

MicroFocus

A Macro Look at Micro Issues

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Introduction

Welcome once again! You'll notice a few changes in this issue of MicroFocus as we move into a new era with our new company — Siemens Healthcare Diagnostics. Although the look and feel of this newsletter will be different, MicroScan's commitment to education remains the same. We look forward to new opportunities to better meet your needs as a member of the Siemens family.

There certainly is no shortage of recommendations for identifying, reducing, preventing and reporting the spread of antibiotic-resistant bacterial pathogens. Evolving guidance significantly impacts current laboratory practice. Dr. J. Michael Janda provides a great discussion on the effects of healthcare-associated infections (HAI), and insertion of community-associated strains of methicillin-resistant *Staphylococcus aureus* (MRSA) into the hospital environment. I think you'll appreciate his down-to-earth synopsis of current HAI-related public health issues and overview of current and pending legislation.

As an integral part of managing infections in healthcare institutions, clinicians reach for their antibiograms nearly every day for information about appropriate empiric therapy choices. The focused approach for antibiogram

generation utilized at the University of Louisville Hospital illustrates how stratified data can be presented in a beneficial manner to help guide critical decisions. Chuck Johnson and Dr. James Snyder share their institution's processes for managing this important data. It is clear that each laboratory, in conjunction with infection control and the pharmacy, needs to establish data reporting decisions based on the scope of available data as well as the unique requirements of their institution.

We continue to receive many requests for Clinical Laboratory Standards Institute (CLSI) updates. In this issue, we've included a checklist summarizing the 2008 CLSI Antimicrobial Susceptibility Testing recommendations. You can use this tool as a concise way to document your review of the latest AST guidelines.

In our ASM booth in Boston this year we had a great line-up of speakers. The presentations will be posted online for continuing education credit this summer. The sessions encompassed a diverse mix of subjects: MRSA — from initiating a surveillance program to the impact and differences between healthcare- and community-acquired strains, susceptibility test considerations for coagulase-negative staphylococci, detection of ESBLs when ampC

The Changing Face of Healthcare-Associated Infections (HAIs) and MRSA in the United States

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Currently, the CDC estimates that over 1.7 million HAIs occur annually in the United States with approximately 99,000 associated deaths.

Although MRSA had emerged as an important healthcare-associated pathogen in the 1960s³ it was only in the early 1980s that it made its first appearance as a community-associated pathogen with a reported outbreak of disease in intravenous drug abusers in Detroit.⁴

Healthcare-associated infections (HAIs) or the older term “nosocomial infections” have been a major concern of hospitals, medical centers and long-term care facilities for decades. The importance of HAIs has long been recognized in that the Centers for Disease Control and Prevention (CDC) has monitored HAIs through the National Nosocomial Infections Surveillance System (NNIS) for years.¹ While NNIS was initially established with 62 hospitals in 1970, by year 2000 the number of participating centers had ballooned to more than 225. Through NNIS, recommendations on performance improvement and infection control strategies were developed for such HAIs as surgical site (SSI) and bloodstream infections (BSI). In 2005, this long-standing infrastructure was replaced by the National Healthcare Safety Network which not only includes NNIS but also the Dialysis Surveillance Network (DSN) and the National Surveillance of Healthcare Workers (NaSH). Their first report of data collected during calendar year 2006 was released in 2007.²

Currently, the CDC estimates that over 1.7 million HAIs occur annually in the United States with approximately 99,000 associated deaths (<http://www.cdc.gov/ncidod/dhqp/hai.html>). Of all HAIs, approximately one-third involved the urinary tract, slightly over one-fifth are associated with surgical site infection (SSI) and another 30% are almost equally divided between bloodstream infection (BSI) and pneumonia. Each HAI has dramatic ramifications for both patients and healthcare practitioners alike, resulting in extended hospitalizations and monitoring, possible additional medical testing, and required intervention in the form of antimicrobial chemotherapy. These additional economic consequences do not even take into account such things as loss of productivity in person-years, possible

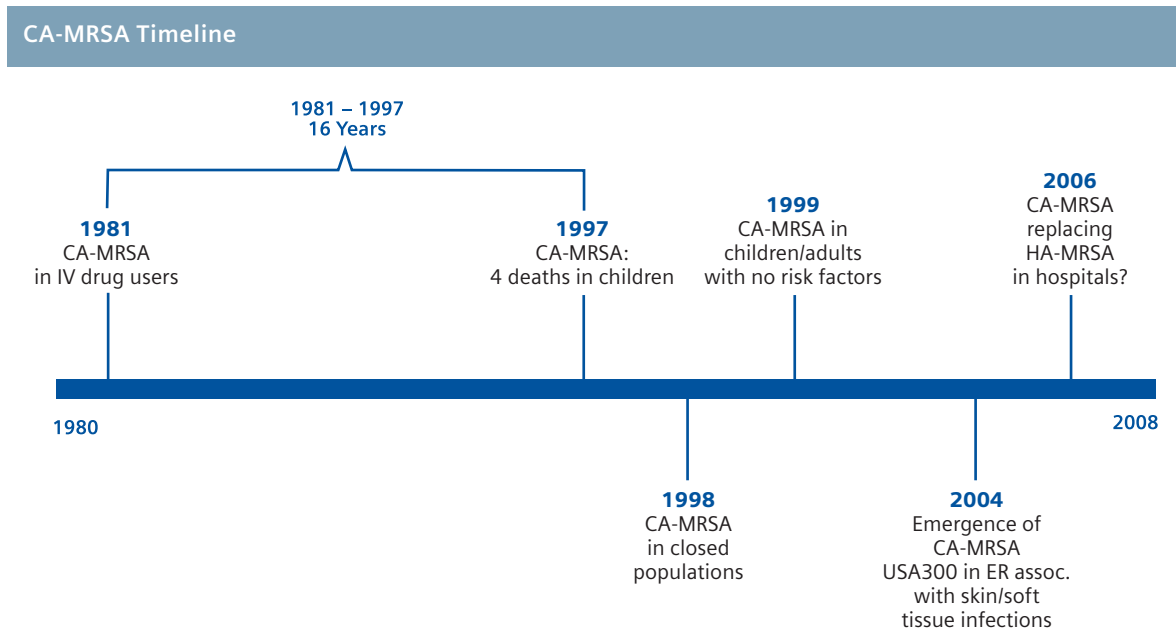
increasing drug resistance in HAIs, and subsequent litigation. HAIs are simply “Pandora’s Box” in their most frightening form.

The Changing “Face” of HAIs: CA-MRSA

As far back as the 1980’s and even into the early 1990’s, HAIs were considered to be an institutional problem restricted to hospital environments and certain subsets of patients with serious underlying disease, lengthy hospitalizations, or those undergoing medical procedures such as surgery and catheterization. While HAI outbreaks did occur sometimes over protracted periods of time in some centers, these typically involved limited numbers of persons and did not affect the community at large. The public health sector, per se, did not view this as a serious threat outside of those environs.

This philosophy radically changed with the onset of community-associated MRSA (CA-MRSA) in the general population in the early 1980s. Although MRSA had emerged as an important healthcare-associated pathogen in the 1960s³ it was only in the early 1980s that it made its first appearance as a community-associated pathogen with a reported outbreak of disease in intravenous drug abusers in Detroit.⁴ Subsequent to that report, CA-MRSA seemed to remain dormant more or less for approximately 16 years until the late 1990s when several outbreaks of CA-MRSA erupted in clustered groups including Indian reservations, prisons, the military, the homeless and daycare centers (Figure 1). Once CA-MRSA emerged in these closed populations it began to spread like wildfire into other groups including persons participating in contact sports and most recently, in men who have sex with men. By 2002 – 2004, CA-MRSA was a major cause of skin and soft tissue infections in the community in persons with no known risk factors and was no

Figure 1



longer confined to hospital settings. An even more alarming trend has been the spread and expansion of a predominant unique clone with a designated pulsed field gel electrophoresis (PFGE) pattern (USA300) as the major cause of CA-MRSA in the United States.⁵ This rapid expansion seems to parallel a similar phenomenon that occurred in the 1950s when penicillin-resistant *S. aureus* pandemics appeared and were predominantly caused by phage-type 80/81.⁶

In the recent past, CA-MRSA infections were distinct from hospital-acquired MRSA (HA-MRSA) in regards to patient populations, disease settings and phenotypes and genotypes of infecting strains. CA-MRSA strains in the past were predominantly found in the community in individuals with skin and soft-tissue infections but no underlying illness. Isolates contained the subtype IV staphylococcal chromosome cassette (SCC) *mec* genes and often additionally harbored the Panton-Valentine toxin. CA-MRSA strains were typically more

susceptible to a number of antimicrobial agents than HA-MRSA including clindamycin, fluoroquinolones, gentamicin, and trimethoprim-sulfamethoxazole. In contrast, HA-MRSA strains were in healthcare settings in seriously ill persons with life-threatening infections. HA-MRSA isolates, in contrast to CA-MRSA strains, belonged to different SCC *mec* subtypes, lacked the Panton-Valentine toxin, and were much more resistant to the antibiotics described above.

This clearly demarcated line between CA-MRSA and HA-MRSA infections is rapidly changing during recent years. A national prevalence study of MRSA in inpatients at over 1,200 health care facilities conducted in 2006 found that 30% of strains analyzed had a phenotype that was more consistent with CA-MRSA.⁷ Seybold et al. has also recently reported that the CA-MRSA USA300 genotype caused 34% of BSI in a major public hospital in Atlanta Georgia in 2004.⁸ This latter study has been followed by a report from an inner city hospital in

By 2002 – 2004, CA-MRSA was a major cause of skin and soft tissue infections in the community in persons with no known risk factors and was no longer confined to hospital settings.

Table 1

Potential Steps in the Evolution and spread of CA-MRSA

Step	Process	Year
1	MRSA in hospitals	1960s
2	Introduction of HA-MRSA into community	Late 1970s
3	Development of CA-MRSA strains	1982
4	Emergence and clonal spread of subtypes	1997
5	Rapid emergence	2000
6	Endemicity and epidemics	2003
7	Re-introduction into hospitals	2006
8	Altered virulence, new subtypes	?

CA-MRSA is now established in open communities and it will take years if not decades to significantly reduce or eradicate this pathogen in established reservoirs.¹¹

Chicago of BSI between 2000 and 2006. Although the total hospital-onset MRSA BSI rate remained relatively stable over the six-year period, the percentage of CA-MRSA causing BSI rose from 24% to 49%.⁹ These results suggest that strains are co-mingling, if not replacing HA-MRSA, in many if not most major medical centers today.

Issues and Concerns

Table 1 lists a number of the steps MRSA isolates have undergone in morphing from a hospital to also a community-associated pathogen with enhanced virulence characteristics. Of critical importance in this process are steps 3–5 where MRSA developed into a more versatile microbe able to colonize, persist and multiply in the community. Complete genome sequencing of one USA300 strain suggests that endemic CA-MRSA may have possibly arisen by horizontal gene exchange with *S. epidermidis* receiving essential genetic elements for survival at low pH on human skin and within phagocytic cells.¹⁰ This event coupled with its sudden rapid clonal expansion and emergence has led to its increasing

incidence in community-associated infections that we now face.⁶

Emergence of CA-MRSA has enormous ramifications for both healthy persons and those hospitalized. CA-MRSA is now established in open communities and it will take years if not decades to significantly reduce or eradicate this pathogen in established reservoirs.¹¹ Published studies already cited suggest that this genotype is now being introduced into tertiary care facilities and public hospitals with the possibility it may also spread to smaller local community medical centers.^{7,8,9} CA-MRSA strains in these settings with enhanced virulence capabilities may also acquire increasing resistance to drugs that have been effective in the past, increasing both morbidity and mortality in these backgrounds. A frightening addendum to this assumption is the recent spread of methicillin-susceptible *S. aureus* (MSSA) USA300 strains in the community and its linkage to higher frequencies of invasive infections in children.¹² Finally, there are at present very few antimicrobial agents useful in treating invasive MRSA infections (vancomycin, trimethoprim-sulfamethoxazole, linezolid) and it is unclear whether or not the pharmaceutical

industry will be able to develop new drugs to add to this limited arsenal, although several investigational drugs such as ceftobiprole and ceftaroline seem to hold some promise. If increased frequency of resistance to front-line therapies such as vancomycin emerges, serious HA-MRSA or CA-MRSA infections could become untreatable.

The Clinical and Public Health Challenge

One of the formidable challenges we all face is to develop a systematic effort to identify, control and prevent HA-MRSA and CA-MRSA in the United States. This challenge has several major obstacles. A 2007 study of over 1200 healthcare facilities found that only 29% of surveyed hospitals performed active surveillance for MRSA.⁷ Of those sites, over half performed routine culture only, clearly not the most sensitive nor rapid method to detect MRSA. Other studies suggest that few coordinated efforts have been made to reduce the transmission and number of MRSA HAIs and control the spread of multi-resistant strains in the hospital environment.¹³ The best available evidence we currently have is that the scope and magnitude of the MRSA problem is underreported and underappreciated and that current efforts fall increasingly short in dealing with this immense issue.

A number of steps need to be taken to begin to curb the prevalence and incidence of MRSA infections on a national basis. To understand the scope and magnitude of MRSA infections, one potential public health approach to this important issue would be to develop a surveillance model for collecting and collating data at the state level regarding *S. aureus* and MRSA infections.¹⁴ Collected annual data would then be disseminated to medical facilities through periodic surveillance reports.

To accomplish such an aggressive approach requires legislative action at the state and/or federal level.

MRSA Regulations at the State and Federal Level

The driving force behind HAI legislation has been the lack of success in controlling MRSA from a silo approach and the failure of many institutions to develop adequate infection control surveillance practices and policies. To deal with this mammoth issue, states have begun to require MRSA reporting in various forms through the regulatory process. In 2006, two states (Illinois, Maryland) authored legislation that if passed would require active surveillance and/or screening for MRSA. Public Act 095-312 of Illinois (SB0233) would create the "MRSA Screening and Reporting Act" that would require all hospitals to establish MRSA control programs and for the Health Department to compile aggregate data on total numbers of MRSA infections reported on admission or during their hospital stay. Such an approach however has not always received consensus support as both the Society for Healthcare Epidemiology (SHEA) and the Association for Professionals in Infection Control and Epidemiology (APIC) do not favor the regulatory route in regards to active screening for MRSA, VRE, and other HAIs.¹⁵

Despite concerns, the clear trend on both the state and federal levels is towards some types of regulation concerning MRSA. In addition to those already on the book for VISA/VRSA and *S. aureus* infections in neonates, Table 2 highlights those states with current reporting regulations involving MRSA.¹⁴ On February 13, 2008, a new California mandate required reporting of severe or fatal *S. aureus* infections (MSRA, MSSA) in previously healthy persons by

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A California Senate bill (SB 1058) introduced on January 7, 2008, would, if approved into law, establish the Medical Facility and Infection Control and Prevention Act requiring the screening of certain patients (surgery, ICU, others) for MRSA and would establish an Internet-based reporting system.

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Table 2

State Reporting Regulations on MRSA		
Reporting Regulation	No. States	States
Invasive or Fatal MRSA (case reports)	11	California, Connecticut, Delaware, Georgia, Iowa, Maine, Minnesota, North Dakota, South Dakota, Tennessee, Virginia
Invasive or Fatal MRSA (lab only)	4	Arkansas, Colorado (Denver), Nebraska, South Carolina
Invasive or Fatal MRSA (outbreak only)	3	Michigan, Missouri, Wyoming
TOTAL	18	

Data obtained from reference 14 and Internet searches

healthcare providers to local health departments. A California Senate bill (SB 1058) introduced on January 7, 2008, would, if approved into law, establish the Medical Facility and Infection Control and Prevention Act requiring the screening of certain patients (surgery, ICU, others) for MRSA and would establish an Internet-based reporting system. A number of other states have some type of reporting regulations in the pipeline and have chartered advisory commissions to advise regarding infection control policies or develop infection control plans. These states include Illinois, New Jersey, North Carolina, Pennsylvania (HB No. 2041), and Texas.

Federal legislation has lagged significantly behind that proposed by several states but a couple of bills are noteworthy. S. 2313 sponsored by Brown (D-OH) and Hatch (R-UT) would establish the STAAR (Strategies to Address Antimicrobial Resistance) Act to develop comprehensive and strategic approaches to combat antimicrobial resistance. It is supported by a wide range of healthcare organizations including the AMA, IDSA, APHA, SHEA, APIC and PIDS. A second bill, if enacted into law, (S. 2525) co-sponsored by

Menéndez (D-NJ) and Durbin (D-IL) and introduced on December 19, 2007, would establish the MRSA Infection Prevention and Patient Protection Act. Under this Act a list of best practices to deal with MRSA would be developed, plus it would require all acute health care facilities to screen patients entering ICUs or other high-risk departments for MRSA. Sec. 3 (b) (3) of this Act would also require a report to Congress no later than January 1, 2009, on whether payment adjustments should be made under title XVIII of the Social Security Act to assist hospitals in defraying the cost of screening for and treating MRSA infections.

Final Thoughts

It is very clear that past practices will be insufficient in addressing the expanding MRSA problem. The changing face of how HAIs impact us is not only represented by MRSA but other agents such as *Clostridium difficile* associated diarrhea (CDAD) where hypervirulent clones are emerging that are less responsive to treatment and are causing more cases of community-associated disease.¹⁶ Methods must be improved to detect, treat, and report MRSA and other important HAIs.

Several approaches seem likely. A number of states have already passed legislation requiring MRSA reporting and others are likely to follow suit. A logical next step and one already implemented on a very limited basis in a couple of states is to require MRSA isolates from serious or fatal infections to be forwarded to State Health Departments by laboratories. Proposals such as the Illinois Public Act 095-312 and Senate bill S. 2525 requiring MRSA screening of some/all hospital patients will, if approved, change the "silo approach" to a more global strategy. These policies will require major changes in healthcare settings from infection control practices, to judicious use of antimicrobial therapy, and rapid and specific methods to detect MRSA as part of a more robust screening program. At issue, of course, is the cost involved and potential reimbursement. The introduction of possible federal legislation that would cover reimbursement issues is promising but many bills introduced never make it out of committee. How we approach control and reduction of MRSA infections from a clinical and public health standpoint in hospitals and communities may well portend how successful we will be able to deal with future HAI pathogens.

References:

- Richards C, Emori TG, Edwards J, Fridkin S, Tolson J, Gaynes R. Characteristics of hospitals and infection control professionals participating in the National Nosocomial Infections Surveillance System. 1999. *Am J Infect Control* 2001;29:400-403.
- Edwards JR, Peterson KD, Andrus ML, Tolson JS, Goulding JS, Dudeck MA, Mincey RB, Pollack DA, Horan TC. National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. *Am J Infect Control* 2007;35:290-301.
- Gorwitz RJ. A review of community-associated methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections. *Pediatr Infect Dis J* 2008;27:1-7.
- Saravolatz LD, Markowitz N, Arking L, Pohlod D, Fisher E. Methicillin-resistant *Staphylococcus aureus*: epidemiologic observations during a community-acquired outbreak. *Ann Intern Med* 1982;96:11-16.
- King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA clone 300 as the predominant cause of skin and soft-tissue infections. *Ann Intern Med* 2006; 144:309-317.
- Kennedy AD, Otto M, Braughton KR, Whitney AR, Mathema B, Mediavilla JR, Byrne KA, Parkins LD, Tenover FC, Kreiswirth BN, Musser JM, DeLeo FR. Epidemic community-associated methicillin-resistant *Staphylococcus aureus*: recent clonal expansion and diversification. *Proc Nat Acad Sci* 2008;105:1327-1332.
- Jarvis WR, Schlosser JA, Chinn RY, Tweeten S, Jackson M. National prevalence of methicillin-resistant *Staphylococcus aureus* in inpatients at US health care facilities, 2006. *Am J Infect Control* 2007;35:631-637.
- Seybold U, Kourbatova EV, Johnson JG, Halvose SJ, Wang YF, King MD, Ray SM, Blumberg HM. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections. *Clin Infect Dis* 2006;42:647-656.
- Popovich KJ, Weinstein RA, Hota B. Are community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) strains replacing traditional nosocomial MRSA strains? *Clin Infect Dis* 2008;46:787-794.
- Diep BA, Gill SR, Chang RF, Phan TH, Davidson MG, Lin F, Lin J, Carleton HA, Mongodin EF, Sensabaugh GF, Perdreau-Remington F. Complete genome sequence of USA300, an epidemic clone of community-acquired methicillin-resistant *Staphylococcus aureus*. *Lancet* 2006;367:731-739.
- Kluytmans-VandenBergh MFQ, Kluytmans JAJW. Community-acquired methicillin-resistant *Staphylococcus aureus*: current perspectives. *Clin Microbiol Infect* 2006;12(Suppl 1):9-15.
- McCaskill ML, Mason Jr EO, Kaplan SL, Hammerman W, Lamberth LB, Hulten KG. Increase of the USA300 clone among community-acquired methicillin-susceptible *Staphylococcus aureus* causing invasive infections. *Pediatr Infect Dis J* 2007;26: 1122-1127.
- Muto CA. Methicillin-resistant *Staphylococcus aureus* control: we didn't start the fire, but it's time to put it out. *Infect Control Hosp Epidemiol* 2006;27:111-115.
- Simons H, Alcabes P. A model for surveillance of methicillin-resistant *Staphylococcus aureus*. *Pub Hlth Rep* 2008;123:21-29.
- Weber SG, Huang SS, Oriola S, Huskins WC, Noskin GA, Harriman K, Olmsted RN, Bonten M, Lundstrom T, Climo MW, Roughmann M-C, Murphy CL, Karchmer TB. Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: position statement from the joint SHEA and APIC task force. *Am J Infect Control* 2007;35:73-85.
- Oldfield 3rd EC. *Clostridium difficile*-associated diarrhea: resurgence with a vengeance. *Rev Gastroenterol Disord* 2006;6:79-96.

The Importance of the Focused Antibioqram

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One of the more frustrating challenges that confront the clinical microbiologist is our inability to participate in “real-time” reporting for most of the results we are tasked to provide.

The antibiogram, defined by the Clinical and Laboratory Standards Institute (CLSI) as “a cumulative antimicrobial susceptibility test data summary,”¹ is the primary method by which most clinical microbiology laboratories disseminate historical data. Use of the antibiogram serves many purposes including serving as a guide in selecting empiric therapy and tracking resistance trends. Methods used to gather the data and the design of an institution’s antibiogram report should reflect its intended purpose.

One of the more frustrating challenges that confront the clinical microbiologist is our inability to participate in “real-time” reporting for most of the results we are tasked to provide. While our chemistry and hematology counterparts regularly phone stat results to the Operating Room and Emergency Department, microbiologists are constrained by the culture process in which conclusive data may not be available for days or even weeks. By the time we inform the clinician regarding the nature of the organism they are treating, and how to treat it, the patient has improved, been discharged or has undergone some other intervention. With the advent of new technologies such as fluorometric testing and PCR, the time necessary to provide some of these answers has decreased but in most cases microbiology results continue to provide confirmatory, rather than diagnostic, information.

Over the years this realization has caused many clinical microbiologists to redefine their role on the medical team. In addition to maintaining their proficiency in culture interpretation, susceptibility testing and Gram stain evaluation, the clinical microbiologist must also achieve a level of proficiency as a data assimilator and statistician.

The University of Louisville Hospital (ULH) is a tertiary care teaching facility that supports a wide range of services including a Level I Trauma Center, regional cancer center, burn unit, extensive bone marrow transplant services, HIV clinic and OB/GYN clinic. To meet the specific needs of each of these unique patient populations, ULH has generated unit-specific antibiograms for over 20 years. As needs have evolved during this time period, so have the designs of the antibiogram. Some of the factors that have warranted consideration include physical changes (remodeling and redefining of the Intensive Care Units [ICU], addition of new wards, construction of new clinics), service-oriented changes (expanding some services, reducing or eliminating others), changes in formularies, and even changes in resistance patterns within the community (e.g., community-associated MRSA and multi-drug-resistant [MDR] *Acinetobacter* spp.). Two general categories of antibiograms are provided at ULH, and focused antibiograms reside within this framework.

Published antibiograms

Published antibiograms are produced specifically to guide the medical staff in selection of empiric therapy. The selective reporting policy in use at ULH provides information only for antimicrobial agents that are on formulary for which we do not want to restrict utilization. Currently we publish antibiograms for the following units and patient populations:

- Combined ICU data [MICU, SICU, CCU, burn unit, neurology]
- Healthcare-associated non-ICU isolate data
- Community-associated isolate data
- Oncology

Figure 1

Review of *Enterobacter cloacae* isolated from ICU vs. non-ICU cultures

	Total # isolates	Data = %S											
		Ampicillin/Sulbactam	Piperacillin/Tazo	Ceftriaxone	Cefepime	Imipenem	Aztreonam	Gentamicin	Tobramycin	Amikacin	Ciprofloxacin	Levofloxacin	Trimeth/Sulfa
<i>Enterobacter cloacae</i> (Non-ICU)	48	25	77	67	91	100	69	81	83	100	77	79	88
<i>Enterobacter cloacae</i> (ICU)	58	45	90	83	91	100	79	90	88	100	88	90	98

These antibiograms are printed on pocket cards and made available to all medical staff. Pharmacy also posts the data on the facility intranet so each antibiogram may be accessed from any network terminal within the hospital. Published antibiograms are updated and printed annually. Information related to major changes or trends that occur within the year and are observed in the course of regular monitoring may be disseminated with updates on the electronic version of the antibiograms.

By releasing separate reports for each target population several issues are addressed simultaneously. The first issue is the reporting of accurate information tailored to any differences between patient groups. In reviewing *Pseudomonas aeruginosa* vs. imipenem in 2007, there was a 68% susceptibility rate for our healthcare-associated non-ICU population but an 89% susceptibility rate for our ambulatory population (out-patient clinics, emergency medicine, etc.). This is a marked difference that would have been missed if we had looked at the 79% rate obtained when all data was averaged (Table 1).

A more thorough illustration of differences in organism susceptibility profiles can be seen with a review of *Enterobacter cloacae* isolated from ICU vs. non-ICU cultures (Figure 1).

This type of report allows us to address different treatment philosophies based on service, such as the inclusion of more broad-spectrum antibiotics for oncology or more oral antibiotics for ambulatory. By being able to restrict the antibiotics reported, clinicians can be guided towards agents that are more effective for primary empiric therapy consideration. This approach helps steer the clinician away from antibiotics with a history of inducing resistance, those that are being held in reserve for more resistant organisms, or directs them to options that are simply less expensive but still clinically applicable. Some clinicians find unit specific antibiograms helpful while formulating a differential diagnosis. By correlating the organism rate with a clinical picture, it is possible to determine which organisms may be the more likely pathogens causing an infection within a given population.

Unpublished antibiograms

Unpublished antibiograms are created for use by Microbiology, Infectious Disease, Infection Control and Pharmacy to track trends, monitor resistance rates in special cases, and perform direct surveillance. They generally comprise a broader range of data that includes an unrestricted list of antimicrobials, organisms tested using alternative

Table 1

Susceptibility Rates	
<i>Pseudomonas aeruginosa</i>	Imipenem-S
Combined	79%
Healthcare-associated non-ICU	68%
Ambulatory	89%

The increased accuracy of the data contained in a unit-specific antibiogram is more likely to contribute to the selection of successful choices of empiric agents.

Patients treated by a service or services with similar antibiotic protocols often have similar resistance patterns.

methodologies, isolates tested for surveillance purposes only, histograms trending MIC values, and comparative data (trends over time). They are maintained by the microbiology staff and made available through printed reports and network access to Infectious Disease and pharmacy. This data is collected on an as needed basis. Some of our current unpublished antibiograms include:

- An antifungalgram summarizing the percent susceptible including histograms demonstrating MIC distributions for all yeast tested for the previous calendar year.
- Beta-hemolytic streptococcus surveillance on 50-100 isolates collected and batch tested once/year for trending purposes.
- A summary of clindamycin resistance in *S. aureus* based on results from the D-zone test to detect inducible resistance.
- A summary of *S. aureus* vancomycin MIC surveillance tested using a method with an expanded MIC range.

Though it is sometimes a timely and complicated process to collect, analyze, and stratify data in this manner, access to these data promote a wide variety of benefits. The primary benefit is improved patient care, which should be the fundamental goal of any medical institution or group. The increased accuracy of the data contained in a unit-specific antibiogram is more likely to contribute to the selection of successful choices of empiric agents. An additional benefit is an overall reduction in hospital costs. Better empiric choices equate to faster recovery times which reduce overall hospital days. Minimizing use of inappropriate antibiotics eases antibiotic pressure in the facility which contributes

to a reduction in the development of resistance. All of these factors play a part in decreasing costs within the hospital (Figure 2).

Unit-specific antibiograms, as the name implies, are reports that summarize data collected from a specific unit in a healthcare facility. Other focused antibiograms can be used to summarize data using any commonly defined parameters. Some of these parameters may reflect patient age, gender, diagnosis, specimen source, or any combination thereof. For example, the data may represent all oncology patients in a facility. It may also represent all surgical patients. Having a goal in mind is essential when deciding how best to organize your data. Identifying groups that are likely to have infections with similar organisms and similar resistance patterns is important. Factors to consider include antibiotic usage, exposure to common staff, and location in the facility.

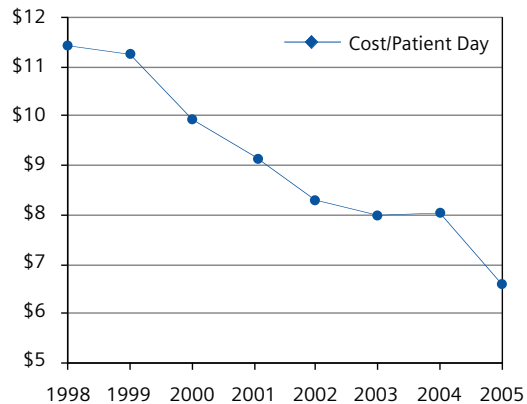
A common practice is to separate community-associated (CA) and healthcare-associated (HA) isolates. It is widely felt that HA isolates demonstrate increased resistance when compared with their CA counterparts. If the goal of the antibiogram is to demonstrate potential variances in these populations, then a strategy must be developed for differentiating that data. What defines a HA isolate? Is a CA isolate a "true" community-associated isolate or a patient admitted from another healthcare facility or long-term care facility (e.g. nursing home)? If so, the assumption of less resistance for these organisms may not apply.

Patients treated by a service or services with similar antibiotic protocols often have similar resistance patterns. For example, the oncology antibiogram at

Figure 2

Antimicrobial Drug Usage Statistics: University of Louisville Hospital, 1998 - 2005

Year	Total \$	Annual Patient Days	Cost/Patient Day
1998	\$1,111,616	na	\$11.44
1999	\$1,245,343	na	\$11.25
2000	\$1,159,226	na	\$9.93
2001	\$1,090,215	118,923	\$9.17
2002	\$1,027,003	123,805	\$8.29
2003	\$1,040,703	129,943	\$8.01
2004	\$1,033,144	128,252	\$8.04
2005	\$944,107	143,629	\$6.57



ULH contains data from three groups: oncology inpatients, outpatients that come to our oncology unit for treatment or surveillance, and patients from our regional cancer center — a facility in a separate building on our medical campus. While all of these patients may be exposed to different environments, they are all treated prophylactically with the same basic antibiotic regimen. In addition, the oncology teams are more likely to use the same guidelines when identifying or treating actual infections. An antibiogram based on this same premise reflects all-inclusive intensive care unit (ICU) data. ULH does not operate “closed” ICU units — patients requiring intensive care are placed in service-specific units whenever possible, but may be moved between various ICUs depending on available bed space. Therefore, the organism incidence and resistance patterns found are unique and different than those in the non-ICU areas of the hospital. For this reason the HA isolates can reliably be divided into ICU and non-ICU. We know this by doing a more intense analysis of the data looking at individual units or ICU’s before deciding what to combine to verify consistency in the data.

So then why, if we are analyzing and calculating the individual data anyway, do we just not publish those reports? Why do we go to the trouble of combining the data? We found that streamlining the data for routine use reduces confusion for most medical staff, reserving the more complex assessment for specialists. In addition, we had to take into account the more restrictive recommendations in the CLSI guidelines for publishing and presenting cumulative AST data, document M39-A2.

CLSI document M39-A2¹ made two recommendations that had a far-reaching effect on published antibiograms at ULH.

- “...for the purposes of guiding clinical decisions about empiric therapy of initial infections, include the first isolate of a given species per patient per analysis period (e.g., year), irrespective of body site, antimicrobial susceptibility profile, or other phenotypic characteristics (e.g., biotype).”
- “It is best to report bacteria for which 30 or more isolates of a given species are available.”

So then why, if we are analyzing and calculating the individual data anyway, do we just not publish those reports? Why do we go to the trouble of combining the data?

The consequence of these recommendations was an overall reduction in the numbers of isolates available to include in our antibiograms. For ULH the problem was compounded in the early 2000s when it was decided to separate the healthcare-associated isolates from the community-associated isolates using the “3-day rule” (only organisms isolated from patients who had been admitted >72 hours would be considered healthcare-associated). For this reason we employ different techniques to comply with the new CLSI guidance to meet the 30-isolate rule. Combining units with similar data is one of those techniques. Others include reporting data collected over a longer time span (such as 18 or 24 months) or combining different species of the same genus together (see clarifying notations in Figure 3). Be aware that for each of these techniques the data must be scrutinized carefully to insure the presentation of information that reflects the current status. For instance, if 24 months’ worth of data is analyzed to obtain 30 isolates, but there is a concurrent and significant shift in resistance patterns from one year to the next, then combining the data would not reflect the susceptibilities for isolates recently encountered. The resultant data reflects a “watered down” effect. The same logic applies if the option pursued is to combine multiple species into one genus, but the data indicates a huge difference in routine resistance patterns between the two most commonly isolated species in that group (Figure 3).

Once the goals are identified and a strategy is in place, the next step is to determine which tools will be used to assimilate and analyze the data. Many Laboratory Information Systems (LIS) provide tools to generate antibiograms, but often these are limited in flexibility and complicated to set up. The ULH microbiology department uses a combination of software, each with their own strengths and weaknesses.

MicroScan® LabPro — The data management software for the MicroScan system is a powerful tool with a fully customizable alert system, instrument interface, and flexible data entry options which provide the ability to work with data acquired from MicroScan instrument systems or manually entered test results from off-line testing. It will generate three basic epidemiology reports, each of which can be further segmented:

- **Antimicrobial % Susceptibility Profile Report** (the report most commonly used for antibiograms)
- **Cumulative % Inhibited by Antimicrobial Level Report** (similar to a histogram or MIC90 report)
- **Bacterial Incidence Report**

The reports are robust although there is limited ability to customize the actual format. This constraint is overshadowed by two of the software’s most effective reporting features, the query system and the export function. The LabPro data management system employs a robust search engine that enables data queries based on almost any parameter or combination of parameters. In fact the user is limited in search capabilities only by the fields of data entered into the system either by LIS interface or manually. If the data is entered into LabPro, then it is available for user-defined queries and data extraction. And the list of data fields available in LabPro is extensive. The second feature allows export of data as a text file in nearly any configuration. This text file can then be easily converted by any spreadsheet or database software that can read text files. When these two features are combined the user has an almost limitless ability to extract any data in a usable format.

Microsoft® Excel — This is a very powerful tool for those proficient in the use of spreadsheet software. It

Figure 3

Presentation of Combined Data

Healthcare Associated Isolates – ICU Patients		Data = %S																	
	Total # isolates	Ampicillin	Ampicillin/Sulbactam	Oxacillin*	Piperacillin/Tazo	Cefazolin	Ceftriaxone	Cefepime	Imipenem	Aztreonam	Gentamicin	Tobramycin	Amikacin	Ciprofloxacin	Levofloxacin	Clindamycin	Tetracycline	Trimeth/Sulfa	Vancomycin
<i>Enterococcus faecalis</i>	65	100									83**								100
<i>Staphylococcus aureus</i>	292			51	51											85	95	100	100
MRSA Only	151			0	0											74	95	99	100
<i>Staphylococcus, coagulase-negative</i>	65			26	26														100
<i>Streptococcus pneumoniae</i>	71						96/90 ¹								100		80	68	100
<i>Acinetobacter spp.</i>	67		36				21	27	70	11	36	52	57	33	33				39
<i>Enterobacter aerogenes</i> ***	62		67		97		86	98	100	90	98	98	100	100	100				100
<i>Enterobacter cloacae</i>	58		45		90		83	91	100	79	90	88	100	88	90				98
<i>Escherichia coli</i>	144	56	57		96	89	98	98	100	97	92	92	99	80	81		83	83	
<i>Klebsiella pneumoniae</i>	63		82		92	89	92	92	100	91	98	92	94	92	92				92
<i>Proteus mirabilis</i> ***	33	94	97		100	94	100	100	100	97	91	94	97	88	91				91
<i>Pseudomonas aeruginosa</i>	71				79			76	76	75	75	83	83	72	70				
<i>Serratia marcesans</i> ***	52		10		81		96	100	100	86	94	86	100	98	100				98

* Nafcillin is the formulary equivalent of oxacillin

** Synergy likely when used with ampicillin or vancomycin

*** Represents 2006 and 2007 data

1 non-meningeal/meningeal breakpoints

allows importing and conversion of data with a minimal amount of effort. Once imported, data analysis can be performed either manually or through the use of pivot tables. The true strength of Excel is the user's ability to generate graphs and charts and the flexibility to use the charts and data in customizable reports.

WHONET — Distributed through the World Health Organization, WHONET software is a Windows®-based application that was designed to

manage and analyze microbiology data. It can be downloaded free of charge from the WHO web site at: <http://www.who.int/drugresistance/whonetsoftware/en/>. The software contains a module that converts the MicroScan export to a custom data file. It takes some effort to set up the conversion module for your laboratory, but once the process is complete it does not have to be repeated and the conversion is easy. Once files are converted, WHONET provides a wide array of analysis tools which facilitate

data analysis based on any filters required to generate a unit-specific antibiogram. The analysis features are extensive, although sometimes a little overwhelming. The only significant limitation with the software is a lack of suitable customizable printed reports. The data, once analyzed, must be copied into some other software to print reports. Where WHONET shines, however, is in its ability to analyze multiple data files at once. It is simple to compare data files from different time periods or even data files from different institutions, which may be in different formats or derived from multiple source files. You can even analyze blocks of data that span several source files, for example, all urines from a clinic over the past three years.

These are only three examples of the software tools available. Each institution will need to determine which tools best meet their needs based on their goals, resources, and user expertise.

Looking ahead

Every day medical and technological advances give us hope of cures for many of the old and new diseases we face, however it is doubtful there will ever be a “cure” or “immunization” that eliminates bacterial infections. While it is incumbent upon pharmaceutical companies to stay vigilant in their development of new antibiotics while balancing R&D activities in support of financial commitments, healthcare givers must also be vigilant to safeguard the useful life of existing antibiotics. In the face of increasing resistance, the need for a team approach to provide oversight in the most effective use of these agents must be recognized. A team can better provide stewardship in the use of antibiotics — to reduce resistance of existing antibiotics by minimizing misuse or overuse, to assure new antibiotics are utilized properly, or to provide direction in cases of highly resistant organisms or complex infections which require multi-antibiotic regimens. Antibiotic

stewardship in a healthcare setting is no longer just the responsibility of the clinician or pharmacist — it takes a concentrated team effort of many disciplines including the microbiology laboratory. As the eyes and ears of the team, the microbiology laboratory can provide accurate and statistically significant data on antimicrobial resistance that will allow the team to make appropriate decisions and recommendations. One of our clinicians is often quoted as saying, “There is a gold mine of data available in microbiology. We just have to be able to get to it and understand it.”

Reference:

1. Clinical Laboratory Standards Institute. 2005. Analysis and presentation of cumulative antimicrobial susceptibility test data. M39-A2. Second edition. Approved guideline. CLSI, Wayne, PA. 19087-1898. USA. Vol 25. 28:2-15.

Introduction

continued from page 1

beta-lactamases are present, Hepatitis C diagnostic challenges, and more. When the presentations are available we will notify you via email and provide a link to the website, so stay tuned!

MicroScan Microbiology Systems is excited to be entering our 30th year of providing bacterial identification, antimicrobial susceptibility testing products and informatics solutions for your laboratory. We are also pleased that MicroFocus is entering its 3rd year of publication, and that many of you

find it to be a useful supplement to your daily routine. Please let us know about topics of interest and other ways we can continue to make this a relevant and useful tool. If you have an interest in becoming an author, please e-mail me directly.

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Commentary:

Interconnected Roles of Microbiology and Infection Control

This issue contains important and timely articles dealing with the evolving issue of antimicrobial resistance. Dr. Mike Janda reviews the topic from a Public Health point of view and summarizes legislative activities regarding Healthcare Associated Infections (HAIs). Dr. Janda uses MRSA as an example to emphasize his points. If there is a positive aspect regarding HAIs, it is the public attention to MRSA infections. As the lay public gains knowledge and pressures state and federal officials to take action, legislation is being developed. Are state and/or federal regulations necessary to control HAIs? Many believe that in regard to MRSA, "the horse is out of the barn." MRSA colonization has become established in a high percentage of people. Do we need a "universal precautions" position and assume all patients are colonized and strict enforcement of good infection control practices is the only practical route? Emphasis should be on education and good infection control practices. SHEA (Society for Healthcare Epidemiology of America) and APIC (Association for Professionals in Infection Control and Epidemiology) do not support legislation to mandate use of active surveillance cultures to screen for MRSA. They support research and educational efforts and strategies for the prevention of infection. On the other hand, others favor thorough screening of all newly admitted patients and possibly weekly testing of high risk patients for organisms like MRSA. Colonized patients would be isolated &/or treated topically, as indicated by institution practice. These actions would be very expensive, but advocates claim that there would be savings in the long run with reduced infections and hospital length of stay. If the latter position is adopted, the microbiology budget must be adequately adjusted for the extra cost. Microbiology should not be expected to absorb the cost for these non-billable procedures.

The continuous development and spread of antimicrobial resistance among bacterial pathogens requires documentation and analysis. Clinical microbiologists as producers and owners of this data have assumed responsibility for producing antibiogram reports. The reports have been produced, in some form or other, for greater than 25 years. I remember working on antibiograms in the mid-1970s. These reports provide information for empiric therapy, assistance for formulary decisions, and they serve as an educational tool. Dr. Snyder and his team from the University of Louisville Hospital provide us with a detailed and practical description of antibiograms. The importance of extracting and analyzing specific versions for individual wards, services, ICUs, Outreach, etc. provides specific information which can be lost when all data is combined for the entire institutional report. Each institution must make several basic decisions as to what is included and which areas or services need individual antibiogram reports. Which antimicrobial drugs are included? All drugs tested, or only those you routinely report on your susceptibility report? Infectious Diseases, Pharmacy and Microbiology personnel should be involved in the decision, and if your institution has an Antimicrobial Committee, it should guide the process. Focused antibiograms can provide very helpful specific data for empiric therapy. The antimicrobial choice is more likely to be successful the more specific the antibiogram. A potential problem of focused reports, especially for smaller institutions, is the need to have a sufficient number of isolates. Otherwise, one or two resistant isolates will greatly change the results. For example, two resistant isolates out of ten will result in a 20% change in data, while two out of 50 would only cause a 4% change. This is why a minimum of 30 isolates is recommended. Another recommendation



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is to only count the first isolate from repeated positive cultures from a patient. This is intended to keep from overcalling resistance, since succeeding isolates tend to be more resistant. Empiric therapy should be based on initial isolates and not selected resistant strains. However, it must be pointed out that from an Infection Control point of view, every resistant strain must be included in an analysis when judging the potential for spread of resistant strains. Infection control needs to keep abreast of each culture result for tracking the incidence of all resistance within the institution. As pointed out in the articles in this edition, the role of the Microbiology Laboratory continues to expand. These laboratories offer vital services in developing and analyzing crucial documentation needed for current patient treatment. Their continued role must be supported if we are to get the upper hand in control of infections and antimicrobial resistance.

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