Diatherix | Eurofins Clinical Diagnostics



TECHNICAL BULLETIN: The Impact of Antibiotic Resistance on the Outcome and Costs of Patient Care

"The optimism of the early period of antimicrobial discovery has been tempered by the emergence of bacterial strains with resistance to these therapeutics. Today, clinically important bacteria are characterized not only by single drug resistance but also by multiple antibiotic resistance— the legacy of past decades of antimicrobial use and misuse. Drug resistance presents an ever-increasing global public health threat that involves all major microbial pathogens and antimicrobial drugs."[1]

The Problem and Solution

The problem of resistance to conventional antibiotics is now being referred to as the world's most pressing public health problem.[2] The overuse and misuse of antibiotics threatens the clinical usefulness of drugs that are critical to patient care.[3] The Centers for Disease Control and Prevention (CDC) now estimates that 50% of all antibiotics prescribed in the United States are either unnecessary or inappropriate.[4] The question then is, "how can this trend of overuse and misuse be reversed"? The answer to reducing antibiotic overuse may be to increase the availability of better diagnostic tests, particularly for infections that are often difficult to treat.

In collaboration with Thermo Fisher Scientific, Diatherix Eurofins has developed a multiplex platform that rapidly detects specific antibiotic-resistant genes in clinical specimens; either directly from the infectious process or from culture isolates obtained in the microbiology laboratory. Diatherix Eurofins ABRx™ Antibiotic Resistance Panel provides detection of seventeen highly inclusive gene types (over 100 subtypes) associated with resistance to three major groups of antibiotics: beta-lactams (penicillins, cephalosporins, carbapenems, and oxacillins), quinolones, and macrolides. Identifying antibiotic-resistant genes that affect a specific antibiotic class is important, particularly if an antibiotic of the affected class is prescribed and it causes the expression of antibiotic-resistant genes that may cause treatment failure (Table 1). Consideration to avoid the antibiotic or the antibiotic class should be given when the pertinent gene resistance mechanism is detected within the infection.

There is a clear distinction between results obtained from gene resistance testing directly from clinical specimens and the phenotypic susceptibility testing provided in the typical clinical microbiology laboratory. Routine phenotypic testing is based on the selected colony that has been isolated and identified from the clinical specimen as well as the susceptibility of the organism utilizing established breakpoints. There is the potential for multiple sources of variation and error in both the pre-analytical and analytical portions of routine culture technology. The variations may include the viability of the organisms, the presence of antibiotics, and the ability of the microbiologist on staff to accurately identify the organisms responsible for the infection from a highly colorized surface.

Analytical and diagnostic challenges to consider when using molecular testing methods include the correlation of phenotypic resistance patterns from culture based methods with the gene resistance detection of the ABRx Panel. Further, antibiotic-resistant genes detected in an infectious process may not always be associated with a specific organism; particularly in polymicrobial infections. In addition, questions on how rapidly gene resistance mechanisms may arise when subjected to antibiotic pressure cannot be determined. Lastly, specimen collection will occasionally be a problem; particularly when screening patients for gene resistance caused by organisms that may be both commensal and pathogenic (pathobionts).

The Final Cost to Healthcare

The cost of antibiotic overuse and misuse to the U.S. healthcare system is multifaceted, and has taken a substantial toll on the healthcare system. According to the IMS Health global database, the expenditures for antibiotics in the U.S. in 2009 exceeded $10.7 billion. The majority of this cost ($6.6 billion or 61.5%) was attributed to prescriptions for patients seen in routine outpatient practices. The classes of antibiotics most often used in these outpatient settings were fluoroquinolones and beta-lactams.[5]

The Centers for Medicare and Medicaid Services (CMS) circulated regulations commencing October 1, 2008, which prospectively denies payment for selected conditions occurring during the hospital stay and are not present upon admission.[6] The infectious Diseases Society of America (IDSA) estimates that each healthcare-associated infection (HAI) averages an additional $15,000 per incident; with an annual total cost to the U.S. healthcare system of $30.5 billion. Many of these HAIs are caused by antibiotic-resistant pathogens and studies have concluded that the annual cost to hospitals associated with infections caused by these antibiotic-resistant organisms only compounds the problem. The IDSA estimates that the U.S. healthcare system bears the added financial burden for antibiotic-resistant infections that are estimated to cost an additional $21 to $34 billion and more than 8 million additional days of hospitalization.[7]

In a recent review article, the relationship between antimicrobial resistance and patient outcomes in the healthcare environment were addressed. The article underscored the impact that delayed or inadequate therapy had on treating infections in patients with severe underlying disease. In effect, patients with infections that are caused by antibiotic-resistant organisms have higher morbidity, increased length of stay, and higher treatment costs when compared to patients with infections caused by antimicrobial susceptible organisms. Patients with infected surgical sites (SSIs) had significantly greater mortality, longer length of stay, and higher treatment costs when compared to patients without SSIs. (Figure 1). In addition, the outcomes of patients with other infections caused by extended spectrum beta lactamase (ESBL) producing *Escherichia coli* and *Klebsiella pneumoniae* showed a similar impact on mortality, length of stay, and overall treatment costs (Figure 2). Moreover, these findings were also seen with infections caused by cephalosporin-resistant Enterobacter species acquired during the hospital stay (Figure 3).[8]

In Summary

Although antibiotics have been used to treat patients for more than seven decades, we are now experiencing an alarming emergence of antibiotic resistance. The relative decline of new and novel antibiotics being introduced for treating infections over the past two decades compounds the precarious position that we face (Figure 4).[7] Diatherix Eurofins and Thermo Fisher are dedicated to advancing education and support of the antimicrobial stewardship movement so that we may preserve the effectiveness of existing antibiotics both in the U.S. and abroad.

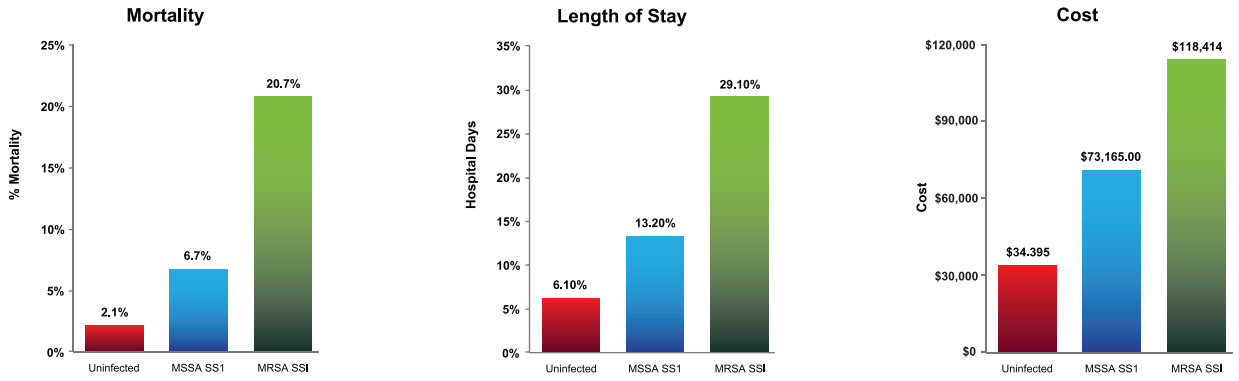

Figure 1. Surgical Site Infection Outcomes Related to Methicillin Resistant *S. aureus*

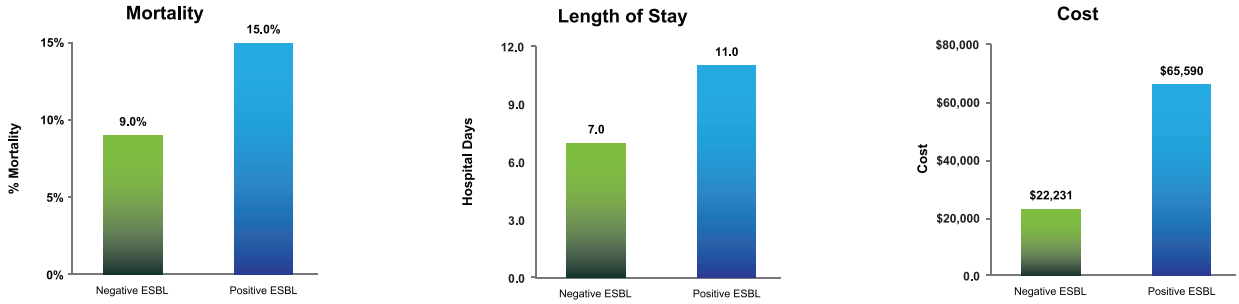

Figure 2. Outcomes Related to *E. coli* and *K. pneumoniae* Infections with ESBLs

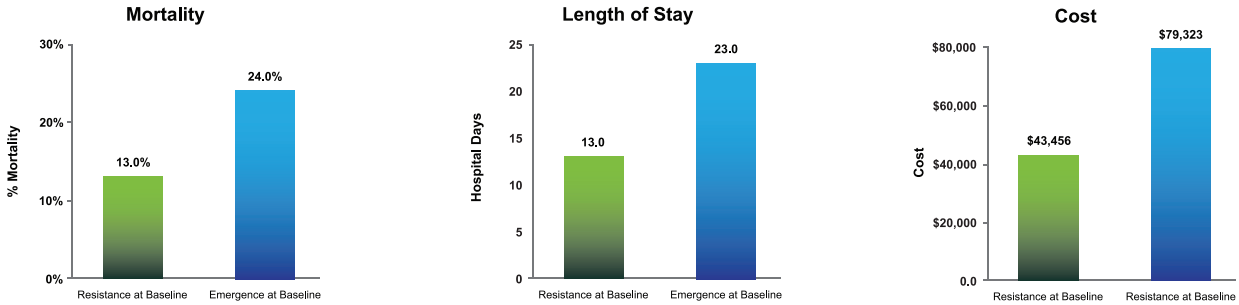

Figure 3. Outcomes Related to the Emergence of Cephalosporin Resistant *Enterobacter sp.*

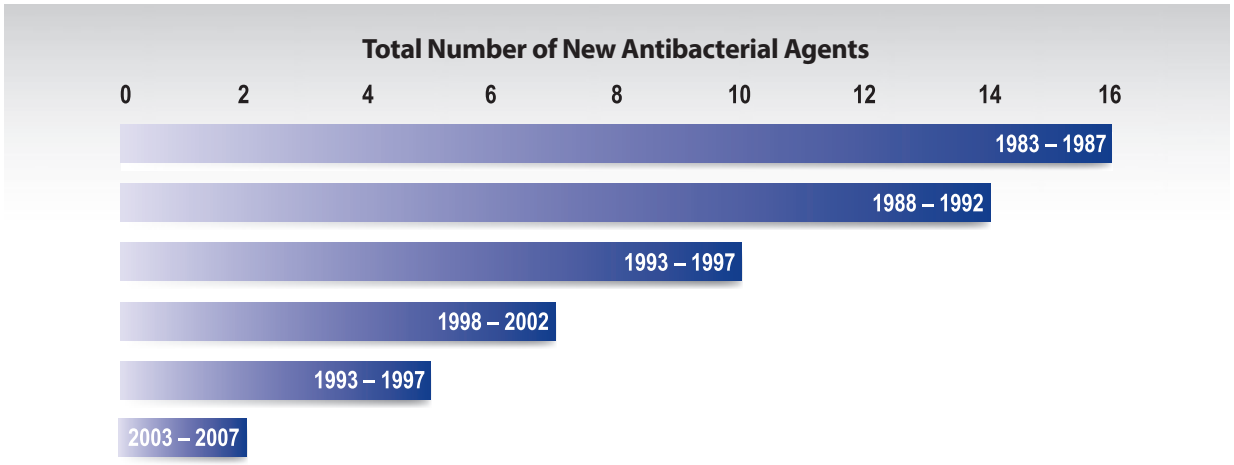

Figure 4. The Dramatic Decline in New and Innovative Antibiotic Production

Table 1. Antibiotic Class Avoidance Based Upon Gene Resistance Detection on the ABRx Panel

Antibiotic Class	Mechanism of Gene Resistance Action	Molecular Class	Panel Target	Antibiotic Class Avoidance
β-Lactam	Breaks β-lactam ring through hydrolysis, deactivating the molecule's antibacterial properties	Class A β-lactamase	CTX-M Group 1	cephalosporins, penicillins, aztreonam
			CTX-M Group 2	
			CTX-M Group 8/25	
			CTX-M Group 9	
			KPC	carbapenems, cephalosporins, penicillins, β-lactamase inhibitors, aztreonam
		Class B metallo-β-lactamase	IMP	carbapenems, cephalosporins, penicillins, β-lactamase inhibitors
			VIM	
			NDM	
		AmpC β-lactamase	FOX	cephalosporins, penicillins, β-lactamase inhibitors
		Class D oxacillinase	OXA-1	cloxacillin, oxacillin, penicillins
			OXA-48	carbapenems, extended spectrum cephalosporins, penicillins, β-lactamase inhibitors
		Minor ESBL	PER	extended spectrum cephalosporins, penicillins, aztreonam
			VEB	
			GES	carbapenems, cephamycins, extended spectrum cephalosporins, penicillins
Macrolide	Methylation on 23S ribosome affects antibiotic binding	Erythromycin ribosomal methylase	ermB	macrolides (erythromycin, clindamycin, azithromycin)
Fluoroquinolone	Binds to and reduces affinity of DNA gyrase and topoisomerase to antibiotic	Pentapeptide repeat protein	qnrA	fluoroquinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin)
			qnrS	

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