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COMMENTARY

Will Regulatory and Financial Considerations Dampen Innovation in the Clinical Microbiology Laboratory?

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ABSTRACT **Over a million prosthetic joints are placed in patients in the United States annually. Of those that fail, 25% will be due to infection, with an estimated cost approaching 1 billion dollars. Despite the clinical and economic importance of these infections, the techniques for their detection are relatively insensitive. An innovative method for detecting these infections by using blood culture bottles (BCB) to culture specimens of periprosthetic tissue (PPT) was described in a recent article [T. N. Peel, et al., mBio 7(1):e01776-15, 2016, doi:10.1128/mBio.01776-15]. There are two potential stumbling blocks to the widespread implementation of this innovation. First, the FDA judges such an application of BCB as an "off-label use" and as such, a laboratory-developed test (LDT). LDTs are coming under greater scrutiny by the FDA and may require extensive, costly validation studies in laboratories that adopt this methodology. Second, the Center for Medicare and Medicaid Services has established a Hospital Acquired Condition Reduction Act under which institutions performing in the lowest quartile forfeit 1% of their Medicare reimbursement. Hospital-acquired infections are an important component of this quality metric. Although prosthetic joint infection (PJI) rates are not currently a hospital quality metric, given their cost and increasing frequency, it is reasonable to expect that they may become one. Will those with financial oversight allow an innovative technique that will require an expensive validation and may put the institution at risk for loss of CMS reimbursement?**

Currently, close to a million joint replacements are performed annually in the United States (1). As the population ages in the industrialized world, it is estimated that the number of joint replacements will increase by three- to fivefold over the next two decades (1). A common complication of this surgery is infections due to biofilm-producing organisms (1). These infections occur in 1 to 2% of these patients and are estimated to cause as many as 25% of prosthetic joint revisions (1, 2). This number appears to be increasing, in part because two risk factors for prosthetic joint infections (PJI), obesity and diabetes, are increasing (1, 2). One of the challenges faced by clinicians caring for these patients is that a significant number of patients with clinical and laboratory signs of infection do have not organisms detected by culture (1, 3).

In 2007, a Mayo Clinic research group led by R. Patel published a landmark paper (4) in which they described a novel technique that used vortexing and sonication of a removed prosthesis as a means to diagnose PJI. This method proved significantly more sensitive than the standard culture techniques commonly used at that time, although more than 20% of specimens from patients with clinical signs of infection remained culture negative. A partial explanation for this insensitivity was the observation that at least some patients had received antimicrobials in the two weeks prior to culture. Despite its enhanced sensitivity and excellent specificity, this method has not been widely adopted because of its complexity and equipment requirements.

Over the past decade, the Mayo group has continued to explore both conventional and molecular methods as a means of enhancing the detection of PJI. Surprisingly, in many cases, molecular methods have not proven to provide a significance advance in PJI detection (5). There are apparently three problems with these methods. Sanger-based sequencing of broad-range targets, such as the 16S rRNA gene, cannot be used for mixed infections and also require extremely stringent collection techniques to avoid contamination. Next-generation sequencing, while promising, is expensive, requires significant technical and bioinformatics expertise, and is impractical for most clinical laboratories. Multiplex assays for the detection of potential PJI pathogens are the most promising approach but are challenging due to the breadth of organisms that could be either pathogens or contaminating flora. The clinical sensitivity and specificity of these assays still need optimization before routine implementation.

The latest innovation by the Mayo group is described in a recent article in mBio (6). In this study, they extend two previous studies using blood culture bottles (BCB) for the detection of PJI (7, 8). The method described is to culture periprosthetic tissue (PPT) that has been processed using a Stomacher device. This process is believed to release organisms from tissue, including those growing in biofilms, but does not lyse them. One milliliter of fluid is then added to both an aerobic and an anaerobic BCB and cultured for either 7 (aerobic) or 14 days (anaerobic). The authors applied a novel statistical method, Bayesian latent class modeling (LCM), to judge the sensitivity and specificity of this novel BCB approach in comparison to those of standard agar and broth PPT cultures. They also compared the different culture methods to the IDSA PJI criteria. Using the Bayesian LCM method, the authors found the BCB method to be more sensitive and specific than standard PPT methods. When using the IDSA criteria as the diagnostic truth, both culture methods proved less sensitive but had similar specificity, although the BCB method had superior sensitivity. The BCB-based method has two distinct advantages over the standard culture methods. First, the time to organism detec-

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tion is decreased, although how much this would improve clinical outcomes is unclear. Second, the method allows automated monitoring of the culture, making this method much less labor intensive after the initial processing, which would be essentially the same for the methods being compared.

While the authors are commended for applying a routine, widely available culture method (blood culture bottles) to a new specimen type to increase sensitivity and time to result, this approach presents challenges for many laboratories. The inoculation of PPT into BCB is considered an "off-label" use of BCBs, meaning it is not FDA-approved/cleared. As such, clinical laboratories must undergo significant verification and validation requirements to implement this approach. Many laboratories do not have the volume of specimens or the number of positive specimens that are received at Mayo Clinic. Therefore, a rigorous verification process is unlikely even at many academic medical centers. An additional concern is whether the application of BCBs to detect PJIs is considered a laboratory-developed test (LDT). As an LDT, the FDA might apply specific regulatory standards that must be met prior to implementation, which will further limit the potential impact of this approach.

Beyond the LDT issue, another challenge may be on the horizon for the adoption of this novel culture method. The Center for Medicare and Medicaid Services (CMS), using data collected by the National Health Safety Network (NHSN), has established the Hospital Acquired Condition (HAC) Reduction Program. Hospitals that fall into the lowest quartile of this program face a 1% reduction of their CMS payments, which means potential loses of millions of dollars in reimbursements for large health care facilities (9). Current key contributors to this score are central-line-associated bloodstream infection and catheter-associated urinary tract infection rates. In fiscal year (FY) 2016, hospital-acquired *Clostridium difficile* infection rates will be added. The numbers of prosthetic joint procedures, many of which are paid for by CMS, are rapidly increasing. It is generally agreed that most PJI are HAC, with a projected cost by 2020 of 1.62 billion dollars annually (1). Given the huge amount of dollars at stake, it seems quite feasible that PJI may become a target of the HAC Reduction Program. Although the BCB method is more sensitive, in the reported study, 26 patients not meeting IDSA criteria for PJI had microorganisms isolated from single PPT specimens cultured in BCBs. Particularly problematic is the observation that organisms that are part of the skin microbiota, coagulase-negative staphylococci, viridans group streptococci, and *Propionibacterium* spp. may be found in as many as 50% of positive prosthetic joint cultures (1). Most are judged to be "true pathogens" in this carefully conducted research study, but will this observation hold true if this method is widely adopted? Will future PJI clinical practice guidelines (3) recommend BCB culture of PPT as their standard method for detecting PJI infection, especially since there is not a true microbiologic gold standard for the diagnosis of these infections? What will be the NHSN definition of a PJI on which CMS will make their determination of quality: will it be the standard PPT culture method (2 positive cultures containing skin microbiota organisms such as coagulase-negative staphylococci, viridans group streptococci, and *Propionibacterium* spp. or one positive PPT culture with typically pathogenic organisms such as *Streptococcus aureus* and aerobic Gram-negative bacilli)? Will BCB monitored by automated blood culture instruments supplant aerobic and anaerobic plate and broth cultures for PJI, given FDA scrutiny of LDTs (6–8)?

A final question concerns laboratories being under pressure from hospital administrators worried about the potential financial impact of increased PJI rates. Will such administrators be leery of using innovative methods that are off-label applications of FDA-approved diagnostic devices, such as an automated blood culture instrument? One potential solution is for automated blood culture instrument manufacturers to seek FDA approval of novel applications of their automated blood culture instruments. So far, manufacturers have been reluctant to do this, with only one company seeking approval of culture of donated platelets for quality control purposes. This represents a significant market for BCB despite the fact that joint, pericardial, pleural, ascites, and peritoneal dialysis fluids are routinely cultured "off label" in BCB at many institutions.

This study (6) appears to be a useful and practical advance in the diagnosis of PJIs. Clinical microbiologists need to be aware of nonlaboratory issues that may have impacts on current and future laboratory innovation.

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