RESEARCH CAVEATS

Authors: Holger Rohde, Karan Goswami

QUESTION 1: Is there a distinct microbiome in the joints?

RECOMMENDATION: It remains unclear whether the native joint or a joint after arthroplasty can be considered a microbiological niche in which specific organisms reside without causing any manifestation of infection. However, given the innocuous character of microorganisms (such as coagulase-negative *Staphylococcus*, *Cutibacterium* species) recovered from clinical specimens in the context of aseptic loosening it appears plausible to hypothesize that chronic colonization of devices can occur and be of long-lasting nature before signs and symptoms of clinical infection occur, if they occur at all. Further studies are needed to determine the clinical relevance of microorganisms or microbial dysbiosis detected within joints, without apparent clinical features of infection, ensuring clinical correlation, long-term follow-up and multicenter validation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 80%, Disagree: 7%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

The term microbiome (or microbiota) is defined as the entity of microorganisms that colonize the human body. It is well-known that defined ecological niches (e.g., the gut, the skin, the oral cavity) can carry groups of microorganisms that differ dramatically in their specific composition [1,2]. There is growing evidence that the specific microbiome composition might be associated with defined clinical pictures or even support the development of illness, but without causing invasive disease [3].

However, in most cases the microbiome/microbiota would be considered to be beneficial for the host [4,5]. This commensal microbiome is expected to be found in niches of the human body traditionally regarded as non-sterile. In contrast, detection of commensal bacteria in sterile body sites (e.g., joints) would be regarded best as an artifact resulting from sample contamination or as evidence for a pathology evolving under certain predisposing conditions (e.g., immune suppression, foreign material implantation). Thus, in the current understanding, detection of single or multiple species originating from human microbiota in sterile body compartments would be primarily regarded as mono- or poly-microbial infection rather than as evidence for colonization. The physiologic or non-pathogenic presence of bacteria within the joint would therefore represent a groundbreaking change of current dogmas in microbiology.

In the face of these considerations, the general question under review comprises several distinct sub-questions: (1) Is there chronic microbial colonization in the joint, and can colonization occur without presence of foreign devices (i.e., an artificial niche)? (2) Can microorganisms establish chronic joint colonization without inducing infectious pathology or sequelae? (3) If so, are joints colonized by one or more species? (4) Can patterns of colonization be identified that predict defined clinical characteristics?

(1) Without doubt, there is chronic persistent colonization of joints in the presence of an implanted device. In fact, this is a basic characteristic of almost all infections caused by more innocuous (less virulent) organisms derived from the skin microbiota and able to form a biofilm [6]. There is limited data available as to which extent native joints also can also harbor such microorganisms. Evidence supporting this hypothesis comes from studies in which joint fluids from apparently uninfected individuals were microbiologically analyzed. Furthermore, some studies identified bacteria by culture or the strict protocols of molecular techniques from shoulder joint fluids [7–9]. Here, a relevant number of samples taken from patients without evidence for infection grew *C. acnes*. Unfortunately, in most of these studies it remains unclear if detection of *C. acnes* indeed represents colonization of the joint or rather was a consequence of contamination by skin flora due to insufficient skin washing procedures [10]. Moreover, since joint aspirates were performed for medical reasons, it is unclear if detection of bacteria would also be possible in individuals without any clinical evidence of infectious shoulder pathology.

(2) A hallmark of device-associated infection is a chronic persistent course with only low-grade inflammation. This course is most likely a direct consequence of biological traits related to microorganisms derived from resident skin microbiota – namely mechanisms that support persistence on the skin without inducing a relevant inflammatory response. In such a scenario, chronic colonization of foreign devices indeed could potentially occur through masking of the pathogen from effectors of the host immune system [11,12]. Some studies investigating explanted prosthetic devices from patients with periprosthetic joint infection (PJI) or aseptic loosening of a joint found small numbers of cases in which bacteria were unambiguously identified from the sample but that didn't show any sign of infection according to current standards (e.g., elevated C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), polymorphonuclear (PMN) cell tissue infiltration) [13–17]. However, of major importance, it is questionable if indeed such cases can be truly regarded as valid evidence for asymptomatic colonization of a device since assignment to the aseptic failure group is based on current algorithms to define PJI. While it remains open whether loosening of the implant can potentially be the only evident sign for an infection, it certainly is unclear if these patients would not have developed disease or PJI according to current case definitions if they remained untreated [18–20]. The relevant control group to test the hypothesis of chronic asymptomatic implant colonization has not yet been investigated, but would be completely asymptomatic

patients with implants in situ. Importantly, in future investigations and especially those applying molecular techniques strict protocols for sample processing, application of DNA-free consumables and process analysis (i.e., inhibitor controls) need to be applied.

(3) and (4) Building on the aspects discussed above, at present it remains unclear if the term "microbiome" is appropriate to describe microorganisms in native joints or after arthroplasty. Some evidence suggests, nevertheless, that more than one organism can potentially colonize artificial surfaces. It will be of major importance to unravel the extent of polymicrobial colonization and the potential importance of interspecies cooperation in future projects (making use of next-generation/metagenomic sequencing techniques and advanced microscopy methods [21]).

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QUESTION 2: Has the profile of organisms causing surgical site infection/periprosthetic joint infection (SSI/PJI) following orthopaedic procedures changed over recent years?

RECOMMENDATION: While the majority of organisms causing SSI/PJI continue to be staphylococcal species, the prevalence of resistant pathogens and atypical organisms continues to rise. In particular, incidence of methicillin-resistant *Staphylococcal aureus* (MRSA) is increasing. Isolated studies have reported an increased prevalence of culture-negative PJI. Further work regarding the flux in organism profile is needed, as it may confer significant antibiotic selection implications.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

Data sources

Medline, Embase, Web of Science, Cochrane Library and reference lists of relevant studies from inception to February 10, 2018.

Selection criteria

Studies included were observational (prospective cohort, nested case-control or case-control, retrospective cohort) studies, case series and randomized controlled trials (RCTs) that have evaluated organism profile in PJI over time in patients undergoing orthopaedic procedures.

Review methods

Investigators screened and extracted data. We were not able to present a meta-analysis of the data. Thus, we present a narrative synthesis based on related data available.

Results

Of 113 potentially relevant citations, we found 23 relevant articles. Studies were observational and retrospective in design.

RATIONALE

Peersman et al. described that the predominant infectious organisms seen in 6,489 knee replacements were gram-positive (*Staphylococcus aureus, Staphylococcus epidermidis and Group B Streptococcus*) [1]. While current literature differs regarding specific percentages, there is consensus that gram-positive aerobic bacteria continue to remain the most common offending organisms [2–4].

In an aggregate of 14 studies examining 2,436 joints, *Staphylococcus aureus* represented 27% of all prosthetic joint infections, coagulase-negative *Staphylococcus* represented 27%, *Streptococcus* species were represented at 8%, *Enterococcus* species were represented at 3%, aerobic gram-negative bacilli made up 9%, anaerobic bacteria comprised 4%, culture-negative PJI was responsible for 14% and polymicrobial infection represented 15% [3–18]. In a study analyzing organism profile at 2 separate referral centers, *Staphylococcus aureus* remained the most prominent offending organism at 26.9% of cases [19]. Additional studies are congruent with the findings reported by by Aggarwal et al. [2,19–21].

However, prevalence of resistant organisms continues to increase. In 2005, Ip et al. described a retrospective case series in which they described the bacterial isolates from 1995 to 2003 [22]. They noted that no isolates from 1995 and 1996 were multiple-drug resistant, a change observed in the later years [22]. McLawhorn et al. showed MRSA and methicillin-susceptible *S. epidermidis* (MRSE) combined to account for 18.1% of PJI pathogens in the United States [23]. Interestingly, a study analyzing prevalence of causative organisms at two separate tertiary centers showed methicillin resistance as significantly more common in the US than in Europe [19].

In summary, the mainstay of organisms causing SSI/PJI continue to be staphylococcal. The prevalence of resistant pathogens and atypical organisms also continues to rise. The prevalence of methicillin-resistant *Staphylococus aureus* and culture-negative infection is also increasing. Further work regarding SSI/PJI organism profile is needed, as it may confer significant antibiotic selection implications.

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QUESTION 3: What methods can the Food and Drug Administration (FDA) and other regulatory bodies use to evaluate the efficacy of novel anti-infective technologies?

RECOMMENDATION: The FDA and other regulatory bodies can use in vitro cell culture methods to evaluate the antimicrobial efficacy against pathogens, followed by animal studies to evaluate osseointegration issues and a subsequent osteomyelitis/periprosthetic joint infection (PJI) animal model to evaluate the in vivo efficacy. However, clinical trials may be required for clearance or approval of some novel anti-infective technologies.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 80%, Disagree: 3%, Abstain: 17% (Super Majority, Strong Consensus)

RATIONALE

Human clinical trials of anti-infective technologies are inherently difficult to perform according to Lazzarini et al. [1], due to the low incidence of implant-associated infections, the heterogeneous patient population, various treatment options in arthroplasty, the surrounding tissue condition after debridement and the broad range of causative pathogens and associated virulence patterns [2]. A cascade of in vitro cell culture methods and especially meaningful experimental animal models have to serve to fill this inevitable gap [1].

During the development of anti-infective biomaterials and devices and the determination of their anti-microbial properties, reliable in vitro test methods are essential to characterize implant surfaces [1,3]. In any evaluation procedure, cell proliferation has to be included as an important step in the course of infection [3]. For appropriate anti-microbial efficacy testing the independent aspects adhesion, proliferation and detection of bactericidal activity shall be considered in a consistent approach [3,4].

In the almost identical anti-microbial test methods, described with Japanese Industrial Standard (JIS) Z 2801:2010 and the International Organization for Standardization (ISO) 22196:2011 standards, the bacteria are applied onto the sample surface and covered under a sterile film, whereas for the American Society for Testing and Materials (ASTM) E 2180 test method the bacteria are applied as a thin agar slurry film. After 24 hours, by recovering vital bacteria from the samples, both test methods' anti-microbial efficacy is determined as the difference between the untreated reference and the anti-microbial sample. The major limitations are the required sample size (ISO 22196 5 x 5 cm, ASTM 3 x 3 cm) and the flat and smooth surface geometry, which is often not a given for orthopaedic implants [4]. In addition, hydrophobic surfaces can be unsuitable for testing according to ISO 22196, and the applied agar film (ASTM E 2180) can be too thick for non-leaching surface bound anti-microbials, thus leading to false-negative results.

Proliferation assay-based methods, first described by Bechert et al. [3], measure the antimicrobial efficacy based on the reproduction and release of daughter cells, monitoring the growth activity of these offspring bacteria over time. The main advantage of the proliferation-based assays is a broad applicability to flexible sample geometries (e.g., 2D and 3D), surface properties (e.g., smooth, textured, porous) and test conditions (e.g., leaching and non-leaching) [3–5]. Moreover, this method allows a parallelized investigation of many different setups in one test run ensuring a direct comparability, which results in increased explanatory power and higher sensitivity as given in the ISO and ASTM test methods [3,4]. However, the interpretation of test results is somehow more sophisticated, since growth of the offspring bacteria is analyzed rather than the vital cells on the sample surface [3,4]. In case of more complex surface structures and 3D geometries, which is the case for orthopaedic implants, the most reliable test method is a proliferation-based assay [4]. An important additional aspect is the contact of the implant to body fluids (such as blood, serum or interstitial liquid), having typically a high concentration of proteins, covering the device surface by a protein layer, which can have an impact on the antimicrobial performance of the material. Moreover, the influence of sterilization, aging degradation and persistence of the anti-microbial effect should be examined and testing should always be performed at least against gram-positive and gram-negative bacteria strains [4]. However, a direct transferability of in vitro results to in vivo performance is not stringently given. Thus, animal data are required to substantiate the antimicrobial efficacy in vivo.

To demonstrate unimpaired osseointegration for implant materials and surfaces that are modified by new anti-infective technologies in hip and knee arthroplasty, an appropriate animal study should be performed using controls based on long-term, clinically-established implant surfaces for cementless fixation, and also the base material and surface structure without the anti-infective treatment. Eto et al. [6] described a rat model with intramedullary implantation of a titanium rod to evaluate the osteoconductivity and osteogenesis in the meta- and diaphyseal region of the distal femur for experimental silver-oxide-containing hydroxyapatide coatings. They examined the implant anchorage strength at 2, 4 and 12 weeks post-implantation in a pull-out test, and performed a histological examination using a contralateral femur implantation with the same surface [6]. Analyzing the surface coverage with bone, they used this procedure to quantify the active peri-implant osteogenesis and osteoconductivity in the meta- and diaphysis of the femur in a comparison of anti-microbial surface treatments to a clinically-established hydroxyapatite (HA) coating [6]. Combining biomechanical and histological examinations, the model by Eto et al. [6] is valuable during the development phase of new anti-microbial implant surfaces to detect favorable solutions. The limitations of size, not allowing for testing multiple implants simultaneously and also significant dissimilarities between rat and human bone make a rat model unsuitable for clinically relevant osseo-integration testing [7].

To evaluate new anti-microbial surface solutions for a clinical use in orthopaedic implants, their biocompatibility, peri-implant osteogenesis, osteoconductivity and ability of osseointegration should be tested in an animal model of a higher species, like sheep, goat, pig or dog [7,8]. Preferably a load-bearing model of the proximal tibia or distal femur in direct implantation site, or autologous left-right comparison should be performed, in reference to a clinically established surface (e.g., HA or porous coating) under a mid-term implantation duration of at least 26 weeks, to evaluate the osseointegration in a substantiated manner [7–10].

Animal models with osteomyelitis have been used previously to investigate potential treatment options using implants. After a review of the existing literature, it was found that a wide variety of osteomyelitis animal models exist [9]. However, no ideal single animal model exists to address implant

associated osteomyelitis. Therefore, we propose that researchers and clinicians should ask indication and disease-specific questions and build on established appropriate animal models capable of answering their questions and enabling translations to the clinical situation [9]. Traditional methods to quantify bacterial load via colony forming unit (CFU) assays should be replaced with in vivo bio-luminescent imaging and radiological outcome quantification. New anti-microbial treatments should be evaluated in regard to the host immune response utilizing biomarkers, and shoud be based on new technologies like the detection of bacteria by fluorescent in-situ hybridization in bone infection [9,11].

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QUESTION 4: What are some of the emerging pre-clinical methods for evaluating novel antimicrobial technologies?

RECOMMENDATION: At present, most in vitro testing provides limited insight into the potential of novel antimicrobial technologies. More recently, in vitro models that incorporate animal or human tissue are emerging to test adherence and colonization to devices in contact with human tissues. Further development and validation of these models is needed, as well as approaches to include the element of human immune response.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 81%, Disagree: 2%, Abstain: 17% (Super Majority, Strong Consensus)

RATIONALE

The Food and Drug Administration (FDA) held a workshop in 2014 on antimicrobial/antibiofilm technologies and has published a white paper on the workshop outcomes [1] as well as a book chapter in 2016 [2]. The FDA recognizes the public health impact of medical device associated infections including prosthetic joint infections. There are two types of pre-clinical antimicrobial effectiveness testing: in vitro and in vivo. In this response, in vitro testing is addressed.

In Vitro Testing

At present, most in vitro testing provides limited insight into the potential of novel antimicrobial technologies. Most Clinical and Laboratory Standards Institute (CLSI) and United States Pharmacopeia (USP) tests (e.g., CLSI M02-A11, CLSI M07-A9 and USP 51) are for planktonic bacteria and/or are not ideal for medical device technologies. Some of the newer American Society for Testing and Materials (ASTM) methods are focused on creation of reproducible microbial biofilms for testing, but are not specifically developed with methods and endpoints that are appropriate for medical devices. Medical devices have a range of patient contact types (e.g., indwelling, transcutaneous and implanted) and duration (e.g., prolonged vs. permanent contact). A notable consideration for permanent contact implants is how to identify an effective dose that can prevent biofilm formation where multiple applications of the antimicrobial are not feasible). Therefore, modification and careful development of protocols to demonstrate in vitro effectiveness is necessary for specific medical device applications.

Differences based on material properties are more easily detected in adhesion studies since they are typically conducted using short times while in saline, where bacterial growth is minimal. Thus, adhesion testing is better suited for comparing early stage bacterial interactions with different antimicrobial technologies or libraries of materials. The ASTM E2647 drip flow reactor or similar type flow systems have been used to study early stage bacterial adhesion and biofilm formation [3,4]. An alternative approach to adhesion testing is to put samples in microtiter plates with an orbital incubator and to extract colonies after testing the antimicrobial strategy [5]. While this approach is simpler to set up and does not require sophisticated and costly confocal microscopy equipment to visualize cells, it is an endpoint method rather than a real-time approach. There may also be limitations due to the extraction technique employed and the presence of viable but non-culturable (VBNC) bacteria. When testing adhesion, one should keep in mind that

surfaces which initially repel bacteria may fail after some period of time due to buildup on the surface, fouling by dead bacteria and interactions with bodily fluid and tissues.

For longer-term biofilm testing, the ASTM E2562 CDC flow reactor is a lab-scale model suitable for testing coupons from medical devices or entire small devices [6]. It has been used extensively in the literature for testing antimicrobial device technologies. A limitation of this approach is that bacteria are typically provided continuous nutrients so that a mature and fully-saturated biofilm is achieved. This can reduce the sensitivity for comparing between similar materials with slight differences, such as different types of patterned/textured surfaces. The ASTM E2799 minimum biofilm eradication concentration (MBEC) assay is a higher throughput format than the CDC reactor, but requires modification to be used with medical devices [7]. It is challenging to perform successfully due to the number of steps and requires significant work to optimize for each material and strain.

Two promising in vitro approaches that have the potential to increase realism in testing are human cell-based co-culture and ex vivo tissue models. Bacterial co-culture with human cells is challenging and its use for testing is still in experimental development. It can include human tissue cells [8] and/or human immune cells [9]. A more achievable approach at this time is ex vivo tissue-based models. The use of ex vivo porcine skin explants has shown great promise as a tool to study the development of more mature biofilms with greater resistance to antimicrobials [9–11]. The next logical step is the use of human tissue models such as a recent article showing how the use of human epithelial tissues has yielded valuable information on the fitness of bacteria to adhere to and colonize human cells [12]. Such models could potentially allow for simulation of the tissues in contact with an orthopaedic implant for evaluation of antibiofilm stratgies.

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QUESTION 5: Does an animal model for periprosthetic joint infection (PJI) exist?

RECOMMENDATION: Yes, there are several animal models using different species and implant designs that have claimed to pertain to PJI. However, the majority of these models are not representative of clinical PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 4%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Despite its increasing prevalence, our fundamental understanding of how bacteria enter the human prosthetic joint, establish biofilm, resist immune response and overcome clinical treatment remains limited. Establishing representative animal models of human disease has led to translational breakthroughs in medical fields such as immunology [1], toxicology [2], oncology [3] and orthopaedics specifically have led to the introduction of novel therapies such as for fracture healing [4] and for improved osseointegration surfaces [5] in joint reconstruction. With such examples, it is conceivable that a clinically representative animal model of PJI could improve our understanding of the pathogenesis of PJI and consequently lead to novel strategies for PJI prevention and treatment.

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify published animal models described to be representative of PJI. The majority were in mice (14) [6–19], with rabbit (5) [20–24], rat (2) [25,26], sheep or ovine (2) [27,28] and dog or canine (1) [29] comprising the species utilized. Utilizing large-animal models such as dogs and sheep permit more frequent serum analyses and involve bony architecture that contains osteons and Haversian systems, which are similar to human bone [30].

However, larger animals have more porous bone that turns over more rapidly compared to humans, making metrics such as osseointegration and osteolysis more difficult to interpret [31]. Smaller animal models are advantageous due to their substantially lower-running costs and, uniquely thus far in the case of mice, the possibility of genetic manipulation to reproduce human disease states [32,33]. However, rodent immune systems are mostly rich in lymphocytes, a stark difference from the largely neutrophil-based immune response found in humans [34]. There currently is no consensus on which animal species is ideal for modeling PJI.

The majority of studies failed to utilize implants that effectively recreate the periprosthetic environment, characterized by the implant separating the articular space from the intramedullary space, or that bear load. The most popular choice was a stainless steel wire inserted retrograde into the femoral canal [6–9,11–13,16–18,24–26,35,36], an implant which does not bear load, is not of the same material as arthroplasty implants, is mechanically loose and fails to recreate the periprosthetic space. The second most popular choice was a titanium screw (with or without a washer) placed across the proximal tibial cortex [14,15,23,28,37], an implant which bears load and uses a correct arthroplasty material, but does not involve the medullary canal and preserves articular cartilage. Three articles utilized implants that bore weight and separated the articular and medullary spaces [19,21,22]. However, two of these articles utilized a silicone implant [21,22] and only one utilized the correct titanium alloy used in clinical arthroplasty implants [19]. This latter example was the only model that fulfilled implant-related criteria. Troublingly, two articles made cortical bone windows and utilized no metal or plastic-based implants whatsoever [10,20].

Almost all studies (23) involved gram-positive organisms including methicillin-sensitive *Staphylococcus aureus* (MSSA) [7–9,11–21,24,25,28], methicillin-resistant *Staphylococcus aureus* (MRSA) [6,22,23,26], and *Staphylococcus epidermidis* [10]. All bacteria utilized in retrieved studies were commercially available strains. There is incomplete information pertaining to the biofilm-forming ability of these strains and, to our knowledge, no study used bacteria derived directly from clinical PJI. The most common method of bacterial inoculation involved injecting bacteria into the articular space following implant insertion and wound closure [7–9,11,12,16,17,21–23,26,28]. Alternatives that share clinical relevance included injecting bacteria into the medullary canal prior to implant insertion [10,18,20,24], pipetting bacteria onto the implant immediately after insertion [6], and administering bacteria intravenously [13,25]. Another method which is not clinically representative is to culture the implant in bacterial broth for 24 hours, permitting biofilm to form on the surface prior to insertion [14,15].

Methodology to determine bacterial viability varied across the retrieved articles, but was not restricted to model type. More comprehensive analyses were identified in mouse-based studies, with biofilm architecture, bacterial colony counting on tissues and implant surfaces and descriptions of immune responses being collectively described in several studies. To date, no non-mouse based study has included quantitative measurements of bacteria, biofilm, and host immune response.

Mouse-based models of PJI are currently the most popular and provide the most comprehensive methodology for PJI-related investigations. Unfortunately, the majority of these models fail to utilize implants that function like their clinical counterparts. This finding is disappointing considering the successful animal models available in orthopaedics for trauma [38] and sports-related conditions [39].

Although intramedullary pins remain popular in PJI-themed models, they have obvious deficiencies when trying to represent arthroplasty components and have been confused in representing osteomyelitis and septic arthritis [10,15]. Carli et al. proposed four criteria that all animal models of PJI should meet: (1) modeling should be performed in animals with comparable musculoskeletal and immunological properties to humans, (2) utilized implants should be of clinically relevant materials, (3) models should use clinically relatable bacteria that can form biofilms on implant surfaces and (4) methodology should include quantitative measurements of bacteria, biofilm and host immune response [40]. One animal model [19] currently fulfills this criteria. Unfortunately, this model has only recently been introduced and requires further validation with the testing of prophylactic or therapeutic PJI investigations.

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QUESTION 6: Are there any concerns regarding the use of joint registries or administrative databases to conduct infection studies?

RECOMMENDATION: Yes. Infections are of a multi-factorial character and currently, national joint registries alone do not provide adequate data for a comprehensive approach to infection research.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 91%, Disagree: 6%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

National joint registries are platforms for aggregating various data on surgical procedures and their subsequent outcomes. The data can be used for further research and also as a means of direct feedback to contributing clinicians via the annual reports.

The systematic review performed generated 19 articles conducting infection research using a national joint registry alone. The utilization of national registries enables a nationwide study setting with large populations. Analyses of these large study sets can identify trends of statistical significance of which further research may be targeted. The 19 identified articles examine various aspects of infection. Three articles have investigated the incidence of infection over time and indicated that the incidence of prosthetic joint infection (PJI) has increased [1–3]. Registry datasets have also been used to study the risk of revision secondary to infection, the burden of revision due to infection and the risk factors for infection in primary arthroplasty [4–9]. Other

studies have evaluated prosthetic components and intraoperative details with regards to infection risk [10–16]. One study reported on the of risk re-revision in four different surgical procedures used to treat infection [17].

The annual reports and data collection forms available on the websites of eight established national joint registries were reviewed [18]. It appears that reporting on infections varies between the registries [19–28]. Further, the definition of infection is inconsistent in the registries, and there is no distinction between superficial infections and deep periprosthetic infections. Patients with infections who were not subject to revision or other reoperations are not captured within these databases. Some registries report infection as revision procedures for infection, defined as all procedures manipulating, exchanging or removing prosthesis parts [21–23]. Other registries report on all open procedures, regardless of exchange, addition or removal of implant components [19,20,24,25]. The remaining categorize procedures due to infection in their own manner [26–28].

It could be argued that with infections being of a multi-factorial nature, the data collected in the registries alone is not sufficient enough to conduct comprehensive infection-based research (Appendix A). With a few exceptions (e.g., Swedish Knee Arthroplasty Register), there is no information on factors such as causative pathogen or antibiotic regime. However, this information can be obtained by performing linkage studies with several registries, such as joint, microbiological and drug registries. In Denmark, Sweden, and Finland, such studies have been conducted to investigate PJI [29–33]. Using a linkage of databases, Gundtoft et al. found a 40% higher incidence of infection after total hip arthroplasty (THA) than registries have previously reported alone [29]. In Sweden, Lindgren et al. reported on a method to investigate the incidence of infection by linking the national drug registry with the national hip joint registry [33]. Holleyman et al. have also used a combination of the National Joint Registry database for England and Wales (NJR) and a register on microbiology data to study which microbes cause PJI [34,35]. Also in Sweden, the Knee Arthroplasty Register conducted a study where data on microbiology and antibiotics was requested from centers for the included patients. The study found that there was a 75% success rate after debridement, exchange of tibial insert and antibiotics in infected total knee arthroplasty (TKA) [36].

Different registries vary in how they report, define and analyze infection rates in their annual reports; thereby making it difficult to conduct a representative comparison across the registry websites. Similar to revision burden being used as a means of comparing registries, Springer et al. used annual reports from six national arthroplasty registries to investigate the infection burden in each registry [3]. Infection burden has been concluded to be a possible way of comparing the success between registries. However, the inconsistency in data collection and definition in the annual reports throughout the registries make it problematic to compare and interpret infection within registries. Additionally, infection burden has been suggested to be underestimated in national joint registries [37–39].

Jämsen et al. conducted a study to estimate the rate of infection following TKA in Finland and came to the conclusion that the incidence of revision TKA secondary to infection seemed to be underestimated [37]. Two studies of the national joint registry in New Zealand came to the same conclusion [38,39]. The registries report on completeness of registered data in their annual reports but do not specifically report on the completeness of reported infection procedures. Validation of data reported on infection to the registries is important in order to maintain a high data quality within these databases. To our knowledge, validation studies on infection have also been conducted within the Danish and Swedish national joint registries [40,41].

Although there are limitations, we believe that registries will play an important role in future infection research. A harmonization of infection definition and data collection is desirable. We also believe collaborative research linking data from national joint, national drug and microbiological registries will provide a more comprehensive approach to infection research.

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APPENDIX A. Variables Collected By Major Arthroplasty Registers

VARIABLE	HIPS							
	AUS	CAN	DEN*	NJR	NEW**	NOR	SWE	FIN
Sex	X	X	X	X	X	X	X	X
Age	X	X	X	X	X	X	X	X
ASA	X			X	X	X	X	X
Other comorb. Score								
Height	X			X	X		X	X
Weight	X			X	X		X	X
Hospital	X	X	X	X		X	X	X

Surgeon	X	X		X		X	X	X
Date	X	X	X	X	X	X	X	X
Previous hip surgery			X			X		X
Primary diagnosis	X	X	X	X	X	X	X	X
Primary procedure details	X	X	X	X	X	X	X	X
Laterality	X	X	X	X		X	X	X
Revision diagnosis	X	X	X	X	X	X	X	X
Type of procedure			X	X		X	X	X
Surgical Approach	X		X		X	X	X	X
Patient positioning				X		X		
MIS						X		
Implant details	X	X	X	X	X	X	X	X
Type of fixation	X	X	X	X	X	X	X	X
Fixation details		X	X	X				
Charnley class							X	
Type of OR			X		X	X		
OR attire			X					
Operative time			X		X	X		X
Perioperative complication				X		X		X
Navigation/Robotics	X							
Bone Loss			X			X		
Trochanteric osteotomy			X	X		X		
Image derived instrumentation	X							
Functional group			X					
Harris Hip Score			X					
Antibiotic prophylaxis			X		X			X
Thrombosis prophylaxis			X	X				X
Type of anaesthesia			X	X				X
Drainage use								X
Bone transplantation				X	X			
Surgeon experience				X	X			X

*Not available on website, but summarized on Danish Orthopaedic Common Database (DOF).

**Not available on website, based on annual reports.

VARIABLE	KNEES							
	AUS	CAN	DEN*	NJR	NEW**	NOR	SWE	FIN
Sex	X	X	X	X	X	X	X	X
Age	X	X	X	X	X	X	X	X
ASA	X			X	X	X	X	X
Other comorb. score								
Height	X			X	X		X	X
Weight	X		X	X	X		X	X
Hospital	X	X	X	X		X	X	X
Surgeon	X	X		X		X	X	X
Date	X	X	X	X	X	X	X	X
Previous knee surgery			X			X	X	
Primary Diagnosis	X	X	X	X	X	X	X	X
Primary procedure details	X	X		X	X	X	X	X
Knee score			X					
Functional group			X					
Laterality	X	X	X	X		X	X	X
Revision diagnosis	X	X	X	X	X	X	X	X
Type of reoperation			X	X		X	X	
Surgical approach	X		X	X	X	X		X
Bloodlessness			X				X	
Positioning						X		
MIS						X	X	
Implant details	X	X	X	X	X	X	X	X
Type of fixation	X	X	X	X		X	X	X
Fixation details		X	X	X			X	X
Type of Operating Room			X		X	X		
Operation time						X	X	X
Perioperative complication			X	X		X		X

Navigation/Robotics	X						X	
Bone loss						X		
Image derived instrumentation	X							
Patella component	X			X				
Spacer use	X							
Bone transplantations			X	X				
Thrombo-prophylaxis				X			X	X
Local infiltration analgesia							X	
Drainage use							X	X
Peroperative antibiotics							X	X
Surgeon experience				X				X
Type of anaesthesia				X			X	X
Patient specific instruments				X				

*Not available on website, but summarized on DOF.

**Not available on website, based on annual reports.