BASIC SCIENCE

Inflatable Penile Prostheses Implantation: Does Antibiotic Exposure Matter?

Ryan M. Chanyi, PhD,[1,2,3] Raidh Alzubaidi, MD,[1] Everett J. Y. Leung, BSc,[2] Hannah B. Wilcox, BSc,[2] Gerald B. Brock, MD,[1,2] and Jeremy P. Burton, PhD[1,2,3]

ABSTRACT

Background: Inflatable penile prosthetic (IPP) infections are unusual but carry high patient morbidity and healthcare costs.

Aim: To increase the bactericidal effect of IPP tubing material to prevent future bacterial infections and to determine whether this effect is time-dependent.

Methods: A modified disk diffusion assay was developed to measure the zones of inhibition against *Escherichia coli*, *Proteus mirabilis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* when tubing was immersed in gentamycin, ampicillin, tetracycline, kanamycin, erythromycin, or ciprofloxacin. To further assess the efficacy of this approach, IPP tubing was exposed to ampicillin or ciprofloxacin for 30 seconds, 2 minutes, 10 minutes, or 60 minutes.

Outcomes: Bacterial zones of inhibition against IPP tubing material exposed to various treatments.

Results: IPP tubing was more effective against Gram-positive bacteria (*S aureus* and *S epidermidis*) then Gram-negative bacteria (*E coli* and *P mirabilis*). Immersing IPP tubing material in ampicillin or ciprofloxacin increased bactericidal effect of tubing material against Gram-positive and Gram-negative bacteria, respectively. The observed inhibitory effect was time dependent.

Clinical Translation: Exposing IPP to a specific antimicrobial directly before implantation increases the bactericidal properties of the material, potentially decreasing the likelihood of infection.

Strengths & Limitations: This study is limited in that it is in vitro experimentation observing the effect of a single strain of each bacterium. Although the strains used were clinically relevant, further analysis is required to determine whether these results were strain specific.

Conclusion: Immersing IPP material into an antibiotic solution, such as ampicillin or ciprofloxacin, increases the bactericidal properties and may aid in the prevention of infection. **Chanyi RM, Alzubaidi R, Leung EJY, Wilcox HB, Brock GB, Burton JP. Inflatable Penile Prostheses Implantation: Does Antibiotic Exposure Matter? Sex Med 2018;6;248–254.**

Key words: Inflatable Penile Prosthesis; IPP; Infection; Antibiotic Use; Infection Prevention

INTRODUCTION

Any foreign material that is inserted into the body is at risk of increasing a patient's chance of developing a bacterial infection. If a bacterium binds to an abiotic surface, the methods our body uses to resist an infection are diminished. There has been a great deal of advancement in the development of biomaterials that prevent bacterial infections. Earlier literature showed infection rates of 3% for nondiabetic virgin, 8% for diabetic virgin, and 10% for revision operations.[1] Infection rates for virgin IPPs have typically been approximately 1% to 3%, but published rates have been significantly higher in revision surgery or when reconstructive procedures are involved.[2]

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[1]Division of Urology, Department of Surgery, The University of Western Ontario, London, Ontario, Canada;

[2]Department of Microbiology and Immunology, Schulich School of Medicine and Dentistry, The University of Western Ontario, London, Ontario, Canada;

[3]Canadian Centre for Human Microbiome and Probiotic Research, Lawson Health Research Institute, London, Ontario, Canada

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IPP as a treatment option for erectile dysfunction provides a high rate of patient satisfaction and success in salvaging erectile function among a cohort of men unresponsive to phosphodiesterase type 5 inhibitors or other pharmaceutical options or for whom they cannot be used. One would surmise that a device that remains in a patient for years would regularly become infected. Surprisingly, IPPs have an incredibly low infection rate (1% to 3%) despite remaining in a patient for more than 10 years.[3]

Perfecting surgical techniques and implementing standardized preoperative cleaning procedures have been key features in preventing infections, yet they still occur.[4] This risk of device infection drastically increases if the implant requires a redo-corrective surgery: rates are as high as 21.7% if the surgery also includes penile reconstruction.[5] Therefore every measure is taken to prevent infection, and the material used in the prosthesis have been developed to inhibit bacterial growth and adherence.

One of the more popular devices, developed by American Medical Systems (AMS, Minnetonka, MN, USA, now owned by Boston Scientific Corp, Marlborough, MA, USA), uses tubing material containing InhibiZone.[6] This is an antibiotic-impregnated material that elutes a mixture of rifampin and minocycline over time. The most prevalent bacteria found to cause infection in IPP implants are Gram-positive, coagulase-negative *Staphylococcus* species. Overall, the use of antimicrobial-impregnated materials decreases the incidence of infection by 50%.[7] Due to the high cost associated with infection, monetary and patient morbidity, as well as the decreased efficacy against Gram-negative organisms, devices are treated with antibiotics either in the factory as ready to use (AMS) or just before the insertion at the day of surgery (Coloplast Corp, Minneapolis, MN, USA). The goal of this study was to determine whether additional antibiotic use increased efficacy against urinary pathogens. It was also assessed whether bacterial inhibition increased the longer the material was immersed in the solution.

MATERIAL AND METHODS

Bacterial Strains, Media, and Culture Conditions

Escherichia coli 67, *Staphylococcus aureus* Newman and *Staphylococcus epidermidis* 3399 were maintained on 1.5% LB agar. Due to the swarming motility of *Proteus mirabilis* 296, it was maintained on non-swarming agar plates (10 g/L tryptone, 5 g/L yeast extract, 0.4 g/L sodium chloride, 20 g/L agar; NSA). When required, all bacterial cultures were grown overnight in liquid LB medium at 37°C, with shaking at 180 rpm.

Modified Disk Diffusion Assay (M-DDA)

To assess the antimicrobial activity of the penile tubing material, a modified disk diffusion assay was developed. Tubing material was sectioned into uniformly thin, 1-mm disks. Tubing material was briefly sterilized with anhydrous ethanol and immediately dried under ultraviolet light to remove residual ethanol. Preliminary experiments demonstrated this did not alter the antimicrobial properties of AMS tubing nor the ability for Coloplast tubing to bind ciprofloxacin or ampicillin. Bacterial cultures were grown overnight in LB medium at 37°C. Cultures were spread onto 1.5% LB agar plates except for *P mirabilis* 296 that was plated onto NSA using a cotton swab. Sections of tubing material were immersed for 5 minutes in gentamycin (15 μg/mL), ampicillin (100 μg/mL), tetracycline (10 μg/mL), kanamycin (50 μg/mL), erythromycin (25 μg/mL), or ciprofloxacin (10 μg/mL). Sections were blotted to remove residual liquid and placed onto the inoculated agar plates. To assess bacterial sensitivity to the antibiotic, cotton discs were immersed in the same antibiotic solution. Tubing material placed in sterile phosphate buffered saline solution was used as a negative control to demonstrate the bactericidal effect of tubing material alone. Plates were incubated overnight at 37°C, and the zone of inhibition was analyzed.

Time-Dependent M-DDA

The modified disk diffusion assay described above was performed with some minor changes. Tubing sections were treated with either ampicillin (100 μg/mL) or ciprofloxacin (10 μg/mL) for 30 seconds, 2 minutes, 10 minutes, or 1 hour. After soaking, the excess antibiotic solution was removed, and the disks were pressed lightly onto the agar. As a bacterial growth control, 1 disk was soaked for each time point in LB medium. Each time point consisted of 3 replicates for each bacterium; this was repeated in triplicate. Zones of inhibition were measured after plates were incubated overnight at 37°C.

Statistical Methods

GraphPad Prism software (GraphPad Software, La Jolla, CA, USA) was used to determine statistical significance by either 1- or 2-way analysis of variance (ANOVA) with the appropriate post-hoc test depending upon the distribution of the data.

RESULTS

Antimicrobial Activity of Inflatable Penile Prosthesis Tubing

The AMS 700 IPP tubing is an antibiotic-impregnated material containing InhibiZone (Boston Scientific Corp), a mixture of minocycline and rifampin. To assess the antimicrobial activity of the material, 2 Gram-negative and 2 Gram-positive bacteria were chosen. *E coli* 67 and *P mirabilis* 296 are both Gram-negative uropathogens used previously in the laboratory to assess bacterial adherence to abiotic surfaces. *S aureus* Newman is a Gram-positive pathogen isolated from tubercular osteomyelitis,[8] whereas *S epidermidis* 3399 is a commensal human skin isolate. The tubing material was more effective at inhibiting the growth of the Gram-positive bacteria and did not appear to inhibit the Gram-negative uropathogens (Figure 1). There was no statistical significance in the ability of the tubing to inhibit *S aureus* more than the non-pathogenic *S epidermidis*.

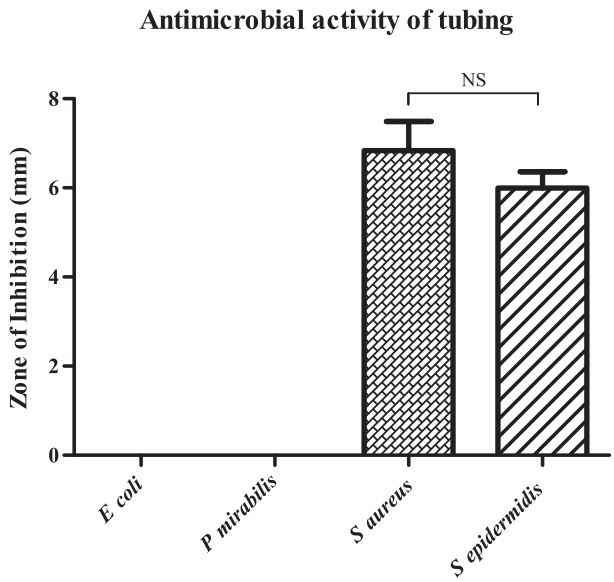

Figure 1. Antimicrobial activity of IPP tubing. IPP tubing could inhibit the growth of *S aureus* and *S epidermidis* but was unable to inhibit *E coli* or *P mirabilis*. There was no significant difference between the inhibition of *Staphylococcus* species. Statistical significance was measured using 1-way ANOVA with Tukey's test. Error bars represent the standard error.

Antibiotic Profiling with IPP Tubing

To interpret the M-DDA, each bacterium's antibiotic susceptibility was tested against a panel of antibacterial agents. Table 1 summarizes the level of resistance or susceptibility of each bacterium to the panel of antibiotics. Overall, the 4 bacterial strains were resistant or showed intermediary resistance to gentamycin, tetracycline, kanamycin, erythromycin and rifampin. *E coli* and *P mirabilis* were susceptible to ciprofloxacin; *S aureus* and *S epidermidis* showed intermediate resistance. *E coli* and *P mirabilis* were resistant to minocycline; however, *S aureus* and *S epidermidis* were susceptible. All bacteria tested were susceptible to ampicillin.

The IPP tubing material was immersed in the different antibiotic solutions and placed on a plate previously inoculated with one of the bacteria. In comparison to tubing material alone, *E coli* (Figure 2A) and *P mirabilis* (Figure 2B) were not further inhibited by the use of gentamycin, tetracycline and erythromycin. Both showed slight inhibition when exposed to ampicillin and variable inhibition with kanamycin. There was a significant increase in the zone of inhibition when ciprofloxacin was used ($P < .001$). As expected, these trends closely follow the bacterial antibiotic susceptibility profile (Table 1). Contrary to the Gram-negative bacteria, *S aureus* (Figure 2C) and *S epidermidis* (Figure 2D) were inhibited by the tubing material itself. However, immersing the IPP material in gentamycin, tetracycline, kanamycin, erythromycin or ciprofloxacin did not significantly increase the zone of inhibition for either bacterium (Figure 2C, D). For both Gram-positive species, the zones of inhibition were significantly increased when the IPP material was immersed in ampicillin. Again, these trends closely follow the bacterial antibiotic susceptibility listed in Table 1.

Time-Dependent M-DDA

Due to the previous promising results that using ampicillin or ciprofloxacin may aid in preventing bacterial infection of IPP material, it was assessed whether time played a factor in this process. Figure 3A shows ampicillin has a significantly larger zone of inhibition against *S aureus* with a 30-second incubation time compared to 60 minutes ($P < .05$). This trend was also observed for *E coli* and possibly for *S epidermidis*; however, this was not significant. Variable results were observed for ciprofloxacin (Figure 3B). Incubating the material for 2 minutes or longer showed significantly larger zones of inhibition against *E coli* ($P < .05$). In contrast, the shorter incubation times of 30 seconds and 2 minutes showed significantly larger zones of inhibition against *S aureus* ($P < .01$). Both *P mirabilis* and *S epidermidis* were unaffected by the changes in incubation time.

DISCUSSION

In the context of surgeries requiring the implantation of a foreign material into the human body, IPPs have an incredibly low rate of infection and other complications. However, this does not prohibit the search for improving surgical and/or procedural processes in the operating room. With an aging population that brings with it an increasing number of comorbidities, many

Table 1. Bacterial susceptibility to common antibiotics

Antibiotic	Concentration (μg/mL)	*E coli*	*P mirabilis*	*S aureus*	*S epidermidis*
Gentamycin	15	R	R	R	R
Ampicillin	100	S	S	S	R
Tetracycline	10	R	R	R	R
Kanamycin	50	I	R	R	R
Erythromycin	25	R	R	I	I
Ciprofloxacin	10	S	S	I	I
Minocycline	30	R	R	S	S
Rifampin	5	R	R	I	R

I = intermediate; R = resistant; S = susceptible.

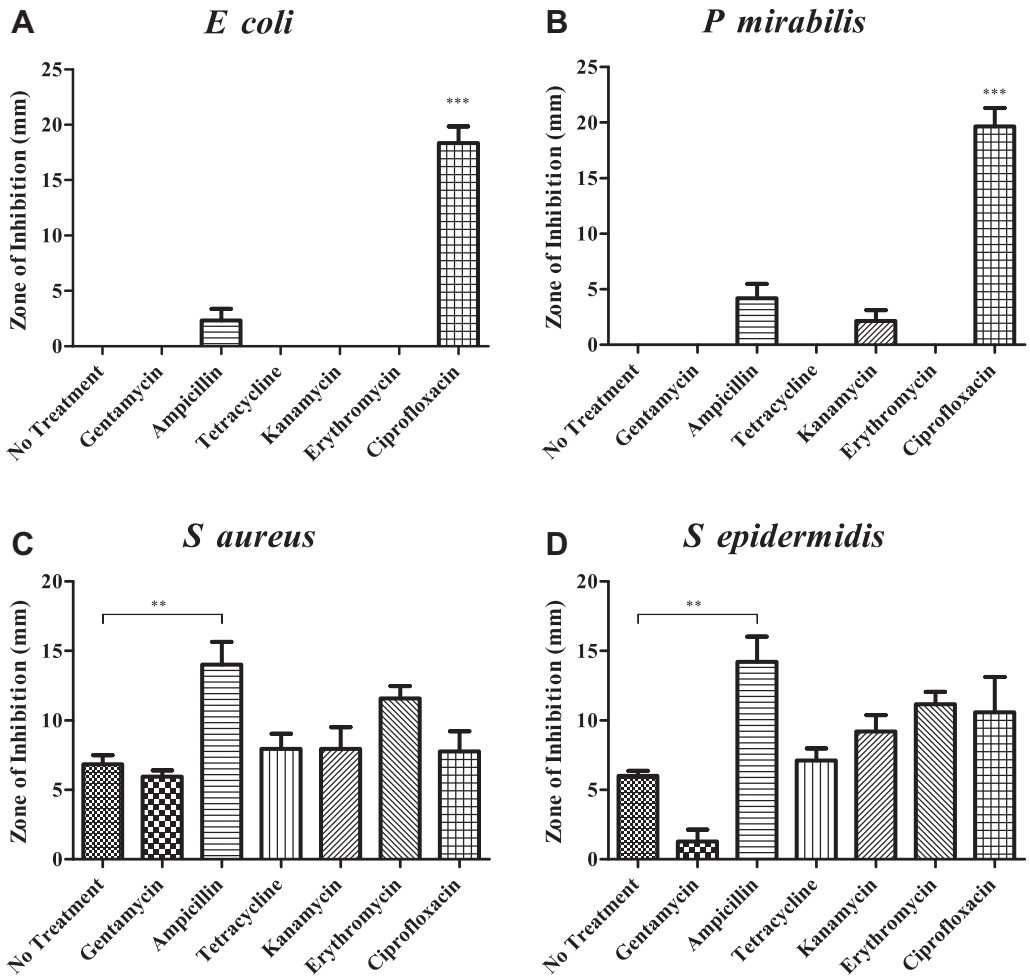

Figure 2. Modified disk-diffusion assay measuring the bacterial zones of inhibition when IPP tubing was exposed to a panel of antibiotics. A) *E coli*; B) *P mirabilis*; C) *S aureus*; and D) *S epidermidis*. Statistical significance was measured using 1-way ANOVA with Dunnett's Multiple Comparison test. $^{**}P < .01$, $^{***}P < .001$. Error bars represent the standard error.

studies have focussed on developing surgical procedures to limit the rate of complications.[9–11] The goal of this study was to determine if the implanted material could be improved.

There are many different types of IPPs with the most common being the 3-piece IPP due to its superior functionality characterized by excellent rigidity, girth expansion and flaccidity. In this study, AMS 700 tubing material containing InhibiZone was analyzed because this is the most popular device being used on site. Other devices have different surface properties, such as the Coloplast Titan that takes advantage of a hydrophilic surface. For this reason, Coloplast material was used to compare with the AMS tubing. This IPP requires it to be immersed in a water-soluble antibiotic solution so that the antibiotic can adhere to the surface and prevent infection. Although the AMS IPPs are not immersed in an antibiotic solution, we wanted to analyze whether this process would influence the ability of the IPP tubing to inhibit bacterial growth.

Regardless of the device (AMS 700 or Coloplast Titan) or the surgical procedure being used (ie device placement), bacterial infections occur. The primary cause of most infections belongs to the coagulase-negative staphylococcal species, a large group comprising more than 45 distinct species. These bacteria are commensal skin inhabitants that generally do not cause disease; however, there has been an increase in antibiotic resistance among members of this group.[12] *S epidermidis* is the most common member isolated from human samples. Although *S aureus* is coagulase-positive, it is the most notorious skin-associated pathogen, causing diseases ranging from impetigo to necrotizing fasciitis and sepsis. It is also the hallmark for bacterial inhibition used in previous literature to measure the efficacy of IPP material.[13]

Although antimicrobial susceptibility is strain dependent and different members of the same bacterial species can respond dramatically differently to antibiotics, the bacterial strains used in this study responded in the same manner as those previously published.[14] Although using rifampin- and minocycline-impregnated catheters and not IPPs, the number of infections by Gram-positive bacteria was decreased compared with in

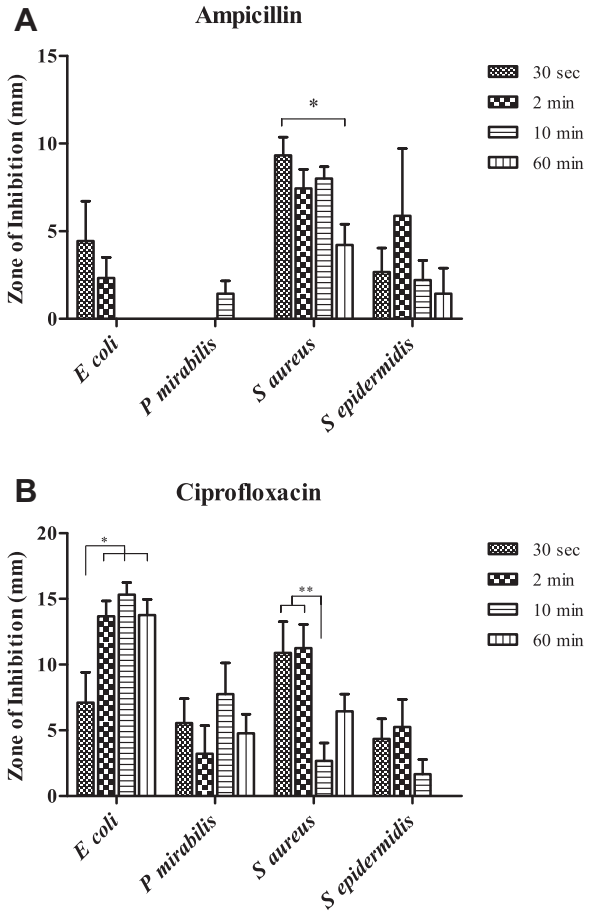

Figure 3. Modified disk-diffusion assay measuring the bacterial zones of inhibition when IPP tubing was exposed to (A) ampicillin or (B) ciprofloxacin for 30 seconds, 2 minutes, 10 minutes or 60 minutes. Values represent means ± standard error, n = 9. Statistical significance was measured by a 2-way ANOVA with a Bonferroni post-hoc test. *$P < .05$; **$P < .01$. Error bars represent the standard error.

controls (38.2% vs 7.1%), but the impregnated material did not aid in preventing Gram-negative bacteriuria (47.1% vs 46.4%) nor candiduria (2.9% vs 3.6%).[14] The tubing material alone was unable to inhibit both Gram-negative bacteria tested (*E coli* and *P mirabilis*) but did show good ability to prevent the growth of *S aureus* and *S epidermidis*.

When assessing bacterial susceptibility to a panel of antibiotics, both *E coli* and *P mirabilis* were susceptible to ampicillin and ciprofloxacin and resistant (or intermediate) to gentamycin, tetracycline, kanamycin, erythromycin, minocycline and rifampin. Similarly, *S aureus* and *S epidermidis* showed very similar susceptibility profiles being resistant (or intermediate) to all antibiotics tested, except that *S aureus* was susceptibility to ampicillin and both were susceptible to minocycline. It is interesting that the only bacterium not isolated from a clinical infection, *S epidermidis* 3399, showed the greatest level of resistance. This is typically a commensal skin inhabitant that aids in preventing pathogens from colonizing the host. The emergence of increased resistance may signal that these bacteria may not be as harmless as originally believed. Scientists can no longer easily classify those that cause disease versus those that do not. It is already being observed that infections caused by opportunistic pathogens is increasing.[15]

These antibiotic profiles were mirrored when assessing the ability of IPP tubing immersed in each antibiotic to inhibit each respective bacterium. This suggests that although the tubing contains an antibiotic-impregnated layer of minocycline and rifampin, other antibiotics can adhere onto the tubing itself. *S epidermidis* was resistant to ampicillin; however, when exposed to IPP tubing immersed in ampicillin, there was a significant increase in the zone of inhibition compared with tubing alone. It is possible that minocycline and rifampin can increase the stress on *S epidermidis* such that an antibiotic to which it is resistant is now much more effective. The same principle applies to the use of Septra (Pfizer, New York, NY, USA), a combination of sulfamethoxazole and trimethoprim. With the increase of antibiotic resistance, these combinatorial regimens have become commonplace and will probably need to include others before novel therapeutic agents arrive.[16]

Before implantation the Coloplast device is dipped into an antibiotic solution to allow the hydrophilic surface to bind the antibiotic. Although the AMS device is not, this would be an easy way to include an additional antibiotic. Although ampicillin was effective at inhibiting *S aureus* and *S epidermidis* with AMS tubing and is a hydrophilic antibiotic, it did not appreciably adhere to the Coloplast material enough to effectively increase bacterial zones of inhibition. This is probably due to the small surface area on the tubing sections not binding enough antibiotic to be effective. It does not mean the antibiotic was unable to adhere. When ciprofloxacin was added, both AMS and Coloplast materials increased bacterial zones of inhibition of *E coli* and *P mirabilis*.

Typically, the IPP would not remain in the solution for an extended period. Based on the results presented in this study, 2 minutes' incubation would be sufficient for the antibiotic to be effective. When immersed in ampicillin the IPP's bactericidal effect was decreased. It is likely that the InhibiZone coating was leaching out of the device and might be further exacerbated by ampicillin. However, the device manufacturer's literature suggests that the impregnated design elutes for a period of time (14 days) after implantation and suggests that a relatively short period of time in a solution would not totally remove this capability. Further analysis would be required to determine whether this were the case. Regardless, it is very unlikely that the device would remain in solution for an extended period because, the longer the device is removed from the sterile packaging, the higher its risk of contamination.

The surgeon and supporting staff in an operating room try to create the most sterile environment possible. They do a very good job at this; however, no surface is ever truly sterile for very long. Scientists once thought that, without an active infection,

urine and even human tissues were sterile; this has been proven false.[17,18] This does not imply that more harsh practices need to be used to prevent infection. Scientists are beginning to understand that most bacteria do not cause disease but instead may act to benefit the host. In another study, culturable bacteria could not be recovered after the washing procedure before surgery. By the end of surgery, 9 different bacterial species were found on the incision site after it was closed (R.M. Chanyi et al, unpublished data, 2016). These included *S epidermidis*, as well as 4 other coagulase-negative *Staphylococcus* species: *S capitis*, *S caprae*, *S petrasii* and *S pettenkoferi*. It is possible these may be due to contamination during the surgical procedure; however, from what is now known, it is likely these may reside in deeper tissue and become exposed during surgery.[19] In a retrospective multi-institutional study comprising 25 institutes, anaerobes, *Candida* and methicillin-resistant *S aureus* comprised nearly one third of positive cultures.[20] In this study, neither anaerobes nor *Candida* would have been isolated based on the incubation conditions, and *S aureus* was not detected.

CONCLUSION

Overall, this preclinical study has shown that adding an additional antibiotic solution is likely to greatly enhance the broader bactericidal effect of the device against the less commonly experienced causes of infection. Although additional antibiotics are not a long-term fix given the problems of bacterial resistance, this study does provide assurance to those who may already use this practice. This study does not account for the effect of surgical techniques, postoperative antibiotics, drain insertion, antibiotic washout of the operative field, or patient factors but suggests that antibiotic dipping is likely to provide additional benefit, especially if the patient is at a greater risk of infection (ie recurrent urinary tract infections or diabetes).

Corresponding Author: Jeremy P. Burton, Lawson Health Research Institute, St Joseph's Hospital, 268 Grosvenor St, London, ON, N6A 4V2, Canada. Tel: 1 (519) 646 6100 ext. 61365; Fax: 1 (519) 432 7367; E-mail: jeremy.burton@lawsonresearch.com

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Jeremy Burton, Gerald Brock, Ryan Chanyi

(b) Acquisition of Data
Ryan Chanyi, Raidh Alzubaidi, Everett Leung, Hannah Wilcox, Gerald Brock, Jeremy Burton

(c) Analysis and Interpretation of Data
Ryan Chanyi, Raidh Alzubaidi, Everett Leung, Hannah Wilcox, Gerald Brock, Jeremy Burton

Category 2

(a) Drafting the Article
Ryan Chanyi, Gerald Brock, Jeremy Burton

(b) Revising It for Intellectual Content
Ryan Chanyi, Gerald Brock, Jeremy Burton

Category 3

(a) Final Approval of the Completed Article
Ryan Chanyi, Raidh Alzubaidi, Everett Leung, Hannah Wilcox, Gerald Brock, Jeremy Burton

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