

Research Paper

# Meta-analysis of sonicate fluid in blood culture bottles for diagnosing periprosthetic joint infection

Cheng Li<sup>1</sup>, Nora Renz<sup>1</sup>, Cristina Ojeda Thies<sup>2</sup>, Andrej Trampuz<sup>1</sup>✉

1. Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Center for Musculoskeletal Surgery (CMSC), Berlin, Germany

2. Hospital Universitario 12 de Octubre, Madrid, Spain

✉ Corresponding author: Andrej Trampuz, MD., Center for Musculoskeletal Surgery, Charité - University Medicine Berlin, Charitéplatz 1, D-10117 Berlin, Germany. Email: andrej.trampuz@charite.de

© Ivyspring International Publisher. This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY-NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>). See <http://ivyspring.com/terms> for full terms and conditions.

Received: 2018.09.05; Accepted: 2018.10.29; Published: 2018.12.24

## Abstract

**Introduction:** Periprosthetic joint infection (PJI) is the most serious complication after arthroplasty, and the diagnosis of PJI is still challenging with modern medical technology. To improve the diagnostic rate, combined diagnostic methods are gradually beginning to be used to diagnose PJI. Sonication is one accurate way to diagnose PJI, but there is minimal research regarding the diagnostic value of sonicate fluid (SF) in blood culture bottles (BCB). Therefore, we evaluated this combined diagnostic method by meta-analysis.

**Methods:** We searched English publications in electronic databases regarding the use of sonicate fluid in blood culture bottles (SF-BCB) for diagnosing PJI, screened the literature according to inclusion criteria, assessed the quality of the selected literature, and collected information regarding SF-BCB.

**Results:** This meta-analysis includes 4 studies that evaluated SF-BCB for the diagnosis of PJI. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) are 0.85 (95% Confidence interval [CI], 0.77 to 0.91), 0.86 (CI, 0.81 to 0.91), 5.34 (CI, 3.13 to 9.11), 0.16 (CI, 0.06 to 0.48) and 39.01 (CI, 9.04 to 168.35), respectively. The area under the curve (AUC) of the summary receiver operating characteristic (SROC) is 0.9186 (standard error, 0.0205).

**Conclusion:** SF-BCB has great value for the microbiological diagnosis of PJ, especially for patients with prior antibiotic treatment.

Key words: Arthroplasty, Periprosthetic joint infection, Diagnose, Blood culture bottles, Sonicate, Meta-analysis

## Introduction

Early diagnosis and bacterial detection during PJI are the key to successful treatment [1]. However, because there is no gold standard to diagnose the existence of biofilms on the surface of a joint prosthesis, the diagnosis of PJI is difficult [2]. So far, comprehensive analyses with some effective diagnostic methods seem to be the best options for diagnosing PJI. Sonicate fluid culture (SFC) is a valuable assessment tool for PJI. SFC dislodges the biofilm on the implant surface through low frequency

ultrasound, which preserves the activity of the microorganism [3]. The high sensitivity and specificity of SFC at different locations with PJI have been reported [4, 5]. In knee prostheses, the sensitivity and specificity are 90.6% and 100%, respectively, and in hip prostheses, the sensitivity and specificity are 87% and 100%, respectively. In elbow prostheses, the sensitivity and specificity are 89% and 100%, respectively.

However, at the early stage of PJI, sonication

might be not helpful for diagnosis [4, 6]. Prieto-Borja L et al. [7] found that SFC is not superior to periprosthetic tissue culture and synovial fluid culture in the early stages of PJI. However, the sensitivity of SFC is significantly increased if diagnosis is delayed. In order to improve the accuracy of PJI diagnose, PCR, microcalorimetry and SF-BCB techniques have been published [8, 9, 10].

The culture result of synovial fluid culture in BCB is better than growth on an agar plate, so synovial fluid culture in BCB is already used regularly [11]. However, studies regarding the use of SF-BCB for the diagnosis of PJI are uncommon [10, 12-15], and thus, the diagnostic validity of SF-BCB is still unclear. Therefore, we performed a meta-analysis to evaluate the effectiveness of SF-BCB for diagnosing PJI.

## Methods

### Search strategy

We searched English publications from the electronic databases of PubMed, Medline, and Web of Science until 30 April 2018 using the following medical subject headings (MeSH) or keywords: "periprosthetic joint infection OR prosthetic joint infection OR orthopaedic implant infection", "sonication fluid OR sonicate fluid OR sonication", and "blood culture vials OR blood culture bottles OR blood culture system". We also reviewed the references in eligible studies and the studies that cited the eligible studies in Google Scholar.

### Inclusion criteria

The selected articles had to meet the following inclusion criteria:

1. The diagnosis of PJI is based on criteria from the Musculoskeletal Infection Society (MSIS), the European Bone and Joint Infection Society (EBJIS) and the Infectious Diseases Society of America (IDSA) [17]; or strong evidence of infection, such as the presence of a sinus tract, purulence around the prosthesis, acute inflammation in periprosthetic tissue, or microbial growth in the synovial fluid, periprosthetic tissue samples, or SF.

2. The numbers of true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) values are clear, and the computed results of sensitivity and specificity are identical to the article described.

3. Only human studies in English are included.

4. Each of the selected studies contains at least 15 cases.

### Quality assessment

Two reviewers independently screened the retrieved clinical studies for inclusion criteria,

extracted data from all studies, and conducted a quality evaluation. The methodological quality of the selected studies was evaluated by using the diagnostic accuracy studies tool (QUADAS-2) [16], which is specifically developed for systematic reviews focusing on diagnostic accuracy. When confronted with disagreements, a third reviewer adjudicated.

### Data extraction

The following information in the articles was collected: first author, year of publication, country, enrolment period, number of infected cases, location, whether antibiotics were used, diagnostic criteria or method, sonication procedure, and the sensitivity and specificity of SF-BCB.

### Statistical analysis

For the analysis of the diagnostic value of SF-BCB, all statistical analysis are conducted using Meta-Disc software (version 1.4). The specificity, sensitivity, PLR, NLR, DOR and AUC of SROC are assessed. The percentage of the total variation across studies is described by the  $I^2$  statistic, which indicates the existence of significant heterogeneity when the value exceeds 50%. The value of  $I^2$  ranges from 0 to 100%, with 0 implying no observed heterogeneity and larger values indicating increasing heterogeneity. The analysis of heterogeneity between studies is conducted using the  $\chi^2$  test. If there is no significant heterogeneity across studies ( $P > 0.1$ ,  $I^2 \leq 50\%$ ), the analysis is performed using a fixed-effects model; otherwise, the random effects model ( $P \leq 0.1$ ,  $I^2 > 50\%$ ) is used.

## Results

Ninety-six articles are identified by the literature search. After literature review of the title, the abstract and the full text of the articles, 4 studies are included in the diagnostic meta-analysis [10, 12-14], including 3 articles from European countries (Germany, Spain, and Greece) and 1 study from China. The flow diagram is shown in Figure 1. As a result, 118 prosthetic joint infection cases are included in the meta-analysis. The detailed characteristics of each study are described in Table 1. The graphical summary of the methodological assessment based on the QUADAS-2 quality assessment for the recruited studies in the meta-analysis is illustrated in Figures 2 and 3.

Significant heterogeneity is found in the sensitivity ( $I^2 = 79.9\%$ ), specificity ( $I^2 = 67.7\%$ ), PLR ( $I^2 = 46.3\%$ ), NLR ( $I^2 = 78.2\%$ ) and DOR ( $I^2 = 72.7\%$ ). Thus, the random-effects model is used. No heterogeneity is found in PLR ( $I^2 = 46.3\%$ ), and the fix-effects model is applied. The pooled sensitivity,

specificity, PLR, NLR, and DOR estimates for the detection of PJI using SF-BCB are 0.85 (95% CI, 0.77 to 0.91), 0.86 (CI, 0.81 to 0.91), 5.34 (CI, 3.13 to 9.11), 0.16 (CI, 0.06 to 0.48), and 39.01 (CI, 9.04 to 168.35), respectively (Figure 4, Figure 5, Figure 6, Figure 7 and

Figure 8). The SROC plot shows the summary sensitivity and specificity under 95% confidence and prediction regions, with an AUC of 0.9186 (standard error, 0.0205) (Figure 9).

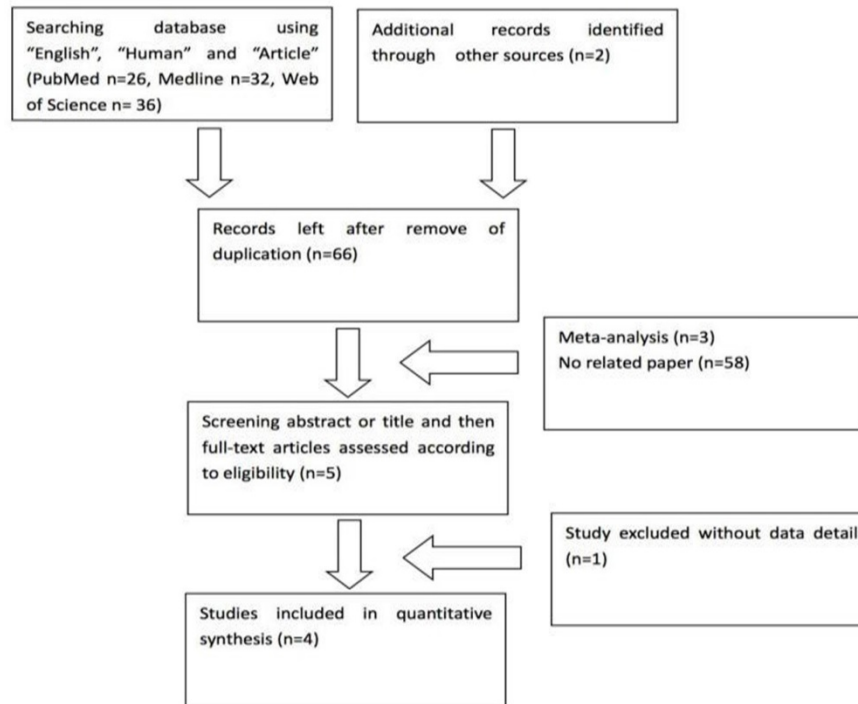


Figure 1. Flow diagram of the included studies

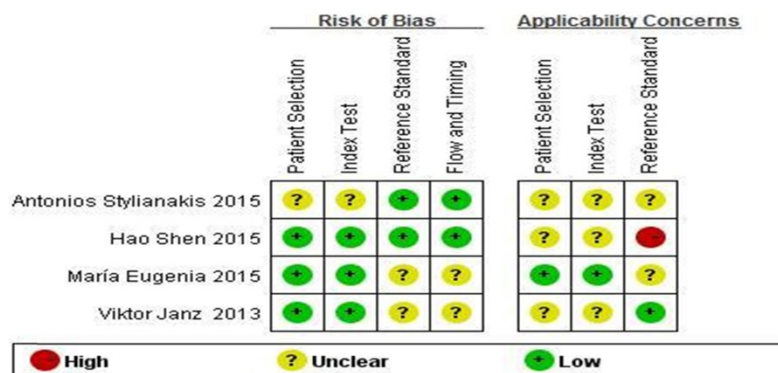


Figure 2. Methodological quality summary

Table 1. The detail characteristics of the included studies

Reference	Country	Enrollment period	Infected Cases	Location	Received antibiotics	Solution for implant	Diagnostic standard†	Vortex	Sonication	Centrifugation	Sensitivity	Specificity
Viktor Janz (2013) [13]	Germany	October 2010 - March 2011	23	hip and knee	No	Ringer's solution	P, H, IOF, M	30 seconds	3 min	No	91%	81%
María Eugenia Portillo (2015) [12]	Spain	June 2013 - December 2013	18	joint prosthesis	YES	NA‡	C, P, H, IOF	30 seconds+30 seconds*	1 min	No	100%	100%
Hao Shen (2015) [10]	China	August 2011 and May 2014	50	Knee 20, hip 30	YES	Ringer's solution	P, H, IOF, M	30 seconds+30 seconds	10 min	10 min	88%	87%
Antonios Stylianakis (2018) [14]	Greece	September 2011 and April 2015	27	hip and knee	YES	Ringer's solution	P, H	30 seconds+30 seconds	5 min	30 seconds	62.96%	83.91%

\* vortex before and after sonication †C, clinical signs of infection; P, presence sinus tract or purulence around the prosthesis; H, histological examination; IOF, intraoperative finding; M, microbiological or laboratory examination. ‡ NA, not available

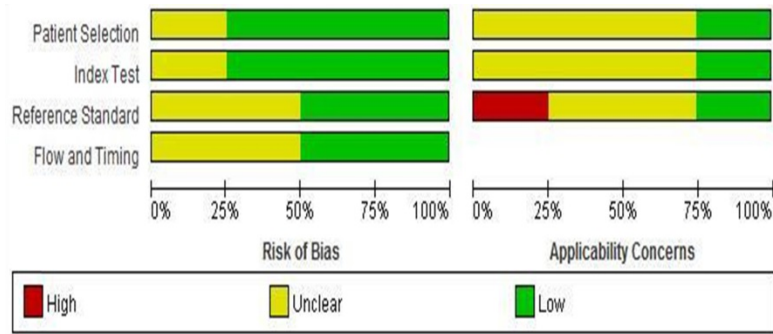


Figure 3. Methodological quality graph

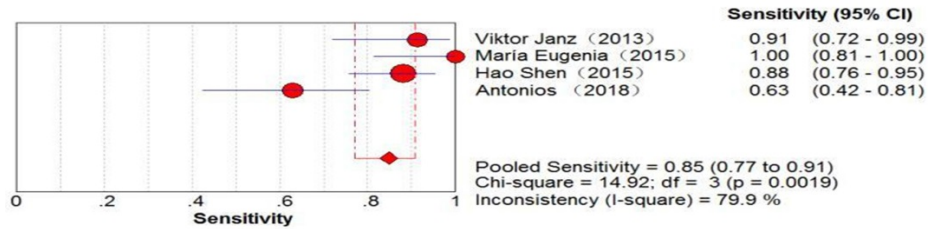


Figure 4. Forest plots of sensitivity of SF-BCB for PJI diagnosis

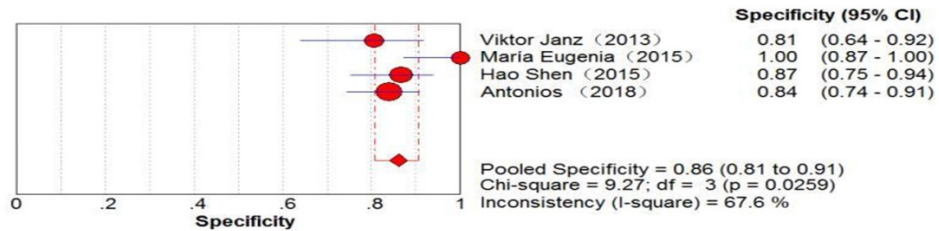


Figure 5. Forest plots of specificity of SF-BCB for PJI diagnosis

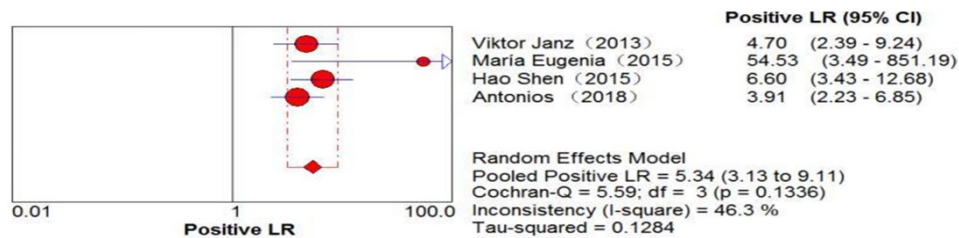


Figure 6. Forest plots of PLR of SF-BCB for PJI diagnosis

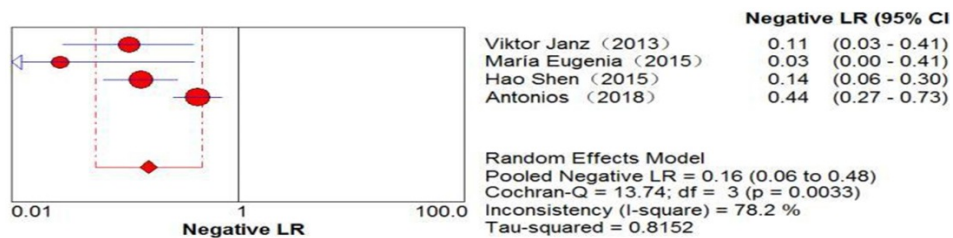


Figure 7. Forest plots of NLR of SF-BCB for PJI diagnosis

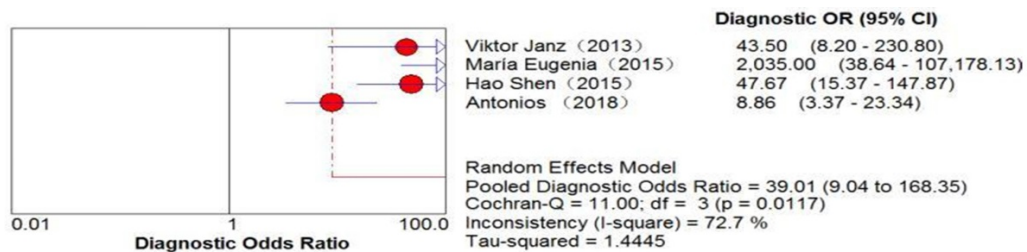


Figure 8. Forest plots of DOR of SF-BCB for PJI diagnosis

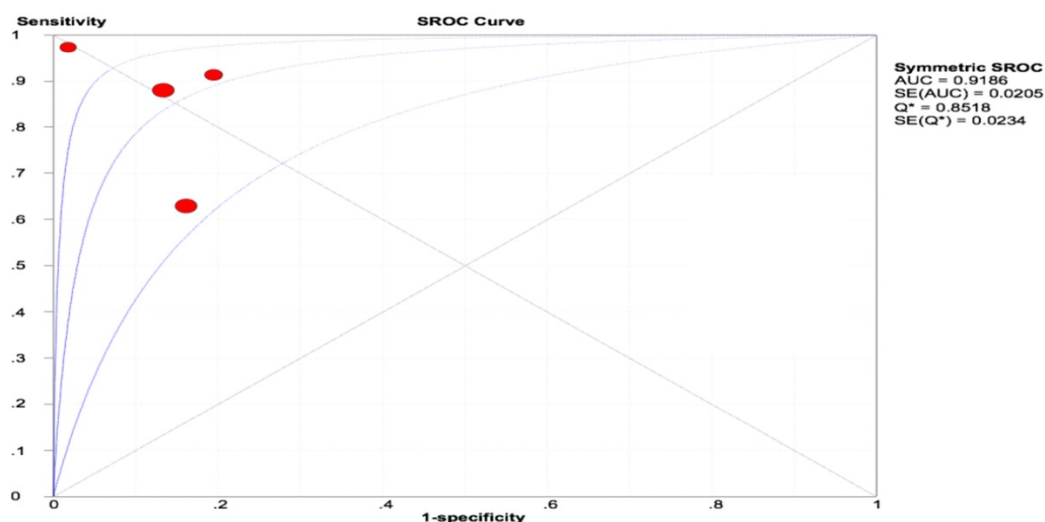


Figure 9. SROC of SF-BCB for PJI diagnosis

## Discussion

Various diagnostic methods of PJI have been published, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial fluid leukocyte count and neutrophil percentage, histopathological examination, periprosthetic tissue culture, and sonication [17]. Discovering pathogenic bacteria is undoubtedly the core, but the range of diagnostic accuracy in traditional cultures is 39% - 70%. Moreover, culture-negative results present a challenge for diagnosing PJI. The cure rate of culture-negative PJI is low (69.2%), and serious complications such as amputation or death might occur. The major reason for culture-negative results in PJI is antibiotic usage before sample collection [20]. However, sonication could improve diagnostic accuracy in those patients that have already used antibiotics.

Sonication dislodges adherent bacteria from prostheses. This easy and valuable technology is used routinely in diagnosing PJI, and it is also included in the diagnostic criteria of the EBJIS [18]. One meta-analysis of 16 SFC studies [19] shows the sensitivity is 79% (95% CI = 0.76 - 0.81), and the specificity is 95% (CI = 0.94 - 0.96). SFC is more sensitive than tissue culture, even in patients that received antibiotic therapy up to 14 days prior.

The improved combination method of SF-BCB for the diagnosis of PJI has been reported in recent years, and the sensitivity of SF-BCB is greater than conventional SFC (100% versus 87%). In the case of previous antibiotic treatment before sample collection, the culture sensitivity of SF-BCB is higher than that of SFC [12]. SF-BCB can detect more positive growth than conventional SFC (101 cases versus 51 cases). SF-BCB can reduce culture time, as well; the

average culture time in SF-BCB is shorter than that of SFC (2.9 days versus 4.2 days) [15].

The diagnostic methods of SF-BCB and of synovial fluid into BCB have been reported in the diagnosis of PJI [10]. The sensitivity of SFC and of synovial fluid culture in BCB are 88% and 64%, respectively. In the cases of patients who received antibiotics within the 14 days before surgery, the percentage of positive cultures in SF and synovial fluid are 81% and 52%, respectively. In the cases of patients without antibiotic treatment, the percentage of positive cultures in SF and synovial fluid are 93% and 72%, respectively. SF-BCB has a better capability of detecting microorganisms than synovial fluid in BCB, but the specificity of synovial fluid is better than SF-BCB (98% versus 87%). Another study also states that the percentage of positive cultures in SFC-BCB is higher than in synovial fluid in BCB (44% versus 22%), but the average duration of positive growth in synovial fluid is shortened to 1.8 days, compared with 2.9 days in SF [15].

Compared to traditional tissue culture, SF-BCB is more sensitive but less specific in patients with previous antibiotic therapy (62.96% to 40.74%, 83.91% to 96.55%) or without previous antibiotic therapy (91% to 75%, 81% to 100%) [13, 14]. In recent research, the sensitivity and specificity of tissue culture in BCB are lower than in conventional SFC; whether in the hip and knee (65.1% to 69.8%, 98% to 100%) or in the shoulder and elbow (72.2% to 88.9%, 87.5% to 100%) [21].

With the development of molecular biological techniques, PCR has been applied to the diagnosis of PJI. Its advantages include short culture time (< 5 hours), automation, high sensitivity and specificity, and the ability to easily distinguish PJI from aseptic loosening [9, 22]. Comparing to SF-BCB, the

sensitivity of PCR is 59.26% and the sensitivity of SF-BCB is 62.96%, respectively, and the specificity of PCR and SF-BCB are close [14].

In our study, the pooled sensitivity is 0.85 (CI = 0.77 - 0.91), the specificity is 0.86 (CI = 0.81 - 0.91), the PLR is 5.34 (CI = 3.13 - 9.11), the NLR is 0.16 (CI = 0.06 - 0.48), and the DOR is 39.01 (CI = 9.04 - 168.35). The AUC value of the SROC curve is 0.9186. SF-BCB is a valuable microbiological diagnosis for PJI with high sensitivity, even in patients who received antibiotic treatment within 14 days of surgery. BCB allows the automated detection of microbial growth technology, and it reduces 60.1% of the work hours for laboratory staff compared with conventional techniques. It is also a cost-saving method [23].

This study has some limitations. First, there are only 4 articles with cases included in our meta-analysis, although we set the standard at a minimum of 15 cases in each study. Second, in three-quarters of the studies, some patients received antibiotic treatment within 14 days of surgery. This could impact culture results, but it also suggests that SF-BCB has an acceptable sensitivity and specificity after antibiotic therapy. Third, in our study, the diagnostic standards are different, and this might negatively influence diagnostic accuracy. Renz N et al [24] use three definition criteria to assess the value of Alpha defensin lateral flow (ADLF) test for diagnosing PJI, the results of sensitivity for ADLF test are 84%, 67%, 54% with different definition criteria. Fourth, sonication has a non-standard methodology. Some research methods include vortex and sonication (without centrifugation) [13, 25]. Some scholars use vortexing, sonication and centrifugation as a standard method [26]. Vortexing or centrifugation with sonication could improve the culture result [26, 27]. A subgroup of meta-analyses [28] also shows that the sonication method with vortexing or centrifugation has better culture results than without vortexing or centrifugation.

## Conclusions

The results of the meta-analysis show that SF-BCB has great value for the microbiological diagnosis of PJI. Its capability of detecting pathogens is better than conventional tissue culture, conventional SF, SF-PCR and synovial fluid in BCB, especially for patients with previous antibiotic treatment.

## Abbreviations

PJI: Periprosthetic joint infection; SF: sonicate fluid; BCB: blood culture bottles; SF-BCB: sonicate fluid in blood culture bottles; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR:

Diagnostic odds ratio; CI: Confidence interval; AUC: Area under the curve; SROC: Summary receiver operating characteristic; SFC: Sonicate fluid culture; MeSH: medical subject headings; TP: true-positive; TN: true-negative; FP: false-positive; FN: false-negative; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; EBJS: European bone and joint infection society; MSIS: Musculoskeletal Infection Society; IDSA: Infectious Diseases Society of America; ADLF: Alpha defensin lateral flow.

## Acknowledgments

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité – Universitätsmedizin Berlin.

## Competing Interests

The authors have declared that no competing interest exists.

## References

- Sendi, Lötscher PO, Kessler B, Graber P, Zimmerli W, Clauss M. Debridement and implant retention in the management of hip periprosthetic joint infection. *Bone & Joint Journal*. 2017;99-B(3):330-336.
- Gbejuade HO, Lovering AM, Webb JC. The role of microbial biofilms in prosthetic joint infections. *Acta Orthopaedica*. 2015;86(2):147-58.
- Pitt WG, Ross SA. Ultrasound increases the rate of bacterial cell growth. *Biotechnol Prog*. 2003;19(3):1038-44.
- Puig-Verdié L, Alentorn-Geli E, González-Cuevas A, et al. Implant sonication increases the diagnostic accuracy of infection in patients with delayed, but not early, orthopaedic implant failure. *Bone Joint J*. 2013;95-B(2):244-9.
- Vergidis P, Greenwood-Quaintance KE, Sanchez-Sotelo J, et al. Implant sonication for the diagnosis of prosthetic elbow infection. *J Shoulder Elbow Surg*. 2011;20(8):1275-81.
- Van Diek FM, Albers CGM, Van Hooff ML, Meis JF, Goosen JHM. Low sensitivity of implant sonication when screening for infection in revision surgery. *Acta Orthop*. 2017;88(3):294-299.
- Prieto-Borja L, Auñón A, Blanco A, et al. Evaluation of the use of sonication of retrieved implants for the diagnosis of prosthetic joint infection in a routine setting. *Eur J Clin Microbiol Infect Dis*. 2018;37(4):715-722.
- Borens O, Yusuf E, Steinrücken J, Trampuz A. Accurate and early diagnosis of orthopedic device-related infection by microbial heat production and sonication. *J Orthop Res*. 2013;31(11):1700-3.
- Renz N, Cabric S, Morgenstern C, Schuetz MA, Trampuz A. Value of PCR in sonication fluid for the diagnosis of orthopedic hardware-associated infections: Has the molecular era arrived? *Injury*. 2018;49(4):806-811.
- Shen H, Tang J, Wang Q, Jiang Y, Zhang X. Sonication of Explanted Prosthesis Combined with Incubation in BD Bactec Bottles for Pathogen-Based Diagnosis of Prosthetic Joint Infection. *J Clin Microbiol*. 2015;53(3):777-81.
- Hughes JG, Vetter EA, Patel R, et al. Culture with BACTEC Peds Plus/F bottle compared with conventional methods for detection of bacteria in synovial fluid. *J Clin Microbiol*. 2001;39(12):4468-71.
- Portillo ME, Salvadó M, Trampuz A, et al. Improved diagnosis of orthopedic implant-associated infection by inoculation of sonication fluid into blood culture bottles. *J Clin Microbiol*. 2015;53(5):1622-7.
- Janz V, Wassilew GI, Hasart O, Matziolis G, Tohtz S, Perka C. Evaluation of sonicate fluid cultures in comparison to histological analysis of the periprosthetic membrane for the detection of periprosthetic joint infection. *Int Orthop*. 2013;37(5):931-6.
- Stylianakis A, Schinas G, Thomaidis PC, et al. Combination of conventional culture, vial culture, and broad-range PCR of sonication fluid for the diagnosis of prosthetic joint infection. *Diagn Microbiol Infect Dis*. 2018;92(1):13-18.
- Janz V, Trampuz A, Perka CF, Wassilew GI. Reduced culture time and improved isolation rate through culture of sonicate fluid in blood culture bottles. *Technol Health Care*. 2017;25(4):635-640.
- Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
- Li C, Renz N, Trampuz A. Management of Periprosthetic Joint Infection. *Hip Pelvis*. 2018;30(3):138-146.

18. Corvec S, Portillo ME, Pasticci B M, Borens O, Trampuz A. Epidemiology and new developments in the diagnosis of prosthetic joint infection. *Int J Artif Organs*. 2012;35(10):923-34.
19. Liu H, Zhang Y, Li L, Zou HC. The application of sonication in diagnosis of periprosthetic joint infection. *Eur J Clin Microbiol Infect Dis*. 2017;36(1):1-9.
20. Parvizi J, Erkocak OF, Della Valle CJ. Culture-negative periprosthetic joint infection. *J Bone Joint Surg Am*. 2014;96(5):430-436.
21. Yan Q, Karau MJ, Greenwood-Quaintance KE, et al. Comparison of the Diagnostic Accuracy of Periprosthetic Tissue Culture in Blood Culture Bottles to Prosthesis Sonication Fluid Culture for Diagnosis of Prosthetic Joint Infection using Bayesian Latent Class Modeling and IDSA PJI Criteria for Classification. *J Clin Microbiol*. 2018;56(6):e00319-18.
22. Portillo ME, Salvadó M, Sorli L, et al. Multiplex PCR of sonication fluid accurately differentiates between prosthetic joint infection and aseptic failure. *J Infect*. 2012;65(6):541-8.
23. Peel TN, Sedarski JA, Dylla BL, et al. Laboratory Workflow Analysis of Culture of Periprosthetic Tissues in Blood Culture Bottles. *J Clin Microbiol*. 2017;55(9):2817-2826.
24. Renz N, Yermak K, Perka C, Trampuz A. Alpha Defensin Lateral Flow Test for Diagnosis of Periprosthetic Joint Infection: Not a Screening but a Confirmatory Test. *J Bone Joint Surg Am*. 2018;100(9):742-750.
25. Achermann Y, Vogt M, Leunig M, Wüst J, Trampuz A. Improved diagnosis of periprosthetic joint infection by multiplex PCR of sonication fluid from removed implants. *J Clin Microbiol*. 2010;48(4):1208-14.
26. Zitron R, Wajsfeld T, Klautau GB, et al. Concentration of sonication fluid through centrifugation is superior to membrane filtration for the microbial diagnosis of orthopedic implant-associated infection. *J Clin Microbiol*. 2016;54(3):788-90.
27. Portillo ME, Salvadó M, Trampuz A, et al. Sonication versus vortexing of implants for diagnosis of prosthetic joint infection. *J Clin Microbiol*. 2013;51(2):591-4.
28. Zhai Z, Li H, Qin A, et al. Meta-Analysis of Sonication Fluid Samples from Prosthetic Components for Diagnosis of Infection after Total Joint Arthroplasty. *J Clin Microbiol*. 2014;52(5):1730-6.