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Q&A

Identifying Antibiotic-Resistant Bacteria in Hospitalized Patients: What Is the Role of Active-Surveillance Cultures?

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Antibiotic-resistant bacteria are an important cause of morbidity and mortality among hospitalized patients throughout the world. Controlling the emergence and spread of these organisms in healthcare settings requires multiple strategies, including strict attention to hand hygiene, vigilant disinfection of equipment and the environment, efforts to promote antimicrobial stewardship, and adherence to evidence-based bundles of care practices to prevent infections associated with the use of invasive devices such as central venous catheters and ventilators. Multiple studies have demonstrated that identification of patients who are colonized with organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA)[7] and vancomycin-resistant enterococci (VRE), in conjunction with the use of contact precautions when caring for those who are colonized, can reduce rates of colonization and infection with these bacteria. Active-surveillance cultures (ASCs) for these organisms are currently recommended for hospitalized patients at high risk of carriage. Questions remain, however, regarding which specific populations should be screened, the optimal screening method, and which organisms should be targeted for ASC. In this Q&A, 5 experts with different roles in infection prevention and microbiology [including adult (S.S.H.) and pediatric (A.M.M.) hospital epidemiologists from the US and Europe (S.H.), an infection preventionist (S.A.D.), and a microbiology laboratory director (A.J.M.)] have been asked to comment on several unresolved issues regarding the use of ASC as a strategy to prevent the transmission of multidrug-resistant organisms (MDROs) in hospitals.

The 2006 Healthcare Infection Control Practices Advisory Committee guideline for the management of MDROs in healthcare settings notes that the target populations for ASC are not well defined. In what patient populations do ASCs make the most sense, and why are there differences between the "search and destroy" approach used in Europe and what is typically done in the United States?

Susan Huang: ASC has been shown to be beneficial in high-risk hospitalized populations where screening can newly identify a substantial proportion of MDRO carriers and trigger contact precautions, decolonization strategies, or both. This strategy has most commonly been applied to the intensive care unit (ICU) setting and has been shown to reduce transmission and bloodstream infection due to MRSA in observational studies.

The Dutch search-and-destroy approach is a comprehensive ASC and decolonization approach that is intended to trace contacts of all MRSA carriers identified in healthcare settings. All patient and healthcare worker contacts undergo intensive screening, followed by isolation and decolonization. This strategy has been credited with the decline of epidemic MRSA type 16 in that region. In the US, it has not been customary or practical to screen healthcare workers who come in contact with MRSA-positive patients. This is in part

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[7] Nonstandard abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; ASC, active-surveillance culture; MDRO, multidrug-resistant organism; ICU, intensive care unit; CRE, carbapenem-resistant Enterobacteriaceae.

due to evidence suggesting that MRSA strains carried by healthcare workers are uncommonly the source of transmission in healthcare settings. In the US, the focus has been on preventing transmission through contact precautions and high-compliance hand hygiene during patient care. More recently, the focus in the US is increasingly directed toward decolonization of high-risk patients during hospitalization.

Stephan Harbarth: The search-and-destroy approach has been successfully used to control MRSA in a few European countries (e.g., the Netherlands, Denmark) and is currently applied to VRE, multiresistant *Acinetobacter* spp and carbapenem-resistant Enterobacteriaceae (CRE) in several others (e.g., France, Switzerland). Nevertheless, large regional differences remain between different European regions. The differences between the US and Western Europe regarding the implementation of ASC can be explained by different determinants, including (1) public health considerations and priorities, (2) availability of on-site microbiology laboratories, (3) factors related to healthcare systems and the influence of the market-driven healthcare industry, (4) cultural factors (e.g., proactive prevention vs reactive control measures), (5) local infection control practices and knowledge, (6) available resources dedicated to hospital hygiene, (7) legal constraints (e.g., mandatory MRSA screening in England), and (8) political commitment.

Several strategies have been documented in the literature as being successful in the prevention and control of MDRO transmission. Whereas it is unclear which bundles of interventions are effective, there is a clear suggestion that multiple simultaneous interventions, including ASC targeted at patients at high risk of MRDO carriage, can be effective in reducing MDRO infections. Existing evidence supports ASC as cost-beneficial in decreasing cross-infection of MDROs, especially in ICUs and units with high MDRO prevalence and low hand-hygiene compliance.

Aaron Milstone: A distinction needs to be made between outbreaks and periods of endemic MDRO transmission. During outbreaks or clusters of MDRO infections, ASCs have been used successfully with other interventions to prevent transmission and interrupt outbreaks. During endemic periods, it is clear that ASC improves detection of patients colonized with MDROs

who can serve as a reservoir of transmission. ASC makes most sense in an area or population with a high colonization prevalence of an organism or a population at particularly high risk for infection. For example, neonates in the ICU are at high risk for *S. aureus* infections, due to prolonged lengths of stay, in-dwelling devices, and frequent procedures. Identifying carriers in this population may be important if there is evidence that patients are the source of ongoing transmission in the unit. A key difference between ASC and search and destroy is that ASC is often not combined with a "destroy" component. Attempting decolonization or eradication of colonization is less common in the US than it is in Europe. Simply identifying a patient as colonized with an MDRO does not protect that patient from developing a subsequent infection, and it does not remove that reservoir from the unit.

Susan Dolan: I have found a targeted approach at our facility to be useful. ASCs are used in our ICUs and in patients scheduled for surgery involving an implant (e.g., orthopedic surgery, neurosurgery, cardiothoracic surgery). In our ICUs, patients are screened upon admission and isolated pending results. For our surgical patients, their surgical antimicrobial prophylaxis is altered upon finding MRSA on their presurgical screen. We have also used ASC for patients admitted to our rehabilitation unit who have transferred from outside facilities, because of an increased prevalence of MRSA in this patient population. Unless mandated by legislation, most US facilities that utilize ASC have targeted their implementation to specific patient populations or units on the basis of their risk assessment. In addition to ASC, it is very important to assure that the basic infection prevention and control principles are in place and adhered to (e.g., hand hygiene, transmission-based isolation precautions, proper donning and removal of personal protective equipment, environmental and equipment cleaning and disinfection, and worker education).

Several diagnostic approaches are available for detecting MRSA colonization from clinical samples, including culture-based methods and more-rapid technology, such as the PCR. Does the benefit of the shorter turnaround time provided by PCR justify the increased cost?

Alexander McAdam: The cost–benefit analysis for selecting a method to detect MRSA colonization is complex and should include all costs to the institution and patient. Laboratory directors can find comprehensive analysis difficult when under pressure to reduce laboratory expenses. In addition to differences in reporting time and cost, there are other things to consider. First, the sensitivity of PCR for MRSA is slightly greater than that of culture if a rapid (1-day) culture method is used. More sensitive culture methods take longer (up to 3 days). Second, some PCR tests are FDA approved only for use with nasal swabs. Testing other body sites in addition to nares increases the detection of MRSA colonization, but this will increase cost. Testing these body sites must be validated for the PCR test. Third, PCR for MRSA can have low positive predictive values, particularly in populations with a low prevalence of colonization. In some studies, the positive predictive values of PCR were only 60%–70%, meaning that 30% to 40% of the positive results were false positives. Use of PCR to detect MRSA might require confirming positive results by culture.

Stephan Harbarth: Ultrarapid MRSA screening (<2 h) is not a mandatory prerequisite to reduce MRSA infections. There is a lack of robust evidence that detection within 2 h is better than within 24–36 h. Molecular methods are probably best suited for targeted MRSA screening in ICUs. Furthermore, settings with a very high prevalence of MRSA colonization (>10% of MRSA-positive patients on admission) may find universal PCR-based screening cost-effective and, in some cases, cost-saving. However, PCR-based MRSA screening is not needed for everyone and not cost-effective in most settings in Europe. The local MRSA epidemiology, competing infection control strategies (e.g., hand hygiene promotion), and economic constraints are important to consider before introducing PCR-based methods on a broad, routine basis.

Susan Dolan: Using newer technologies, we have decreased turnaround time to about 3 h from receipt of specimen to the verified result. This improvement has eliminated a substantial amount of time during which patients who are not colonized need to remain in isolation pending results. In an ICU setting, this cuts down tremendously on personal protective wear (e.g., gowns, gloves), is less cumbersome for staff, and saves them time when entering and leaving the room. More importantly, we have seen a positive benefit for parents of our pediatric patients, who no longer have to wait several days for a result and don't have to adhere to the constraints of isolation for their child.

Much less is known about ASC for gram-negative bacteria compared with MRSA or VRE. Do you see a role for ASC for multidrug-resistant gram-negatives? If so, which organisms should we be looking for?

Stephan Harbarth: Yes, ASCs are important to control specific gram-negative MDROs, including CRE. Throughout Europe, active CRE-screening policies have been established by defining patients at high risk of CRE carriage. Currently, these risk factors mainly consist of previous contacts with medical facilities in countries with ongoing outbreaks or endemic occurrence of CRE (e.g., Israel, Greece, and Italy). For patients transferred from these regions, preemptive isolation while the CRE-screening results are awaited is highly recommended. Similarly, in settings in the United States with low prevalence and localized CRE outbreaks, the aim of infection control measures should be the complete eradication of CRE, according to an adaptation of the classic search-and-destroy strategy, whereby patients considered to be at high risk of CRE carriage are isolated upon hospital admission pending the results of admission screening by rectal swabs or stool cultures. The latest fatal outbreak of carbapenem-resistant *Klebsiella pneumoniae* at the US National Institutes of Health Clinical Center unfortunately best underscores the importance of stringent infection control precautions including aggressive ASC. CRE screening, cohorting, and contact isolation were effective measures that eventually stopped the outbreak, since infection control practitioners failed to appreciate that the most important transmitters of CRE were asymptomatic carriers and not sick cases.

Aaron Milstone: At this time, I see a very limited role for ASC for multidrug-resistant gram-negatives in children. Outbreaks in neonatal ICUs have been seen with high morbidity and mortality, so a cluster of infections in high-risk settings should prompt consideration of ASC. However, given the overall low prevalence of multidrug-resistant gram-negatives in hospitalized children, the value of ASC remains unknown. Children who come to the US for quaternary care from

areas of high endemicity may be at increased likelihood of multidrug-resistant gram-negative colonization, but without knowledge of their local epidemiology, determining what organisms to screen for is a challenge. Our biggest limitation is that there is no one test to identify a patient colonized with a multidrug-resistant gram-negative. We can identify extended-spectrum β-lactamase producers and CRE, but testing is complicated and often is performed only at reference laboratories. Standard infection control measures and antibiotic stewardship should remain our first line of defense against these emerging organisms.

Alexander McAdam: Compared to MRSA or VRE, we know little about the best methods for ASC for multidrug-resistant gram-negative bacilli. It is important to understand this limitation when deciding whether and how to screen for multidrug-resistant gram-negative bacilli. We do not know what body sites to test, how often to test, or what culture method to use for high-sensitivity screening. Screening for enteric gram-negative bacilli (e.g., *Escherichia coli* and *K. pneumoniae*) is usually done with rectal swab specimens; however, additionally testing other specimens, such as urine, could significantly increase detection of colonized or infected patients. Testing for nonenteric gram-negative bacilli (e.g., *Acinetobacter baumannii*) is more complex, because there is not one body site that these organisms usually colonize. Furthermore, little is known about the best culture conditions for multidrug-resistant gram-negative bacilli. The Centers for Disease Control and Prevention recently published a method for detection of carbapenemase-producing *Klebsiella* and *E. coli*, and there are now commercial media available for detection of some multidrug-resistant gram-negative bacilli. Investigators should consider including questions about methods for ASC in their larger projects in this area. Such questions could often be answered with a minimum of additional work in the context of an outbreak investigation.

Many states now have legislative mandates requiring hospitals to perform ASC. Are these mandates helpful in the effort to curb the spread of antibiotic-resistant bacteria, or have legislators overstepped their bounds?

Susan Huang: The state legislative mandates surrounding healthcare-associated infections in general and ASC in particular have been very helpful in drawing attention to the need for directed efforts and successful prevention strategies to reduce healthcare-associated infections as a top-ten cause of death in the US. Legislation produces action and standardization as hospitals strive to comply with state laws and has propelled and compelled action in ways not otherwise attainable with good intentions alone.

However, it is important to note that legislation may be problematic in keeping up with scientific change. For instance, our recent 43-hospital trial that found universal decolonization in adult ICUs to be superior to ASC plus targeted decolonization raises the important question about whether legislation can be rapidly modified in response to the results of major trials. If not, then legislation may be enforcing out-of-date practice.

Stephan Harbarth: In Europe, compulsory surveillance and public reporting of MRSA infection rates, as well as mandatory ASC for MRSA carriage upon admission, have been introduced only in England. The overall reported incidence of MRSA bloodstream infections in England fell by 56% between 2004 and 2008. The role of mandatory MRSA screening, introduced gradually after 2007, in this impressive reduction of MRSA rates remains controversial. Many factors have probably contributed to the noted decrease in MRSA bloodstream infections, including development of infection-control structures, campaigns to promote hand hygiene and evidence-based practice, and political pressure. Of note, a fall in the incidence of MRSA infections has been observed not only in England but also in many Western European countries without mandatory universal MRSA screening.

Susan Dolan: Legislation can be most helpful when it supports the core elements of infection prevention processes. Targeting a specific organism may not be the most effective or efficient approach. Facilities should utilize their financial and human resources to target, identify, and prevent the acquisition and spread of organisms identified as concerning for their own patient population.

Aaron Milstone: Like all prevention strategies, the decision to perform ASC should be made after a careful risk assessment within an institution. The main limitation of a legislative mandate to perform ASC is that it trumps a risk assessment made by an institution. When early legislation was introduced, the US and the world were seeing a dramatic increase in the numbers of MRSA infections in hospitalized and healthy patients alike. Now, with years of investigation about these programs, studies of ASC for MRSA prevention, for example, have not consistently shown a benefit to curb the spread of endemic MRSA in acute-care settings. ASC as part of a comprehensive control strategy may provide some benefit, but legislators do not mandate a comprehensive approach, they simply mandate ASC. These mandates do not allow healthcare facilities to conduct a

risk assessment, ensure implementation, and enforce compliance with standard control measures (hand hygiene, cleaning and disinfection, education of healthcare workers, identifying patients readmitted or transferred with known MRSA, etc.). In an environment of limited resources devoted to infection prevention, ASC could be considered a special approach for preventing MRSA transmission to be considered when transmission continues despite basic prevention measures.

An alternative approach for hospitals is to eliminate ASC in favor of universal decolonization for selected patient populations. What are the risks and benefits of this approach?

Susan Huang: Our recent large cluster randomized trial, the REDUCE MRSA Trial, has demonstrated that universal decolonization without screening is superior to screening plus targeted decolonization of MRSA carriers in reducing MRSA clinical cultures and bloodstream infections due to all pathogens. These results were presented at IDWeek 2012 and suggest that a universal approach targeting all pathogens should be seriously considered as best practice, rather than ASC. Given this finding, ASC should not be adopted as best practice in adult ICUs. Formal cost-effectiveness evaluations will be forthcoming for this trial but are not currently available. Nevertheless, the 44% reduction in all-pathogen bloodstream infection is compelling. Careful surveillance for the emergence of resistance to decolonizing agents will be important. Fortunately, decolonizing agents are not used for disease treatment, so the loss of a therapeutic agent is not at stake.

Stephan Harbarth: Universal decolonization and chlorhexidine body washes for all patients, independent of their MDRO carriage status, are currently fashionable subjects in the US. However, many European experts are reluctant to use this preventive approach on a broader basis outside of outbreak settings. They are concerned about the selection of resistant strains, especially related to increasing mupirocin and chlorhexidine use. Resistance to these agents will certainly increase in the United States in the next 5 years and render less effective an essential preventive measure for surgical patients at high risk of postoperative MRSA infection.

Aaron Milstone: The concept of a "universal" approach is rapidly spreading in infection control. This concept is emerging through the use of universal barriers (donning gloves, or gowns and gloves, for all patient contact) and universal treatment (daily chlorhexidine bathing and/or intranasal mupirocin application for all patients). These approaches are referred to as horizontal infection control measures that may prevent the spread of all organisms, not simply MRSA. Data are emerging on the efficacy of these universal approaches. A number of outstanding issues remain, including: (1) Are they cost-effective to prevent undesired outcomes? (2) Will antibiotic resistance and/or antiseptic resistance emerge with universal application? (3) Are these treatments safe in all populations (e.g., safety of off-label use of mupirocin and chlorhexidine in neonates, negative psychosocial outcomes, etc.)? Although these universal approaches have great promise, additional surveillance and outcome data are needed before they should be widely implemented.

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