


RESEARCH ARTICLE

Periprosthetic infections: How do we diagnose and treat? Results of an online survey and comparison with international recommendations

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Objective: Endoprosthetic replacement surgery of hip and knee joints is widely performed, but always carries the risk of developing periprosthetic infection (PPI). Treatment of PPI is lengthy and demanding for the patient, often involving multiple surgeries as well as lengthy drug therapies. Remediation is not always successful despite extensive therapy.

Methods: An online survey was used to investigate whether the therapeutic measures implemented in German hospitals are based on international treatment recommendations. For this purpose, German physicians who regularly treat periprosthetic infections in their clinics were asked to complete an online questionnaire. The questionnaire asked about internal hospital procedures. These were then compared with international recommendations.

Results: With a response rate of 10.9%, the questionnaire shows agreement with the international recommendations in large parts of the operative and medicinal procedures. In preoperative imaging for example, two-plane radiographs are the standard. Similarly, the participants' approach to preoperative specimen collection, incubation time, and operative management (regarding one- or two-stage approach to septic joint) reflects the recommendations.

Deviations were particularly evident in the area of laboratory diagnostics, where the erythrocyte sedimentation rate (ESR) is determined in only 17.1%, contrary to the recommendations. Whereas procalcitonin (PCT) and blood culture sampling takes place regularly. Clear differences emerge in the use of drains, which, contrary to the recommendations, are used very regularly (almost 70%).

In this survey, the time intervals between the onset of infection symptoms and the start of therapy (prosthesis-preserving therapy) is shown to be longer than recommended internationally.

Conclusion: In summary, however, the recommended approaches of the international groups in most respects are followed, a high willingness of respondents to collaborate with local infectious disease specialists demonstrates the complexity of the disease.

Key words: Arthroplasty exchange; Compliance to guideline; Online survey; Periprosthetic joint infection

Introduction

The rising number of total joint replacement (TJR) surgeries is both, promising and challenging. Hip arthroplasty was named the surgery of the century¹ since it is able to alleviate arthrosis pain, which is of increasing importance due to the demographic development. Perioperative risks are

calculable for healthy and compliant patients, but not for older and frail ones.

Complication rates for elective hip arthroplasty implantation range from 2% to 10%, including aseptic loosening (36.5%), joint dislocation (17.7%), and periprosthetic infection (PPI) (15.3%)^{2,3}. In knee arthroplasty PPI is even

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the leading complication with 25.2%.³ Particularly in multimorbid patients a significantly higher risk of must be expected. Although age alone does not appear to increase the risk of PPI, elderly patients have increased risk factors that favor infections (i.e., coagulopathy, cardiopulmonary disease, diabetes mellitus, neoplasia, immunosuppressive therapy)^{4,5}.

Diagnosis of PPI can be challenging. It is often based on single factors, none of which can be seen as a definite proof of infection.

For PPI of the hip and knee diagnostic algorithms and treatment recommendations are based on international guidelines or consensus recommendations, so on expert opinion. Evidence is limited due to lacking large randomized controlled trials. Bouaziz *et al.* 2018 showed that non-compliance with Infectious Diseases Society of America (IDSA) guidelines in methicillin-susceptible *Staphylococcus aureus* (MSSA) joint infection implies an increased treatment failure⁶. It is unclear whether international recommendations are implemented at all in medical routine care. For this purpose, an online survey was conducted to find out about everyday medical practice in the management of septic and aseptic TJR procedures in German hospitals, in order to compare this with the current guideline and consensus recommendations.

Methods

German hospitals performing endoprosthesis implantations and also treating the complication of PPI were asked to complete an online questionnaire. For this questionnaire two Internet-based German hospital lists (“Weiße Liste” = portal of the Bertelsmann Foundation and “VDEK-Klinikliste” = basis of the quality reports of the hospitals) were used in order to identify hospitals performing endoprosthesis implantations and also treating the complication of PPI. The key word search was “endoprosthesis” or the coding ICD T84 (T84.5 Infection/inflammatory reaction due to a joint endoprosthesis; T84.6 Infection/inflammatory reaction due to internal osteosynthesis device [any site]; T84.7 Infection/inflammatory reaction due to other orthopaedic endoprostheses, implants, or grafts) of the Diagnosis Related Groups (DRG) system.

These clinics were contacted using the Internet survey platform “ClinicalSurveys.net” and asked to complete an online questionnaire on the topic of prosthesis infection. ClinicalSurveys.net uses a customized version of Globalpark’s internationally acclaimed EFS Survey and EFS Leadership technology for an easy-to-use online documentation system. It provides a straightforward, high-performance documentation system.

The questionnaire was designed in interview style as multiple choice. Open questions were avoided. The questionnaire included the topics:

1. Standard diagnostics to confirm/exclude infection.
2. Treatment strategy for non-infective exchange procedures.
3. Treatment strategy in case of proven infection.

The questionnaire could be completed online, further inquiries of the interviewees were possible by mail. The data were collected with the system’s own documentation and evaluated epidemiologically. To ensure interobserver reliability, the data and their analysis were checked by two independent investigators.

International guidelines or consensus recommendations used for comparison were:

1. Italian Society of Infectious Tropical Diseases (SIMIT). “Italian guidelines for the diagnosis and infectious disease management of osteomyelitis and prosthetic joint infections in adults” 2009.⁷
2. Société de Pathologie Infectieuse de Lange Française (SPLIF). “Recommendations for bone and joint prosthetic device infections in clinical practice (prosthesis, implants, osteosynthesis)” 2010.⁸
3. American Academy of Orthopaedic Surgeons (AAOS). “The diagnosis of periprosthetic joint infections of the hip and knee – guideline and evidence report.” 2010 [short version⁹; long version¹⁰ American Academy of Orthopaedic Surgeons (AAOS). “Diagnosis and prevention of periprosthetic joint infections – clinical practice guideline.” 2019.¹¹
4. Infectious Diseases Society of America (IDSA), “Diagnosis and management of prosthetic joint infection: clinical practice guidelines.” 2012¹²
5. International Consensus Group (Philadelphia Consensus), “Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection.” 2013.¹³ International Consensus Group (Philadelphia Consensus), “Proceedings of the Second International Consensus Meeting on Periprosthetic Joint Infection” 2019.¹⁴

The AAOS 2019¹¹ and Philadelphia Consensus 2019¹⁴ literature was published after the online survey was conducted. Statistical analysis was descriptive.

Results

One thousand sixty-nine hospitals performing endoprosthetic procedures (including PPI treatment) were contacted. After several requests of completion, the questionnaire was fully completed by 117 clinics (10.9%). Out of these 51.3% were primary care hospitals and 49.6% had a bed count of less than 50 beds. Of the institutions, 52.1% were certified as a Endoprosthesis Center (EPC), including 16.2% Maximum care Endoprosthesis Centers (EPCmax).

On average, the clinics perform more primary TJR procedures than revision or exchange procedures. Case numbers of most clinics are between 100 and 250 primary hip TJR/year. Hip arthroplasty exchanges are performed less frequently than 50 times/year by 78.6% of respondents (Fig. 1).

In 64.1% of the hospitals, surgical procedures are conducted by only one to three surgeons.

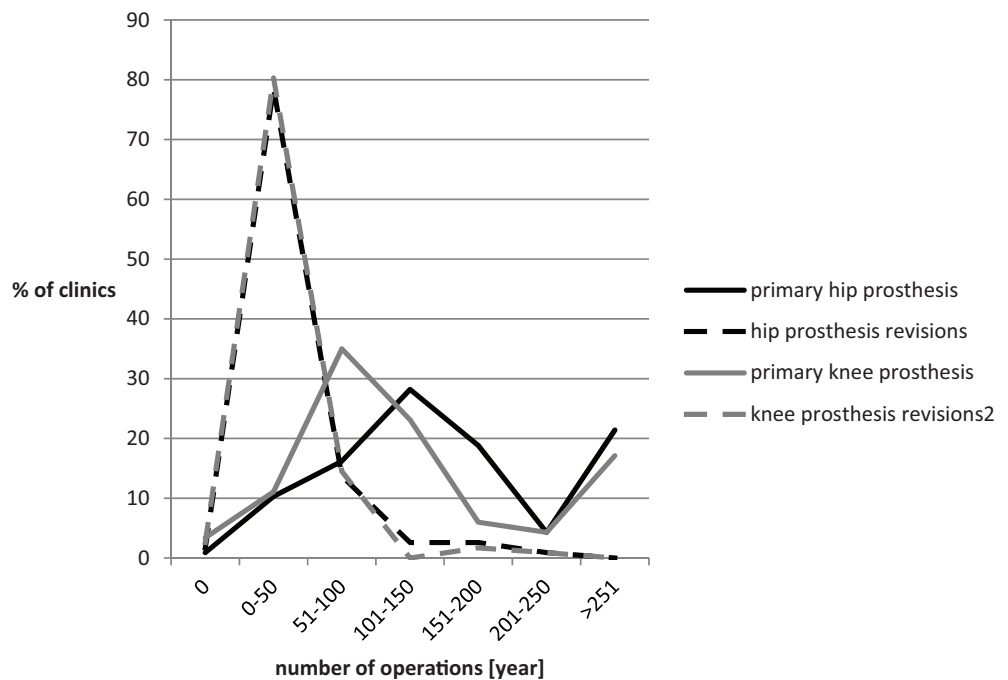


Fig. 1 Case numbers of endoprosthetic procedures. On average, the clinics performed more primary endoprosthetic procedures than exchange procedures. The case numbers of most clinics were between 100 and 250 primary hip TEPs/year. Hip TEP exchanges were performed less frequently than 50 times/year by 78.6% of respondents.

Preoperative laboratory diagnostics prior to endoprosthesis exchange classified as non-infectious

Blood count (99.1%) and CRP (98.3%) were determined by almost all clinics. ESR (erythrocyte sedimentation rate) was measured much less frequently (17.1%), with 50.4% of respondents reported never determining ESR.

Interleukins were rarely (less than 5%) used as routine values. In 15.4% blood cultures, in procalcitonin (PCT) was determined. Additionally, clinics reported about considering PCT sampling before surgery on an individual basis in 70.1%. Blood culture collection was part of routine diagnostics in 74.4% after individual decisions.

Preoperative imaging diagnosis before endoprosthesis exchange classified as non-infectious

In 98.3% of cases, a two-plane x-ray of the joint was performed preoperatively. Skeletal scintigraphy, computed tomography (CT), or joint ultrasound was routinely performed in 7.7%, 8.5%, 7.7%, respectively. However, on individual decisions, imaging was considered more regularly: skeletal scintigraphy 76.1%, CT 76.1%, ultrasound 59.0%, magnetic resonance imaging = MRI 62.4%. Thereby, based on the available questionnaire data, a tendency towards more and more detailed diagnostics in the larger hospitals surveyed could be identified.

Sampling prior to arthroplasty exchange classified as non-infectious

Fifty-nine per cent of the clinics routinely take a sample from the joint cavity before a planned endoprosthetic exchange. Mostly a joint puncture is performed (72.6%), followed by arthroscopic synovial sampling (14.2%;

Table 1). If antibiotic therapy had been given preoperatively, 90.6% of respondents pause it before sampling (Table 1). In most clinics collected specimens are

TABLE 1 Kind of sample taking, antibiotics pause and time of sample cultivation

Variabel	Expression	Total
Sampling performed before prosthesis change		117 (100)
Always		69 (59,0)
Individual decision		44 (37,6)
Never		2 (1,7)
No specification		2 (1,7)
If sampling: method of sampling		113 (96,6)
Joint puncture		82 (72,6)
Mini-arthrotomy		7 (6,2)
Arthroscopic synovial-sampling		16 (14,2)
Arthrotomy		8 (7,1)
No specification		0 (0,0)
Antibiotic break before sampling [days]		
No		7 (6,0)
0-7		12 (10,3)
8-14		44 (37,6)
>14		50 (42,7)
No specification		4 (3,4)
Incubation time [days]		
1-7		3 (2,6)
8-14		75 (64,1)
15-21		29 (24,8)
>21		6 (5,1)
No specification		4 (3,4)

Indication of whether and in what way samples are taken before prosthesis change, as well as whether and how long antibiotics were paused before sampling; indication of how long the samples taken were cultivated.

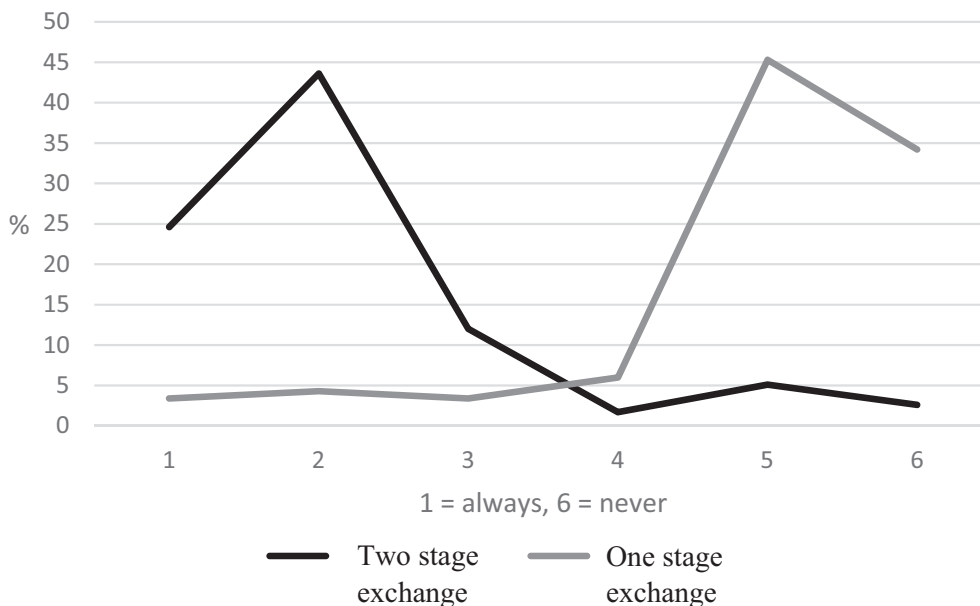


Fig. 2 Revision strategie of clinics. When a prosthesis change is required, the majority of clinics used two stage revision (black graph), not one stage exchanges (grey graph).

incubated between 8–14 days (64.1%), while nearly one third of the institutions report about an incubation time of more than 14 days; Table 1).

During the operative procedure, 94.9% recollect samples for microbiological and pathological examination, in most of the cases 4–6 samples for microbiology (51.4%) and 1–3 samples for pathology (76.6%). The prosthesis is rarely given for sonication in patients previously classified as non-infectious (6.8%).

Operative and medical treatment in case of PPI

The decision of prosthesis preservation in the infected state is limited by the time between symptom onset and therapy initiation; these periods varied from 0 to more than 6 weeks in this survey. When prosthesis replacement is required, the majority of clinics opt for a two-stage approach (79.5%; Fig. 2). Prosthesis reimplantation occurs after 15 to 42 days (“short interval”; 55.6%) or after 29 to 56 days (“long interval” after completion of antibiotic treatment; 64.1%).

Joint spacers are used by 92.3% of the hospitals surveyed for two-stage approach, regardless of the length of the prosthesis-free interval. Spacers are mostly specified as self-modeled, antibiotic-piled spacers (50.9%). In 53.7% of cases, an exchange of the spacer was not performed, regardless of the period the spacer was in place. Before planned prosthesis replantation, 74.1% of the respondents took samples from the joint cavity also with inserted joint spacers.

Independently of the type of operation (prosthesis preservation or exchange), intraoperative tissue samples were collected for microbiologic and pathologic examination (97.4%); most commonly 4–6 samples for microbiology (61.4%) and 1–3 samples for pathology (75.4%). Respondents (51.8%) reported maintaining an accurate specimen collection protocol. Respondents (87.7%) did not have polymerase chain reaction (PCR) testing in their routine testing

program. Only 9.4% performed sonication of the prosthesis, out of this 72.7% sent the prosthesis to external laboratories for this purpose.

Drains were routinely inserted in 69.2% of the clinics, with more than two drains in more than half of the cases (52.8%).

In 82.9% of cases, an interdisciplinary treatment planning including antibiotic therapy was carried out in cooperation with infectiologists and/or microbiologists. Most participants oralized the initial intravenous antibiotic administration based on individual criteria after 2 weeks (65%). Different information was given on the total duration of therapy, as well as on the chosen antibiotics and their dosages.

Discussion

Based on the structures of the hospitals that completed the questionnaire, this study appears to be a comparable sample to the average German hospitals, despite the small number of cases. In the study by Hoell *et al.* 2012¹⁵, similar structures (average number of beds, level of care) were represented. Whether the survey results can thus be considered representative is not certain, but can be assumed.

The rather small number of surgeons who complete procedures corresponds to the advantage offered by increasing specialization¹⁶. A concentration on a few surgeons bundles the available knowledge as well as the surgical experience, thus leading to fast and safe surgery with fewer complications and cost reduction for the hospital. However, the problem arises that the training of younger colleagues is made more difficult. In addition, the small number of “experts” in a clinic makes it more difficult to provide care, especially for surgical complications, which can occur on weekends or holidays when perhaps none of the experts are on background duty. Long-term absence experts (e.g., due to illness, parental leave, etc.) can additionally impair patient care in this model.

Preoperative laboratory diagnostics prior to endoprosthesis exchange classified as non-infectious

The preoperative determination of blood count and CRP performed at almost all clinics is in line with the advice of almost all existing guidelines and consensus recommendations⁷⁻¹⁴. However, the ESR, which is widely recommended as a preoperative laboratory diagnostic, is rarely examined. This seems incomprehensible considering the fact that ESR is a low-cost laboratory value and can provide another indication of a possible underlying infection in the patient. Similarly, the study by Hoell *et al.*¹⁵ also shows an infrequent use of ESR.

For standard diagnostic purposes, if patients not judged to be septic, PCT and blood cultures are determined frequently. Moreover, on an individual basis, percentage PCT- and blood culture determination is very high. This reflects the importance of these laboratory values, although these two laboratory tests are seldomly mentioned in international recommendations as preoperative standard⁷⁻¹⁴. Osmon *et al.* 2013¹² recommend blood culture collections in febrile or septic patients. However, the study by Cheung *et al.* 2012 shows that in spondylitis, blood culture collection can detect a causal pathogen in 25% to 59% of cases¹⁷. This could be one of the reasons why this examination is also frequently performed in the context of prosthesis exchanges, even if a frequent pathogen detection in the context of a sub-clinical periprosthetic infection has not yet been shown.

Preoperative imaging diagnosis prior to endoprosthesis exchange classified as non-infectious

The use of preoperative imaging is in line with international recommendations⁷⁻¹⁴. Here, only the two-plane X-ray is recommended as a routine diagnostic procedure since it is frequently available, inexpensive, and reproducible. According to Tande *et al.* 2014, periosteal bone growth, for example, can be used to conclude PPI with high specificity¹⁸.

Sample collection prior to arthroplasty exchange classified as non-infectious

The mentioned sample collection from the joint prior to planned arthroplasty exchange by joint puncture is in line with the recommendation of international guidelines and consensus papers⁷⁻¹⁴. Joint puncture offers the advantage that it can be performed quickly and safely. Based on the cell count, a questionable infection can be verified (or refused), and in addition, incubation of the punctate can succeed in microbiological pathogen detection in many cases^{8,12,18-20}. More invasive procedures for sampling, for example by excision, are performed secondarily by survey participants as recommended in the literature, for example for punctio sicca⁷⁻¹⁴. The second most common reported procedure is arthroscopic synovial sampling. This way of sample collection is particularly essential to detect the pathogen in case of a (low-grade) infection, significantly influencing the surgical procedure. In cases of a difficult-to-treat pathogen a single-stage prosthesis exchange is not recommended²¹.

To increase the validity of sampling, the antibiotic pause is recommended approximately 2 weeks before sampling^{8,12,18-20}. This advice is followed by almost half of participants. The long incubation period of the collected samples recommended in the literature^{8,22} is also found practically applied in this survey (Table 1).

The collection of tissue samples during the prosthesis exchange itself, practiced here in 95%, as well as type and number of samples, is in line with the international recommendation⁷⁻¹⁴. Regarding sonication, the guidelines do not yet specify a clear recommendation.

Surgical and medicinal procedure in case of proven infection of the prosthesis

According to the guidelines, 80% performed the two-stage prosthesis exchange, the recommended gold standard in the case of proven infection of an endoprosthesis. According to the Philadelphia Consensus, one-stage prosthesis replacement in the infection situation is acceptable in the case of local infection, known pathogen with effective, readily bio-available antibiotics and good bone/soft tissue mantle²², but it does not currently appear to be practiced regularly in everyday practice even under suitable conditions.

The prosthesis-free interval to be observed in two-stage alternation (“short”, “long”) is not clearly defined in the literature; periods between 2 and 6 weeks are usually mentioned. Similar time periods are named in the respondents interviewed here.

The use of drains is divergent to the literature recommendation. In particular, due to the higher probability of transfusion, the use of drains is only recommended in exceptional cases. However, more than two thirds of the respondents routinely insert drains, in more than half of the cases even more than two drains.

According to the 2010 SPLIF recommendation⁸, more than 92% of the hospitals surveyed in this survey use joint spacers regardless of the length of the prosthesis-free interval, mostly self-formed, antibiotic-laden. This reduces costs compared with the use of prefabricated spacers and additionally allows targeting of the added antibiotics to the detected pathogen. However, forming your own spacers requires slightly more operating time. The Philadelphia Consensus sees no advantage or disadvantage in self-formed versus purchased spacers²².

Mostly, a planned spacer exchange does not occur, regardless of how long the spacer is in place. Before the planned replantation, most of the respondents take samples from the joint, despite the inserted, potentially still antibiotic-releasing joint spacers. This is not supported by the Philadelphia Consensus. However, this could be explained by a high requirement of eradication before a new artificial joint is implanted. This is in line with the fact that the respondents seem to be very “respectful” of the septic single-stage change. However, the disadvantage of sampling with the spacer in place is the fact that a negative result only conveys a false sense of security, as the pathogen receiving

therapy may simply not be culturally detected due to local antibiotic release. Only a positive pathogen detection is to be considered a certainty. In addition, any surgical intervention on the joint, even the seemingly “harmless” sampling, poses a risk for the introduction of new pathogens.

When attempting a prosthesis-preserving procedure, this survey found time periods of up to 6 weeks between symptom onset and therapy initiation. In the literature, a period of 3, maximum 4 weeks is usually used here^{7–14,22}. The longer time frame is almost certainly due to the fact that prosthesis replacement is more invasive than prosthesis preservation. Trying to prevent the prosthesis exchange can be interpreted from the point of view that prosthesis replacement is still possible after a failed preservation attempt. Therefore, no surgical option is lost by an initial attempt to retain the prosthesis, but time is lost. However, especially in older patients with limited mobility due to infection, one would prefer mobilizing the patient as quick as possible during therapy in order to avoid secondary complications such as thrombosis, muscle atrophy, etc. This could explain why many surgeons do not attempt to retain the prosthesis and why many surgeons try to maintain the prosthesis “if at all possible” in order to spare the patient the phase of bed confinement that a two-stage exchange often entails. However, there is a risk if the attempt to maintain the prosthesis fails, the patient’s mobility is impaired for a longer period of time.

In almost all cases tissue samples are taken intraoperatively for microbiological and pathological examination. The type and number of the samples is consistent with the procedure described in guidelines and consensus recommendations^{7–14}. Of note is the high number of clinics (>50%) that follow an accurate sampling protocol. This can improve the usability and informative value of samples and is therefore advocated in the literature^{8,23}.

Nearly 90% of the respondents do not routinely perform a PCR examination as an additive to the microbiological examination of the tissue samples. This is understandable, as it is an expensive examination, which is also not (yet) firmly integrated in the guidelines^{12,19}. In the future, however, the addition of a PCR examination to the microbiological examinations can presumably improve pathogen detection, especially in antibiotic-pretreated patients.

Only a few clinics perform sonication of the prosthesis, which is probably due to the mostly lacking technical possibility in-house. Sonication involves a high technical effort and has so far only been recommended in exceptional cases in the guidelines²². According to Portillo *et al.* 2014²⁴, a similar specificity and sensitivity in pathogen detection can be achieved by simply shaking the prosthesis parts in sterile fluid with subsequent cultivation of the fluid. Further studies remain to be conducted in this area.

According to international literature and recommendations, treatment planning is done mostly in cooperation with infectiologists and/or microbiologists^{8,12,18,23,25,26}. Based on individual criteria, most participants oralize the initial intravenous antibiotic administration at the latest after 2 weeks

(65%). There have been no relevant studies on the duration of i.v. antibiotic administration with PPIs, so the Philadelphia Consensus does not specify a time period as a recommendation. The IDSA recommends 2–6 weeks⁷, and the SPLIF recommends 15 days (for prosthesis-preserving therapy)⁸. Li *et al.* 2019, with the publication of the OVIVA trial results, show that early oral antibiotics are at least not inferior to IV administration, as long as drugs with good bioavailability and bone penetrance are available²⁷.

Various information is given in the survey on the total duration of therapy in the case of a prosthesis-preserving concept and prosthesis replacement, as well as on the antibiotics used and their dosages. There are also no clear guidelines in the recommendations on the duration of treatment in the case of a prosthesis-preserving therapy concept. The IDSA and SIMIT Guidelines^{7,12} mention periods of 3 months for hip arthroplasty and 6 months for knee arthroplasty, while the SPLIF 2010 and ESCMID^{8,23} recommend 6 to 12 weeks of antibiotic therapy duration. The Philadelphia Consensus does not specify a recommended time period²². Regarding the antibiotics used as well as their dosage, the information provided by the respondents is largely in line with international recommendations. Pathogen- and resistance-adapted treatment is important here, for which interdisciplinary therapy planning is necessary. In the future, this collaboration can be further improved by the use of special interdisciplinary treatment meetings, such as an osteomyelitis board, which have already been established in a few hospitals.

Conclusion

Overall, the high willingness of respondents to cooperate with non-surgical infection specialists shows how complex the clinical picture of PPI is. Therapeutic success can be achieved on an interdisciplinary basis, but treatment is lengthy, costly, and complex. According to this survey, the existing international recommendations, which are often not evidence-based but at least experience-based, seem to be implemented to the greatest possible extent in everyday orthopedic surgery in Germany. Further findings in the form of randomized studies are urgently needed to improve both the diagnosis and the therapy of PPI in the future.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors. All authors are in agreement with the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' Contributions

C.O.L. and A.G. conducted the survey and made the evaluation. P.E. gave the inspiration for the survey.

C.O.L. and A.Y. wrote the article. All authors have read and approved the final submitted manuscript.

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