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Original Article

Proposal and clinical validation of a perioperative algorithm enhancing antimicrobial stewardship in substitution urethroplasty

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Abstract *Objective:* To evaluate the impact of a standardized antibiotic stewardship protocol on three subsequent endpoints in patients undergoing urethroplasty.
Methods: Men undergoing bulbar substitution urethroplasty between January 2009 and December 2016 were stratified by urine culture (UCx) at the time of surgery (sterile *vs.* non-sterile) and were subjected to a standardized algorithm for urinalysis and antimicrobial therapy. We performed quantitative and qualitative exploration of UCx results and the microbial spectrum. The ability of the algorithm to improve antibiotic stewardship was tested by three endpoints: (a) immediate (UCx 2 days postoperatively), (b) short-term (21-day infectious complications), and (c) long-term (retreatment-free survival [RFS]). Statistical analyses included

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bivariate comparisons. The Kaplan–Meier estimators were used to compare RFS between the groups. The multivariable Cox regression was used to evaluate the independent effect of UCx status at the time of surgery on RFS.
Results: Of 374 men, 235 (63%) had a sterile and 139 (37%) a non-sterile culture at the time of surgery. The proportion of sterile cultures at the time of surgery (63%) was significantly improved to 82% 2 days postoperatively ($p<0.001$). There were 16 (4.3%) patients with infectious complications with no difference between patients with sterile versus non-sterile culture ($p=0.6$). At median follow-up of 29 months, there was no difference in RFS (84%) between patients with sterile versus non-sterile culture ($p=0.3$). Positive UCx was not a predictor of recurrence after multivariable adjustment ($p=0.5$).
Conclusion: A standardized protocol such as the one introduced improves antibiotic stewardship through frequent testing and culture-specific treatment. This is crucial in avoiding unnecessary antimicrobial treatment, and reducing infectious events and adverse effects of a positive UCx on long-term stricture recurrence.

1. Introduction

Male urethral stricture disease carries a significant burden on quality of life caused by urinary obstruction and subsequent complications. Stricture etiology comprises traumatic, infectious, iatrogenic, and idiopathic causes and the incidence is estimated to be up to 627 per 100 000 males [1]. In approximately half of the patients, the anterior urethra, particularly the bulbar urethra, is affected [2]. Open reconstructive surgery is routinely performed and represents the gold standard treatment in longer or complex strictures and in refractory cases after endoscopy [2,3]. Infectious complications can compromise the perioperative course of treatment and deteriorate the postoperative surgical outcome following urethroplasty [4]. To prevent such complications, many reconstructive urologists advocate for the administration of antibiotic prophylaxis extending up to 21 days postoperatively until catheter removal [5,6], despite uncertainties regarding the advantages of universal antibiotic usage in patients dependent on indwelling catheters postoperatively [7]. The lack of both evidence and standardization results in a scarcity of guideline recommendations leading to substantial heterogeneity of antimicrobial administration in the perioperative urethroplasty setting [6,8].

Extensive antimicrobial treatment is known to cause antimicrobial resistance, prolonged hospitalization, increased mortality, and health care costs [9]. In addition, clostridium difficile infections are linked to overuse of antibiotic therapy. Consequently, emphasizing antibiotic stewardship (ABS) becomes critically important to circumvent unnecessary antimicrobial treatment, mitigate patient risks, and address global resistance patterns overall. This focus is especially pertinent in reconstructive urology, a field where patients frequently rely on indwelling catheterization [5,9–12].

Given the limited evidence on rational ABS programs in urethral reconstruction, we aimed to introduce a standardized algorithm for perioperative ABS and to investigate the effect of such distinct measures on immediate, short-term, and long-term outcomes after one-stage substitution urethroplasty.

2. Patients and methods

2.1. Study population

This study was approved by the ethics committee of the Medical Council of Hamburg (PV4123) and was a retrospective analysis of 1039 patients who had undergone one-stage buccal mucosal graft urethroplasty between January 2009 and December 2016. Data extraction and collection were performed according to local laws (Hamburgisches Krankenhausgesetz, HmbKHG §12.1). To allow for a homogeneous and comparable cohort and for the purpose of our analysis we excluded 423 patients with non-bulbar or lichen sclerosus-associated strictures, 45 patients undergoing a procedure other than ventral onlay, 33 with a history of pelvic radiotherapy, five with prior hypospadias repair, and 159 with missing data regarding the relevant perioperative urine culture (UCx) examination.

2.2. Perioperative urinalysis and ABS workflow

Patients who underwent urethral stricture surgery were subjected to our standard operating procedure for perioperative urinalysis and antimicrobial treatment, which is in detail depicted in Fig. 1. In short, UCx-1 was taken 7–10 days prior to surgery in the outpatient clinic or with the private practitioner and antimicrobial therapy was initiated 5 days prior to surgery in case of microbial detection according to UCx-1 pathogens and sensitivity results. On the preoperative day, an extensive urinalysis was performed by dipstick and UCx-2 in all patients, irrespective of the UCx-1 result. Urethroplasty was postponed in case of nitrite positivity and/or significant leukocyturia ($^{++/+++}$) in dipstick analysis confirmed by positive microscopic urine sediment analysis. All patients underwent intraoperative intravenous

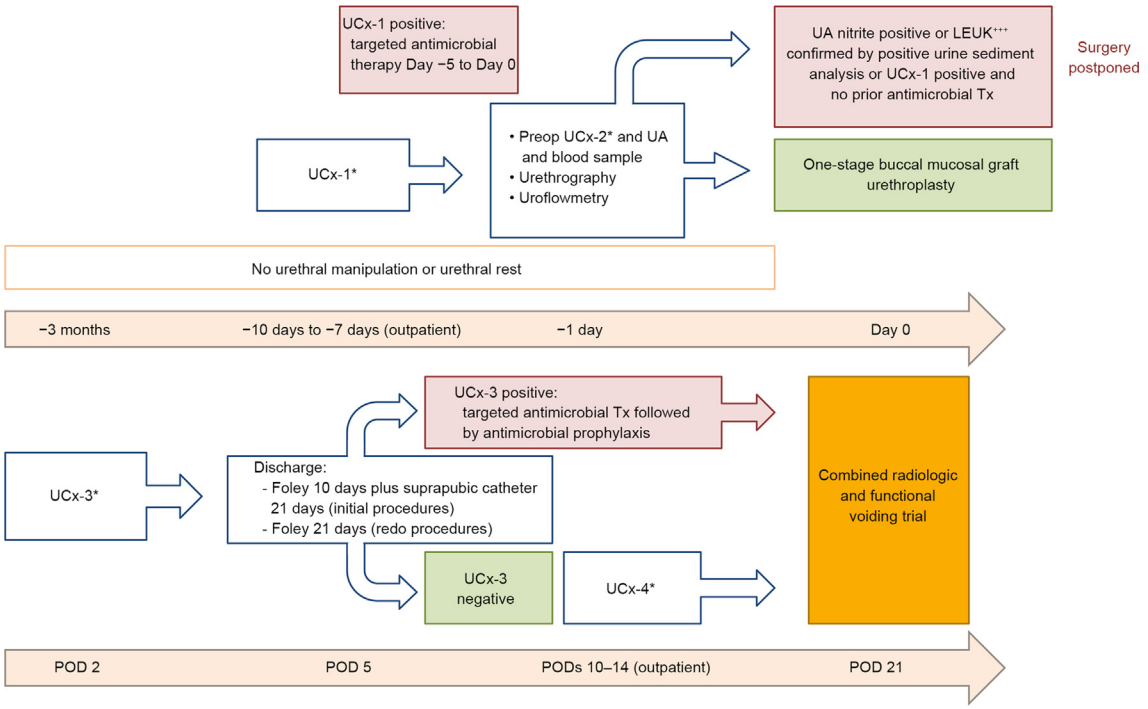

Figure 1 The flowchart of a standardized perioperative algorithm regarding frequent urinalysis and culture-specific targeted treatment, which is applied to patients undergoing urethral reconstruction at the Department of Urology at the University Medical Center Hamburg-Eppendorf. The day indications in the diagram refer to the days before (*i.e.*, −1 day means 1 day prior to surgery) and after the surgery, with "Day 0" representing the day of the surgery. POD, postoperative Day; UA, urinalysis; UCx, urine culture; $LEUK^{+++}$, leukocytes significantly positive; Tx, therapy; Preop, preoperative. * Each UCx with a positive finding implicates targeted culture-specific antimicrobial therapy for ±5 days.

administration of a single dose of 1.5 g cefuroxime. Results of preoperative UCx-2 were regularly available at postoperative Day (POD) 2, and targeted therapy was initiated in case of *de novo* bacteriuria, or previous treatment was adjusted respectively. UCx-3 was submitted on POD 2, the result was available on POD 4 and again, targeted antimicrobial therapy was initiated for 5 days or adapted according to microbiological results and sensitivity testing. Patients were commonly discharged on POD 5. In case of a positive UCx-3, antimicrobial therapy was initiated. In general, targeted antimicrobial therapy was performed for 5 days.

In case of targeted therapy according to perioperative testing (UCx-2 and/or UCx-3), patients were advised to undergo a subsequent antimicrobial prophylaxis (nitrofurantoin 100 mg once daily) up to POD 21. If UCx-3 was negative, patients were discharged without antimicrobial treatment.

Patients and urologists were advised to submit UCx-4 on PODs 10—14 and to treat according to microbiological results in case of bacterial positivity. Thereby, sterile urine conditions should be ensured for the combined radiologic and functional voiding trial at POD 21 (Fig. 1).

2.3. Evaluations, surgical procedures, and perioperative management

Prior to surgery, all men were evaluated by medical history, physical examination, uroflowmetry, post-void residual volume, and combined urethrography (retrograde and voiding urethrography). Ventral onlay buccal mucosal graft urethroplasty was performed for bulbar stricture repair [13] according to a standardized perioperative pathway [14,15]. Postoperatively combined suprapubic (21 days) plus transurethral catheterization (10 days), and a transurethral catheterization only (21 days) were performed for primary and redo cases, respectively. At POD 21, a combined voiding trial including urethrography was conducted to assess urethral patency and early functional outcomes [14].

2.4. Study endpoints and the follow-up

We sought to investigate the effect of the implementation of an institutionally standardized ABS algorithm on immediate, short-term, and long-term outcomes after urethroplasty. First, the immediate endpoint was defined as the UCx-3 result at POD 2, as it mirrors the instant and first outcome of preoperative ABS management. Second, the short-term endpoint was defined as the occurrence of any infectious complication (wound and significant urinary tract infection [UTI]) at POD 21 to evaluate the effectiveness of postoperative ABS management on the clinical course within the first 3 weeks postoperatively until catheter removal. Third, the long-term endpoint was defined as functional recurrence, which was defined as stricture retreatment, to investigate the relevance of a positive UCx at the time of surgery on stricture recurrence in the context of a strict ABS algorithm [16]. A cross-sectional postoperative follow-up was performed by mail and phone using standardized questionnaires.

2.5. Covariables

Baseline characteristics consisted of age at surgery, history of previous urethral surgery, presence of any urinary catheter at admission, and preoperative urine dipstick analysis. A positive urine dipstick was defined as one of the following measures being positive: nitrite, leukocytes, hemoglobin, or erythrocytes. Intraoperative parameters included operative time and graft length.

2.6. Statistical analyses

First, patients were stratified by findings from UCx-2 into sterile and non-sterile urine. UCx-2 was chosen as baseline UCx, as it most adequately represents the actual intraoperative urinary status, given that UCx-2 was submitted on the day prior to surgery. Baseline and intraoperative characteristics were compared between the groups using medians and interquartile ranges (IQRs) for continuous variables and frequencies and proportions for categorical variables.

Second, we performed a detailed qualitative analysis to identify and report the microbial spectrum in patients with a positive UCx-2 at the time of surgery.

Third, we tested the association of the urinary status at the time of surgery (*i.e.*, UCx-2) with our immediate and short-term study endpoints by bivariate analyses. For all descriptive analyses, differences between groups were evaluated using the Mann–Whitney *U* test, Pearson's Chi-squared test, or Fisher's exact test when samples were less than 10, as appropriate.

Fourth, reverse Kaplan–Meier estimates were calculated for follow-up time in censored patients. The effect of a positive UCx-2 at the time of surgery on the long-term outcome (retreatment-free survival) was tested by Kaplan–Meier analyses and equality of the curves was evaluated by the logrank test. Furthermore, a multivariable bootstrap-corrected (200 repetitions) Cox regression model was computed to evaluate the independent effect of UCx-2 status on stricture retreatment, after adjusting for age, history of previous urethral surgery, catheter at admission, and graft length.

All analyses were performed using Stata® (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LLC). Two-sided statistical significance was defined as a *p*-value of less than 0.05.

3. Results

3.1. Baseline and intraoperative characteristics

Patient characteristics are summarized in Table 1. Median patient age was 52 (IQR 38–65) years and a total of 309 (83%) men had undergone previous urethral stricture treatment (17% urethroplasty). Median operative time and graft length were 66 (IQR 57–82) min and 4.5 (IQR 4.0–5.0) cm, respectively. Overall, 102 (27%) men presented with suprapubic catheter at admission, and preoperative urine dipstick was positive in 169 (45%) patients.

UCx-2 was positive in 139 (37%) patients. Of those, 70 (50%) and 69 (50%) patients showed bacterial counts of $\leq 10^3$ colony-forming units (cfu)/mL and $\geq 10^4$ cfu/mL, respectively. Compared to patients with a sterile UCx-2, patients with positive UCx-2 were older (median age 54 years *vs.* 49 years; $p=0.022$), and presented more frequently with an indwelling catheter (38% *vs.* 21%; $p<0.001$) or a positive urine dipstick at admission (60% *vs.* 37%; $p<0.001$).

A detailed qualitative analysis of the urinary culture status at the time of surgery is depicted in Fig. 2. In the 139 patients with positive UCx-2, gram-positive cocci (63%) and enterobacteriaceae (22%) were the most frequent microbes.

3.2. The association of urinary status at the time of surgery and immediate, short-term, and long-term outcomes

The number of patients with sterile UCx findings at the time of surgery (UCx-2 sterile in 63%) was significantly improved to 82% in UCx-3 at POD 2 ($p<0.001$). Overall, infectious complications were reported in 16 patients (4.3%; 14 significant UTIs and two wound infections), which resulted in

Table 1 Baseline and intraoperative characteristics in 374 men undergoing one-stage buccal mucosal graft urethroplasty stratified according to preoperative UCx (the UCx-2) results.

Patient characteristic	Overall cohort[a]	Sterile[a]	Non-sterile[a]	*p*-Value
Patient	374 (100)	235 (63)	139 (37)	–
Age at surgery, year	52 (38–65)	49 (36–63)	54 (43–68)	0.022
History of previous urethral surgery				0.9
None	65 (17)	40 (17)	25 (18)	
DVIU	246 (66)	157 (67)	89 (64)	
Urethroplasty	63 (17)	38 (16)	25 (18)	
Catheter at admission	102 (27)	49 (21)	53 (38)	<0.001
Preoperative urine dipstick positive[b]	169 (45)	86 (37)	83 (60)	<0.001
Operative time, min	66 (57–82)	66 (57–83)	66 (57–82)	0.6
Graft length, cm	4.5 (4.0–5.0)	4.0 (4.0–5.0)	5.0 (4.0–5.0)	0.3

DVIU, direct vision internal urethrotomy; UCx, urine culture; –, not applicable.
[a] Values are presented as median (interquartile range) or *n* (%), and total percentages may not be 100% due to rounding.
[b] Nitrite, leukocytes, hemoglobin, or erythrocytes positive.

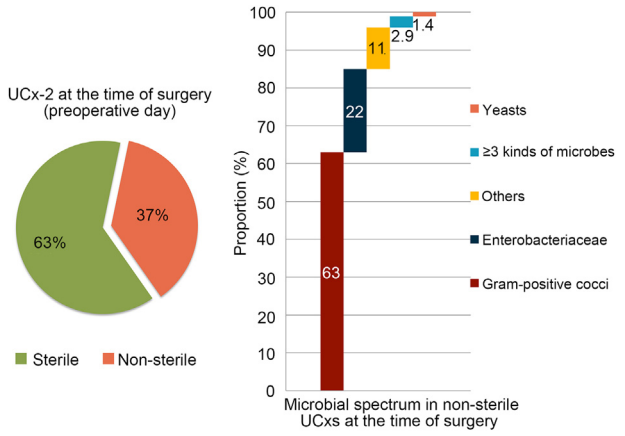

Figure 2 Graphic representation of patients presenting with a non-sterile urine culture at the time of surgery and the microbial spectrum in such patients; UCx, urine culture.

postponing urethrography initially scheduled for POD 21. There was no significant difference in the occurrence of infectious complications between patients with sterile versus non-sterile UCx-2 at the time of surgery ($p=0.6$; Table 2).

Overall, 69 (18%) patients were lost to follow-up, and at a median follow-up of 29 (IQR 15—50) months, retreatment-free survival was 84%. In the Kaplan—Meier analysis, there was no difference regarding functional recurrence between patients with sterile versus non-sterile UCx-2 at the time of surgery ($p=0.3$; Supplementary Fig. 1). Those findings were confirmed in the bootstrap-corrected Cox regression analysis after adjusting for age, catheter at admission, previous stricture treatment, and graft length. A positive UCx-2 was thereby not an independent predictor of functional recurrence in above-mentioned ABS algorithm (hazard ratio 1.23; 95% confidence interval 0.67—2.27; $p=0.5$; Supplementary Table 1).

4. Discussion

ABS programs aim at reducing unintended consequences of antimicrobial use such as healthcare-associated infections including clostridium difficile, toxicity, selection of virulent organisms, and emergence of resistant bacterial strains while optimizing the clinical outcome and ensuring cost-effective therapy [17,18]. Asymptomatic bacteriuria (ABU) is common and mostly corresponds to colonization. It is even discussed to have a protective effect regarding clinically relevant, superinfecting, and symptomatic UTIs [19]. Therefore, ABU should only be treated in patients with proven benefit, to avoid the risk of promoting antimicrobial resistance and eradicating a potentially protective ABU strain.

Contemporary urological guidelines recommend screening for and treating ABU in patients prior to urologic procedures entering the urinary tract and breaching the mucosa [4,20]. Such antimicrobial treatment should be tailored and not be empirically administered. However, a specific recommendation for patients scheduled for urethroplasty is lacking. These patients often present with indwelling catheters or suffer from post-void residual urine and commonly present with ABU. Furthermore, all patients rely on extended postoperative catheterization for up to 21 days.

We established and implemented a standardized perioperative framework for urinary testing and antimicrobial treatment at predefined time points in the pre- and post-operative courses. This algorithm aims at both outcome improvement and reducing unnecessary or untargeted antimicrobial treatment in the management of urethroplasty patients. Despite thorough testing 7—10 days prior to urethroplasty and targeted antimicrobial therapy in case of microbial detection, a positive UCx was still found in more than one-third of all patients at the time of surgery. This finding underscores the problem of the imperfect sensitivity of pre-surgery urinalysis (urine dipstick and microscopy), where certain patients may not be detected beforehand and consequently present with a positive UCx at the time of surgery. These preoperative UCx (UCx-2) results showed gram-positive cocci and gram-negative rods as the most frequent microbes. Others reported comparable preoperative bacterial patterns regardless of the presence or absence of an indwelling catheter [21]. Intriguingly, a positive UCx at the time of surgery did not translate into more frequent infectious complications or inferior postoperative short-term and long-term outcomes after urethroplasty in such patients. This effect can be explained by strict adherence to the proposed urinary testing algorithm, enabling effective antimicrobial targeted treatment including the evaluation of resistance and sensitivity patterns at three critical perioperative time points. Our hypothesis is supported by our observation that the

Table 2 Bivariate analyses of preoperative UCx (the UCx-2) findings with immediate and short-term outcomes in 374 men undergoing one-stage bulbar buccal mucosal graft urethroplasty.

Immediate and short-term outcomes	Overall cohort[a]	Sterile[a]	Non-sterile[a]	*p*-Value
UCx-3 at POD 2				<0.001
Sterile	334 (89)	220 (94)	114 (82)	
Non-sterile	40 (11)	15 (6)	25 (18)	
Infectious complication[b]	16 (4.3)	9 (3.8)	7 (5.0)	0.6

POD, postoperative Day; UCx, urine culture.
[a] Values are presented as *n* (%), and total percentages may not be 100% due to rounding.
[b] Evaluated at the time of a radiographic and functional voiding trial at POD 21; significant urinary tract infections or wound infections were considered infectious complications and urethrography was postponed accordingly.

postoperative UCx-3 at POD 2 was sterile in 82% of our cohort. This outcome may be attributed to both the targeted therapy following UCx-2 and the intraoperative single-shot antibiotic treatment. Consequently, this finding enables approximately four out of five patients to be discharged without the necessity of antibiotic prophylaxis.

Early postoperative infectious complications including UTIs and wound infections were observed in 4.3% of our cohort. Kim et al. [12] reported postoperative UTIs in 6.7% and wound infection in 4.1% (overall 11%) of a heterogeneous cohort including 390 patients following urethroplasty using nitrofurantoin prophylaxis until catheter removal. In addition, two doses of ciprofloxacin or trimethoprim and sulfamethoxazole were applied 1 day prior to catheter removal. In a recent follow-up publication implementing a second cohort of 510 patients who received only two dosages of antibiotics (ciprofloxacin or trimethoprim and sulfamethoxazole) prior to catheter removal, UTIs and wound infections were reported in 3.9% and 3.7% of the cohort (overall 7.6%) within 30 days, respectively [22].

A recent study by Bischoff et al. [23] identified residence in nursing homes, male gender, hospitalization within the last 30 days, renal transplantation, antibiotic treatment within the last 30 days, an indwelling urinary catheter, and recurrent UTIs as risk factors for multidrug resistance in patients with UTIs. Patients following urethroplasty meet several of these risk factors. Our proposed algorithm therefore aims to ensure targeted antibiotic treatment if needed at any perioperative time point and has thereby the potential to mitigate the risk of multidrug resistance in this vulnerable cohort.

While UCx-1 is in line with current recommendations for the management of patients with urethroplasty, extensive preoperative urine evaluation including UCx-2 the day before surgery and UCx-3 on POD 2 reduces untargeted antimicrobial treatment and postoperative complications. Although ABU was observed in a relevant number of patients, the risk of relevant UTIs at the time of surgery is minimized by postponing urethroplasty in patients with untreated UTIs related to UCx-1 or evidence of significant bacteriuria or signs of florid infections preoperatively. This might be reflected by mainly low counts of cfu/mL and by 82% of patients with a sterile UCx-2. Ultimately, the use and timing of UCx-4 follow current recommendations from the American Urological Association and the European Association of Urology [3,20].

A direct comparison of our postoperative outcomes to other reported data is difficult since the definition of a positive UCx and UTI is not consistent between different research groups. Baas et al. [10] defined a UTI as $>10^6$ cfu/mL or reported lower urinary tract symptoms treated with empiric antibiotics. Others defined a UTI as a febrile infection with bacteriuria and symptoms [21]. Manjunath et al. [11] defined a UTI as positive urine-culture with $>10^3$ cfu/mL of one organism. At our institution, we respond to any bacterial detection by UCx, given that urethroplasty represents a procedure breaching the mucosa and the need of postoperative extended catheterization. Infectious complications might be a risk factor for impaired postoperative outcomes of reconstructive surgery. The literature in this regard is scarce. However, ABU and UTIs are known to cause perianastomotic inflammatory response with impaired healing of urethral anastomosis [24].

A substantial strength of our current publication is the homogeneous and comparable cohort including only patients with bulbar ventral onlay urethroplasty. However, our study is not devoid of limitations. Various surgical approaches adopted at different centers could potentially yield divergent surgical outcomes and infection rates. By concentrating on a single center's population, we aimed to eliminate differing perioperative treatment protocols as a potential confounding factor. However, future research on perioperative antibiotic prophylaxis post-urethroplasty should incorporate comparisons among diverse surgical techniques. It is important to note that our present series primarily focused on a cohort of men undergoing substitution urethroplasty. Regrettably, comprehensive details regarding bacterial species and counts in preoperative outpatient urine cultures were unavailable. Therefore, we were unable to assess the correlations or changes in more detailed bacteriuria characteristics between cultures pre- and post-therapy. Further limitations of our study are retrospective data acquisition and the absence of a control group, which does not allow for direct causal inferences.

5. Conclusion

We successfully subjected a perioperative algorithm including frequent urine testing and targeted, culture-specific therapy to patients undergoing urethral reconstruction. The proposed algorithm proved efficient in mitigating potential adverse effects of a positive UCx at the time of surgery, as no impairment of postoperative immediate, short-term, or long-term outcomes was observed. Pending external validation of this or other distinct algorithms to improve ABS in reconstructive urology, our concept may aid in reducing unnecessary and untargeted antibiotic treatment in patients undergoing urethroplasty.

Author contributions

Study concept and design: Phillip Marks, Benedikt Kranzbühler, Malte W. Vetterlein.
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Data analysis: Malte W. Vetterlein.
Drafting of the manuscript: Phillip Marks, Benedikt Kranzbühler, Malte W. Vetterlein.
Critical revision of the manuscript: Tim A. Ludwig, Liucheng Ding, Frederik König, Lennart Kühnke, Roland Dahlem, Margit Fisch.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2024.01.003.

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