

An update on antibiotic prophylaxis in TRUS-guided prostate biopsy

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Since its inception in the 1980s, transrectal ultrasound (TRUS)-guided prostate biopsy has remained the standard tool for the histological diagnosis of prostate cancer. There are several advantages to this technique which have led to the widespread use of TRUS in the diagnosis of prostate cancer, such as availability of cost-effective equipment, ease of training, and the ability to undertake this under local anaesthesia in an outpatient-based setting.

The procedure involves the insertion of an ultrasound probe into the rectum; this is used to measure the dimensions of the prostate, after which a suitable local anaesthetic is given and the biopsy 'gun' is used to take the required biopsies of the prostate.

Infection, haematuria, dysuria, haematospermia and blood in the stools are common complications seen in patients following TRUS-guided prostate biopsy. Infection and its consequences, such as sepsis, is a significant concern and this review is focused on the evidence for strategies that may help reduce this risk.

The process of taking prostate biopsies through the rectum is inevitably associated with a high probability of introducing anaerobic or aerobic organisms into the blood stream and the prostate tissue. The most commonly introduced organisms include *escherichia coli*, *streptococcus faecalis* and *bacteroides* species which are the common organisms found within the gastrointestinal tract. TRUS biopsy has

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been found to be associated with a risk of bacteriuria (44%) and bacteraemia (16%) [1], though clinically significant infection is low when prophylactic antibiotics are used [2]. One study has reported the incidence of post TRUS biopsy urinary tract infection (UTI) to be between 2% and 6% with approximately 30–50% of these patients having accompanying bacteraemia [3,4]. Severe sepsis, which has been noted in 0.1–2.2% of cases following TRUS biopsy, is frequently accompanied by bacteraemia [3].

There is no general consensus on which particular patients are at an increased risk of infective complications. However, some of the risk factors identified are:

- Patients with UTI – the risk of septicaemia will be increased and consideration should be given to deferring the procedure until after treatment of the infection.
- Patients with a recent history of travel to a country where there is a higher rate of ciprofloxacin resistance.
- Patients with a history of urinary retention or with long-term catheter use.
- Patients with a recent history of prostatitis (with use of ciprofloxacin).
- Patients with a previous hospital admission.
- Patients with diabetes mellitus, on steroid medications, or immunocompromised – these patients may be at increased risk of infection and should be considered for a longer course of antibiotics.
- Nursing home residents.
- Obese patients [5].
- Risk of endocarditis (previous rheumatic fever, heart valve replacement or endocarditis [6].

Various antibiotic strategies

Combination vs. mono therapy

In an attempt to make prophylaxis more effective, some centres have looked at combining the standard fluoroquinolones with different antibiotics, such as ceftriaxone, gentamicin and metronidazole [8] based on evidence

to suggest that the combined use of any of these antibiotics is superior to their single use [9]. Most combination antibiotic therapies focus on delivering a fluoroquinolone orally, augmented with another intravenous antibiotic. Some studies have suggested this strategy to be no more effective than mono-antibiotic therapy, but these have arguably evaluated lower doses of the intravenous antibiotic. An IV infusion of gentamicin 80mg, in addition to oral fluoroquinolone, was shown not to convey extra protection than just using fluoroquinolone alone [10]. However, when the combined regimen included IV gentamicin 250mg, benefits above that of only oral fluoroquinolones were seen [11]. Indeed, the same effect was also demonstrated with cefuroxime 1.5g IV [12], and with ceftriaxone 1g [13]. However, the matter is complicated by the fact that about 30% of fluoroquinolone-resistant *E coli* are also resistant to gentamicin [14]. Consequent ineffectual cover for this group of organisms could, apart from exposing the patient to a higher risk of infection and sepsis, be a dangerous slippery slope by potentially leading to more resistant strains.

Single-dose vs. multiple dose and long-term vs. short-term

The evidence for single-dose regimens (administered on the day of the procedure, 30–60 minutes before the biopsy) compared to multi-dose regimens (oral antibiotics taken across a number of days before and after the procedure) is far more contested. There is evidence that suggests that the use of multiple dose regimens confers a greater protection against infection rates, particularly the use of norfloxacin one week prior to procedure [15]. Norfloxacin used for three days post procedure was also shown to significantly reduce infection rates [16]. The beneficial effect of multiple dose regimens is also evidenced when combination therapies are used for a longer time [17], although a potential bias in this publication is that the ciprofloxacin and metronidazole combination was administered two hours prior to the procedure, which is arguably

not the optimum time for adequate prophylaxis.

Overall, it does seem that the majority of evidence does not support the use of multiple dose regimens. This was most convincingly shown when one team of researchers followed infection rates at both 5 and 15 days post biopsy [18,19] and found little statistical difference when comparing it to single dose regimens. Though this phenomenon is most studied with the use of ciprofloxacin [20,21], it was also demonstrated with other antibiotics, and with both oral and intravenous use [22].

When can alternative antibiotics be considered?

The use of alternative antibiotics, such as carbapenam, amikacin or fosfomycin, has also been studied in TRUS-guided prostate biopsies. These antibiotics have been shown to significantly reduce the risk of sepsis post biopsy. The resistance to these broad spectrum antibiotics in the rectal flora is very low and therefore they are good alternatives to the fluoroquinolones used in standard practice. However, in the long term the widespread use of such non-standard regimes may lead to increased resistance to these antibiotics and therefore diminish our options for the treatment of sepsis post TRUS biopsy.

Targeted antibiotic therapy

The widespread use of broad-spectrum antibiotics has led to the development of multi-drug resistant E coli; therefore, the shortest course of the appropriate antibiotic to protect the patient from serious clinical consequences is desirable. The percentage of fluoroquinolone-resistant E coli recovered from urinary tract infections has increased 4.4 fold from 2004 to 2006 [4,23]. In addition, fluoroquinolone-resistant E coli in rectal flora is a risk factor for infectious complications after TRUS-guided biopsy [16,24]. One of the mechanisms of fluoroquinolone resistance is the activity of extended spectrum beta lactamases (ESBL) that enzymatically mediate resistance to extended-spectrum third-generation cephalosporins and monobactams, while not affecting carbapenems [25].

It has been shown through several case-control studies that the previous use of third-generation cephalosporins and fluoroquinolones remains an independent risk factor for infections caused by ESBL-producing organisms, compared to treatment-naïve patients [26]. Antibiotic consumption within 30 days has been shown to be associated with an increased risk of post TRUS biopsy infection

“More recently resistant forms of bacteria have become more prevalent, which calls for different strategies to be looked at when deciding on appropriate prophylaxis.”

secondary to ESBL producing organisms [27]. Another study demonstrated that previous use of fluoroquinolones also increased the risk of ESBL-producing E coli and K pneumonia infections [28].

A case-control retrospective cohort study conducted by Akduman et al. [29] compared those patients who had received prolonged courses of antibiotics to those who had not. A three-week course of levofloxacin was used to treat a sudden increase in prostate specific antigen (PSA) in asymptomatic patients, based on the assumption that this was a consequence of prostatitis and that the use of antibiotics may reverse the PSA reading and thereby reduce the need for a biopsy. The authors reported a staggering 3% overall rate of sepsis in this study. Among those patients who became septic, 65% had received three weeks of levofloxacin treatment, compared with 35% who did not receive levofloxacin. They reported that 100% of the isolates were resistant to fluoroquinolones and, even more worryingly, about half of them were also ESBL producers. ESBL bacteria are more difficult to treat because they are resistant to many drugs, including cephalosporin.

Ciprofloxacin-resistance has been reported in a wide range, from 6.5% to 75.5%. As discussed earlier, ciprofloxacin-resistant E coli has been implicated in increased risk of post-biopsy infectious complications, and consequently a better understanding of the mechanism of this is required. The cellular events for development of resistance are thought to be:

- Mutation in the target enzyme DNA gyrase.
- Changes in cell wall porin size (decreased penetration).
- Active efflux.

Some of the risk factors for colonisation with quinolone-resistant strain are:

- Increasing age.
- Travel to developing countries where resistance is prevalent.
- Prior quinolone use, presumably via alteration of gut flora.

Horcajada et al. proposed three broad mechanisms for the emergence of resistant

E coli: unmasking of present resistant bacteria in low numbers, acquisition of new resistant bacteria, and selection of intermediate strains to become resistant [30].

One of the proposed preventative measures to reduce post-biopsy infection due to fluoroquinolone-resistant E coli is to tailor antibiotic prophylaxis by performing pre-biopsy rectal culture in high-risk patients. This would provide a method of choosing targeted antibiotics by identifying resistant strains [31,32]. Although attractive, there are however difficulties with this approach. When a targeted prophylaxis is used for TRUS biopsy, the rectal culture needs to be performed before TRUS biopsy to allow time for microbiological cultures and antimicrobial sensitivity results. The time interval between the rectal culture and biopsy has not been clearly established, and there is concern that the flora might change over time and with age, although this may not be as relevant in the short term [33,34]. There are also no statistical measures of performance for screening rectal cultures for the purpose of targeted prophylaxis.

Nevertheless, the potential benefit of knowing the fluoroquinolone-resistance status of a patient is three-fold:

- To potentially prevent post biopsy infection.
- To reduce the use of fluoroquinolones when they may be ineffective.
- To avoid the development of further antibiotic resistance.

A systematic review has shown that targeted antibiotic therapy prior to TRUS-guided prostate biopsy reduces the risk of urosepsis in areas with a high prevalence of fluoroquinolone resistance, facilitated by pre-biopsy swabs [31]. The availability of PCR would enable results to be obtained rapidly.

Other preventive measures

Alternative approaches to the TRUS biopsy procedure are being considered to overcome the drawbacks of the standard procedure. Infectious complications could be reduced by avoiding the rectal route altogether and employing a trans-perineal route, which is increasingly being used for targeted and saturation biopsies. However,

this approach is disadvantaged by the requirement for general anaesthesia and the relatively fewer number of urologists who are able to perform this procedure, which precludes its use indiscriminately for all men with an elevated serum PSA. The use of narrower criteria for selection of men considered at high-risk of developing prostate cancer and the use of pre-biopsy MRI criteria are other options.

Furthermore, the use of iodine / povidone soaked swabs has a distinct beneficial effect. Studies have shown that the use of iodine swabs, when in combination with prophylactic antibiotics, dramatically decreases both the amount of bacteria cultured and the infection rates post biopsy [35].

Enemas to cleanse the rectum are also used in certain centres prior to TRUS-guided biopsies. The rationale behind using this method is to decrease the number of microbes present within the rectum pre-biopsy. However, no significant positive outcomes have been demonstrated so far from this intervention.

Conclusion

There is no doubt that antibiotics reduce the risk of infective complications following prostate biopsy. The length of antibiotic therapy will depend on the patient's risk factors and the local policies or pathways. In healthy individuals or those with minimal risk factors it is appropriate to prescribe a single dose or a one-day regimen. Antibiotics other than quinolones should be considered for prophylaxis during TRUS biopsy based on a knowledge of local quinolone resistance and individual risk factors. Consideration should also be given for rectal swabs prior to biopsy to be able to offer targeted prophylaxis.

What is clear though is that we need to find ways of augmenting the current use of fluoroquinolones, whether it is by using combination therapy, targeted antibiotics, or the use of iodine-soaked swabs.

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Declaration of competing interests:
None declared.