Preventing Lethal Hospital Outbreaks of Antibiotic-Resistant Bacteria

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In 2011, a strain of *Klebsiella pneumoniae* resistant to multiple antibiotics, including carbapenems, was identified in the intensive care unit (ICU) of the Clinical Center of the National Institutes of Health (NIH).[1] This organism has since colonized at least 19 patients and may have caused seven deaths among patients with severe coexisting conditions. Although the spread of the organism was traced through clinical epidemiologic investigation and whole-genome sequencing, it was curtailed by "rigorous infection-control procedures." What does this episode tell us about how to mitigate the risk of future outbreaks?

The threat of infections due to multidrug-resistant organisms (MDROs) is increasing. Methicillin-resistant *Staphylococcus aureus* (MRSA) has attracted the most attention, but multidrug-resistant gram-negative rods (MDR-GNRs) are more menacing. No effective drugs are available to treat some life-threatening MDR-GNR infections, and there are few new antimicrobials in development. Resistance to cephalosporins is so widespread that many clinicians turn to carbapenems for serious infections, but as their use has increased, so has resistance. The problem is not confined to enteric gram negatives, as physicians faced with treating patients infected with acinetobacter, pseudomonas, and other pan-resistant strains are discovering. Resistance that develops in one corner of the world can spread quickly, as demonstrated by MDR-GNRs containing New Delhi metallo-beta-lactamase 1.

In the NIH outbreak, molecular epidemiologic investigation provided insights into the spread and increasing antibiotic resistance of klebsiella. But the truth is that we already know how MDROs spread. Reliable adherence to basic infection control practices is the key to interrupting transmission in our hospitals.

MDROs are transmitted mainly on the hands of caregivers who do not practice effective hand hygiene after every contact with patients and their environment. Once hospitals have trained clinical personnel, verified that they know how to use alcohol-based hand rubs and soap and water, and placed full, operating dispensers and sinks where personnel can use them during routine care, anything less than complete adherence to hand-hygiene guidelines constitutes a violation of sound practice and requires accountability. Since some MDROs (especially gram-positive bacteria and acinetobacter) can survive for prolonged periods, fastidious cleaning and disinfection are also essential. In the NIH outbreak, klebsiella survived on a ventilator that had been cleaned three times with two different disinfectants. Environmental services personnel are as much a part of the MDRO containment net as doctors and nurses. Environmental infection control is not the place for hospitals to cut corners when scrutinizing their bottom line.

Most ICU infections — even in severely immunosuppressed patients — are attributable to invasive devices, such as central venous catheters, ventilators, and urinary catheters. We know how to prevent these infections; even in patients colonized with MDROs, infection is unlikely if we adhere to established practices. Although progress in reducing harm related to infections in U.S. hospitals has been slow, rates of central-line–associated bloodstream infections are decreasing through reliable application of evidence-based "bundles" of care practices and decision-support checklists, especially when combined with strong leadership commitment, teamwork, communication, peer behavior norms, real-time feedback of adherence data, and accountability.

Overuse of antibiotics promotes resistance in individual hospitals and contributes to the global emergence and spread of MDROs. Limited progress has been made despite the fact that sound guidance has been available for more than 15 years.[2] "Antimicrobial stewardship" — structured guidance and support for responsible selection and utilization of antimicrobial agents — is gaining traction in the United States and abroad, although evidence that stewardship programs

Interventions for Reducing Antibiotic Exposure in Hospitals.

Intervention	Comments
Promote clear, accessible decision support for appropriate duration of antibiotic therapy	Target common diagnoses and provide links to evidence
Use standardized order sets	Clearly define the appropriate antimicrobial agent, dose, and duration of treatment
Make the antibiotic indication visible at the point of care	Potential strategies include requiring the indication to be specified at the time the order is written and highlighting the indication on the medication administration record
Include start day, day of treatment, and expected duration in documentation of patient care	Provide visible reminders of the amount of antibiotic received and expected, facilitating awareness and daily decision making
Implement an antibiotic "time out" after 72 hours of treatment	Promotes timely, team-based assessment of whether antibiotic therapy can be discontinued or de-escalated
Send appropriate cultures before starting antibiotics	Positive cultures help to tailor regimens to the narrowest spectrum appropriate; negative cultures reduce clinicians' anxiety about discontinuing unnecessary therapy
Implement prospective-audit-with-feedback strategies and build an organizational culture in which feedback is viewed as valuable input toward enhancing safety and quality of care	Engages frontline clinicians and tracks progress

are having an effect on the development of resistance (as opposed to other outcomes, such as *Clostridium difficile* infections, the cost of antibiotics, or the suffering and costs associated with adverse drug events) remains sparse. Because reduced antibiotic use should be associated with less resistance, embedding the major tenets of stewardship into routine frontline work is essential. Antimicrobial stewardship encompasses a broad array of strategies,[3] but a parsimonious set of interventions aimed at reducing exposure to antibiotics may have the greatest effect on resistance (see table).

The klebsiella that killed patients at the NIH was brought in by a patient transferred from a New York City hospital. It took microbiologists 4 weeks to acquire screening media that had been validated for cultures from the rectum — the most important site of colonization for enteric gram-negative organisms. Although selective media have been developed for identifying organisms that produce extended-spectrum beta-lactamases or *K. pneumoniae* carbapenemase, they have not been approved by the Food and Drug Administration and are not in common use in the United States. We urgently need screening media (or real-time genomic tests) that can be deployed quickly to identify patients who are colonized with MDROs that surveillance networks have identified as emerging threats. In essence, hospitals should create a cordon sanitaire to identify and isolate patients transferred from other hospitals or chronic care facilities, especially when they come from communities where specific MDROs are known to be problematic. Facilities transferring patients should notify the receiving institution about their antibiotic-resistance problems.

Customized screening media can also be used for "ring containment" should patients be exposed to other patients who have been colonized. Some have advocated screening of all patients on admission for certain MDROs, especially MRSA. The cost-effectiveness of this approach remains controversial; screening for only one organism while ignoring other potentially lethal and difficult-to-treat bacteria seems imprudent. The challenge is even more complicated for gram negatives; it remains unclear which organisms merit isolation precautions, and there is no validated method whereby colonized patients can be "screened off" of precautions. This knowledge gap is especially problematic with regard to children, for whom extended isolation poses unique challenges. Studies focused on the duration of colonization and the effectiveness of targeted screen-

ing for MDR-GNRs are desperately needed.

Incorporating these fundamental prevention and control practices into the daily life of the hospital is difficult, as demonstrated by persistently low rates of adherence even in the country's most prestigious institutions. The Department of Health and Human Services and many organizations have invested heavily in programs aimed at improving performance, but hospitals often approach each infection individually rather than redesigning frontline systems to facilitate adherence to best practices — for example, incorporating a set of critical practices, such as timely removal of invasive devices and "de-escalation" of antibiotic treatment (including narrowing or discontinuing antibiotics once culture results are available), into a bedside checklist. Multidisciplinary care pathways can incorporate standing-order sets, checklists, and prompts (such as alerts to consider "sedation vacation" for ventilated patients) that can facilitate not only adherence but also real-time data collection and feedback that reinforce social norms. Enhanced data collection can be accomplished through "random audits"[4] that target one key aspect of evidence-based care at least weekly on rounds, with the team checking adherence on a simple form at each bedside and sharing a tally and strategies for improvement at the end of rounds. This data collection should be a seamless part of work, not extra labor performed by someone else.

Even fastidious adherence to evidence-based practice does not guarantee immunity from MDR-GNR outbreaks. Although relatively rare, these outbreaks require ongoing vigilance, rapid epidemiologic investigation, and prompt response.[5] Common-source outbreaks caused by contaminated solutions or equipment still occur despite advances in sterilization and disinfection, elimination of multidose containers, and procedures designed to minimize contamination during use. New resistant pathogens may emerge suddenly and escape the growing global surveillance network, arriving at the hospital door unheralded. But if hospitals develop reliable, evidence-based systems to minimize the MDRO threat, they will be able to refocus on developing innovative approaches to intercepting and mitigating new dangers.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Microbial Stowaways in Topical Antiseptic Products

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In the 1970s, the Food and Drug Administration (FDA) developed regulatory pathways for a number of active drug ingredients that were on the market but had not been approved by the FDA. Antiseptic drug products fall into one class of drugs that was included in the regulations that resulted from the expert reviews of the 1970s. At the time, it was assumed that antiseptic drug products were free of microbial contamination because of their pharmacologic activity. The need for sterile manufacture for these products was therefore not considered. In recent years, however, there have been published reports linking outbreaks of infection to antiseptic products that