Editorial

Prosthetic joint infections—a need for consolidation?

During the last couple of years several articles on prosthetic joint infection (PJI) have been published in *Acta Orthopaedica*, ranging for example from papers on experimental studies, new surgical techniques, diagnostic modalities, risk factors, retrospective studies on treatment results, and registry studies (Geurts et al. 2013, Søe et al. 2013, Metso et al. 2014, Buttaro et al. 2015, Holmberg et al. 2015, Lübbeke et al 2016). This probably reflects that PJI is the most important complication of prosthetic surgery.

This issue of *Acta Orthopaedica* presents 4 new studies on different aspects of PJI. Zhu et al. (2016) compared data on the rate of PJI reported to the New Zealand Joint Registry (NZJR) with the "true" rate of PJI, identified by audit of hospital records (discharge and operation codes). Less than two-third of PJIs were reported to the NZJR. Similar rates of underestimation of PJI in arthroplasty registries have also been reported from the Nordic countries (Witsø 2015).

2 other articles in this issue of Acta Orthopaedica present data on the results of surgical treatment of PJI (Janssen et al. 2016, Lindberg-Larsen et al. 2016). The first one is a registry study from Denmark on 105 partial and 215 two-stage revisions, and the other one is a retrospective study from the Netherlands, presenting the results of 120 two-stage revisions performed at one center. It is rather impressive that the group from the Netherlands has presented more or less complete data on patients operated over a time span of 25 years. However, the fact that such a long time is needed to study treatment results is of course also a problem. A randomized clinical trial (RCT) should have been the ideal approach when comparing different surgical treatments of PJI, such as 1-stage and 2-stage prosthetic revision. Until now, no such study has been performed (Beswick et al. 2012, Strange et al. 2016). To get a sufficient number of patients is a major problem when conducting RCTs in orthopedic surgery (Bernstein et al. 2003). In the near future we will hopefully have the results of randomized multicenter trials comparing 1- and 2-stage revision of infected prostheses (Strange et al. 2016).

In addition, randomized trials comparing the results of different antibiotic regimes in cases of PJI have been difficult to conduct. One such example was the study on rifampin by Zimmerli et al. (1998). The study has been cited more than 560 times (Scopus), and has had a large impact on orthopedic surgeons and infectious disease specialists. The study compared antibiotic treatments in patients with an orthopedic implant infection due to staphylococci. After initial debridement, the patients underwent 2 weeks of intravenous therapy using either flucloxacillin/vancomycin with rifampin or flucloxacillin/vancomycin with placebo, followed by either ciprofloxacin-rifampin or ciprofloxacin-placebo orally. When calculating the number of patients who would have been included in the study (the sample size), the cure rate in the placebo group (patients receiving standard antibiotic therapy) was estimated to be 20% compared to 75% in the study (rifampin) group. 5 years were required to conduct the study. In all, 33 patients were included, many of whom (18) had an infected osteosynthesis. Not all patients were operated, and there were 9 dropouts. At follow-up at minimum 15 months, the cure rate was 12/12 in the rifampin group and 7/12 in the placebo group.

During the past decade, several studies on the use of rifampin in the treatment of PJI have been published, most of them retrospective in design and involving rather few patients (Soriano et al. 2006, El Helou et al. 2010, Senneville et al. 2011). In a prospective multicenter study in which 117 patients with PJI were included, the use of rifampin was not associated with a successful outcome (Cobo et al. 2011). The success rate of soft tissue revision and antibiotic treatment, with or without rifampicin, is 50–80% (Byren et al. 2009, Romano et al. 2012, Geurts et al. 2013, Holmberg et al. 2015, Westberg et al. 2015). It is therefore justified to perform a new randomized trial with more than 33 patients to clarify the role of rifampin in the treatment of PJI. It should be remembered that rifampin is first and foremost a drug used in the treatment of tuberculosis, and every effort should be made to avoid inappropriate use of it.

Another aspect of the studies on PJI presented in this issue of *Acta Orthopaedica* is related to the definition of a PJI. In the study from the Netherlands (Janssen et al. 2016), the Mayo criteria for the diagnosis of PJI were applied (Berbari et al. 1998). Currently, the most common definition of a PJI is probably that suggested by Parvizi et al. (2011). To some it may come as a surprise that neither sonication of extracted prosthesis/prosthetic parts nor molecular diagnostics, such as PCR, is included in that diagnostic armamentarium. According to the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection (ICPJI) (2013a) there was even a "strong consensus" that routine sonication and molecular techniques (such as PCR) do not have a role in the diagnosis of PJI. During the last decade, a change of attitude regarding the pathophysiology of prosthetic failure/loosening appears to have occurred. 10 years ago, it was hypothesized that septic prosthetic failure/loosening was grossly underestimated, and the term "aseptic loosening" was even questioned (Nelson et al. 2005, Waldvogel 2007). In that context, the results of some

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studies were rather central. Trampuz et al. (2007) compared the results of culture from periprosthetic tissue and culture from sonication fluid from extracted prosthetic parts in 79 patients with PJI. The overall sensitivity of culture from sonication fluid was superior to that of culture from tissue—79% and 61%, respectively. In 23 patients where the antibiotic free interval before surgery was less than 2 weeks (i.e. 4–14 days), the sensitivity of culture from sonication fluid and of culture from tissue was 87% and 48%, respectively. However, in patients where 5 or more tissue biopsies had been cultured, the overall sensitivity of culture from sonication fluid and of culture from tissue biopsies was similar (79% vs. 73%). According to supplementary data on 14 patients with positive sonication fluid cultures and negative tissue cultures, culture using synovial fluid had been performed in 7 patients, 6 of which had a positive culture (i.e. the same bacterium as that cultured from sonication fluid). Only 1 patient had negative culture from synovial fluid and a positive culture from sonication fluid. In this patient, sonicate culture showed growth of *Staphylococcus aureus*, which was also cultured in 1 out of 4 tissue biopsies. It is also interesting that in 13 of 14 patients with positive sonication fluid cultures and negative cultures from tissue, the causative microbe had been identified in previous cultures from tissue biopsies and synovial fluid. Of the 17 study patients with PJI and negative cultures from sonication fluid, 1 patient had growth of yeast from joint fluid and from 1 tissue culture, and 1 patient had growth of *S. aureus* from joint fluid. In The New England Journal of Medicine's Journal Watch, it was commented that if the above-mentioned "supplementary data" were to be considered, there would be no difference in sensitivity between sonication fluid culture and culture from tissue biopsies/synovial fluid—and that the clinical importance of these findings was unclear (Diekema 2007).

Tunney et al. (1999) reported on 120 patients who underwent revision of a hip prosthesis. All patients had received antibiotic prophylaxis before tissue sampling. Culture from tissue biopsies showed bacterial growth in 5 of 120 (4%) of the cases, culture from sonication fluid was positive in 21 of 120 (18%) of the cases, and PCR was positive in 85 of 118 (72%) of the cases.

These findings have been difficult to reproduce in prospective studies (Moojen et al. 2010, Bjerkan et al. 2012, Bémer et al. 2014). On the contrary, molecular diagnostics do not identify more PJIs than culture from tissue biopsies and joint fluid. It appears that most cases of aseptic prosthetic loosening *are* aseptic. In addition, the results of a recent study showed that identification of bacterial DNA by 16S rRNA PCR in cases of revision for suspected aseptic loosening does not influence the survival of the revision prosthesis (Boot et al. 2015). This should, however, not be interpreted as though there is no room for improvement when it comes to methods for diagnosing a PJI (Bémer et al. 2016, Peel et al. 2016), or that sonication or molecular diagnostics should not be used in special situations (ICPJI 2013b). In this issue of *Acta Orthopaedica*, Rak et al. (2106) present the results of a prospective clinical study where 2 different methods were used for diagnosis of a PJI in cases of early, delayed, and late infection. Sonication fluid and periprosthetic tissue where subjected to molecular analysis (16S rRNA PCR). 27 of 29 cases of PJI were identified after molecular analysis of sonication fluid, as compared to 22 of 27 cases when periprosthetic tissue was used for culture ($p = 0.06$). Due to the lack of a clear statistically significant difference, the authors conclude that "further investigation is required to improve detection of bacteria in patients with so-called aseptic failure".

The final conclusion from the study by Lindberg-Larsen et al. (2016) presented in this issue of *Acta Orthopaedica* is that revision surgery of infected prostheses should be centralized to high-volume centers. It is easy to agree on that point of view, but the possibility of centralization will probably differ from country to country. During the last few years, a vast number of unusual bacteria have been reported to be causative microbes in PJI, such as *Bordetella holmesii, Actinobaculum schaalii,* and *Trueperella bernardiae* (Humphrey et al. 2015, Jacquiet et al. 2015, Gilarranz et al. 2016). This in itself calls for centralization of chronically infected prosthetic revisions to hospitals where specialists in infectious medicine and medical microbiology are included in the multidisciplinary team.

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