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Rapid Diagnostics and Antimicrobial Resistance in the ICU

The need to address the problem of antimicrobial resistance, the importance of faster diagnosis of bacterial infections and an overview of rapid diagnostic testing.

Antimicrobial resistance (AMR) is rapidly increasing on a global scale. The discovery of penicillin revolutionised the field of medicine, providing safe harbour from the most pressing threats of the time—infectious diseases. However, the threat of AMR has now escalated to a degree that it has become a major priority for national public health agencies, such as the Centers for Disease Control and Prevention (CDC) in the United States, and the World Health Organization (WHO). Just over one hundred years after the discovery of our first antibiotic, we are quickly running out of treatment options for some organisms. In the battle against bacteria, we are in danger of losing.

How did we get here? The cause of antimicrobial resistance is multifactorial, stemming from microbes' innate ability to develop resistance when exposed to evolutionary pressure. Even when not expressed, microbes carry resistance genes that allow them to modify antibiotics, remove the drugs from their cytosol via efflux pumps, or alter their targets to prevent drug activity (Jian et al. 2021; Hutchings et al. 2019). Constant exposure to antibiotics, such as through injudicious use in healthcare, begets more antimicrobial resistance.

Antimicrobials are commonly prescribed in outpatient, inpatient, and intensive care settings. Numerous studies have now established that timely initiation of antimicrobials with appropriate activity in serious infections, specifically sepsis and septic shock, leads to marked reductions in mortality. However, the heterogenous presentation of bacterial infections, which often overlap with other causes of non-bacterial sepsis (e.g., viral and fungal infections), and the inevitable delay in obtaining definitive diagnosis can lead to administration of inappropriate and often unnecessary antibiotics. Up to a third of patients treated with broad-spectrum antibiotics for suspected bacterial infections in emergency departments are ultimately diagnosed with non-infectious or viral illnesses (Shappell et al. 2021). These concerns are only magnified in countries where over the counter antibiotic purchasing can lead to unprecedented levels of antibiotic misuse.

How do we become better? Like the cause of antimicrobial resistance, the fix must also be multifactorial. The easiest and most immediately feasible place to start is to become faster in our diagnosis of bacterial infections, as well as recognition of antimicrobial resistance. Traditional culture-based diagnostics are key to the identification of bacterial infection but can require several hours to days to provide actionable data. Other biomarkers, such as procalcitonin, have been studied in the hope of distinguishing between bacterial and viral infection, but these markers have thus far fallen short of their aims and may correlate better with disease severity rather than aetiology (Self et al. 2017).

In order to guide therapy, assays must be rapid, accurate, and actionable. Recently, rapid molecular tests have shown promise in providing faster and more reliable information to guide clinical decisions. The majority of these assays are based on nucleic acid amplification tests (NAAT) and semi-quantitatively detect bacterial genetic material or protein end-products to identify causes of infection. With some assays, there is the potential to detect genetic determinants of antimicrobial resistance as well. Some of the molecular tests currently available still rely on the growth of bacteria in traditional cultures but can then accelerate the process of identifying the bacteria from 24-72 hours when using culture methods to a matter of hours (Ecker et al. 2010). More novel methods, such as next-generation sequencing (NGS), can bypass the need for culture entirely by identifying cell-free non-human DNA targets within whole blood samples to identify pathogen-derived genetic sequences. Though some of these tests are not yet commercially available for clinical use (or require too much time to be actionable in the ICU), they show promise for future improvements in our ability to rapidly identify and treat infections (Grumaz et al. 2019).

There are a variety of syndromically-based rapid molecular assays available for use in clinical practice, including upper and lower respiratory tract, gastrointestinal, urinary, neurological, and bloodstream infections. Polymerase chain reaction (PCR) assays available for the diagnosis of lower respiratory tract infections may be able to detect pathogens with significantly greater

sensitivity (and speed) when compared with routine culture-based testing, with sensitivities as high as 74% when compared to 44% by cultures (Enne et al. 2022). When testing sputum specimens with higher leukocyte counts on conventional staining, PCR testing has an even greater yield and can detect pathogens at lower leukocyte counts than traditional cultures (Rand et al. 2021).

Another common problem encountered in clinical practice is that of culture-negative pneumonia. Many factors can result in the inability to isolate an organism in a culture, including recent antibiotic exposure or a high inoculum of normal throat flora. Even in this situation, molecular pneumonia panels can identify bacterial targets in 63% more bronchoalveolar lavage samples than traditional cultures (Buchan et al. 2020).

There is a wider variety of rapid molecular tests available in the arena of bloodstream infections. Rapid blood culture identification systems, including the Verigene (Luminex, Austin, Texas, USA) and FilmArray BCID (BioFire Diagnostics, Salt Lake City, Utah, USA) panels, detect key genes to identify bacteria as well as common beta-lactam resistance markers. These tests lack the amplification step of PCR-based tests, and as such require a threshold inoculum in order to identify bacteria, roughly correlating with a positive blood culture; nonetheless, the time to identify both bacterial species and beta-lactam resistance can be reduced by 24-48 hours with these panels (Claeys et al. 2021).

Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) is an adaptation of nuclear magnetic resonance testing for the identification of bacteria. Different bacterial molecules have unique mass spectra, which confer to them different times-of-flight when accelerated through a detector. The MALDI-portion of the test confers ionic charge to the molecules to allow for their acceleration. Already in widespread clinical use, MALDI-TOF is currently being actively developed to detect antimicrobial resistance patterns as well (Croxatto et al. 2012).

"rapid molecular tests have shown promise in providing faster and more reliable information to guide clinical decisions"

Next-generation sequencing (NGS), also known as high-throughput sequencing, can identify billions of DNA sequences simultaneously from clinical samples. NGS can be used to detect non-human cell-free DNA (cfDNA) from whole blood samples and is therefore non-pathogen specific, in comparison to PCR-based tests which are limited in only being able to detect specific, targeted organisms. However, NGS is also limited by its ability to distinguish human genomic material, such as that hosted within circulating leukocytes, versus non-human material. This shortcoming can be bypassed by using targets unique to pathogens, such as the 16S rRNA gene, by comparing a patient's cfDNA with those of healthy controls, or first depleting the sample of human genetic material (Gu et al. 2019).

In terms of clinical applications, rapid molecular assays can provide clinically actionable information with potential for faster de-escalation of antibiotic therapy. PCR-based pneumonia panels have shown faster test result times and shorter antibiotic therapy times after the implementation of these assays compared to prior (Rogers et al. 2015). These tests, however, require integration with strong antimicrobial stewardship practices. In one series, up to 48% of patients in one study underwent appropriate de-escalation of antibiotics based on test results, but 16% of patients in the same study underwent inappropriate escalation or continuation of therapy despite clear test results. Good stewardship requires better tests but also better implementation (Buchan et al. 2020).

As we work to improve our clinical use of antibiotics in human medicine, we must work as a global health community to improve and reduce the use of antibiotics in veterinary medicine and agriculture. Recognising the strong interconnection between humans, animals, and the environment, CDC and global partners have developed One Health, a project that works to establish mutual goals and projects to combat emerging infectious disease threats, including AMR. Through focused education regarding wise antibiotic use, close monitoring of antibiotic use and waste, and careful surveillance of emerging resistance, we can improve care for all patients.

Conflict of Interest

None. ■

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