Antibiotic Commonsense

Molecular diagnostic technologies improve patient care & antibiotic stewardship

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According to the Centers for Disease Control and Prevention (CDC), 47 million unnecessary antibiotic prescriptions are written in the United States every year[1]. The misunderstanding about the use of antibiotics is still the leading cause of antibiotic resistance. Raising awareness of good antibiotic use requires strong collaboration between health professionals, policymakers, and the public[2]. In addition, recent technical advances in microbial identification with high accuracy and short turnaround time have revolutionized the diagnosis and treatment of infectious diseases. Timely differentiation between major pathogen groups – viruses, bacteria, fungi, and parasites – prevents misuse or overuse of antimicrobials. Detection of highly resistant pathogens at early stages of infection facilitates optimal of antimicrobial use, reduction of mortality and hospital length of stay, effective infection control, and cost savings for the patient and the hospital system.

Viral Infection

Conventional viral culture for diagnosing influenza and other respiratory viruses such as respiratory syncytial virus (RSV), adenovirus, and parainfluenza is laborious, slow, and not sensitive. The cytopathic effect of conventional culture that indicates the presence of a virus may take several days[3]. The long turnaround time of culture contradicts the optimal administration window of antiviral drug: oseltamivir should be taken within 48 hours of flu symptom onset[4]. While awaiting results of lab testing, the physician may also admit the patient to the hospital and/or offer empirical therapy based on the severity of the symptoms[5,6]. On the other hand, rapid influenza diagnostic tests (RIDTs) based on antigen detection have a fast turnaround time, but their sensitivity is only about 50 – 70%[7]. When influenza is prevalent (40%), the negative predictive value (NPV) of RIDT is only about 70 – 80%. In other words, a negative test result does not necessarily rule out infection.

Nucleic acid amplification tests (NAATs) have significantly shortened the time to diagnose respiratory viral diseases. The targets of such assays range from influenza virus alone to a panel of viruses that commonly cause respiratory illness. Some of the NAATs that can be performed as point-of-care tests have turnaround times as short as 30 minutes[8], with sensitivity and specificity that outperforms those of conventional viral culture and rapid antigen assay[9,10]. Early detection of influenza by NAATs is associated with significantly lower odds ratios for admission, length of stay, antimicrobial duration, and number of chest radiographs[11]. For infectious gastroenteritis, certain NAATs are now able to detect astrovirus and sapovirus, two pathogens previously not commonly detected[12]. Early diagnosis of a viral etiology helps reduce the unnecessary use of antibiotics.

Bacterial Infection

The emergence of multidrug-resistant (MDR) bacteria has continued to be a major threat to public health. Just to list a few examples: methicillin resistance caused by *mecA*, *mecC* genes; vancomycin resistance caused by *vanA*, *vanB* genes; carbapenem resistance caused by carbapenemases KPC, NDM, OXA, IMP, VIM ...

the list goes on and on. The detection of these MDR bacteria using NAATs is generally reliable. The sensitivity ranges from 92% - 100%, while the specificity ranges from 94% - 100%[13-15]. The short turnaround time of NAATs allows more effective antibiotic administration (5 hours vs 15 hours, P<0.001) compared to conventional methods[16]. Cases diagnosed by NAATs also had faster (48 hours vs 63 hours, P=0.034) and higher rate of antimicrobial de-escalation (52% vs 34%). In addition, the fast turnaround time of NAATs to identify Gram positive organisms, for example, *Staphylococcus aureus* vs coagulase negative *Staphylococcus*, helps the provider distinguish true infection from blood culture contamination, which in turn reduces readmission rates and unnecessary treatment. Diagnosis of *C. difficile* infection (CDI) using NAATs has been made more sensitive and effective using enzyme immunoassay[17]. It is still debatable whether using a single-step algorithm or two-step algorithm is more cost-effective to diagnose of CDI, but it has been shown that the use of NAATs favors a reduction in patient isolation days compared to *C. difficile* toxin A/B immunoassay (364 vs 1,022; P<0.00001) and a reduction in the duration of empirical metronidazole for patients with negative test results (P=0.02)[18].

Fungal and Parasitic Infection

The use of NAATs allow accurate detection of fungal and parasitic pathogens not only from diarrheal stool specimen, but also from sterile sites for invasive infections. Septic shock due to invasive candidiasis is a near fatal condition. The latest molecular technologies for diagnosing bloodstream infection (BSI) by *Candida* have significantly improved turnaround time – the diagnosis can be performed directly from blood specimens instead of a positive blood culture. The use of such technology can potentially reduce the number of unnecessarily treated patients (low-to-moderate-risk) by 98% relative to that with empirical treatment[19]. Serious fungal infections are expensive to treat and involve long hospital stays, so these technologies can be cost-effective given a high prevalence of *Candida* BSI[19].

Limitations of molecular technologies

While molecular technologies improve diagnostic performance, turnaround time, and patient outcomes, it is also important to understand their limitations. NAATs can only detect the targets designed as part of the assay – a new test would need to be developed to detect any new/rare strains or resistance markers. For example, the outbreak of carbapenemase-producing *Klebsiella pneumoniae* associated with endoscopic retrograde cholangiopancreatography was due to OXA-232, a carbapenemase that was detected by whole genome sequencing but is not targeted by existing diagnostic NAATs[20]. An inadequate database of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) leads to the misidentification of bioterrorism agents such as *Burkholderia pseudomallei*[21]. A positive result of a NAAT for toxigenic *C. difficile* might indicate colonization rather than infection; misinterpretation of the result could lead to unnecessary treatment[22]. If not used carefully, high-resolution molecular sequencing technology, may create nomenclatural instability and confusion[23]. Lastly, the adoption of molecular technologies should not replace the conventional culture system, as the isolation of pathogens is still critical for conducting epidemiological studies and for susceptibility studies. Laboratory test results must be correlated with the clinical findings to help clinical decision making.

In summary, molecular technologies have not only revolutionized the field of microbiology, they have also had tremendous impact on treatment of infections, patient care, infection control and prevention, and overall hospital operation. There is no doubt that laboratories are adopting more and more molecular technologies to provide better quality of service, and, in particular, to advance antibiotic stewardship.

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