Rapid Molecular Diagnostics: Supporting CDC’s Four Core Actions to Fight Antimicrobial Resistance

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Antibiotics are among the most widely used, and misused, therapies in medicine. While the advent of the antibiotic era profoundly altered both the practice of medicine and the way we view medicine as a healing art, the impact of injudicious and inappropriate antibiotic use has considerable consequences to individuals and society.

The Infectious Diseases Society of America (IDSA) has published accepted standards for the use of antimicrobial therapy. Important considerations for antimicrobial use include:

• Accurate diagnosis of infection
• Use of definitive versus empiric therapy
• Identifying opportunities to switch to narrow-spectrum, cost-effective oral agents for the shortest duration necessary
• Understanding antimicrobial drug and host characteristics that influence antimicrobial activity
• Recognizing antimicrobial adverse events
• Understanding the significance of antimicrobial stewardship—when to consult infectious disease specialists and identifying situations when antimicrobial therapy is not needed

The IDSA states that, “By following these general principles, all practicing physicians should be able to use antimicrobial agents in a responsible manner that benefits both the individual patient and the community.”

The clinical practice of medicine, however, is laden with complexity that can impede guideline adherence. Because microbiological results often do not become available for 24 to 72 hours, initial therapy for infection is often empiric and guided by the clinical presentation. For the critically ill, delays in antibiotic treatment for even one hour are associated with poor outcomes, including greater morbidity, increased mortality, and increased length of stay. If the patient is stable, the directive is to withhold antibiotics until laboratory results become available, but this rarely occurs. Instead, physicians are often forced to make empiric decisions without the benefit of crucial data to guide decision-making.

A year-long study of antibiotic prescribing for adults in the outpatient setting estimated that out of 40 million people who were given antibiotics, only one-third needed them. Two-thirds of prescriptions were unnecessary and resulted in essentially wasted therapy. In a separate study, 57% of children with acute respiratory infections were prescribed antibiotics, but only 27% had bacterial infections. In these cases, the inability to quickly and accurately confirm whether the causative pathogen was bacterial or viral directly resulted in higher healthcare costs and ineffective resource utilization, including inappropriate antibiotic use which is the driving force for development of antimicrobial resistance (AMR). Increases in antibiotic use directly correlate with the presence of non-susceptible bacterial strains.

The Centers for Disease Control and Prevention (CDC) estimates that in the United States, more than two million people are sickened every year with antibiotic-resistant infections and at least 23,000 die as a result. The CDC stresses that these estimates are based on conservative assumptions and are likely minimum estimates and represent the best approximations that can be derived from available data. In addition, almost 250,000 people each year require hospital care and at least 14,000 people die each year in the United States from *Clostridium difficile* (*C. difficile*) infections, which are known to be related to antibiotic use. Many of these infections could have been prevented with more judicious antibiotic use. Meanwhile, the total economic cost of AMR in the United States in today’s dollars is estimated at more than $22 billion per year for direct healthcare costs and $39 billion per year with the inclusion of lost productivity.

So why does such inappropriate antibiotic prescribing behavior occur? In the host of factors, diagnostic uncertainty is a major culprit.

The clinical presentations of viral and bacterial infections are often indistinguishable. The care expected at point-of-service is in direct conflict with the obligatory delay of waiting for culture results that is currently required by standard, sometimes outdated, culture techniques. This is despite the exponential advances in technology over the past decades. Hence, many patients receive empiric antimicrobial therapy to address suspected infections instead of appropriate therapy directed by unequivocal identification of a specific infectious agent.

The practical outcome of diagnostic uncertainty has been well articulated. The pediatric literature shows that antibiotic overuse and
misuse are extremely common—50% of antibiotics are erroneously prescribed for a viral infection. This can result in adverse effects from the antibiotic and promote bacterial resistance. But, the problem of diagnostic uncertainty is not one-sided. In contrast, 20% of pediatric patients with a bacterial infection do not receive timely antibiotics leading to possible disease prolongation, complications and even hospitalization.6

The bottom line is that empiric therapeutic decision making without proper and timely diagnostic results may lead to ineffective therapy resulting in serious consequences for the patient. Empiric therapy may also result in selection for so-called “superbugs” and increased morbidity and mortality that will only get worse moving forward. Thus, CDC has declared the complex problem of AMR a serious threat today, which will result in potential catastrophic consequences with continued inaction. In like respect, the World Health Organization (WHO) has stated that, “A post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century,” threatening the achievements of modern medicine.9

Aggressive action is needed now to prevent both the spread of existing resistance and development of new resistance mechanisms. To combat AMR, the CDC has identified 4 core actions, all of which can be addressed through rapid molecular diagnostics (Figure 1).

**Preventing Infections and the Spread of Resistance**

Preventing infection not only obviates the need for antibiotics, which by definition is the ultimate prevention strategy for AMR, but also limits the spread of infections caused by resistant organisms. There are many ways that drug-resistant infections can be prevented. Immunization, handwashing, safe food preparation, infection control and prevention practices, and judicious antibiotic use were all identified by the CDC as effective preventative measures.

To fulfill this goal, the CDC has established various policy initiatives: (1) tracking resistance and prescribing patterns at national, regional and local levels; (2) providing guidance to healthcare facilities interested in better antibiotic use; and (3) working to prevent all patient infections through infection control guidelines, assistance implementing these guidelines, and laboratory expertise.

Policy initiatives represent efforts on the macro level. Rapid molecular diagnostics provide a parallel method to attack the problem of resistance spread on the micro level at point of care. Tests are currently available to identify those organisms the CDC considers the most urgent and serious threats, including assays for the detection of MRSA, C. difficile, carbapenem-resistant organisms, vancomycin-resistant enterococci and drug-resistant tuberculosis.10

Use of rapid and accurate molecular diagnostics enables real-time identification of organisms, including drug-resistant isolates. This greatly improves “time to result,” allowing clinicians and infection prevention professionals to quickly identify, isolate and better manage patients colonized or infected with drug-resistant organisms—thereby limiting the spread of resistance. Unfortunately, developments in rapid molecular testing in many cases have outpaced clinician awareness and uptake.11

**Disease Surveillance**

In today’s information age, data represent an expanding set of powerful opportunities. As many as 70% of clinical decisions may be informed by data from the medical laboratory and the vast amount of data being created is growing at an exponential pace. Managing this significant volume of information quickly, correctly and securely is increasingly more difficult and complex; however, the challenge isn’t in simply making the data available. The ability to access and share meaningful insights from the wealth of information the laboratory generates is a necessity.

Too often healthcare professionals have limited visibility to the information they need to optimize patient care. To operate successfully in today’s healthcare environment, clinicians require immediate access to patient information. Irrespective of centralized or decentralized testing environments, the process of collecting and managing the volume of information flow quickly, correctly and securely is difficult and complex. Individual hospitals, large health systems and public health agencies in remote or urban settings alike are realizing the benefits a single, unified warehouse of information can provide.
The advent of rapid molecular diagnostics permits active disease surveillance in real time. This is achieved through the combination of (1) real-time actionable test results within and across sites of care; and (2) mobile data reporting through seamless, secure and scalable digital connectivity solutions. Active tracking allows for rapid information sharing to help monitor, manage and reduce the spread of infection resulting in better epidemiologic surveillance to improve patient treatment and outcomes. This approach is in contrast to paper-based recording systems that are slow and error prone. Editing, transmission and translation of data from paper reports inherently causes delays and errors that contribute to the cost, complexity and inaccuracy of data and its interpretation.\(^{13}\)

As an example of the benefits of active disease surveillance, in 2010 the WHO endorsed a novel test for tuberculosis (TB), Xpert\textsuperscript{®} MTB/ RIF. It is an automated, cartridge-based nucleic amplification assay for the simultaneous detection of TB and rifampin resistance directly from sputum. Compared to culture that can take up to three months to provide a result, Xpert MTB/RIF was anticipated to revolutionize TB care and control by providing an accurate diagnosis for many patients in less than two hours. Now more than 5,000 systems and 15 million Xpert MTB/RIF cartridges have been procured under the WHO Global TB Programme. The large number of systems in place created a unique opportunity to track and monitor the prevalence of TB infections and the spread of rifampin resistance.

To complement the novel TB test and enhance disease surveillance, a proprietary connectivity platform was implemented in South Africa to stratify high-risk populations based on epidemiological trends and geographic variations to detect and monitor “hotspots” of disease and drug resistance (Figure 2). The result was that a comprehensive, 360° view of testing information strengthened disease surveillance, monitoring and reporting capabilities in a secure, compliant and sustainable manner. In short, public health officials in South Africa were able to utilize TB laboratory data to better direct resources to manage TB spread in country, particularly in those areas where multidrug-resistant TB was prevalent.

\section*{Antibiotic Stewardship}

An important action needed to slow the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Despite broad conversations about AMR policy and dramatic advances in diagnostic technologies, most patients with suspected infections receive empiric antimicrobial therapy rather than appropriate therapy directed by rapid identification and characterization of the infectious agent. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate, as noted by the CDC.\(^\text{9}\) Given data clearly demonstrating that antibiotic use directly correlates with development of resistant clones, even slowing the rate of inappropriate and unnecessary antibiotic use should slow the spread of resistant bacteria. This concept has been termed antibiotic stewardship and is defined as, “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration.”\(^{1,3}\)

Antibiotic stewardship is essential, but behavioral change is not easy. People must be given information and an acceptable action plan to drive and solidify that change. Rapid diagnostics can transform the way antibiotics are used by providing objective data for antimicrobial stewardship programs to improve outcomes and prevent the emergence of resistant organisms.\(^\text{3}\) Specifically, rapid molecular diagnostics can answer critical, actionable questions at point of care:

\begin{itemize}
\item Is the infection causing the illness bacterial or viral?
\item If bacterial, what type of bacteria is causing the infection?
\item To which antibiotics are the bacterial species susceptible and resistant?
\end{itemize}

Published data demonstrate the clinical and economic value of antibiotic stewardship programs that utilize rapid diagnostic testing. Parta and colleagues evaluated the Xpert\textsuperscript{®} MRSA/SA BC assay in comparison to traditional methods and showed that patients without S. aureus bacteremia had a significant decrease in inappropriate antibiotic therapy and a 44.6-hour reduction in the mean time to appropriate therapy.\(^{15}\) Similarly, both Bauer et al.,\(^{16}\) and Wong and colleagues\(^{17}\)—using the same Xpert MRSA/SA BC assay showed statistically significant reductions in conversion time from empiric treatment to appropriate therapy, total antibiotic exposure, hospital length of stay, and hospital costs when testing was combined with timely intervention.

Importantly, simply using rapid molecular diagnostics is not enough. Rapid diagnostic tests are of little value if an antimicrobial stewardship program does not have, “a role as an active messenger and educator of the results.”\(^\text{18}\) For example, Bauer et al. also reported on a study that failed to demonstrate improved patient outcomes or a decrease in antibiotic use with utilization of a rapid microbiologic test despite the test’s accuracy because of the absence of an effective implementation strategy.\(^{18}\) Hence, it is the combination of rapid microbiologic tests and antimicrobial stewardship that is required to demonstrate significant improvement in patient outcomes and antimicrobial use.
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Development of New Diagnostics

The need for development of new antibiotics is absolute. Resistance formation in bacteria and viruses is part of natural selection and will never be eradicated. Because inappropriate and overuse of antibiotics is a core driver of resistance formation through selection pressure, it must be managed. Development of new drugs and diagnostics, by necessity, will be a component of timely delivery of optimal therapy. To spur innovation, multiple organizations across the world have sponsored large financial prizes:

- The Longitude Prize (UK): £10 million prize for a point-of-care diagnostic test that will help solve the problem of global antibiotic resistance fulfilling the goal of conserving antibiotics for future generations by revolutionizing the delivery of global healthcare. The prize announcement calls for the diagnostic innovation to be “accurate, rapid, affordable and easy to use anywhere in the world.” Submissions are accepted on a rolling basis until a winner is chosen. The final deadline for submission is September 30, 2019.
- Antimicrobial Resistance, Rapid, Point-of-Care Diagnostic Test Challenge (US): $20 million prize sponsored by the National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA) (with support from the CDC and FDA) to facilitate development of rapid, point-of-care diagnostic tests for healthcare providers to identify highly resistant bacterial infections.

The fact that very sizable awards have been offered for developing new diagnostics underscore the need for new, faster diagnostic options.

Conclusion

As healthcare providers and stewards, should we accept two-thirds of cancer patients receiving the wrong chemotherapy? Should you accept having your doctor diagnose your child’s illness correctly only one-third of the time? We can and must do better, bridging the gap between guidance on infectious disease treatment and implementation of practical standards of care. The principles underlying efforts to combat AMR are beyond debate. The goals of these efforts are to improve care and prevent AMR from becoming an even greater public health emergency. National and international policies, as articulated by the CDC’s Four Core Actions, are a critical path to fighting resistance formation and improving healthcare. In a time defined by advances in technology, greater utilization and integration of tools and technologies is another pathway for improvement.

While the therapeutic and societal value associated with combating AMR is clear, significant challenges remain. Political action and policy implementation are critical. Yet, without rapid diagnostics, it is much more difficult for clinicians to give the right drugs to the right patient in a timely manner. More universal implementation of rapid molecular diagnostics at point of care will require demonstration of both the cost and clinical effectiveness of the tests in well controlled studies. Bringing efficiency to healthcare informatics will also be required, as we do not yet do an adequate job integrating the rapid diagnostic options we have today. The good news is that these issues have been articulated, their urgency has been stated, public policies have been created, and technological advancements redefining clinical decision-making at point of care are underway.

REFERENCES

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