The Essential Role of Clinical Microbiology Laboratories in Antimicrobial Stewardship

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Antimicrobial stewardship programs (ASPs) aid physicians in providing optimal antimicrobial therapy to their patients, prescribing the right antimicrobial regimen to the right patient for the right period of time—and avoiding unnecessary antimicrobial use. Ultimately, ASPs aim to improve patient outcomes while limiting adverse drug events and antimicrobial resistance (1). ASPs also have been shown to save resources and money. ASPs and prescribing physicians depend on information and guidance from the clinical microbiology laboratory in order to accomplish these goals, making the laboratory vital to patient care and the success of ASPs.

Three Keys for the Lab in Antimicrobial Stewardship

Antibiogram Reporting

Clinical microbiology laboratories conduct surveillance on local antimicrobial resistance trends among microbial pathogens. The collection, organization, and communication of resistance data culminates in the creation of an antibiogram. Antibiograms provide critical information to ASPs and prescribing physicians on institutional susceptibility patterns.

For example, when physicians treat patients with presumed infectious diseases, they must consider which microbial pathogens are most likely to be involved given a patient's history, severity of illness, and location of suspected infection. They also must consider which antimicrobials are most likely to cover those serious pathogens and prescribe accordingly. However, physicians typically do not have patient-specific information when ordering the initial antimicrobial agent. This type of antimicrobial prescribing based on a physician's best

estimate of potential offending pathogens is called empiric therapy.

Empiric therapy should be broad enough to cover the pathogens that are most likely to be involved. This is especially important for certain infections such as bacteremia in critically ill patients, where there is clear data that patients have a greater chance of survival if their empiric antimicrobial regimen covers their infecting pathogen. However, unnecessarily broad empiric therapy also carries risks. For example, an increase in the incidence of adverse drug events, acquisition of Clostridium difficile infection, development of antimicrobial resistance, and increased healthcare costs have all been linked to inappropriate antimicrobial use.

Individual physicians can refer to their institution's antibiogram for guidance on which antimicrobials are most likely to effectively treat which pathogens, thereby optimizing empiric antimicrobial therapy. Many ASPs use antibiograms to develop institution-specific guidelines for prescribing physicians. ASPs can also use their local antibiograms to make decisions about which antimicrobials should or should not be on their institution's drug formulary.

Most laboratories provide institution-wide antibiograms that report on the susceptibility of clinically relevant microbial pathogens to various antibiotics over a defined period of time (Figure 1). Some laboratories also prepare more specific antibiograms. For example, antibiograms can be prepared for distinct patient care locations such as medical intensive care units (ICUs), surgical ICUs, burn ICUs, or outpatient settings. Antibiograms can also be organized by clinical condition such as urinary tract infection (UTI) or by certain underlying diseases such as cystic fibrosis.

Given the important function that these antibiograms have in patient care, their quality is essential. Laboratories can ensure useful and accurate antibiograms by adhering to the guidelines for cumulative susceptibility reporting from the Clinical and Laboratory Standards Institute (CLSI) (2).

Patient-Specific Information

Laboratories provide patient-specific information by identifying microbial pathogens and performing antimicrobial susceptibility testing. This information is necessary so that empiric antimicrobial therapy can be narrowed appropriately. Antimicrobial prescribing that targets isolated pathogens is called directed therapy. Directed therapy typically carries less risk for developing antimicrobial resistance and adverse drug events, and often is more effective and less expensive. Further, patient-specific information that confirms the absence of pathogens enables physicians to discontinue antimicrobials

entirely. The time that it takes a laboratory to report this information directly impacts the duration of empiric antimicrobial therapy, the time to directed therapy, or discontinuation of unnecessary therapy.

Consider the case of a critically ill patient with sepsis. In such instances, patients are typically started on a broad, empiric antimicrobial regimen that contains three or more antimicrobial drugs, such as piperacillin-tazobactam plus amikacin plus vancomycin. If that patient's blood cultures reveal methicillin-sensitive Staphylococcus aureus, his or her antimicrobial regimen can be significantly narrowed to only one, narrow-spectrum antimicrobial, such as nafcillin.

Additionally, some ASPs have incorporated biomarkers such as procalcitonin into guidelines to help differentiate infectious from non-infectious causes of inflammation, and to complement other methods for determining antimicrobial courses and durations. The procalcitonin value has been shown to be an effective tool in decreasing antimicrobial use in patients with acute respiratory infections and in shortening the duration of antimicrobial regimens in ICU patients with sepsis.

Specimen and Reporting Quality

Laboratory guidelines, policies, and procedures that ensure high-quality specimen processing have an important role in limiting unnecessary antimicrobial use. For instance, guidance on methods to promote appropriate specimen collection directly affects the reliability and applicability of testing results. Procedures for rejecting improperly submitted specimens and that limit the work-up of organisms that are likely to be contaminants decrease unnecessary antimicrobial use and are both critical to patient safety (3). Finally, clinical microbiology laboratories can work directly with ASPs to jointly create guidelines, ensuring optimal results communication to physicians.

Improving Patient Care With Rapid Diagnostics

Over the past decade, there have been several advances in rapid diagnostic testing. Examples of these techniques are matrix-assisted laser desorption ionization time-of-flight mass spectometry (MALDI-TOF MS), peptide nucleic acid-fluorescence in situ hybridization (PNA-FISH) technology, quantitative polymerase chain reaction (qPCR) assays, and multiplex nucleic acid assays. Compared to standard techniques that require 48–72 hours for final results, these methods can greatly reduce the time to pathogen identification by providing final organism identification within hours of growth.

In order to capitalize on the benefits of this decreased time to identification, several ASP interventions are useful. For

example, ASPs develop institutional guidelines on how to use the test results, educate providers on the new testing techniques and appropriate application, ensure direct notification of positive results to clinicians, and provide support for clinicians as questions arise. When used with ASP interventions, rapid diagnostics improve patient care by decreasing overall antimicrobial use, the time to directed or optimal antimicrobial therapy, the length of hospital stays, and by decreasing overall healthcare costs (4,5).

MALDI-TOF MS systems enable identification of any one of a large number of organisms from positive cultures of different body sites in as little as 0.2 hours. Several studies have reported a favorable impact of MALDI-TOF technology on patient care when used in combination with ASP interventions. One study demonstrated an improved time to optimal antimicrobial therapy by 43 hours, decrease in ICU stay by 6.6 days, and a 5.8% decrease in mortality (6). Of note, while MALDI-TOF MS systems allow for very rapid organism identification, they do not yield any information on antimicrobial susceptibilities.

PNA-FISH tests employ fluorescein-labeled probes that target pathogen-specific RNA and can yield results 0.3–4 hours after a blood culture bottle signals growth. Several studies have demonstrated improvements in various patient care parameters when ASP interventions are coupled with PNA-FISH testing. Many of these studies were performed using an S. aureus single probe. However, PNA-FISH testing has also been used for other pathogens, including Candida spp., and the ability to distinguish different Candida spp. can result in a quicker transition from expensive, empiric antifungal therapy to optimal or directed antifungal therapy. For example, the Yeast Traffic Light PNA-FISH assay (AdvanDx) can identify five different Candida species, which have variable sensitivity to fluconazole. Specifically, one study demonstrated pathogen identification 3.8 days earlier, a 1.7 day decrease in time to directed antifungal therapy, a 1-day decrease in time to microbial clearance, and an estimated $415 cost-savings per patient (7).

qPCR assays accurately distinguish S. aureus from other types of staphylococci and identify the presence of methicillin-resistance genes (mecA and SCCmec) from blood culture samples within 2 hours from the time microbial growth is demonstrated. The use of qPCR testing in conjunction with ASP interventions also has been shown to decrease unnecessary antimicrobial use. One study demonstrated a decrease in time to directed antimicrobial therapy by 1.7 days, a decrease in mean hospital length of stay by 6.2 days, and a mean decrease in hospital cost of $21,387 (8).

Multiplex nucleic acid assays can be used to test simultaneously for the presence of multiple organisms as well as select yeast species within 1–2.5 hours from the time of culture positivity. While multiplex nucleic acid assays do not give detailed susceptibility data, they do detect several resistance markers such as mecA, vanA, vanB, KPC, NDM, CTX-M, VIM, IMP, and OXA.

Multiplex nucleic acid assays have been shown to positively impact patient care when combined with ASP interventions. Specifically, one study reported a decrease in the time to directed antimicrobial therapy by approximately 1 day, a decrease in average length of hospital stay by 21.7 days, and a decrease in average hospital costs by $60,729 in patients with enterococcal bacteremia (9).

One major shortcoming of most currently available rapid diagnostic testing is their limited information on antimicrobial susceptibility. While some of these technologies are able to identify resistance markers, which are helpful in particular instances such as methicillin-resistant S. aureus and vancomycin-resistant enterococci, full antimicrobial susceptibility data is not yet readily available. The quicker that information is available, the sooner antimicrobial prescribing decisions can be made and an individual patient's antimicrobial regimen can be optimized. Another limitation of currently available rapid diagnostic testing methods to evaluate patients with presumed bacteremia is that they can only be performed after a culture system has detected microbial growth. Ultimately, the use of point-of-care molecular diagnostics on whole blood specimens would significantly decrease time to organism identification, but those capabilities are not yet available.

Communication Is Key

Effective communication between the clinical microbiology laboratory and prescribing physicians is essential for optimizing antimicrobial regimens and delivering safe patient care. This communication may take several forms, including verbal and written test results reporting. It is imperative that reporting be timely, clear, understandable, and accessible to prescribing physicians. Laboratories should have procedures in place to ensure effective communication, and these procedures should be reviewed and updated regularly.

Further, ASPs can play an important role in enhancing communication among microbiology laboratories, ASPs, and clinicians. The benefit of effective communication is particularly apparent when new diagnostic testing is introduced. ASPs can act as a clinical liaison to the microbiology laboratory to review microbiology laboratory reporting procedures and provide

insights and advice on how reported data will likely be interpreted or used in the clinical setting.

When laboratories implement a new test, they must plan to educate clinicians to ensure accurate interpretation and appropriate use of results. ASPs provide clinical support and guidance on how results should be used to optimize antimicrobial therapy, ensure timely and effective communication of laboratory results, see that therapy modifications occur in a timely fashion, and provide clarifications and reassurance to providers.

Importantly, when communication fails, new technology may not translate into improved patient care. One study illustrated this concept and reported that when a single-probe S. aureus PNA-FISH assay was introduced without administrative support for active reporting or the ASP's team input, no impact on patient care was realized even though test results were verbally communicated within 60 minutes to a relevant licensed care provider and documented in the electronic medical record (10). In contrast, several other studies have demonstrated a significant, positive impact on patient care when the introduction of rapid diagnostic testing was coupled with ASP interventions. The importance of effective communication and communication support is logical as rapid diagnostics are of limited utility if their results are unclear, not known, or not acted upon promptly.

Clear communication is essential in creating antibiograms. ASPs and clinical microbiology laboratories should work together to determine the most useful and feasible method for organizing, analyzing, and reporting cumulative susceptibility data given the local patient populations and institution specific nuances of microbial resistance. Since ASPs often make suggestions on empiric antimicrobial therapy, either informally or through local guidelines, it is important that they understand how the susceptibility data is generated and to which patient populations it may or may not apply.

Finally, open communication between clinicians and laboratory personnel should be encouraged. This communication may include direct conversations and questions about an individual patient's results. But it can also take the form of a structured educational initiative such as laboratory rounds where a mutual exchange of information takes place. While laboratory rounds are not feasible at many institutions due to limited time and manpower, both clinicians and laboratory personnel find them enlightening. Even a 20 or 30-minute session on a weekly, biweekly, or monthly basis can make a difference. During laboratory rounds, a representative from the clinical microbiology laboratory shares one or more laboratory specimens with clinicians (i.e. a culture plate from a patient with a clinical specimen growing S. pneumoniae or a MALDI-TOF

demonstration) and explains the methods, procedures, and limitations of clinical microbial testing. Likewise, the clinician provides a clinical context for laboratory personnel, particularly if he or she is familiar with the patient whose specimen is being processed.

Conclusion

The clinical microbiology laboratory plays a critical role in the success of antimicrobial stewardship efforts by providing essential information for accurately diagnosing and treating patients with infectious diseases. Institution-wide antimicrobial resistance surveillance reported in the form of antibiograms informs decisions for empiric antimicrobial therapy, and timely and accurate patient-specific pathogen isolation and susceptibility data inform directed antimicrobial therapy. Coupling clinical microbiology laboratory information with ASP interventions leads to the best antimicrobial use for individual patients and on an institutional level. Finally, each clinical laboratory professional has the ability to directly and positively affect patient care by ensuring accurate specimen processing and timely, effective verbal and written communication with clinicians and ASPs.

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