The role of BioFire Joint Infection Panel in diagnosing periprosthetic hip and knee joint infections in patients with unclear conventional microbiological results

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Aims

This study aimed to evaluate the BioFire Joint Infection (JI) Panel in cases of hip and knee periprosthetic joint infection (PJI) where conventional microbiology is unclear, and to assess its role as a complementary intraoperative diagnostic tool.

Methods

Five groups representing common microbiological scenarios in hip and knee revision arthroplasty were selected from our arthroplasty registry, prospectively maintained PJI databases, and biobank: 1) unexpected-negative cultures (UNCs), 2) unexpected-positive cultures (UPCs), 3) single-positive intraoperative cultures (SPCs), and 4) clearly septic and 5) aseptic cases. In total, 268 archived synovial fluid samples from 195 patients who underwent acute/chronic revision total hip or knee arthroplasty were included. Cases were classified according to the International Consensus Meeting 2018 criteria. JI panel evaluation of synovial fluid was performed, and the results were compared with cultures.

Results

The JI panel detected microorganisms in 7/48 (14.5%) and 15/67 (22.4%) cases related to UNCs and SPCs, respectively, but not in cases of UPCs. The correlation between JI panel detection and infection classification criteria for early/late acute and chronic PJI was 46.6%, 73%, and 40%, respectively. Overall, the JI panel identified 12.6% additional microorganisms and three new species. The JI panel pathogen identification showed a sensitivity and specificity of 41.4% (95% confidence interval (CI) 33.7 to 49.5) and 91.1% (95% CI 84.7 to 94.9), respectively. In total, 19/195 (9.7%) could have been managed differently and more accurately upon JI panel evaluation.

Conclusion

Despite its microbial limitation, JI panel demonstrated clinical usefulness by complementing the traditional methods based on multiple cultures, particularly in PJI with unclear microbiological results.

Article focus

- This study used the BioFire Joint Infection (JI) panel technology to evaluate 268 archived synovial fluid samples related to revision cases following total hip and knee arthroplasty with unclear microbiological results.

Bone & Joint Research

Key messages

- The JI panel helped to resolve cases with unclear microbiological results related to unexpected-negative cultures, unexpected-positive cultures, and single-intraoperative positive cultures.
- The JI panel identified additional microorganisms compared to conventional microbiology in patients on antibiotic therapy and in recurrent cases.
- The results obtained with the JI panel suggest that this molecular approach may be useful as an intraoperative diagnostic tool (especially in late acute cases), but should not be used as an alternative to the traditional methods based on multiple cultures.

Strengths and limitations

- This is the largest single-centre study using JI panel technology to exclusively evaluate very well characterized patients who underwent revision hip and knee arthroplasty with unclear microbiological results.
- The JI panel has a limited microbial coverage and does not identify relevant periprosthetic joint infection causative microorganisms such as *Staphylococcus epidermidis* and *Cutibacterium acnes*.
- JI panel result was compared with the culture result either in tissue(s) and/or sonication fluid, due to the limited availability of culture results for intraoperative synovial fluid.

Introduction

Culture-based methods are the gold standard for identifying the causative pathogen(s) in hip and knee periprosthetic joint infection (PJI).[1] However, they have limitations, such as generating false-negative results despite clinical and laboratory evidence of PJI while also, in contrast, detecting false-positive microorganism(s).[2-5] Moreover, conventional microbiology tends to underestimate polymicrobial infections, which are often attributed to both fast-growing and indolent bacteria,[6] and to produce single-positive intraoperative cultures (SPCs), the clinical relevance of which is still not fully understood.[7]

Molecular diagnostic techniques may have a complementary role in traditional microbiology.[8,9] The commercial BioFire Joint Infection (JI) panel (BioFire; bioMérieux, USA) uses a multiplex polymerase chain reaction (PCR)-based approach and provides rapid identification in synovial fluid of 31 clinically relevant PJI microorganisms, as well as eight antimicrobial resistance markers.[10]

The JI panel has shown potential clinical utility in the management of suspected native septic arthritis and late acute (haematogenous) PJI.[10-14] However, there are no reports on the use of this technology in cases with unclear microbiological results, particularly in dealing with hip and knee PJI. Furthermore, the relevance of using the JI panel in chronic PJI has not been addressed. Therefore, the aims of the present study were: 1) to evaluate the performance of the JI panel in cases where conventional microbiology is unclear (unexpected-negative cultures (UNCs), unexpected-positive cultures (UPCs), and SPC) using clearly infected and clearly aseptic cohorts as controls; 2) to compare the performance of the JI panel in chronic PJI cases using acute and late acute PJI cohort as controls; and 3) to assess potential impact of synovial fluid on the management of PJI when used as a complementary intraoperative diagnostic tool.

Methods

Study design and selected population

This single-centre retrospective cohort study was conducted in accordance with the Declaration of Helsinki,[15] as well as national and institutional standards. After the institutional review board's approval and patients' informed consent were obtained, we analyzed our institutional arthroplasty registry, prospectively maintained PJI database, and biobank. We selected five groups from several commonly encountered scenarios when dealing with hip and knee revision arthroplasties, particularly: 1) UNC resulting from a clinically septic procedure; 2) UPC obtained from a presumed clinically aseptic procedure; 3) SPC; and control groups from 4) clearly septic and 5) aseptic revisions.

A total of 268 synovial fluid (SF) samples collected from 195 patients who experienced one or multiple episodes of hip and knee PJI met the inclusion criteria. Patients on ongoing antibiotic therapy at the time of specimen collection were prioritized, as they are known to be challenging for conventional microbiology analysis.[16] The selected patients were characterized by sex, age, BMI, type of joint, number of previous revisions, and American Society of Anesthesiologists (ASA) grade.[17] Cases were categorized according to the International Consensus Meeting (ICM) 2018 criteria for PJI classification.[18,19] PJIs were categorized as early acute, late acute, and chronic infections.[20] The baseline characteristics of the 195 selected patients, including demographics and relevant clinical information, are depicted in Table I.

Evaluation of the BioFire film array joint infection panel

SF samples were collected routinely by arthrocentesis under sterile conditions according to the institutional protocol of Orthopaedic Hospital Vienna-Speising, and immediately stored at -80°C in the existing biobank until further analysis. For JI panel assessment, 200 µl of frozen SF was tested under aseptic conditions following the manufacturer's recommendations. The BioFire JI investigational use only (IUO) panel was used to evaluate 211/268 SF samples, and the remaining 57/268 SF samples were evaluated using the in vitro diagnostic (IVD) kit, which was approved by the USA Food and Drug Administration Agency (FDA) during the study. Discrepant results were further investigated by the BioFire R&D group, bioMérieux (France) and Ares Genetics (Austria) using microorganism-specific PCR followed by sequencing.

Microbiological analysis

Conventional microbiological analysis of SF, intraoperative periprosthetic tissues, and sonication fluid resulting from sonication and vortexing of explanted devices was conducted under aerobic and anaerobic conditions as previously described.[21]

Statistical analysis

Sensitivity was calculated as the percentage of accurate positive and negative JI panel findings compared with the ICM 2018 infection diagnosis classification criteria and conventional microbiological analysis, respectively. For the latter, the

Table I. Demographics and clinical profile of the patients.

Baseline characteristics	Total
Patients, n	195
Male, n (%)	82/195 (42.1)
Female, n (%)	113/195 (57.9)
Mean age, yrs (SD)	70.24 (2.5)
Mean BMI, kg/m^2 (SD)	30.62 (8.62)
THAs, n (%)	59/195 (30.3)
TKAs, n (%)	136/195 (69.7)
ASA grade, n (%)*	
I	9/268 (3.3)
II	172/268 (64.2)
III	87/268 (32.5)
Synovial fluid samples, n	268
Samples collected from patients on antibiotic therapy, n (%)†	122/268 (45.5)
ICM 2018 PJI criteria, n (%)	
Infected	141/268 (52.6)
Chronic	84/141 (59.6)
Early acute	31/141 (22.0)
Late acute	26/141 (18.4)
Non-infected	89/268 (33.2)
Inconclusive	38/268 (14.2)
Single-positive cultures, n (%)	
Infected	25/141 (18.4)
Non-infected	32/89 (36)
Inconclusive	10/38 (26.3)
Median number of previous revisions (IQR)	2 (0 to 2)

*The ASA grade was determined per case and not per patient. The population selected for the study included recurrent patients who had more than one synovial fluid sample evaluated in the study. These patients underwent multiple revision surgeries with changes in ASA grade over time.

†The high number of samples collected from patients on ongoing antibiotic therapy was specifically chosen for the study to increase the number of cases that may have been particularly problematic for conventional microbiological analysis.

ASA, American Society of Anesthesiologists; ICM, International Consensus Meeting; IQR, interquartile range; PJI, periprosthetic joint infection; SD, standard deviation; THA, total hip arthroplasty; TKA, total knee arthroplasty.

comparison was based on the availability of the culture results from specimens collected during the relevant procedure. As most orthopaedic centres, such as ours, do not routinely send SF from revision surgeries for microbiological analysis,[22] the comparison of microbial detection between the JI panel result in frozen SF and the corresponding original microbiological result in SF was made for only 57/268 SF samples. For the remaining 211/268 archived SF samples, the comparison had to be made between the JI panel result in SF and the initial microbiological findings in tissue(s) and/or sonication fluid obtained from the same procedure. SF samples were divided into culture-negative and culture-positive groups; the latter group was further subdivided into culture-positive with at least one JI 'on-panel' microorganism, and culture-positive with JI 'off-panel' microorganism(s). This comprehensive classification allowed an in-depth evaluation of the JI panel in detecting the relevant PJI-causative microorganisms, thus reflecting the microbiological scenarios observed in PJI cases. Specificity was determined as the percentage of accurate negative JI panel results compared with culture-based results and infection diagnostic classification. Analyses were performed separately for 'on-panel' culture-positive cases only and JI 'on-panel' culture-positive cases including 'off-panel' JI microorganisms for an overall assessment. Binomial confidence intervals (CIs) were calculated using the Wilson method. Differences in distributions of a JI-positive result in early/late acute and chronic infections were assessed using chi-squared tests with standardized residuals. A significance level of $p < 0.05$ was used.

Results

Performance of the BioFire JI panel technology in cases with unclear conventional microbiological results

Overall, the study included two main groups according to whether the initial microbiological analysis was performed either on SF only (Figure 1a) or on tissue(s) and/or sonication fluid (Figure 1b) only at the time of the specific procedure. A total of 146/268 (54.5%) SF samples associated with culture-positive and 122/268 (45.5%) culture-negative cases, classified as infected, non-infected, and inconclusive cases, were evaluated. As shown in Figures 1a and 1b, the JI panel yielded a total of 61/146 (41.8%) and 10/122 (8.2%) positive JI panel results, respectively. Overall, 7/48 (14.5%) cases of UNCs and 15/67 (22.4%) cases of single-intraoperative cultures had a positive microorganism detection using the JI panel technology. Negative JI panel results were found among all the selected cases related to UPCs. Further analysis of the infected group (Figure 1c) showed good correlation between a JI panel-positive detection and PJI classification in late acute infections (17/26; 73.1%), but lower percentages of positive JI panel yields in early acute (14/30; 46.7%) and chronic (34/85; 40%) infections. Chi-squared tests showed a significant difference in the distribution of JI panel results between the early acute, late acute, and chronic infection groups (χ^2 (2) = 8.7; p = 0.013). The frequency of positive JI panel results was significantly higher in the late acute infection group (p = 0.004), while negative results were significantly more frequent in the chronic infection group (p = 0.028).

Positive JI panel detections were found in two SF samples from the inconclusive culture-negative groups (Figures 1a and 1b), which would have been reclassified as infected by ICM-2018 upon JI panel evaluation. The concordance between JI panel positive results and PJI classification showed a sensitivity of 47.5% (95% CI 39.5 to 55.7) and a specificity of 96.8% (95% CI 92.2 to 98.8).

Microorganism(s) detection by the BioFire JI panel

In total, the BioFire JI panel identified 21 additional microorganisms in the five cohorts selected for this study, adding 12.6% to the original pool of 167 microorganisms listed in

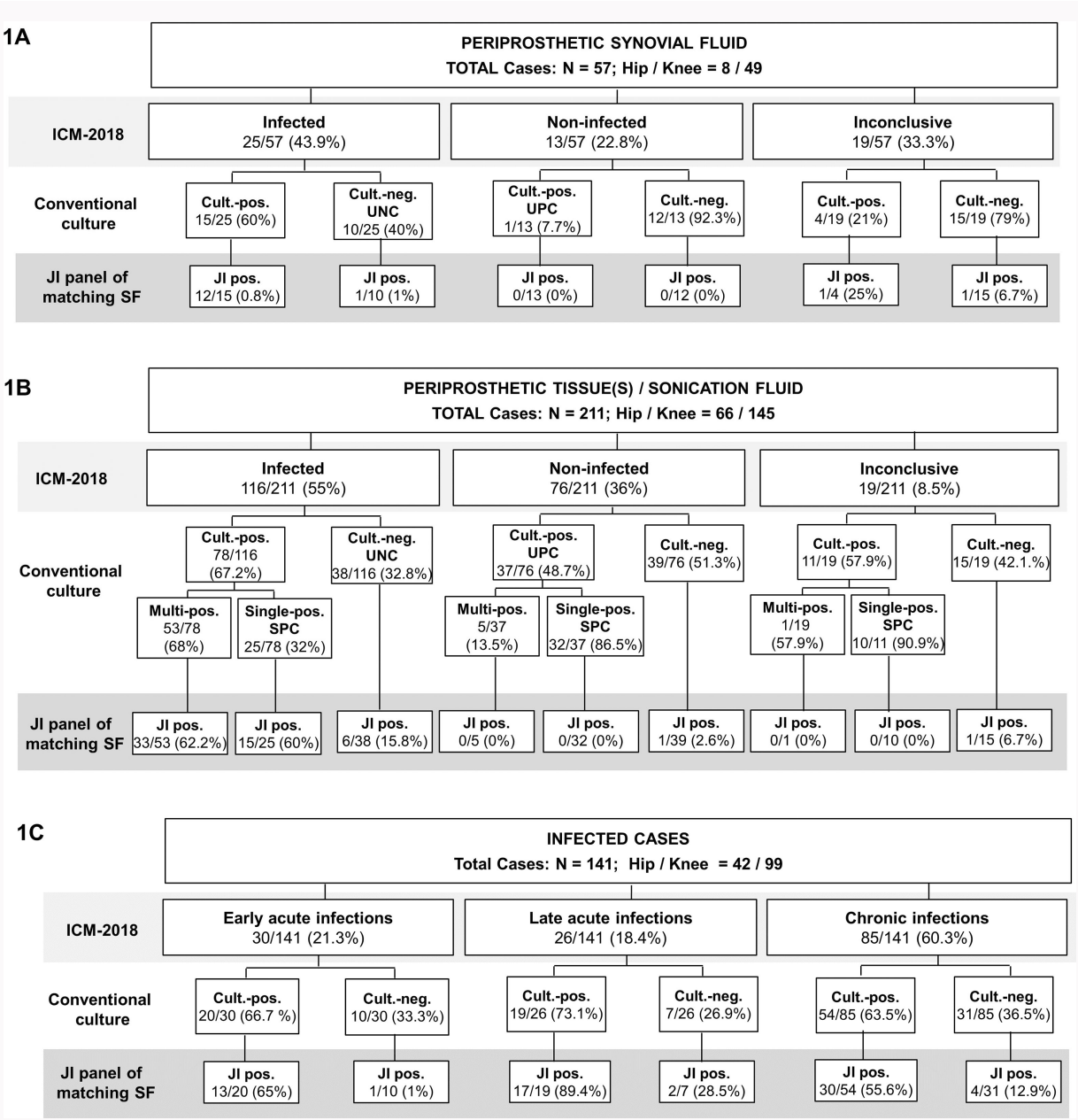

Fig. 1

Performance of the BioFire Joint Infection (JI) panel technology (bioMérieux) in periprosthetic hip and knee cases with unclear microbiological results. The number of positive JI panel results was compared with the number of positive (culture-positive) and negative (culture-negative) results initially obtained (at the time of the specific procedure) by conventional culture either on a) synovial fluid (SF) only or on b) tissue(s) and/or sonication fluid only from infected, non-infected, and inconclusive cases. c) Percentage of positive agreement between JI panel-positive results and PJI classification according to International Consensus Meeting (ICM) 2018 criteria, including early acute, late acute, and chronic infections. Cult.-neg., culture-negative; Cult.-pos., culture-positive; JI pos., JI-positive; Multi-pos., multi-positive; Single-pos., single-positive; UNC, unexpected negative-culture; UPC, unexpected positive-culture.

Supplementary Table i. The three newly identified species – *Finegoldia magna*, Peptinophilus, and *Anaerococcus prevotii* – represent an additional 7% of the 43 species originally included (Supplementary Tables ii and iii). The 21 microorganisms were detected in 16/268 (5.97%) SF samples and categorized into five groups (Supplementary Table iv).

Figure 2 shows the distribution of positive JI panel results among culture-negative and positive cases with JI 'on-panel' and 'off-panel' microorganisms (Figure 2).

All evaluated SF samples with an initial 'on-panel' positive detection by conventional microbiological analysis (Figure 2a) yielded a JI panel-positive result matching with the microorganism identified. In two of those SF specimens, additional pathogens were detected. In the group of SF samples related to cases where microbiological analysis was only performed on tissue(s) and/or sonication fluid culture (Figure 2b), the percentage of positive agreement (PPA) between culture-positive attributed to JI 'on-panel' microorganisms and the JI panel evaluation result was 47/67 (70%). In one case, the JI panel identified a different microorganism from the *S. capitis* isolate initially detected by culture; in three other cases additional microorganisms were found. Details of each discrepant case are shown in Table II.

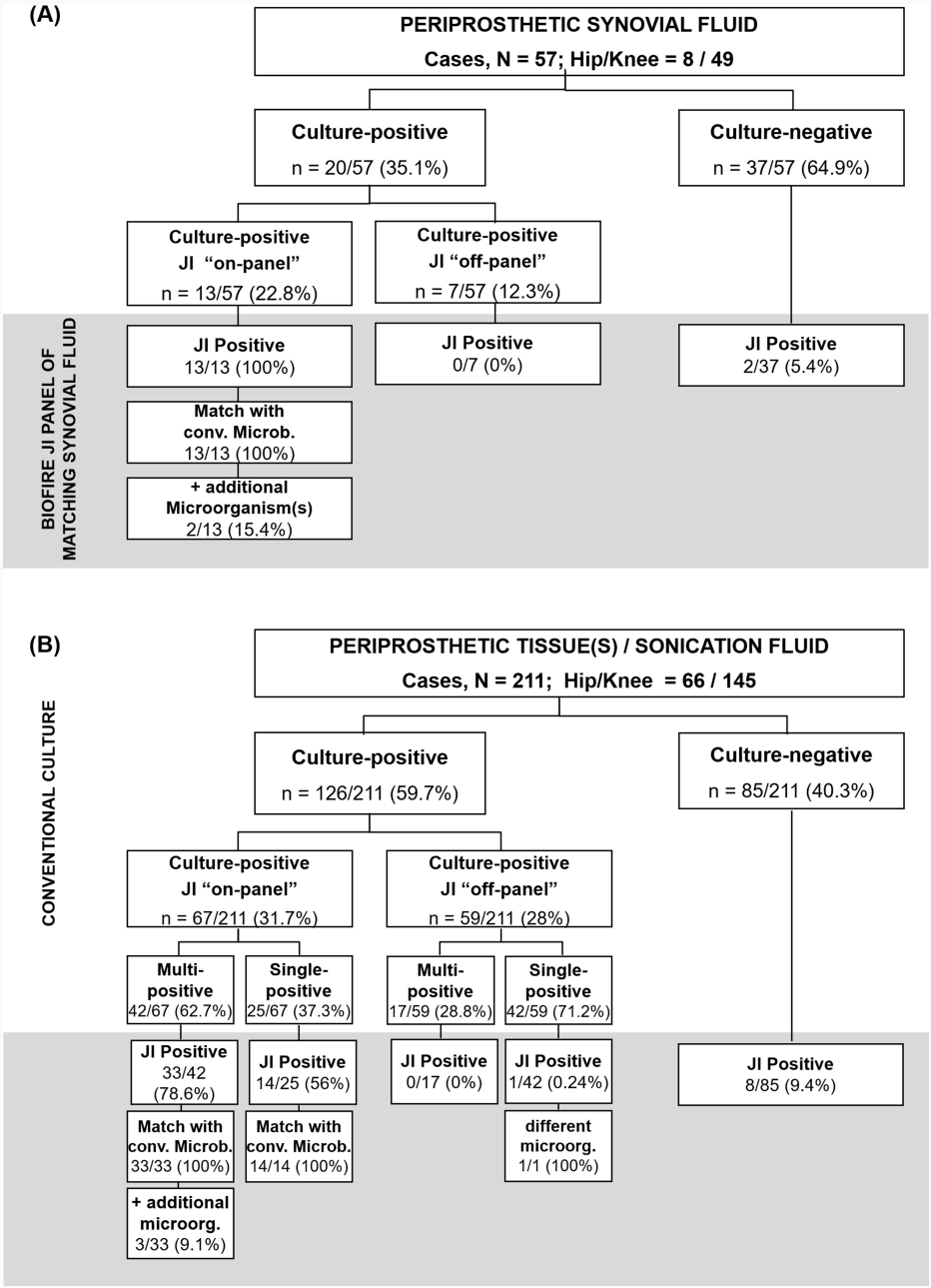

Fig. 2

Comparison of results obtained using conventional microbiology methods and the BioFire Joint Infection (JI) panel technology when the comparison of the matched synovial fluid (SF) was made either a) to the SF culture result, or b) to the culture result(s) of tissue(s) and/or sonication fluid. Cases were classified as JI 'on-panel', 'off-panel', and culture-negative according to the initial culture results. JI positive, positive detection with the JI panel; match with conv. Microb. (concordant with conventional microbiology), concordant result between JI panel and culture methods; match with conv. + additional microorg. (concordant with conventional microbiology + additional microorganisms), concordant result between JI panel and microbiological analysis with additional microorganisms; different microorg. (different microorganisms), JI panel positive result with a different microorganism than that identified by culture.

Overall, 13/16 (81.2%) of the discrepant SF specimens were obtained from patients who were receiving antibiotics at the time of specimen collection. Furthermore, 3/10 (30%) patients from the culture-negative group with a JI panel-positive result (Table II; group A) returned to our institution with persistent infections caused by the JI panel-positive finding. Similarly, 2/5 (40%) of the patients in the monomicrobial group with a polymicrobial JI panel result (Table II; group B) returned to our institution with persistent infections with one of the additional microorganisms identified by the JI panel.

In 5/14 (36%) SF specimens from the JI 'on-panel' SPC group with matching results, the match was with a microorganism present in sonication fluid at a concentration of ≤ 50 colony-forming units (CFUs)/ml.

In total, 16/20 (80%) SF samples related to the culture-positive JI 'on-panel' group with JI negative result (Supplementary Table v) were further investigated by microorganism-specific PCR followed by sequencing and confirmed negative. The remaining 4/20 (20%) discordant results could not be further evaluated due to insufficient SF volume to perform the assay. Overall, 19/195 (9.7%) patients

Table II. Additional microorganisms and new species detected by BioFire Joint Infection panel technology for each discordant synovial fluid sample. Discrepant results were noted in culture-negative cases, monomicrobial infected cases, and single-intraoperative culture cases. All 16 cases with discordant results were confirmed by specific microorganism polymerase chain reaction followed by sequencing.

Result	Conventional microbiology	JI panel	ICM-2018 classification
Negative to positive microbiological result			
1	None	*Streptococcus* spp	Infected
2	None	*Streptococcus* spp	Infected
3	None	*Streptococcus agalactiae*	Infected
4	None	*Staphylococcus lugdunensis*	Infected
5	None	*Staphylococcus lugdunensis*	Infected
6	None	*Staphylococcus aureus* (MSSA)	Non-infected
7	None	*Candida albicans*	Inconclusive
8	None	*Staphylococcus aureus* (MSSA)	Infected
9	None	*Streptococcus* spp	Inconclusive
10	None	*Streptococcus agalactiae*	Infected
Monomicrobial with additional microbiological result(s)			
1	*Staphylococcus aureus* (MSSA)	*Staphylococcus aureus* (MSSA), *Enterococcus faecium* (VRE)	Infected
2	*Proteus mirabilis*	*Proteus* spp, *Staphylococcus aureus* (MSSA), *Anaerococcus prevotii*, *Finegoldia magna*, *Peptoniphilus*	Infected
3	*Enterococcus faecalis* (VSE)	*Enterococcus faecalis* (VSE), *Fineglodia magna, Peptoniphilus, Streptococcus* spp	Infected
4	*Candida albicans*	*Candida albicans, Staphylococcus aureus* (MSSA)	Infected
5	*Staphylococcus aureus* (MSSA)	*Staphylococcus aureus* (MSSA), *Proteus* spp	Infected
SPC in sonication fluid with additional microorganism			
1	*Staphylococcus capitis*	*Staphylococcus aureus* (MSSA)	Infected

ICM, International Consensus Meeting; JI, joint infection; MSSA, methicillin-susceptible *Staphylococcus aureus*; SPC, single-positive culture; VRE, vancomycin-resistant *Enterococcus*; VSE, vancomycin-susceptible *Enterococcus*.

could have been managed differently and more accurately if the JI panel results had been readily available at the time of specimen collection.

The determination of sensitivity and specificity for the JI 'on-panel' microorganism using the JI panel technology showed values of 75.0% (95% CI 65.4 to 83.3) and 91.8% (95% CI 85.6 to 95.5), respectively, while with the inclusion of 'off-panel' pathogens, the determined values were 41.4% (95% CI 33.7 to 49.5) and 91.1% (95% CI 84.7 to 94.9), respectively.

A positive JI panel yield was also found in three SF samples from the culture-negative group, one non-infected SF with *S. aureus* MSSA and two SF inconclusive cases with *C. albicans* and *Streptococcus* spp, respectively.

Antibiotic resistance markers

Three types of resistance markers were detected by the JI panel in seven SF samples as follows: (4/7) *mecA* (confirmed methicillin-resistant *Staphyloccocus aureus* (MRSA) by routine culture), (2/7) *ctx-M* (*E. coli* ESBL confirmed by culture results), and (1/7) *E. faecium vanA/B* (negative in culture). All resistance markers detected by culture were also identified by the JI panel.

Discussion

In this study, the BioFire JI Panel identified additional, diverse, and some difficult-to-grow JI 'on-panel' pathogens in cases with unclear microbiological results, specifically in cases of UNCs and SPCs. Overall, 9.7% of patients (n = 19/195) may have received a different treatment at the time of the JI panel evaluation. In the UNC group, the JI panel yielded a total of seven positive detections: all correlated with patients receiving antibiotics at the time of specimen collection, highlighting the utility of the JI panel technology in patients undergoing antibiotic therapy. A total of 15/67 (22.3%) of the cases from the SPC group were reclassified as clearly infected by the ICM 2018 major infection criteria, due to

an accurate match between the conventional microbiology results in either one tissue or sonication fluid and the JI panel result in SF.[18,19] In 5/15 (33.3%) of these infected SPC cases, the bacterial concentration in the sonication fluid was ≤ 50 CFUs/ml, which could potentially have been initially regarded as a false-positive.[23] For two inconclusive cases and seven non-infected UPC cases, all related to a JI 'on-panel' SPC, the JI panel evaluation of concordant SF yielded a negative result. Considering that the conventional microbiological analysis of all collected tissues and sonication fluid correlating with these cases yielded a negative-culture result, the identified SPCs are suggestive of contamination. Of these nine patients, only two were treated with antibiotics.

Furthermore, the JI panel showed additional value in the identification of polymicrobial infections. A total of six new polymicrobial cases were identified among the infected group, five of which were associated with 'recurrent' patients who had experienced multiple episodes of PJI, revision surgeries, and had undergone several rounds of antibiotic therapy. Previous studies have suggested that treatment failure after a second-stage procedure may be partly due to an incomplete initial diagnosis of complex polymicrobial infections that were not initially captured by culture.[21,24] Although microbiological analysis of multiple tissues and sonication fluid is a significantly more accurate method than SF itself, our study suggests that microbiological analysis of intraoperative SF may be considered as a complementary diagnostic tool. The SF result may help to confirm a suspected PJI, and elucidate the clinical relevance of SPCs and UPCs. Additionally, the likelihood of positive detections in cases of UNC and multiple detections in cases of monomicrobial infections might be enhanced. The use of molecular techniques, which provide faster results and require much smaller volumes than those recommended for conventional microbiology (often limiting SF evaluation in hip PJI cases), could be a valuable option.

The PPA between a positive JI detection and a diagnosed PJI was good for late acute cases, but low for early acute (as described by Schoenmakers et al)[11] and chronic cases. The low concordance rate may be due to the high incidence of early acute and chronic *S. epidermidis* infections at our institution. Due to the limitation of the JI panel in detecting PJI caused by highly prevalent JI 'off-panel' pathogens,[25] the overall PPA between a positive JI detection and a diagnosed PJI was only 47.5%. Nevertheless, two culture-negative cases would have been reclassified as infected according to the ICM 2018 criteria due to a positive JI panel detection. One of these two patients returned to our institution with an infection caused by *Streptococcus oralis*, the same genus detected in the corresponding archived SF by the JI panel.

At 41.7%, the overall sensitivity of the JI panel for culture-positive cases was poor. This finding is consistent with other previous studies conducted.[10-12] At our institution, approximately 60% of PJI causative microorganisms are not covered by the JI panel, with the most prevalent being *S. epidermidis*, followed by other coagulase-negative staphylococci. This microbiological profile is similar to that reported by most orthopaedic centres.[26] However, the sensitivity of the JI panel may be subjective and dependent on the country in which the JI panel technology is offered.[27–29]

Negative JI panel detections were found in 20 culture-positive infected cases caused by at least one JI 'on-panel' microorganism(s). Possible explanations for the misdetection of the 'on-panel' microorganism could be either a drastic reduction in bacterial load due to long-term freezing of the SF, or a true negative microbiological result in the SF. One recent report in the literature has demonstrated microbiological differences in the SF, tissue(s), and implant in the same case of PJI.[30]

There are some limitations of the study. First, due to its retrospective design, there is a selection bias. Second, the patient population was heterogeneous. Third, for some patients, not all the required test results were available for the assessment of the infection criteria. Fourth, the JI panel technology provided a limited microbiological spectrum. Lastly, the availability of initial culture results for SF was low, as in the majority of orthopaedic centres (including ours), microbiological analysis is only performed on periprosthetic tissues and sonication fluid.[22]

Therefore, for the majority of the SF samples evaluated, the JI panel result was not compared with the culture result in SF, but rather with tissue(s) and/or sonication fluid. Nevertheless, this is the largest single-centre study using JI panel technology to evaluate patients who underwent hip and knee revision arthroplasty.

In conclusion, regardless of limited microbial coverage, the JI panel technology offered clinical advantages in microbiologically challenging PJI cases. In recurrent patients, and those undergoing antibiotic therapy including second-stage revision, molecular diagnostics should be used to prevent poor outcomes due to inadequate pathogen identification. However, this molecular approach should be used as a complementary microbiological intraoperative diagnostic tool rather than an alternative to the traditional multiple culture-based methods.

Supplementary material

Five tables are combined, covering the selected microbial spectrum for the study, the conventional microbiological results of synovial fluid compared with the joint infection (JI) panel evaluation of matched synovial fluid, the conventional microbiological results of tissue(s) and/or synovial fluid compared with the JI panel evaluation of matched synovial fluid, the overall changes in the initial microbiological spectrum after the JI panel evaluation, and the 20 negative JI panel results in the culture-positive group with 'on-panel' microorganisms.

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Data sharing

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