Facing multidrug-resistant pathogens in periprosthetic joint infections with self-administered outpatient parenteral antimicrobial therapy—A prospective cohort study

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Abstract
A key factor in the successful management of periprosthetic joint infection (PJI) besides the surgical regime is a consistent antimicrobial therapy. Recently, oral versus intravenous (IV) antibiotics for bone and joint infection trial demonstrated the noninferiority of oral antimicrobial therapy compared to IV, implying that an early transition to oral administration is reasonable. It is likely that the international consensus meeting of musculoskeletal Infections and the European Bone and Joint Infection Society will consider these findings. However, rising levels of antimicrobial resistance are challenging and recommendations for dealing with multidrug-resistant (MDR) pathogens resistant to oral antibiotics are lacking. This study focuses on establishing guidance towards their management in PJI. From December 2015 to June 2019, patients with MDR pathogens were included in a single-center prospective cohort study and treated with self-administered outpatient parenteral antimicrobial therapy (S-OPAT) based on a two-stage revision strategy. Demographics, pathogens, antimicrobial agents, and outcomes were recorded. A total of 1738 outpatient days in 26 patients were analyzed. The incidence of pathogens resistant to oral antibiotics in PJI was 4%, most frequently encountered were staphylococcus epidermidis. The Kaplan–Meier-estimated infection-free survival after 3 years was 90% (95% confidence interval, 84.6%–95.5%). We recorded adverse events in 6 of 54 (11%) S-OPAT episodes (3.45/1000 S-OPAT days). (i) S-OPAT in two-stage revision arthroplasty to counter increasing numbers of MDR pathogens resistant to oral agents can achieve a high infection eradication rate and (ii) should therefore be taken into account at the next society’s consensus treatment updates.

KEYWORDS
DTT, MDR pathogen, OPAT, PJI, two-stage revision

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INTRODUCTION

Periprosthetic joint infection (PJI) is a major complication in total hip arthroplasty and total knee arthroplasty (THA/TKA). It occurs in 1%–2% of all primary arthroplasties and in around 4% of revision arthroplasties.1-4 Various management concepts coexist, but until now a gold standard has not been established. In addition, guidelines for dealing with multidrug-resistant (MDR) pathogens are lacking, leading to controversial discussions due to the increasing relevance of these pathogens.

While in North America the current definition and treatment of PJI mainly follows the recommendations of the International Consensus Meeting (ICM) and are based on the Musculoskeletal Infection Society criteria, the current guidelines of the American Academy of Orthopaedic Surgeons (AAOS), and the Infection Disease Society of America (IDSA), in Europe the criteria of the PRO-IMPLANT Foundation as well as the European Bone and Joint Infection Society (EBJIS) consensus, are widely adopted. All of the proposed strategies share the common belief that successful and permanent absence of infection can only be achieved through the combination of a consistent surgical strategy and susceptibility-guided and biofilm-active antimicrobial therapy.

Regardless of the procedure used, such as debridement, antibiotics, irrigation, and retention of the prosthesis, single-stage or multistage revision, patients with a normal postoperative course, declining inflammatory parameters, and dry wound conditions can be discharged to outpatient care after having been successfully switched from parenteral to oral antimicrobial therapy.5-7 Even though the optimal point for switching from parenteral to oral administration remains unknown, this approach is consistent with the 2019 oral versus intravenous (IV) antibiotics for bone and joint infection (OVIDA) randomized trial, which challenged the practice of prolonged IV therapy. The noninferiority of oral antimicrobial therapy was demonstrated, implying that an early transition to oral administration is a reasonable alternative to prolonged IV therapy.8

It is likely that the recently published results of the OVIVA trial will influence the upcoming guidelines of the different associations and societies, leading to a rethink of the role of oral antibiotic therapy. However, there may still be a mandatory indication for prolonged IV therapy in the case of MDR pathogens. More than a million THAs and TKAs are performed in the United States annually. It is estimated that the number will almost double by 2030.9 In addition, the incidence of revision hip and knee arthroplasty due to infections is projected to increase in the same time period.10 Both will lead to an enlarged absolute number of mixed infections or difficult-to-treat (DTT) pathogens showing multidrug resistance, which will take up a larger proportion in specialized departments for PJI. Susceptibility-guided optimized oral antimicrobial therapy can often not be achieved for these infecting organisms. This situation occurs if the oral bioavailability is not sufficient to ensure reliable infection eradication, even at the highest doses, if the suitable agents are only available as IV medications due to antimicrobial resistance, or if oral susceptibility-guided therapy comprises only antibiotic agents with solely bacteriostatic action (Table 1).

Since the optimal duration of IV antimicrobial treatment is unclear, prolonged IV therapy was preferred in the past (IDSA guideline) and has been a driver for outpatient parenteral antimicrobial therapy (OPAT) services. However, there is a lack of published studies investigating the use of OPAT in a homogeneous PJI population and to the best of our knowledge, no prospective study has been carried out in this setting. If PJI cases are considered in OPAT studies, they are generally counted among the group of bone and joint infections, which is a heterogeneous collection of cases and encompasses widely mixed infection types. In addition to PJI, spondylodiscitis, osteomyelitis and diabetic foot syndrome are frequently included, leading to different treatment concepts.11,12 For a more targeted investigation, a well-defined study design using a homogeneous PJI cohort is required.

Currently, there are no published guidelines for the treatment of MDR organisms that cannot be controlled by oral medications. This leads to prolonged hospitalization associated with higher costs or compromises are made when selecting the antibiotic agent, which, in turn, increases the risk of persistent infection and treatment failure. Administering OPAT represents a viable alternative and provide a positive economic benefit for the patient, the health insurance company, and the hospital. The available data do not allow any conclusions to be drawn regarding whether OPAT is useful in patients with MDR-PJI. The cure rate of MDR-PJI patients who underwent OPAT was never investigated in comparison to PJI cohorts in general. Therefore, the aims of this study were (i) to describe the outcome of treating MDR pathogens in PJI with OPAT in two-stage revision arthroplasty and (ii) to establish guidance towards the management of MDR-PJI resistant to oral antimicrobial therapy.

1.1 Outpatient parenteral antimicrobial therapy

The administration of OPAT was first introduced in the 1970s in the US and has been successfully implemented in numerous European countries, Asia, Australia, South America, and Canada.13-23 The success is based on two randomized trials comparing OPAT with inpatient care in the setting of skin and soft tissue infections (SSTIs).24,25 In both, patient satisfaction improved without significant differences for outcomes, duration time, or complications. In addition, there are several retrospective series that investigated its use for bone and joint infections,11,12,26,27 SSTI,28,29 and infective endocarditis.30-32

| TABLE 1 | OPAT for PJI |
|---|---|
| Criteria | |
| o Susceptibility-matched antimicrobial agents only available for IV administration | |
| o Inadequate oral bioavailability | |
| o Oral antibiotics with solely bacteriostatic activity | |

Abbreviations: IV, intravenous; OPAT, outpatient parenteral antimicrobial therapy; PJI, parenteral antimicrobial therapy.
1.2 | Intravascular access and service structure

We implemented a self-administered OPAT (S-OPAT) service structure. Recent studies verified the safety of this approach, including severe infections. It enables the use of antimicrobial agents that necessitate multiple daily dosing and is, therefore, ideal for the treatment of PJI. Thorough patient selection with profound education and continuous support are basic requirements.33–35

Four types of IV access devices are the most common for OPAT use: peripheral lines, midline catheters, peripherally inserted central catheters (PICCs), and short- or long-term central venous catheters (CVCs), including tunneled CVCs and subcutaneous ports.36,37

2 | METHODS

2.1 | Study design

Data for analysis were obtained from a prospective single-center cohort study, level of evidence II. All patients with PJI who received S-OPAT for treatment of MDR pathogens between December 2015 and June 2019 were included. The management of PJI followed a standardized comprehensive algorithm using a two-stage revision procedure with a duration of a prosthesis-free interval of 6 weeks.

Data analysis was performed using the Statistical Package for Social Sciences software (IBM Statistics Version 24). Descriptive statistical results (mean, median, standard deviation, range, and percent) were collected to describe the outcome, complications, and for comparison. The study protocol was reviewed and approved by the institutional ethics committee (18-6604 - BR). The study was approved by the German Clinical Trial Register (reference number DRKS00021135).

2.2 | Definitions

The inclusion criterion was the detection of a pathogen that could not be optimally treated with oral antibiotics according to the PRO-IMPLANT Foundation based on the management concept of Zimmerli et al.1 and adapted by Trampuz et al.1,6,38,39 Table 2 shows our standard antimicrobial treatment concept, modified after Izakovicova et al.40 The pathogens were reliably identified from multiple tissue samples taken intraoperatively.

When a patient is discharged to S-OPAT, it is classified as an S-OPAT episode. Two S-OPAT episodes per patient are typically expected in two-stage revision arthroplasty. Catheter-related complications (CRC) (Table 3) and adverse drug reactions (ADRs) are the two major adverse events that can occur and were recorded.

The definition for successfully treated PJI was based on the Delphi panel international multidisciplinary consensus.51 Therefore, treatment was considered as successful if all of the following criteria were fulfilled at the latest follow-up examination: (i) infection eradication, characterized by a healed wound without fistula persistens, drainage, or pain, and no infection recurrence caused by the same organism; (ii) no subsequent surgical intervention for persistent or perioperative infection after revision surgery; and (iii) no occurrence of PJI-related mortality.41 In addition, after the termination of OPAT, no oral antibiotics were continued.

2.3 | Diagnosis

A thorough physical examination with respect to the soft tissue condition was carried out and radiographs were made. Laboratory tests, including diagnostic arthrocentesis, were performed. In addition, histopathology and microbiological samples were analyzed. After removal, the prosthesis underwent sonication to increase the accuracy of the microbiologic diagnosis.42 PJI was diagnosed by applying the proposed EBJIS criteria (Table 4).43

2.4 | Treatment

After confirming the diagnosis, all implants, cement remnants, and foreign material were removed, as well as infected soft tissue and bone. Irrigation and debridement of all surrounding tissue layers were conducted. Cement spacers were used in temporary arthrodesis of the knee for stabilization, dead-space management, and local antimicrobial treatment, as part of a standardized two-stage revision concept.

Antimicrobial treatment was initiated intraoperatively after taking at least five tissue samples and synovial aspiration. All patients underwent standardized antimicrobial therapy that was based on the previously published concepts of Zimmerli et al.,1 the PRO-IMPLANT Foundation, and EBJIS.1,6,38,39 IV antimicrobial therapy was routinely continued for 2 weeks postoperatively. Upon the detection of MDR pathogens and proof that oral antimicrobial therapy would not be sufficient (Table 1), S-OPAT was initialized before discharge. A long prosthesis-free interval of ≥6 weeks due to the presence of MDR pathogens was used. All patients received antimicrobial therapy until reimplantation (i.e., without an antibiotic-free period and diagnostic aspiration). During reimplantation, one more thorough debridement procedure was performed, and multiple tissue samples were collected. After implantation of the prosthesis, a general IV treatment followed until patients showed a normal postoperative course, declining inflammatory parameters and dry wound conditions at which point they were discharged to S-OPAT, if possible with oral biofilm-active therapy. The total antimicrobial treatment duration was at least 12 weeks (Figure 1).

2.5 | Choice of catheter and placement

PICC and midline catheters were used in this study. PICC lines are inserted into the basilic or cephalic vein and terminate in the superior vena cava or upper portion of the right atrium. Subsequently, a native chest radiograph is obtained to verify the correct position of the
**TABLE 2**  Antimicrobial treatment (reproduced with permission from the pocket guide to diagnosis and treatment of PJI, PRO-IMPLANT Foundation)

### Empirical antimicrobial therapy

- Ampicillin/sulbactam 3 × 3 g IV or amoxicillin/clavulanic acid 3 × 1.2 g IV (+vancomycin 2 × 1 g IV in septic patients, known MRSA carriers, multiple previous surgeries, suspected low-grade infection)

#### Interval/suppressive therapy

| Microorganism                          | Antimicrobial agent* (check pathogen susceptibility before) |
|----------------------------------------|------------------------------------------------------------|
| Staphylococcus spp.                    | Cotrimoxazole, doxycyclin, clindamycin                   |
| Streptococcus spp.                     | Amoxicillin, clindamycin, levofloxacin                    |
| Enterococcus spp.                      | Amoxicillin (linezolid)                                   |
| Anaerobes (Gram-positive)              | Clindamycin, amoxicillin, doxycycline                     |
| Anaerobes (Gram-negative)              | Metronidazole, clindamycin                               |
| Gram-negative organisms                | Ciprofloxacin, cotrimoxazole                             |
| Fungi (Candida spp.)                   | Fluconazole                                               |

#### Targeted eradication therapy (de-escalate as soon as the pathogen is known)

| Microorganism                          | Antimicrobial agent* (check pathogen susceptibility before) | Dose* | Route |
|----------------------------------------|------------------------------------------------------------|-------|-------|
| Staphylococcus spp.                    | Fluoxacin*                                                 | 4 × 2 g | IV    |
| Oxacillin-/methicillin-susceptible      | (±Fosfomycin*) for 2 weeks, followed by (according to susceptibility) | (3 x 5 g) | IV    |
|                                        | Rifampin* +                                               | 2 × 450 mg | p.o.  |
|                                        | Levofloxacin or                                           | 2 × 500 mg | p.o.  |
|                                        | Cotrimoxazole or                                          | 3 × 960 mg | p.o.  |
|                                        | Doxycyclin or                                             | 2 × 100 mg | p.o.  |
|                                        | Fusidic acid                                              | 3 × 500 mg | p.o.  |
| Oxacillin-/methicillin-resistant        | Daptomycin or                                             | 1 × 8 mg/kg | IV    |
|                                        | Vancomycin*                                               | 2 × 1 g | IV    |
|                                        | (±Fosfomycin*)                                             | (3 x 5 g) | IV    |
|                                        | for 2 weeks, followed by an oral rifampin combination as above |       |       |
|                                        | Rifampin-resistant                                       | Intravenous treatment according susceptibility for 2 weeks, followed by long-term suppression for ≥ 1 year |     |       |
| Streptococcus spp.                     | Penicillin G* or                                          | 4 × 5 million U | IV    |
|                                        | Ceftriaxon                                                 | 1 × 2 g | IV    |
|                                        | for 2–3 weeks, followed by:                               |       |       |
|                                        | Amoxicillin or                                            | 3 × 1000 mg | p.o.  |
|                                        | Levofoxacin                                               | 2 × 500 mg | p.o.  |
|                                        | (consider suppression for ≥1 year)                       |       |       |

(Continues)
### TABLE 2 (Continued)

**Targeted eradication therapy (de-escalate as soon as the pathogen is known)**

| Microorganism | Antimicrobial agent | Dose | Route |
|---------------|---------------------|------|-------|
| **Enterococcus spp.** | | | |
| Penicillin-susceptible | Ampicillin + | 4 × 2 g | IV |
| | Gentamicin | 1 × 120 mg | IV |
| | (± Fosfomycin) for 2–3 weeks, followed by: | | |
| | Amoxicillin | 3 × 1000 mg | p.o. |
| Penicillin-resistant | Vancomycin | 2 × 1 g | IV |
| | Daptomycin + | 1 × 10 mg/kg | IV |
| | Gentamicin | 1 × 120 mg | IV |
| | (± Fosfomycin) | (3 × 5 g) | IV |
| | 2–4 weeks, followed by | | |
| | Linezolid (maximum 4 weeks) | 2 × 600 mg | p.o. |
| Vancomycin-resistant enterococci | Individual; removal of the implant or life-long suppression necessary | | |

| **Gram-negative** | | | |
| Enterobacteriaceae (Escherichia coli, Klebsiella, Enterobacter, etc.) | Ciprofloxacin | 2 × 750 mg | p.o. |
| Nonfermenters (Pseudomonas aeruginosa, Acinetobacter spp.) | Piperacillin/tazobactam or Meropenem or Ceftazidim + Tobramycin (or Gentamicin) for 2–3 weeks, followed by: | 3 × 4.5 g | IV |
| | | 3 × 1 g | IV |
| | | 3 × 2 g | IV |
| | | 1 × 300 mg | IV |
| Ciprofloxacin-resistant | Depending on susceptibility: meropenem 3 × 1 g, colistin 3 × 3 million U, and/or fosfomycin 3 × 5 g IV, followed by oral suppression. | | |

| **Anaerobes** | | | |
| Gram-positive (Cutibacterium, Peptostreptococcus, Finegoldia magna) | Penicillin G or Ceftriaxone for 2 weeks, followed by: Rifampin + Doxycycline or Amoxicillin | 4 × 5 million U | IV |
| | | 1 × 2 g | IV |
| | | 2 × 450 mg | p.o. |
| | | 2 × 100 mg | p.o. |
| | | 3 × 1000 mg | p.o. |
| Gram-negative (Bacteroides, Fusobacterium) | Ampicillin/sulbactam for 2 weeks, followed by Metronidazol | 3 × 3 g | IV |
| | | 3 × 400 or 500 mg | p.o. |
| Microorganism | Antimicrobial agent | Dose | Route |
|---------------|---------------------|------|-------|
| *Candida* spp. | Caspofungin or Anidulafungin for 1–2 weeks, followed by: Fluconazole (suppression for ≥1 year) | 1 × 70 mg | IV |
| Fluconazole-susceptible | | 1 × 100 mg (first day: 200 mg) | IV |
| | | 1 × 400 mg | p.o. |
| Fluconazole-resistant | Individual (e.g., with voriconazole 2 × 200 mg p.o.); removal of the implant or long-term suppression | | |

**Culture-negative**
- Ampicillin/subactamc for 2 weeks, followed by:
  - Rifampine
  - Levofloxacin
- 2 × 450 mg
- 2 × 500 mg
- p.o.

**Abbreviations:**
- CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IV, intravenously; MRSA, methicillin-resistant *Staphylococcus aureus*; p.o., per os.
- aTotal duration of therapy: 12 weeks, usually 2 weeks IV, followed by oral route.
- bLaboratory testing 2 × weekly: Leukocytes, CRP, creatinine/eGFR, liver transaminases. Dose-adjustment according to renal function and body weight (<40/>100 kg).
- cPenicillin allergy of non-type 1 (e.g., skin rash): cefazolin (3 × 2 g IV). In case of anaphylaxis (type 1-allergy such as Quincke’s edema, bronchospasm, anaphylactic shock), or cephalosporin allergy: vancomycin (2 × 1 g IV) or daptomycin (1 × 8 mg/kg IV). Ampicillin/subactam is equivalent to amoxicillin/clavulanic acid (3 × 2.2 g IV).
- dFor fosfomycin, the 5 g dosage form is only available in Germany. In all other countries, 2, 4, and 8 g dosage forms for IV fosfomycin are available. A daily dosage of 12–24 g IV fosfomycin is licensed.
- eRifampin is administered only after reimplantation, not in the interval. Add it to intravenous treatment as soon as wounds are dry and drains removed; in patients aged >75 years, rifampin is reduced to 2 × 300 mg p.o.
- fCheck vancomycin through concentration (take blood before next dose) at least 1 × weekly; therapeutic range: 15–20 μg/ml.
- gGive only if gentamicin high-level (HL) is tested susceptible (consult the microbiologist). In gentamicin, HL-resistant *E. faecalis* gentamicin is exchanged with ceftriaxone (1 × 2 g IV).
- hAdd IV treatment (piperacillin/tazobactam 3 × 4.5 g or ceftriaxon 1 × 2 g or meropenem 3 × 1 g IV) in the first postoperative days (until the wound is dry).
- iAfter a loading dose of 70 mg on Day 1, reduce the dose to 50 mg in patients weighing <80 kg from Day 2.
catheter tip immediately above the cavoatrial junction. The same approach for insertion of a midline catheter, except the tip remains in the peripheral circulation. We followed the current guidelines of the National Commission for Hospital Hygiene and Infection Prevention.44,45

2.6 | Home care setting

To establish S-OPAT, we followed the recommendations of the British Society for Antimicrobial Chemotherapy (BSAC)46 and the clinical practice guidelines published by IDSA.47 Regardless of the antibiotic agent used, patients visited their general practitioners or the hospital at least once a week for follow-up clinical examination and laboratory testing and to investigate any CRC or ADRs events.

A provider of outpatient infusion therapy was responsible for filling the elastomeric pumps with the antimicrobial treatment, delivering, dressing changes at weekly intervals, and follow-up wound inspections. Patients and relatives were trained to independently apply OPAT. Between administrations, a 200 IU/2 ml heparin block was applied.

2.7 | Outcome analysis

Patients were seen in the outpatient clinic after 3, 6, and 12 months and annually thereafter. Clinical, laboratory, and radiological evaluations were performed by a specialized orthopedic surgeon. In addition, each case was discussed with an infectious disease specialist.

3 | RESULTS

Since December 2015, a total of 27 patients have been included in the prospective cohort. Three patients were lost to follow-up, after successful reimplantation. One patient deceased due to a non-PJI-related cause. Overall, we recorded 54 S-OPAT episodes with a completed treatment algorithm in 26 patients and analyzed the outcome with a follow-up of 23. None of the patients experienced unplanned readmittance during OPAT.

3.1 | Patient demographics

The mean patient age was 66 ± 15 years, with a mean American Society of Anesthesiologists score of III, Charlson comorbidity index of 5, and a body mass index of 29; 19 (70%) were female. In one patient, both THA’s were exchanged during the same stay and in another, a TKA and THA exchange on the ipsilateral side was conducted. Overall, we treated PJI in 17 TKA’s and in 12 THA’s. The mean total duration of OPAT was 66 ± 26 days. We recorded a total of 1738 outpatient days. One patient obtained 213 OPAT days before reimplantation, due to critical soft tissue (Table 5).

TABLE 3  Diagnostic criteria for catheter-related events

| Criteria | Sensitivity | Specificity |
|----------|-------------|-------------|
| Superficial inflammation at the insertion site without signs of systemic infection/line infection | | |
| Catheter-related bloodstream infection | | |
| Thrombosis: Symptomatic deep venous thrombosis, confirmed by ultrasound scan | | |
| Mechanical nerve irritation | | |
| Displacement and/or accidental removal of the catheter | | |

TABLE 4  Diagnostic criteria for periprosthetic joint infection (reproduced with permission from the pocket guide to diagnosis and treatment of PJI, PRO-IMPLANT Foundation)

| Test                                      | Criteria                                      | Sensitivity | Specificity |
|-------------------------------------------|-----------------------------------------------|-------------|-------------|
| Clinical futures                          | Sinus tract or purulence around prosthesis\(^a\) | 20%-30%     | 100%        |
| Leukocyte count in synovial fluid         | >2000 leukocytes/µl or >70% granulocytes (PMN)\(^b\) | ~90%        | ~90%        |
| Periprosthetic tissue histology           | Inflammation (≥23 granulocytes per 10 high-power fields)\(^c\) | 73%         | 95%         |
| Microbiology                              | Microbial growth in                           |             |             |
|                                          | Synovial fluid or                             | 45%-75%     | 95%         |
|                                          | ≥2 Tissue samples or                          | 60%-80%     | 92%         |
|                                          | Sonication fluid (> 50 CFU/ml)\(^e\)         | 80%-90%     | 95%         |

Note: Periprosthetic joint infection is diagnosed, if ≥1 criterion is fulfilled. Adopted with kind permission of the PRO-IMPLANT Foundation. Abbreviations: CFU, colony-forming unit; PJI, periprosthetic joint infection; PMN, polymorphonuclear neutrophils.

\(^a\)Metal-on-metal bearing components can simulate pus (“pseudopus”), leukocyte count is usually normal (metal debris is visible).

\(^b\)Leukocyte count can be high without infection in the first 6 weeks after surgery, in rheumatic joint disease (including crystalopathy), periprosthetic fracture, or luxation. Leukocyte count should be determined within 24 h after aspiration using microscopy or automated counter; clotted specimens are treated with 10 µl hyaluronidase.

\(^c\)Classification after Krenn and Morawietz61: PJI corresponds to type 2 or type 3.

\(^d\)For highly virulent organisms (e.g., Staphylococcus aureus, Streptococci, E. coli) or patients under antibiotics, one positive sample confirms infection.

\(^e\)Under antibiotics, for S. aureus and anaerobes, <50 CFU/ml can be significant.
cases the susceptibility of the causative pathogens was vancomycin and meropenem in Gram-negative pathogens. The deceased patient is included in the pathogen evaluation.

Appropriate antimicrobial therapy was selected based on the results of susceptibility testing with the first preferential of a bactericidal treatment. The most frequently used antimicrobial agent in Gram-positive pathogens was vancomycin and meropenem in Gram-negative (Table 6).

We identified 17 classic DTT pathogens with resistance to oral biofilm-active therapy, including one fungal PJI. In patients with a mixed infection (n = 22), the additional pathogens were preferably treated with an additive oral antimicrobial therapy, in line with the concept of the PRO-IMPLANT Foundation. An oral biofilm-active therapy with rifampin was carried out after reimplantation of the new prosthesis in 10 patients with Gram-positive causative pathogens.

Regarding the indication for S-OPAT (Table 1), we noticed in 14 (54%) cases the susceptibility-matched antimicrobial agents were only available for IV administration. Oral antibiotics with solely bacteriostatic activity were the reason for OPAT in 11 (42%) patients, while inadequate oral bioavailability was only noticed once.

3.3 | Adverse events

Overall, adverse events were recorded in 6 of 54 (11%) S-OPAT episodes. Five CRCs occurred (9%), giving a line-associated complication rate of 2.88 per 1000 S-OPAT days. In detail, we observed three midline catheter occlusions in two patients, leading to an exchange, as well as one midline catheter and one PICC-associated superficial thrombophlebitis. The catheters were removed and regular treatment was terminated a few days before scheduled.

An ADR was noted in one patient (2%; 0.43 per 1000 S-OPAT days). After 2 weeks of vancomycin use, acute renal impairment occurred. Antibiotic administration was paused for 3 days and then switched to daptomycin. The patient was able to remain in outpatient treatment. No critical or life-threatening complications were observed.

3.4 | Outcome

All 23 patients successfully completed their treatment. Hitherto, we have recorded two reinfections; these occurred within the first year after reimplantation. Due to a complex mixed infection with three pathogens, including candida, and severe compromised bone and soft tissue, in the end only a transfemoral amputation was possible for infection control. In the second failure, the microorganisms causing reinfection was not the same as isolated initially and could be treated orally. Following the consensus of successful PJI treatment by Diaz-Ledzema et al., the case was counted as reinfection, even if a new haematogenous infection is likely. Both failures were observed in patients with initial proven staphylococcus epidermidis and resistance to rifampicin.

In six patients, poor bone and soft tissue conditions led to revision surgery, which combines the advantage of a second thorough debridement with benefits of spacer exchange, providing local high antimicrobial drug level, was carried out. Additional reconstructive surgery was frequently necessary in these patients. This was the reason for markedly extended periods of wound healing leading to prolonged antimicrobial treatment.

Two elderly patients with multiple revisions in their patient history showed extensor mechanism insufficiency in combination with large bone defects and compromised soft tissues conditions. Therefore, a knee arthrodesis with a cementless intramedullary nail was conducted as part of a two-stage revision procedure, after detailed discussion.

At a mean follow-up of 29 months, successful infection eradication as measured by the Delphi-based consensus definition was achieved in 91% of cases. The Kaplan-Meier-estimated infection-free survival after 3 years was 90% (95% confidence interval, 84.6%–95.5%). The survivorship of these patients is illustrated in Figure 2.

4 | DISCUSSION

4.1 | S-OPAT in PJI with MDR pathogens

According to the BSAC and IDSA guidelines, OPAT should only be considered if the patient care would not be better met in an inpatient...
TABLE 5 Patient demographic, OPAT characteristics, microbiology, and outcomes

| Variables                        | Values          |
|----------------------------------|-----------------|
| n                                | 27              |
| Deceased                         | 1               |
| Age (years)                      | 66/72 ± 15      |
| BMI                              | 29/27 ± 10      |
| CCI                              | 5/4 ± 3         |
| ASA                              | 3/3 ± 1         |
| ASA I                            | 1               |
| ASA II                           | 10              |
| ASA III                          | 13              |
| ASA IV                           | 2               |
| Patients with S-OPAT             | 26              |
| PICC                             | 12              |
| Midline                          | 14              |
| Episodes                         | 54              |
| Total S-OPAT days                | 1738            |
| Total duration of OPATab         | 64/66 ± 26      |
| ‣ Two-stage exchangeab           | 50/41 ± 34      |
| ‣ Multistage exchangeab          | 101/64 ± 84     |
| Adverse events                   | 6 (11%)         |
| ‣ Catheter-related               | 5 (9%)          |
| ‣ Adverse drug reaction          | 1 (2%)          |
| Microbiology                     |                 |
| › Monomicrobial                  | 4               |
| › Polymicrobial                  | 22              |
| › No possibility of biofilm-active therapy (DTT) | 17         |
| Lost to FU                       | 3               |
| Treatment failure                | 2               |
| Revisions                        | 6               |
| Infection-free at latest FU      | 21 (91%)        |
| Time to reimplantation (day)na   | 105/70 ± 88     |
| ‣ Without revisionana            | 64/59 ± 25      |
| ‣ Patients with revisionana      | 174/135 ± 115   |
| TKA                              | 17d             |
| THA                              | 12d             |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; DTT, difficult-to-treat; FU, follow-up; PICC, peripherally inserted central catheters; S-OPAT, self-administered outpatient parenteral antimicrobial therapy; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Complication rate per 1000 S-OPAT days.

setting. Antimicrobial therapy should be evaluated by an infectious disease specialist and, if possible, switched to an appropriate orally administered agent.46,47 This is consistent with the new findings of the OVIVA trial, showing no superiority of IV antimicrobial therapy compared to oral administration.5 At the time of the current ICM recommendations, the OVIVA results had not yet been published and were, therefore, not taken into account. Anyways, the results were already expected, an adjustment of the therapy recommendations can be assumed. ICM briefly pointed out OPAT as part of a multidisciplinary or interdisciplinary approach in the treatment of PJI. However, they did not mention the indication because the currently available data are insufficient and more evidence in this area is needed.7

Despite the numerous OPAT reports, there is a lack of robust data for the use of OPAT for patients with PJI. This situation has arisen due to the absence of well-defined study designs and the inclusion of PJIs with bone and joint infections, creating widely heterogeneous cohorts with mixed infection types and different treatment concepts. To the best of our knowledge, OPAT has not been studied in conjunction with MDR pathogens.

We identified few publications dealing with OPAT in PJI. However, only one study examined PJI patients exclusively. The others contained heterogeneous OPAT patient populations in which PJI also occurred. All of these studies had a retrospective study design. Mackintosh et al.12 and Duggal et al. showed poor infection-free survival, with 71% and 64%, respectively, in a short follow-up time. The remaining authors did not record outcomes and follow-up individually for patients with PJI. In addition, the treatment protocol for PJI was not presented in any publication; therefore, the relevance of these studies is quite limited, and it is difficult to compare their results to ours. However, OPAT is generally a safe treatment with a low amount of complications when considering the available data from heterogeneous patient populations.11,12,24,24,25,33 (Table 7).

Our cohort had an overall adverse event rate of 3.45 per 1000 S-OPAT days (11%). Our rate of line-related complications (2.88 per 1000 S-OPAT days) is comparable to other OPAT studies (3.2–5.3 per 1000 catheter days).48–52 The frequency of ARD varied substantially in previous studies, from 0.5% to 9.8%. In our study, this was 3%, which is within this range.40,49,51,53,54 Gastrointestinal symptoms are one of the most common ARD. We would only have recorded these, if they had led to an interruption of the therapy; this may be considered as a limitation. No critical or life-threatening complications were observed, which is consistent with the mortalities found in the literature (often ≤1%).20,49,52 We recorded 54 S-OPAT episodes, which is comparable with other cohort studies but not with register studies (Table 7). No patients were readmitted during the course of the study treatment procedures (Figure 1). This is in contrast to other recent studies, showing a general OPAT readmission rate varying from 3.6% to 12.6%40,48,49,58 and a specific S-OPAT readmission rate of 10.5%.33
Comparing the outcome

Our focus was the management of MDR pathogens resistant to all eligible oral antibiotics in PJI. Increasing numbers of primary total joint arthroplasties and revisions of hip and knee arthroplasty due to infections,9,10 will lead to enlarged number of these microorganisms. Between December 2015 and June 2019, those pathogens were identified in 27 out of 650 patients with PJI (4%). Therefore, their occurrence is markedly higher than fungal PJI, which has been reported in approximately 1% of all PJIs.59

Even if these pathogens occur only rarely, there is a controversial discussion on how to treat them. The presented collective has not enough power for a subgroup analysis between knees and hips, midline versus PICC, or detailed demographic analyses and we are aware that this leads to heterogeneity within our collective. However, we were able to present some fundamental findings, helping to treat these pathogens.

Although two-stage revision arthroplasty for the treatment of PJI has been evaluated and is well known, comparing different studies remains difficult due to varied definitions of failure and the lack of standardization. Cure rates in larger cohorts are reported between 76% and 92%. The clinical outcomes in our cohort were excellent with a 91% infection eradication. The mean follow-up of 29 months, considered as short-term follow-up defined by the Delphi panel,41 is promising. Our results showed similar eradication rates in patients with MDR-PJI including DTT pathogens compared to non-MDR-PJI. The most frequently microorganism were Staphylococcus epidermidis followed by Gram-negative E. coli and Klebsiella pneumoniae. We conducted two-stage revision procedures with long intervals (6 weeks), as proposed by Zimmerli et al.,1 because of the identified pathogens. Further investigations are necessary to determine whether a short interval can be similarly effective in MDR-PJI.

Our study has some limitations. We only investigated a short-term follow-up and 23 patients is a small sample size. Subcohort analyses, for example, between demographic parameters, THA versus TKA, and midline catheter versus PICC would be markedly underpowered and were, therefore, omitted. However, some fundamental conclusions could be drawn. Prospective multicentre trials are needed to confirm our findings using our proposed treatment method to eradicate MDR pathogens in patients with PJI.

### TABLE 6 Antimicrobial therapy of identified microorganisms

| Microorganism (n = 27) | No. (%) | Prevalent used antimicrobial agent(s) |
|------------------------|---------|-------------------------------------|
| **Gram-positive pathogens (n = 13)** | | |
| Staphylococcus epidermidis (MRSE) | 10 (37) | Vancomycin  Fosfomycin  Daptomycin |
| Staphylococcus aureus (MRSA) | 1 (4) | Vancomycin  Fosfomycin  Daptomycin |
| Enterococcus faecium (VRE) | 2 (7) | Gentamicin  Fosfomycin |
| **Gram-negative pathogens (n = 14)** | | |
| Escherichia coli (3MRGN) | 5 (19) | Meropenem |
| Klebsiella pneumoniae | 4 (15) | |
| Klebsiella pneumoniae (3MRGN) | 3 (11) | Meropenem |
| Klebsiella pneumoniae (4MRGN) | 1 (4) | Colistin  Gentamicin |
| Klebsiella oxytoca (3MRGN) | 1 (4) | Meropenem |
| Pseudomonas aeruginosa (MRGN) | 1 (4) | Ceftazidim  Tobramycin  Fosfomycin |
| Enterobacter cloacae complex (3MRGN) | 1 (4) | Meropenem |
| Serratia marcescens (3MRGN) | 1 (4) | Meropenem |
| Proteus mirabilis (3MRGN) | 1 (4) | Meropenem |

Abbreviations: MRGN, multiresistant Gram-negative; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; VRE, vancomycin-resistant enterococci.

*Rounded values.*

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**FIGURE 2** Infection-free survival of 23 multidrug-resistant periprosthetic joint infection at 3 years with 90%; dotted lines: 95% confidence interval [Color figure can be viewed at wileyonlinelibrary.com]
TABLE 7  OPAT: Bone and joint infection

| Authors                  | Study period | OPAT episodes | Patients total | PJI | S-OPATa | Follow-upb | OPAT durationb | Outcome %c,d | Design         |
|--------------------------|--------------|---------------|----------------|-----|---------|-------------|----------------|--------------|----------------|
| Matthews et al.55        | 1993–2005    | 2059          | 1621           | 447 | 92      | None        | Unknown        | Unknown      | Retrospective |
| Duggal et al.56          | Jul–Dec 2007 | 74            | 74             | 74  | None    | 12 weeks    | Unknown        | 78           | Retrospective |
| Mackintosh et al.57      | 2001–2005    | Unknown       | 198            | 65  | Unknown | 60 weeks    | Unknown        | 71           | Retrospective |
| Esposito et al.11        | 2003–2005    | Unknown       | 239            | 45  | 3       | 30 days     | Unknown        | Unknown      | Retrospective |
| Kieran et al.51          | 2006–2009    | 60            | 56             | ≤2  | ≤2c    | None        | 12            | Unknown      | Unknown        |
| Upton et al.52           | 2000–2002    | 107           | 100            | 4   | Unknown | None        | 30            | Unknown      | Retrospective |
| Frieler et al. (2020)   | 2015–2019    | 56            | 27             | 27  | 27      | 117 weeks   | 37            | 91           | Prospective   |

Abbreviations: PJI, periprosthetic joint infection; S-OPAT, self-administered outpatient parenteral antimicrobial therapy.
· Values are related to PJI.
· Values are given as the mean.
· Infection free survival.
· Unclear whether one patient was treated twice or 2 patients once.
· S-OPAT solely to treat MDR pathogens.

5 | CONCLUSION

S-OPAT in two-stage revision arthroplasty appears to be a viable treatment method for counteracting the increasing number of MDR pathogens resistant to every eligible oral antibiotics in chronic PJIs—a trend that shows no sign of slowing.

Our treatment strategy can be combined with the common management concepts of ICM, IDSA, AAOS, EBJIS, and PRO-IMPLANT Foundation. For the treatment of non-MDR pathogens, we recommend implementing the findings of the OVIVA trial; OPAT should only be used if inevitable.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Sven Frieler, Yannik Hanusrichter, Petri Bellova, Jan Geßmann, Thomas A. Schildhauer, and Hinnerk Baecker contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

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