European Association of Urology (EAU) Position Paper on the Prevention of Infectious Complications Following Prostate Biopsy

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Preface

The EAU Urological Infections Guidelines Panel has recently published a large two-part systematic review (SR) and meta-analysis (MA) of randomized controlled trials (RCTs) on the use of antibiotic and non-antibiotic interventions for the prevention of infectious complications related to prostate biopsies (PBs) [1, 2]. The aim of this article is to summarize the available evidence and provide clinicians with practical recommendations on how to reduce infection rates after PB (**Figure 1**).

The right indication for & how to minimize unnecessary biopsies

The indication for PB is based on prostate-specific antigen (PSA) level and/or suspicious digital rectal examination (DRE) and/or imaging. The decision to perform a biopsy should be taken following a PSA control ideally performed in the same laboratory as the original test. The patient's age, existing comorbidities and risk stratification should also be considered [3]. With the wide availability and increasing experience with prostate MRI, there is growing evidence that MRI diagnostics can be used to prevent unnecessary PBs and their associated complications [4]. Explicitly, a meta-analysis of 6 RCTs showed that antibiotic therapy for PSA reduction is unhelpful and does not prevent unnecessary biopsies [5].

Patients at risk of developing post-biopsy infections

Personalized Medicine plays a crucial role in contemporary clinical practice. In patients who require PBs, personalized medicine requires identifying men at high risk for biopsy-related infectious complications beforehand and adapting management accordingly. This will reduce peri-procedural morbidity and mortality rates.
The EAU SR and MA, summarized evidence from a total 143 RCTs reporting multiple risk factors (**Supplementary Table 1**). A notable variation in reported risk factors was observed across the studies. Although some of the studies randomized patients with risk factors into different arms, clear recommendations on the practical management of patients at high risk for PB-complications based on risk stratification could not be provided [1, 2].

Why you should use transperineal biopsy

A MA of 7 RCTs showed that transperineal PBs were associated with significantly fewer infectious complications (RR 0.55, 95% CI: 0.33 to 0.92) compared to transrectal PBs [2]. In addition, a SR including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal PBs, respectively [6]. A population-based study from the UK (n=73,630) showed lower re-admission rates for sepsis in patients who had transperineal versus transrectal PBs (1.0% vs 1.4%) [7].
These results are not surprising, as they align with the surgical principle that the least contaminating approach should be followed in order to reduce the rate of infectious complications. Available evidence highlights that it is time for the urological community to switch from a transrectal to transperineal PB approach despite any possible logistical challenges [8]. To date, no RCT has been published investigating different antibiotic prophylaxis regimens for transperineal PBs; however, some cohort studies have reported intravenous prophylaxis with cefazolin.

Antibiotic prophylaxis in transrectal biopsy – use of fluoroquinolones suspended by the European Commission

Perioperative antibiotic prophylaxis with fluoroquinolones was the gold standard for many years due to their excellent pharmacokinetics in prostatic tissue and their low resistance rates. However, widespread and uncontrolled usage of fluoroquinolones has resulted in increasingly high resistance rates. Ultimately, the era of fluoroquinolones in PB prophylaxis was brought to an end by the European Commission in March 2019 with the suspension of the indication for perioperative antibiotic prophylaxis due to the risks of chronic severe side effects [9]. This legally binding decision is applicable in all EU countries.

If local fluoroquinolone resistance rates are low, fluoroquinolone prophylaxis is possible; however, the use of fluoroquinolones in this setting falls outside the EU directive. Furthermore, no validated fluoroquinolone resistance threshold has been identified. A minimum of a full-day course of fluoroquinolone prophylaxis should be offered, as the MA showed that a single dose was significantly inferior [1].

However, our recent SR showed that empirical prophylaxis with fluoroquinolones was inferior to both targeted (RR 1.81, 95% CI: 1.28 to 2.55) and augmented antibiotic prophylaxis (RR 2.10, 95% CI: 1.53 to 2.88) [1].

Antibiotic prophylaxis in transrectal biopsy – alternatives to fluoroquinolones

Regarding alternative options for antibiotic prophylaxis, two RCTs investigated ***aminoglycosides*** (gentamicin 3 mg/kg i.v. before biopsy; amikacin 15 mg/kg i.m. 1 to 2 h before biopsy), two RCTs investigated ***cephalosporins*** (ceftriaxone 1 g i.m. 0.5 h before biopsy; cefixime 400 mg p.o/day for 3 days starting the day before biopsy) and 3 RCTs ***fosfomycin trometamol*** (each 3 g p.o. 24 h before plus after biopsy; 3 g p.o. the night before biopsy; 3 g p.o. 1 h before biopsy) versus fluoroquinolones. Aminoglycosides and cephalosporins were comparable to fluoroquinolones with regard to infectious complications, while fosfomycin trometamol led to significantly reduced number of infections (RR 0.49, 95% CI: 0.27 to 0.87) [1].

The value of ***fosfomycin trometamol*** was confirmed in 3 independent meta-analyses, each including 4-5 studies, with non-randomized trials as well as studies conducted in countries with high fluoroquinolone resistance [10-12]. In contrast, in a recent large Canadian nested case-control study with more than 9000 patients, fosfomycin trometamol (single dose as well as two doses) was inferior to ciprofloxacin (3 days or single dose), which limits the generalizability of the use of fosfomycin trometamol [13]. In its implementing decision C(2020) 3966 final of June 2020, the EU commission sees a positive benefit in the use of fosfomycin trometamol as PB antibiotic prophylaxis, but requested additional pharmacokinetic and pharmacodynamic studies to support the use of a second dose 24 hours after PB.

Targeted prophylaxis was originally introduced to offer an alternative antibiotic agent in case of fluoroquinolone resistance from a rectal swab/ stool culture [14]. Fluoroquinolone resistance ranged from 18 to 83% in the 6 available RCTs included in the panel's SR[1]. However, 4 out of these 6 studies did not provide detailed information on type, dosage and duration of prophylaxis in the targeted prophylaxis group. It remains unclear whether non-fluoroquinolones were used in cases without fluoroquinolone resistance [1]. Meaning that targeted prophylaxis has only been s investigated in the context of fluoroquinolone prophylaxis and there is no RCT available to date that does not use fluoroquinolones as baseline prophylaxis.

Augmented prophylaxis, describes the use of two or more different classes of antibiotics. Although it contradicts the principles of antibiotic stewardship, the reason for its use is the broadening of the antibacterial spectrum to cover possible resistance to a single substance. However, out of the ten available RCTs on augmented prophylaxis, eight studies combined a fluoroquinolone with another antibiotic. Only two older studies used alternative combinations (**Table 1**). Therefore, no recommendation can be made, on the basis of RCTs, as to which non-fluoroquinolone using combinations are superior to the use of mono prophylaxis. A recent non-RCT multicenter study has investigated the effect of local antibiogram-based augmented antibiotic prophylaxis. It reported that the use of an augmented antibiotic prophylaxis based on the local resistance patterns could reduce infectious complications by 53% relative to the historical rate, but again most combinations included a fluoroquinolone [15].

Non-antibiotic strategies when transrectal biopsy is performed

If a transrectal PB is performed, rectal preparation with povidone-iodine is highly recommended, as this is associated with a significantly reduced number of infectious complications (RR 0.50, 95% CI 0.38-0.65) [2]. On the other hand, no advantage could be shown for the use of an enema [2]. Furthermore, the number of biopsy cores, the use of local anaesthesia in the form of periprostatic nerve block (PPNB), number of injections for PPNB, needle guide type, needle disinfection, and needle type had no influence on the rate of infectious complications [2].

Take home message

The transperineal approach is preferred to reduce PB-related infections. Fluoroquinolones are suspended for prophylaxis of PB in the EU; therefore, alternative antibiotics based on local resistance, or targeted prophylaxis, in conjunction with povidone-iodine rectal preparation are recommended for transrectal PB.

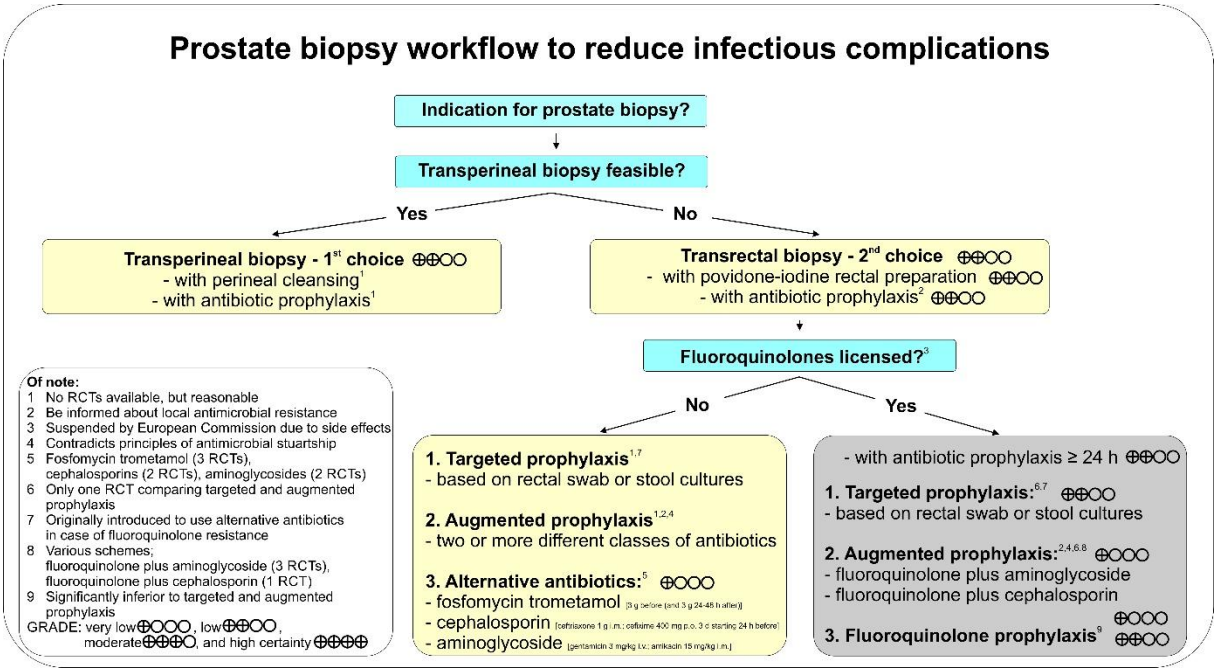

Figure 1 Suggested workflow on how to reduce post biopsy infections. GRADE Working Group grades of evidence.
High certainty: (⊕⊕⊕⊕) we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: (⊕⊕⊕⊖) we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: (⊕⊕⊖⊖) our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: (⊕⊖⊖⊖) we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 1 Overview of randomized controlled trials investigating standard prophylaxis vs. augmented prophylaxis

Study, Year	Patients	Country	Study period	Antibiotic classes		Detailed prophylaxis	
				Standard	Augmented	Standard	Augmented
Bosquet, 2006	71 vs. 85	Spain	2004	Aminoglycoside	Aminoglycoside plus fluoroquinolone	TOB 100 mg i.v. 30 min before and i.m. 8 h after	TOB 100 mg i.v. 30 min before and i.m. 8 h after plus CIP 500 mg p.o. bid for 3 d starting 30 min before
Chan, 2012	179 vs. 188	China	2007 - 2009	Penicillin	Penicillin plus fluoroquinolone	AMC 1000 mg p.o. bid for 36 h starting 2 h before	AMC 1000 mg plus CIP 250 mg p.o. bid for 36 h starting 2 h before
Ergakov, 2013	40 vs. 40	Russia	2013	Fluoroquinolone	Nitroimidazole plus azithromycin plus antifungal azole	PEF 400 mg p.o. bid for 5 d starting 1 d before	SEC/AZM/FLC p.o. qd for 6 days starting 1 d before
Fahmy, 2016	202 vs. 210	Egypt	2012-2015	Fosfomycin	Fluoroquinolone plus nitroimidazole	FOF 3000 mg p.o. 1–2 h before	CIP 500 mg and MTZ 500 mg p.o. 1 h before
Fong, 1991	47 vs. 54	Canada	1984 - 1989	Cotrimoxazole	Aminoglycoside plus nitroimidazole	SXT 320 mg/1600 mg p.o. 1 h before	NET 1.5 mg/kg i.v. and MTZ 500 mg p.o. 1 h before
Izadpanahi, 2017	225 vs. 225	Iran	2010 - 2013	Fluoroquinolone plus nitroimidazole	Fluoroquinolone plus nitroimidazole plus cephalosporin plus aminoglycoside	CIP 500 mg p.o. bid and MTZ 500 mg p.o. tid for 5 d starting the day before	CIP 500 mg p.o. bid plus MTZ 500 mg p.o. tid for 5 d starting the day before plus CRO 1 g i.v. plus AMK 5mg/kg i.m. 30–60 minutes before
Miyazaki, 2016	230 vs. 217	Japan	2007 - 2009	Fluoroquinolone	Fluoroquinolone plus aminoglycoside	LVX p.o. 2 h before	LVX p.o. 2 h before plus AMK 30 min i.v. before
Pace, 2012	70 vs. 65	Italy	2010 - 2011	Fluoroquinolone	Fluoroquinolone plus cephalosporin	CIP 1000 mg p.o qd for 5 d starting the evening before	CIP 1000 mg p.o. qd for 5 d starting the evening before plus CRO 1 g as periprostatic nerve block 15 min before biopsy
Vaz, 1994	10 vs. 10	Brazil	Not reported	Fluoroquinolone	Fluoroquinolone plus nitroimidazole	LOM 400 mg p.o. qd for 2 d starting 3 h before	LOM 400 mg p.o. qd plus MTZ 500 mg p.o. tid for 2 d starting 3 h before
Elshal, 2018	163 vs. 166	Egypt	2015 - 2017	Fluoroquinolone	Fluoroquinolone plus aminoglycoside	CIP 500 mg p.o. bid for 3 d starting the day before	CIP 500 mg p.o. bid for 3 d starting the day before plus GEN 160 mg i.v. just before

Amoxicillin-clavulanic acid=AMC, Azithromycin=AZM, Amikacin=AMK, Ciprofloxacin=CIP, Ceftriaxone=CRO, Fluconazole=FLC, Fosfomycin=FOF, Gentamycin=GEN, Lomefloxacin=LOM, Levofloxacin=LVX, Metronidazole=MTZ, Netilmycin=NET, Pefloxacin=PEF, Secnidazole=SEC, Trimethoprim-sulfamethoxazole=SXT, Tobramycin=TOB, qd=once a day, bid= two times a day, tid= three times a day, qid= four times a day, h=hour(s), d=day(s), studies with fluoroquinolone are marked in grey

Supplementary Table 1 Reported risk factors rendering patients susceptible to develop post-biopsy infections

Reported risk factors
Allergy to antibiotics
ASA score >3
Bladder stones
Chronic prostatitis
Concomitant or previous antibiotic therapy
Diabetes mellitus
Fluoroquinolone resistance
History of chemotherapy
Immunosuppression
Impaired renal or liver function
Indwelling catheter
Infections (acute or chronic) of any cause
Noncompliance with antibiotic prophylaxis
Previous prostate biopsy
Previous recent endoscopic manipulation
Previous sepsis
Previous urinary retention
Positive prebiopsy urine culture/leukocyturia/urinary tract infection
Prosthetic devices
Severe cardiopulmonary dysfunction
Transrectal biopsy
Travel history to countries with high antibiotic resistance
Uncontrolled hypertension
Valvular heart disease
Voiding dysfunction

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