REVIEW

Journal of Clinical Microbiology and Infectious Diseases (*JCMID*) 2021, Volume 1, Number 1: 24-27

Published By : the Indonesian Society for Clinical Microbiology

The current trend for prosthetic joint infection diagnosis from culture to molecular: a literature review

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Received: 2021-06-01
Accepted: 2021-06-30
Published: 2021-07-02

ABSTRACT

Pathogen identification in prosthetic joint infection is necessary to achieve optimal patient management. The specimens for diagnosis of prosthetic joint infection could be the synovial fluid, the tissue obtained intraoperatively, and the biofilm from the implanted prosthesis. Because of the low sensitivity of the conventional specimen culture method, the preanalytic treatment of the specimen was widely studied to increase the yield of detection. This review aimed to describe the current specimen processing methods used in the clinical setting to increase the pathogen detection rate. A blood culture bottle, tissue homogenization, and explanted prosthesis sonication were the most studied methods with a good result. Molecular methods were also developed to reduce the time of pathogen detection. MALDI-TOF was studied to reduce identification time after a positive culture. Other molecular methods such as polymerase chain reaction and next-generation sequencing were studied to omit the culture step and reduce detection time. However, the impracticality and the inconsistent sensitivity of certain specimens from the molecular methods limit its application in the clinical setting. Specimen culture remains as a crucial step in the current prosthetic joint infection, with the improvement of the molecular methods toward a better prosthetic joint infection diagnosis.

Keywords: culture, diagnosis, molecular, prosthetic joint infection
Cite This Article: Natasha, A., Wahid, M., Sudarmono, P. 2021. The current trend for prosthetic joint infection diagnosis from culture to molecular: a literature review. *Journal of Clinical Microbiology and Infectious Diseases* 1(1): 24-27.

INTRODUCTION

Prosthetic joint infection (PJI) is an emerging problem since the procedure became more frequently performed in many hospitals in Indonesia. The cumulative incidence of PJI in 2009 was around 1%–2% over the lifetime of the prosthetic joint patient. It is depending on the type of prosthesis and the surgery indication.[1] In Indonesia, the infection also reported to occur in 1% to 2 % of total knee and hip arthroplasty.[2] For the diagnosis, the Musculoskeletal Infection Society and Infectious Diseases Society of America developed a consensus of periprosthetic joint infection (PJI) criteria, which included: a sinus tract was found communicating with the prosthesis, a pathogen isolated by culture from at least two different tissue or fluid samples obtained from the affected prosthetic joint, of the following criteria: elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration, elevated synovial leukocyte count, elevated synovial neutrophil percentage, presence of purulence in the affected joint, isolation of a microorganism in one culture of periprosthetic tissue or fluid, or greater than five neutrophils per high-power field in 5 high power fields observed from histologic analysis of periprosthetic tissue.[1,3]

The pathogens which frequently cause the PJI are coagulase-negative *Staphylococci*, *Staphylococcus aureus*, *Streptococcus sp.*, *Enterococcus sp.*, *Escherichia coli, Pseudomonas aeruginosa, Enterobacteriaceae*, and *Candida sp.*[4,5] The pathogenesis of PJI was related to microorganism growth in biofilm and produced low-grade inflammation.[4] The microorganism could reach the site by direct inoculation during the procedure, *per continuitatem* from the infected adjacent soft tissue, or hematogenous/lymphomatous from distant foci of infection such as urinary tract or respiratory tract infection.[4] Since the common pathogen of PJI had low virulence, embedded in biofilm, and produce low-grade inflammation, the diagnosis and microorganism detection became very difficult. It was reported that around 7% to 30% of culture results were negative.[4,6] Without guidance from the identified pathogens, the unfit antibiotic selection could prolong the recovery and cause more damage to the patients. To this day, much research is projected to optimize the culture and molecular method in detecting pathogens. This review will describe the current technology in culture

and molecular methods for the diagnosis of PJI.

DISCUSSION

Culture Method for the Prosthetic Joint Infection

Once the patient is admitted to the orthopedic division with suspected PJI, a diagnostic arthrocentesis should be performed unless the diagnosis is evident clinically and surgery is planned, and antimicrobials can be safely withheld prior to surgery.[1] The synovial fluid was then sent for inflammatory cell counts and cultured in two conditions, aerobic and anaerobic.[1] Blood culture is necessary if the patient had a fever.[1] After the PJI is confirmed and surgery is planned, at least 3 to a maximum of 5 to 6 intraoperative tissue samples or the explanted prosthesis itself should be submitted and individually processed for aerobic and anaerobic culture at the time of surgical debridement or prosthesis removal.[1,7] If the inflammation is mild, more samples should be obtained to increase the sensitivity since the number of organisms might be low and scattered patchily around the prosthesis.[4] However, more than six specimens were reported not to improve the diagnostic yield but could increase the numbers of false-positive results.[8]

Several methods were introduced to increase the sensitivity of synovial fluid and tissue culture. Preanalytic specimens processing such as direct inoculation of synovial fluid to blood culture bottles, tissue homogenization before inoculation to blood culture bottles, and sonication of the explanted prosthesis before inoculation were widely studied to improve sensitivity and specificity. Synovial fluid culture by using the blood culture bottles was reported to increase the sensitivity and specificity of the PJI diagnosis.[9] Cohen et al. reported synovial culture using BACTEC blood culture bottles, compared to agar plates, gave a faster response time and broader identification spectrum.[10] The superiority of blood culture bottles also utilized for tissue culture. The tissue was homogenized before inoculated to a blood culture bottle.[11] The mechanical homogenization was reported better than manual milling for tissue treatment before inoculation.[12] Hughes et al. study showed a better sensitivity of tissue suspension culture using BACTEC blood culture bottles than direct inoculation on the agar plates.[13] Peel et al. also reported inoculation into blood culture bottles would result in an estimated reduction of 60.1% in the total laboratory staff time required, lower total cost, and better accuracy.[7] And the last one is the sonication of the explanted prosthesis. The sonication is aimed to dislodge and disaggregate the biofilm bacteria.[14] Several studies reported a better sensitivity of culture from the fluid of sonicated prosthesis compared to tissue culture.[14-17] Unlike tissue and synovial fluid, the current fluid culture from sonicated prostheses is not inoculated to the blood culture bottle but still uses the routine agar plates. The culture methods started with the inoculation of 0.1 ml concentrated sonicate fluid onto sheep blood and chocolate agar, and both were incubated in aerobic and anaerobic conditions.[15] A single colony growing on a plate is equivalent to one colony per 10 ml sonicate fluid, with a cutoff value of ≥20 CFU/10 ml was defined as positive for sonicating fluid cultures.[14,15,17]

The drawbacks of culture methods are the risk of negative culture results, the risk of contamination, and the impracticality of some specimen processing methods. First, the negative culture could occur when the microorganism is fastidious or challenging to culture, such as *Mycobacterium sp.* and *Ureaplasma sp.*[6] The negative result could also occur if the specimens are not adequate in volumes, the inflammation is low, or when antibiotics already administer to the patients.[1,6] Therefore, withholding antimicrobial therapy for at least two weeks before culture increases the likelihood of recovering an organism.[1] Second, contamination could occur when the specimen's processing is not conducted under aseptic conditions.[18] The last downside of culture is the impracticality of processing methods such as mechanical homogenization of tissue and sonication of explanted prosthesis, since these methods need specific instruments and sterile compartments during the process.[11] However, isolating pathogen and obtain susceptibility testing from the specimen would assist the clinician in selecting the right antibiotics and reduce the irrational use of antibiotics.[7] Therefore, specimen culture is critical in PJI diagnosis.

Molecular Method for the Prosthetic Joint Infection

Because of the considerable amount of time needed for culture and the problem in culture-negative PJI, several molecular methods became the target of much PJI research. The methods revolved between reducing the time of identification after the positive blood culture or eliminating the culture process.

To reduce the time of identification from the positive culture, Kuo et al. were using MALDI-TOF. They reported a significant reduction in time for identification with direct MALDI-TOF (directly using the fluid from the positive blood culture bottle).[19] However, the direct MALDI-TOF methods were less sensitive when compared to the routine MALDI-TOF (using subculture from the positive blood culture bottle), and the time needed for routine MALDI-TOF was two times higher than the direct MALDI-TOF.[19]

The other methods which projected directly to skip the specimen culture step are the polymerase chain reaction (PCR) and the metagenomic next-generation sequencing (mNGS). Polymerase chain reactions were studied using multiple primers simultaneously or using primer targeted to the 16S rRNA.[20-24] The specimens included in the studies were synovial fluid, tissue, and the fluid of sonicated prosthesis. The sensitivity results mainly were superior compared to the conventional culture method.[19,21,23,24] Although PCR is known for its sensitivity, there are several downsides in the method. Morgenstern et al. reported the multiplex PCR sensitivity was not significantly different with synovial fluid culture (60% vs 54%).[20] And the use of a broad primer, with 16S rRNA as the target, would need amplicon sequencing as the additional step to identify the pathogen. Lane et al. also reported the low sensitivity of PCR to identify *Staphylococcus aureus* and *Streptococcus sp.* when using the 16S rRNA as the primer.[25] Hence, the clinical use of multiplex PCR and broad primer PCR currently limited to identify rare pathogens, when the inflammation was low, or when the culture was

negative.[20,21,26-28]

The latest trend in molecular methods is next-generation sequencing. The metagenomic approach is used to identify the target pathogen blindly. Wang et al. reported a better sensitivity of mNGS compared with comprehensive primer PCR.[22] Cai et al. study also showed a higher sensitivity of mNGS than conventional culture.[29] However, mNGS needs a specific instrument and technician with advanced bioinformatic knowledge for the analysis. It is impractical for the current situation. Nevertheless, mNGS had been reported as a valuable method for identifying pathogen from the culture-negative PJI, and the result was used to guide for a targeted antibiotic selection, which gave a favorable outcome.[30]

CONCLUSION

The current technology provides better options and quality diagnostic methods. To increase the sensitivity of culture methods, preanalytical treatment of specimens had resulted in a broader yield of pathogen isolation. The molecular methods showed promising results, but their usage was still limited due to impracticality and inconsistent sensitivity in a particular specimen. Thus, the culture method is still a pivotal step in PJI diagnosis and the current trend of research is pushing the molecular methods to be more useful in the future.

DISCLOSURES

Conflict of Interest

All authors declare no conflict of interest.

AUTHOR CONTRIBUTION

All authors contribute equally.

FUNDING

We declare that no financial supports or funding obtained for this study.

ETHICAL STATEMENT

Not applicable

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