CONCISE COMMUNICATION

Bacterial Contamination of an Automated Pharmacy Robot Used for Intravenous Medication Preparation

David Cluck, PharmD;[1] John C. Williamson, PharmD;[1] Marty Glasgo, BSPharm;[1] Daniel Diekema, MD;[2] Robert Sherertz, MD[1]

Multiple cultures were positive for *Bacillus cereus* during routine quality assurance testing of a pharmacy robot that prepares intravenous medications. An investigation confirmed bacterial contamination of the robot as well as drug product made by the robot. The process and outcomes of the investigation are described in this report.

Infect Control Hosp Epidemiol 2012;33(5):517-520

Healthcare systems today are steadily increasing their use of advanced technology and automation. Recent advances have facilitated the use of automation in drug distribution and preparation, including intravenous medications. The integration of such automation into the pharmacy workflow results in a multitude of benefits, including increased productivity and efficiency as well as improved patient safety. In 2008, Wake Forest Baptist Medical Center implemented the Intellifill i.v. (Baxa) for the preparation of small-volume intravenous medications. This report describes an investigation of bacterial contamination of this robot.

ROBOT DESCRIPTION

The Intellifill i.v. automates the preparation of small-volume intravenous medications with minimal human manipulation of drug product. Medications are prepared in an aseptic environment that meets US Pharmacopeial Convention 797 quality system requirements, whether used inside or outside the pharmacy's clean room.

The Intellifill i.v. prepares medications by extracting drug product from a bulk source and aliquoting it to syringes. The bulk source can be vials (vial mode) or large-volume intravenous bags (reservoir mode). During vial mode, empty syringes are uncapped and held in place on a dial. Before filling the syringe, the bulk vial is uncapped and swabbed with isopropyl alcohol by inverting the vial and rubbing its septum across an alcohol soaked wick (Figure 1). A needle is then inserted into the vial through the septum, and a pump facilitates aspiration of the dose required to fill each syringe. A similar process occurs in reservoir mode. However, the reservoir mode does not utilize a needle since there is no septum to puncture. Instead, a large-volume bag is placed within the machine and attached to tubing that facilitates flow of drug from the bag to the syringes.

Many steps are taken to prevent contamination. Operators are appropriately garbed when manipulating the robot, including sterile gown, head cover, gloves, and mask. The robot automatically signals users to conduct routine cleaning. The cleaning process includes wiping surfaces manually with 70% isopropyl alcohol as well as "fogging" with alcohol, using a spray bottle to clean parts not easily accessible. In addition, certain parts of the machine are changed routinely, such as lines used to transfer drug from vial to syringe. Last, air flowing throughout the robot's chamber is filtered by a high-efficiency particulate air filter with positive pressure air flow.

When vial mode is in operation, the needle used to puncture vials is rinsed inside and out at a centrally located washing station (Figures 1, 2). To rinse the outside of the needle, it is inserted into a cannula at the washing station that is filled with sterile water. To rinse the inside of the needle, the machine directs sterile water to flow through the needle. Water coming out of the needle and overflow from the cannula are drained into a basin and ultimately through a tube to a container held in a separate, nonsterile compartment of the machine.

QUALITY ASSURANCE

As part of the quality assurance process, 10 syringes of product are prepared using trypticase soy broth (TSB) instead of actual drug. This is referred to as media challenge. The prepared TSB syringes are incubated for 7 days and then inspected for microbial contamination by assessing turbidity. Media challenges are run immediately after cleaning (before machine use) and 24 hours after the machine has been used (just before the next scheduled cleaning).

To assess surface bioburden, agar paddles are pressed against 7 locations specified by the manufacturer. To assess air quality, an agar paddle is placed in each corner of the robot's compartment, exposed for 30–60 minutes, and then incubated for 7 days. The air samples are not expected to have any growth. In contrast, some users allow up to 5 colony forming units on paddles applied to surfaces that are frequently handled (eg, doors). These air and contact samples must be monitored at least weekly both before and after the robot has been cleaned.

PROBLEM IDENTIFICATION

The Intellifill i.v. has been in use at Wake Forest Baptist Medical Center since 2008. During a 2-week period in early December 2010, 13 out of 20 TSB syringes prepared after cleaning were turbid. Three out of 10 were turbid the first week, followed by 10 out of 10 the next week. All positives were prepared in vial mode. This prompted the immediate suspension of both vial and reservoir mode operations. In addition, drug product prepared at this time was quarantined. Samples of the drug product were frozen for future testing.

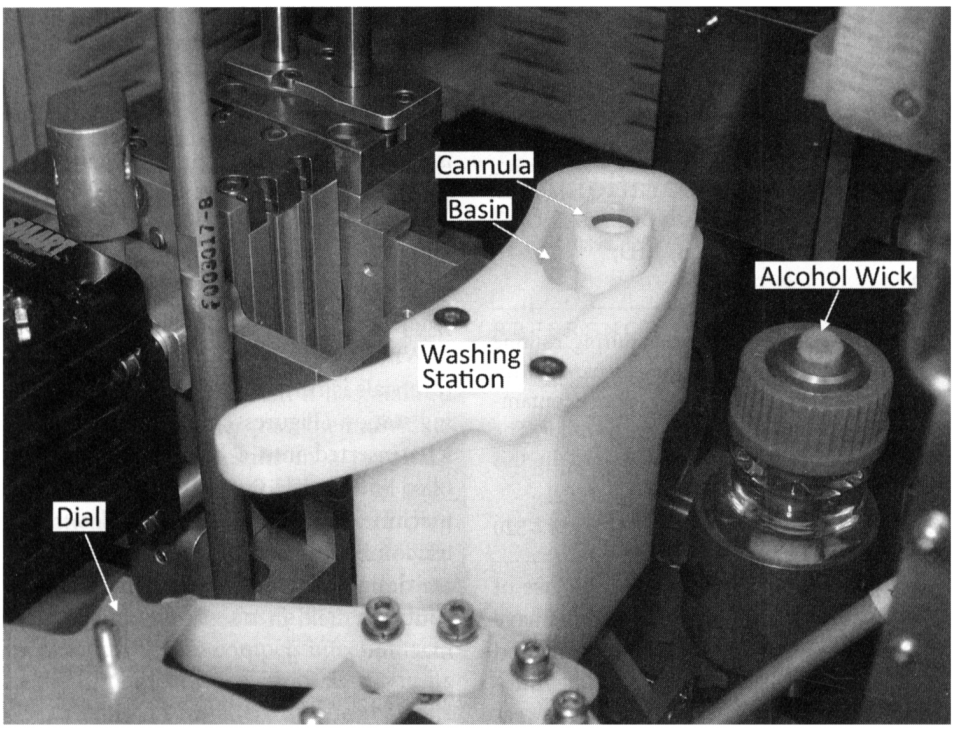

FIGURE 1. Washing station and alcohol wick. A color version of this figure is available in the online edition of the journal.

Culture of the TSB syringes revealed *Bacillus cereus*. Air and contact samples obtained at this time were negative.

INVESTIGATION

A review of pharmacy records indicated that 10 doses of drug product had been dispensed from pharmacy before the TSB syringes were found to be positive. An examination of the electronic medical record of these 10 patients revealed no positive blood cultures, and none of the patients developed signs or symptoms of infection. A list of patients who had positive blood cultures for *Bacillus* species before the discovery of contaminated TSB syringes was obtained from the clinical microbiology lab. None of these patients received drug product prepared by the Intellifill i.v.

To determine the source of contamination, a series of cultures was obtained at various sites within the Intellifill i.v. apparatus. Initially, cultures were obtained of the dial and the cap of the wick bottle. Cultures of these sites were negative. Subsequently, the isopropyl alcohol used in the robot's operation was investigated, in part due to a recent recall of isopropyl alcohol pads that were contaminated by *Bacillus*.[1,2] Four alcohol sources were cultured: the wick bottle, the spray bottle used in cleaning, and 2 bulk bottles of alcohol (1 fresh and 1 opened). A small aliquot of 2–4 mL from each source was placed in a 40-mL blood culture bottle (VersaTREK Instrumentation, Trek Diagnostic Systems) and sent to the clinical microbiology laboratory for processing in the same way clinical samples are processed. All cultures of alcohol were negative.

Finally, cultures were obtained at the washing station, since this served as a drain to an external, nonsterile container. In addition, it was well known by Intellifill i.v. operators that the container had a foul smell occasionally, suggesting the presence of bacteria. Two cultures were obtained at the washing station (Figure 1): the rim of the basin and the top of the cannula used to rinse the outside of the needle. Both of these cultures were positive with *Bacillus cereus*.

With a possible source of contamination identified, further cultures around the washing station were obtained to determine the extent of contamination, including the floor of the washing station, the top of the drainage tube (where it connects to the drain), the bottom of the drainage tube (where it connects to an external container), and the floor of the robot's compartment adjacent to the washing station. All of these cultures were positive for *Bacillus cereus*.

The isolates were frozen and sent to a reference laboratory for typing using pulsed field gel electrophoresis (PFGE).[3] All isolates from the Intellifill i.v. apparatus, all isolates from TSB samples, and 3 of 6 isolates from drug product (lidocaine) had indistinguishable PFGE patterns. The other 3 isolates from drug product were not related and may represent another contaminant that was not present in sufficient quantity to be detected in quality control sampling or were introduced during processing of the samples.

DISCUSSION

To our knowledge, this is the first published report of a pharmacy robot being contaminated with *Bacillus* with resultant

https://doi.org/10.1086/665316 Published online by Cambridge University Press

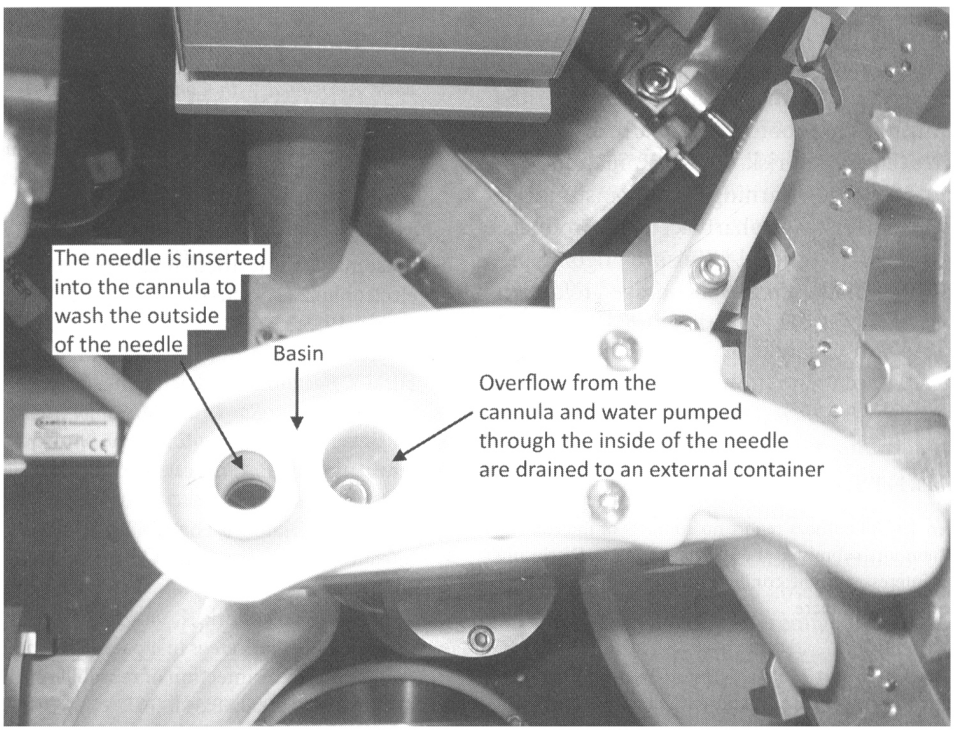

FIGURE 2. Overhead view of washing station. A color version of this figure is available in the online edition of the journal.

contamination of intravenous drug product. *Bacillus* is a gram-positive, spore-forming bacterium that is becoming increasingly prevalent as a cause of healthcare-associated infections. Its spore-forming ability provides difficulties with disinfection. *Bacillus* outbreaks have been reported in association with contaminated hospital linens, nonsterile gloves, reused towels, reusable ventilator airflow sensors, ventilator circuits, contaminated calcium gluconate solution, contaminated washer/decontaminator, and contaminated alcohol prep pads.[2,4-10] Especially pertinent to this investigation is the fact that *Bacillus* spores are not killed by alcohol or most commonly used disinfectants, and this has played a role in 1 outbreak[2] and 1 pseudo-outbreak.[11]

We feel that the washing station of the Intellifill i.v. was the source of contamination. It was the only culture-positive site, and the PFGE results implicate this site, as evidenced by a pattern matching those found in TSB and drug product. That being said, we may never know how the organism was first introduced into the sterile environment of the robot. There is risk of contamination from human hands associated with cleaning and setup. Objects are routinely exchanged within the compartment, such as tubing, drug vials, and intravenous fluid bags. Although the contents are sterile, the outside of drug vials and fluid bags are not.

Once the organism was introduced, the tubing from the washing station to the external container may be what allowed the organism to persist. The washing station and the tubing to the container are not routinely cleaned beyond exposure to alcohol during fogging. The drainage container is not considered a sterile part of the robot, which allows it to serve as a reservoir to seed the washing station, particularly if biofilm develops in the drain tubing. The company's recommendations to monitor the robot's environment do not involve surface testing of the washing station, and air sampling at the corners of the robot compartment could miss the washing station as a source of contamination because it is located in the center of the compartment. Furthermore, the company has no defined schedule for exchanging the tubing or the container.

The implications of contaminated intravenous product are potentially severe, most notably life-threatening bloodstream infections. Fortunately, the contamination was identified early, and no patient was harmed. The quality assurance methodology recommended by the manufacturer helped to prevent any adverse events. In retrospect, the risk could have been reduced further if media challenge was performed after each batch and drug product was quarantined until media challenge cultures return negative. However, potential delays in product availability must be considered before implementing this practice. Drugs with a short expiration date may no longer be suitable for production using Intellifill i.v. Rapid, nonculture bacterial detection techniques could be utilized to reduce turnaround time, but validation at a low level of contamination would be necessary.

To prevent other users of Intellifill i.v. from experiencing the same problem, the manufacturer should consider establishing a formal procedure for cleaning and maintaining the washing station, with more detailed recommendations to

https://doi.org/10.1086/665316 Published online by Cambridge University Press

change the drain tube, the container, and possibly the washing station itself. In addition, it is reasonable to expand existing quality assurance recommendations to include surface testing of the washing station and air sampling in the center of the compartment. Last, using the robot in the pharmacy's clean room could further decrease the risk of contamination.

Our findings should serve as a warning to other institutions that use automated systems to make pharmaceutical products. Quality assurance methods are critical to ensure ongoing patient safety. Likewise, manufacturers are encouraged to design such products that minimize risks of microbial contamination.

ACKNOWLEDGMENTS

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Affiliations: 1. Wake Forest Baptist Health, Winston-Salem, North Carolina; 2. Departments of Internal Medicine and Pathology, University of Iowa Carver College of Medicine, Iowa City, Iowa.

Address correspondence to David Cluck, PharmD, Bill Gatton College of Pharmacy, ETSU, Department of Pharmacy Practice, Box 70657, Johnson City, TN 37614 (cluckd@etsu.edu).

Received August 17, 2011; accepted November 24, 2011; electronically published March 16, 2012.

 0899-823X/2012/3305-0013$15.00. DOI: 10.1086/665316

REFERENCES

1. US Food and Drug Administration. *Triad Group Issues a Voluntary Nationwide Recall of All Lots of Alcohol Prep Pads, Alcohol Swabs, and Alcohol Swabsticks due to Potential Microbial Contamination.* Silver Spring, MD: US Food and Drug Administration, January 5, 2011. http://www.fda.gov/safety/recalls/ucm239219.htm. Accessed August 15, 2011.
2. Dolan SA, Dowell E, Littlehorn C, et al. Bacillus cereus *Bacteremia Associated with Contaminated Alcohol Prep Pads: Outbreak Investigation Followed by International Product Recall.* In: Program and abstracts of the Annual Scientific Meeting of the Society for Healthcare Epidemiology of America; April 1–4, 2011; Dallas, TX. Abstract LB 16.
3. Tenover FC, Arbeit RD, Goering RV, et al. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol* 1995;33:2233–2239.
4. Sasahara T, Hayashi S, Morisawa Y, Sakihama T, Yoshimura A, Hirai Y. *Bacillus cereus* bacteremia outbreak due to contaminated hospital linens. *Eur J Clin Microbiol Infect Dis* 2011;30:219–226.
5. Jeurissen A, Weyers L, Cossey V, Muller J, Schuermans A. Dissemination of *Bacillus cereus* in the burn unit due to contaminated non-sterile gloves. *J Hosp Infect* 2010;76:92–93.
6. Dohmae S, Okubo T, Higuchi W, et al. *Bacillus cereus* nosocomial infection from reused towels in Japan. *J Hosp Infect* 2008;69:361–367.
7. Kalpoe JS, Hogenbirk K, van Maarseveen NM, et al. Dissemination of *Bacillus cereus* in a paediatric intensive care unit traced to insufficient disinfection of reusable ventilator air-flow sensors. *J Hosp Infect* 2008;68:341–347.
8. Gray J, George RH, Durbin GM, Ewer AK, Hocking MD, Morgan ME. An outbreak of *Bacillus cereus* respiratory tract infections on a neonatal unit due to contaminated ventilator circuits. *J Hosp Infect* 1999;41:19–22.
9. Thuler LC, Velasco E, de Souza Martins CA, et al. An outbreak of *Bacillus* species in a cancer hospital. *Infect Control Hosp Epidemiol* 1998;19:856–858.
10. Bryce EA, Smith JA, Tweeddale M, Andruschak BJ, Maxwell MR. Dissemination of *Bacillus cereus* in an intensive care unit. *Infect Control Hosp Epidemiol* 1993;14:459–462.
11. Hsueh PR, Teng LJ, Yang PC, Pan HL, Ho SW, Luh KT. Nosocomial pseudoepidemic caused by *Bacillus cereus* traced to contaminated ethyl alcohol from a liquor factory. *J Clin Microbiol* 1999;37:2280–2284.