Carbapenem-Resistant Enterobacteriaceae: A Call for Cultural Change

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Starting in the summer of 2011, a cluster of infections caused by carbapenem-resistant Enterobacteriaceae (CRE) occurred in the National Institutes of Health Clinical Center (NIHCC). Over 15 months, 18 patients acquired a single CRE strain and 7 highly immunocompromised patients died of CRE infection. Four patients' bloodstream isolates became resistant to all antibiotics. Aggressive and costly implementation of multiple infection control interventions (**Table**) (1) ultimately controlled transmission. Carbapenem-resistant Enterobacteriaceae infections have become a major threat to health care facilities throughout the world and can be particularly devastating for immunosuppressed patients, with mortality rates exceeding 50% (1). Our experience with this devastating cluster (2) led us not only to reflect on the past but also to envision a way forward in managing CRE and other multidrug-resistant organisms more effectively.

Although equipment and environmental surfaces are probably important in spreading these organisms, our experience leads us to believe that the key to controlling the spread of CRE is meticulous adherence to infection control protocols, particularly hand hygiene. Observations in the mid-19th century by Oliver Wendell Holmes and Ignaz Semmelweis about the role of health care personnel in transmitting infection provide a humbling backdrop to the current struggles with multidrug-resistant organisms (3, 4).

Although the health care industry has had more than 150 years to assimilate these facts, it has not sufficiently modified its culture to establish hand hygiene as a fully consistent patient care behavior (5). Without effective antimicrobials, we must rely on primary prevention strategies (for example, handwashing) to reduce transmission.

We can no longer accept a permissive culture that condones shortcuts and does not place the highest premium on patient safety. We need a true cultural revolution in infection control. The time for this transformation is ripe, given the current increased focus on patient safety, evidence-based medicine, and adherence to practice guidelines that can provide a platform from which to launch such a revolution. Its success will depend on several distinct elements, each of which played a significant role in our CRE struggles.

First, complete vigilance and scrupulous consistency in adhering to infection prevention principles is critical. Templates for human performance at this level of precision can be found in other high-reliability organizations (for example, air traffic control, computer manufacturing, and the nuclear power industry). Such discipline must be incorporated into health care with equal rigor. Examples of this vigilance include the effective use of targeted microbial surveillance and direct monitoring of each health care provider's adherence to infection control precautions that have been proven to interrupt pathogen transmission. Both strategies were essential components of our NIHCC interventions. As our cluster unfolded, we broadened microbial surveillance from taking cultures only from ICU patients to including all hospitalized medical–surgical patients; patients transferred from other institutions; and, ultimately, all hospitalized patients. We hired monitors to observe directly that required precautions were followed 100% of the time in the care of CRE-colonized patients. On the basis of our prior experience (6), we concluded that around-the-clock direct observation was the only way to assure adherence. Whereas direct observation is costly and labor-intensive, the margin of error for adherence is infinitesimally small and the cost of nonadherence (patient morbidity and mortality) is unacceptably high.

Second, progress in molecular medicine (specifically, molecular diagnostics and genomics) may allow us to investigate problems efficiently and with greater scientific specificity and credibility than before (7). Such techniques will rapidly broaden the health care epidemiology science base and also permit hospitals to initiate investigations while the "'trail is still warm." In our cluster, we relied heavily on existing rapid diagnostic methods, such as mass spectroscopy, and developed innovative ways for rapidly identifying CRE in patient specimens, including newer technologies for direct identification in submitted specimens. This accelerated the process from days to minutes. Although some of these technologies are currently experimental or prohibitively expensive, they will probably become more accessible in the coming months or years.

In our cluster, whole-genome sequencing provided definitive insight into a web of silent transmission that would have been almost impossible to elucidate by any other technique. By integrating single-nucleotide variations in patients' isolates with data from epidemiologic investigations, our collaborators created a definitive transmission map that helped identify where our safety net had failed. This prompted us to broaden microbial surveillance and redouble efforts to monitor adherence to infection control precautions.

Third, we need strategies to preserve the existing antimicrobial armamentarium. Such strategies should focus on improving institutional antimicrobial stewardship and implementing molecular diagnostic techniques that allow precise and rapid targeting of therapies for infectious pathogens to facilitate prompt modulation of broad-spectrum, empirical coverage to targeted, narrow-spectrum therapy (8, 9).

The fourth critical element relates to the development of new antimicrobials. The number of "new molecular entity" antimicrobials currently available for practice is strikingly small. Novel drugs targeting unique enzymes that

Table. **Interventions Used to Combat the Spread of CRE at the NIHCC**

Intervention	Basis	Comment
Careful engagement of all stakeholders involved in the care of infected and colonized patients	Guideline (1)	Critical to successful implementation of prevention and control measures
Communication with hospital staff, campus staff, local and state public health authorities, and patients about issues relating to the outbreak that are relevant to each group	Guideline (1)	Critical to successful engagement of stakeholders
Aggressive microbial surveillance		
Microbial surveillance of all patients who are admitted to medical, surgical, or pediatric wards of the hospital, with empirical isolation and additional surveillance of patients who have been hospitalized in the United States in the past week or abroad in the past 6 mo	Guideline (1)	Crucial for identifying new cases and preventing transmission from patients who have had potentially high-risk exposures
Targeted, twice-weekly microbial surveillance of patients hospitalized in the highest-risk units	Empirical	Frequency driven by the severity of illness/immunosuppression
Monthly whole-house microbial surveillance of all medical–surgical patients	Guideline (1)	Crucial for identifying new cases/transmission
Use of selective media to identify resistant pathogens	Guideline (1)	Selective media are expensive
Sampling multiple sites on each patient to decrease sampling error and capture different pathogens in their respective niches	Empirical	Driven by local microbiology; prior outbreaks of other multidrug-resistant organisms
Rapid identification of resistant organisms (e.g., MALDI-TOF MS)	Routine at NIHCC	Equipment expensive; output extremely rapid and remarkably useful
Rapid characterization of resistance mechanisms (for example, PCR testing for carbapenemase genes)	Guideline (1)	–
Whole-genome sequencing to characterize the spread and investigate mechanisms of health care–associated spread	Investigational	Did not "unravel" our outbreak but identified silent transmission and changed our strategy (see text for details)
Implementation of enhanced contact precautions for all infected or colonized patients	Empirical	Intensity of the intervention due to the severity of illness/immunosuppression
Geographic and personnel cohorting	Guideline (1)	Difficult to implement for some categories of personnel
Equipment dedicated to be used solely for cohorted patients, to the extent possible	Guideline (1)	–
Daily chlorhexidine baths for patients	Guideline (1)	Unable to determine efficacy in our setting
Monitoring adherence to all infection control precautions, including unwavering attention to performance of appropriate hand hygiene procedures	Empirical	Strategy was useful in prior outbreak (6), and implementation was associated with improved adherence
Attention to the details of environmental disinfection, including consideration of use of new decontamination technologies (e.g., hydrogen peroxide vapor or ultraviolet light)	Empirical	Intensity of the intervention due to the severity of illness/immunosuppression of our patients; a minuscule inoculum may ultimately prove lethal

CRE = carbapenem-resistant Enterobacteriaceae; MALDI-TOF MS = matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; NIHCC = National Institutes of Health Clinical Center; PCR = polymerase chain reaction.

produce resistance, such as carbapenemases or metallo-β-lactamases, may extend the useful life of existing antimicrobials. Development of such therapeutic compounds must be an integral part of the revolution in medical culture (10).

The fifth critical element relates to changes in administrative culture, even in times of constrained resources. Institutions must provide appropriate support for patient safety and infection prevention activities. During our CRE outbreak, our hospital administration restructured priorities in real time to provide needed personnel and financial support.

Finally, we must develop effective strategies to convince health care personnel and the public of the significance of these issues in a way that leads to enduring changes in behavior without promoting fear. During our outbreak, we received telephone calls asking whether it was safe to drive past the NIH campus. In another instance, a visit from corporate executives to another facility on our campus was cancelled because of fear that they might contract CRE.

Our experience with CRE is being mirrored at institutions around the country, and CRE are already endemic in hospitals along the U.S. East Coast. We all await, with trepidation, the occurrence of similar outbreaks caused by the "New Delhi metallo-β-lactamase producers."

Advances in molecular technology have armed us with new diagnostic strategies. Given the increased focus on drug development, we hope that the near future will also bring the development of new antimicrobials (10). For the short term, however, we must modify health care behavior to provide the highest possible levels of patient safety, at least in part by embracing changes proposed more than 150 years ago.

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