology.* 2011;78:250-255.

49. Arslan H, Azap OK, Ergonul O, Timurkaynak F, Urinary Tract Infection Study G. Risk factors for ciprofloxacin resistance among Escherichia coli strains isolated from community-acquired urinary tract infections in Turkey. *J Antimicrob Chemother.* 2005;56:914-918.

50. Dumford D, 3rd, Suwantarat N, Bhasker V, et al. Outbreak of fluoroquinolone-resistant Escherichia coli infections after transrectal ultrasound-guided biopsy of the prostate. *Infect Control Hosp Epidemiol.* 2013;34:269-273.

51. Carlson WH, Bell DG, Lawen JG, Rendon RA. Multi-drug resistant E.coli urosepsis in physicians following transrectal ultrasound guided prostate biopsies--three cases including one death. *Can J Urol.* 2010;17:5135-5137.

52. Kamdar C, Mooppan UMM, Gulmi FA, Kim H. Multi-Drug-Resistant Bacteremia After Transrectal Ultrasound Guided Prostate Biopsies in Hospital Employees and Their Relatives. *Urology.* 2008;72:34-36.

53. Losco G, Studd R, Blackmore T. Ertapenem prophylaxis reduces sepsis after transrectal biopsy of the prostate. *BJU Int.* 2014;113 Suppl 2:69-72.

54. Lindstedt S, Lindstrom U, Ljunggren E, Wullt B, Grabe M. Single-dose antibiotic prophylaxis in core prostate biopsy: Impact of timing and identification of risk factors. *Eur Urol.* 2006;50:832-837.

55. Simsir A, Kismali E, Mammadov R, Gunaydin G, Cal C. Is it possible to predict sepsis, the most serious complication in prostate biopsy? *Urol Int.* 2010;84:395-399.

56. Anastasiadis E, van der Meulen J, Emberton M. Hospital admissions after transrectal ultrasound-guided biopsy of the prostate in men diagnosed with prostate cancer: a database analysis in England. *Int J Urol.* 2015;22:181-186.

57. Luong B, Danforth T, Visnjevac O, Suraf M, Duff M, Chevli KK. Reduction in hospital admissions with the addition of prophylactic intramuscular ceftriaxone before transrectal ultrasonography-guided prostate biopsies. *Urology.* 2015;85:511-516.

58. Sahin C, Eryildirim B, Cetinel AC, et al. Does metabolic syndrome increase the risk of infective complications after prostate biopsy? A critical evaluation. *Int Urol Nephrol.* 2015;47:423-429.

59. Tsu JH, Ma WK, Chan WK, et al. Prevalence and predictive factors of harboring fluoroquinolone-resistant and extended-spectrum beta-lactamase-producing

rectal flora in Hong Kong Chinese men undergoing transrectal ultrasound-guided prostate biopsy. *Urology.* 2015;85:15-21.

60. Suwantarat N, Dumford DM, 3rd, Ponce-Terashima R, et al. Modification of antimicrobial prophylaxis based on rectal culture results to prevent fluoroquinolone-resistant Escherichia coli infections after prostate biopsy. *Infect Control Hosp Epidemiol.* 2013;34:973-976.

61. Borkowetz A, Platzek I, Toma M, et al. Comparison of systematic transrectal biopsy to transperineal magnetic resonance imaging/ultrasound-fusion biopsy for the diagnosis of prostate cancer. *BJU Int.* 2015;116:873-879.

62. Hossack T, Patel MI, Huo A, et al. Location and pathological characteristics of cancers in radical prostatectomy specimens identified by transperineal biopsy compared to transrectal biopsy. *J Urol.* 2012;188:781-785.

63. Ong WL, Weerakoon M, Huang S, et al. Transperineal biopsy prostate cancer detection in first biopsy and repeat biopsy after negative transrectal ultrasound-guided biopsy: the Victorian Transperineal Biopsy Collaboration experience. *BJU Int.* 2015;116:568-576.

64. Dundee PE, Grummet JP, Murphy DG. Transperineal prostate biopsy: template-guided or freehand? *BJU Int.* 2015;115:681-683.

65. Grummet JP, Weerakoon M, Huang S, et al. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? *BJU Int.* 2014;114:384-388.

66. Grabe M, Bartoletti R, Bjerklund-Johansen TE, et al. *Guidelines on urological infections.* Vol 2014. Arnhem, The Netherlands.: European Association of Urology (EAU); 2014.

67. Namekawa T, Fukasawa S, Komaru A, et al. Prospective evaluation of the safety of transrectal ultrasound-guided transperineal prostate biopsy based on adverse events. *Int J Clin Oncol.* 2015;20:1185-1191.

68. Mai Z, Yan W, Zhou Y, et al. Transperineal template-guided prostate biopsy: 10 years of experience. *BJU Int.* 2016;117:424-429.

69. Pepe P, Aragona F. Morbidity after transperineal prostate biopsy in 3000 patients undergoing 12 vs 18 vs more than 24 needle cores. *Urology.* 2013;81:1142-1146.

70. Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. *Eur Urol.* 2014;66:22-29.

71. Radtke JP, Teber D, Hohenfellner M, Hadaschik BA. The current and future role of magnetic resonance imaging in prostate cancer detection and management. *Transl Androl Urol.* 2015;4:326-341.

72. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol.* 2006;175:1605-1612.

73. Berger AP, Gozzi C, Steiner H, et al. Complication rate of transrectal ultrasound guided prostate biopsy: a comparison among 3 protocols with 6, 10 and 15 cores. *J Urol.* 2004;171:1478-1480; discussion 1480-1471.

74. Scattoni V, Maccagnano C, Zanni G, et al. Is extended and saturation biopsy necessary? *Int J Urol.* 2010;17:432-447.

75. Inal GH, Oztekin VC, Ugurlu O, Kosan M, Akdemir O, Cetinkaya M. Sixteen gauge needles improve specimen quality but not cancer detection rate in transrectal ultrasound-guided 10-core prostate biopsies. *Prostate Cancer Prostatic Dis.* 2008;11:270-273.

76. Ukimura O, Coleman JA, de la Taille A, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. *Eur Urol.* 2013;63:214-230.

77. Ehdaie B, Vertosick E, Spaliviero M, et al. The impact of repeat biopsies on infectious complications in men with prostate cancer on active surveillance. *J Urol.* 2014;191:660-664.

78. Liss MA, Nakamura KK, Meuleners R, Kolla SB, Dash A, Peterson EM. Screening rectal culture to identify fluoroquinolone-resistant organisms before transrectal prostate biopsy: do the culture results between office visit and biopsy correlate? *Urology.* 2013;82:67-71.

79. Cohen JE, Landis P, Trock BJ, et al. Fluoroquinolone resistance in the rectal carriage of men in an active surveillance cohort: longitudinal analysis. *J Urol.* 2015;193:552-556.

80. Bokhorst LP, Lepisto I, Kakehi Y, et al. Complications after prostate biopsies in men on active surveillance and its effects on receiving further biopsies in the Prostate cancer Research International: Active Surveillance (PRIAS) study. *BJU Int.* 2016;118:366-371.

81. Liss MA, Nakamura KK, Peterson EM. Comparison of broth enhancement to direct plating for screening of rectal cultures for ciprofloxacin-resistant Escherichia coli. *J Clin Microbiol.* 2013;51:249-252.

82. Dai J, Leone A, Mermel L, et al. Rectal Swab Culture–directed Antimicrobial Prophylaxis for Prostate Biopsy and Risk of Postprocedure Infection: A Cohort Study. *Urology.*85:8-14.

83. Walker JT, Singla N, Roehrborn CG. Reducing Infectious Complications Following Transrectal Ultrasound-guided Prostate Biopsy: A Systematic Review. *Rev Urol.* 2016;18:73-89.

84. Liss MA, Gillis K, Sakamoto K, Fierer J. Fluoroquinolone resistance colonization from initial to repeat prostate biopsy. *J Clin Urol.* 2016;9:392-396.

85. Taylor AK, Zembower TR, Nadler RB, et al. Targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound guided prostate biopsy is associated with reduced incidence of postoperative infectious complications and cost of care. *J Urol.* 2012;187:1275-1279.

86. Davis M, Sofer M, Kim SS, Soloway MS. The procedure of transrectal ultrasound guided biopsy of the prostate: a survey of patient preparation and biopsy technique. *J Urol.* 2002;167:566-570.

87. Pattana-arun J, Wolff BG. Benefits of povidone-iodine solution in colorectal operations: science or legend. *Dis Colon Rectum.* 2008;51:966-971.

88. Pu C, Bai Y, Yuan H, et al. Reducing the risk of infection for transrectal prostate biopsy with povidone-iodine: a systematic review and meta-analysis. *Int Urol Nephrol.* 2014;46:1691-1698.

89. Gyorfi JR, Otteni C, Brown K, et al. Peri-procedural povidone-iodine rectal preparation reduces microorganism counts and infectious complications following ultrasound-guided needle biopsy of the prostate. *World J Urol.* 2014;32:905-909.

90. Ryu JW, Jung SI, Ahn JH, et al. Povidone-iodine rectal cleansing and targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound-guided prostate biopsy are associated with reduced incidence of postoperative infectious complications. *Int Urol Nephrol.* 2016.

91. Abughosh Z, Margolick J, Goldenberg SL, et al. A prospective randomized trial of povidone-iodine prophylactic cleansing of the rectum before transrectal ultrasound guided prostate biopsy. *J Urol.* 2013;189:1326-1331.

92. Park DS, Hwang JH, Choi DK, et al. Control of infective complications of transrectal prostate biopsy. *Surg Infect.* 2014;15:431-436.

93. Lindert KA, Kabalin JN, Terris MK. Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. *J Urol.* 2000;164:76-80.

94. Jeon SS, Woo SH, Hyun JH, Choi HY, Chai SE. Bisacodyl rectal preparation can decrease infectious complications of transrectal ultrasound-guided prostate biopsy. *Urology.* 2003;62:461-466.

95. Carey JM, Korman HJ. Transrectal ultrasound guided biopsy of the prostate. Do enemas decrease clinically significant complications? *J Urol.* 2001;166:82-85.

96. De Nunzio C, Lombardo R, Presicce F, et al. Transrectal-ultrasound prostatic biopsy preparation: rectal enema vs. mechanical bowel preparation. *Cent European J Urol.* 2015;68:223-228.

97. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2007;60:913-920.

98. Tumbarello M, Sanguinetti M, Montuori E, et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae: importance of inadequate initial antimicrobial treatment. *Antimicrob Agents Chemother.* 2007;51:1987-1994.

99. Trecarichi EM, Cauda R, Tumbarello M. Detecting risk and predicting patient mortality in patients with extended-spectrum beta-lactamase-producing Enterobacteriaceae bloodstream infections. *Future Microbiol.* 2012;7:1173-1189.

100. Rogers BA, Ingram PR, Runnegar N, et al. Community-onset Escherichia coli infection resistant to expanded-spectrum cephalosporins in low-prevalence countries. *Antimicrob Agents Chemother.* 2014;58:2126-2134.

101. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect.* 2012;18:268-281.

102. Zowawi HM, Forde BM, Alfaresi M, et al. Stepwise evolution of pandrug-resistance in Klebsiella pneumoniae. *Sci Rep.* 2015;5:15082.

103. Williamson DA, Freeman JT, Roberts SA, et al. Rectal colonization with New Delhi metallo-beta-lactamase-1-producing Escherichia coli prior to transrectal ultrasound (TRUS)-guided prostate biopsy. *J Antimicrob Chemother.* 2013;68:2957-2959.

104. Tumbarello M, Trecarichi EM, Bassetti M, et al. Identifying patients harboring extended-spectrum-beta-lactamase-producing Enterobacteriaceae on hospital admission: derivation and validation of a scoring system. *Antimicrob Agents Chemother.* 2011;55:3485-3490.

105. Johnson SW, Anderson DJ, May DB, Drew RH. Utility of a clinical risk factor scoring model in predicting infection with extended-spectrum beta-lactamase-producing enterobacteriaceae on hospital admission. *Infect Control Hosp Epidemiol.* 2013;34:385-392.

106. Goodman KE, Lessler J, Cosgrove SE, et al. A Clinical Decision Tree to Predict Whether a Bacteremic Patient Is Infected With an Extended-Spectrum beta-Lactamase-Producing Organism. *Clin Infect Dis.* 2016;63:896-903.

107. Gottesman T, Yossepowich O, Harari-Schwartz O, Tsivian A, Idler J, Dan M. The Value of Rectal Cultures in Treatment of Sepsis Following Post-Transrectal Ultrasound-Guided Prostate Biopsy. *Urol Int.* 2015;95:177-182.

108. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41:580-637.

109. Antimicrobial resistance surveillance in Europe 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: European Centre for Disease Prevention and Control; 2015.

110. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev.* 2005;18:657-686.

111. Pitout JD. Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. *Drugs.* 2010;70:313-333.

112. Zowawi HM, Harris PN, Roberts MJ, et al. The emerging threat of multidrug-resistant Gram-negative bacteria in urology. *Nat Rev Urol.* 2015;12:570-584.

113. Senol S, Tasbakan M, Pullukcu H, et al. Carbapenem versus fosfomycin tromethanol in the treatment of extended-spectrum beta-lactamase-producing Escherichia coli-related complicated lower urinary tract infection. *J Chemother.* 2010;22:355-357.

114. Gardiner BJ, Mahony AA, Ellis AG, et al. Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? *Clin Infect Dis.* 2014;58:e101-105.

115. Rhodes NJ, Gardiner BJ, Neely MN, et al. Optimal timing of oral fosfomycin administration for pre-prostate biopsy prophylaxis. *J Antimicrob Chemother.* 2015;70:2068-2073.

116. Lampri N, Galani I, Poulakou G, et al. Mecillinam/clavulanate combination: a possible option for the treatment of community-acquired uncomplicated urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. *J Antimicrob Chemother.* 2012;67:2424-2428.

117. Adams-Haduch JM, Potoski BA, Sidjabat HE, Paterson DL, Doi Y. Activity of temocillin against KPC-producing Klebsiella pneumoniae and Escherichia coli. *Antimicrob Agents Chemother.* 2009;53:2700-2701.

118. Balakrishnan I, Smith G. Comment on: The national burden of infections after prostate biopsy in England and Wales: a wake-up call for better prevention. *J Antimicrob Chemother.* 2013;68:2418-2419.

119. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. *Clin Infect Dis.* 2016;63:754-762.

120. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet.* 2015;385:1949-1956.

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

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

Table 1: Summary of risk factors and proposed TRUBP Risk assessment questionnaire. Risk factors should be considered when determining the optimal biopsy approach and use of adjunctive prevention measures to reduce biopsy-related complication. A risk assessment questionnaire may help identify patients at an increased risk of biopsy-related complication. Adapted from Loeb et al[3] and Losco et al[51].

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

Table 2: Recommendations for assessment and prevention of prostate biopsy related infection arising from this collaborative systematic review. Studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) using a system used in the EAU guidelines (2015) modified from the Oxford Centre for Evidence-based Medicine[23].

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 *without* risk factors may proceed to TRUS biopsy using quinolone-based prophlyaxis 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 *with* 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 prophlyaxis according to culture results, AND/OR	2A	B

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

Table 3: Management summary for patients presenting with post-TRUBP sepsis. Empiric treatment should be region- or hospital-specific and continue until in vitro susceptibilities become available. Culture-directed treatment is dependent on the 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 *in vitro*)			
Enterobacteriaceae – non-MDR strains	• Gentamicin • Ceftriaxone	• 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	• Carbapenems • Piperacillin-tazobactam[2] • Aminoglycoside (may be	• Fosfomycin • Temocillin • Pivmecillinam	If piperacillin-tazobactam is used should

	susceptible to amikacin, but frequently gentamicin resistant) • Ceftolozane/tazobactam • Ceftazidime/avibactam	• Amoxicillin-clavulanate[2] • (Co-trimoxazole or Fluoroquinolone but often resistant)	be dosed maximally (e.g. 4.5g 6-hourly). Generally aminoglycosides should only be given for <48h and not used as monotherapy. Cefepime should be dosed at 2g Q8h if normal renal function
AmpC-producing Enterobacteriaceae (e.g. *Enterobacter cloacae/aerogenes*, *Citrobacter freundii, Serratia marcescens, Morganella morganii*)	• Carbapenems • Cefepime • Piperacillin-tazobactam (if susceptible, but resistance can develop in complex infections) • Aminoglycosides • Ceftazidime/avibactam	• Co-trimoxazole or trimethoprim • Fluoroquinolone • Fosfomycin • Temocillin	
Pseudomonas aeruginosa	• Piperacillin-tazobactam • Ceftazidime • Cefepime • (All +/- aminoglycoside)	Fluoroquinolone (Only oral agent active against *Pseudomonas* spp.)	
Carbapenem-resistant / XDR organisms	• Ceftazidime/avibactam: (for KPC, some OXA-type carbapenemase; **not** NDM or IMP types) • Ceftolozane/tazobactam: often effective for MDR-*Pseudomonas* spp.	Usually very few oral options available Fosfomycin may be effective	Seek specialist advice; carbapenems may still be used if dosed to maximise exposure (e.g. extended

	• Combination therapy: e.g. carbapenem + polymixin (or aminoglycoside, e.g. amikacin); dual carbapenems		infusions) with reference to the MIC, or used in combination

[1] Consider IV to oral switch once patient is afebrile, with resolved clinical signs of sepsis, tolerating oral intake, gastrointestinal absorption is not compromised and source control has been achieved; longer IV duration may be required if positive blood cultures or other complications (e.g. undrained abscess). Total duration is typically 7-14 days

[2] If susceptible in vitro: use against ESBL-producers is controversial, specialist advice is recommended