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Comparing the Effectiveness of Two Culture Media Techniques in the Diagnosis of Prosthetic Joint Infection

Protez Eklem Enfeksiyonunun Tanısında İki Kültür Ortamı Tekniğinin Etkinliğinin Karşılaştırılması

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Abstract

Aim: When infectious diseases are suspected, culture studies ensure the selection of the appropriate antimicrobial treatment and confirm the diagnosis. There are various differences in medium, sample collection technique, enrichment, and evaluation techniques. Culture sampling makes important contributions to the diagnosis and treatment of prosthetic joint infections, the frequency of which has increased in recent years as a result of the increased rate of arthroplasty. After evaluating the preoperative and intraoperative criteria together, prosthetic joint infections can be diagnosed in suspected cases without culture positivity. This study aims to evaluate different culture samplings efficiency for the diagnosis of prosthetic joint infection.

Material and Method: This study retrospectively evaluated 946 patients who had been sampled in our department between January 2005 and May 2015. These patients were divided into two groups according to their final diagnoses: group one (prosthetic joint infection) and group two (suspected but non-infected prosthetic joint replacement). Considering patients' final diagnoses, this study aimed to compare the results of the blood culture bottle (BCB) method and the standard sterile fluid culture method.

Results: When cultivated in a blood culture flask, the sensitivity of the culture test was 28.09%, specificity was 95.77%, and accuracy was 58.13%. When cultivated in a solid medium, sensitivity was 10.11%, specificity was 100%, and accuracy was 50%.

Conclusions: When prosthetic joint infection is suspected, BCB usage is a preferable, safer method compared to the standard sterile fluid culture method because it has the power to isolate more bacteria with a higher diagnostic value.

Keywords: Bacterial identification, blood culture bottles, culture assay, diagnostic accuracy, prosthetic joint infection

Öz

Amaç: Bulaşıcı hastalıklardan şüphelenildiğinde, kültür çalışmaları uygun antimikrobiyal tedavinin seçilmesini sağlar ve tanıyı doğrular. Ortam, örnek toplama tekniği, zenginleştirme ve değerlendirme tekniklerinde çeşitli farklılıklar vardır. Kültür örneklemesi, son yıllarda artroplasti oranının artmasıyla sıklığı artan protez eklem enfeksiyonlarının tanı ve tedavisine önemli katkılar sağlar. Ameliyat öncesi ve sırasındaki kriterlerin birlikte değerlendirilmesiyle, şüpheli vakalarda kültür pozitifliği olmadan protez eklem enfeksiyonları teşhis edilebilir. Bu çalışma, protez eklem enfeksiyonunun tanısı için farklı kültür örneklemelerinin etkinliğini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada, Ocak 2005 ile Mayıs 2015 arasında bölümümüzde örneklenen 946 hasta retrospektif olarak değerlendirildi. Bu hastalar nihai tanılarına göre iki gruba ayrıldı: birinci grup (protez eklem enfeksiyonu) ve ikinci grup (şüpheli ancak enfekte olmayan protez eklem replasmanı). Hastaların son tanıları göz önünde bulundurularak, bu çalışmada kan kültürü şişesi (BCB) yöntemi ile standart steril sıvı kültür yönteminin sonuçları karşılaştırılmıştır.

Bulgular: Kan kültürü şişesinde kültür yapıldığında, kültür testinin duyarlılığı %28,09, özgüllüğü %95,77 ve doğruluğu %58,13 olarak bulunmuştur. Katı bir ortamda kültür yapıldığında, duyarlılığı %10,11, özgüllüğü %100 ve doğruluğu %50 olarak bulunmuştur.

Sonuç: Protez eklem enfeksiyonundan şüphelenildiğinde, BCB kullanımı daha yüksek tanı değerine sahip daha fazla bakteri izole etme gücüne sahip olduğundan standart steril sıvı kültür yöntemine kıyasla tercih edilen, daha güvenli bir yöntemdir.

Anahtar Kelimeler: Bakteriyel tanımlama, kan kültürü şişeleri, kültür testi, protez eklem enfeksiyonu, tanısal doğruluk

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INTRODUCTION

Bacterial isolation in musculoskeletal system infections positively contributes to diagnosis and treatment direction. The increase in the prevalence of prosthetic joint infection (PJI), secondary to the increase in arthroplasty rates in recent years, suggests that this issue will remain relevant.[1]

PJI after primary arthroplasty has been reported at a rate of 1.5-2.5%. It is the most common cause of implant failure within the first five years after knee arthroplasty.[2] In cases of suspected PJI, a culture examination of synovial fluid is a routinely performed standard practice. Flora contamination, low-virulence bacteria, and uninterrupted antibiotherapy before joint aspiration can lead to uncertainty in culture sampling results.[3,4]

For PJI, the time of diagnosis affects the choice of treatment. It is generally accepted that infections observed within the first four weeks are called "early PJIs," while infections observed after the fourth week are called "late PJIs".[5,6] Apart from acute cases, PJIs are usually treated with staged surgeries that require implant removal. For this reason, it is important to reach a rapid diagnosis in cases that are suspected during the early period of infection.

Culture negativities are more common, especially in late-stage and delayed PJIs, due to the presence of a biofilm layer.[1] These negativities are usually caused by low-virulence bacteria.[2] Late PJI may be caused by low-virulent skin flora (coagulase-negative staphylococci, *Propionibacterium* species, and coryneform bacteria).[2–4] The long incubation time requirements of bacteries in late-stage prosthetic infections may lead to culture negativities and their presence in the normal skin flora may lead to a misdiagnosis as contamination.[5]

The importance of the culture is not limited to diagnosis; the culture and antibiogram are also important for guiding antibiotic therapy after implant removal and for determining the antibiotics in the spacer that will be applied into the joint during debridement-implant removal surgery.

Sampling type (tissue sampling, tissue swab samples, synovial fluid aspirate, implant sonication), incubation time, and medium type (solid, semi-solid, liquid, blood culture bottle) may affect the results of culture sampling.[7-12]

In the selection of media, the blood culture bottle (BCB) has the advantages of being easily obtained in many centers and of being able to offer a more objective evaluation of the automated system. It has been established that cultivation in a BCB contributes positively to non-blood sterile body fluid sampling.[13,14]

Despite all technical innovations, different types of specimens, long incubation periods, and enrichment methods, there are still patients who are diagnosed with prosthetic infections without reproduction in culture. This condition is defined as culture-negative PJI.

Culture-negative PJIs have been reported at relatively high rates, especially in late-stage PJIs. For this reason, the need to set out various criteria has emerged to define this group of patients. The most well-known of these criteria was defined by the Musculoskeletal Infection Society (MSIS) working group in 2011 and subsequently included in clinical practice.[15] These criteria were redefined in 2018.[16]

According to the 2011 MSIS criteria, the diagnosis of PJI can be performed under three main titles (**Table 1**).

Table 1. 2011 Musculoskeletal Infection Society (MSIS) criteria[15]

Main Criteria Group	Criteria	Status of meeting criteria	Final diagnosis
1.	The presence of sinus tract infections associated with the prosthesis	Positive	PJI
2.	The same pathogen is detected in two different samples	Positive	PJI
3.	**a)** Increased erythrocyte sedimentation rate (ESR) or C-Reactive Protein (CRP) in serum; **b)** Increased leukocyte count in synovial fluid; **c)** Increased neutrophil percentage in synovial fluid (PMN%); **d)** Presence of purulence in the affected joint; **e)** Reproduction in a single culture; **f)** More than five neutrophils appear per area at 400 x magnification	Presence of 4 or more	PJI

When these criteria are evaluated, the diagnosis of PJI can be made without culture positivity. Judging from the modifications to the criteria in 2018, it can be observed that the effectiveness of intraoperative findings increased and that the diagnosis of PJI can still be made without culture positivity.[16]

This group of patients, who have to be diagnosed without culture positivity, may benefit from different practices that will contribute to pathogen isolation. Choosing culture methods with higher sensitivity, specificity, and accuracy may positively contribute to PJI diagnosis.

This study compares the results of standard sterile body fluid culture and transplantation to a BCB by sampling synovial fluid of patients suspected of having a PJI. Furthermore, this study aimed to consider whether the patients' final diagnoses were PJI while comparing the diagnostic efficiency of their examinations.

The hypothesis of this study was the following: In the preliminary diagnosis of PJI, sowing into a blood culture bottle in synovial fluid sampling provides a greater number and variety of bacterial isolation.

MATERIAL AND METHOD

Before to the start of the study, approval was obtained from the institutional ethics committee with decision number 20-KAEK-092. This retrospective study examined patients' blood culture samplings between January 2005 and May 2015.

Patients with suspicious findings for PJI (joint pain, warmth, erythema, induration, oedema at the incision site, persistent wound drainage, wound dehiscence, joint effusion and/or fever) who had a sterile joint fluid culture performed from their synovial fluid samples and who agreed to participate in the study were

included in the study. Patients with oncological bone diseases who had undergone a tumour resection prosthesis, patients with a follow-up period of less than 2 years and those who had lost follow-up, patients who were taking immunomodulating drugs and patients who had taken antibiotics within the last seven days were not included in the study.

The following data were evaluated: the presence of sinus tracts, culture results, serum CRP and ESR values, synovial leukocyte count, synovial leukocyte ratio, the presence of purulence during surgery, and the neutrophil count per area at 400 times magnification.

When we started our study, it was found that 946 blood culture tests were performed at the Orthopaedics and Traumatology Clinic. 728 samples that were performed for reasons other than suspected PJI and did not contain synovial fluid samples were excluded from the study in the first phase. 218 samples collected with suspected PJI were analysed according to the MSIS criteria described in 2011. 160 patients with sufficient data in the hospital records who met the criteria were included in the study.

All samples included in the study were taken under fluoroscopy control in the operating room after appropriate sterilization and draping.

The patients included in the study were divided into two groups according to their MSIS criteria. Group I comprised patients diagnosed with PJI, while Group II comprised patients suspected of having PJI but not infected. Group I patients underwent two-stage revision arthroplasty, while Group II patients were treated conservatively and patients whose symptoms did not improve underwent one-stage revision arthroplasty.

A second study was performed based on the results of bacteriological examinations of synovial fluid samples collected with BCB and standard medium. Accordingly, the sowing with BCB was analysed in two groups as group B and the sowing with conventional medium in group C and the growth results were recorded.

In Group B, samples were inoculated and incubated in Bactec 9240 (Becton Dickinson, USA) automated blood culture system at 35°C for 7 days. Bottles that showed a positive signal were subjected to Gram staining and subcultured on Blood agar (Himedia, India) and Eosin Methylene-blue Lactose Sucrose (EMB) agar (Himedia, India) plates and incubated in 35°C for 24 hours. Identificatian of isolates were performed by conventional methods and the automated VITEK2® system (bioMerieux, France).

In Group C sample was subjected to Blood agar and EMB agar plates and incubated in 35°C for 24 hours. Identificatian of isolates were performed by conventional methods and the automated VITEK2® system (bioMerieux, France).

The results of culture sampling were tested with diagnostic parameters (sensitivity, specificity, positive predictive value and negative predictive value, diagnostic accuracy). The day bacteria isolation in positive cultures was also recorded.

Statistical Analysis

Each descriptor for the two groups of anchors is represented as average±standard deviation. Averages were compared using the independent sample t-test. The significance test of the difference between the two means or one-way analysis of variance (ANOVA) was used. P values less than 0.05 were accepted as statistically significant. The diagnostic test evaluation calculator was used to evaluate diagnostic tests. All statistical analyses were performed using the software package IBM SPSS Statistics 19 (SPSS Inc., an IBM Co., Somers, NY).

RESULTS

The analysis of the results of the culture samples taken from the patients, the characteristics of the wound site and the laboratory results from the hospital database showed that 89 (55.6%) patients were diagnosed with PJI and belonged to group I, while 71 (44.4%) patients belonged to group II.

Group I included 60 knee arthroplasty cases and 29 hip arthroplasty cases, while Group II included 52 cases of knee arthroplasty and 19 cases of hip arthroplasty. (p>0.05)

The average age of the patients in Group I was 67.58 (± 7.16) years and 64.91 (± 9.74) years in Group II. (p >0.05)

Four-eyed tables were prepared to examine whether patients were diagnosed with PJI and to determine the culture results (**Table 2**).

Table 2. Distribution of examination results according to final diagnosis

	Positive	Negative	Total
Technique 1			
Positive	25	3	28
Negative	64	68	132
Total	89	71	160
Technique 2			
Positive	9	0	9
Negative	80	71	151
Total	89	71	160
Evaluation together			
Positive	25	3	28
Negative	64	68	132
Total	89	71	160

Diagnostic test evaluation was performed according to technique one, technique two, and the evaluation of both techniques together. The sensitivity of technique B was 28.09%, with a specificity of 95.77%, a positive likelihood ratio of 6.65, a negative likelihood ratio of 0.75, a prevalence of 55.63, a positive predictive value of 89.29%, and an accuracy of 58.13%. The sensitivity of technique C was 10,11%, with a specificity of 100%, a positive likelihood ratio of 0, a negative likelihood ratio of 0.9, a prevalence of 55.63%, a positive predictive value of 100%, and an accuracy of 50%. When evaluated together, the diagnostic results of both tests were the same as when sowed only in a blood culture bottle (**Table 3**).

Table 3. Diagnostic test results according to culture techniques

Statistics	Result	95% Trust Interval
Technique 1		
Sensitivity	28.09%	19.07% - 38.62%
Specificity	95.77%	88.14% - 99.12%
Positive Likelihood Rate	6.65	2.09 - 21.13
Negative Likelihood Rate	0.75	0.65 - 0.86
Prevalence	55.63%	47.57% - 63.47%
Positive Predictive Value	89.29%	72.39% - 96.36%
Negative Predictive Value	51.52%	48.05% - 54.97%
Accuracy	58.13%	50.08% - 65.87%
Technique 2		
Sensitivity	10.11%	4.73% - 18.33%
Specificity	100%	94.94% - 100%
Positive Likelihood Rate		
Negative Likelihood Rate	0.9	0.84% - 0.96%
Prevalence	55.63%	47.57% - 63.47%
Positive Predictive Value	100%	
Negative Predictive Value	47.02%	45.29% - 48.76%
Accuracy	50%	42% - 58%
Evaluation together		
Sensitivity	28.09%	19.07% - 38.62%
Specificity	95.77%	88.14% - 99.12%
Positive Likelihood Rate	6.65	2.09 - 21.13
Negative Likelihood Rate	0.75	0.65 - 0.86
Prevalence	55.63%	47.57% - 63.47%
Positive Predictive Value	89.29%	72.39% - 96.36%
Negative Predictive Value	51.52%	48.05% - 54.97%
Accuracy	58.13%	50.08% - 65.87%

While the mean bacterial isolation day with technique B was 3.72±1.59, it was calculated as 2.2±0.45 for technique C (**Table 4**).

Table 4. Reproduction days with different techniques by species

Pathogen	Reproduction Day	
	n	Avg.±SD
Technique 1		
Acinetobacter baumanni	1	5±.
Brucella spp.	3	6±0
E. coli	1	3±.
Enterococcus faecium	2	4.5±0.71
Salmonella species	1	5±.
Staphylococcus aureus	7	2.86±0.69
Staphylococcus capitis ssp urealyticus	1	4±.
Staphylococcus chromogenes	2	2.5±0.71
Staphylococcus epidermidis	5	2.6±0.89
Staphylococcus hominis	1	3±.
Staphylococcus warneri	1	8±.
Total	25	3.72±1.59
Technique 2		
Acinetobacter baumanni	0	.±.
Brucella spp.	0	.±.
E. coli	1	2.±.0
Enterococcus faecium	2	3.±.0
Salmonella species	0	.±.
Staphylococcus aureus	4	2.25±0.5
Staphylococcus capitis ssp urealyticus	0	.±.
Staphylococcus chromogenes	1	2±.0
Staphylococcus epidermidis	0	.±.
Staphylococcus hominis	0	.±.
Staphylococcus warneri	0	.±.
Total	8	2.2±0.45

In 13 different patients, seven different bacteria were produced only in technique B, namely *Acinetobacter baumanni*i, *Brucella* ssp., *Salmonella* ssp., *Staphylococcus capitis Ureolyticus* ssp., *Staphylococcus epidermidis*, *Staphylococcus hominis*, and *Staphylococcus warneri* (**Table 5**).

Table 5. Results of samples with reproduction only in the blood culture bottle technique

Pathogen	Reproductive positivity
Acinetobacter baumanni	1
Brucella spp	3
Salmonella species	1
Staphylococcus capitis ssp urealyticus	1
Staphylococcus epidermidis	5
Staphylococcus hominis	1
Staphylococcus warneri	1
Total	13

DISCUSSION

Looking at our results, we found that we diagnosed PJI in 89 patients as a result of cultures from aspiration of synovial fluid performed when PJI was suspected. In the tests performed with BCB, it was found that 13 patients grew bacteria that could not be obtained in the cultures performed with conventional media. Nowadays, the problem can be solved with less morbidity by diagnosing joint surgery and prosthesis infections, which increase in parallel, at an early stage and performing interventions before a biofilm layer forms.

The classical method used for culture evaluation in sterile body fluids other than blood is to sow different solid mediums without enrichment. Concentration-enhancing methods such as filtration or centrifugation can be used before planting.[11] If necessary, the need to check reproduction daily after planting on standard media and to conduct a subculture study represent additional burdens on the laboratory. For this reason, systems that will reduce laboratory workload and contribute to international standardization are frequently needed.

A study by Von Essen has revealed that patients who presented to the rheumatology clinic due to the synovial effusion retrospectively analyzed the culture results and that the cultivation made in the blood culture bottle yielded a greater variety of culture positivity compared to the solid medium and swab cultures.[17] Although this patient population, which was referred to the rheumatology clinic without PJI, is different from that evaluated in our study, sensitivity of cultivation to the BCB medium was also higher.

Çetin et al. have compared the evaluation of sterile body fluids with conventional culture cultivation and blood culture bottle systems and pointed out that blood culture bottle systems are faster and more diverse, emphasizing that bacteria such as *Brucella* and *Streptococcus pneumoniae* only grow in BCB systems.[18] Similarly, in this study, *Staphylococcus warneri*, *Staphylococcus capitis*, *Ureolyticus* ssp., *Staphylococcus*

epidermidis, *Staphylococcus hominis*, *Brucella* ssp., and *Salmonella* ssp. were only produced in the blood culture bottle, suggesting that this technique has higher pathogen sensitivity when comparing sterile fluid culture technique.

Birgisson et al. have reported that in case series consisting of five pediatric patients with septic arthritis, osteomyelitis and sepsis, Kingella kingea isolation was only successful via cultivation in the blood culture bottle.[19] Similarly, Yagupsky et al. have reported a high frequency of Kingella kingea infection obtained only by the blood culture system in the synovial fluid analysis.[20] Many bacteria did not reproduce in standard sterile body fluid culture procedure but concominant blood culture bottle procedure results were positive. The fact that *Staphylococcus epidermidis*, which is frequently isolated in PJI, was detected only in the cultivation of the BCB in five different patients suggests that direct cultivation alone can be misleading.[21,22]

In this study, the presence of *Brucella* spp. and *Staphilococcus epidermidis* were only detected using the BCB technique which suggests that this technique is more preferable for PJI diagnosis. In 13 different patients, seven different bacteria were produced only in the BCB technique suggesting that the contribution of the standard sterile fluid culture assessment technique is limited in the diagnosis of PJI.

Therefore, the results of this study suggest that BCB usage is beneficial in diagnosing PJI. Similar to this finding, BCB usage was found to be favorable in the sampling of pleural fluid[23] and synovial fluid.[24,25]

With the exceptions of the positive predictive value and the negative likelihood values, all diagnostic tests of standard sterile fluid culture assessment have found lower than the BCB technique. The low pathogen diversity of standard sterile fluid method suggests that this technique's contribution to diagnosing PJI is limited.

The main limitation of this study was the retrospective design of the criteria assessment for patients suspected of having PJI. Considering that the patients with synovial sampling were clinically observed for at least two years, the authors of this study concluded that this limitation did not adversely affect the study's results.

CONCLUSION

In the case of suspected PJI, BCB usage is a preferable and safe method that has the power to isolate more bacteria with higher diagnostic value and a greater variety of microorganisms.

Increasing rates of PJI suggest that diagnostic accuracy will become more important issue. Improvement of microbiological identification contributes both diagnosis and treatment of PJI.

Microbiological identification studies performed using only sterile fluid technique may lead to limitations in the diagnosis of PJI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziosmanpaşa University Clinical Research Ethics Committee (Date: 30.04.2020, Decision No: 20-KAEK-092).
Informed Consent: Informed consent for this study was obtained from all subjects for this study.
Referee Evaluation Process: Externally peer-reviewed.
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