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Microorganism Profiles of Penile Prosthesis Removed for Infection, Erosion, and Mechanical Malfunction Based on Next-Generation Sequencing.

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1 **Title:** Microorganism Profiles of Penile Prosthesis Removed for Infection, Erosion, And
2 Mechanical Malfunction Based on Next-Generation Sequencing
3

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14 BACKGROUND: Next-generation sequencing (NGS) is an emerging technology that may
15 allow for more sensitive and sophisticated microbial testing of the microbiota of penile
16 prostheses (PP).

17

18 AIM: To describe the microorganism profiles of PP explanted for infection, erosion, and
19 mechanical malfunction using NGS.

20

21 METHODS: All patients who underwent PP removal by two physicians at two institutions
22 were identified. Differences in alpha diversity (i.e., number of species detected, species
23 diversity across samples) and microbiome compositional profiles (Bray-Curtis community
24 dissimilarities) across samples were assessed using ANOVA and PERMANOVA,
25 respectively.

26

27 OUTCOMES: Number of species detected, species diversity across samples, and microbiome
28 compositional profiles.

29

30 RESULTS: A total of 83 patients who underwent device removal for infection (n=8, 10%),
31 erosion (n=5, 6%), and mechanical malfunction (n=70, 84%) were included. When
32 considering all studies, 56% (n=48) of NGS and 29% (n=24) of standard cultures resulted
33 positive for presence of microorganisms. Culture only detected the most abundant NGS
34 species in 62.5% (n=5) of infected devices. Species richness and microbiome compositional
35 profiles varied by surgical indication, but not by age, race, diabetes status, or implant
36 duration. Most frequent organisms by surgical indication were *Pseudomonas aeruginosa*
37 (infection), *Staphylococcus epidermidis* (erosion), and *Escherichia coli* (mechanical
38 malfunction). The highest relative abundance organisms were *P. aeruginosa* (infection),

39 *Corynebacterium jeikeium* (erosion), and *E. coli* (mechanical malfunction). ~~GS Vancomycin~~
40 ~~and gentamicin provide the most comprehensive coverage against these organisms.~~

41 ~~Minocycline and rifampin do not cover the most abundant organisms for infection and~~
42 ~~erosion.~~

43

44 CLINICAL IMPLICATION: Identifying microbiome profiles of PP removed for infection,
45 erosion, and mechanical malfunction may guide the selection of peri-operative antibiotics and
46 PP antibiotic coatings or hydrophilic dip solutions for each individual scenario.

47

48 STRENGTHS AND LIMITATIONS: While this is the first study to utilize next-generation
49 sequencing to evaluate penile prosthesis biofilm, the clinical significance of these findings
50 has yet to be determined. A prospective, randomized trial aimed at evaluating the clinical
51 significance of NGS in patients with PP infection is currently underway.

52

53 CONCLUSIONS: NGS testing identified distinct microbiome profiles of PP removed for
54 infection, erosion, and mechanical malfunction.

55

56 Keywords: Penile prosthesis; penile implant; infection; culture; next-generation sequencing;
57 ~~polymerase chain reaction~~

58 INTRODUCTION

59

60 Penile prosthesis (PP) implantation has emerged as the mainstay surgical treatment
61 for medically refractory erectile dysfunction (ED). Substantial improvements in the efficacy
62 and durability of PP over past decades have allowed a large and growing volume of patients
63 to undergo PP surgery.(1) However, PP infection remains one of the most feared
64 postoperative complications and places a significant economic burden on the healthcare
65 system, with reported cost of management being six times that of the initial placement.(2)
66 Significant efforts, such as infection retardant coatings on implants, better skin prep
67 techniques, revision washout, and implementation of the “no-touch” surgical technique, have
68 been utilized to optimize the management and reduce the risk of this complication.(3)

69 As evidence has shown that traditional infection rates of revision surgeries have a
70 much higher rate of infection at 10.0 – 13.3% when compared to virgin cases at 0.5 – 2.0%,
71 surgeons have attempted to use standard culture of the devices to help guide antibiotic
72 therapy for revisions patients.(4) However, recent multi-institutional data evaluating
73 clinically infected device explantations have reported device cultures showing no growth or
74 non-specific growth in up to 33% of cases.(5) This may be attributed to flaws in the culture
75 collection technique, the difficult nature of identifying and growing certain biofilm-
76 associated microorganisms, or the administration of antibiotics before culture acquisition.(6)
77 Regardless, this makes tailoring of the antibiotic regimen challenging.

78 Emerging technology has allowed for more sensitive and sophisticated testing and
79 may be useful in the setting of genitourinary prostheses infections. One of the most promising
80 advances in this realm is rapid molecular sequencing. Polymerase chain reaction (PCR) is the
81 most familiar technology, which is a fast and inexpensive technique that amplifies small
82 segments of DNA targets and may detect a comprehensive group of microorganisms and
83 even resistance genes. This technology is already clinically available for blood cultures,

84 respiratory panels, pneumonia, meningitis, and may play a role in improving patient
85 outcomes and decrease surgical complications in patients with infected PP.(7) Next-
86 generation sequencing (NGS), also referred to as high throughput sequencing, is a technology
87 which allows for hundreds to thousands of strands of DNA to be sequenced in parallel.
88 Unlike PCR, which is limited to evaluating pre-determined targets, NGS uses bioinformatics
89 to piece DNA fragments together and compare the sequences to reference genome
90 databanks.(8) NGS may help to provide a more global understanding of biofilms and
91 microorganisms found on PP. Herein, we aim to describe the microorganism profiles of PP
92 explanted for infection, erosion, and mechanical malfunction using ~~PCR~~ and NGS molecular
93 techniques.

94

95 MATERIALS AND METHODS

96 Study Design and Patient Population

97 Institutional review board approval was obtained to perform a retrospective review of
98 consecutive patients undergoing PP explant procedures from January 2015 to January 2019
99 by two physicians at two institutions (IRB# TJU 20E.509 & WK 18.0002). Patients
100 undergoing PP explantations were included regardless of indication for surgery (infection,
101 erosion, and mechanical malfunction). Patients undergoing planned device explantation with
102 or without replacement underwent routine preoperative testing, including a urinalysis and if
103 positive, a urine culture. Positive cultures were treated with a seven-day course of culture-
104 specific antibiotics preoperatively. Perioperative antibiotics were administered in accordance
105 with the American Urological Association (AUA) Guidelines using vancomycin and
106 gentamicin unless clinically contraindicated.(9, 10) Postoperatively, patients were given 5-7
107 days of trimethoprim/sulfamethoxazole or culture-specific antibiotics based on preoperative

108 urine cultures. Revision surgery was performed using either the penoscrotal or infrapubic
109 method, but was not always performed by the same surgeon who performed the initial
110 placement.(11) The antibiotic impregnated outer layer, InhibiZone™, was utilized for the
111 AMS 700™ inflatable PP, while vancomycin and gentamicin were the hydrophilic solution
112 of choice for the Titan® Touch inflatable PP. Vancomycin and gentamicin mixed in normal
113 saline was also the irrigation fluid of choice at the time of implantation.

114

115 Intraoperative Sample Collection and Molecular Testing

116 At the time of explantation, surgeons minimized device contact with neighboring skin
117 to decrease the potential risk of contamination by normal skin flora. Sterile gauze was used to
118 swab the removed devices. The swabs were stored in sterile containers and shipped overnight
119 at ambient temperature for NGS testing (MicroGenDX, Lubbock, TX). A second specimen or
120 the explanted device was sent to the respective institutional microbiology laboratory for
121 routine aerobic and anaerobic culture.

122 NGS of 16s ribosomal RNA was performed using an Illumina MiSeq sequencing
123 platform (Illumina, San Diego, CA). For this, variable regions 1-2 of 16S rDNA gene were
124 amplified and prepared into libraries for sequencing following molecular methods outlined in
125 Tipton et al. but using primers 28F and 388R.(12, 13) Bioinformatic processing followed that
126 reported by Cook et al. and McDonald et al.(8, 14) Generated sequences of microorganisms
127 were compared with an in-house curated species database and an agreement of over 90%
128 between the database and the sequence results as necessary to report a positive result.
129 Bacteria and fungi were reported as relative abundances within each specimen (with 2%
130 being the minimum threshold of reporting).

131 Prior to statistical analysis all NGS sample results were compared to their
132 corresponding controls which were a combination of DNA extraction controls ~~and no-~~

133 ~~template PCR controls~~. NGS detection for control samples were first transformed to relative
134 abundances and then compared to matched samples. If the sample and control both had
135 detection for a given microbe, the read counts of the sample were depleted proportional to the
136 relative abundance in the control. Also, any detection of *Pelomonas*
137 *saccharophila* and *Ralstonia pickettii* were eliminated because they are known common
138 reagent contaminants.

139

140 Data and Statistical Analysis

141 Patient demographics and etiologies for device explantation were abstracted.
142 Etiologies were broadly classified by infection (e.g. gross infection), erosion (e.g. urethral
143 erosion, tubing or pump extrusion), or mechanical malfunction (e.g. fluid leak, floppy glans,
144 impending erosion, cylinder resizing). Standard culture and NGS results were documented as
145 “yes” for presence of microorganisms, or “no” for absence of organisms. Microorganism
146 species identifications and relative abundances were documented.

147 Differences in number of species detected (richness) and species diversity (expressed
148 as the exponential function of the Shannon diversity metric, i.e., Hill₁ numbers) across
149 samples explained by age, ethnicity, diabetes status, implant duration, and year of implant
150 removal were assessed using ANOVA with Type III sum of squares and backward stepwise
151 selection. Differences in microbiome compositional profiles among samples were calculated
152 with Bray-Curtis community dissimilarities, and Permutational Analysis of Variance
153 (PERMANOVA) was used to test for the effect of the sample variables mentioned above for
154 ANOVA.(15, 16) An ordination was performed by principal coordinates analysis using Bray-
155 Curtis distances. Tests for differences in the relative abundance of species depending on
156 indication classification were conducted using Analysis of Compositions of Microbiomes

157 with Bias Correction (ANCOM-BC).(17) Chi-squared tests were used to assess relationships
158 between etiologies and microorganism detection rate. Statistical analyses were performed
159 using R statistical software.

160

161 RESULTS

162 Patient Demographics

163 From a total of 110 patients, 83 patients, with a median age of 69 (interquartile range:
164 17) years with both NGS and culture results, were included in this study. Indication for
165 device removal included infection (n=8, 10%), erosion (n=5, 6%), and mechanical
166 malfunction (n=70, 84%). The median time from PP implant to explant was 28 (interquartile
167 range: 43.5) months. Of the devices removed, only one was a malleable PP, while the other
168 82 were inflatable PP. At the time of explant, 68 (82%) underwent device replacement, four
169 of which were malleable PP, while the other 64 were inflatable PP. Eight (9.6%) patients had
170 a concomitant artificial urinary sphincter device that was explanted at the time of revision
171 surgery.

172

173 Standard Culture and Rapid Molecular Testing Results

174 Of the 83 devices, 48 (56%) NGS studies and 24 (29%) standard cultures resulted
175 positive for detection of microorganisms ($p < 0.001$). Among the 8 infected cases, all NGS and
176 culture studies tested positive. Focusing specifically on the 8 infected samples there were 14
177 culture positive microorganisms, and 6 (42%) of these culture detections were also found in
178 the corresponding patient's NGS result. Making the same comparison at the genus level
179 resulted in 8 (57%) of these culture detections (8 of 14) also occurring in the NGS results.
180 When culture did detect a species and genus reported by NGS, culture detected the most
181 abundant NGS species and genus in 5 (63%) of 8 patients.

182 Among the 5 erosion cases, 4 (80%) NGS studies and 4 (80%) cultures studies tested
183 positive (with one instance of NGS being negative and another instance of culture being
184 negative). Among the 70 mechanical malfunction cases, 36 (51%) NGS studies and 12 (17%)
185 culture studies tested positive. Considering patients with only mechanical malfunction, NGS
186 and culture were both negative in 29 studies (41%) and both positive in 8 cases (11%).

187 Time for ~~PCR~~, NGS and standard culture finalized reporting times were assessed
188 specifically in infection and erosion cases from one institution. ~~PCR studies returned at a~~
189 ~~mean of 1 day, which was significantly faster than NGS and culture (both $p < 0.01$).~~ NGS
190 results returned at a mean 5 days compared to 7 days for finalized conventional culture
191 results ($p=0.12$). ~~Quantitative PCR also assessed for antibiotic resistance genes, which were~~
192 ~~detected in 2 cases. Tetracycline resistance was identified in an infected device and~~
193 ~~methicillin resistance was identified in an eroded device. No resistance genes were detected~~
194 ~~in devices removed for mechanical malfunction.~~

195

196 Microorganism Profiles

197 Richness, defined as the number of species present in a sample, was calculated for all
198 NGS positive samples and effect of surgical indication, age, race, diabetes status, and implant
199 duration on observed richness values was assessed (Figure 1). Only surgical indication was
200 significant ($F=16.01$, $p < 0.01$), but time to surgery was the next most influential, albeit not
201 significant ($F=3.04$, $p=0.09$). For Hill₁, which is an alpha measure that encapsulates both
202 richness and evenness of species relative abundances of microbiota profiles, results were
203 similar to those for observed richness values only with surgical indication being the only
204 significant variable ($F=23.98$, $p < 0.01$), and diabetes being the next most influential, albeit not
205 significant ($F=2.08$, $p=0.16$).

206 The most frequent organisms by surgical indication (infection, erosion, and
207 mechanical malfunction) were *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and
208 *Escherichia coli*, respectively (Figure 2). The highest relative abundant organisms by
209 infection, erosion, and mechanical indications for revision surgery were *P. aeruginosa*,
210 *Corynebacterium jeikeium*, and *E. coli*, respectively (Figure 3). Common implant antibiotic
211 coatings and dip combinations against the most frequent and abundant organisms were
212 broadly reviewed (Table 1).

213 Fungal elements were identified in two NGS specimens that were not identified in
214 corresponding standard cultures. *Verticillium sp.* was identified by NGS in one mechanically
215 failed implant from a diabetic patient, while *Malassezia restricta* was identified by NGS in an
216 infected implant from a non-diabetic patient. *Candida parapsilosis* was identified by standard
217 culture in one infected implant from a non-diabetic patient that was not detected by NGS.

218 Microbiome compositional profiles varied by surgical indication ($F=2.03$, $p<0.01$),
219 but not by age, race, or diabetic status. Each surgical indication was then compared post hoc,
220 revealing that infection and erosion samples did not significantly differ compositionally
221 ($p=0.58$) but did significantly differ from mechanical malfunction samples (both $p<0.01$)
222 (Figure 4). Relative abundances of species that were significant through differential
223 abundance testing comparing indication types are exhibited in Figure 5.

224

225 DISCUSSION

226 Rapid molecular testing is an emerging technology that may allow for more sensitive
227 and sophisticated microbial testing compared to standard techniques. We found that NGS
228 may best play a role in identifying microorganisms in devices explanted due to infection or
229 erosion rather than a mechanical malfunction etiology due to its higher positivity rates for
230 those surgical indications. While it may not seem surprising that infected explants were more

231 likely to yield positive results, Henry et al. previously demonstrated that up to 70% of
232 patients with clinically uninfected penile prosthesis can grow positive bacteria cultures at the
233 time of reoperation.(18) Likewise, we found that 51% of NGS and 17% of standard culture
234 studies of uninfected devices in our cohort detected microorganisms. However, this was a
235 much lower rate when compared to NGS and standard cultures results of their infected
236 counterparts (both 100%).

237 When comparing the timings to results reporting in one institution, we found that
238 NGS testing results were reported at a slightly faster rate than culture results, although this
239 difference was not statistically significant. ~~Most notably, PCR results could be returned~~
240 ~~within hours of receipt of the specimen.~~ Clinically, this may allow for prompt tailoring of
241 antibiotics or antifungals and earlier targeted antimicrobial therapy, ~~and identification of~~
242 ~~resistance genes.~~ Furthermore, NGS assesses for both bacterial and fungal organisms
243 simultaneously, eliminating the long wait for fungal culture results to finalize. Although
244 immediate versus delayed salvage of an implant has not been shown to make a difference,
245 perhaps earlier detection of the causative organisms and assurance that the correct antibiotics
246 are being administered may allow urologists to more confidently proceed with salvage
247 treatments.(19)

248 NGS provides an opportunity to better understand the microbiota on PP and may
249 better described how specific groups may be at risk for infection. The presence of biofilm
250 formation on the implanted device is thought to be a predisposing factor for infection in
251 patients undergoing revision surgery.(18, 20-22) Removal of the primary device may disrupt
252 biofilm and allow previously sequestered bacteria to be released and adhere to the new
253 implant causing clinical infection.(23) In this present study, *E. coli* was the most frequent and
254 abundant organism on devices replaced for mechanical malfunction, contrary to the historical
255 paradigm of coagulase-negative *Staphylococcus* being the dominant species of PP

256 biofilms.(3, 20, 24, 25) The use of antibiotic coated devices and antibiotic irrigation may
257 have reduced the coagulase-negative *Staphylococcus*, but allowed more virulent organism to
258 become predominant as a result. Characterizing biofilm on PP is also a clinical imperative
259 since it may additionally be linked to mechanical failures resulting in decreased device
260 longevity and increased need for revision surgery.(26)

261 The most conservative treatment of an infected or eroded PP is complete removal
262 with delayed implantation, which may result in corporal fibrosis, decreased penile length, and
263 a potentially challenging replacement surgery. The challenge is that not all eroded devices are
264 infected, even though they may be treated as such. Isolated single component removal and
265 replacement has been described for eroded tubing and pumps in small cases series.(27, 28)
266 Salvage washout with malleable or inflatable PP replacement is also feasible with potential
267 infection-free rates of 93%; however, its use is currently limited to only 17.3% of infected
268 cases.(19, 29)

269 An improved characterization of microbiota profiles of PPs may help to increase
270 utilization and success of salvage treatments by guiding the selection of peri-operative
271 antibiotics for systemic use and PP antibiotic and antifungal coatings or hydrophilic dip
272 solutions. For example, in this study, virulent, Gram-negative *Pseudomonas aeruginosa* was
273 the most frequent and abundant organisms on infected implants, while skin flora,
274 *Staphylococcus epidermidis* (most frequent) and *Corynebacterium jeikeium* (most abundant),
275 were identified predominantly on eroded implants. When common implant antibiotic coatings
276 and dip combinations were broadly reviewed, vancomycin and gentamicin would provide the
277 best coverage for infected and eroded implants which is consistent with a recent large multi-
278 center review.(30) Interestingly, the most abundant organisms for infection and erosion were
279 not covered by the combination of minocycline and rifampin, a common infection retardant

280 ~~coating~~. Fungal elements were also detected in our study which reiterates the call to identify
281 the clinical value of incorporating antifungals in PP surgery.(5)

282 NGS detected additional microorganisms not detected on standard cultures and may
283 be more informative. For example, when focusing specifically on infected devices, culture
284 only detected the most abundant NGS species in 62.5% (n=5). Additionally, when looking at
285 the individual result reports, we found that the overall trend was that NGS tended to detect a
286 polymicrobial profile, while the results demonstrated by cultures were mostly
287 monomicrobial. Gross et al. similarly identified that 25% of culture-positive infection also
288 showed polymicrobial growth.(5) Interestingly, while this has yet to be established in the
289 urologic literature, treatment of polymicrobial infections has been shown to have lower
290 success rates compared with monomicrobial infections in infected periprosthetic joints within
291 the orthopedic literature.(31, 32) NGS may help to provide a better understanding of the
292 predominant organism (abundance data) on PP and help to established whether these profiles
293 are truly polymicrobial and require treatment, or rather an infection with a dominant species
294 with the other organisms acting in concert.(33)

295 Our study is not without limitations. Best techniques for sampling the microbiota of
296 PP and proper controls are still in development. Swabbing the implants may be not sufficient
297 to dislodge microorganisms and may be an incomplete assessment of the microbial
298 microenvironment. Controls were not utilized at the time of surgery to ensure microbes on
299 the gauze were not contaminants from the field. Therefore, detected organisms may not
300 represent a clinically significant infection and may reflect a contamination during device
301 removal. Direct susceptibility testing was also not performed for NGS results and this made it
302 difficult to compare the rates of bacterial composition and antibiotic resistance in our study.
303 Samples were shipped overnight at ambient temperatures which may affect DNA integrity,
304 and factoring was not performed for varying biomass between specimens during molecular

305 testing. In addition, no clinical studies have yet been performed showing that treating
306 organisms identified in this study will have a positive clinical effect. A prospective,
307 randomized trial aimed at evaluating the clinical significance of NGS in patients with PP
308 infection and erosion is being performed. Despite these limitations, NGS was utilized to
309 further characterize the microbiome profiles of PP removed for infection, erosion, and
310 mechanical malfunction.

311

312 CONCLUSIONS

313 NGS helped to further characterize distinct microbiomes of PP removed for infection,
314 erosion, and mechanical malfunction. The clinical potential of NGS is most useful in patients
315 with infected and eroded devices, compared to devices removed for mechanical malfunction.
316 ~~PCR shows promise in rapidly detecting clinically significant organisms and resistance genes~~
317 ~~in PP infections. A prospective, randomized trial aimed at evaluating the clinical significance~~
318 ~~of NGS in patients with PP infection is being performed.~~

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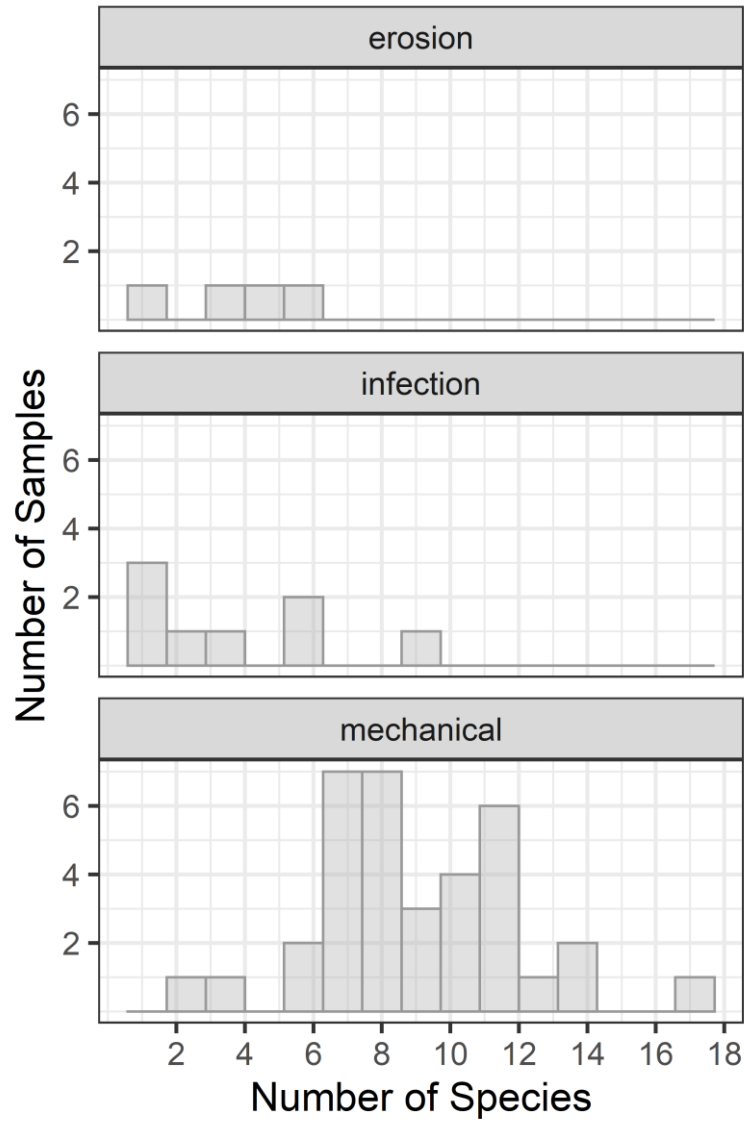
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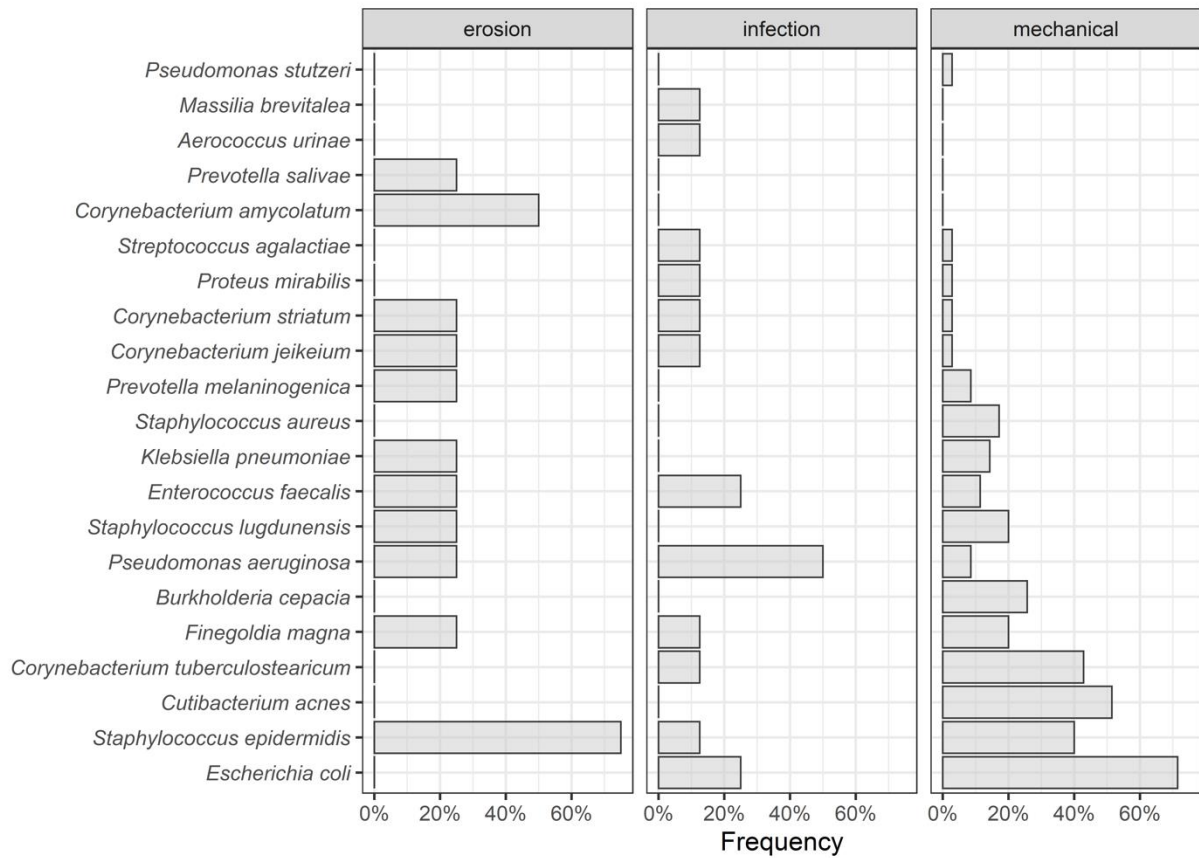
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Figure 1. Histogram of species richness by surgical indication for penile prosthesis removal.



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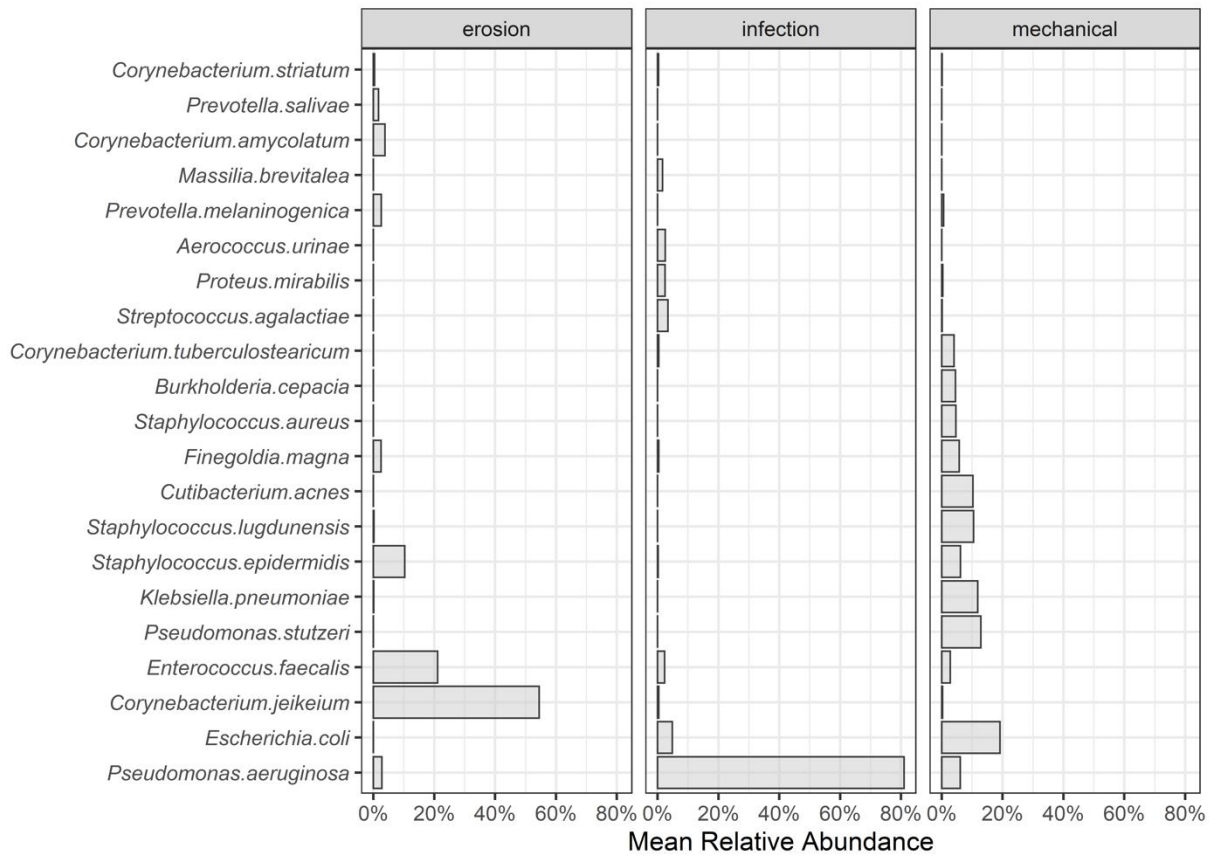
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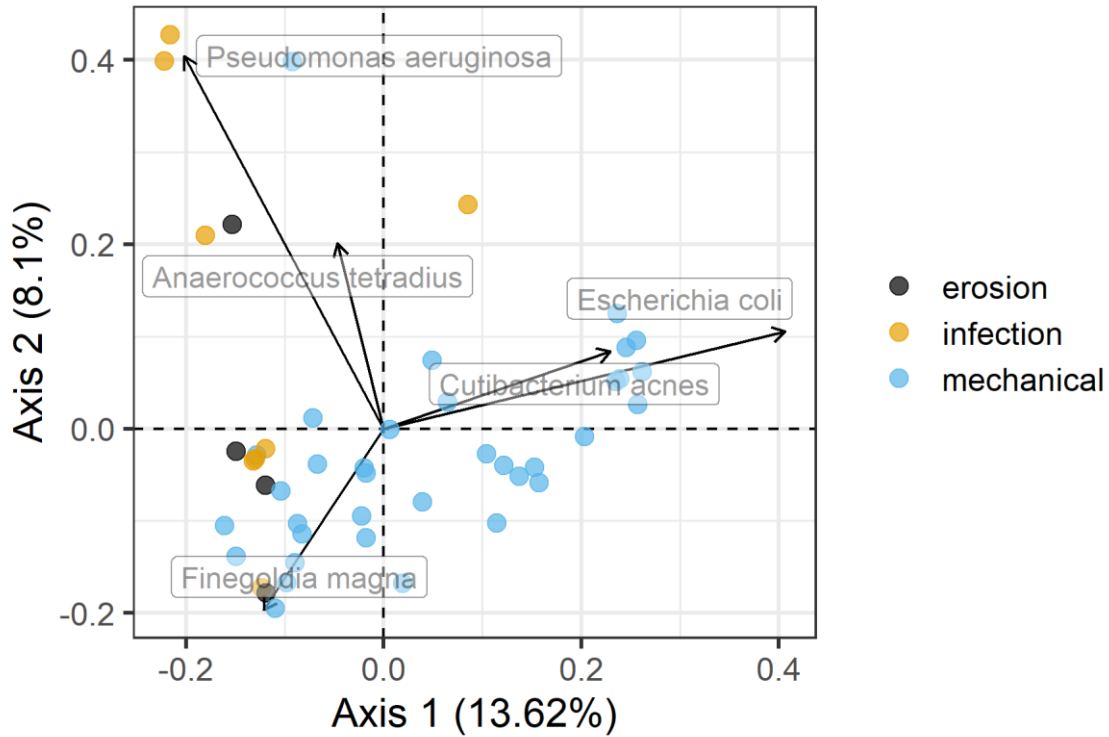
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Figure 2. Bar chart of frequency of the most common species within each surgical indication for penile prosthesis removal. For this illustration the top 10 most common species within infection, erosion, and mechanical malfunction indications were identified, which resulted in 21 unique species.



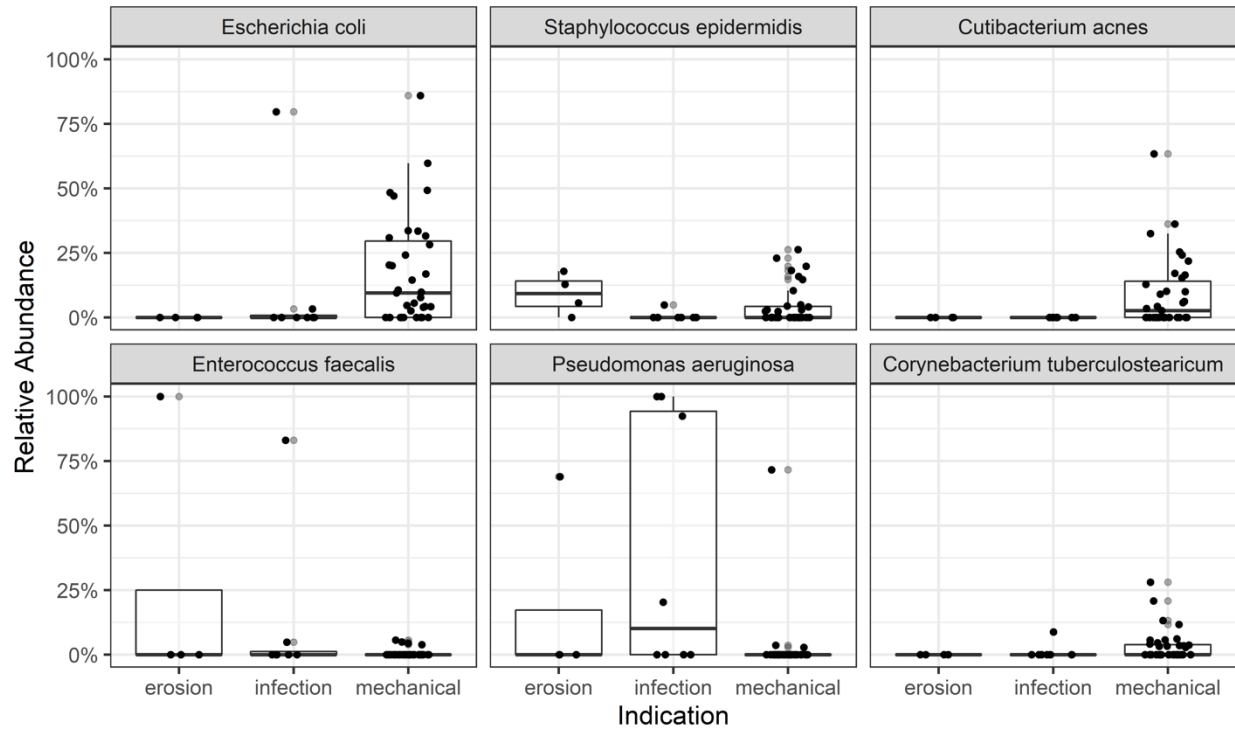
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Figure 3. Bar chart of mean relative abundances of the most common species within each surgical indication for penile prosthesis removal. For this illustration the top 10 most common species within infection, erosion, and mechanical malfunction indications were identified, which resulted in 21 unique species.



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458 Figure 4. Principal coordinates analysis based on Bray-Curtis Dissimilarities. Species that
459 had the strongest correlation with the first two axes are illustrated. The species evaluated for
460 plotting were those previously identified to be the most common in the study. The direction
461 and length of the arrow for each species represents increasing relative abundance of the
462 corresponding species for samples in that area of the plot.



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465 Figure 5. Box and dot plots of relative abundances of species that were significant through

466 differential abundance testing comparing indication types. Each dot represents values for

467 individual samples. The boxes of the boxplots are defined by 25th and 75th quartiles, the

468 horizontal lines within boxes are medians, and whiskers calculated as 1.5 times the

interquartile range.

469 Table 1. Coverage of common antibiotic coatings/dips against the most abundant and
 470 frequent organisms based on surgical indication.
 471

	Infected	Eroded		Mechanical Malfunction
	<i>P. aeruginosa</i>	<i>S. epidermidis</i>	<i>C. jeikeium</i>	<i>E. coli</i>
	<i>Most abundant and frequent organism</i>	<i>Most frequent organism</i>	<i>Most abundant organism</i>	<i>Most abundant and frequent organism</i>
Coverage of Common Antibiotic Coatings/Dips				
Minocycline/Rifampin		X		X
Gentamicin/Rifampin	X	X		X
Gentamicin/Vancomycin	X	X	X	X
Gentamicin/Bacitracin	X			X
Rifampin/trimethoprim/sulfamethoxazole		X		X

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