Are conventional microbiological diagnostics sufficiently expedient in the era of rapid diagnostics? Evaluation of conventional microbiological diagnostics of orthopedic implant-associated infections (OIAI)

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The majority of orthopedic procedures include the use of implants, which increase the risk of infection due to the reduced number of bacteria needed to establish an infection (Zimmerli et al. 1982). Orthopedic implant-associated infections (OIAI) are infrequent per se, with an overall surgical site infection rate following implant surgery of 3% (Skråmm et al. 2012). However, the number of patients undergoing orthopedic implant surgery is high and increasing (Norwegian National Advisory Unit on Arthroplasty and Hip Fractures 2020).

A microbiological diagnosis is vital for providing the best treatment, with regards to both surgical options and providing targeted and narrow-spectrum antimicrobial therapy (Beam and Osmon 2018). Today’s conventional diagnostics include microbiological culturing of 5 biopsies from each infected patient on several different media for at least 5 days dependent on growing and dividing bacteria (Bergh et al. 2011, Osmon et al. 2013). More rapid diagnostic tools are being developed, but with varying degrees of sensitivity and specificity (Bonanzinga et al. 2017, Jun and Jianghua 2018, Aamot et al. 2019).

We assessed time to (a) pathogen identification, (b) antibiotic susceptibility patterns, and (c) targeted antibiotic treatment using conventional microbiological diagnostics of OIAI in a consecutive series of patients.

Patients and methods
This retrospective cohort study included all patients aged ≥ 18 years operated for acute OIAI (including prosthetic joint infections, fracture implants, and osteotomy implants) undergoing first revision surgery in 2017–2018 at Akershus University Hospital (Ahus), Norway. Ahus is Norway’s largest acute care hospital serving > 10% of the Norwegian population (5.4 million).
Committee on Antimicrobial Susceptibility Testing EUCAST was performed according to the guideline from the European Compass for flexControl v3.4. Antibiotic susceptibility testing was performed using MALDI-TOF MS Biotyper (Bruker Daltonik GmbH, Bremen, Germany, MBT 6903 MSP Library, MBT Compass v4.1.70.1, laser desorption ionization time of flight (MALDI-TOF) using net with subsequent seeding as previous described (Aamot et al. 2019). Antibiotic susceptibility testing was performed by homogenizing up to 5 tissue samples individually with mortar and pestle in heart infusion broth (HIB) in a type 2 microbiological safety cabinet with subsequent seeding as previous described (Aamot et al. 2019). Incubation was terminated after 5 days following consensus (Parvizi et al. 2013) unless slow growing bacteria, such as Cutibacterium acnes, were suspected to be clinically relevant. The incubation period was prolonged to 14 days in such cases. Cultivation results have previously been published in 13 patients (Aamot et al. 2019). Empirical treatment was based on national guidelines (Norwegian Directorate of Health, 2020) and distributed intraoperatively after biopsy. For prosthetic joint infections (PJI), the empirical treatment was vancomycin, ciproxin, and/or dicloxacillin. For other implant infections, the empirical treatment was penicillinase-resistant penicillin. 11 patients received non-empirical, targeted treatment prior to surgery due to previously diagnosed bloodstream infections or unrelated concurrent joint infections.

**Ethics, funding, and potential conflicts of interest.**
This study was approved by the Data Protection Officer (2018-105) at Akershus University Hospital. This study did not receive grants from public, commercial, or not-for-profit sectors. The authors report no conflict of interests.

**Results**
Of the 123 patients included, 62 (50%) patients were female. The median age was 71 years (25–95).

**Time to microbiology results (Table 1)**
Pathogens were identified after a median of 59 hours (2.5 days) and antibiotic recommendations were available after a median of 84 hours (3.5 days). Culturing results were finalized within a median of 141 hours (6 days).

**Pathogens causing infections and culture-negative samples (Table 2)**
Confirmed infection, defined by positive cultivation results, was observed in 109/123 (89%) patients. The remaining 14/123 (11%) patients had inconclusive/negative cultivation, of whom 4 patients had received antibiotic treatment prior to revision surgery. Monomicrobial infections were most common, identified in 79/109 (72%) patients. **S. aureus** and **S. epidermidis** were the most frequent pathogens. None of the **S. aureus** isolates and 10/18 of the **S. epidermidis** isolates were resistant to mexiticillin. 8 of 76 patients undergoing surgery during the microbiology lab’s opening hours had culture-negative biopsies, whereas 6...
of 47 patients undergoing surgery outside opening hours had culture-negative biopsies. Similar results were seen in patients’ biopsies requiring pre-cultivation in broth (6/76 versus 3/47).

Change of treatment

111/123 (90%) patients were given empirical treatment. Of the remaining 12/123 (10%) patients, 11 patients received targeted treatment based on previous infections and 1 patient did not receive any antibiotic treatment prior to cultivation results as infection was considered unlikely. Of the 109 patients with culture-positive results, antibiotic treatment was changed to targeted and narrowed treatment in 66 (61%) patients within a median of 4 days (0–24) based on the antibiotic treatment recommendations.

Discussion

Our study confirms that conventional microbial diagnostics of OIAIs is comprehensive and time-consuming with a median of 2.5 days to pathogen identification and a median of 3.5 days to antibiotic recommendation. In addition, we identified a delay of median 4 days from when antibiotic recommendations were given to clinicians to when treatment was changed.

The lengthy time to results may be explained by a combination of several factors. The bacteria require time to multiply. In addition, 11% of the patients showed inconclusive or negative culturing, which involves 5 days of culturing before termination. Of the 109 patients with culture-positive results, 9 patients had positive samples only after pre-cultivation in broth. Pre-cultivation prolongs cultivation by 2 days. Lack of concurrence between the time of surgery and the opening hours of the microbiology lab may also prolong time to results. Biopsies taken after the lab’s opening hours were not cultivated until the following day in 47/123 patients. However, the concurrence between opening hours and time of surgery did not seem to affect the cultivation outcome. The frequency of inconclusive/negative results and positive results only after broth pre-cultivation did not differ among those patients with surgery performed before 16:00 compared with after 16:00.

Staphylococci are the most frequently reported causes of orthopedic implant infections (Arciola et al. 2018), as was confirmed by our study.

Of the 109 patients with culture-positive results, 66 received targeted treatment after receiving antibiotic resistance patterns. The majority of patients received better targeted antibiotic treatment, which may have led to more efficient treatment and reduced induction of antibiotic resistance. However, the response time from notification of antibiotic susceptibility results to the actual change of antibiotic treatment took a median of 4 days. This delayed response may negate the benefit of future rapid diagnostics. In our hospital, the microbiological results are sent electronically to the patient’s medical records immediately upon approval. Our continuous efforts to reduce the time to microbiological results will come to naught without clinicians reacting accordingly. Such optimization may also be relevant in diagnostics and treatment of other patient groups and types of infections.

As a retrospective study, this work is limited by the information already registered in the patients’ journals at the time of care. Furthermore, this study was carried out in a country with a low prevalence of antibiotic resistance, so empirical treatment success may not be comparable to countries with a higher antibiotic resistance load. The study’s strengths lie in the number of patients included, as OIAI is infrequent, and the patients coming from an unselected patient population.

As the majority of patients had culture-positive biopsies, more rapid diagnostics could improve time to targeted treatment and may potentially improve clinical outcome. Our study was not designed for patient-reported outcome measures (PROMS), but the obvious benefits would be faster diagnosis, and simpler, less resource-demanding care. An additional potential advantage is the reduction of antibiotic resistance development through more targeted and narrow-spectrum antibiotic treatment. This will require further investigation.

In conclusion, in taking 2.5 days for pathogen identification and 3.5 days for targeted treatment advice, conventional microbiological diagnostics of OIAI are not sufficiently expedient. Same-day diagnostics may contribute to rapid targeted treatment and more favorable clinical outcomes, but the delayed response from clinicians on the treatment recommendations needs to be addressed.
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