Molecular techniques v. conventional culture: Should there really be a debate?

Lower respiratory tract infection is one of the most important communicable causes of death worldwide.[1] In South Africa, community-acquired pneumonia (CAP) ranks among the top 10 causes of death, surpassed only by tuberculosis as the leading infective cause.[2] In a well-known study in patients with septic shock, a frequent complication of CAP, it was found that each hour's delay in initiating appropriate antimicrobial therapy was associated with a 7.6% decrease in survival.[3] It is therefore critically important for antimicrobial treatment for severe CAP to be instituted timeously. For this reason, antimicrobial therapy is often prescribed before microbial culture results are available. Empirical therapeutic options for CAP target the most common aetiological pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella* species, *Chlamydia pneumoniae* and *Moraxella catarrhalis*.[4] There are, however, a growing number of multidrug-resistant bacterial species that complicate decisions on empirical therapy. Inappropriate broad-spectrum antibiotic use not only results in increased mortality, but can also inadvertently contribute to the development of antimicrobial resistance. Antimicrobial stewardship principles dictate that every effort should be made to de-escalate to a narrower-spectrum antimicrobial agent as soon as a causative organism is identified and antimicrobial susceptibility results are available. Traditional microbial culture methods, however, require organisms to first grow on culture medium in the laboratory before antimicrobial susceptibility testing can be performed. This process can take 48 - 72 hours, invariably resulting in either prolonged inappropriate broad-spectrum antimicrobial agents being used before de-escalation is possible, or prescribing empirical therapy to which the causative organism is resistant.

Molecular techniques have the potential to significantly reduce the time to identify potential pathogenic organisms. Multiplex molecular assays, such as the Biofire FilmArray Pneumonia Panel, use nucleic acid amplification techniques to detect genes of more than 20 different organisms with a single test run. The positive and negative agreement with conventional culture results are >96%.[5] These techniques allow for fast identification of potential pathogenic organisms, both bacteria and viruses, as well as the presence of resistance genes within 2 hours.[6] As part of antimicrobial stewardship practices, Buchan *et al.*[7] found that the Biofire FilmArray Pneumonia Panel result had the potential for antibiotic adjustment in 70.7% of patients hospitalised with lower respiratory tract infections.

Most of the studies on molecular techniques for pneumonia were conducted in hospitalised or intensive care unit patients, usually in higher-income settings. In the current issue of *AJTCCM*, Worodria *et al.*[8] compared the diagnostic yield of the BioFire FilmArray Pneumonia Panel with conventional culture techniques in hospitalised patients with HIV in a low-income setting. They found that <25% of patients with CAP had a positive sputum culture, whereas the FilmArray Pneumonia Panel could detect a possible bacterial aetiology in 83.2% of patients. The FilmArray Pneumonia Panel improved the diagnostic yield by 64.5%. A viral pathogen could be detected in 49.5% of patients, with 44.9% of patients having both bacterial and viral infections detectable by the polymerase chain reaction (PCR) method. More than one pathogen was identified with PCR in 56.0% of patients who had a positive sputum culture, suggesting mixed infections. Antimicrobial resistance could be detected in 58.8% of patients using sputum cultures, whereas PCR could detect resistance genes in 79.3%.

The investigators rightly point out that the study did not assess the clinical outcomes of the patients, and the impact of molecular testing on important outcomes such as morbidity or mortality could therefore not be evaluated. A well-known and important drawback of molecular testing is the difficulty in differentiating between infection and mere colonisation. Furthermore, the Biofire FilmArray Pneumonia Panel does not include testing for important opportunistic infections such as *Pneumocystis jirovecii* or *Mycobacterium tuberculosis*. The attending clinician should therefore specifically request tests for these organisms.

The advantages of molecular techniques in terms of turnaround time, increased diagnostic yield and detection of viruses as a cause for CAP, as well as the detection of resistance genes, are clear. Why is it then that molecular tests are not routinely performed in the current era of increasing antimicrobial resistance, especially in low-income settings? Cost associated with molecular tests may still be a significant barrier. It may also be that there is still concern regarding a lack of understanding or interpretation of results, especially in patients with mixed infections or limited symptoms in whom detected pathogens may simply be colonisers. Interestingly, despite these potential barriers, PCR-based methods are already well established in diagnosing and managing pulmonary tuberculosis in low-income settings. Conventional culture remains important for phenotypic susceptibility testing and therefore still has a vital role. It is, however, high time for molecular techniques to be incorporated in the diagnostic algorithms for CAP to the benefit of our patients.

S D Maasdorp, MB ChB, MMed (Int Med), FCP (SA), Cert Pulmonology (SA), PhD
Department of Internal Medicine, School of Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa
maasdorpsd1@gmail.com

B van der Westhuizen, MB ChB, MMed (Micro), FC Path (SA) Micro, DTM&H
Department of Microbiology, School of Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

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