Labs take new role in antibiotic stewardship, championing improved diagnoses, guiding therapy, saving lives, and cutting costs

By Joe Romano

Optimizing antibiotic therapy and antibiotic stewardship is a mantra often chanted, yet together they seldom get the necessary recognition as a common denominator that mutually impacts departments hospital-wide. Unfortunately, laboratories are not always typically perceived as central actors who take *the* leading role to drive the overall success of a hospital enterprise by facilitating a key paradigm shift in antibiotic management. As a result, the inappropriate use of antimicrobial agents in the form of under- or over-treatment of infections is a common problem; and optimizing antibiotic therapy for patients continues to pose a major challenge.[1]

What is the problem, and how did we get here?

Unnecessary use or overuse of antibiotics is associated with significant increases in healthcare costs, hospital length of stay, and the development of pathogens that are resistant to many types of antibiotic therapy.[2-4] The failure to *promptly deliver* or *quickly administer* antibiotic therapy to patients with potentially life-threatening infections is associated with increased morbidity and mortality.[5-8]

To exacerbate the problem, hospital physicians are confronted with patients every day who potentially have life-threatening bloodstream infections. As a result, clinicians are typically forced to decide which antibiotic, if any, should be administered to the patient. In order to appropriately cover a wide variety of increasingly resistant pathogens, broad-spectrum antibiotic therapy is frequently administered when blood-culture results are reported as positive and an infection is suspected.

Moreover, bacteremia is also a leading cause of infection among hospitalized patients. Staphylococci are the most frequent bloodstream isolates, accounting for more than 50 of positive bloodstream cultures.[9-10] Although coagulase negative staphylococci (CoNS) are commonly isolated from blood, only a minority of such cultures represent true infection.[11] Conversely, blood cultures growing *Staphylococcus aureus* almost invariably signify true bacteremia and may be associated with severe complications, including foci of secondary infection at distant sites such as bones, joints, endovascular structures, and the central nervous system. Furthermore, a majority of nosocomial *S aureus* bloodstream infections are now caused by MRSA strains.[10]

Delay in the institution of appropriate therapy in patients with *S aureus* sepsis may lead to catastrophic complications, including bacterial seeding of deep tissues; such delays are associated with increased hospital costs, length of hospitalization, and death.[8,12,13] As more clinical and microbiological data becomes available, antimicrobial therapy is narrowed or discontinued, yet — in the interim — antibiotic stewardship yields to the practical and immediate need to essentially treat the patient and administer a broad-spectrum of drugs before a proper diagnosis is secured.

New approaches to improve antibiotic stewardship

Antibiotic administration practices have become a major focus of antibiotic-stewardship quality-improvement programs at many hospitals. The pressures to provide prompt and effective antibiotic therapy to patients most likely to benefit from it while minimizing the unnecessary use of antibiotics have spurred alternative approaches to improve antibiotic stewardship.

One target of antibiotic-reduction efforts has been the over-utilization of broad anti-staphylococcal agents, particularly vancomycin. These antibiotics are generally started when a Gram-positive infection is suspected on clinical grounds or when bacterial stain and/or cultures show Gram-positive cocci. An important diagnostic and therapeutic branch point occurs when clinicians try to differentiate true staphylococcal bacteremia from blood-culture contamination. Physicians often prescribe an anti-staphylococcal antibiotic for patients with blood cultures growing Gram-positive cocci in clusters.

When using traditional laboratory techniques, identification of the organism as *S aureus*, or the more benign CoNS may take up to 48 hours. Earlier differentiation between *S aureus* and CoNS facilitates implementation of more targeted antibiotic therapy and improved overall antibiotic-stewardship programs. To truly change and improve these programs, however, faster and more rapid diagnostics must be integrated into laboratories — and their results must be more expeditiously delivered to attending physicians — to facilitate this paradigm shift.

Enabling the paradigm shift

To address this need, clinical laboratories and microbiologists are frequently relying on more rapid diagnostic tests to detect *S aureus* and improve antibiotic steward-

ship. Given the time and resource constraints facing microbiologists, very rapid methods for the detection of *S aureus*-specific nucleic-acid sequences, such as peptide nucleic-acid fluorescence *in situ* hybridization (PNA FISH), are used. PNA FISH tests enable microbiology labs to provide rapid and accurate identification of bloodstream pathogens directly from positive blood cultures in hours instead of days, providing the following benefits:

- rapidly differentiate *S aureus* from CoNS in bloodstream isolates;
- allow faster diagnoses and more accurate antibiotic-therapy selection; and
- guide dramatic improvements in antibiotic stewardship that results in improved patient outcomes and healthcare-resource utilization.

Antibiotic stewardship also depends on improved communication between labs, treating clinicians

The communication of laboratory results to the treating clinician closes the loop initiated at the time of blood-culture draw. In a study of 509 episodes of clinically significant bloodstream infections, therapeutic interventions typically occurred at the time of phlebotomy and after notification of Gram-stain results by telephone.[14] The clinical value of rapid diagnostic tests depends on an expeditious reporting of the results to the treating clinician.[15] The rapid reporting of results, coupled with education regarding the implications of *S aureus* vs. CoNS, can significantly affect resource utilization and clinical outcomes.

Forrest, et al, reported that in the context of an antimicrobial utilization team, the use of a rapid diagnostic technique (PNA FISH) to identify *S aureus* was associated with a significant reduction in median length of hospital stay from six to four days (P<0.05; 95 confidence interval [CI], 0.95-1.87), a trend toward less use of vancomycin, and a decrease in associated hospital costs of approximately $4,000 per patient.[16] Ly, et al, demonstrated that the rapid reporting of *S aureus* PNA FISH results was associated with a reduction in overall mortality (8 vs. 17; P=0.05) and in duration of antibiotic use in patients with CoNS (median, 2.5 days; P=0.01).[17]

These studies suggest that an approach whereby accurate microbiology data is rapidly generated, disseminated, interpreted, and acted upon by a highly integrated healthcare team can leverage the combination of rapid diagnostics and antibiotic stewardship to guide therapy, enhance appropriate use of antibiotics, and improve patient outcomes.

The optimization of antibiotic therapy in hospitalized patients coupled with the need for improved antibiotic stewardship will continue to be a major challenge that new assays and procedures are beginning to meet in the laboratory.[18] The coming years are expected to bring further advances in the rapid detection of bloodstream microbes and the identification of resistant strains. Optimizing the effects of these advances will require the delivery of results from the diagnostic laboratory to clinicians in a more timely fashion. Coupling advances

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in diagnostic techniques with current and emerging communication technology will facilitate this process.

As data accumulate regarding the effect on clinical outcomes of rapid diagnostics and clinician notification, these strategies are expected to replace the slower, traditional methods. To truly change and improve these programs, however, faster and more rapid diagnostics must be integrated in laboratories, and test results must be more expeditiously delivered to attending physicians. □

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