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AUA-recommended Antibiotic Prophylaxis for Primary Penile Implantation Results in a Higher, Not Lower, Risk for Postoperative Infection: A Multicenter Analysis

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Study Need and Importance: In 2008 the AUA published a Best Practice Statement on Urologic Surgery Antibiotic Prophylaxis that recommended an aminoglycoside and vancomycin or a first-/second-generation cephalosporin for penile prosthesis placement. This recommendation was based on orthopedic and general surgery literature due to a lack of high-level urological evidence. The combination of vancomycin and gentamicin has since become the most commonly used regimen for inflatable penile prosthesis (IPP) prophylaxis, as noted in a number of subsequent studies. Recent research has questioned the efficacy of these suggested regimens in high-risk patients. We sought to evaluate the efficacy of the most commonly used AUA-recommended regimen among all patients undergoing primary IPP placement.

What We Found: In a large multicenter study, we found vancomycin plus gentamicin was associated with an increased risk of implant infection in multivariable analysis (HR: 2.7, 95%CI: 1.4 to 5.4, $P = .004$; part A of Figure) compared to all other regimens. The addition of an antifungal to the antibacterial regimen decreased the risk of infection by 92%. In a subgroup analysis, there was no statistically significant difference between weight-based and low-dose (80 mg) gentamicin dosing (part B of Figure).

Limitations: The main limitations of this study are its retrospective nature and inherent selection bias. A large portion of patients who received vancomycin plus gentamicin also received an antifungal, which may bias the hazards ratio. Additionally, we were not able to account for other infection reduction strategies.

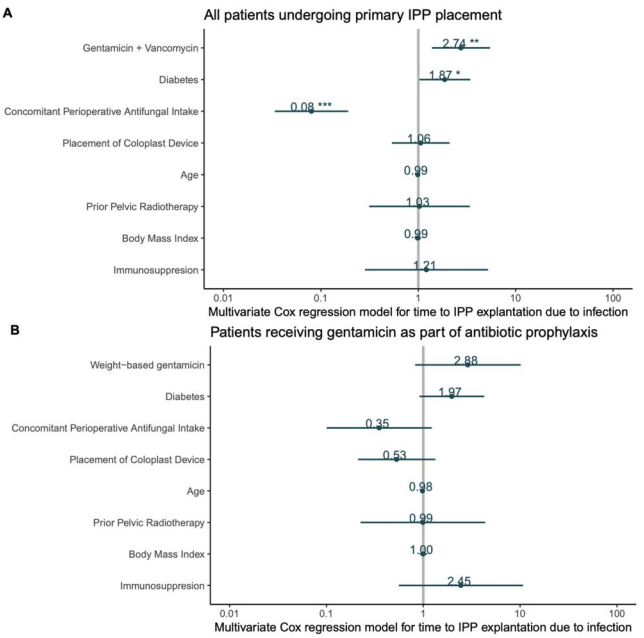

Figure. A, All patients undergoing primary inflatable penile prosthesis (IPP) placement. B, Patients receiving gentamicin as part of antibiotic prophylaxis. All asterisks indicate statistically significant findings.

Interpretation for Patient Care: Our findings provide a strong rationale for the addition of an antifungal to antibacterial coverage in all men undergoing IPP placement. Tailoring antimicrobial prophylaxis to local infection trends and antibiogram data may be the most effective and data driven option for IPP infection prevention.

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AUA-recommended Antibiotic Prophylaxis for Primary Penile Implantation Results in a Higher, Not Lower, Risk for Postoperative Infection: A Multicenter Analysis

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Purpose: Our aim was to determine if the AUA-recommended prophylaxis (vancomycin + gentamicin alone) for primary inflatable penile prosthesis surgery is associated with a higher infection risk than nonstandard regimens.

Materials and Methods: We performed a multicenter, retrospective study of patients undergoing primary inflatable penile prosthesis surgery. Patients were divided into those receiving vancomycin + gentamicin alone and those receiving any other regimen. A Cox proportional-hazards model was constructed adjusted for major predictors. A subgroup analysis to identify the appropriate dosage of gentamicin was also performed.

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Results: A total of 4,161 patients underwent primary inflatable penile prosthesis placement (2,411 received vancomycin + gentamicin alone and 1,750 received other regimens). The infection rate was similar between groups, 1% vs 1.2% for standard vs nonstandard prophylaxis. In the multivariable analysis, vancomycin + gentamicin (HR: 2.7, 95% CI: 1.4 to 5.4, $P = .004$) and diabetes (HR: 1.9, 95% CI: 1.03 to 3.4, $P = .04$) were significantly associated with a higher risk of infection. Antifungals (HR: 0.08, 95% CI: 0.03 to 0.19, $P < .001$) were associated with lower risk of infection. There was no statistically significant difference in infection rate between weight-based gentamicin compared to 80 mg gentamicin (HR: 2.9, 95% CI: 0.83 to 10, $P = .1$).

Conclusions: Vancomycin + gentamicin alone for antibiotic prophylaxis for primary inflatable penile prosthesis surgery is associated with a higher infection risk than nonstandard antibiotic regimens while antifungal use is associated with lower infection risk. A critical review of the recommended antimicrobial prophylactic regimens is needed. Prospective research is needed to further elucidate best practices in inflatable penile prosthesis antimicrobial prophylaxis.

Key Words: erectile dysfunction, penile prosthesis, infections

Penile prosthesis surgery is the gold standard treatment of refractory erectile dysfunction that has traditionally been associated with a high satisfaction rate and excellent long-term device survival.[1,2] Implant infection is one of the most feared complications, but occurs in only 1%-6% of patients undergoing penile prosthesis surgery with higher rates in diabetics and revision cases.[3,4] Device infection can be associated with the need for further surgery, sexual dysfunction, penile length loss, and medicolegal implications.[5,6]

Due to the devastating impacts of inflatable penile prosthesis (IPP) infections, surgeons take many steps to decrease infection, including the use of antibiotic impregnated/coated devices, antiseptic surgical scrub, no-touch technique, wound irrigation, and perioperative antimicrobial prophylaxis. There is heterogeneity among the recommendations for perioperative antimicrobial prophylaxis in patients undergoing IPP surgery. The AUA recommends specific regimens with gentamicin plus vancomycin or a first-/second-generation cephalosporin.[7,8] Among these regimens, vancomycin and gentamicin is the most commonly used.[9] The European Association of Urology (EAU), however, previously recommended a second-/third-generation cephalosporin or a penicillin agent with anti-penicillinase activity.[9,10] Nevertheless, recent evidence suggested regimens that have been recommended by the AUA and EAU may be associated with a higher postoperative infection rate than nonstandard regimens.[4,9] Accordingly, the EAU no longer publishes specific guidance on perioperative prophylaxis, leaving surgeons with only the AUA recommendation regarding specific regimens. Recent evidence also suggests the use of antifungal agents, especially in high-risk groups, may provide more robust prophylaxis;[4] however, the role of antifungals in patients undergoing primary IPP surgery remains unclear.

Previously, our multi-institutional collaborative demonstrated the standard AUA antimicrobial prophylaxis was less effective than an aggregate of comparator regimens in men with diabetes.[4] Here, our aim was to evaluate the AUA antimicrobial prophylaxis in all men undergoing IPP placement. We hypothesized that vancomycin plus gentamicin alone would be associated with a higher risk of infection while the use of antifungals would be associated with lower risk in primary IPP placement.

MATERIALS AND METHODS

Study Design

A total of 4,161 patients who underwent primary IPP surgery between July 2016 and July 2021 were included in this multicenter, retrospective cohort study. A total of 16 different institutions from the United States, Europe, and Korea submitted patients. All included institutions were sexual medicine referral centers and all surgeries were performed by experienced prosthetic surgeons. This study was conducted based on the Declaration of Helsinki and was approved by the Institutional Review Board of each center. Findings were reported based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement.[11]

Selection Criteria

Our goal was to assess antibiotic prophylaxis in the patient undergoing routine, primary IPP placement. Predefined inclusion criteria were patients undergoing primary IPP surgery due to erectile dysfunction with data availability for perioperative antibiotic administration and for study outcomes. The exclusion criteria comprised the following groups due to their higher risk for infection: (1) concomitant correction of penile curvature with any adjunct surgical treatment (plication or grafting), and (2) concomitant or prior correction of urinary incontinence with any adjunct surgical treatment (sling, artificial urinary sphincter, mini-jupette).

Study Protocol

The electronic medical record of each institution served as the primary data sources and all data were pooled for analysis. The last follow-up evaluation was defined as the last clinical evaluation of the patient from the surgeon who performed the IPP implantation. Data on baseline, intraoperative, and postoperative characteristics, as well as on the type and dosage of perioperative antibiotic prophylaxis, were extracted. Groups consisted of patients who received recommended antibiotic prophylaxis (vancomycin plus

gentamicin alone), vs patients who received any other antibiotic prophylaxis.

Study Outcomes

The primary outcome was the time to postoperative device explant and/or salvage due to infection in patients undergoing perioperative antibiotic prophylaxis with vancomycin plus gentamicin vs other antibiotic regimens. Secondary outcomes were: (1) the effect of patient baseline and perioperative characteristics on time to device explanation due to infection, (2) the microorganisms involved in infection, and (3) the management of patients with device infection.

We performed a subgroup analysis in patients in both groups who received gentamicin as part of perioperative antibiotic prophylaxis, aiming to compare weight-based dosage vs 80 mg dosage of gentamicin.

Statistical Analysis

Continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables as frequencies and percentages. Evaluation of normality and between-group comparisons were performed with the corresponding statistical tests. Univariate regression models were applied to identify potential predictors for time to device explanation. Based on clinical relevance, type of perioperative antibiotic prophylaxis, use of antifungals, age, device manufacturer, cylinder size, diabetes, hypertension, smoking, BMI, Charlson Comorbidity Index, immunosuppression, Peyronie's disease, vascular disease, prior use of intracavernosal injections, prior radical prostatectomy, prior pelvic radiotherapy, and prior priapism were selected as potential estimates for postoperative explant. A Cox proportional-hazards model was constructed adjusted for perioperative antibiotic prophylaxis, antifungal prophylaxis, age, device manufacturer, diabetes, BMI, immunosuppression, and prior pelvic radiotherapy. Included independent variables were chosen based on both clinical predictors (age, diabetes, BMI, immunosuppression, and prior pelvic radiotherapy) and statistical significance (perioperative antibiotic prophylaxis, antifungal prophylaxis, and device manufacturer) in the univariate analysis determined by a $P < .05$. For all associations, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Proportional hazards assumption was tested with the goodness of fit test ($P < .05$) and with graphical procedures using Kaplan-Meier curves. When discordances between the goodness of fit test and the graphical procedures occurred, observed vs predicted curves and log-minus-log plots were performed to resolve any discrepancies. All statistical tests were undertaken using the R statistical software (version 3.6.3).

RESULTS

Baseline Characteristics

We included 4,161 patients undergoing primary IPP placement. The mean age of these patients was 61.9±10.5 years, mean BMI 29.8±3.7 kg/m^2, and mean Charlson Comorbidity Index 2.6±2.2. A total of 1,423 (34.2%) patients had diabetes, 2,023 (48.6%) had hypertension, and 665 (17.4%) were smokers. Of note, 2,962 (71.2%) patients received a Coloplast device and 1,199 (28.8%) had a Boston Scientific device. Infrapubic, penoscrotal, and subcoronal approaches were used in 46.6%, 40.3%, and 13.3%, respectively. Overall, 2,411 (57.9%) patients received vancomycin plus gentamicin, whereas 1,750 (42.1%) patients received another, nonrecommended antibiotic prophylaxis regimen. These antibiotic regimens comprised, in most cases, a third antibiotic over gentamicin and vancomycin (not including antifungals), as well as a gentamicin- or a quinolone-based regimen. The nonrecommended antibiotic prophylaxis regimens are illustrated in Supplementary Material 1 (https://www.jurology.com). The baseline characteristics of all included patients are depicted in Table 1 and Supplementary Material 2 (https://www.jurology.com).

Predictors of Infection

At a median follow-up of 9 months (IQR: 2-19), 47 patients underwent device explantation due to infection. Of these, 25 occurred in the gentamicin and vancomycin group and 22 in the other antibiotic group. The median follow-up of patients without any device infection was 13 months (IQR: 6 to 23) in the vancomycin plus gentamicin group and 3 months (IQR: 2 to 11) in the other regimen group. In the univariate Cox proportional-hazards analysis, the use of gentamicin and vancomycin alone was significantly associated with lower risk of infection compared to other regimens (HR: 0.51, 95% CI: 0.28 to 0.93, $P = .03$). Similarly, placement of a Coloplast device (HR: 0.43, 95% CI: 0.23 to 0.8, $P = .008$), as well as concomitant use of antifungals (HR: 0.17, 95% CI: 0.08 to 0.33, $P < .001$) were also associated with lower risk of infection. The presence of diabetes was not associated with higher risk of device explantation due to infection (HR: 1.7, 95% CI: 0.94 to 3, $P = .08$) in univariate analysis (Table 2).

Subsequently, a multivariable Cox proportional-hazards model was performed adjusted for perioperative antibiotic prophylaxis, concomitant intake of antifungals, age, type of device, diabetes, BMI, immunosuppression, and prior pelvic radiotherapy. After adjusting for these variables, the use of vancomycin and gentamicin alone was significantly associated with higher risk of infection (HR: 2.7, 95% CI: 1.4 to 5.4, $P = .004$). Diabetes was significantly associated with higher risk of infection (HR: 1.9, 95% CI: 1.03 to 3.4, $P = .04$) and concomitant intake of antifungals (HR: 0.08, 95% CI: 0.03 to 0.19, $P < .001$) was associated with a 92% reduction in the risk of infection. In multivariable analysis, Coloplast and Boston Scientific devices were associated with similar risk of infection (HR: 1.1, 95% CI: 0.54 to 2.1, $P = .9$). The risk of device explantation due to infection was 2.7 times higher in patients receiving vancomycin and gentamicin alone. The corresponding Cox proportional-hazards analysis can be seen in Table 2.

Table 1. *Baseline Characteristics of the Study Participants Based on the Type of Perioperative Antibiotic Prophylaxis Administered*

Characteristic	Gentamicin + vancomycin, n = 2,411	Other regimens, n = 1,750	*P* value
Age, mean±SD, y	62±11	61±9.7	**< .001**
Race, No. (%)			**< .001**
Asian	16 (0.7)	695 (40)	
Black	1,135 (47)	133 (7.6)	
Caucasian	1,029 (43)	717 (41)	
Hispanic	207 (8.6)	63 (3.6)	
Other	24 (1)	142 (8.1)	
Diabetes, No. (%)	834 (35)	589 (34)	.6
Hypertension, No. (%)	1,011 (42)	1,012 (58)	**< .001**
Vascular disease, No. (%)	482 (20)	312 (18)	.09
Body mass index, mean±SD, kg/m^2	30±3.9	29±3.5	**< .001**
Charlson Comorbidity Index, mean±SD	3.3±2.2	2.1±2.1	**< .001**
Immunosuppressed, No. (%)	69 (2.9)	27 (1.5)	**.007**
Smoker, No. (%)	359 (17)	306 (18)	.7
Radical prostatectomy, No. (%)	342 (14)	291 (17)	**.03**
Pelvic radiotherapy, No. (%)	105 (4.4)	75 (4.3)	> .9
Peyronie's disease, No. (%)	340 (16)	204 (12)	**< .001**
Priapism, No. (%)	79 (3.4)	33 (1.9)	**.005**
Shunt for priapism management, No. (%)	12 (16)	12 (41)	**.01**
Intracavernosal injections, No. (%)	391 (16)	532 (50)	**< .001**
Perioperative antifungal intake, No. (%)	2,009 (83)	100 (5.7)	**< .001**
Type of device, No. (%)			**< .001**
AMS	300 (12)	899 (51)	
Coloplast	2,111 (88)	851 (49)	
Cylinder size, mean±SD, cm	20±1.9	19±2.4	**< .001**
Intraoperative approach, No. (%)			**< .001**
Infrapubic	1,797 (75)	134 (7.7)	
Penoscrotal	612 (25)	1,064 (61)	
Subcoronal	2 (0.1)	552 (32)	

Abbreviations: AMS, Boston Scientific inflatable penile prosthesis device; SD, standard deviation.
Bold *P* values are statistically significant (< .05).

In the subgroup analysis of gentamicin dosing, 2,511 patients received 80 mg of gentamicin while 913 (27%) received weight-based dosage. In the Cox proportional-hazards analysis adjusted for gentamicin dosage, use of antifungals, age, type of device, diabetes, BMI, immunosuppression, and prior pelvic radiotherapy, the use of weight-based gentamicin compared to 80 mg gentamicin was associated with similar risk of infection (HR: 2.9, 95% CI: 0.83 to 10, $P = .1$; Table 3).

Cultured Microorganisms and Management of Infection

Intraoperative cultures were obtained in all cases and identified 19 different microorganisms. Twenty-six (64%) cultures were positive, while multiple microorganisms were identified in 19%. *Staphylococcus aureus* and *Escherichia coli* were most frequently cultured (Table 4). The most common management of implant infection was device salvage with a malleable

Table 2. *Univariate and Multivariable Cox Proportional Hazards Models for Time to Device Explantation Due to Infection*

	HR	95% CI	*P* value	HR	95% CI	*P* value
Gentamicin + vancomycin	0.51	0.28, 0.93	**.03**	2.7	1.4, 5.4	**.004**
Charlson Comorbidity Index	0.97	0.82, 1.1	.7			
Intracavernosal injections	1.3	0.66, 2.4	.5			
Coloplast device	0.43	0.23, 0.8	**.008**	1.1	0.54, 2.1	.9
Cylinder diameter	0.95	0.82, 1.1	.5			
Age	1	0.97, 1.02	.8	0.99	0.96, 1.01	.3
Diabetes	1.7	0.94, 3	.08	1.9	1.03, 3.4	**.04**
Hypertension	1.1	0.63, 2	.7			
Body mass index	0.96	0.9, 1.04	.3	0.99	0.92, 1.1	.7
Vascular disease	0.96	0.49, 1.9	.9			
Perioperative antifungal intake	0.17	0.08, 0.33	**< .001**	0.08	0.03, 0.19	**< .001**
Immunosuppressed	1.5	0.35, 6	.6	1.2	0.28, 5.2	.8
Smoker	1.4	0.71, 2.8	.3			
Radical prostatectomy	1.3	0.63, 2.7	.5			
Pelvic radiotherapy	1.4	0.42, 4.4	.6	1	0.31, 3.4	> .9
Peyronie's disease	0.74	0.31, 1.8	.5			
Priapism	1.4	0.33, 5.8	.7			

Abbreviations: CI, confidence interval; HR, hazard ratio.
Bold *P* values are statistically significant (< .05).

Table 3. *Univariate and Multivariable Cox Proportional Hazards Models for Device Explantation Due to Infection in Patients Receiving Gentamicin as Part of Perioperative Antibiotic Prophylaxis*

	Univariate Cox regression model			Multivariable Cox regression model		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
Weight-based gentamicin	8.1	3.6, 18	**< .001**	2.9	0.83, 10	.1
Charlson Comorbidity Index	0.97	0.72, 1.3	.8			
Intracavernosal injections	0.99	0.37, 2.7	>.9			
Coloplast device	0.17	0.08, 0.39	**< .001**	0.53	0.21, 1.3	.2
Cylinder diameter	0.85	0.71, 1.02	.09			
Age	1	0.96, 1.03	.8	0.98	0.95, 1.02	.3
Diabetes	2.1	1.01, 4.5	**.047**	2	0.91, 4.2	.08
Hypertension	1.2	0.55, 2.4	.7			
Body mass index	0.99	0.9, 1.1	.8	1	0.92, 1.1	> .9
Vascular disease	0.34	0.08, 1.4	.14			
Perioperative antifungal intake	0.12	0.05, 0.27	**< .001**	0.35	0.1, 1.2	.1
Immunosuppressed	3.6	0.85, 15	.08	2.5	0.56, 11	.2
Smoker	0.75	0.22, 2.5	.6			
Radical prostatectomy	1.1	0.38, 3.2	.9			
Pelvic radiotherapy	1.8	0.41, 7.5	.4	0.99	0.23, 4.3	> .9
Peyronie's disease	0.38	0.09, 1.6	.2			

Abbreviations: CI, confidence interval; HR, hazard ratio.
Bold *P* values are statistically significant (< .05).

prosthesis (40%; Table 4). Explantation without consecutive salvage treatments was performed in 38% of cases and 21% were salvaged with IPP.

DISCUSSION

In this multicenter retrospective cohort study, we found that vancomycin and gentamicin alone are not reliable as a standard prophylaxis regimen in men undergoing primary IPP placement. Patients who received vancomycin and gentamicin alone as recommended by the AUA Best Practice Statement had 2.7 increased risk of developing an implant infection. Importantly, we also found antifungals significantly decreased the risk of infection by 92%. Prosthetic surgeons may consider adding antifungals to their perioperative prophylaxis regimen for all patients.

Table 4. *Cultured Microorganisms and Management of Device Infection Caused by Them*

Characteristic	Gentamicin + vancomycin, n = 25	Other regimens, n = 22
Cultured microorganism, No. (%)		
Achromobacter	1 (4)	0
Candida spp	1 (4)	0
Coagulase-negative Staphylococcus spp	0	1 (4.5)
Coagulase-negative Staphylococcus spp, Diphtheroid	1 (4)	1 (4.5)
Enterococcus faecalis, Klebsiella pneumoniae	0	1 (4.5)
Escherichia coli	5 (20)	0
Escherichia coli, Staphylococcus epidermidis	0	1 (4.5)
Finegoldia magna	1 (4)	0
Group B Streptococcus spp	1 (4)	1 (4.5)
Klebsiella pneumoniae	1 (4)	0
No microrganism idenitifed	5 (20)	11 (50)
Peptococcus	0	1 (4.5)
Prevotella bivia	0	1 (4.5)
Propionibacterium avidum, Streptococcus intermedius	0	1 (4.5)
Pseudomonas aeruginosa, Klebsiella oxytoca	0	1 (4.5)
Serratia marcescens	0	1 (4.5)
Staphylococcus aureus	7 (28)	1 (4.5)
Staphylococcus aureus, Haemophilus parainfluenzae	1 (4)	0
Staphylococcus epidermidis, Group B Streptococcus spp	1 (4)	0
Management of device infection, No. (%)		
Explant and salvage with IPP	2 (8)	8 (36)
Explant and salvage with malleable prosthesis	10 (40)	9 (41)
Explant only	13 (52)	5 (23)

Abbreviations: IPP, inflatable penile prosthesis; spp, species.

In 2008, the AUA published the Best Practice Statement on antimicrobial prophylaxis, which was revised in 2020.[7,12] This statement recommends the use of gentamicin plus a first-/second-generation cephalosporin or vancomycin.[12] In 2017, Gross and colleagues found that a cephalosporin plus gentamicin only covered 62% of penile implant infections; however, this could be increased to 86% with the use of vancomycin instead of a cephalosporin due to MRSA (methicillin-resistant *Staphylococcus aureus*) infections.[9] Vancomycin plus gentamicin alone has poor coverage of anaerobes[9] which may partially account for the higher infection rate. It is possible that the addition of a third antibiotic to vancomycin/gentamicin regimens which covers anaerobes may provide superior coverage; however, this should be balanced with antibiotic stewardship to limit antibiotic resistance. Vancomycin plus gentamicin has become the most commonly used regimen among prosthetic surgeons.[4,9] Therefore, we chose to test the most widely used regimen recommended by the AUA (vancomycin plus gentamicin alone) against all other regimens. Multiple series have demonstrated the risks of fungal infections in diabetics undergoing penile prosthesis placement as well as the important role of antifungals in this high-risk group.[4,13] However, our results suggest that all patients may benefit from antifungal prophylaxis, the use of which was associated with a

significant reduction in overall infection risk. The AUA, EAU, or International Consultation on Sexual Medicine recommendation for prosthetic cases does not discuss the role of antifungal prophylaxis. It is surprising that we found such a profound impact of antifungal prophylaxis despite only 2.1% of infections in this series from *Candida*. However, no organism was identified in 34% of implant infections. It is possible that many of these were fungal infections since different techniques are used to isolate fungi from bacteria in culture. Our findings suggest infection rates can further be reduced by thoughtful antibiotic selection and the use of antifungals.

Recent literature demonstrated 89% of patients receiving gentamicin prophylaxis for urological surgery do not receive guideline-recommended weight-based dosing.[14] In our series, there was no statistically significant difference in weight-based vs low-dose gentamicin on implant infections in multivariable analysis; however, our study may be underpowered to detect a difference. Xie et al reported no difference in toxicity in a comparative analysis of over 800 patients receiving low-dose (80 mg) vs weight-based dosing of gentamicin.[15] There was a higher incidence of infection in the low-dose gentamicin group (1.22% vs 0.74%), although this was not significant. The optimal dosing of gentamicin remains unclear but our series was unable to demonstrate a difference between groups. However, in the absence of strong evidence suggesting adverse outcomes or toxicity with weight-based dosing, there appears to be little to no harm of weight-based dosing. One concern with low-dose gentamicin remains that underdosing of antimicrobials can lead to antibiotic resistance.[16]

We found *E coli* and *S aureus* to be the most frequently cultured organisms in our cohort. Our findings are consistent with prior work demonstrating these as common pathogens of penile implants.[9,17,18] Although *E coli* and *S aureus* were the most common pathogens in our series, vancomycin and gentamicin alone were still associated with a higher infection risk. It is possible that local resistance patterns may account for these findings. However, recent work using next-generation sequencing found *Pseudomonas* and *Enterococcus* as the most common organisms in implant infections.[19] This group found that traditional cultures only detected the most abundant organism on next-generation sequencing in 63% of cases.[19] This technology rapidly sequences billions of nucleic acid fragments to identify microorganisms present.[20] One of the limitations to this technology is the ability to decipher pathogenic organisms from those contributing to the biofilm which are known to be present on noninfected devices.[20,21] Recent studies using culture and scanning confocal electron microscopy to detect microorganisms on explanted devices from patients without clinical infection have also added uncertainty to our understanding of the relevant microbiology in IPP failure and infection.[22] In our series, no organism was identified by culture in one-third of cases. In order to determine the optimal prophylactic regimen for penile implant surgery, we first must better understand which detected organisms represent true pathogens. Additionally, as antibiotic resistance becomes of greater concern, no 1 regimen is likely to be best in all regions of the world. Tailoring individual regimens to local antibiograms may provide more effective postoperative infection prevention than current guidelines. The current AUA recommendation does not account for local resistance patterns, and also has poor anaerobic coverage.[9] Taken together, the present study and our prior research point out that there is no clear choice for perioperative antibiotics in IPP patients. Our data show the need for a randomized controlled prospective clinical trial to answer the questions our data have raised.

Our study is limited by its retrospective design and inherent selection bias. This study is not powered or designed to determine the most optimal antimicrobial regimen. The use of antifungals was imbalanced between groups with more patients in the vancomycin and gentamicin group also receiving antifungal prophylaxis compared to those receiving other regimens. Since antifungals were associated with a large reduction in infection risk, the imbalance between groups may confound our findings. All surgeons in our study were high-volume, experienced prosthetic surgeons and our findings may not be representative of other practices. We were not able to account for other infection reduction strategies such as shaving, no-touch techniques, reduced operative time, and surgical scrub/prep. Further, we could not account for postoperative oral antibiotics which may have been prescribed on discharge. We defined implant infection as those requiring device explantation since this is the gold standard treatment. We did not include patients who had postoperative infections treated with antibiotics alone without explantation. It is possible we may have missed infections by this strict definition; however, we feel it is very rare that a patient with a device infection can be salvaged by antibiotics alone. Surgeons who use nonstandard regimens may have already tailored their practice to local antibiograms or infection history, and this selection bias may account for our findings. We also did not gather data on overall morbidity and mortality. *Clostridium difficile* infection, allergic reactions, and other antibiotic-associated adverse events may be important considerations in this patient population, and prophylactic regimens may be differentially associated with these. Additionally, we provide the largest analysis of guideline-recommended prophylactic vancomycin and gentamicin on postoperative IPP infections in the published literature. Further, after controlling for confounding variables, the use of antifungals and nonstandard antibiotic regimens

were independently associated with a decreased risk of infection.

CONCLUSIONS

The use of vancomycin and gentamicin alone for antimicrobial prophylaxis in primary penile implant surgery is independently associated with a greater risk of implant infection, while the use of antifungals decreases the risk of infection. Our findings suggest the need for a critical review of the AUA antimicrobial recommendations and tailoring prophylactic regimens to local infection trends and antibiograms.

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EDITORIAL COMMENTS

In the modern era, inflatable penile prosthesis (IPP) infection is a challenging phenomenon to study due to the rarity of infection events. Hundreds, if not thousands, of cases are required to draw a clinically significant conclusion. Accordingly, the authors of this large, multi-institutional study must be congratulated on their real-world analysis of IPP antibiotic protocols.

In this study, standard AUA antibiotic prophylaxis was compared to all alternative regimens in 4,161 primary IPP placements followed for 13 months. The primary outcome was time to device explantation or salvage due to infection.

First, it is important to consider that standard AUA antibiotic prophylaxis does specify use of a first- or second-generation cephalosporin—which was included with "other" regimens in this analysis. Therefore, while a conclusion can be made regarding infection rate using vancomycin and gentamicin, it is

somewhat inaccurate to broaden the terminology to all "standard AUA prophylaxis regimens."

Second, one cannot make the assumption that vancomycin plus gentamicin has a higher infection rate than any alternative antibiotic prophylaxis regimen, as the alternative regimens were all grouped together. Review of the supplementary material reveals 19 different alternative regimens, most commonly vancomycin plus gentamicin plus "other." "Other" regimens also included gentamicin plus cephalosporin (which is part of the standard AUA prophylaxis recommendation) and quinolone-based regimens which are quite different in their mechanisms. While it is possible that one of these regimens is more efficacious than vancomycin plus gentamicin, such a conclusion may not be appropriate based on pooled analysis.

The most important takeaway of this paper is the importance of re-evaluating local antibiograms and infection prevention protocols. As technologies such as next-generation sequencing become readily available to hospitals and researchers, and our understanding of prosthetic biofilms grows, we will continue to bolster infection reduction strategies in this space.

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The authors have written a multicenter, retrospective study of 4,161 patients undergoing primary inflatable penile prosthesis (IPP) surgery stratifying patients into 2 groups: those who received AUA guidelines' recommended prophylaxis (vancomycin + gentamicin alone) and those who received any other regimen. They conclude that the guidelines' recommendation is associated with higher infection rates than other regimens, that additive antifungal usage lowers infection risk, and that a critical review of the recommended antimicrobial prophylactic regimens should be done.

The authors should be applauded for their hard work and impressive numbers. The guideline panels based their recommendation on the existing publications and isolate identification techniques that were available to them at that time. As surgeons and devices have "improved" their tactics in the fight against infections—alcohol-based skin preps, infection retardant coatings, minimizing skin contact, etc—the biome has adjusted as discussed in several publications over the last 5 years.

Until recently, studies have used culture methods to identify microbial species present during revision penile prostheses surgery. Next-generation sequencing (NGS) compares DNA to identify isolates and report relative abundances. NGS compared to traditional culture methods has been done in the otolaryngology and ortho literature with culture only showing the correct high abundance isolate about 30% of the time.[1] NGS is being considered the gold standard for isolate identification in other medical specialties: orthopedics, infectious disease, and wound care.[2] Dr Costerton, the Godfather of biofilm research, summarized "Culture methods are no longer used for the detection and identification of bacteria, in many fields of Microbiology…"[3] Future guideline panels for IPP antimicrobial prophylaxis could consider newer NGS data for their decision making.

As it applies to the conclusion on additive antifungal usage, I give all my IPP patients antifungal prophylaxis and would advise doing likewise, especially if you live in a hot, humid climate.

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The authors retrospectively reviewed 4,161 patients from 16 institutions across the U.S., Europe, and Korea and found that vancomycin and gentamicin alone for primary penile prosthesis placement on multivariable analysis was associated with a higher infection risk (HR 2.74) than other perioperative

antibiotic regimens and that diabetes was associated with an increased risk of infection (HR 1.9). Another important finding of the study is that antifungals were associated with a lower risk of infection (HR 0.08). It is important to note that many of the patients included in the alternative regimen group received a third antibiotic in addition to gentamicin and vancomycin.

There are limitations to the study including the retrospective nature, different baseline patient characteristics, and that we do not know many intraoperative variables or if patients received additional postoperative antibiotics. However, within these limitations, this study contributes to the growing body of literature supporting the addition of antifungals to perioperative antibiotic regimens for penile prosthesis. Intriguingly, the most frequently cultured organisms from explanted devices were *Staphylococcus aureus* and *Escherichia coli*, and only 1 explant grew *Candida* and no anaerobes. A prior study assessing culture data from 227 explanted infected inflatable penile prostheses found 11% *Candida* and 10.5% anaerobes[1] and other studies have grown *Pseudomonas aeruginosa*, staphylococcal species, and *E coli,*[2] but still around 30% often have no growth. Overall, the data suggest that the addition of anaerobic and antifungal coverage to the standard vancomycin and gentamicin regimen may help reduce inflatable penile prosthesis infections in select patients but continued research in this domain is still needed.

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I applaud these authors for questioning the existing dogma of vancomycin and gentamicin for routine penile implant surgery. The authors compile a mountain of data from over 4,000 virgin penile implants. In summary, they find that the routine use of the AUA antimicrobial recommendation of vancomycin and gentamicin for routine prophylaxis may increase infection risk in penile implant surgery. A more definitive finding is that routine use of antifungal prophylaxis decreases penile implant infection risk.

The use of vancomycin and gentamicin for routine prophylaxis in penile implant surgery is fraught with multiple issues outside of the findings in this paper. Vancomycin needs to run over an hour and can take another hour to reach appropriate tissue levels. Patients may develop "red man syndrome" as the vancomycin infuses, causing providers to scramble for alternative gram-positive coverage in the preop unit. The renal load for vancomycin and gentamicin is considerable and only more tenuous if administering nonsteroidal anti-inflammatory drugs for perioperative multimodal anesthesia.

With this work, the authors provide data and rationale to consider alternatives to the AUA antimicrobial prophylaxis. While the paper certainly cannot determine the ideal prophylaxis for all patients, implanters should consider their local resistance patterns along with patient factors. Many men pursuing penile implant have considerable medical comorbidities and renal insufficiency at baseline, and I caution implanters against using vancomycin and gentamicin in men with already strained renal function.

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REPLY BY AUTHORS

We appreciate the thoughtful editorial comments and the efforts of our reviewers. We note with concern that Bole and Bajic have erroneously mischaracterized some of the aims and conclusions of our study. They are correct that it cannot be assumed vancomycin plus gentamicin has a higher infection rate than any other specific regimen. That conclusion exists only in their editorial comment, and not in the findings of our paper.

We found that vancomycin plus gentamicin alone was associated with a greater risk of infection compared to all other regimens. We did not attempt to compare the efficacy of vancomycin plus gentamicin to other individual regimens. We concluded that the use of vancomycin plus gentamicin alone is independently associated with a greater risk of implant infection and a critical review of the AUA antimicrobial recommendations may be warranted.

Bole and Bajic are also correct that gentamicin combined with a first-/second-generation cephalosporin is another recommendation listed in the AUA Best Practice Statement, but this is relevant only as a semantic observation. The combination of gentamicin and a first-/second-generation cephalosporin is obsolescent in contemporary implant surgery given the lack of MRSA (methicillin-resistant *Staphylococcus aureus*) coverage. We evaluated the efficacy of vancomycin plus gentamicin because this combination is the most widely used and the most effective of the recommendations listed in the AUA Best Practice Statement.[1,2]

Our study is the latest in a growing body of literature questioning the AUA's recommendation of vancomycin and gentamicin. Prosthetic urologists are unfortunately left with more uncertainty regarding the ideal intravenous antimicrobial prophylaxis. We advocate for tailoring regimens based on local infection history and local antibiograms. The addition of an antifungal to antibacterial prophylaxis is also prudent, as noted in all the editorial comments.

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