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Antimicrobial Prophylaxis in Transurethral Resection of the Prostate: Results of a Randomized Trial

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Abbreviations and Acronyms

AMP = antimicrobial prophylaxis
EAU = European Association of Urology
FQ = fluoroquinolone
RCT = randomized controlled trial
TURP = transurethral resection of the prostate
WBC = white blood cells

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Purpose: We sought to determine whether omitting antimicrobial prophylaxis is safe in patients undergoing transurethral resection of the prostate without preoperative pyuria and a preoperative catheter.

Materials and Methods: We conducted a multicenter randomized controlled trial from September 17, 2017 until December 31, 2019 in 5 hospitals. Patients with pyuria (>100 white blood cells/ml) and a preoperative indwelling catheter were excluded. Postoperative fever was defined as a body temperature ≥38.3C. A noninferiority design was used with a 6% noninferiority margin and null hypothesis (H0) that the infection risk is at least 6% higher in the experimental (E) than in the control (C) group; H0: C (antimicrobial prophylaxis group) − E (no antimicrobial prophylaxis group) ≥ Δ (6% noninferiority margin). A multivariable, logistic regression was performed regarding posttransurethral resection of the prostate fever and antimicrobial prophylaxis with co-variates: (clot-)retention and operating time. The R Project® for statistical computing was used and a p value of 0.05 was considered as statistically significant.

Results: Of the patients 474 were included for multivariable analysis and 211/474 (44.5%) received antimicrobial prophylaxis vs 263/474 (55.5%) patients without antimicrobial prophylaxis. Antibiotics were fluoroquinolones in 140/211 (66.4%), cephazolin in 58/211 (27.5%) and amikacin in 13/211 (6.2%) patients. Fever occurred in 9/211 (4.4%) patients with antimicrobial prophylaxis vs 13/263 (4.9%) without antimicrobial prophylaxis (p=0.8, risk difference 0.006 [95% CI −0.003−0.06, relative risk 1.16]). We were able to exclude a meaningful increase in harm associated with omitting antimicrobial prophylaxis (p=0.4; adjusted risk difference 0.016 [95% CI −0.02−0.05]).

Conclusions: Our data demonstrate the safety of omitting antimicrobial prophylaxis in patients undergoing transurethral resection of the prostate without preoperative pyuria and a preoperative indwelling catheter.

Key Words: transurethral resection of prostate; randomized controlled trial; fever; drug resistance, microbial; antibiotic prophylaxis

TRANSURETHRAL resection of the prostate remains the gold standard in the surgical treatment of moderate benign prostatic hyperplasia. Postoperative fever can occur in 26% of procedures and antimicrobial prophylaxis is used to reduce the infection rate.[1]

The AUA (American Urological Association) and European Association of Urology recommend AMP in TURP, based on level 1a guidelines.[2,3]

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The AUA guidelines recommend a single dose of cephazolin or trimethoprim+sulphamethoxazole as primary choice. The EAU guidelines don't recommend specific AMP for TURP because of local diversity in microbial resistance. The Belgian guidelines (BAP-COC) recommend a single dose of fluoroquinolones although our large, prospective cohort trial in 506 consecutive patients undergoing TURP showed a preoperative urinary FQ resistance of 69.2% in Eschericea coli, questioning these local guidelines.[4,5]

Cai proved that using single-dose AMP instead of a prolonged AMP course, reduced antibiotic usage without increasing postoperative infections and also lowered the prevalence of resistant uropathogens.[6]

The overuse and misuse of antibiotics is an important factor in microbial resistance and this study was an important step forward in antimicrobial stewardship.

A reduction in total antibiotic consumption remains the "Holy Grail" in antimicrobial stewardship, since even a single dose of antibiotics can increase microbial resistance.[7,8] We observed a low infectious complication rate of 2.9% in 506 patients undergoing TURP without AMP and without a preoperative catheter or pyuria (>100 white blood cells/ml) in our prospective cohort trial in 2017.

The lack of randomization was a major study weakness and this randomized controlled trial investigates the safety of omitting AMP in a subgroup of patients undergoing TURP to obtain a reduction in antibiotic use.

MATERIALS AND METHODS

A RCT in 5 hospitals was initiated from September 17, 2017 until December 31, 2019 after approval by the Ethical Committee of Jessa Hasselt (B243201733480) and receiving EudraCT number 2017-004870-32.

A urine sample was collected at hospital arrival and patients with pyuria (>100 WBC/ml) were excluded. The 100 WBC/ml cutoff for pyuria was chosen in accordance with our microbiologists and based on laboratory guidelines.[9] Patients with a preoperative catheter were also excluded because of the possible colonization of the urine.

All patients underwent TURP with a bipolar resectoscope (Olympus®) and had a rinsing catheter that was removed after 2 or 3 days, depending on hospital protocol and degree of hematuria. No antibiotics were systematically prescribed after catheter removal.

Patients were seen at the followup consultation 3 weeks after surgery, where postoperative antibiotic usage was explicitly checked.

The patients in the AMP group received single-use FQs, which depending on institutional habits was cipro (400 mg/200 ml) or levofloxacin (500 mg/100 ml).

In case of recent (<6 months) FQ use or FQ intolerance, a single dose of cephazolin (2 gm) was used. In the rare case of recent use of FQ and penicillin intolerance, amikacin (1 gm/100 ml) was given.

The primary study endpoint was postoperative fever, defined by Fraser as a body temperature ≥38.3C, within 3 weeks of the operation (time to followup consultation).[10]

Septicaemia was defined as fever in combination with hypotension (>40 mmHg drop from baseline systolic pressure) or an elevated lactate (>1 mmol/l).[11]

The following parameters were documented during hospitalization: pain score, body temperature, blood pressure, pulse, saturation and respiratory rate. Patients were informed at discharge that a re-admission to the hospital was mandatory in case fever or chills developed. Initial fever measurement at home was performed by the patient or general practitioner and checked upon hospital admission.

Data collection included hospital site, date of surgery, age, prostate volume (measured by ultrasound), operating time, resected prostate volume, pathological infection (chronic or acute inflammation/infection in histology report), postoperative fever, (clot) retention and catheter time. Diabetes mellitus type 2 was also registered as specific comorbidity.

A 1:1 randomization was intended in a control group with antimicrobial prophylaxis and an experimental group without antibiotics.

Randomization was performed by "flip a coin" in 4 hospitals. One center used a variation on block randomization due to practical reasons and patients received AMP every first 6 months of the study and no AMP in the next following 6 months and so on. Flip a coin is the most common and basic method of randomization and can be trusted in large clinical research to generate similar numbers of subjects among groups.[12]

All standardized bias measures (age, hospital site, prostate volume) were below 0.25 standard deviation, which is considered as an acceptable maximum value of imbalance according to Ho.[13] Allocation concealment in this single-blinded study was achieved by using a password-controlled computer database.

A noninferiority design with null hypothesis H0: C (control) − E (experimental) ≥ Δ and alternative hypothesis H1: C − E<Δ was used. The alternative hypothesis (H1) states that the experimental therapy (E=no AMP) may have a negative effect compared to the active control (C=AMP) but by no more than Δ (noninferiority margin).[14] The noninferiority margin (Δ) was based on both clinical judgement and statistical reasoning.

Qiang described a probability of postoperative high fever (body temperature >38.5C) in patients with AMP of 2.6% vs 13.5% (risk difference −0.11, 95% CI [−0.2−−0.06]) in patients without AMP.[1] The probability of developing post-TURP fever in total fever (>37.2C) was 22.5% in patients with AMP vs 26.9% (risk difference −0.05, 95% CI [−0.09−−0.01]) no AMP.

A 6% margin was chosen as a clinically relevant cutoff between 4.4% and 10.9% in postoperative fever reduction following TURP. A power analysis was performed and an estimated effect size of 450 patients was calculated with an attrition rate of 10%, alpha 0.05 and a power of 80%. The null and alternative hypothesis as such were H0: AMP (C) − no AMP (E) ≥ 6% (Δ) and H1: AMP (C) − no AMP (E) < 6% (Δ) respectively.

A multivariable, logistic regression was performed regarding AMP and post-TURP fever with co-variates; (clot-)

retention and prolonged operating time (>52 minutes). The cutoff for prolonged operating time was based on the findings by Colau.[15]

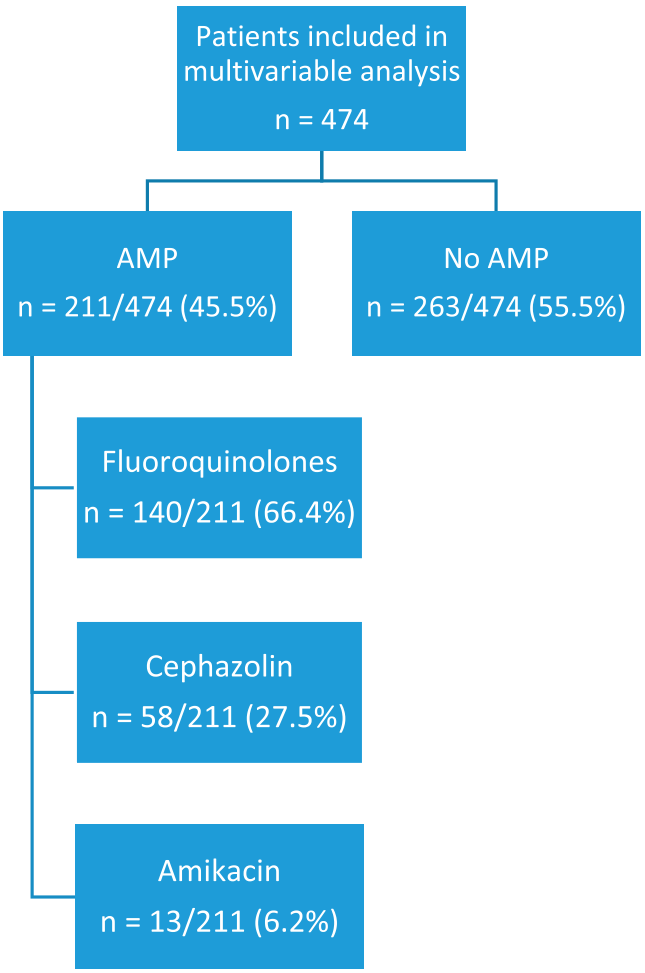
The R Project for statistical computing was used and a p value of 0.05 was considered as statistically significant.

RESULTS

At 5 centers 607 patients were recruited from September 17, 2017 until December 31, 2019.

Of the patients 118 were excluded from analysis because of preoperative pyuria (>100 WBC/ml), missing data or no followup visit and 15 more patients were excluded because of postoperative antibiotic usage, prescribed by the general practitioner, in the absence of fever.

Thus 474 patients were included for analysis and 211/474 (44.5%) patients received AMP vs 263/474 (55.5%) patients without AMP. The administered antibiotics were fluoroquinolones in 140/211 (66.4%), cephazolin in 58/211 (27.5%) and amikacin in 13/211 (6.2%) patients (see figure).



Randomization and antibiotic regimens of patients included in multivariable analysis.

The demographics regarding age, prostate volume, operating time, resected tissue volume, pathological infection of the tissue, catheter time, (clot-) retention, diabetes mellitus type 2 and postoperative fever in both groups are shown in the table.

Of the patients without AMP 13/263 (4.9%; 95% CI 2.8–8.4) developed postoperative fever compared to 9/211 (4.3%; 95% CI 2.2–8) patients with AMP (p=0.8). A risk difference of 0.006 (95% CI −0.003–0.06) was calculated with a relative risk of 1.16 of developing post-TURP fever without AMP.

Of the patients in the AMP group 12/13 (92.3%) developed fever during hospitalization and 1/13 (7.7%) after discharge compared to 7/9 (77.7%) patients without AMP during hospitalization and 2/9 (22.2%) after discharge.

Of the patients with postoperative fever 1/211 (0.47%) developed septicaemia in the AMP group vs 1/263 (0.4%) patient in the nonAMP group (p >0.9).

A multivariable, logistic regression was performed investigating the effect on postoperative fever by AMP and as covariates a prolonged operating time (>52 minutes) and (clot-) retention.

Omitting AMP caused no significant increase in postoperative fever (p=0.4), nor did a prolonged operating time (p=0.6) and (clot-) retention (p=0.9). The adjusted risk difference and 95% CI for omitting AMP in this multivariable analysis was 0.016 (−0.02–0.05).

DISCUSSION

TURP remains the gold standard in the surgical treatment of moderate benign prostatic hyperplasia. Postoperative fever (>37.2C) is a feared complication and can occur in 26% of patients undergoing TURP and high degree fever (>38.5C body temperature) in 13.5%.[1]

AMP is widely used to reduce postoperative fever but the benefits should exceed the disadvantages such as increased cost, allergic reactions, side effects of the medication and potential increase in microbial resistance.

Antimicrobial prophylaxis in TURP is rather well documented and the EAU guidelines have a level Ia evidence to support AMP in TURP.

The guidelines, however, are mainly based on 3 studies (a meta-analysis, systematic review and a RCT) published between 2002 and 2005.[1,16,17]

Berry and Barratt described in their meta-analysis of 4,260 patients a subset of 1,979 patients regarding postoperative septicaemia (persistent body temperature >38.5C, rigors and elevated C-reactive protein).[16] The rate of postoperative septicaemia lowered from 4% without AMP to 0.9% to 2% in patients with AMP. However, none of the included trials mentioned a significant decrease in postoperative septicaemia as outcome and no subanalysis of postoperative fever was performed.

Demographics of the AMP and no AMP groups regarding age, prostate volume, operating time, resected tissue volume, diabetes mellitus type 2, catheter time, postoperative fever and clot retention

	AMP Group	No AMP Group
No. pts	211	263
Median yrs age (Q1–Q4; IQR)	72 (64–76; 12)	72.5 (63–74; 11)
Median gm prostate vol (Q1–Q4; IQR)	54 (38–70; 32)	50 (38–65; 27)
Median mins operating time (Q1–Q4; IQR)	45 (35–60; 25)	43 (30–52; 22)
Median gm resected tissue vol (Q1–Q4; IQR)	20 (11–32; 21)	19.3 (10–30; 20)
% Pathological infection (95% CI)	9.5 (6.2–14.3)	8.7 (5.9–12.8)
% Diabetes mellitus type 2 (95% CI)	5.7 (3.2–9.8)	4.2 (2.8–7.4)
Median days catheter time (Q1–Q4; IQR)	2 (2–2; 0)	2 (2–2; 0)
% Postop fever (95% CI)	4.3 (2.2–8)	4.9 (2.8–8.4)
% (Clot) retention (95% CI)	6.2 (3.6–10.3)	4.9 (2.8–8.4)

A total of 28 studies published between 1966 and 2002 regarding TURP complications and AMP in patients with a preoperative urine sample less than 100,000 bacteria per ml were included in the systematic review by Qiang et al in 2005.[1] Only 6/28 studies investigated postoperative fever after TURP and a risk difference of −0.11 (13.5% vs 2.6%) was observed in reducing high grade fever (>38.5C) and a reduction in total fever (>37.2C) of 4.4% (26.9% vs 22.5%) in favor of AMP.

The authors conclude that a reduction in high grade fever appears to be of clinical significance but the benefits should be weighed against a 2.6-fold increase in side effects and the potential for the development of antibiotic resistant uropathogens.[1]

Wagenlehner et al published the most recent RCT to date about AMP in TURP in 2005.[17] Primary and secondary endpoints were postoperative bacteriuria after 5–7 days and 3–5 weeks. The tertiary endpoint was the rate of infectious (postoperative fever >38.5C, shivering, epididymitis, pyelonephritis) and noninfectious complications.

Due to slow recruitment only 400 patients of 480 prospected for inclusion were recruited at 14 centers with a range of 2–96 patients per center, and 376 patients were definitively included until postoperative day 5–7 and 336 until week 3 to 5.

Of the patients 302 received AMP (levofloxacin or trimethoprim + sulphamethoxazole) and 74 patients had placebo in a 2:2:1 ratio.

No significant difference was observed in overall complication rate between the AMP and placebo group. Although this study was well conducted, postoperative fever was only a subanalysis of the tertiary endpoint. The authors also state that the study is underpowered and only a low number of patients without AMP was included (74/376) due to the 2:2:1 ratio of randomization.

These studies showed a small benefit for AMP in reducing postoperative fever but also state that the use of prophylaxis should be weighed against the increase of adverse events, costs and potential for developing antibiotic resistant organisms.

Overuse and misuse of prophylactic antibiotics can increase antimicrobial resistance, which is a threat for global health care. This has led to the concept of antimicrobial stewardship, aiming for optimal clinical outcomes and restricting the development of resistant uropathogens.[2]

Cai et al performed an important study in support of antimicrobial stewardship.[6] A protocol for adherence to the EAU guidelines was created and data of 2,619 urological procedures (open, laparoscopic, endoscopic) before and 3,529 after protocol implementation were compared. Postoperative infection was defined as the presence of symptoms related to urinary tract infection and confirmed by microbiological analysis or surgical site infection. No significant difference was observed in symptomatic postoperative infection between both groups after and before protocol implementation (180/3529 [5.1%] vs 117/2619 [4.5%]; p = 0.3). The AB-resistance rate in E. coli to ciprofloxacin also decreased significantly (32.3% vs 19.1%; p = 0.03) after protocol introduction.

These data support the safety of single-use AMP course in urological procedures and the positive impact on antimicrobial resistance but it is important to note that only 100 patients undergoing TURP before and 128 after protocol implementation were included and no specific results for TURP were published.[6]

Although the evolution from a prolonged AMP course to single-use AMP is encouraging, the "Holy Grail" of antimicrobial stewardship remains a reduction in total antibiotic use since even single-use AMP can increase antimicrobial resistance.[7,8]

The impact of single-use antibiotics on microbial resistance was investigated by Wagenlehner et al in 2000.[8] A prospective analysis was performed on the level of ciprofloxacin resistance on fecal E. coli in 105 patients and showed that the E. coli resistance to ciprofloxacin increased from 3% to 12% (p = 0.05) after a single dose of 500 mg ciprofloxacin orally.

Due to disabling and potentially permanent side effects on the tendons, muscles, joints, nerves and central nervous system, the use of FQ is becoming controversial. The U.S. Food and Drug Administration (FDA) approved changes in 2016 to the labels of fluoroquinolones for systemic use and revised the Boxed Warning (FDA's strongest warning) with an update in December 2018 about the risk of aortic aneurysm associated with fluoroquinolone use.[5,18]

We performed a prospective cohort trial in 506 patients undergoing TURP in 2017, investigating

the safety of omitting AMP in a subset of patients. Only 67/506 patients received AMP either because they had a preoperative catheter (56/67, 83.5%) or preoperative pyuria (11/67, 16.4%), defined as >100 WBC/ml. A remarkable high fluoroquinolone resistance rate of 69.2% in E. coli was observed in the patients with preoperative pyuria. Postoperative fever was present in 13/439 (2.9%) patients without antibiotic prophylaxis vs 7/67 (10.4%) patients with AMP. Although these data were solid and questioned the use of FQ as antibiotic prophylaxis in TURP, the lack of randomization was a major weakness.[5]

This large, multicenter RCT was set up to investigate our earlier findings and to assess the safety of omitting AMP in patients undergoing TURP without a preoperative catheter and in the absence of preoperative pyuria. Multivariable, logistic regression showed no meaningful increase in harm associated with omitting AMP ($p=0.4$) and adjusted difference 0.016 (95% CI −0.02–0.05). These results support a safe reduction in antibiotic use in TURP prophylaxis, avoiding the potential impact on microbial resistance next to the side effects/allergic reactions and increased costs of antibiotics. Our multicenter study is adequately powered and has a clearly defined endpoint (postoperative fever). One center used a different randomization method, with possible temporal trends, which could be the cause of the slight imbalance in numbers in both groups. This can be considered as a study weakness but this is nearly inevitable in multicenter studies and an additional analysis was performed to confirm adequate randomization.

CONCLUSIONS

This study demonstrates the safety of omitting AMP in patients undergoing TURP without preoperative pyuria and a preoperative catheter. These findings support a reduction in antibiotic use, which in turn reduces side effects/allergic reactions of antibiotics and the potential impact on microbial resistance. This way, the study could be another step forward in antimicrobial stewardship.

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EDITORIAL COMMENTS

This group from Belgium has produced a clinical study with rigorous design and powered it well to present a clinical situation for the urological community to consider. The urological surgeon is

concerned about a violation of the urethral mucosa but a study like this makes the reader question, "What is the critical point to minimize infection in the perioperative period of an elective endoscopic procedure with significant breaks in normal tissue barriers?"[1] The answer possibly lies in the recognition that there are multiple time points in the perioperative period where intervention makes a difference, and those key points likely carry different relative weights of patient risk.

The investigators have controlled for preoperative factors with strict urinalyses criteria and excluding patients with indwelling foley catheters. We know that documenting preoperative, sterile urine is important to care standards but investigations into the urinary microbiome may change practice. We know that it probably takes several weeks for the urethral mucosa to be restored after TURP but long durations of postoperative antibiotics are a thing of the past.

Urologists have been active participants in the efforts to modify antibiotic stewardship for our procedures. An excellent example is the modification of the guidelines for local procedures where office cystoscopy is done without prophylaxis and prostate biopsies done with a single dose of fluoroquinolone.[1] More relevant to this study is the evolution of antibiotic choice for elective procedures with a break in the normal tissue barrier. At Loyola Medical Center a third generation cephalosporin (cefriaxone) has replaced cephalexin. In addition to recognition of regional antibiograms, another important reason this drug might become more effective is the prolonged half-life compared to its second generation companion. The published literature seems to support antibiotic prophylaxis at the time of catheter manipulation/removal after TURP.[2]

I think this study also highlights that clinically significant, postoperative sepsis after elective bladder outlet procedures like TURP is a rare occurrence. My main critique of this European study is that it has very little chance of changing clinical practice for the simple reason that hospitals and surgeons are held to quality measures that include the use of preoperative antibiotics. Said another way, in the United States, "perioperative antibiotics are here to stay." But sometimes good science is good because it leaves us with good questions and the implication that there is certainly more work to be done. This publication, the investigators, and study participants are a good example.

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The authors present an extremely well done and thought-provoking study which recapitulates naturalistic exposure as pertaining to antibiotic use in TURP. Despite prior recommendations from well-conceived guidelines (references 2 and 3 in article), they determine no benefit for perioperative antimicrobial use in a well-defined multicenter randomized population undergoing this surgical intervention. They correctly stress not only the necessity for temporal but also absolute dose reduction in antimicrobial use as prime tenets of antibiotic stewardship. Two groups of variables possibly confound this conclusion: one being those related to comorbidities and potential impact on patient immunological integrity, the second being variability in postoperative urinary catheter dwell time (and potential manipulation such as irrigation). Therefore, the conclusion must be drawn that antibiotic use should be considered within the broader aspect of coherent and consistent systematized care delivery (antimicrobial stewardship). Previously, urology has been slow to adopt antibiotic indication and use modifications, but is now rapidly reconsidering strategies (and remediations thereof) such as prolonged suppression (intermittent self-start and host optimization), perioperative duration of exposure (strict criteria as to time frame for surgical parenteral administration), and indicated use and class of specific agents (adoption of stricter criteria for clean and clean contaminated procedures, avoidance of liberal use of fluoroquinolones; references 2 and 3 in article). However, as noted in guidelines such as those created by the Centers for Disese Cotrol and Prevention,[1] antibiotic use must be considered within the framework of organizational surveillance and response to untoward

infection related issues such as surgical site infection and antibiotic associated diarrhea. Such roadmaps provide the direction for continuous quality improvement in this arena.

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