Scoring against MRSA—studies shed light on what works

Anne Paxton

August 2014—A race for prevention may lack the drama of a race for the cure. But to fight methicillin-resistant Staphylococcus aureus and other multidrug- resistant organisms, hospitals really have no choice. A disease with a higher number of annual U.S. deaths than for salmonella, tuberculosis, influenza, and HIV put together, MRSA can only be tamed with prevention.

Despite the fact that U.S. guidelines for the past 10 years have not considered active screening as essential, in 2012, 59 percent of hospitals were screening for MRSA. The question is: Which strategies do the best job of forestalling the infection and spread of organisms like MRSA that are difficult, if not impossible, to treat?

“Traditionally, very few randomized trials have been funded on MRSA strategies,” says Anthony Harris, MD, MPH, medical director of infection control at the University of Maryland Medical Center and professor at the University of Maryland School of Medicine. “But in the last half decade, we’re fortunate that the Agency for Healthcare Research and Quality, the National Institutes of Health, and the CDC have sponsored some trials.”
Results from two large-scale randomized clinical trials published in the past 14 months are shedding light on what works in MRSA prevention. Both the REDUCE MRSA trial of universal decolonization (Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate MRSA) and the BUGG trial (Benefits of Universal Gowning and Gloving) will inevitably change the role of the clinical microbiology laboratory as hospitals absorb the trials’ lessons and adjust their MRSA protocols.

The timing is appropriate for a number of reasons—but especially because studies giving better guidance on best practices are coming out just as the Centers for Medicare and Medicaid Services is about to raise the stakes significantly. The agency will start cutting Medicare payments to hospitals whose hospital-acquired condition rates, including infections, are out of line. From Oct. 1, 2014 through Sept. 30, 2015, hospitals getting the penalty will lose one percent of each Medicare payment.

Of those hospital-acquired conditions, MRSA may be the one with the highest profile. But a major issue in MRSA prevention is whether efforts should be directed at individual pathogens, or at people who are highly susceptible to multiple pathogens. The REDUCE MRSA study, published in June 2013, specifically addresses this question by looking at intensive-care unit patients as being especially vulnerable to infection. (Huang SS, et al. N Engl J Med. 2013: 368:2255–2265).

Dr. Platt

REDUCE MRSA involved 75,000 people who were in hospital ICUs that were randomized to one of the three evaluated regimens. “It is the largest study of its type that has ever been conducted,” says principal investigator Richard Platt, MD, MSC, professor and chair of the Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute.

The study demonstrated a substantial improvement in its primary outcome, which was clinical isolates of MRSA

associated with universal decolonization, and a substantial reduction in one of its major secondary aims, which was all-cause bacteremia. “The results were quantitatively impressive in terms of the magnitude of reduction in disease burden, and we think they will have substantial value in guiding clinical practice,” Dr. Platt says.

Participating hospital ICUs were assigned to three regimens tested in REDUCE MRSA. In arm one, all admissions were screened for MRSA and isolated if the screen or the history were positive, which is the baseline practice currently at most U.S. hospitals. Arm two was targeted decolonization, meaning the screen-and-isolate policy plus decolonization by mupirocin and daily chlorhexidine baths for five days. Arm three was universal decolonization, with no screening: All patients were decolonized, and isolation was ordered if a positive clinical isolate was reported.

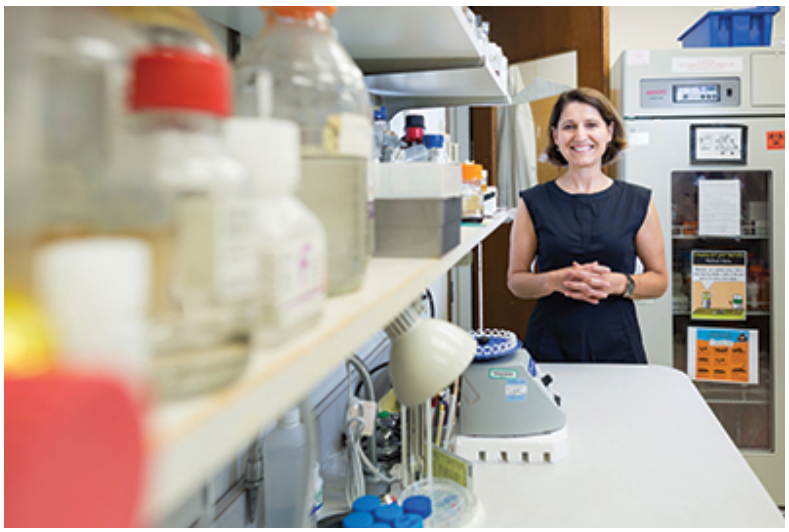
When the study was completed, “It was pretty clear that both of the other intervention arms were better than arm one, the surveillance culture/isolation-if-positive protocol,” Dr. Platt says. But the study found that the third arm, universal decolonization, was preferable. “It was both better and easier. It was less costly to implement and yielded a better result.”

When they set out, the researchers did not know what the results of their study would be, but he finds the results plausible. “The technique of doing the surveillance cultures and isolation if positive means that under the best of circumstances, it’s a day or two before you know the person is positive and you begin isolation. That assumes the surveillance mechanism is 100 percent sensitive, which it may not be.”

“So it might miss some people who are actually positive. That’s a reason that the regimen would reduce the amount of spread from patient to patient in the ICU. But in addition, the decolonization regimen reduces the level of bacterial colonization that a person has, so that might reduce the chance of the patient becoming sick with his or her own flora.”

It’s important to note, Dr. Platt says, that REDUCE MRSA was a “pragmatic embedded” trial, meaning it was implemented in the hospital sites in the way it would normally be used in hospitals employing their regular clinical teams, not on-site research staff.

Several studies, he says, have had results consistent with the idea that universal decolonization is beneficial, and many hospitals are evaluating adoption of the protocol. However, the fact that so many states require hospitals to do surveillance cultures to prevent MRSA is a potential problem.



Dr. Hayden recommends that laboratories do baseline testing, then serial testing every six months or every year, working with infection control to test isolates from patients exposed to mupirocin. “High-level resistance to mupirocin is clearly a concern,” she says. “It’s

associated with decolonization failure, and that's really what you want to avoid."

"That certainly changes the economics in an important way," Dr. Platt says. He doesn't support the requirement to perform cultures. "There was never strong evidence that you got better outcomes, and I believe the results of this study show the best way to prevent complications is to decolonize everybody. In that case, the results of culture wouldn't guide any clinical decision-making, so I don't see it as being useful."

The evidence for universal decolonization, on the other hand, is "pretty powerful," he emphasizes, and hospitals should seriously consider it as a standard way to take care of their patients.

"It's not a change you can make by fiat in the hospital, because there's some equipment and training that's needed. But it's well within the capabilities of ICUs. In our experience, the ICUs that adopted it once they made the switch didn't find it overly burdensome. Basically every patient gets bathed in the ICU every day unless there's a reason not to do it, so we are not adding a new practice."

His colleagues are now completing a study of the same decolonization protocol for general medicine and general surgery outside the ICU. "We expect to have an answer on that fairly soon." He also notes there's an important question still to explore: whether patients known to be colonized with MRSA would benefit from a decolonization regimen after they are discharged.

But just as MRSA evolved from antibiotic use, the possibility of antibiotic resistance developing from prevention strategies remains quite real, and part of the REDUCE MRSA trial was devoted to this potential outcome. As a co-investigator of the REDUCE MRSA trial, Rush University Medical Center's microbiology laboratory's role was to do susceptibility testing on the collected isolates to look for potential adverse consequences of the universal decolonization approach. (Rush received about 4,500 MRSA isolates to test; results of the laboratory's work will be presented in October in an oral abstract session at IDWeek 2014.)

Mupirocin is a nasal formulation approved by the FDA for eradication of MRSA colonization, so it is used in nasal decolonization. But mupirocin resistance can be a problem. Worldwide it ranges from 4.6 percent to 17.8 percent, and although it's relatively low in the U.S. (four to five percent), it may be on the increase.

"We're trying to learn from the mistakes related to MRSA and VRE [vancomycin-resistant Enterobacteriaceae], where we let things get out of control by not having a coordinated regional approach," says Mary Hayden, MD, professor of medicine and pathology and director of Rush's Division of Clinical Microbiology. Rush University Medical Center is one of the CDC Prevention Epicenters (Robert A. Weinstein, MD, PI), and Dr. Hayden's laboratory has worked on identifying hot spots of carbapenem-resistant Enterobacteriaceae in long-term and short-stay acute care hospitals and has done focused interventions to control the organism.

Coordinated regional approaches were uncommon 25 years ago when VRE first emerged and individual hospitals tried to battle it, Dr. Hayden says. "I think now we're smarter, and to address organisms like CRE, we've been trying to control the problem by working with our public health department and other hospitals."

"Laboratory detection is important and [CRE is] much more difficult to detect than some of the other organisms we have dealt with in the past," she says, noting that CRE involves multiple genera and multiple species of bacteria. "It's not like MRSA where it's Staphylococcus aureus and there is one mechanism of resistance; with CRE there are multiple mechanisms of resistance."

Moreover, sometimes the organisms don't express at very high levels, so they can be difficult to detect, she adds. The Clinical and Laboratory Standards Institute has lowered the breakpoint for carbapenems, and that has helped, but it has not solved the problem.

"The lower breakpoints don't solve the problem," Dr. Hayden explains, "because although it improves our ability to

detect CRE, it doesn't allow us to identify the mechanisms of resistance—production of carbapenemases—that are most important epidemiologically and that we want to focus our control efforts on."
For facilities that are planning to use universal decolonization, she believes that serial prevalence surveillance, particularly for mupirocin resistance, is necessary. "If you are using universal chlorhexidine, it's probably OK right now to leave surveillance to researchers and the public health authorities, but mupirocin is more concerning if you are using it as part of the universal decolonization bundle. You're putting a lot of selective pressure and could be driving resistance."

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A number of studies in the research literature suggest that the use of mupirocin drives mupirocin resistance. For example, a New Zealand study showed a surge in resistance after mupirocin was made available over the counter (Upton A, et al. J Antimicrob Chemother. 2003;51:613–617). "High-level resistance to mupirocin is clearly a concern. It's associated with decolonization failure, and that's really what you want to avoid," Dr. Hayden says.

Since mupirocin is an antibiotic, it's natural for clinical laboratories to test for it, and breakpoints, ranges, and testing conditions have been established. But chlorhexidine gluconate (CHG) is a biocide or antiseptic, and testing antiseptic resistance requires a different approach from antibiotic resistance, Dr. Hayden points out.

"It was a challenge to attempt chlorhexidine susceptibility testing, because it's not something clinical labs are set up to do," she says. "So what we did in REDUCE MRSA was extrapolate testing methods for antibiotic susceptibility testing to chlorhexidine, then try to determine the breakpoints based on published research."

"For MRSA, almost all MICs fall within 1 to 4 mg/L, and when using CHG to bathe patients, we would say an MIC of 8 mg/L shows resistance because it falls outside the natural range. But whether that's a relevant resistance is very unclear. It's still very rare worldwide for anybody to report elevated MIC with CHG in staphylococci, and some people say we should define resistance by the presence of a particular gene called qacA."

One particular strain of MRSA seems to be able to survive particularly well even when there's a lot of chlorhexidine around, Dr. Hayden explains. "Whether or not that has to do with the MIC or there's some other feature of the organism that allows a survival advantage is not clear to me. But there is this particular epidemic strain that's described in England and other parts of the world, and that may be selected by use of a lot of CHG. It's really an open question."

At Rush, where the protocol even before the REDUCE MRSA study has been to do CHG bathing and not add mupirocin, the laboratory tests CHG susceptibility as a research tool, but finds it "vanishingly rare," she says.

"Our site was involved in some very early trials of CHG which demonstrated that it had benefits even beyond MRSA eradication, associated with decreased central-line–associated bloodstream infections. So we've been using it for many years in our ICUs, but we haven't added mupirocin because of concerns about development of mupirocin resistance."

If hospitals choose to use mupirocin, she recommends that the laboratory do susceptibility testing. However, she does not think that mupirocin is on any of the commercial panels, so hospital laboratories may find it difficult to perform the test without sending it to a reference laboratory.

While community MRSA has remained stable or perhaps increased in the past few years, health-care–associated MRSA has declined, Dr. Hayden says, because of all the attention to MRSA control and to health-associated infections such as central-line–associated bloodstream infections. As far as emerging threats are concerned, most states have carbapenem-resistant Enterobacteriaceae organisms but they're in low prevalence. "That's good news and means we should continue to work hard to have a concerted regional and national effort to control CRE and not let it get out of hand as it did for VRE and MRSA."

She believes less active surveillance will be done over time for MRSA in general. But a number of states mandate

screening for MRSA on high-risk patients. “So in my lab, because screening is mandated in Illinois, we will continue doing surveillance whether we think it’s effective or not. But I think there is a sentiment toward more of these universal horizontal approaches to control—rather than focusing on a particular organism, we’re focusing on decreasing infections overall. I think that is gaining momentum and labs will probably see less screening unless it’s required or your hospital feels strongly about it.”

Active surveillance for CRE will depend on local prevalence and the population the hospital serves. “In my hospital. we have a lot of transplant patients, and we want to keep CRE out of those populations. They have a very high risk of significant morbidity and mortality from these pathogens.”

“We’ve been able to determine that the patients most likely to carry CRE when they come to our hospital are coming from another facility, so we’ve been screening patients who are admitted from another facility for CRE, although we are not finding very much.”

But deciding how far the lab needs to go to identify CRE can be tricky, she adds. “Some labs will just be able to confirm a pathogen is CRE, others will determine the molecular mechanism, and some may want to refer isolates if they think there is a cluster or an increase. It depends on the capacity of the lab.”

Dr. Harris

The benefits of universal gowning and gloving as a precaution have been debated, but the $5 million BUGG study involving 20 ICUs, conducted in the same time frame as the REDUCE MRSA study, has given supporters and skeptics a substantial amount of data for the first time (Harris AD, et al. JAMA. 2013;310:1571–1580). “There hasn’t really been anything of this magnitude in the past,” says the University of Maryland’s Dr. Harris. “We’ve done previous studies that show how the bacterium is transmitted from patient to patient, but this intervention had never been studied previously in a randomized trial.”

The BUGG study tested whether going to 100 percent health care worker gowning and gloving for ICU patients could prevent the spread of antibiotic-resistant bacteria. Gowning and gloving is not at all mandatory at present. “The CDC only recommends use of gloves and gowns or contact precautions for patients with antibiotic-resistant bacteria. So in the average ICU in this country, five to 40 percent of patients could be on such contact precautions, with a national average of about 10 percent.”

The question BUGG tested was: “In an ICU where you don’t know all the patients who have MRSA or VRE, are there advantages to being more aggressive and having the workers wear gowns and gloves for all patients with whom they come in contact and thus prevent the spread of antibiotic-resistant bacteria?” Dr. Harris says.

Logistically, such a protocol may sound difficult, but at Dr. Harris’ hospital, health care workers in some ICUs have been doing universal gowning and gloving for almost a decade. “There are barriers to health care workers accepting an idea of intervention that requires this kind of behavior change,” he concedes. But in the study, “once we got over the hurdles of their initial reaction, I actually think it was fairly well done, if you look at our intervention sites. They were compliant over 85 percent of the time with gowns and over 86 percent with gloves. And we had a fair number of sites that stayed on universal gowns and gloves after the study ended.”

One reason for that uptake was that the study showed the universal gowns and gloves brought a significant drop in MRSA acquisition—40 percent—although not in VRE rate, which did not improve. “It was surprising we did not have

any effect on VRE, but on the flip side, the magnitude of the effect on MRSA was larger than we expected; it was very robust."

Another significant study outcome was that universal gowning and gloving did not lead to more adverse events, contrary to expectations by some that it would impede the work of doctors and nurses. "We did see that health care workers went in and out of rooms one less visit per hour. But there was no difference in hand washing on room entry, and there was actually an increase in hand washing compliance on room exit."

The cost of this intervention— $150,000 to $250,000 a year for an ICU of average size—has scared off some hospitals, but Dr. Harris thinks hospitals generally are not taking the long view and considering that 20 to 50 percent of patients who are colonized with MRSA develop an infection, which is much more costly by comparison.

The cost-effectiveness of gowning and gloving versus other interventions remains to be assessed. Still, Dr. Harris believes gowning and gloving is one of the most effective interventions that have been shown to work in reducing MRSA. "The uptake nationally has been less than I think was anticipated because of some falsely negative perceptions that contact precautions lead to more adverse events, which we have disproved in this study."

If he had to pick one strategy to address MRSA, it would be screening and isolation or decolonization, says epidemiologist Lance Peterson, MD, director of microbiology and infectious disease research at NorthShore University Health System in Chicago's northern suburbs. NorthShore's MRSA rates are remarkably low, a fraction of average rates, Dr. Peterson says, and he credits active surveillance that extends beyond the ICU.

The protocol goes back to August 2005, when NorthShore started doing universal admission surveillance and reduced the rates of disease by 50 percent within three months. Within three years, the hospital saw a 70 percent reduction in total MRSA disease during hospitalization and 30 days post-discharge.

The program, which uses a computer algorithm to predict who needs to be tested, then treats the patient with nasal mupirocin twice daily for five days with chlorhexidine bathing, "is just kind of self-sustaining," he says. "On each admission we take the nasal swab inside the nose, it's sent to the lab, and we run a real-time PCR assay. And now the prediction rule has been built into our Epic electronic medical record system and runs in the background telling us who needs testing," says Dr. Peterson, who is a clinical professor at the University of Chicago.

Convincing the hospital to spend the extra money on surveillance has made universal screening controversial. But Dr. Peterson doesn't think it should be, since the first eight years of NorthShore's MRSA containment program prevented 813 infections.

"We found that, estimating very conservatively, each MRSA infection added $24,000 to the cost of an admission, because of the longer length of stay and additional care, so if you look at our net recovery of finances, we reduced the cost by $2 million per year." It would be very helpful if Medicare reimbursed for the testing, he adds.

The law in Illinois, as in about a dozen other states, requires screening and isolation only for ICU patients, and most Illinois hospitals continue to screen and isolate only that group. The Veterans Affairs hospitals in the state and across the country started doing universal surveillance about a year and a half after NorthShore, and have published extensively on their positive results.

One benchmark of the hospital's success with MRSA: "Each year the Joint Commission requires hospitals to do an annual assessment on our most important active problems, and MRSA is not on our list anymore."

But every approach has its controversies, Dr. Peterson notes. "There's been a lot of attention focused on hand hygiene, and it's important. But if you look at the data, one cluster randomized trial in Canada showed increasing hand hygiene didn't help. A Swiss study showed it lowered disease, but if you read the study carefully, you can't really tell if the benefits were due to hand hygiene or a comprehensive surveillance program they started at the same time."

The difficulty, he says, is MRSA is hardy. “It sticks around in the environment a long time, and if you happen to be colonized, every time you touch someone you can transmit about a billion organisms.”

The vast majority of studies have shown surveillance and decolonization were the only thing that reduced MRSA infections when there was a relatively low rate of MRSA to start with, he says. “I think the data is overwhelming that this works. It may not be what everybody wants to do, but from an evidence-based medical standpoint, it’s desirable that people look seriously at their own MRSA rates.”

A simple way to calculate whether rates are high is to use the formula from the Illinois Hospital Report Card, which hospitals are required to submit, he says. It takes the positive blood cultures from the microbiology lab for patients on day two or later of hospitalization and divides it by patient days for the hospital. “If your rates are high, do something, even if it’s just screening and isolation.”

Dr. Peterson agrees that the BUGG study showed significant impact of universal gowning and gloving on MRSA rates. But he points out that the combined change in MRSA plus VRE acquisition in the BUGG study was not different between intervention and controls, and he doesn’t consider 100 percent gowning and gloving to be practical. His view: “It’s hard enough to get people to be compliant when you’re doing it only for known positives.”

Dr. Platt, too, reserves judgment about universal gowning and gloving. “At the end of the day, we will probably have to do a formal comparison to know how universal gowning and gloving stacks up against universal decolonization in terms of microbiologic outcomes and clinical outcomes for the patient,” he says.

Dr. Platt believes that universal decolonization without routine surveillance deserves serious consideration by most hospitals. “The hospitals in which we did our study, we believe, were highly representative of mainstream U.S. hospitals, and we therefore think that the big reductions we saw in MRSA rates are likely ones that other hospitals could achieve.”

Whichever protocol hospitals choose, the progress toward more concerted, evidence-based MRSA strategies is undeniable. “We’re finally moving the field ahead,” says Dr. Harris. “It’s what hospital epidemiologists and infectious disease physicians have been pushing for.”n
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