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EDITORIAL

Infectious complications after prostate biopsy: Time to rethink our clinical practice

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Abstract

Prostate biopsy is a very common procedure performed worldwide which still represents the only way for prostate cancer diagnosis and reference point for subsequent treatments. Even if transrectal prostate biopsy is considered a safe procedure, it may be accompanied by infective complications, ranging from asymptomatic bacteriuria to symptomatic urinary tract infections and sepsis. During the recent decade we observed an increasing number of infectious complications and subsequent hospitalizations after and transrectal prostate biopsy. The most probable reason for the increasing rate of infectious complications after prostate biopsy is the increasing antimicrobial resistance, especially to the current first-line recommended fluoroquinolone antibiotics. We believe the time has come to re-think our current practice of diagnosing prostate cancer. We need to focus on the selection of patients at higher risk of infective complications, on microbiological sampling of the faecal flora prior to biopsy to identify resistance to specific agents, on the number of biopsy cores, on the biopsy route (perineal or transrectal approach) and, finally, consider alternative antibiotics with improved susceptibility to be used for prophylaxis.

Key words: Prostate cancer; Prostate biopsy; Transrectal biopsy; Rectal swab; Antibiotic prophylaxis

Core tip: Transrectal biopsy of the prostate is generally considered a safe procedure used for obtaining tissue samples for the histological diagnosis of prostate carcinoma. However, in the last years we observed a higher rate of infective complications, ranging from asymptomatic bacteriuria to sepsis that continued

to be the principal cause of hospital admission after procedure. The higher rate of sepsis could be due to the emerging resistance to fluorquinolones, in particular to ciprofloxacin. New strategies for antibacterial prophylaxis need to be purposed.

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INTRODUCTION

Prostate biopsy is currently an indispensable method for the diagnosis of the prostate cancer and the transrectal approach is most commonly used by European urologists[1-3]. Even if transrectal biopsy of the prostate (TR-PB) is generally considered a secure method, it may be accompanied by several clinical complications, like bleeding due to the biopsy trauma or, more frequently, infective complications ranging from asymptomatic bacteriuria to symptomatic urinary tract infections and sepsi[4]. Although infective complications after TR-PB are well identified and a recent systematic review showed a significant reduction in the risk of bacteriuria compared with placebo[5], an higher rate of infective complications after transrectal biopsy of the prostate has been recently reported in several countries[6,7]. Today, the infective complications after TR-PB represent an important challenge for the urologist and a life-threatening risk for the patient, in particular due to the increased rate of antibiotic resistant bacteria.

STATE OF ART: INTERNATIONAL GUIDELINES

The European Association of Urology (EAU) guidelines suggests using fluoroquinolones and trimethoprim/sulfamethoxazole as appropriate antibiotics for prophylaxis[8]. Moreover, the best practice policy statement on urologic surgery antimicrobial prophylaxis, edited by American Urological Association, suggest to perform antibiotic prophylaxis in all patients by using ciprofloxacin in single dose[9]. However a recent survey showed a total of forty-eight diverse schedules utilizing 13 different antibiotics, ranging from a single oral dose of ciprofloxacin before TR-PB, to intravenous cefuroxime and enema with metronidazole before the procedure, with subsequent doses of oral cephalexin[4,10,11]. There are huge cost variations among the prophylactic regimens[4]. In this sense, there is a clear lack of standardization of antibiotic prophylaxis for transrectal prostate biopsy. The favorable pharmacokinetic and pharmacodynamic characteristics of fluoroquinolones are important reasons for the recommendations given in the EAU guidelines on prostate biopsies[8]. Fluoroquinolones reaches high concentrations in prostate tissue and prostatic secretions[8]. Moreover, orally administered fluoroquinolones reach high concentrations in the prostate tissue that are sufficient for the treatment of chronic bacterial prostatitis[12].

ACTUAL SCENARIO: THE INCREASING NUMBER OF INFECTIVE COMPLICATIONS AND THE ROLE OF EMERGING RESISTANT BACTERIAL STRAINS

Despite fluoroquinolones being the most prescribed drug for TR-PB prophylaxis, in line with EAU guidelines[8], the hospital admissions due to complications after TR-PB have significantly increased during the last 10 years[13]. The recently published results of the Global Prevalence Study of Infections in Urology study found a high rate of symptomatic urinary tract infections (5.2%) and a significant rate of hospitalization (3.1%)[3]. Interesting, in the same study, Wagenlehner *et al*[3] reported that fluoroquinolones were used in 98.2% of patients, in accordance with the EAU guidelines, but the resistance rate against fluoroquinolones was seen in 60% of all isolated bacterial strains. Now is the time to ask what the clinical consequences of these data are. Several studies showed that the higher risk of infection is due to an increase in ciprofloxacin resistance in *Escherichia coli* and hence a associated reduce in the efficacy of prophylaxis with ciprofloxacin in patients undergoing TR-PB[14]. The current increasing rate of fluoroquinolone resistant organisms has become a significant contemporary health crisis. This emergency is due both to the abuse and over-prescription of antibiotics and the limited development of new molecules with subsequent reduced number of new antibiotics in the pipelines of pharmaceutical companies[13]. Some authors hypothesize that the observed increase prevalence of ciprofloxacin resistant *Escherichia coli* strains isolated from patients with urinary tract infections reflects changes in the strains colonizing the patients' gastrointestinal tracts[15]. In fact, a recent study showed that 22.0% of patients who had undergone TR-PB, harbored ciprofloxacin-resistant *Escherichia coli* strains[16]. Moreover, they found that faecal carriage of *Escherichia coli* strains resistant to fluoroquinolone was a important risk factor for infective complications after TR-PB[16].

ALTERNATIVE STRATEGIES TO DECREASE INFECTIVE COMPLICATIONS

In order to decrease the frequency of infective complications after prostate biopsy, some strategies have been purposed and evaluated: (1) risk assessment for selecting patients at higher risk for infective complications; (2) microbiological evaluation of the faecal flora prior to biopsy to identify resistance to specific agents; (3) number of biopsy cores and the use of

targeted, image fusion guided biopsies; (4) change of biopsy route (perineal approach); and (5) alternative molecules with enhanced susceptibility.

Risk assessment to selecting patients at higher risk for infective complications

Loeb *et al*[17] in 17472 men who had undergone prostate biopsy and 134977 controls, showing that age, race, region, year, and Charlson comorbidity score are independent prognostic factors to use for assess the risk of hospitalization. Moreover, they highlighted other two independent prognostic factors for developing febrile complications due to urinary tract infections after TR-PB: prostate enlargement and diabetes[17]. Moreover, it is well known that hyperglycemia-related impairment of the immune response may lead to an increase in post-biopsy infections[14]. Assessment of comorbidity is important to identify patients at higher risk of infective complications after prostate biopsy. Finally, it is well known that the prevalence of resistant bacteria is different among countries. For this reason, travelling to countries with high prevalence of resistant bacteria was associated with colonization and may be considered a risk factor for developing infective complications after prostate biopsy. However, we have no data about it in the current literature.

Microbiological evaluation of the faecal flora prior to biopsy to identify resistance to specific agents

Based on the previous evidences, some researchers proposed doing rectal swab culture test before prostate biopsy to isolate and characterize all fluoroquinolone-resistant strains from patients' rectal flora[18]. In line with this hypothesis, Taylor *et al*[18] planned a longitudinal cohort study of 457 men receiving targeted antibiotic prophylaxis based on microbiological evaluation of the rectal flora as compared with empirical antibiotic prophylaxis. They did not find any statistically significant differences between the two groups in terms of number of infective complications. On the other hand, the targeted antibiotic prophylaxis obtained a cost saving of $4499 due to the prevention of a significant number of infectious complications after the procedure[18]. In particular, they found a cost benefit ratio of 38:1 if compared to the indiscriminate use of fluorquinolone-based antibiotic prophylaxis[18]. Moreover, Williamson found that a specific fluoroquinolone-resistant *Escherichia coli* strain (*E. coli* ST131) was an significant cause of sepsis after TR-PB[19]. These reports have significant clinical relevance and should be taken into account as it has been shown that faecal fluoroquinolone resistant *Escherichia coli* can be selected even by only one dose of oral 500 mg ciprofloxacin given as prophylaxis before transrectal biopsy of the prostate[20]. Furthermore, the use of fluoroquinolones in the 6 mo period before prostate biopsy has also been shown to be associated with a higher risk of faecal carriage of fluoroquinolone-resistant *Escherichia coli* strains[16]. Recently, Taylor *et al*[21] evaluated the prevalence of ciprofloxacin-resistant strains in patients who had undergone TR-PB and estimated the subsequent risk of infectious complications after TR-PB with peri-operative ciprofloxacin prophylaxis. They collected a pre and post biopsy rectal swab and urine culture and analyzed the susceptibility to the most commonly used antibiotics[21]. Among 865 investigated patients, *Escherichia coli* was the most common strain (80.9%) and accounted for 90.6% of ciprofloxacin resistant specimens while the rate of ciprofloxacin-resistant coliforms in general was 19%[21]. Infectious complications occurred in 3.6% of patients and 48% of these patients had ciprofloxacin resistant bacteria at pre-biopsy microbiological evaluation of the rectal flora. Their findings strongly indicate that the increasing prevalence of infection rate after TR-PB is due to an increasing prevalence of ciprofloxacin-resistant *E. coli* in the rectal flora[21]. Paralleling the worldwide increase of fluoroquinolone resistance in enterobacteria faecal fluoroquinolone-resistant bacteria can indeed explain the increase of infective complications after TR-PB[3]. But what about giving a course of a customized prophylaxis regimen prior to a transrectal prostate biopsy based of the findings of the microbiological evaluation of the rectal flora? Some aspects should be addressed. Firstly, rectal swab would represent a significant difficulty for clinical microbiology laboratories and might fail to identify ciprofloxacin-sensitive isolates with intermediate MICs. Secondly, there is a relative instability of ciprofloxacin in specific microbiological procedures, and there is no commercially accessible ciprofloxacin containing media[14].

Number of biopsy cores and the use of targeted, image fusion guided biopsies

Recently, some authors have addressed the importance of the number of biopsy cores taken. Wagenlehner *et al*[3] identified the number of biopsy cores to be the only important risk factor for the development of symptomatic urinary tract infections after prostate biopsy. This finding was confirmed by Dodds *et al*[22] who observed an increased rate of complications after prostate biopsy in 2080 patients, highlighting the number of biopsy cores as one of the main risk factor for patients' hospitalization. On the other hand, a randomized trial of 6 *vs* 12 core biopsies reported no significant differences in terms of febrile complications[23]. The authors concluded that prostate biopsy with 12-cores is generally well tolerated and can be safely performed with no significant difference in pain or morbidity compared to the procedure with 6-cores[23]. The jury is still out regarding the importance of number of biopsies for the risk of infective complications.

Change of biopsy route (perineal approach)

Even if several authors showed that no important differences in the number of complications were found between the transperineal or transrectal approach, the transperineal approach has been considered an

alternative strategy to decrease the infective complications[13,24,25]. Recently, Grummet *et al*[26], evaluating the rate of hospital admission for sepsis after transperineal biopsy of the prostate, found that the rate of hospital re-admission for infective complications was zero. Moreover, the international data suggested a negligible rate of sepsis by using transperineal biopsy[27]. In conclusion, although transrectal prostate biopsy is handy, inexpensive and quick to perform, the transperianeal road should now be considered as an alternative approach, not only to patients undergoing repeat prostate biopsy, but also to all patients in whom a high risk of infective complication has found.

Alternative molecules with enhanced susceptibility

Another important aspect to discuss is an interesting finding from the Carignan's study: among *Escherichia coli* isolated from all patients who underwent TR-PB and deemed susceptible to ciprofloxacin, the MIC increased during the latter period[14]. As already suggested by others, an increasing fluorquinolones resistance and creeping MICs call for a reassessment of the current recommendations on antibiotic prophylaxis[28]. However, the use of alternative antibiotic prophylaxis should still be based on the susceptibility of the most common pathogens and the pharmacokinetic diffusion of the antibiotic within the prostate tissue[3]. The rising resistance to fluoroquinolones, in particular to ciprofloxacin, is the most likely cause of the increasing prevalence of infective complications after TR-PB and new strategies for antibacterial prophylaxis need to be purposed. As reported in several studies, *Escherichia coli* accounts for most of the positive cultures in patients who had undergone TR-PB, and displays a high levels of antimicrobial resistance[7,28]. The authors stress that the highest rates of resistance was seen for trimethoprim sulfamethoxazole and amoxicillin, a fact suggestive of that these molecules should not be used for prophylaxis before the biopsy of the prostate[7,28,29]. An alternative strategy is to try and obtain better treatment through the use of more extended antimicrobial prophylaxis[13]. However, this suggestion should be met with caution, due to the risk of collateral damage and the actual need for lowering the use of broad spectrum antibiotics[20]. Another valid option could be the use of antibiotics with low profile of resistance, such as fosfomycin trometamol. Fosfomycin is a candidate alternative agent for antibiotic prophylaxis in TR-PB having showed elevated activity against MDR Gram-negative bacteria and favorable pharmacokinetic parameters, including an elevated penetration into prostatic tissue[30,31]. In a recent review paper Wagenlehner *et al*[32] argued that fosfomycin trometamol 3 g orally 3 h before and 24 h after, could be used as prophylaxis during traumatic endourological interventions and surgical procedures. For diagnostic procedures one single oral dose might be an alternative if perioperative antibiotic prophylaxis is indicated. Further studies are required in order to settle the role fosfomycin trometamol in the antibiotic prophylaxis before prostate biopsy. New evidence calls for re-consideration of clinical practice and development of better preventive strategies against infectious complications in patients undergoing transrectal prostate biopsy.

From all these evidences it is clear that prostate biopsy policy should be totally revised in order to obtain acceptable prospective results in terms of infective complications, costs saving and patient compliance as recently suggested by Wagenlehner *et al*[33]. In conclusion, before prostate biopsy is decided a exhaustive history should be taken with special attention to risk factors for infectious complications (*i.e.*, diabetes) and for harboring resistant strains (*i.e.*, recent hospitalization, travel to certain geographical regions or antibiotic use)[17,29,34,35].

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