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.

From the Division of Infectious Diseases, Boston Children's Hospital (T.J.S., D.A.G.); the Department of Pediatrics, Harvard Medical School (T.J.S., D.A.G.); and the Departments of Immunology and Infectious Diseases and Epidemiology, Harvard School of Public Health (D.A.G.) — all in Boston; and the Institute for Healthcare Improvement, Cambridge, MA (D.A.G.).

1. Snitkin ES, Zelazny AM, Thomas PJ, et al. Tracking a hospital outbreak of carbapenem-resistant *Klebsiella pneumoniae* with whole-genome sequencing. Sci Transl Med 2012; 4:148ra116.
2. Goldmann DA, Weinstein RA, Wenzel RP, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. JAMA 1996;275: 234-40.
3. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.
4. Ursprung R, Gray JE, Edwards WH, et al. Real-time patient safety audits: improving safety every day. Qual Saf Health Care 2005; 14:284-9.
5. Zawacki A, O'Rourke E, Potter-Bynoe G, Macone A, Harbarth S, Goldmann D. An outbreak of *Pseudomonas aeruginosa* pneumonia and bloodstream infection associated with intermittent otitis externa in a healthcare worker. Infect Control Hosp Epidemiol 2004;25:1083-9.

DOI: 10.1056/NEJMp1212370

Microbial Stowaways in Topical Antiseptic Products

Christina Y. Chang, M.D., M.P.H., and Lesley-Anne Furlong, M.D.

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

were contaminated with microbial organisms, and some products have been recalled for that reason.

The FDA-approved indications for these products include "for preparation of the skin prior to surgery," "for preparation of the skin prior to an injection," and "helps reduce bacteria that potentially can cause skin infection." Off-label uses (e.g., catheter maintenance) are prevalent in clinical practice and have been incorporated into practice guidelines from the Centers for Disease Control and Prevention (CDC). The nonprescription status of topical antiseptic products allows for direct access by consumers, although these products are marketed predominantly to health care facilities. Given their wide use, evidence that topical antiseptic products may become contaminated with microbial organisms (during manufacture or use) — and that they can cause infection at sites of injection, surgery, or existing wounds — has raised concerns.

Outbreaks associated with the use of contaminated antiseptic products (see table) have been reported in journals[1] and to the CDC.[2,3] Clinical infections associated with a variety of approved products have been reported to the FDA as well, and a number of product recalls have ensued.[4] The reported outcomes range from localized infections at injection sites to systemic infections resulting in death. The reports implicate all commonly used antiseptic categories, including alcohol, iodophors, chlorhexidine gluconate, and quaternary ammonium products. Some potentially pathogenic organisms, such as *Bacillus cereus*, *Burkholderia cepacia*, *Pseudomonas aeruginosa*, and *Serratia marcescens*, have been implicated in more than one outbreak.

Although the scope of nosocomial infections associated with contaminated antiseptic products is difficult to assess, it is most likely broader than has been indicated by postmarketing reports and the medical literature. Several factors may limit the identification of infections related to antiseptic products. Health care providers may not consider these products as a potential source of postprocedural infection because they assume that antiseptic properties preclude microbial survival. Cases of contamination might be underreported, since epidemiologic investigation and infection workups require a high index of suspicion on the part of the treating clinician. In addition, single-use containers are typically discarded at the conclusion of a surgical procedure, so the residual product may not be available for investigation when an infection becomes apparent. Confirmation of contamination often requires the testing of other units from the same manufacturing lot as the suspect product; however, contamination may not occur consistently within a lot, confounding the infection workup. Because the background rate of postoperative infection varies with the type of procedure, patient demographic characteristics, and hospital environment, it may be difficult to detect an increase in the rate of postprocedural infections stemming from contaminated antiseptic products. Although the CDC collects data on surgical-site infections on the basis of diagnoses at hospital discharge, infections treated in ambulatory settings may not be captured. Finally, the reporting of nosocomial infections to regulatory agencies is voluntary, and medicolegal considerations and time constraints may deter hospitals and health care providers from reporting.

Outbreaks associated with the use of contaminated antiseptic products have led to some product recalls. Reported outcomes range from localized infections at injection sites to systemic infections resulting in death.

Contamination of antiseptic drug products may occur either during manufacturing (intrinsic contamination) or during manipulations by the end user (extrinsic contamination). Extrinsic contamination can arise from dilution of the product with nonsterile water or from storage in nonsterile containers. Users should also be aware that microbial contamination can occur when they are opening containers or diluting and storing solutions under nonsterile conditions. The period during which a container, once opened, can remain safe from extrinsic contamination is unknown. Awareness on the part of

Infections Associated with Contaminated Antiseptic Products.

Product and Mechanism of Contamination	Clinical Outcome	Responsible Organism*
Iodophor, including povidone-iodine and poloxamer-iodine		
Intrinsic contamination	Peritonitis, replacement of dialysis catheter, pseudoperitonitis, pseudobacteremia, and infection at dialysis catheter insertion site	*Burkholderia cepacia* and *Pseudomonas aeruginosa*
Extrinsic contamination	None reported	—
Alcohol product		
Intrinsic contamination	Pseudobacteremia	*Bacillus cereus*
Extrinsic contamination	Bacteremia	*Burkholderia cepacia*
Chlorhexidine gluconate alone or with cetrimide		
Intrinsic contamination	None confirmed	—
Extrinsic contamination	Death, bacteremia, removal of indwelling central venous catheter in patients with cancer, replacement of dialysis catheter, pseudobacteremia, wound infection, and colonization	*Burkholderia cepacia*, *Achromobacter xylosoxidans*, *Ralstonia pickettii*, and *Serratia marcescens*
Quaternary ammonium compound, including benzalkonium chloride and benzethonium chloride		
Intrinsic contamination	None confirmed	—
Extrinsic contamination	Death, bacteremia, septic arthritis requiring prolonged antibiotic therapy (occasionally necessitating surgery), and injection-site infection	*Burkholderia cepacia* and *Mycobacterium abscessus*

* Responsible organisms are listed only for cases in which genetic-fingerprinting methods have confirmed the source of contamination. Contamination of antiseptic drug products may occur either during manufacturing (intrinsic contamination) or during manipulations by the end user (extrinsic contamination).

users may reduce the likelihood that multidose antiseptic products will become contaminated.

In August 2009, the FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee considered whether sterile conditions of manufacture should be mandated for topical antiseptic products intended for use on nonintact skin.[5] Advisory committee members discussed the uncertainties of the costs and benefits and noted that the extent of the clinical problem was unclear. The committee also raised concerns about whether potential requirements for sterile manufacture might adversely affect the purity and quality of active ingredients or the integrity of product packaging. The committee did not come to a final decision, but they observed that the labels of two foreign-made topical chlorhexidine gluconate products claimed that they had been manufactured under sterile conditions.

The FDA is continuing to evaluate the issues surrounding a requirement for the sterile manufacture of antiseptic products. It is important that health care providers be aware that topical antiseptic products, if contaminated, pose a risk of infection and that particular microbes isolated from clinical specimens have been traced to the contamination of such products (see table). The isolation of unusual organisms (e.g., *Bacillus cereus*) after the use of topical antiseptic products should trigger an investigation of possible contamination stemming from an antiseptic product.

We also encourage the prompt reporting of pertinent findings

to the FDA to help us better understand the causes and scope of microbial contamination in antiseptic products. Finally, the FDA is holding a public hearing, scheduled for December 12 and 13, 2012, and invites input concerning the microbial contamination of these products.

Editor's note: Further information about the FDA hearing on microbial contamination of topical antiseptic products may be found at www.fda.gov/Drugs/NewsEvents/ucm319621.htm.

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

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

1. Weber DJ, Rutala WA, Sickbert-Bennett EE. Outbreaks associated with contaminated antiseptics and disinfectants. Antimicrob Agents Chemother 2007;51:4217-24.
2. Contamination of alcohol prep pads with *Bacillus cereus* group and *Bacillus* species — Colorado, 2010. MMWR Morb Mortal Wkly Rep 2011;60:347.
3. Allergy injection-associated *Mycobacterium abscessus* outbreak — Texas, 2009 (http://idsa.confex.com/idsa/2010/webprogram/Paper2955.html).
4. Food and Drug Administration. Archive for recalls, market withdrawals & safety alerts (http://www.fda.gov/Safety/Recalls/ArchiveRecalls/default.htm).
5. Meeting transcript from the Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM179891.pdf).

DOI: 10.1056/NEJMp1212680