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ORIGINAL PAPER

Procedure for single-stage implant retention for chronic periprosthetic infection using topical degradable calcium-based antibiotics

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Abstract

Introduction Surgical treatment using DAIR (debridement, systemic antibiotics, and implant retention) can lead to high rates of treatment success in cases of early periprosthetic joint infection (PJI) but can fail in late-onset cases. Supplementary local antibiotic therapy is not yet generally established and lacks evidence-based proof of efficacy. The *aim* of this study was to analyze DAIR outcomes in recurrent PJI cases and patients who are not suitable for a two-stage exchange, using additional degradable calcium-based antibiotics.

Methods All patients fulfilled the Infectious Diseases Society of America (IDSA) guidelines for chronic late-onset PJI but were not suitable for a multistage procedure because of their individual operation risk. A total of 42 patients (mean age, 73 years) were treated using a single-stage algorithm consisting of DAIR, followed by implantation of degradable antibiotics chosen in accordance with an antibiogram. OSTEOSET® (admixed ceftriaxone/vancomycin/tobramycin) and Herafill-Gentamycin® were used as carrier systems. The follow-up period was 23 months (± SD, 10.3). The study is based on institutional review board (IRB) approval.

Results The clinical entities were chronic PJI of the hip (45.2%), knee (28.6%), and knee arthrodesis (26.2%). The bacterial spectrum was composed of *Staphylococcus epidermidis* (29%), *Staphylococcus aureus* (21%), and *Enterococcus faecalis* (21%). 21.4% showed a combination of two or more bacteria. In 73.8%, permanent remission was achieved, while 11.9% showed chronic PJI under implant retention. Implant retention could be achieved in 85.7%.

Conclusion DAIR usually shows low levels of success in difficult-to-treat cases. However, we could demonstrate the successful treatment of patients with recurrent PJI (typically considered DAIR-inappropriate) using degradable antibiogram-based topical calcium-based antibiotics. Over 70% of the cases went to remission and over 85% of the implants could be retained.

Keywords Herafill · OSTEOSET · PJI · Periprosthetic infection · DAIR · Implant retention

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Introduction

The number of endoprosthetic procedures is increasing annually and concomitantly; the number of revision surgeries is on the rise [1–3]. The incidence of periprosthetic joint infection (PJI) following THA procedures increased from 1.99 to 2.18%, and following total knee arthroplasty procedures, PJI increased from 2.05 to 2.18%, in the period from 2001 to 2009 in the USA [4].

To date, there is no international gold standard for the treatment of PJI. The outcome of two-stage revision surgery for implant replacement versus single-stage procedures is being investigated [5–8]. In addition, no definitive guidelines are provided for the different procedures [8, 9]. While the two-stage exchange is considered the most appropriate for chronic difficult-to-treat cases, the single-stage exchange has to fit the hard criteria [10]. A two-stage procedure with long prosthesis-

free intervals is a burden on both the resources of the medical facility and the patient. In most cases average costs are among 100.000USD per patient and treatment. By 2020, an increase in the annual cost of treatment to $1.6 billion is expected in the USA [11]. Complex interdisciplinary treatment strategies with modular implants and treatment-resistant pathogens represent not only a professional but also a financial challenge. Therapy regimens with one- or two-stage implant replacements are on average approximately 3.4–6 times more cost-intensive than the primary implantation itself [11–14]. In the background of limited resources, an approach with shorter intervals and/or single-stage procedures could be considered.

The DAIR procedure (debridement, antibiotics, and implant retention) represents a possibility for early-onset PJI [15, 16].

In addition, mortality increases with increasing numbers of revisions, which can be a problem for multimorbid and elderly patients [17]. Mortality rates for a two-stage revision in elderly patients over 80 years old were shown to be 36.7% [17].

For this reason, strategies are needed to treat periprosthetic infections in multimorbid and elderly people as effective as possible, using a minimal number of operations. In fact, if the patient fulfills the criteria of the Infectious Diseases Society of America (IDSA) guidelines concerning a one-stage septic exchange of the prosthesis, a good outcome can be achieved regarding this single-stage exchange procedure [18–20] whereas treatment concepts for patients who are not suitable for a prosthesis change because of their individual constitution and multimorbidity are lacking. To date, no viable treatment concepts have been developed for implant retention if exchange is not reasonable (multimorbidity, lack of bone stock, lack of consent for exchange). Prompt surgical treatment using DAIR, following strict diagnostic and therapeutic criteria, in patients with suspected PJI, can lead to high rates of success in eradicating the infection [16] but is not as effective in difficult-to-treat cases [21].

Ultimately, an improved DAIR concept for chronic and multimorbid cases is lacking.

Local antibiotic therapy

The DAIR procedure is an evidence-based strategy involving debridement, irrigation, changing of mobile parts like inserts, cups or ball heads, and systemic antibiotic therapy [15, 22, 23]. In addition to surgical debridement and systemic antibiotic treatment, the therapy is supplemented by local antibiotics, mostly guided by the personal experience of the surgeon, with no available formal evidence for efficacy [24, 25]. The local circulation deficit in infections prevents higher antibiotic concentrations at the focus of the infection when using only systemic antibiotics [26]. Used since the 1970s [27, 28], polymethyl methacrylate (PMMA) is today the most widely used carrier system for local antibiotics [29, 30]. However, there are some disadvantages that limit the use of PMMA: First is the need for its surgical removal in a subsequent procedure. Used in bone defects, the non-resorbable PMMA prevents the desired bone from osteointegration [31]. Despite the initial antibiotic potency, the surface of the cement acts as an adhesive for bacteria and can itself lead to bacterial colonization, as well as the development of bacterial resistance and biofilm formation [32, 33]. Furthermore, its unfavourable release and incomplete elution limit a regular deployment [34, 35]. Depending on the used antibiotic, PMMA spheres have release rates between 25 and 50% [36, 37]. In addition to the active substance, the size of the surface participating in the diffusion is decisive. Therefore, the rate of release when used as bone cement decreases to 6–12% [37]. Consequently, degradable antibiotic carriers are increasingly attracting attention [38–40]. Because of their biological properties, removal in a secondary surgery is no longer required and the active ingredient can be completely released. Tobramycin-impregnated calcium sulfate can lead to high local antibiotic concentrations in the therapeutic range up to 28 days after implantation. In vitro studies of the elution characteristics of calcium sulfate showed a peak of release immediately after implantation. From three days, a constant release of active substance in the therapeutic range could be achieved until 22 days [39].

Aim

The aim of the current study is to show the success rate of the DAIR procedure combined with topical calcium-based degradable antibiotics in elderly, multimorbid patients suffering from chronic late-onset PJI, who are not suitable for exchange arthroplasty.

Material and methods

Patient characteristics

Patients with chronic recurrent periprosthetic infection of the hip or knee joint were included. None of the patients fulfilled the criteria for a single-step exchange according to the IDSA guidelines [20]. All patients fulfilled the criteria of a late-onset chronic infection. Patients with early infections, or the possibility of a one -or two-stage replacement, were not included. All patients presented with an ASA 3 or ASA 4 classification and a high operation risk, due to their coexisting disease. None of the patients qualified for a multiple-stage procedure because of their individual operation risk or predictably untreatable lack of bone stock after prosthesis removal. All patients had previously undergone septic revisions or already had septic prosthesis exchange and suffered recurrent PJI.

Over 25% of the patients already had a knee arthrodesis because of recurrent infection. All infected arthrodesis existed of a modular knee arthrodesis system including a tibial and a femoral stem as well as a connecting module (KAM, Brehm, Germany [41]). All patients of the arthrodesis group had at least one infected knee prosthesis before. The study is based on institutional review board (IRB) approval.

Diagnostics

PJI was diagnosed in all patients according to the IDSA guidelines [20]. Effective antibiotic therapy requires reliable bacterial detection; we guaranteed this by taking three to five tissue samples during the surgery and in advance using a sterile joint puncture.

Local degradable antibiotics and surgical procedure

A single-stage procedure included arthrotomy, radical debridement, irrigation, the exchange of mobile parts like inserts, cups, or ball heads (DAIR procedure), and application of local degradable antibiotics matched in accordance with an antibiogram. A systemic antibiotic treatment was carried out in accordance with an antibiogram for the duration of surgical treatment and for six weeks [42] after intervention (Table 1). Rifampicin was used if the bacteria were gram-positive and in the absence of contraindications. The operation started using the existing approach with excision of the old scar and possible fistula passages. This was followed by a renewed radical debridement of the soft tissue and a sequestrectomy of the bones, as well as the exchange of mobile parts. For microbiological and histological diagnostics, three to five tissue samples were taken and degradable antibiotics were applied. A secure closure of the fascia and skin was ensured, in order to achieve the highest possible concentration of active ingredients. The selection of the active antibiotic substance depended on the sensitivity of the exciter or pathogen. If the bacteria were susceptible to tobramycin or gentamycin, OSTEOSET-T® (Wright Medical Technology Inc., Arlington, TN, USA) or Herafill-G40® (Heraeus Medical GmbH, Wehrheim, Germany) was applied. In the case of vancomycin-, ceftriaxone-, or colistin-sensitivity, OSTEOSET® was self-made and mixed with the suitable antibiotic. The current study was restricted to active substances with already well-characterized pharmacokinetics with OSTEOSET® as a carrier material [43, 44]. We previously showed sufficient and safe release from these preparations [45, 46]. The antibiotic in powder form is first dissolved in the fluid contained in the OSTEOSET® kit. Subsequently, OSTEOSET® is admixed and after 60 seconds of rest time, stirred into a paste. This is spread into the silicone molds and is cured. The curing duration depends on the active substance and ranges from 20 to 60 minutes. The antibiotic-impregnated calcium sulfate beads can then be pressed out of the mold and are implanted. Figure 1 shows the application of the mixed antibiotics. The local antibiotics are intended to provide a continuous release of the active substance over a period of four to six weeks, at a sufficient dosage. The calcium sulfate carrier, in the form of hemihydrate $Ca[SO_4]\cdot½H_2O$, shows these pharmacological benefits and demonstrates encouraging results as a resorbable carrier material for antibiotics [43, 44, 47]. As a possible side effect, recent studies describe a possible increase in serum calcium in renal insufficiency [48].

Table 1 Systemic antibiotic administration

	n	%
Ampicillin + Sulbactam	11	26.2
Clindamycin	10	23.8
Doxycyclin	5	11.9
Levofloxacin	3	7.1
Meropenem	3	7.1
Ciprofloxacin	2	4.8
Vancomycin	2	4.8
Fosfomycin	2	4.8
Amoxicillin	2	4.8
Tigacyclin	1	2.4
Piperacillin + Tazobactam	1	2.4
All	42	100
Combination of two antibiotics		
Clindamycin	1	2
Rifampicin	13	31
All	14	33

Characteristics of the local degradable antibiotics in detail

Tobramycin combined with calcium sulfate is offered under the product name OSTEOSET-T® (Wright Medical Technology Inc., Arlington, TN, USA). It contains medical grade calcium sulfate, 4% tobramycin sulfate, and stearic acid as a tableting aid in pellet form. The resorption time of the calcium sulfate is about 30 to 60 days as indexed by the manufacturer. Additionally, there is a calcium sulfate paste as a free-mix kit (OSTEOSET®) for use with alternative water-soluble antibiotics. The third carrier system used in this study consists, apart from calcium sulfate dihydrate, of calcium carbonate, hydrogenated triglyceride, and 1% gentamycin sulfate (Herafill®, Heraeus Medical GmbH, Wehrheim, Germany). The resorption time of the calcium carbonate is indexed as a few months.

OSTEOSET-T® It consists of calcium sulfate hemihydrate and is impregnated with 4% tobramycin. The beads are offered in 10- and 20-g packs containing 400 mg and 800 mg

tobramycin /tobramycin sulfate, corresponding to 262 and 524 tobramycin (salt factor tobramycin/tobramycin sulfate, 0.655) [49].

OSTEOSET-bead kit It contains at least 98% medical grade calcium sulfate dihydrate, as well as dolomite (0.5%), calcium carbonate (0.3%), and mineral aggregates [50–52]. Commercially available packs contain 25 mL of powder and 8 mL of solvent, which are supplied with two silicone molds for curing. The latter consist of two halves each having 30 hemispherical recesses with a diameter of 7 mm. With this product, antibiotics can be added after the antibiogram itself. Figure 1 shows the application. We used vancomycin (4000 mg per bead kit) or ceftriaxone (2000 mg per bead kit). It is also possible to use other antibiotics [45, 53].

Herafill® G40 The beads consist of calcium sulfate dihydrate, calcium carbonate, hydrogenated triglyceride, and gentamycin sulfate. They each weigh 250 mg and contain 1% (equivalent to 2.5 mg) gentamycin (as gentamycin sulfate). They are offered in sizes of 20 and 40 units, and the pack corresponds to a volume of 5 or 10 mL [54].

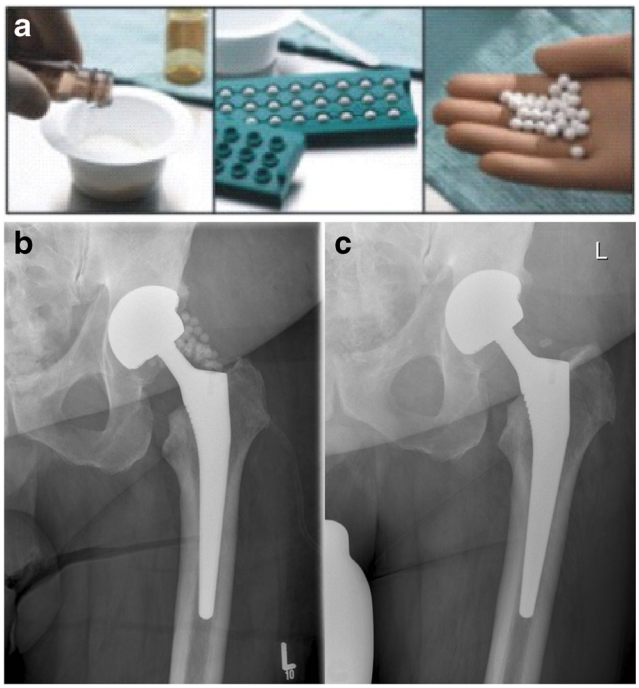

Fig. 1 **a** Application of OSTEOSET-bead kit. Amount of antibiotic per 30 beads: vancomycin 4000 mg or ceftriaxone 2000 mg. Other antibiotic beads were used prefabricated (OSTEOSET-Tobramycin, Herafill-Gentamycin). **b** Surgical single-stage application of beads in periprosthetic joint infection of total hip arthroplasty during DAIR (debridement, systemic antibiotics, and implant retention) procedure. **c** X-ray after 1-year follow-up shows degradation of the beads under implant retention

Systemic antibiotic therapy

A calculated systemic antibiotic therapy was initiated after taking the microbiological samples intra-operatively during the first intervention. The calculated systemic therapy was performed using a broad range of antibiotics which provide good penetration of the soft tissue. The antibiotics were changed 3 days after the procedure in accordance with the results of the actual antibiogram (Table 1). Antibiotics were selected according to the principles of antibiotic stewardship, taking into account sensitivity and tolerability. Since there is no evidence for the superiority of quinolones in PJI, because of their significant side effects and the resulting bacterial resistance, they were only used if no alternative products were available. Six weeks of pathogen-specific highly bioavailable oral antimicrobial therapy was carried out after an initial intravenous therapy. Clinical and laboratory monitoring for efficacy and toxicity was performed. Monitoring of outpatient antimicrobial therapy followed that of published guidelines [55].

Patients monitoring

Monitoring of the patients was carried out in accordance with published guidelines [20, 55]. Evaluation of the patient included a physical examination and examination of wound healing, current clinical symptoms, drug allergies and intolerances, comorbid conditions, prior and current microbiology results from aspirations and surgeries, and antimicrobial therapy for the PJI including local antimicrobial therapy. A test for C-reactive protein (CRP) as well as complete blood count and electrophoresis was performed. A plain radiograph was performed in all patients prior and after the surgery. Blood cultures for aerobic and anaerobic organisms as well as procalcitonin are obtained if fever was present.

Success rate

Success and remission were defined as the absence of clinical, radiological, and biological (i.e., inflammatory markers) signs of infection [20] after a minimum follow-up of 12 months after surgery (mean follow-up period was 23 months). In addition, the need for any surgical intervention after the described single-stage procedure was defined as failure.

Results

Between February 2014 and May 2016, 42 patients were treated using a degradable calcium-based antibiotic in addition to a DAIR procedure. 45.2% suffered a chronic PJI of the hip (n = 19), 28.6% of the knee (n = 12), and 26.2% of a knee arthrodesis (n = 11). The average age was 73 years (54–87 years).

Fifty percent of the patients were male ($n = 21$) and 50% were female ($n = 21$). The mean follow-up period was 23 months (± SD, 10.3), while the minimum follow-up was 12 months.

In 90% of cases, bacteria could be isolated ($n = 36$). The most common bacterium was *Staphylococcus epidermidis* (29%), followed by *Staphylococcus aureus* (21%) and *Enterococcus faecalis* (21%). In 21.4% of the cases, mixed infections with two types of bacteria were found and in one case, three types of bacteria. In fact, certain bacteria were only detected in combination with others (Fig. 2). Systemic antimicrobial therapy administration was performed in accordance with the antibiograms, most frequently using unacid or clindamycin and in one-third of cases using a combination therapy with rifampicin.

Every patient was treated as previously described and a local antibiotic was added. Treatment with vancomycin (45.2%, $n = 19$) and tobramycin (19%, $n = 8$, prefabricated OSTEOSET-T) was most frequently performed, followed by gentamycin (31%, $n = 13$, prefabricated Herafill-G) and ceftriaxone (4.8%, $n = 2$).

In 73.8% of the cases ($n = 31$), remission of the infection was achieved, whereas failure occurred in 26.2% ($n = 11$). These patients who failed treatment (26.2%) showed a reinfection, and either implant retention could be achieved after performing a second DAIR or antibiotic suppression therapy ($n = 5$, 11.9%) or an amputation had been carried out ($n = 6$, 14.2%). These amputations accounted for three amputations of the knee (7.1%) and three Girdlestone procedures of the hip (7.1%). Table 2 shows the overall treatment outcomes. No significant difference between the locally applied drugs was seen with regard to success rate. No side effects related to the use of the antibiotic beads were noted. In between the follow-ups, no one had died.

Discussion

Although local antibiotics and PMMA chains have been used in the treatment of musculoskeletal infections for more than 40 years, evidence for efficacy is lacking. There are several previous studies concerning their use in osteomyelitis. We were able to analyze the application of these local antibiotics for the first time in chronic recurrent osteomyelitis ($n = 93$), and a success rate of 84% was achieved in cases that were not successfully treated previously [45]. In a small case study, Humm et al. [56] reported treatment success in all patients

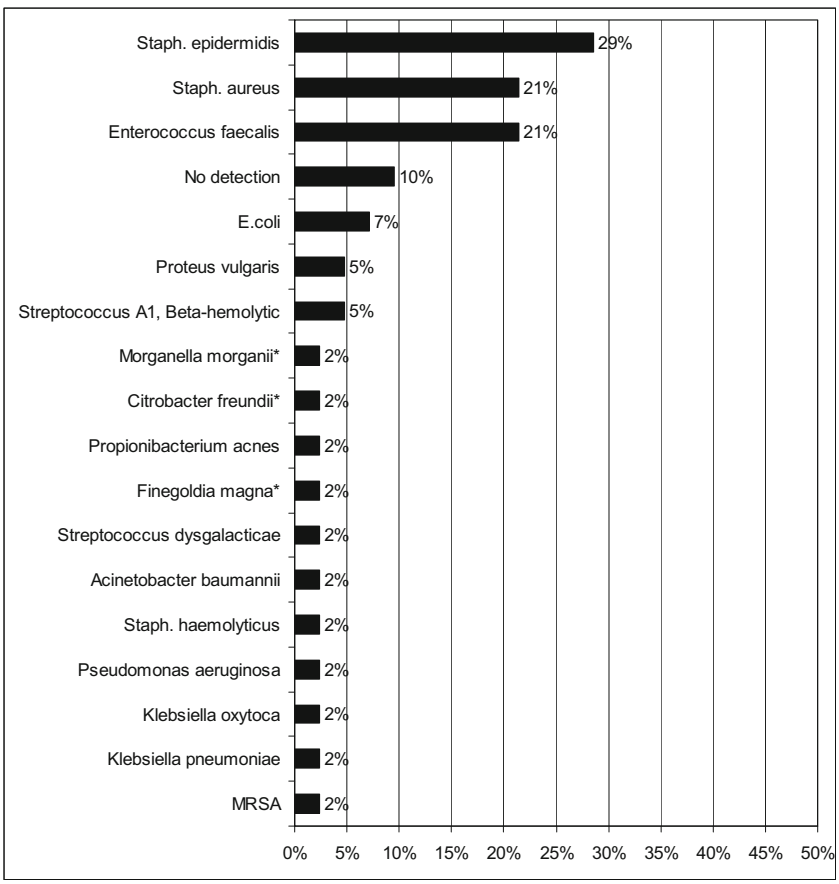

Fig. 2 Bacterial spectrum. Multiple nominations possible, as percentage of 42 cases. Asterisk indicates bacteria that only occurred in combination

Table 2 Treatment outcomes

			Chronic periprosthetic infection of			All
			Hip arthroplasty	Knee arthroplasty	Knee arthrodesis	
Result	Success	*n*	12	11	8	31
		%	63.2	91.7	72.7	73.8
	Chronic PJI	*n*	4	0	1	5
		%	21.1	0.0	9.1	11.9
	Amputation	*n*	0	1	2	3
		%	0.0	8.3	18.2	7.1
	Girdlestone	*n*	3	0	0	3
		%	15.8	0.0	0.0	7.1
All		*n*	19	12	11	42
		%	45.2	28.6	26.2	100

using OSTEOSET-T® in post-traumatic osteomyelitis cases. Ferguson et al. [38] reported a success rate of 90.8% using the same product in a series of 195 cases. Chang et al. [40] compared debridement with or without local antibiotic therapy retrospectively. Simple debridement in this study resulted in a success rate of 60%, whereas in conjunction with OSTEOSET-T®, 80% of the cases went to remission. Because of the small number of cases ($n = 65$), a statistically significant effect was not achieved. Reliable assessments on the use of local antibiotics in PJI, as well as in recurrent cases, even with degradable carriers, are not available so far. To the best of our knowledge, this is the first study which shows the use of calcium-based topical degradable antibiotics in an implant retention procedure for chronic PJI. Sufficient data pertaining to the DAIR procedure are rarely available, particularly concerning indication-appropriate application in the early infection and without antibiogram-appropriate application of local resorbable antibiotic beads. When applied during late chronic infection, the success rate of the DAIR procedure is 28–62% [57]. De Vries et al. found that patients with acute infections showed a better survival compared with those suffering late infections (84.0% vs. 46.6%) [58]. Lora-Tamayo et al. [21] conducted the biggest case study of the DAIR procedure, with 462 cases. They showed the largest series of streptococcal PJI cases managed through DAIR, and the patients showed a worse prognosis than previously reported. Outcomes were evaluable in 444 patients: failure occurred in 187 (42.1%) [40]. Prompt surgical treatment with DAIR, following strict diagnostic and therapeutic criteria, in patients with suspected PJI, can lead to high rates of success in eradicating the infection [16] but is less effective in difficult-to-treat cases [21]. In contrast, high success rates of over 70% could be detected in difficult-to-treat patients in the presented study, using calcium-based degradable antibiotic beads. Mortality rates for a two-stage revision in elderly patients over 80 years old have been shown to be 36.7% [15], whereas in the current study, no mortality was reported over the follow-up period. Tsang et al. currently advised that DAIR procedure should be only considered for an acutely infected arthroplasty when presenting within seven days of the onset of symptoms [59]. However, if the patient is suffering from late-onset PJI and is not suitable for a multistage procedure, because of his individual operation risk, our data shows that degradable, local antibiotics may offer advantages and a reasonable addition for DAIR procedure.

Limitations

Our study has several limitations. The number of cases is limited because of the strict inclusion criteria. The current study has no control group, and a prospective randomized trial showing results that contrast with those from DAIR procedure and without local degradable antibiotics would be valuable. A long-term follow-up could identify late-onset recurrences. We did not monitor local antibiotic release in the current study but have shown sufficient release previously [46].

Conclusion

In summary, degradable, local antibiotics based on calcium sulfate could offer advantages and can be a reasonable addition to already established systems in the treatment of PJI. Over 70% of the cases went to remission and over 85% of the implants could be retained. The pharmacokinetics and dynamics of the carriers, as well as the potential for antibiogram-dependent applications, seem to be significant advantages and appear to contribute to these good results.

Compliance with ethical standards

The study is based on institutional review board (IRB) approval.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dieter C, Wirtz CR, Reichel H, (HRSG.) (eds) (2008) Revisionsendoprothetik der Hüftpfanne, vol 1. Heiko Reichel, Heidelberg
2. Sporer SM, Paprosky WG (2006) The use of a trabecular metal acetabular component and trabecular metal augment for severe acetabular defects. J Arthroplast 21(6 Suppl 2):83–86. https://doi.org/10.1016/j.arth.2006.05.008
3. Yu R, Hofstaetter JG, Sullivan T, Costi K, Howie DW, Solomon LB (2013) Validity and reliability of the Paprosky acetabular defect classification. Clin Orthop Relat Res 471(7):2259–2265. https://doi.org/10.1007/s11999-013-2844-7
4. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J (2012) Economic burden of periprosthetic joint infection in the United States. J Arthroplast 27(8 Suppl):61–65
5. Roger PM, Tabutin J, Blanc V, Leotard S, Brofferio P, Lecule F, Redreau B, Bernard E, Reso Infectio Paca E (2015) Prosthetic joint infection: a pluridisciplinary multi-center audit bridging quality of care and outcome. Med Mal Infect 45(6):229–236. https://doi.org/10.1016/j.medmal.2015.04.003
6. Muhlhofer HM, Schauwecker J, Banke IJ, von Eisenhart-Rothe R (2015) Septic endoprosthesis exchange: preoperative diagnosis and reimplantation. Orthopade 44(12):946–951
7. Maillet M, Pavese P, Bruley D, Seigneurin A, Francois P (2015) Is prosthesis retention effective for chronic infections in hip arthroplasties? A systematic literature review. Eur J Clin Microbiol Infect Dis 34(8):1495–1502. https://doi.org/10.1007/s10096-015-2388-8
8. Yoon YC, Lakhotia D, Oh JK, Moon JG, Prashant K, Shon WY (2015) Is two-stage reimplantation effective for virulent pathogenic infection in a periprosthetic hip? A retrospective analysis. World J Orthop 6(9):712–718. https://doi.org/10.5312/wjo.v6.i9.712
9. Kunutsor SK, Whitehouse MR, Lenguerrand E, Blom AW, Beswick AD, Team I (2016) Re-infection outcomes following one- and two-stage surgical revision of infected knee prosthesis: a systematic review and meta-analysis. PLoS One 11(3):e0151537
10. Wongworawat MD (2013) Clinical faceoff: one- versus two-stage exchange arthroplasty for prosthetic joint infections. Clin Orthop Relat Res 471(6):1750–1753. https://doi.org/10.1007/s11999-013-2882-1
11. Kapadia BH, Banerjee S, Cherian JJ, Bozic KJ, Mont MA (2016) The economic impact of periprosthetic infections after total hip arthroplasty at a specialized tertiary-care center. J Arthroplast. https://doi.org/10.1016/j.arth.2016.01.021
12. Kamath AF, Ong KL, Lau E, Chan V, Vail TP, Rubash HE, Berry DJ, Bozic KJ (2015) Quantifying the burden of revision total joint arthroplasty for periprosthetic infection. J Arthroplast 30(9):1492–1497
13. Lamagni T (2014) Epidemiology and burden of prosthetic joint infections. J Antimicrob Chemother 69(1):5–10
14. Peel TN, Dowsey MM, Buising KL, Liew D, Choong PF (2013) Cost analysis of debridement and retention for management of prosthetic joint infection. Clin Microbiol Infect 19(2):181–186
15. Qasim SN, Swann A, Ashford R (2017) The DAIR (debridement, antibiotics and implant retention) procedure for infected total knee replacement–a literature review. SICOT-J 3
16. Sendi P, Lotscher PO, Kessler B, Graber P, Zimmerli W, Clauss M (2017) Debridement and implant retention in the management of hip periprosthetic joint infection: outcomes following guided and rapid treatment at a single centre. Bone Joint J 99(3):330–336
17. Webb JE, Schleck CD, Larson DR, Lewallen DG, Trousdale RT (2014) Mortality of elderly patients after two-stage reimplantation for total joint infection: a case-control study. J Arthroplast 29(11):2206–2210
18. Leite PS, Figueiredo S, Sousa R (2016) Prosthetic joint infection: report on the one versus two-stage exchange EBJIS survey. J Bone Joint Infect 1:1–6
19. Nagra NS, Hamilton TW, Ganatra S, Murray DW, Pandit H (2016) One-stage versus two-stage exchange arthroplasty for infected total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc 24(10):3106–3114
20. Osmon D, Berbari E, Berendt A, Lew D, Zimmerli W, Steckelberg J, Rao N, Hanssen A, Wilson W, Infectious Diseases Society of A (2013) Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 56(1):e1–e25
21. Lora-Tamayo J, Senneville E, Ribera A, Bernard L, Dupon M, Zeller V, Li HK, Arvieux C, Clauss M, Uckay I, Vigante D, Ferry T, Iribarren JA, Peel TN, Sendi P, Miksic NG, Rodriguez-Pardo D, Del Toro MD, Fernandez-Sampedro M, Dapunt U, Huotari K, Davis JS, Palomino J, Neut D, Clark BM, Gottlieb T, Trebse R, Soriano A, Bahamonde A, Guio L, Rico A, Salles MJC, Pais MJG, Benito N, Riera M, Gomez L, Aboltins CA, Esteban J, Horcajada JP, O'Connell K, Ferrari M, Skaliczki G, Juan RS, Cobo J, Sanchez-Somolinos M, Ramos A, Giannitsioti E, Jover-Saenz A, Baraia-Etxaburu JM, Barbero JM, Choong PFM, Asseray N, Ansart S, Moal GL, Zimmerli W, Ariza J (2017) The not-so-good prognosis of streptococcal periprosthetic joint infection managed by implant retention: the results of a large multicenter study. Clin Infect Dis 64(12):1742–1752
22. Tschudin-Sutter S, Frei R, Dangel M, Jakob M, Balmelli C, Schaefer DJ, Weisser M, Elzi L, Battegay M, Widmer AF (2016) Validation of a treatment algorithm for orthopaedic implant-related infections with device-retention-results from a prospective observational cohort study. Clin Microbiol Infect 22(5):20
23. Kuiper JW, Willink RT, Moojen DJ, van den Bekerom MP, Colen S (2014) Treatment of acute periprosthetic infections with prosthesis retention: review of current concepts. World J Orthop 5(5):667–676
24. Wang J, Calhoun JH, Mader JT (2002) The application of bioimplants in the management of chronic osteomyelitis. Orthopedics 25(11):1247–1252
25. Mader JT, Calhoun J, Cobos J (1997) In vitro evaluation of antibiotic diffusion from antibiotic-impregnated biodegradable beads and polymethylmethacrylate beads. Antimicrob Agents Chemother 41(2):415–418
26. Armstrong DG, Findlow AH, Oyibo SO, Boulton AJ (2001) The use of absorbable antibiotic-impregnated calcium sulphate pellets in the management of diabetic foot infections. Diabet Med 18(11):942–943
27. Klemm K (1979) Gentamicin-PMMA-beads in treating bone and soft tissue infections (author's transl). Zentralbl Chir 104(14):934–942
28. Klemm K, Borner M (1986) Treatment of chronic osteomyelitis with gentamicin PMMA chains. Unfallchirurgie 12(3):128–131
29. Adams K, Couch L, Cierny G, Calhoun J, Mader JT (1992) In vitro and in vivo evaluation of antibiotic diffusion from antibiotic-impregnated polymethylmethacrylate beads. Clin Orthop Relat Res 278:244–252

30. Blaha JD, Calhoun JH, Nelson CL, Henry SL, Seligson D, Esterhai JL Jr, Heppenstall RB, Mader J, Evans RP, Wilkins J et al (1993) Comparison of the clinical efficacy and tolerance of gentamicin PMMA beads on surgical wire versus combined and systemic therapy for osteomyelitis. Clin Orthop Relat Res 295:8–12
31. Walenkamp GH, Kleijn LL, de Leeuw M (1998) Osteomyelitis treated with gentamicin-PMMA beads: 100 patients followed for 1-12 years. Acta Orthop Scand 69(5):518–522
32. Neut D, van de Belt H, Stokroos I, van Horn JR, van der Mei HC, Busscher HJ (2001) Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopaedic revision surgery. J Antimicrob Chemother 47(6):885–891
33. Heybeli N, Oktar FN, Ozyazgan S, Akkan G, Ozsoy S (2003) Low-cost antibiotic loaded systems for developing countries. Technol Health Care 11(3):207–216
34. Kelm J, Anagnostakos K, Regitz T, Schmitt E, Schneider G, Ahlhelm F (2004) MRSA-infections-treatment with intraoperatively produced gentamycin-vancomycin PMMA beads. Chirurg 75(10):988–995. https://doi.org/10.1007/s00104-004-0847-3
35. Nelson CL, Griffin FM, Harrison BH, Cooper RE (1992) In vitro elution characteristics of commercially and noncommercially prepared antibiotic PMMA beads. Clin Orthop Relat Res 284:303–309
36. Walenkamp GH, Vree TB, van Rens TJ (1986) Gentamicin-PMMA beads. Pharmacokinetic and nephrotoxicological study. Clin Orthop Relat Res 205:171–183
37. DiCicco M, Duong T, Chu A, Jansen SA (2003) Tobramycin and gentamycin elution analysis between two in situ polymerizable orthopedic composites. J Biomed Mater Res B Appl Biomater 65(1): 137–149. https://doi.org/10.1002/jbm.b.10528
38. Ferguson JY, Dudareva M, Riley ND, Stubbs D, Atkins BL, McNally MA (2014) The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases. Bone Joint J 96-B(6): 829–836. https://doi.org/10.1302/0301-620X.96B6.32756
39. Turner TM, Urban RM, Hall DJ, Chye PC, Segreti J, Gitelis S (2005) Local and systemic levels of tobramycin delivered from calcium sulfate bone graft substitute pellets. Clin Orthop Relat Res 437:97–104
40. Chang W, Colangeli M, Colangeli S, Di Bella C, Gozzi E, Donati D (2007) Adult osteomyelitis: debridement versus debridement plus Osteoset T pellets. Acta Orthop Belg 73(2):238–243
41. Brehm P (2018) KAM TITAN arthrodesis. Brehm Germany. http://www.peter-brehm.de/en/produkte/knie/kam-titan/. Accessed 12.01.2018
42. Chaussade H, Uckay I, Vuagnat A, Druon J, Gras G, Rosset P, Lipsky BA, Bernard L (2017) Antibiotic therapy duration for prosthetic joint infections treated by debridement and implant retention (DAIR): similar long-term remission for 6 weeks as compared to 12 weeks. Int J Infect Dis 63:37–42
43. Mousset B, Benoit M, Delloye C, Bouillet R, Guillard J (1997) Biodegradable implants for potential use in bone infection. Int Orthop 21:403–408
44. Waterman P, Melissa Barber M, Weintrob AC, Regina VanBrakle M, Howard R, Kozar MP, Andersen R, Wortmann G (2012) The elution of colistimethate sodium from polymethylmethacrylate and calcium phosphate cement beads. Am J Orthop (Belle Mead, NJ) 41(6):256–259
45. Gramlich Y, Walter G, Gils J, Hoffmann R (2017) Early results of adjuvant topical treatment of recurrent osteomyelitis with absorbable antibiotic carriers. Z Orthop Unfall 12(10):0042–112228
46. Fleiter N, Walter G, Bosebeck H, Vogt S, Buchner H, Hirschberger W, Hoffmann R (2014) Clinical use and safety of a novel gentamicin-releasing resorbable bone graft substitute in the treatment of osteomyelitis/osteitis. Bone Joint Res 3(7):223–229
47. Kallala R, Haddad FS (2015) Hypercalcaemia following the use of antibiotic-eluting absorbable calcium sulphate beads in revision arthroplasty for infection. Bone Joint J 97-B(9):1237–1241. https://doi.org/10.1302/0301-620X.97B9.34532
48. Wahl P, Livio F, Jacobi M, Gautier E, Buclin T (2011) Systemic exposure to tobramycin after local antibiotic treatment with calcium sulphate as carrier material. Arch Orthop Trauma Surg 131(5):657–662. https://doi.org/10.1007/s00402-010-1192-2
49. Wright_Medical (Zugang am 28.12.2015) Osteoset® T medicated bone graft substitute technical monograph. Wright Medical Technology, Inc. http://www.ossano.com/Produkter/Bensubstitut/Osteoset/Osteoset.html
50. Gauland C (2011) Managing lower-extremity osteomyelitis locally with surgical debridement and synthetic calcium sulfate antibiotic tablets. Adv Skin Wound Care 24(11):515–523. https://doi.org/10.1097/01.ASW.0000407647.12832.6c
51. Marczak D, Synder M, Sibiński M, Okoń T, Kowalczewski J (2016) The use of calcium carbonate beads containing gentamicin in the second stage septic revision of total knee arthroplasty reduces reinfection rate. Knee 23(2):322–326. https://doi.org/10.1016/j.knee.2015.12.001
52. Tsourvakas S (2012) Local antibiotic therapy in the treatment of bone and soft tissue infections. In: Selected Topics in Plastic Reconstructive Surgery. InTec
53. Strauss A (1999) Lokaler Antibiotikumtraeger aus Kalziumsulfat: Vertraeglichkeit im Gewebe und Pharmakokinetik der angewendeten Antibiotika nach Implantation in Kaninchen. Köhler
54. Hereaus Medical GmbH Werheim Germany (2016) Technical Monograph Herafill. Hereaus Medical Germany. http://heraeus-medical.com/de/produkte_1/knochenersatz/herafill_1.aspx. Accessed 2016
55. Tice AD, Rehm SJ, Dalovisio JR, Bradley JS, Martinelli LP, Graham DR, Gainer RB, Kunkel MJ, Yancey RW, Williams DN (2004) Practice guidelines for outpatient parenteral antimicrobial therapy. Clin Infect Dis 38(12):1651–1671
56. Humm G, Noor S, Bridgeman P, David M, Bose D (2014) Adjuvant treatment of chronic osteomyelitis of the tibia following exogenous trauma using OSTEOSET((R))-T: a review of 21 patients in a regional trauma centre. Strateg Trauma Limb Reconstr 9(3):157–161. https://doi.org/10.1007/s11751-014-0206-y
57. Di Benedetto P, Di Benedetto ED, Salviato D, Beltrame A, Gissoni R, Cainero V, Causero A (2017) Acute periprosthetic knee infection: is there still a role for DAIR? Acta Biomed 88(2 -S):84–91
58. de Vries L, van der Weegen W, Neve WC, Das H, Ridwan BU, Steens J (2016) The effectiveness of debridement, antibiotics and irrigation for periprosthetic joint infections after primary hip and knee arthroplasty. A 15 years retrospective study in two community hospitals in the Netherlands. J Bone Joint Infect 1:20–24
59. Tsang SJ, Ting J, Simpson A, Gaston P (2017) Outcomes following debridement, antibiotics and implant retention in the management of periprosthetic infections of the hip: a review of cohort studies. Bone Joint J 99-B(11):1458–1466. https://doi.org/10.1302/0301-620X.99B11.BJJ-2017-0088.R1