HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2020 July 18.

Published in final edited form as:

Clin Infect Dis. 2019 July 18; 69(3): 445–449. doi:10.1093/cid/ciy910.

Multistate Outbreak of *Burkholderia cepacia* Complex Bloodstream Infections After Exposure to Contaminated Saline Flush Syringes — United States, 2016–2017

Richard B. Brooks[#1,2], **Patrick K. Mitchell**[#1,3], **Jeffrey R. Miller**[3,4], **Amber M. Vasquez**[5], **Jessica Havlicek**[6], **Hannah Lee**[2], **Monica Quinn**[7], **Eleanor Adams**[7], **Deborah Baker**[7], **Rebecca Greeley**[8], **Kathleen Ross**[8], **Irini Daskalaki**[9], **Judy Walrath**[9], **Heather Moulton-Meissner**[10], **Matthew B. Crist**[10], **The *Burkholderia cepacia* Workgroup**

[1]Epidemic Intelligence Service, Division of Scientific Education and Professional Development, Centers for Disease Control and Prevention, Atlanta, GA, USA;

[2]Maryland Department of Health, Baltimore, Maryland, USA;

[3]Pennsylvania Department of Health, Harrisburg, PA, USA;

[4]Division of State and Local Readiness, Centers for Disease Control and Prevention, Atlanta, GA, USA;

[5]Epidemic Intelligence Service, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA;

[6]Baltimore County Health Department, Baltimore, MD, USA;

[7]New York State Department of Health, Albany, NY, USA;

[8]New Jersey Department of Health, Trenton, NJ, USA;

[9]Delaware Department of Health and Social Services, Dover, DE, USA;

[10]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

[#] These authors contributed equally to this work.

Abstract

Background: *Burkholderia cepacia* complex (Bcc) has caused healthcare-associated outbreaks, often in association with contaminated products. The identification of four Bcc bloodstream infections (BSIs) in patients residing at a single skilled nursing facility (SNF) within one week led to an epidemiological investigation to identify additional cases and the outbreak source.

Corresponding author: Richard B. Brooks, 201 W. Preston St., Room 330, Baltimore, MD 21201; zti6@cdc.gov; (410) 767-7395. Alternate corresponding author: Patrick K. Mitchell, 14-2 Dove Drive, Ithaca, NY 14850; Mitchell.patrick.k@gmail.com; (732) 277-4773.

Potential conflicts of interest

All authors: No reported conflicts of interest.

Methods: A case was initially defined as a blood culture yielding Bcc in a SNF resident receiving intravenous therapy after August 1, 2016. Multistate notifications were issued to identify additional cases. Public health authorities performed site visits at facilities with cases to conduct chart reviews and identify possible sources. Pulsed-field gel electrophoresis (PFGE) was performed on isolates from cases and suspect products. Facilities involved in manufacturing suspect products were inspected to assess possible root causes.

Results: An outbreak of 162 Bcc BSIs across 59 nursing facilities in 5 states occurred during September 2016–January 2017. Isolates from patients and pre-filled saline flush syringes were closely related by PFGE, identifying contaminated flushes as the outbreak source and prompting a nationwide recall. Inspection of facilities at the saline flush manufacturer identified deficiencies which might have led to the failure to sterilize a specific case containing a partial lot of product.

Conclusions: Communication and coordination among key stakeholders, including healthcare facilities, public health authorities, and state and federal agencies, led to the rapid identification of an outbreak source and likely prevented many additional infections. Effective processes to ensure the sterilization of injectable products are essential to prevent similar outbreaks in the future.

Summary:

An outbreak of 162 *Burkholderia cepacia* complex bloodstream infections in five states during November 2016–January 2017 was linked to contaminated pre-filled saline flush syringes, highlighting the importance of strong quality control measures in the manufacturing of sterile products.

Keywords

Burkholderia; healthcare-associated infections; outbreak; medical device contamination

Background

The *Burkholderia cepacia* complex (Bcc) is a group of closely related gram-negative, rod-shaped bacteria found in soil and water. Immune system impairment and lung disease, particularly cystic fibrosis, increase the risk of Bcc infection. Bcc can be spread through lapses in infection control, including indirect contact via environmental surfaces. Person-to-person transmission is possible but less common [1]. Additionally, numerous healthcare-associated Bcc outbreaks have been linked to Bcc-contaminated devices and liquid medications [2–6]. During the latter half of 2016, the Centers for Disease Control and Prevention (CDC) was actively investigating a multi-state outbreak of Bcc associated with contaminated liquid docusate sodium [7].

On September 22, 2016, Maryland Department of Health (MDH) was notified about a cluster of four patients admitted to the same hospital during September 12–19 with fever or sepsis with blood cultures positive for Bcc. All four patients resided at a single skilled nursing facility (SNF) in Baltimore County, and all were receiving intravenous (IV) antibiotics through central venous catheters (CVCs) at the SNF prior to symptom onset. We initiated an investigation to determine the scope of the outbreak, identify a source, and prevent additional illness.

Methods

Based on the characteristics of the first four identified cases, a case was initially defined as a blood culture yielding Bcc in a SNF resident receiving IV therapy after August 1, 2016. Given the ongoing CDC investigation into Bcc associated with contaminated docusate at the time, concern for a contaminated product was high, and therefore Maryland issued a multistate notification of their cases through the Epidemic Information Exchange (Epi-X) on September 28 [6]. CDC was contacted to determine whether other cases meeting this definition had been identified in other jurisdictions; CDC also assisted with coordination of the investigation. Through these efforts, additional cases were rapidly identified in Pennsylvania.

Public health authorities in Maryland and Pennsylvania visited affected facilities in late September 2016. The goal of the site visits was to conduct chart review, staff interviews, infection control observations, and evaluation of common product and medication exposures to identify possible infection sources. Detailed information was collected on antibiotic use, and the potential use of recalled products — including oral liquid docusate sodium — implicated in recent Bcc outbreaks. Products identified as potential sources were collected for testing, and the pharmacy that distributed suspect products was contacted for further information. Additional site visits and multi-agency coordinating calls were conducted as the investigation progressed.

Clinical isolates were sent to state public health laboratories or CDC for species confirmation and molecular typing by pulsed-field gel electrophoresis (PFGE) [8]. Suspected, unopened products were cultured, and product isolates also underwent PFGE to determine relatedness to clinical isolates. The U.S. Food and Drug Administration (FDA) investigated to identify potential sources of contamination, including inspection of procedures for and performance of manufacturing, compounding, and product release, receipt, storage, and distribution. The New Jersey Board of Pharmacy (NJBOP) worked with FDA and state health departments to investigate a pharmacy distributing suspect contaminated products.

Results

At the Maryland SNF, no infection prevention breaches were identified that could explain the Bcc cases. Most patients had received IV products through peripherally inserted central catheters (PICCs), many of which had been placed by a third-party agency at the SNF and were maintained by SNF health care providers. No previously recalled products, including docusate, were found. Common exposures identified among patients included presence of PICC lines and receipt of compounded IV antibiotics and saline flushes, though patients lacked documentation of the timing, quantity, and brand(s) of saline flushes they received. All IV products were supplied to the SNF by “Pharmacy A,” a New Jersey-based pharmacy, which serves only long-term and post-acute care facilities [9].

Following the Epi-X notification, the Pennsylvania Department of Health (PADOH) determined that four recently identified cases of Bcc BSI occurred in residents of two SNFs

that were also supplied by Pharmacy A. One patient received no IV antibiotics, but did receive normal saline solution and saline flushes from Pharmacy A. Personnel from Pharmacy A reported that since August 29 they had begun sourcing saline flush from a different manufacturer, Nurse Assist, Inc. (Haltom City, TX), because of a supply shortage.

On October 3, seven unopened Nurse Assist saline flushes from a single lot were cultured by PADOH Bureau of Laboratories and identified Bcc by Gram stain, oxidase, and Vitek® 2 Compact. PFGE performed by MDH on one isolate from these flushes revealed that it was indistinguishable from clinical isolates from patients in Maryland and Pennsylvania (Fig. 1). This PFGE pattern was distinct from those associated with the ongoing Bcc-contaminated docusate sodium outbreak. On October 4, Nurse Assist issued a voluntary recall of all unexpired lots of saline flush syringes, totaling 386,175 syringes nationwide [10]. All units of the implicated lot were shipped to one Pharmacy A distribution center, which was the only lot of Nurse Assist saline flushes dispensed by that distribution center. All identified cases were reported from SNFs served by this distribution center.

On October 5, the initial case definition was revised to require that cases received intravenous care at a facility using Nurse Assist saline flushes. Using this case definition, 162 cases of Bcc BSI with first positive blood culture during September 6, 2016–January 20, 2017 were identified (Fig. 2). Of these, 59 (36%) occurred prior to notification of public health authorities. Cases were identified in 59 facilities in five states (Delaware, Maryland, New Jersey, New York, and Pennsylvania). Median age at time of positive culture was 72 years (n=161). Sixteen (10%) “late onset” cases had the first positive blood culture collected more than one week after the product recall, including one more than 15 weeks after all product was reported to have been removed from the facility where the patient resided. Among 144 cases with available data, 116 (81%) were hospitalized. PFGE typing performed at CDC identified two closely related outbreak-associated patterns — which differed by a single band — in 119/127 (94%) patient isolates and 7/7 (100%) Nurse Assist flush isolates tested from multiple states. Of the 16 “late onset” patient isolates, 10 were typed by PFGE and all matched the outbreak patterns. Patterns identified in this outbreak did not match those from isolates obtained from other products recently recalled due to contamination with Bcc.

FDA inspected Nurse Assist’s facility and collected samples from various manufacturing process points, the water source, and from retained products or returned products. No samples from the implicated lot remained at Nurse Assist, so no undistributed implicated product could be tested by FDA. Samples collected at the manufacturing site did not test positive for Bcc. The inspection did detect other organisms in the processing area, indicating conditions that might have contributed to contamination.

FDA also conducted an inspection at the off-site contract sterilizer. Their findings were not sufficient to identify a root cause of contamination, and the sterilization process was ultimately found to be adequate. However, discrepancies were identified in shipping records between Nurse Assist and the off-site contract sterilizer. On May 8, 2017 FDA issued a warning letter to Nurse Assist identifying the process deficiencies identified during inspection, which included that there was a discrepancy in documentation of the number of

cases of saline flushes manufactured and the number of cases of saline flushes that were sterilized [11].

Discussion

This investigation identified a single lot of contaminated Nurse Assist saline flushes as the likely source of an outbreak of 162 cases of Bcc BSI in 59 facilities in five states. As has been seen in other outbreaks caused by contaminated products, outbreak detection was challenging, as demonstrated by the large number of cases that occurred prior to notification of public health authorities. Distribution of contaminated product to multiple facilities in a large geographic area, resulting in few cases at each individual facility, complicated the recognition of the outbreak; furthermore, lack of documentation specifying which saline flushes patients received complicated identification of populations at risk for exposure. This outbreak resulted in a high hospitalization rate, disruption of medication supply chains at healthcare facilities in multiple states, and the recall of over a quarter million saline flush syringes — likely all preventable outcomes, had appropriate record keeping and quality control procedures been consistently followed by the saline flush manufacturer.

Communication between partners was critical in the investigation. At least two facilities independently identified and reported clusters of suspicious illnesses, leading to the recognition of a broader problem. Collaboration between state and federal agencies enabled rapid identification of the source of the outbreak and the resulting recall likely prevented many additional infections. Through the Epi-X notification and phone conferences among state and federal partners, information regarding the potential source was communicated rapidly. Coordination between the epidemiology and laboratory staff at both PADOH and MDH facilitated prompt recognition and culture of the suspected product, leading to the recall. CDC linked cases and saline flushes from multiple states through PFGE testing. The NJBOP and FDA facilitated the collection of information from Pharmacy A and Nurse Assist, respectively, and FDA identified Nurse Assist manufacturing deficiencies in need of correction to prevent future possible outbreaks.

As has been reported in a previous outbreak associated with saline flushes [12, 13], many cases matching the outbreak PFGE patterns were identified with first positive blood culture weeks after the recall. It is possible that some patients' CVCs were colonized before the recall and that later infections resulted from disturbed biofilm releasing bacteria into the bloodstream [14]. However, on December 14, recalled flushes from the implicated lot were found at a previously affected PA facility during a follow-up visit prompted by reports of new cases after the recall. As such, the most likely explanation is that some recalled flushes were not removed from circulation, resulting in later exposures. In response, a visual guide for distinguishing the recalled Nurse Assist flushes from those manufactured by other companies was produced by PADOH and shared with affected SNFs.

Lack of documentation of which specific flush products were administered to patients created challenges in determining which patients were exposed to contaminated product. Saline flush syringes are regulated by FDA as medical devices, and the administration of individual saline flushes is not typically recorded in patient records; therefore, we were

unable to define a case as infection in a person who was known to have received a Nurse Assist saline flush and instead required that patients reside at a SNF using Nurse Assist saline flushes once the source was identified. Documentation of product identifiers for individual administration of saline flushes (which are regulated by FDA as medical devices), and improved technological means to do so (e.g., use of bar codes), would enhance product tracking and facilitate identification of exposed persons and removal of contaminated products in future outbreaks.

While these measures may help mitigate outbreaks, avoiding source contamination is key to preventing them. An FDA advisory issued May 22, 2017 prompted manufacturers to be alert to Bcc's ability to survive in factory water systems, and advised manufacturers to establish microbiological testing procedures for all production materials and to investigate any results not meeting specifications [15]. For sterile products such as saline flushes, the use of visual indicators to confirm that the sterilization process has been completed might further reduce the risk of Bcc outbreaks linked to such products. For products without a terminal sterilization step, however, Bcc's persistence and outbreak potential necessitate meticulous quality control practices throughout the manufacturing and distribution processes to prevent future outbreaks.

Acknowledgements

The authors would like to acknowledge input and assistance from Jonathan Johnston, David Torpey, and Nivia Facundo at the Maryland Department of Health Laboratories Administration; Ernest Clement and Emily Lutterloh at the New York State Department of Health; Geetha Nattanmai, Sherly Jose, Teresa Passaretti, Elizabeth Nazarian, and Kara Mitchell at the Wadsworth Center, New York State Department of Health; Janet Glowicz and Mark Weng in the Division of Healthcare Quality Promotion at CDC; and Rolieria West-Deadwyler and Paige Gable in the Clinical and Environmental Microbiology Branch at CDC.

Members of The *Burkholderia cepacia* Workgroup include Cara Bicking Kinsey, Allison Longenberger, Sharon Watkins, Brigitte Husband, Lisa Dettinger (Pennsylvania Department of Health); Kelly E. Kline (Pennsylvania Department of Health, CDC/CSTE Applied Epidemiology Fellowship Program); David Blythe, Katherine A. Feldman, Rebecca Perlmutter, Lucy E. Wilson (Maryland Department of Health); Karen Southwick, Jane Greenko, Rafael Fernandez, Sarah Kogut (New York State Department of Health); and Joe Perz (CDC).

Financial support

This work was supported by the Centers for Disease Control and Prevention's Epidemiology and Laboratory Capacity Cooperative Agreement.

References

1. Centers for Disease Control and Prevention. Burkholderia cepacia in Healthcare Settings. Available at: https://www.cdc.gov/hai/organisms/bcepacia.html. Accessed July 6, 2017.
2. Kutty PK, Moody B, Gullion JS, et al. Multistate outbreak of Burkholderia cenocepacia colonization and infection associated with the use of intrinsically contaminated alcohol-free mouthwash. Chest 2007; 132(6): 1825–31. [PubMed: 17925414]
3. Marquez L, Jones KN, Whaley EM, et al. An Outbreak of Burkholderia cepacia Complex Infections Associated with Contaminated Liquid Docusate. Infect Control Hosp Epidemiol 2017; 38(5): 567–73. [PubMed: 28166854]
4. Metcalf P, Newman K, Siegel JD, et al. Notice to readers: nosocomial *Burkholderia cepacia* infections associated with exposure to sublingual probes — Texas, 2004. MMWR Morbidity and Mortality Weekly Report 2004; 53(34): 796.

5. Centers for Disease Control and Prevention. Notice to readers: manufacturer's recall of nasal spray contaminated with Burkholderia cepacia complex. MMWR Morbidity and Mortality Weekly Report 2004; 53(11): 246.

6. Glowicz J, Crist M, Gould C, et al. A multistate investigation of health care-associated Burkholderia cepacia complex infections related to liquid docusate sodium contamination, January-October 2016. Am J Infect Control 2018.

7. Centers for Disease Control and Prevention. Multistate Outbreak of Burkholderia cepacia Infections Associated with Oral Liquid Docusate Sodium. Available at: https://www.cdc.gov/hai/outbreaks/b-cepacia/index.html. Accessed February 1, 2018.

8. Centers for Disease Control and Prevention. Modified Pulse-Net procedure for pulsed-field gel electrophoresis of select gram negative bacilli, 2014:10.

9. PharmScript. About PharmScript Available at: https://pharmscript.com/about-2/. Accessed April 2, 2018.

10. U.S. Food and Drug Administration. Nurse Assist Inc. recalls normal saline flush IV syringes due to possible Burkholderia cepacia bloodstream infections Available at: https://www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm535293.htm. Accessed March 24, 2018.

11. U.S. Food and Drug Administration. Nurse Assist, Inc 5/8/17. Available at: https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm589443.htm. Accessed April 2, 2018.

12. Gershman MD, Kennedy DJ, Noble-Wang J, et al. Multistate outbreak of Pseudomonas fluorescens bloodstream infection after exposure to contaminated heparinized saline flush prepared by a compounding pharmacy. Clin Infect Dis 2008; 47(11): 1372–9. [PubMed: 18937575]

13. McHale J, Clayton J, Kim C, et al. Update: Delayed Onset Pseudomonas fluorescens Bloodstream Infections After Exposure to Contaminated Heparin Flush — Michigan and South Dakota, 2005–2006. Morbidity and Mortality Weekly Report 2006; 55(35): 961–3. [PubMed: 16960550]

14. Gominet M, Compain F, Beloin C, Lebeaux D. Central venous catheters and biofilms: where do we stand in 2017? APMIS 2017; 125(4): 365–75. [PubMed: 28407421]

15. U.S. Food and Drug Administration. FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm559508.htm. Accessed January 29, 2018.

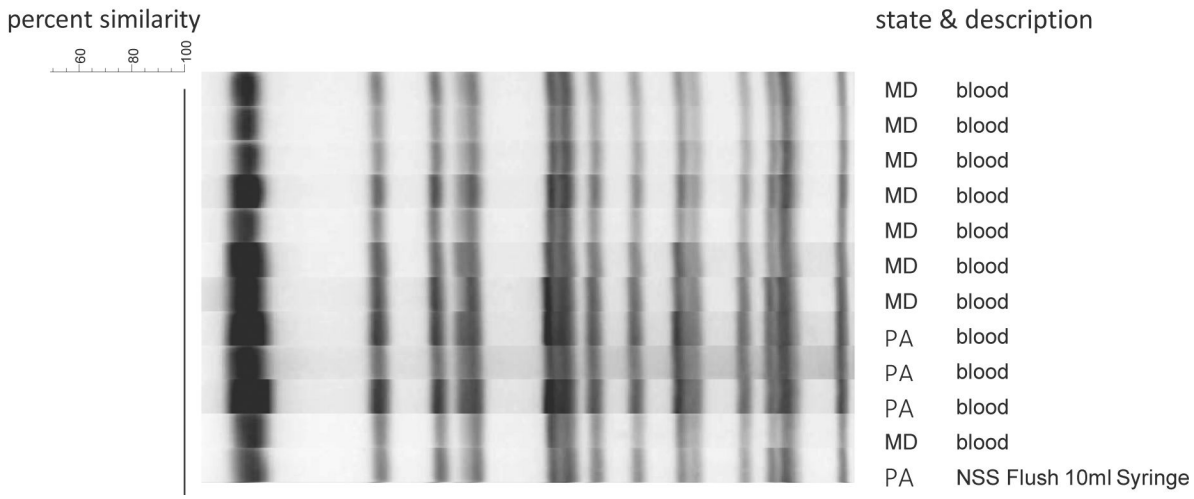

Fig. 1.

Pulsed-field gel electrophoresis (PFGE) patterns for eleven clinical isolates from early Maryland and Pennsylvania clinical cases and one unopened Nurse Assist saline flush showing indistinguishable patterns.

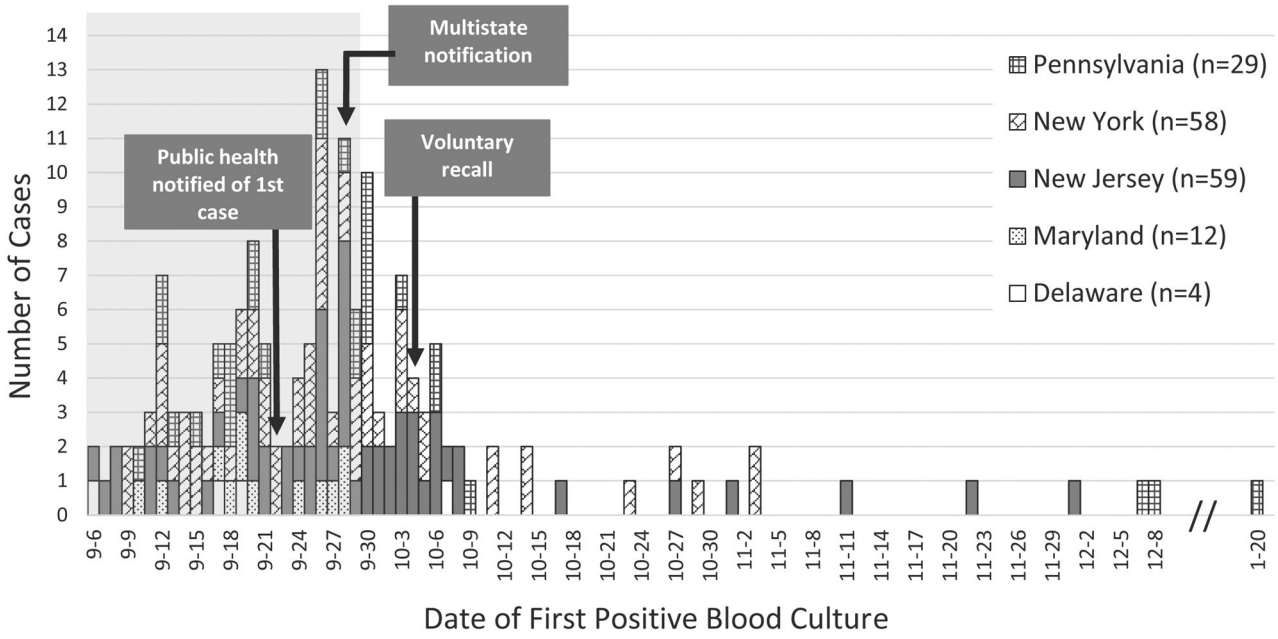

Fig. 2.

Burkholderia cepacia complex bloodstream infections among skilled nursing facility residents by date of first positive blood culture — United States, 2016–2017 (n = 162). The shaded area represents the time period during which there was ongoing distribution of Nurse Assist saline flushes from Pharmacy A.