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Multicenter evaluation of BioFire JI panel related to improved microbiological diagnostics on acute osteoarticular infections

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ABSTRACT

Microbiological diagnosis of osteoarticular infections (OI) is crucial for a successful treatment. A prospective multicenter study including 262 synovial fluids with suspicion of acute OI was performed between July 2021 and October of 2022. BioFire Joint Infection Panel multiplex-PCR test was performed and results were compared with conventional cultures of synovial fluid specimens. In total, 136 microorganisms were detected, and fourteen samples were positive for more than one microorganism. In monomicrobial infections (n = 87) agreement with culture was 69%. In 26 samples, the multiplex PCR yield an additional positive result when culture result was negative. It helped in the detection of fastidious microorganisms as *K. kingae* and *N. gonorrhoeae*. This multiplex PCR has proven to be a useful technique that can be used for patients with high suspicion of acute OI in a rapid and automated manner.

1. Introduction

Osteoarticular infections (OIs) include septic arthritis, prosthetic joint infections (PJIs), osteomyelitis, and spinal infections. They are relatively common infections and cause serious morbidity for the patient (Patel, 2023). They could cause acute sepsis with bone and joint destruction, chronic pain, and permanent disability. They are difficult and expensive to treat, as they often require surgical intervention and prolonged antibiotic treatment (Colston and Atkins, 2018; Sigmund and McNally, 2019). A proper etiological diagnosis is needed to establish a targeted treatment for a successful outcome, especially with the increasing number of multidrug-resistant microorganisms (Colston and Atkins, 2018; Papadopoulos et al., 2019).

Conventional culture methods remain the gold standard for microbiological diagnosis of OI. Culture techniques present several limitations, such as long turn-around time, and false negative results in patients receiving antibiotics. In this scenario, conventional methods have improved their sensitivity using different combinations of culture media, prolonged incubation time, and incorporation of new techniques as sonication (Parvizi et al., 2014; Saeed, 2014; Bellova et al., 2019; Higgins et al., 2022). Despite those advances in microbiological diagnosis, there are still patients with a clinical suspicion of OI with negative culture results (Palan et al., 2019; Parvizi et al., 2014).

In this context, to accelerate diagnosis and ameliorate the sensitivity and specificity of microbiological diagnosis, different molecular techniques have been developed in the past years. These molecular tools include specific PCRs, and multiplex-PCR panels and sequencing analysis of 16S rDNA, (Esteban et al., 2014; Saeed, 2014; Salar-Vidal et al., 2022).

Recently a new kit based in FilmArray technology, the BioFire Joint

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Infection (JI) panel (bioMérieux SA, BioFire Diagnostics, LLC) was approved by the FDA and CE-marked. This test uses a cartridge methodology and includes a total of 31 microorganisms and groups of microorganisms commonly involved in bone and joint infections, and it also allows the detection of eight resistance markers. It can provide results within an hour approximately, and it has shown in the microbiological evaluation great values in terms of sensitivity (90.9%) and specificity (98.5%) (Esteban et al., 2023).

Herein, we evaluate the usefulness of BioFire JI Panel for acute OI diagnosis in different Spanish and Portuguese clinical settings and compare test performance with standard diagnostic methods in the routine of clinical microbiology laboratories.

2. Materials and methods

A prospective multicenter study including synovial fluids leftovers with suspicion of acute OI (Parvizi et al., 2018) was performed between July 2021 and October of 2022 in five Spanish hospitals and one Portuguese hospital, including University Hospital Fundación Jiménez Díaz (Madrid, Spain), University Hospital Ramón y Cajal (Madrid, Spain), University Hospital Marqués de Valdecilla (Santander, Spain), University Hospital Virgen del Rocío (Seville, Spain), University Hospital La Fe (Valencia, Spain) and University Hospital of Coimbra (Coimbra, Portugal). Chronic infection cases were not included in the study.

Fresh samples were processed using the standard-of-care technique. Approximately 200 μL of synovial fluid was used for the BioFire® Joint Infection Panel testing. The test was performed according to the provider's instructions using aseptic techniques. This study was conducted with an investigational-use-only (IUO) version of the panel. The results of the multiplex PCR were not informed to clinicians to not influence patient management. Results of the multiplex-PCR were compared with conventional cultures of synovial fluid specimens. Spanish sites followed the standard procedures validated by the Spanish Society of Clinical Microbiology and Infectious Diseases (Esteban et al., 2009). Briefly, synovial fluid was inoculated in blood agar, chocolate agar, and non-selective anaerobic agar. When there was enough sample volume, it was inoculated in a blood culture bottle. Cultures were incubated for a minimum of five days. We also recorded information about the patient's age, sample source (PJI or native joint), joint type, and additional tests performed as blood culture or tissue culture.

The impact of the joint infection panel result was retrospectively assessed by the bone and joint infection multidisciplinary unit of each center according to whether the result would have modified patient management in terms of the type of therapy, antibiotic choice or duration of the treatment. All the participant hospitals have specific multidisciplinary teams that evaluated the results and decided if the treatment of the patients could have been modified if the PCR results were known in real time.

Statistical analysis was performed using Stata Statistical Software, Release 11 (StataCorp 2009). A pairwise comparison of proportions was done. We considered a level of statistical significance of p-value < 0.05 in all tests.

No approval was requested from the Ethics in Research Committee because no data of the patients are included and no intervention in the patient was performed using the BioFire test results.

3. Results

During the study period a total of 262 synovial fluids were collected. Regarding the distribution of synovial fluid samples by age, most of the patients belonged to the group of > 56 years (60.7%; 159/262), followed by the group between 19 and 55 years (30.5%; 80/262). A total of 56.1% (147/262) of the samples were from male patients. Samples were obtained from native joints (50.3%; 132/262), prosthetic joints (40.1%; 105/262), and osteosynthesis material (9.6%; 25/262). The principal source was the knee (58.4%; 153/262) followed by hip (20.2%; 53/262), shoulder (6.9%; 18/262), wrist (2.7%; 7/262), ankle (2.7%; 7/262), spine (2.7%; 7/262) elbow (2.3%; 6/262), interphalangeal (2.3%; 6/262), and other sources (1.8%; 5/262).

The PCR test detected microorganisms in 101 (38.5%) samples. In total, 136 microorganisms were detected. Fourteen samples were positive for more than one microorganism.

The most detected microorganism was *Staphylococcus aureus* in 45 samples, followed by *Pseudomonas aeruginosa* (10), *Escherichia coli* (8), *Streptococcus agalactiae* (7), *Streptococcus* spp. (7), and *Staphylococcus lugdunensis* (6).

Within the monomicrobial PCR-positive results (87) (Table 1), culture techniques gave 60 concordant results (69%; 60/87). In one case, PCR result was positive for *Parvimonas micra* but the microorganism detected by culture was *Actinomyces europaeus*. In 26 samples, the multiplex-PCR yield an additional positive result when the culture result of the synovial fluid was negative. These microorganisms included *Staphylococcus aureus* (9), *Neisseria gonorrhoeae* (5), *Kingella kingae* (3), *Pseudomonas aeruginosa* (2), *Streptococcus agalactiae* (2), *Streptococcus* spp. (2), *Escherichia coli* (1), *Serratia marcescens* (1), and *Staphylococcus lugdunensis* (1). In eight of those patients the same isolate was identified both by PCR and in blood culture (2) or tissue culture (6).

Positive PCR results regarding age groups are shown in Table 2. The proportion of positive results was significantly higher in the group of < 18 years and 19–56 years compared to the age group of > 56 years (p-value= 0.021; p-value= 0.034). *S. aureus* was the microorganism most often detected in the 19–56 years and > 56 years group. There was a statically significant difference between *S. aureus* detection in the < 18 years group and > 56 years group (p-value= 0.022).

Fourteen polymicrobial results were detected. In twelve cases the PCR test detected additional microorganisms that were missed by culture (Table 3). Five cultures gave a monomicrobial positive result, while the BioFire test gave more than one microorganism. Most of the samples were obtained from osteosynthesis material (7/14), and the main

Table 1
Results of BioFire JI panel and synovial fluid culture in monomicrobial infections.

	BioFire JI Panel	Synovial fluid culture
Positive BioFire JI Panel Positive Synovial fluid culture	*S. aureus* (31) *P. aeruginosa* (6) *E. coli* (5) *S. agalactiae* (4) *E. faecalis* (3) *N. gonorrhoeae* (3) *S. lugdunensis* (3) *C. avidum/granulosum* (1) *K. kingae* (1) *K. pneumoniae* (1) *P. micra* (1) *S. pneumoniae* (1) *S. pyogenes* (1)	*S. aureus* (31) *P. aeruginosa* (6) *E. coli* (5) *S. agalactiae* (4) *E. faecalis* (3) *N. gonorrhoeae* (3) *S. lugdunensis* (3) *C. avidum/granulosum* (1) *K. kingae* (1) *K. pneumoniae* (1) *A. europaeus* (1) *S. pneumoniae* (1) *S. pyogenes* (1)
Positive BioFire JI Panel Negative Synovial fluid culture	*S. aureus* (9) *N. gonorrhoeae* (5) *K. kingae* (3) *P. aeruginosa* (2) *Streptococcus* spp. (2) *S. agalactiae* (2) *E. coli* (1) *S. lugdunensis* (1) *S. marcescens* (1)	
Negative BioFire JI Panel Positive Synovial fluid culture		*E. coli* (2) *S. epidermidis* (2) *S. capitis* (2) *Citrobacter* spp. (1) *N. gonorrhoeae* (1) *S. aureus* (1) *S. caprae* (1) *S. pyogenes* (1) *S. agalactiae* (1)

Table 2
Positive results of BioFire JI panel according to age group.

< 18 years (n = 13)	19–56 years (n = 31)	> 56 years (n = 57)
K. kingae (4)	*S. aureus* (12)	*S. aureus* (26)
P. aeruginosa (2)	*N. gonorrhoeae* (8)	*P. aeruginosa* (6)
S. aureus (2)	*S. lugdunensis* (2)	*E. coli* (6)
C. avidum/C. granulosum (1)	*Streptococcus* spp. (1)	*S. agalactiae* (4)
S. agalactiae (1)	*S. pneumoniae* (1)	*E. faecalis* (3)
Polymicrobial (3)	*S. pyogenes* (1)	*S. lugdunensis* (2)
	S. agalactiae (1)	*K. pneumoniae* (1)
	Polymicrobial (5)	*P. micra* (1)
		S. marcescens (1)
		Streptococcus spp. (1)
		Polymicrobial (6)

Table 3
Results of BioFire JI panel and synovial fluid culture in polymicrobial infections.

Sample	BioFire JI Panel	Synovial fluid culture
1	*Citrobacter*	*Pseudomons aeruginosa*
	Morganella morganii	*Proteus vulgaris*
	Proteus spp.	
	Serratia marcescens	
	Pseudomonas aeruginosa	
	Candida albicans	
2	*Clostridium perfringens*	*Clostridium perfringens*
	Staphylococcus aureus	
3	*Anaerococcus prevotii/vaginalis*	*Actinotignum europaeus*
	Enterococcus faecalis	*Staphylococcus caprae*
	Finegoldia magna	*Enterococcus faecalis*
	Peptoniphilus	*Staphylococcus intermedius*
	Staphylococcus lugdunensis	
	Streptococcus spp.	
4	*Staphylococcus aureus*	*Staphylococcus aureus*
	Morganella morganii	
5	*Klebsiella pneumoniae* group	*Klebsiella pneumoniae*
	Candida spp.	
6	*Escherichia coli*	*Escherichia coli*
	Parvimonas micra	Mixed anaerobe bacteria
	Peptoniphilus	
	Streptococcus spp.	
7	*Anaerococcus prevotii/vaginalis*	*Finegoldia magna*
	Finegoldia magna	*Staphylococcus epidermidis*
	Streptococcus agalactiae	*Streptococcus agalactiae*
8	*Anaerococcus prevotii/vaginalis*	
	Finegoldia magna	
	Peptonophilus	
	Staphylococcus lugdunensis	
9	*Pseudomonas aeruginosa*	
	Streptococcus spp.	
10	*Parvimonas micra*	*Staphylococcus aureus*
	Haemophilus influenzae	
	Staphylococcus aureus	
	Streptococcus spp.	
11	*Enterococcus faecalis*	*Enterococcus faecalis*
	Staphylococcus aureus	*Staphylococcus aureus*
12	*Anaerococcus prevotii/vaginalis*	*Finegoldia magna*
	Finegoldia magna	
	Peptostreptococcus anaerobius	
	Peptoniphilus	
13	*Anaerococcus prevottii/vaginalis,*	*Staphylococcus aureus*
	Finegoldia magna	
	Parvimonas micra	
	Peptoniphilus	
	Staphylococcus aureus	
	Streptococcus spp.	
14	*Enterobacter cloacae* complex	
	Escherichia coli	

affected joint with polymicrobial results was the knee (8/14).

Of the 161 PCR-negative sample results, 148 were also negative by culture resulting in a 91.9% agreement between both techniques. Twelve microorganisms in 12 different samples were isolated in synovial fluid culture but not detected by PCR. Five corresponded to coagulase-negative staphylococci (targets not included in the panel); and the other ones were *Escherichia coli* (2), *Citrobacter* (1), *Neisseria gonorrhoeae* (1), *Staphylococcus aureus* (1), *Streptococcus agalactiae* (1), and *Streptococcus pyogenes* (1). In these patients, *N. gonorrhoeae* and *S. agalactiae* were also grown in tissue culture.

In addition, five resistance mechanism genes were detected for methicillin resistance (4) and carbapenemase production (OXA-48-like) by the multiplex-PCR. Those results were in agreement with the phenotypic antibiotic susceptibility testing performed from cultured bacteria and OXA-48 was also detected using other molecular techniques. According to the expert opinion assessment given by a microbiologist or infectious diseases consultant, the PCR result would have influenced patient management in 36.6% of the cases, especially with positive results (66.3%).

4. Discussion

In the last years, diagnosis of bone and joint infections has experimented important advances that increased the number of patients with an etiologic diagnosis (Salar-Vidal et al., 2022), which implies better therapeutic options for these patients. However, because the number of patients without such diagnosis is still important, new approaches are currently under development (Liu et al., 2022; Salar-Vidal et al., 2022; Xiu et al., 2021). Among these, a new commercial multiplex PCR have appeared in the last years with interesting characteristics.

Our study showed the potential use of the BioFire JI panel to optimize the clinical management of patients with acute OI. Results confirmed that diagnostic yield is improved with the use of the panel in comparison with traditional culture techniques from synovial fluids, especially regarding microorganisms that are difficult to culture and polymicrobial infections. Culture was used as comparison methodology as it is the reference technique used in most of all the microbiological laboratories (Yusuf et al., 2022). In the multicenter evaluation of the panel an improvement over standard culture methods was demonstrated, with a shorter time to results for microorganisms and resistance genes with a high sensitivity/ positive percent agreement and specificity/ negative percent of agreement (Esteban et al., 2023). Of interest, as it has been previously reported (Saeed et al., 2023), it allowed the detection of fastidious-growing culture microorganisms as *K. kingae*, one of the most common pathogens associated with pediatric arthritis, whose incidence may be underestimated, but the use of molecular methods has significantly improved the performance and delay of its diagnosis (Ilharreborde et al., 2009; Slinger et al., 2016). It has been also proved the utility of PCR techniques for gonococcal arthritis diagnosis especially in cases with negative culture (Moussiegt et al., 2022). In our series it identified five *N. gonorrhoeae* and three *K. kingae* cases of septic arthritis that would have been undetected by conventional diagnostic methods.

Regarding the differences between age groups, it was expected to have a higher proportion of positive results in young people as incidence of septic arthritis is higher in children than adults (Donders et al., 2022), and a lower proportion in the > 56 group as PJI have an increased incidence with age but clinical symptoms of some PJI (especially in the elderly) are clinically difficult to distinguish from aseptic failure (Kim and Cho, 2021). There are also differences regarding the microorganisms detected by age groups, most of which can be explained by the epidemiology of osteoarticular infections according to age. *K. kingae* was the microorganism most often detected in the pediatric population in our series according to previous studies (Gené Giralt et al., 2019; Juchler et al., 2018), and *N. gonorrhoeae* has only been detected in the 19–56 age group due to the high prevalence of gonococcal septic arthritis in sexually active patients younger than 40 years (Moussiegt et al., 2022). *S. aureus* was the most detected microorganism in the groups of 19–56 years and > 56 years as it is the most frequent bacteria involved in early postoperative prosthetic joint infection and acute hematogenous prosthetic joint infections (Benito et al., 2019). In addition, *S. aureus* has

been reported as the most common pathogen causing septic arthritis (McBride et al., 2020).

Moreover, it has been proven that using traditional culturing polymicrobial infections may be missed, as it appears in our series (Schulz et al., 2021). Interestingly, the number of anaerobic bacteria detected with the use of the panel is higher in comparison with culture methods. One reason could be the overgrowth of one of the strains that hide the growth of more slowly growing organisms, and previous antimicrobial treatment may also influence the result. This can lead to a delay in starting appropriate treatment that could have been optimized and may be associated with decreased length of stay and costs if the correct organism had been detected earlier (Balada-Llasat et al., 2022).

It was also observed a great concordance in negative results between both techniques, but the BioFire JI panel should not be used to rule out infection as there is limited number of pathogens included and it can give false negative results for the diagnosis of infection. According to expert opinion assessment, a negative result would have not influenced patient management in the majority of the cases (82.8%). It highlights its use as a complementary technique to standard diagnostic methods. On the other hand, a positive result would have had a clinical impact in great number of cases, because changes in the antibiotic treatment schemes and a faster introduction of active antibiotics in the management of the patients. Interestingly, the high percentage of positive results in our series is probably due to a pre-test evaluation of the patients, and only those with a high suspicion index were tested. This approach has been suggested as the most useful one (Auñón et al., 2022), and can have an important impact on clinical management of the patients. It is true that clinical syndrome is essential for the surgical management of the patients, but the knowledge of the etiology (especially before surgery) could have a potential impact in the decision (for example, if a MDR strain or a *Candida* species are detected, or in patients with sepsis or septic shock). Moreover, some cases of these infections are culture-negative ones, and they can be diagnosed only by using molecular techniques, and in these cases such knowledge could impact in the antibiotic selection for these patients. Even in some cases such diagnosis could have an epidemiological impact (such as *N. gonorrhoeae* arthritis). For these reasons, we think that a proper use of this method can be useful in the clinical routine of microbiology laboratories.

Another advantage of the test is its ability to give rapid results in approximately one hour. This contributes to reduce the turnaround time in diagnosis, and it also gives the possibility to use it as a point of care test or even in the intraoperative diagnosis of acute PJI. In regions with high prevalence of multidrug resistance pathogens, the BioFire JI panel has additional value of rapidly detecting methicillin resistance in *S. aureus*, vancomycin resistance in enterococci, and gram-negative bacteria producing extended spectrum beta-lactamases and carbapenemases. It may help in the optimization of antimicrobial therapy with an impact in antimicrobial stewardship. However, its use is not recommended when there is a suspicion of a chronic prosthetic joint infection since pathogens commonly involved in those types of infections as coagulase-negative staphylococci or *Cutibacterium acnes* are not included in the panel. Its usefulness in acute septic arthritis of native and prosthetic joints that are hematogenous in origin has also proven (Schoenmakers et al., 2023).

The main limitation of the study is the lack of detailed clinical data because the study was designed to avoid ethical issues. Another limitation is the fact despite culture methodology used followed standard of care procedures, there could be a bias in the procedures of each hospital included in the study (especially because two different countries have been included), but all the Spanish centers follow standard published protocols (Marin et al., 2010), and these centers included most of the cases.

In conclusion, the BioFire JI panel has demonstrated to be a feasible solution to increase the probability of early and successful diagnosis when the patient meets the diagnostic criteria for an acute OI. Given its high precision of diagnosis in comparison to conventional culturing, the panel could yield higher number of correct pathogen identifications, leading to an optimized surgical revision strategy, antimicrobial stewardship, and improving patient management. However, it should be used alongside the traditional diagnostic methods to detect microorganisms not included in the panel and for antibiotic susceptibility testing.

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This study was performed using PCR kits provided by Biomérieux.

Declaration of Competing Interest

Llanos Salar-Vidal has received speaker honoraria from Werfen. Patricio Favier has received consultant honoraria from Biomérieux Argentina. Jaime Esteban has received speaker honoraria from Biomérieux and Heraeus, and consultant honoraria from Biomérieux. Catarina Chaves, Ileana T. Dianzo-Delgado, Salvador Giner-Almaraz, María José Gómez-Gómez, Guillermo Martín-Gutiérrez, Isabel Pereira, Ana Rodríguez-Fernández, Patricia Ruiz-Garbajosa, and Carlos Salas-Venero declare they have no financial interests.

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