Multiflora and Gram-Negative Microorganisms Predominate in Infections Affecting Pelvic Endoprostheses Following Tumor Resection

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Background: Periprosthetic infections after pelvic reconstruction are common, with reported rates ranging from 11% to 53%. Management of these infections is troublesome, as they commonly necessitate multiple surgical interventions and implant removal. The epidemiology and outcomes of these infections are largely unknown. The aim of this study was to analyze the causative microorganisms and the clinical outcome of treatment in a series of patients with pelvic endoprostheses affected by infection following tumor resection.

Methods: In this retrospective, multicenter cohort study, we identified all patients who developed an infection after endoprosthetic reconstruction in periacetabular tumor resection, between 2003 and 2017. The microorganisms that were isolated during the first debridement were recorded, as were the number of reoperations for ongoing infection, the antimicrobial treatment strategy, and the outcome of treatment.

Results: In a series of 70 patients who underwent pelvic endoprosthetic reconstruction, 18 (26%) developed an infection. The type of pelvic resection according to the Enneking-Dunham classification was type P2-3 in 14 (78%) of these patients and type P2 in 4 (22%). Median follow-up was 66 months. Fourteen (78%) of the 18 patients with infection had a polymicrobial infection. Enterobacteriaceae were identified on culture for 12 (67%). Of a total 42 times that a microorganism was isolated, the identified pathogen was gram-negative in 26 instances (62%). Microorganisms associated with intestinal flora were identified 32 times (76%). At the time of latest follow-up, 9 (50%) of the patients had the original implant in situ. Of these, 2 had a fistula and another 2 were receiving suppressive antibiotic therapy. In the remaining 9 (50%) of the patients, the original implant had been removed. At the time of final follow-up, 3 of these had a second implant in situ. The remaining 6 patients had undergone no secondary reconstruction.

Conclusions: Infections that affect pelvic endoprostheses are predominantly polymicrobial and caused by gram-negative microorganisms, and may be associated with intestinal flora. This differs fundamentally from mono-bacterial gram-positive causes of conventional periprosthetic joint infections and may indicate a different pathogenesis. Our results suggest that prophylaxis and empiric treatment may need to be re-evaluated.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Stemmed acetabular implants are the preferred constructs for reconstruction after periacetabular tumor resection in many centers[1-3]. Early mechanical failure is rare nowadays, but infection that affects the pelvic endoprosthesis is reported to occur in 11% to 53% of cases[1-10]. These infections can be devastating, as they commonly necessitate multiple surgical debridements, removal of implants, or even, although rarely, hindquarter amputation[4]. In general, patients undergoing tumor resection and reconstruction have impaired defenses against infection because of adjuvant chemo- and radiation therapy and disseminated disease. In pelvic reconstruction, poor penetration of systemic antibiotics in, usually, large dead spaces hampers

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TABLE I Baseline Characteristics and Outcome of 18 Patients with an Infection Affecting the Pelvic Endoprosthesis

Patient	Age *(yr)*	Sex	Diagnosis*	Resection Type	Adjuvant Therapy†	Reconstruction	Prophylaxis	Local Antibiotic Prophylaxis
1	55	M	CS gr. 2	P2-3	Rtx post.	LUMiC	Cefazolin, 1 day	—
2	67	F	CS gr. 3	P2-3	—	LUMiC	Cefuroxime, 3 days	—
3	57	M	CS gr. 2	P2	—	Pedestal	Cefazolin, 1 day	—
4	20	M	Osteosarcoma	P2-3	Ctx post.	LUMiC	Cefuroxime, 5 days	—
5	71	F	Met (rectum)	P2	Rtx pre. and post., ctx pre.	LUMiC	Cefuroxime, 3 days	Gentamicin sponges
6	53	F	CS gr. 2	P2-3	—	Pedestal	Cefazolin, 1 day	—
7	68	F	Chondromyxoid fibroma	P2-3	—	LUMiC	Cefazolin, 2 days; cefuroxime 5 days	—
8	72	F	Met (breast)	P2	Rtx pre.	LUMiC	Cefazolin, 1 day; cefuroxime, 1 day; metronidazole, 1 day	Gentamicin sponges
9	34	F	CS gr. 2	P2-3	—	LUMiC	Cefazolin, 1 day; cefuroxime, 5 days; metronidazole, 1 day	—
10	66	F	CS gr. 2	P2-3	—	Pedestal	Cefuroxime, 5 days	—
11	68	M	CS gr. 2	P2-3	—	LUMiC	Cefazolin, 1 day	—
12	67	M	CS gr. 2	P2-3	—	LUMiC	Cefazolin, 1 day; cefuroxime, 5 days	—
13	71	F	CS gr. 2	P2-3	—	LUMiC	Cefamandole, 5 days; metronidazole, 1 day	—
14	21	F	Ewing sarcoma	P2-3	Ctx pre. and post., rtx post.	LUMiC	Cefamandole, 5 days	—
15	63	M	Met (thyroid)	P2	—	LUMiC	Cefamandole, 5 days	—
16	64	M	CS gr. 3	P2-3	—	Pedestal	Cefamandole, 5 days	—
17	35	F	CS gr. 2	P2-3	—	Pedestal	Cefamandole, 5 days	—
18	28	M	Ewing sarcoma	P2-3	Ctx pre. and post.	Pedestal	Cefamandole, 5 days; gentamicin	—

*CS = chondrosarcoma, gr. = grade, and met = metastatic carcinoma. †Rtx = radiation therapy, post. = postoperatively, ctx = chemotherapy, and pre. = preoperatively. ‡*E. cloacae* = *Enterobacter cloacae, E. faecalis* = *Enterococcus faecalis, P. mirabilis* = *Proteus mirabilis, C. acnes* = *Cutibacterium acnes, B. fragilis* = *Bacteroides fragilis, P. magnus* = *Peptostreptococcus magnus, E. coli* = *Escherichia coli, C. innocuum* = *Clostridium innocuum,* gr. = group, *S. epidermidis* = *Staphylococcus epidermidis, P. aeruginosa* = *Pseudomonas aeruginosa, P. bivia* = *Prevotella bivia, S. aureus* = *Staphylococcus aureus, K. oxytoca* = *Klebsiella oxytoca, M. morganii* = *Morganella morganii, K. pneumoniae* = *Klebsiella pneumoniae, C. sedlakii* = *Citrobacter sedlakii, E. faecium* = *Enterococcus faecium,* and CNS = coagulase-negative staphylococci. §DAIR = debridement, antibiotics, and implant retention.

adequate treatment. Furthermore, limited possibility for soft-tissue coverage increases the risk of infection and reduces the chance of successful eradication. Appropriate antibiotic prophylaxis and, in cases of infection, empirical treatment are dependent on the local epidemiology of causative microorganisms. Most centers currently administer prophylactic intravenous cephalosporins for 24 hours to 5 days, sometimes combined with, for example, metronidazole, tobramycin, clindamycin, or vancomycin[1,2,4,11]. Preemptive antibiotics are sometimes continued for a duration of up to 4 weeks[11]. The heterogeneity of treatment strategies illustrates the lack of consensus on prophylaxis and early treatment. The extensive use of antibiotics may lead to increased antimicrobial resistance and impaired effectiveness of prophylactic antibiotic regimens[12,13]. Apart from that, the proximity of the abdominal cavity and perianal region during surgery may influence the spectrum of causative microorganisms in cases of infection affecting pelvic endoprostheses. Angelini et al. evaluated 55 patients with an infection after various types of pelvic reconstructions, and found that 37% of these infections were caused by gram-negative organisms,

TABLE I (*continued*)

Microorganisms†	Time After Implantation *(days)*	Surgical Treatment§	Local Antibiotic Treatment	Final Outcome	Follow-up *(mo)*
E. cloacae, E. faecalis, P. mirabilis	39	DAIR (4×)	Gentamicin beads	Implant in situ, fistula	24
E. cloacae, E. faecalis, C. acnes, B. fragilis	15	DAIR (6×)	Gentamicin beads	Implant in situ	101
E. cloacae, P. magnus	46	DAIR (1×), 2-stage revision	Gentamicin spacer, gentamicin beads	Second implant in situ	116
E. coli, B. fragilis, C. innocuum	94	DAIR (2×)	Gentamicin beads	Implant in situ	69
Gr. G streptococci, *S. epidermidis*	52	DAIR (3×)	Gentamicin beads, gentamicin sponges	Implant in situ, suppressive antibiotics	31
P. aeruginosa, E. cloacae	16	DAIR (2×), 2-stage revision	Gentamicin spacer, gentamicin beads	Type B-II rotationplasty	136
E. cloacae, E. faecalis, P. bivia, P. mirabilis	12	DAIR (4×)	Gentamicin beads	Implant in situ, fistula	42
S. aureus	42	DAIR (1×)	—	Implant in situ, suppressive antibiotics	21
S. epidermidis	55	DAIR (1×)	—	Implant in situ	21
K. oxytoca, M. morganii	12	DAIR (1×)	Gentamicin sponges	Implant in situ	1
M. morganii, P. aeruginosa, P. mirabilis	23	1-stage revision, DAIR (1×)	—	Second implant in situ	13
P. aeruginosa, S. aureus	17	DAIR (2×), 2-stage revision	Gentamicin spacer, gentamicin beads	Second implant in situ	22
Diphtheroids	28	DAIR (1×)	Gentamicin beads	Girdlestone	44
E. coli	93	DAIR (6×)	Gentamicin sponges	Implant in situ	66
E. coli, P. mirabilis, E. faecalis	20	DAIR (6×)	—	Girdlestone, fistula	44
K. pneumoniae, C. sedlakii, P. aeruginosa, S. aureus	14	DAIR (6×)	—	Hindquarter procedure	6
E. faecium, CNS	50	DAIR (1×)	Gentamicin spacer	Girdlestone	113
E. cloacae, E. coli	28	DAIR (3×)	Gentamicin beads	Girdlestone	103

which is unusually high in comparison with infections following conventional hip and knee arthroplasty procedures[4,14]. However, studies focusing specifically on the epidemiology of causative microorganisms and the clinical outcome of infections involving pelvic endoprostheses are currently lacking. Therefore, the aim of this study was to analyze (1) the characteristics of causative microorganisms, (2) the proportion of patients with successful implant retention, and (3) the clinical outcome after implant removal in a series of patients with a pelvic endoprosthesis affected by infection following tumor resection.

Materials and Methods

Study Population

In this retrospective, multicenter cohort study, we queried institutional databases to identify all patients who underwent endoprosthetic reconstruction following periacetabular tumor resection between 2003 and 2017, in 2 tertiary referral centers for orthopaedic oncology. The minimum follow-up among surviving patients was 12 months.

Surgical Procedure

All surgical procedures were performed in operating rooms with laminar air flow. The skin was thoroughly disinfected using chlorhexidine 0.5% in alcohol 70%. For periacetabular resections, we use an extended iliofemoral Smith-Petersen approach. With this approach, the skin incision starts posteriorly and follows the iliac crest to the anterior superior iliac spine, and then angles distally along the line of the femoral artery[5]. When needed, especially in combined P2-3 resections (Enneking-Dunham classification[15]), the incision was modified

to a utilitarian approach providing exposure of the pubic symphysis. During surgery, a double pair of gloves was used. Protective helmets were not used. Pulse lavage was used to rinse the wound intraoperatively. Following tumor resection, during the same operative session, reconstruction using a stemmed acetabular implant was performed to address the pelvic defect. In the first years under study, the Pedestal Cup endoprosthesis (Zimmer) was used[5]. From 2008 onward, the LUMiC prosthesis (Implantcast) was used[1]. Patients in whom an acute infection was suspected underwent surgical lavage and debridement, during which at least 5 samples of periprosthetic purulence and tissue were obtained for culture. A thorough debridement was performed, including mechanical cleaning of the implant and disassembly of endoprosthetic parts, whenever possible.

Antibiotic Regimen

A first or second-generation cephalosporin was administered at least 30 minutes prior to skin incision in all patients and repeated every 3 hours of surgery or in cases in which blood loss exceeded 2 L. In Center 1, cefazolin (1 g) or cefuroxime (1.5 g) was used, and in Center 2, cefamandole (1 g) was used. A subset of patients, dictated by surgeon preference, additionally received prophylactic metronidazole or gentamicin and/or local antibiotic treatment using gentamicin sponges. The prophylactic antibiotics were continued for 1 to 5 days, depending on surgeon preference and variables such as duration of surgery, extent of resection, and patient condition (Table I). Antibiotic-loaded cement, gels, and gentamicin beads were not used as local prophylaxis. In patients with infection, after surgical lavage and debridement, empiric treatment was started immediately after surgery and consisted of flucloxacillin, combined with rifampicin administered up to 5 days after debridement to prevent biofilm formation. Gentamicin was added if the periprosthetic biopsy did not demonstrate a positive Gram stain. Targeted antibiotic therapy was started when culture results were known.

Definitions

An infection affecting the pelvic endoprosthesis was considered to be present if a patient met ≥1 of the following criteria: the presence of pus around the prosthesis, a sinus tract communicating with the prosthesis, at least 2 positive operative culture results with the same microorganism identified, or 1 positive culture result with a virulent microorganism identified. The microorganisms that were isolated during the first debridement for infection were recorded for this study, as were the number of reoperations for ongoing infection, the antimicrobial treatment strategy, and the outcome of treatment. Patients were considered "cured" if the endoprosthesis (the primary or a secondary implant) was in situ at the time of the latest follow-up, no draining fistula was present, and the patient was not receiving suppressive antibiotics. Patients were considered "functionally cured" if the endoprosthesis (primary or secondary implant) was in situ at the time of the latest follow-up, with or without a draining fistula or suppressive antibiotics.

Institutional review board approval was not required for this study according to Dutch law.

Results

A total of 70 patients were identified. Eighteen (26%) developed an infection during follow-up and were included in our analysis. Eight (44%) of the 18 patients were male. The median age at surgery was 64 years (range, 20 to 72 years). Fifteen (83%) of the patients were treated for a primary bone tumor (including 11 chondrosarcomas), and 3 (17%) underwent a pelvic resection for osseous metastases of a distant carcinoma. Four (22%) of the patients received (neo)adjuvant chemotherapy, and 4 (22%) had (neo)adjuvant radiation therapy. The type of pelvic resection according to the Enneking-Dunham classification was P2-3 in 14 (78%) and P2 in 4 (22%)[15]. Twelve (67%) of the patients had reconstruction with use of an LUMiC and 6 (33%), with a Pedestal Cup endoprosthesis. The median follow-up was calculated with the reverse Kaplan-Meier method and was equal to 66 months (95% confidence interval, 26 to 106 months)[16].

TABLE II Isolated Microorganisms*

Pathogen	No. of Times Isolated (%)
Gram-negative Enterobacteriaceae and anaerobic bacteria	26 (62)†
Enterobacter cloacae	6 (33)
Escherichia coli	4 (22)
Proteus mirabilis	4 (22)
Pseudomonas aeruginosa	4 (22)
Morganella morganii	2 (11)
Bacteroides fragilis	2 (11)
Klebsiella pneumoniae	1 (6)
Prevotella bivia	1 (6)
Citrobacter sedlakii	1 (6)
Klebsiella oxytoca	1 (6)
Gram-positive microorganisms	16 (38)†
Enterococcus faecalis	4 (22)
Staphylococcus aureus	3 (17)
Staphylococcus epidermidis	2 (11)
Enterococcus faecium	1 (6)
Clostridium innocuum	1 (6)
Peptostreptococcus magnus	1 (6)
Cutibacterium acnes	1 (6)
Diphtheroids	1 (6)
Coagulase-negative staphylococci	1 (6)
Beta-hemolytic streptococci group G	1 (6)

*The percentages shown are of the total number of patients (n = 18), except where otherwise noted. †The percentage is of the total number of times that a microorganism was isolated (n = 42).

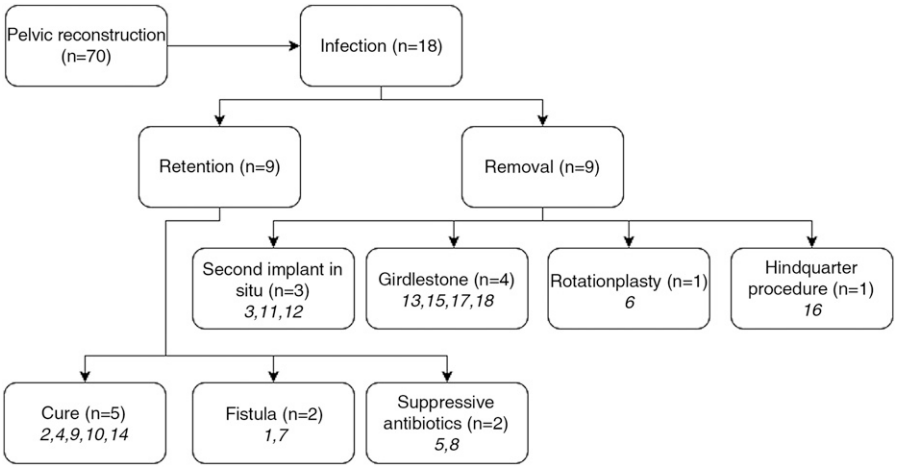

Fig. 1

Outcome of 18 patients with a pelvic endoprosthesis affected by infection. The numbers in italics correspond with the patient numbers in Table I.

The infections (n = 18) were diagnosed at a median of 28 days postoperatively (range, 12 days to 3 months). Fourteen (78%) of the patients had a polymicrobial infection. Enterobacteriaceae were identified on culture for 12 (67%) of the 18 patients. Of a total 42 times that a microorganism was isolated, the identified pathogen was gram-negative in 26 instances (62%) (Table II). Microorganisms associated with intestinal flora were identified 32 times (76%).

At the time of final follow-up, 9 (50%) of the patients had the original implant in situ. Among these patients, 5 (56%) were considered cured (endoprosthesis in situ with no presence of a fistula and no use of suppressive antibiotics) (Fig. 1). Of the remaining 4 patients, 2 had a fistula at latest review (Table I, Patients 1 and 7), and the other 2 patients received suppressive antibiotic therapy; both had no signs of active infection at the time of latest follow-up (Table I, Patients 5 and 8) but suppressive antibiotic therapy was continued because of poor life expectancy (both patients had been treated for a metastatic carcinoma).

In the other 9 patients (50%), the original implant was removed, after a median of 2 months (range, 1 to 43 months). At the time of latest follow-up, 3 of these patients had a second implant in situ (2 after a 2-stage exchange and 1 after a 1-stage exchange). The remaining 6 patients underwent no secondary reconstruction because of limited life expectancy or patient condition, or because the patient did not want to risk developing another infection. Of these, 4 underwent a Girdlestone procedure, 1 had a type B-II rotationplasty[17], and 1 underwent hindquarter amputation because a fistula had developed between a vascular repair and the bladder (Fig. 1). Three of 4 (75%) one and two-stage revisions were successful, without suppressive antibiotic treatment or a fistula.

At review, 8 (44%) of the patients were cured, having the primary or a secondary pelvic endoprosthesis in situ without suppressive antibiotic treatment or the presence of a fistula. When including the 4 cases in which the primary endoprosthesis was in situ but the patient was receiving suppressive antibiotic treatment or had a draining fistula, a total of 12 (67%) of the patients were considered functionally cured (Table I).

Discussion

An infection affecting the endoprosthesis is the most frequent complication after pelvic reconstruction and the predominant cause of reconstruction failure during the first years, irrespective of the technique used[1,4,7,18]. The aim of this study was to analyze the characteristics of the causative microorganisms and the outcome of a surgical and antibiotic treatment strategy in a series of patients with pelvic endoprostheses affected by infection following reconstruction in periacetabular tumor resection. This study showed that the causative microorganisms differ fundamentally from conventional periprosthetic joint infections, in which mono-bacterial, gram-positive infections predominate[19].

The proportion of patients functionally cured (67%) was comparable with that in previous series by Jaiswal et al. (58%)[6] and Guo et al. (75%)[3]. However, Ji et al. reported only 27% functionally cured, which can be explained by the large proportion (80%) of late infections[11]. In the current study, implant retention was achieved for 9 (50%) of the patients, which is comparable to findings in the literature (53% to 75%)[3,6]. Following the treatment strategy for conventional periprosthetic joint infection, we tend to switch to 1 or 2-stage revision treatment after 3 unsuccessful DAIR (debridement, antibiotics, and implant retention) procedures. Although our cohort was limited in numbers, our results nevertheless showed that performing >3 DAIR procedures can be successful. Two of 4 patients who were treated with 6 sequential DAIR procedures had no signs of infection and no fistula or suppressive therapy at latest follow-up. One and two-stage revision was demonstrated to be a feasible treatment strategy, with 3 (75%) of 4 patients successfully cured, without a fistula or suppressive therapy. However, the functional impairment associated with a Girdlestone procedure has to be taken into account. If infection at the prosthesis anchoring site is suspected, we advise not to perform DAIR procedures and, instead, consider 1 or 2-stage revision. The cure rate in our series was relatively low (44%) compared with that for conventional

arthroplasty (>77%) and non-pelvic endoprosthetic reconstruction after tumor resection (60%)[20-22]. This cure rate may underestimate the potential for successful infection eradication, as we regularly chose not to attempt further reconstruction, stop suppressive antibiotics, or revise a persistent fistula in cases of short life expectancy, avoiding the risk of additional surgical procedures and reinfection.

Most hip and knee periprosthetic joint infections are caused by *Staphylococcus aureus* and coagulase-negative staphylococci, together accounting for 50% to 60% of cases[19]. Tande and Patel published data on 1,979 cases of infection following hip arthroplasty procedures, reporting that 14% were polymicrobial and 7% were caused by aerobic gram-negative bacilli[19]. In our series, 78% of the patients had a polymicrobial infection. Also, for 72% of the patients, gram-negative bacteria were identified on culture.

A number of explanations may account for these notable differences. First, the spectrum of microorganisms may be influenced by the surgical approach. For periacetabular tumor resection, part of the incision runs through the inguinal crease and, in that respect, it is comparable with the incision that is used during the direct anterior approach to the hip[23]. Ilchmann et al. recently demonstrated that the direct anterior approach might be associated with a higher risk of gram-negative and polymicrobial infection compared with a lateral approach for conventional hip replacement surgery[24]. They suggested that this may be due to the incision being located close to the groin, which is a highly colonized area. However, the inguinal crease is predominantly colonized by corynebacteriae and staphylococci[25-27].

Second, differences in causative microorganisms might be explained by a different etiology of infection. It is generally believed that most early periprosthetic joint infections are caused by the introduction of microorganisms during surgery[19]. A less-frequent cause of periprosthetic infection is contiguous spread via compromised soft tissue, or via hematogenous seeding[14,19]. As such, high rates of infection can be expected after periacetabular tumor resections: the wound is often large and the surgical procedures are lengthy, while most of the soft-tissue envelope has been resected. Notably, a high rate of intestinal flora was found, which suggests yet another route of bacterial contamination. Bacterial translocation through the intestinal wall has been proposed as a possible explanation, known as "the theory of the leaky gut." This was first described in 1979[28-30]. Opening of the peritoneal cavity with the prosthesis abutting the intestines contributes to the plausibility of this hypothesized route of contamination. However, the peritoneal cavity was not opened in the majority of patients in our study. Although we regard "the theory of the leaky gut" a valid hypothesis, translocation has not definitively been demonstrated to be the cause of pelvic infections.

The chosen prophylactic antibiotic strategy is dependent on many factors, including causative microorganisms. In turn, the spectrum of microorganisms is dependent on the most likely route of infection. Risk of infections associated with the incision site could be reduced by additional antiseptic measures during surgery. Poor penetration of systemic antibiotics in the dead space after tumor resection would potentially justify the use of local antibiotic treatment. Gentamicin beads, cement, gels, and sponges have been used in infection cases in order to achieve high local doses without systemic toxicity[31]. Fisher et al. reported a relatively low risk of infection (11%) after pelvic reconstruction in 27 patients using a large volume of gentamicin-laden cement. They believed that a high concentration of antibiotics around the prosthesis minimized the risk of deep infection[2]. However, although these data are promising, there is no solid evidence to support the use of local antibiotics as prophylaxis in either conventional arthroplasty or pelvic reconstruction. Furthermore, leaving a foreign body in situ remains controversial[32]. Despite poor penetration of antibiotics in dead spaces, and because of the low level of evidence for local antibiotics, systemic treatment should be considered. The polymicrobial flora found in our series may justify the use of a broader spectrum of antibiotic prophylaxis aimed at gram-negative bacteria. Another prophylactic strategy could be selective gut decontamination. If bacterial translocation through the intestinal lumen indeed contributes to the development of infection, reducing intestinal bacterial load may lead to a reduced risk of infection. The effect of selective digestive decontamination (SDD), often used to prevent intensive care unit-acquired infections, has been reported in several large studies[33]. However, its use is still controversial in intensive care medicine[33]. To our knowledge, the use of SDD for infected pelvic endoprosthesis has not been investigated.

Our results suggest that prophylactic antibiotic strategies and empiric treatment may need to be reconsidered. Considering the predominant polymicrobial flora found in our series and the possibility of a route of infection through the intestinal wall, prophylactic measures and empiric treatment should consist of broad-spectrum systemic antibiotics. In addition, local antibiotics should be considered. A clinical trial using SDD as a preventive measure would be of interest. ■

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