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# Diagnostic Microbiology and Infectious Disease

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## Time to positivity of acute and chronic periprosthetic joint infection cultures<sup>☆</sup>

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### ABSTRACT

**Introduction:** A prolonged incubation time is generally recommended for diagnosing periprosthetic joint infections (PJI). However, in literature, no distinction is made between acute and chronic infections.

**Methods:** All patients with a PJI that underwent surgical debridement between November 2015 and February 2019 with or without revision of the prosthesis were retrospectively evaluated. Synovial fluid, 5 intraoperative periprosthetic tissue samples, and the sonicated prosthesis were cultured.

**Results:** Fifty-nine patients were analyzed, including 21 acute PJIs (33 isolates) and 38 chronic PJIs (46 isolates). In acute PJIs, all isolates grew within 5 days, while this took 11 days for chronic PJIs. Sonication fluid showed the shortest time to positivity (78% at day 2) for chronic PJIs, but no difference was observed for acute PJIs compared to tissue cultures.

**Conclusion:** In contrast to cultures from chronic PJIs, acute PJIs do not need a prolonged incubation time and no clear benefit is observed for sonication.

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## 1. Introduction

One of the more serious complications after orthopedic arthroplasty is a periprosthetic joint infection (PJI). Although the incidence of PJI is rather low; around 1% for hip and shoulder prostheses and around 2% for knee prostheses, infection accounts for 15% of the indications for revision surgery of hip implants and 25% for knee implants (Bozic et al., 2009, 2010). PJI can be caused by a plethora of bacterial species with different degrees of virulence. In most cases, virulent bacteria like *Staphylococcus aureus* and Gram negative rods are associated with more acute symptoms like joint effusion, fever and leucocytosis. While less virulent bacteria like *Cutibacterium acnes* and Coagulase Negative Staphylococci (CoNS) are associated with more subtle and chronic symptoms like persisting joint pain. Based on these characteristics and the duration of symptoms, PJIs are classified in acute and chronic infections. In general, acute infections are treated with debridement, antibiotics and implant retention (DAIR) while in chronic infections, the prosthesis needs to be revised (Osmon et al., 2013).

Microbiological diagnosis of PJI is, amongst others, dependent on the bacterial replication rate. In general, virulent bacteria show a faster replication rate, while less virulent bacteria have a slower replication rate

(Schafer et al., 2008). Moreover, in biofilm associated infections, the degree of biofilm formation plays an essential role in replication rate as well. Bacteria within a mature biofilm remain in a dormant state and are therefore, more difficult to cultivate (Wood et al., 2013). Since isolating all causative microorganisms is key for the success of antibiotic treatment, there has been debate about the length of incubation of PJI samples. An incubation time of 10–14 days is the main consensus, dependent upon the culture techniques applied (e.g. use of sonication, incubation of samples in blood culture bottles etc.) (Butler-Wu et al., 2011; Minassian et al., 2014; Portillo et al., 2015; Wolcott and Ehrlich, 2008). However, in literature, no distinction is made between acute and chronic PJIs. Therefore, in this study we evaluated whether time to positivity (TTP) for acute and chronic PJI differs.

## 2. Methods

### 2.1. Study population

All patients who underwent a DAIR procedure or revision surgery at the University Medical Center Groningen between November 2015 and February 2019 were retrospectively evaluated. PJIs were diagnosed according to the criteria proposed by the Musculoskeletal Infection Society (MSIS) (Parvizi et al., 2011, 2018). Culture negative PJIs were excluded. Acute PJIs were defined as either early acute / post-surgical infections (i.e. within 3 months after the index arthroplasty) or late

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acute / hematogenous infections, both with a symptom duration of less than 3 weeks before a DAIR procedure was performed. A chronic PJI was defined as late infections (i.e. more than 3 months after the index arthroplasty) with a symptom duration for more than 3 weeks. Reimplantation cultures and sonication of spacers were excluded from the analysis. Ethical approval by the local ethical committee was not required for this study.

## 2.2. Laboratory procedures

An average of 5 intraoperatively obtained tissue samples, synovial fluid and the orthopedic prosthesis/insert/liner were directly transported to the microbiological laboratory during working hours (including weekends) or cooled at 4 °C outside working hours before transport to the laboratory. Each sample was cultured for 9 to 14 days (laboratory standard is 9 days, but the incubation length could be increased due to weekends or on request of a medical microbiologist) on blood and chocolate agar under aerobic conditions (with 5% CO<sub>2</sub>) and on Brucella blood agar under anaerobic conditions. Synovial fluid and peri-prosthetic tissues were also cultured in fastidious broth (Media products, Groningen, The Netherlands). When >5 mL of synovial fluid was received, synovial fluid was also incubated in blood culture bottles (<10% of cases). All broths were subsequently subcultured on blood and Brucella agar after 7 days of incubation, or earlier when deemed positive. Subcultures were incubated for an additional 2 days. The prosthesis, insert or liner was sonicated for 1 minute at 40,000 Hertz in sterile Ringer lactate. One hundred microliters of the sonication fluid was plated on blood agar plates and 10 mL sonication fluid was incubated in blood culture bottles in a blood culture system (BD BACTEC™), both were incubated for 9 days. Positive blood cultures were subsequently plated on blood agar plates and the bacterial species directly determined using the matrix assisted laser desorption/ionization time-of-flight analyzer (MALDI-ToF) system on bacterial pallet obtained using a BD vacutainer serum separation tube. Cultures were analyzed only during working days.

## 2.3. Data analysis and definitions

To identify polymicrobial infections, all morphologically distinct colonies were identified using the MALDI-ToF system. When isolates were identified as similar species but with a distinct morphology, an antibiogram was made of both isolates. When the antibiogram differed significantly, the isolated were considered as 2 different pathogens.

TTP was set on the day that an isolate was identified by MALDI-ToF (the first day of growth in all cases). To avoid the inclusion of contaminants, positivity was defined as a positive culture that was considered as clinically relevant: a culture was considered as true positive, and thus considered as a confirmed PJI, according to the MSIS criteria (i.e. 2 positive cultures with the same microorganism or 1 positive culture combined with an additional other positive criteria, for example an increased leucocyte count in synovial fluid or positive intraoperative histology) (Parvizi et al., 2011, 2018). If these criteria were not met, a positive culture was considered as a contaminant.

## 3. Results

### 3.1. Study population

We analyzed 237 cases that underwent a DAIR procedure or revision surgery. A total of 107 cases were culture positive. Of the 107 positives, 41 cultures were considered contaminants and 7 were reimplantation cultures as part of a 2-stage revision, leaving a total of 59 confirmed PJIs. Of the 59 cases, 38 were chronic PJIs and 21 were acute PJIs. The 59 cases included 22 knee prosthesis, 34 hip prosthesis, 2 shoulder prosthesis and 1 elbow prosthesis. The 38 chronic PJI cultures yielded 46 microorganisms, while 33 microorganisms were isolated from the 21 acute PJI cultures.

### 3.2. TTP is lower in acute PJI cultures compared to chronic PJI cultures

From all analyzed PJI cultures, 79 unique non-contaminant isolates were identified, with TTP determined by the second positive culture per unique isolate or by the first and only positive culture when combined with additional positive criteria according to MSIS criteria (Parvizi et al., 2011, 2018). Acute PJI cultures ( $N = 33$ ), showed a median TTP of 2 days (range 1–5), with 80% of species identified within 2 days post inoculation and 100% within 5 days (Fig. 1A). Chronic PJI cultures ( $N = 46$ ) also showed a median TTP of 2 days (range 1–11). Although in the chronic cultures, 90% of species were isolated after 4 days of inoculation, it took 11 days before 100% of species were isolated (Fig. 1B).

We additionally analyzed the TTP and culture yield of different sample types. In acute PJIs, sonication fluid and periprosthetic tissue cultures showed a similar total bacterial yield of  $\pm 80\%$ , and TTP of sonication fluid was not shorter compared to tissue cultures (Fig. 1C). However, in 4 acute PJIs, sonication of the mobile parts did identify an additional micro-organism as part of a polymicrobial infection which was not isolated with the other culturing techniques. The bacteria identified included *Corynebacterium amycolatum* and *Staphylococcus haemolyticus*, *S. lugdunensis* and *S. epidermidis*. Culturing synovial fluid did not seem to have clear added benefit (only 33% positivity), but in one case synovial fluid culture proved PJI diagnosis according to MSIS criteria, by the isolation of the second positive sample. In chronic PJIs, sonication fluid showed the fastest culture yield (78% after 2 days and also the highest yield of 93% (Fig. 1D). Periprosthetic tissue cultures had a total yield of 80%, but TTP was longer (52% after 2 days) compared to sonication cultures. Synovial fluid culture showed 43% positivity.

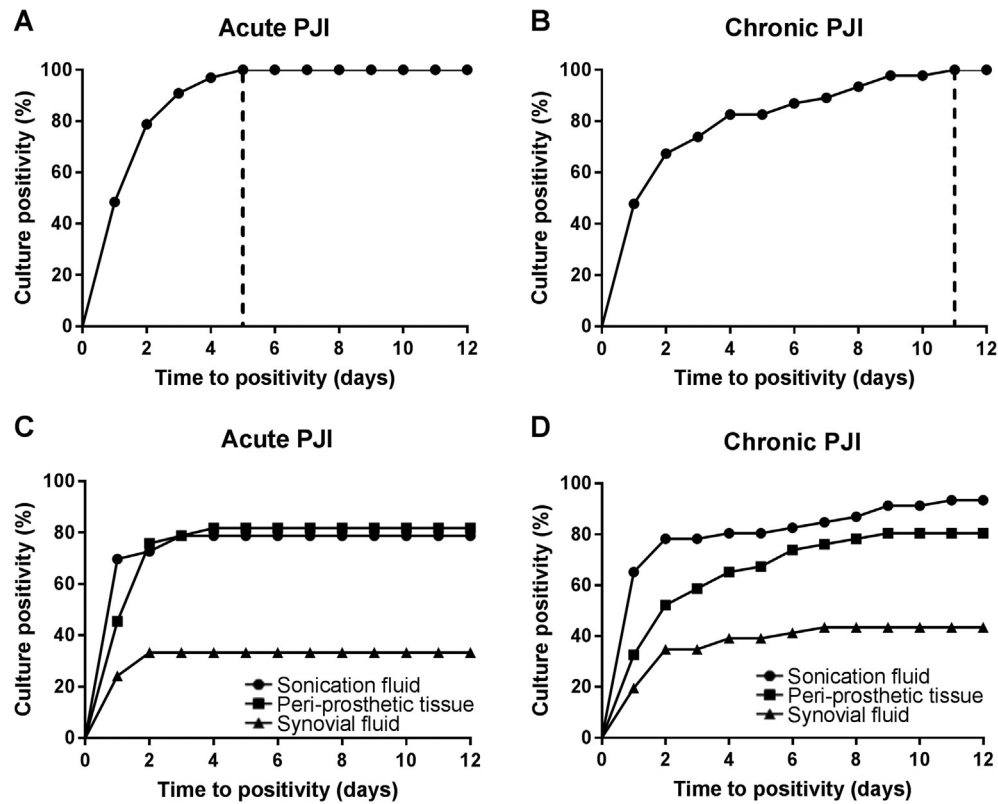
### 3.3. TTP depends on the PJI causing species

We additionally analyzed the TTP in relation to the type of pathogen isolated. A clear difference was seen in TTP between more virulent species like *S. aureus*, Gram negative rods and streptococci, and less virulent species like *C. acnes*, CoNS and aerobic Gram positive rods/others (Fig. 2). Enterococci also showed a short TTP. More than 90% of virulent organisms were isolated on day 1 or 2 after incubation. The CoNS group showed approximately 70% positivity in the first 2 days, while it took 7 days to isolate all CoNS (4 days in acute PJI, 7 days in chronic PJI) (Fig. 2B). *C. acnes* isolates grew from the 4th day on and it took 11 days to isolate all *C. acnes* isolates (Fig. 2F). The growth of aerobic Gram positive rods/others showed a linear isolation curve, with a maximum of 9 days to isolate all species (Fig. 2G). *C. acnes* was solely isolated in chronic PJI cultures, while *Streptococcus* spp. were isolated predominantly in acute PJI cultures (Fig. 2H).

In our study population, 41 cultures were considered contaminants, according to the criteria proposed by the Musculoskeletal Infection Society (MSIS), containing 73 isolates. Species identified as contaminants were either Coagulase negative staphylococci, *Cutibacterium acnes* or Gram positive rods/others. In Coagulase negative staphylococci, most non-contaminants were cultured within 3 days of incubation while more than half the contaminants were isolated from day 4 or later. In contaminated isolates identified as *Cutibacterium acnes* or Gram positive rods/others, the TTP did not show a pattern distinct from non-contaminants. Contaminants were predominantly cultured from agar cultures of sonication fluid and tissue or broth cultures of tissue and synovial fluid, and less from agar cultures from synovial fluid and sonication fluid incubated in blood culture bottles (Supplemental material, fig. S1).

### 3.4. Prosthesis age does not correlate with time to positivity

One of the challenges in the microbiological diagnosis of PJI is culturing sessile bacteria within biofilm. Since biofilm formation is correlated with the time a PJI exists, we investigated the correlation between TTP



**Fig. 1.** Time to positivity for acute and chronic PJI cultures. A-B: Time to positivity (TTP) plotted against the percentage of culture positivity in acute ( $N = 33$ ) (A) and chronic ( $N = 46$ ) (B) PJIs. Culture positivity was defined as the second isolation of a unique bacterium. C-D: TTP plotted for different clinical samples. Dotted line indicates 100% isolation yield.

and the age of the prosthesis provided that the bacteria contaminated the wound during surgery. For this analysis, all hematogenous PJIs were excluded. For all samples tested, we did not observe a correlation between TTP and prosthesis age in acute (Fig. 3A-B) or chronic (Fig. 3C-D) PJI samples.

#### 4. Discussion

A prolonged incubation time of 10 to 14 days is generally recommended for diagnosing PJIs, but in literature no clear distinction is made between acute and chronic PJIs. In this study, we retrospectively analyzed whether TTP differs between acute and chronic infections, and found that the TTP of acute PJI cultures are considerably shorter compared to chronic PJI cultures. In our study, all isolates of acute PJIs grew within 5 days while this took 11 days for chronic PJIs. In addition, in contrast to cultures from chronic PJIs, sonication showed no benefit concerning TTP for acute PJIs.

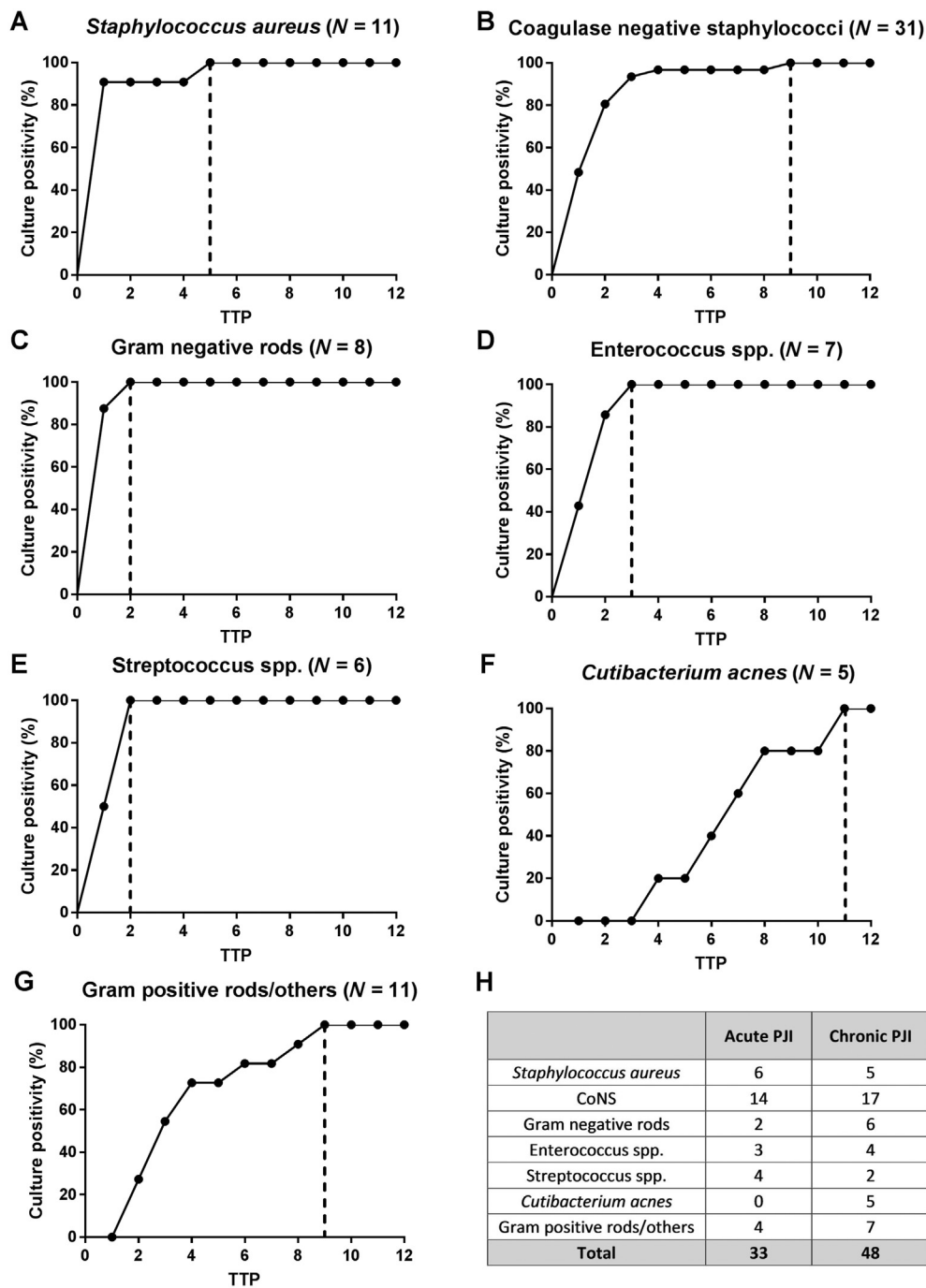
Although it makes sense that a shorter incubation time is sufficient for acute PJIs due to a high bacterial load and the presence of predominantly planktonic bacteria, the coexistence of biofilm may slow the metabolic rate and hamper the TTP. In addition, acute PJIs may involve low virulence microorganisms as well, especially in polymicrobial infections (Lowik et al., 2019; Tsai et al., 2019). Shorter incubation of acute PJI samples might then lead to failure to diagnose infection with low virulent micro-organisms in polymicrobial infections. Nevertheless, our study clearly shows that there are distinct TTP patterns for acute and chronic PJIs, and indicate that prolonged incubation is not needed for acute PJI samples. These findings apply for low virulent microorganisms isolated in acute PJI samples as well (i.e. CoNS and enterococci).

Our results have the potential to reduce the workload of handling PJI cultures in the laboratory and subsequently diagnostic costs, and allow for timely narrowing broad spectrum empiric antibiotic treatment regimens. A recent publication by Deroche et al. advocated that empiric

antibiotics for PJI can be re-evaluated at day 5 for both mono- and polymicrobial infections (Deroche et al., 2019). Our data demonstrate that although the day 5 mark indicated by Deroche et al. may hold true for acute infections, only 80% of pathogens are isolated after 5 days in chronic infections, which is consistent with other findings in literature (Butler-Wu et al., 2011). Although our study was not designed to evaluate the sensitivity of different culture methods in PJI diagnosis, we showed a sensitivity of 79% in acute and 93% in chronic PJI for the culturing of sonication fluid. Former publications on this topic have shown an even higher sensitivity up to 100%, but a pooled sensitivity of 85% in a recent meta-analysis shows that our data is comparable to literature (Li et al., 2018; Portillo et al., 2015).

In addition to the above mentioned results, we demonstrated that sonication of mobile parts in acute PJIs samples did not result in a shorter TTP and in addition, sonication contributed only minimally to the culture yield compared to tissue samples. However, we did observe that sonication of mobile parts resulted in the isolation of unique isolates in polymicrobial infections e.g. CoNS and gram positive rods. Although isolation of these organisms could be due to contamination, PJI with CoNS are known to be a major risk factor for treatment failure after DAIR (Kuiper et al., 2014) and failure to diagnose CoNS in acute PJI could have major consequences in the long run. Therefore sonication of mobile parts should in our opinion be performed despite the minimal extra benefit in TTP and culture yield. We did find a clear benefit of sonication in chronic PJI samples, both in TTP as in total culture yield. The effect of sonication on TTP and culture yield in chronic PJI has been shown before (Portillo et al., 2015; Puig-Verdie et al., 2013) and may be explained by the ability of sonication to destruct the bacterial biofilm, bringing sessile bacteria back into a planktonic state (McConoughey et al., 2014; Tunney et al., 1998). These results show that sonication of implants from chronic PJI patients is of added value in diagnosing PJI and reducing TTP.

Our study has a few limitations. First, according to our local protocol, samples were incubated for a minimum of 9 days. The incubation time

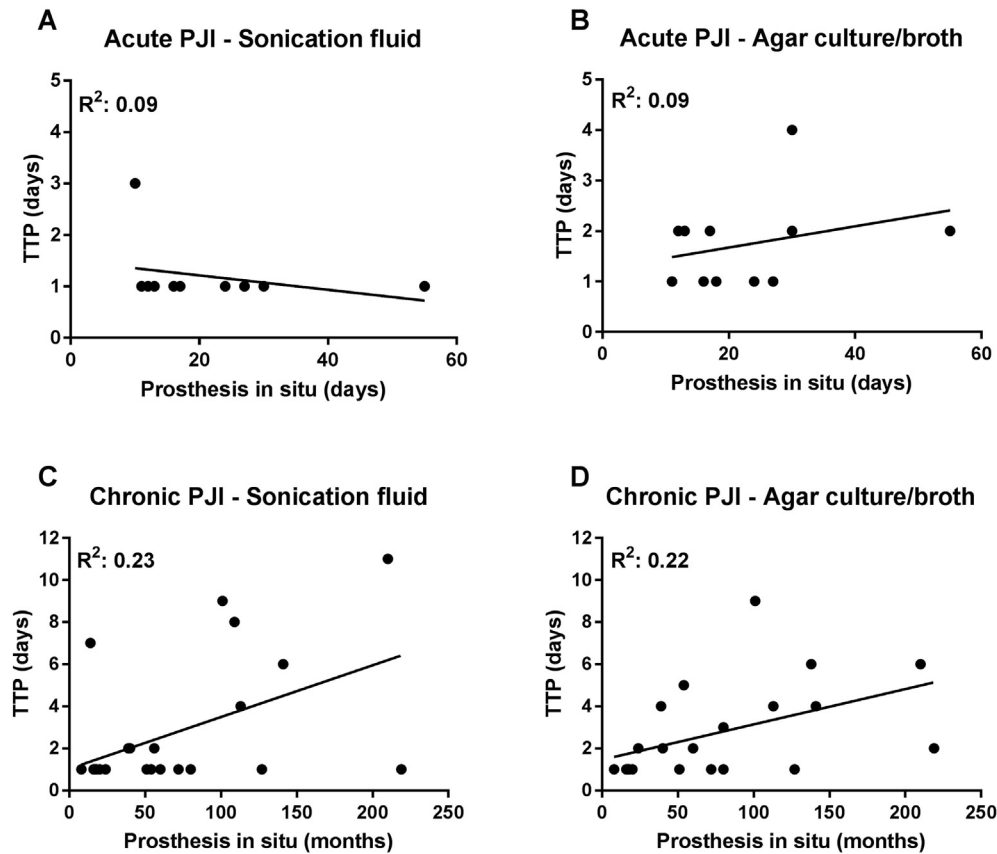


**Fig. 2.** Species specific time to positivity in periprosthetic joint infections. TTP for different bacterial species cultured from PJI samples. More virulent species like *S. aureus* (A), gram negative rods (including: *Enterobacter cloacae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens* and *Citrobacter braakii*) (C), streptococci (E) and enterococci (D) are isolated faster compared to less virulent bacteria like coagulase negative staphylococci (B), *C. acnes* (F) and gram positive rods/others (including: *Corynebacterium* spp., *Abiotrophia defectiva*, *Bacillus pumilus*, *Granulicatella adiacens* and *Bacillus cereus*) (G). Dotted line indicates 100% isolation yield. (H) Isolated bacterial species divided for acute and chronic PJI.

was prolonged to 11 days in weekends or to a maximum of 14 days on request of the medical microbiologist. Not analyzing the cultures during the weekend could potentially bias the TTP in these samples. Furthermore, an average incubation time of 9 days could lead to false negative cultures according to literature stating that *C. acnes* can take up to 14 days to isolate, even when sonication fluid is incubated in blood culture bottles (Butler-Wu et al., 2011; Li et al., 2019). However, in our study, samples from patients suspected for PJI but with a negative culture after 9 days were incubated longer according to guidelines by the International Consensus Meeting (ICM) on Musculoskeletal infections (Ascione et al., 2019). In addition, a prolonged incubation period

might lead to isolation of contaminants, especially caused by *C. acnes* (Bossard et al., 2016), even though a recent meta-analysis did not support that (Li et al., 2018). However, the results of the meta-analysis concerning contaminants have to be analyzed with caution since not all studies elaborated on the criteria used to determine contaminants. Second, our study is of retrospective nature and consists of a relatively small number of patients. Therefore, drawing firm conclusions is difficult, especially on incubation length in chronic PJI's due to a low number of *C. acnes* positive PJI's. Thirdly, despite earlier work showing benefit of incubating synovial fluid in blood culture bottles (Hughes et al., 2001), in our study <10% of synovial fluid was incubated in blood culture





**Fig. 3.** Correlation between prosthesis age and time to positivity. Prosthesis age plotted against time to positivity for acute PJI sonication fluid cultures ( $N = 11$ ) (A) and direct blood agar and broth cultures ( $N = 12$ ) (B) and chronic PJI sonication fluid cultures ( $N = 24$ ) (C) and direct blood agar and broth cultures ( $N = 21$ ) (D).

bottles due to insufficient amounts of synovial fluid received. This might explain the low sensitivity of synovial fluid cultures found in our study.

In conclusion, our data demonstrate that the TTP of acute and chronic PJI cultures has a different dynamic. In acute PJI cultures, 5 days of incubation is sufficient to isolate all micro-organisms, while chronic PJI cultures require 11 days of incubation to reach a 100% yield. Our findings indicate that empiric antibiotic therapy can be re-evaluated after 5 days for acute PJIs. Our findings need to be confirmed in a larger cohort of patients.

#### Declaration of competing interest

The authors have no conflict of interest to declare.

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