OUTBREAK OF CATHETER-ASSOCIATED KLEBSIELLA OXYTOCA AND ENTEROBACTER CLOACAE BLOODSTREAM INFECTIONS IN AN ONCOLOGY CHEMOTHERAPY CENTER

John T. Watson, MD, MSc; Roderick C. Jones, MPH; Alicia M. Siston, MPH; Julio R. Fernandez; Karen Martin, RN, BS, CIC; Elizabeth Beck, MT; Steven Sokalski, DO; Bette J. Jensen; Matthew J. Arduino, DrPH; Arjun Srinivasan, MD; Susan I. Gerber, MD

Background: In March 2004, the Chicago Department of Public Health was notified of a cluster of bloodstream infections with Klebsiella oxytoca and Enterobacter cloacae at a chemotherapy center. Our purpose was to identify the source of the outbreak and prevent further cases.

Methods: The investigation included 103 oncology patients seen at an outpatient oncology chemotherapy center in Chicago during the 16 days before its closure. The outbreak investigation included case identification, retrospective cohort study, review of medical records, microbiologic testing of blood specimens, environmental cultures, and pulsed-field gel electrophoresis. The main outcome measure was infection with K oxytoca, E cloacae, or both, and the Mantel-Haenszel $\chi^2$ test was used to assess risk of infection in relation to presence of central venous catheter.

Results: Among the 103 patients, risk of infection was associated with the presence of central venous catheter (relative risk undefined, $P<.001$). Twenty-seven patients had blood cultures that grew K oxytoca, E cloacae, or both, and all had central venous catheters that were flushed with isotonic sodium chloride solution at the clinic from February 17 through March 3, 2004. Isolates of K oxytoca and E cloacae were matched by pulsed-field gel electrophoresis to K oxytoca and E cloacae isolates obtained from multiple predrawn syringes and from the intravenous fluid and administration set in use in the clinic at the time of its closing.

Conclusions: The injection of contaminated isotonic sodium chloride solution through the venous catheters of attendees at the clinic likely provided the opportunity for bloodstream infections in these 27 case patients. This outbreak highlights the need for continued emphasis on safe injection practices and suggests the need for guidelines and recommendations tailored to outpatient settings.

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Gram-negative bacteria are frequent causes of bloodstream infections (BSIs), accounting for 14% of inpatient BSIs reported to the National Nosocomial Infections Surveillance (NNIS) System from 1992 through 1999. Outbreaks of Enterobacter and Klebsiella in health care settings are generally caused by extrinsic contamination of medications such as albumin, isotonic sodium chloride solution, total parenteral nutrition solutions, intravenous fluids, and aerosolized medications, or by contamination of equipment such as dialysis equipment, digital thermometers, invasive blood pressure-monitoring equipment, and blood gas machines. Gram-negative organisms are known to be a cause of catheter-related BSIs associated with contaminated intravenous fluids.

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Central venous catheters (CVCs) are commonly used in a wide variety of health care settings, both inpatient and outpatient. Variations in quality of CVC care and maintenance, particularly outside of the intensive care unit (ICU), have been noted and have led to calls for interventions to reduce CVC-associated BSIs in non-ICU patients. Administration of intravenous therapy in an outpatient setting, such as a hospital clinic or physician’s office, has been demonstrated to be a significant risk factor for BSI and may be indicative of poor infection-control techniques. Poor hand hygiene can also facili-
tate transmission of pathogens in the health care setting and has been implicated in previous outbreaks of health care–associated gram-negative BSIs. In this article, we describe the investigation of a large outbreak of CVC-associated *Klebsiella oxytoca* and *Enterobacter cloacae* BSIs among outpatients at an oncology chemotherapy clinic and discuss strategies for prevention of BSIs in similar settings.

**METHODS**

**OUTBREAK SUMMARY**

In early March 2004, the Chicago Department of Public Health (CDPH) received a report of 13 cases of bacteremia among attendees at Clinic A, an oncology clinic. Clinic A was located within a freestanding outpatient multispecialty medical facility that was affiliated with a large health care organization and attended by oncology patients undergoing outpatient chemotherapy. This outpatient medical facility was operated independently by physician groups. The report came from the infection-control department at a nearby hospital that was affiliated with the same health care organization and was asked by Clinic A to assist in the investigation. The CDPH and the hospital infection-control department participated in the investigation with assistance from the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention (CDC).

At the time of the initial report to the CDPH, *E cloacae* had been diagnosed in 10 patients, *K oxytoca* in 2, and both organisms in 1. The first case was diagnosed on February 27, 2004, and the recognition of additional cases led to the voluntary closure of Clinic A on March 3, 2004. The 13 affected persons all had indwelling central venous access and had received chemotherapy at the clinic. All were treated with parenteral antibiotics and were recovering. Dates of the most recent use of the CVC at the clinic for the 13 patients ranged from February 17 to March 3, 2004. Our investigative objectives were to confirm the existence of an outbreak, seek the source and mode of transmission of infection, characterize the clinical features and morbidity of infection, and implement control measures.

**EPIDEMIOLOGIC INVESTIGATION**

We defined a case as any patient seen at Clinic A during February or March 2004 with a blood culture that grew *K oxytoca*, *E cloacae*, or both. These cases met the CDC criteria for laboratory-confirmed BSI as defined by the NNIS System. Cases included those with and without clinical symptoms of sepsis. To detect additional cases, we used clinic records to identify patients seen at the clinic during February and March, including patients receiving services that did not involve use of a CVC at the clinic. The patients identified were interviewed by CDPH staff and had blood drawn for culture. Control patients were defined as attendees seen at Clinic A during the outbreak from whom blood cultures did not grow either *K oxytoca* or *E cloacae*. We attempted to obtain the following information on cases and controls: demographics, diagnoses, medications, visits to the clinic, hospitalizations, presence and type of CVC, and recent symptoms of illness. To further define clinical case characteristics, we reviewed the clinic records to obtain information regarding the presence of CVC. We abstracted additional data from the hospital records of the identified case patients, including laboratory and clinical information about admission, hospital course, and treatment information.

**ENVIRONMENTAL INVESTIGATION:**

We conducted interviews with the staff of Clinic A to determine the flow of patients through the clinic; the processes of care in the clinic; and the procedures regarding preparation, storage, and administration of infused products.

**ENVIRONMENTAL SPECIMENS**

To assess potential environmental sources of *K oxytoca* and *E cloacae*, we collected samples of products associated with the infusion process, including medications, syringes that had been prefilled with isotonic sodium chloride solution by the staff and used to flush CVCs, and the bag of isotonic sodium chloride solution and administration set used to fill the syringes that were in use at the time of clinic closure on March 3, 2004. Other products that were cultured included tape, soap, antimicrobial ointment, benzoin, iodine disinfectant, gauze bandages, syringes, valves, and other infusion materials from each lot present in the clinic. The artificial fingernails of 1 clinic nurse were also cultured. In addition, we used sterile, moistened swabs to obtain environmental samples from the sinks, toilet, doorknobs, mixing hood, and counter surfaces. Microbiologic testing was performed at the microbiology laboratory at the hospital assisting with the investigation and at CDC.

**LABORATORY ANALYSIS**

Specimens for blood culture were drawn through CVCs (for those with central venous access) or percutaneously (for those without central venous access). Specimens were inoculated into an enrichment medium (BACTEC; Becton, Dickinson and Company, Franklin Lakes, NJ; or BacT/ALERT; bioMerieux, Durham, NC). All organisms isolated were identified with an automated method (VITEK; bioMerieux; MicroScan; Dade Behring, Inc, West Sacramento, Calif; or ESP; TREK Diagnostic Systems, Inc, Cleveland, Ohio). Isolates were sent to CDC for confirmation of identification. Molecular typing with pulsed-field gel electrophoresis (PFGE) was also performed at CDC as described previously.

**STATISTICAL ANALYSIS**

All data were entered into a database (Access; Microsoft Corp, Redmond, Wash), and descriptive statistics were calculated (Epi Info version 6.04b, Centers for Disease Control and Prevention, Atlanta, Ga). The Mantel-Haenszel χ² test was used to assess risk of infection in relation to presence of CVC.

**RESULTS**

One hundred three patients seen at Clinic A from February 17 to March 3, 2004, were evaluated with blood cultures and assessed for the presence of risk factors. Twenty-seven (26%) had blood cultures positive for *E cloacae* (n = 20), *K oxytoca* (n = 2), or both (n = 5). Of the 27 case patients, 18 (67%) were infected with clinical cultures, and 9 were identified only with surveillance cultures. The 18 case patients with symptoms had signs or symptoms indicative of a BSI (eg, fever, chills, or sweats) before admission. Nine case patients were asymptomatic. All 27 case patients were hospitalized, with a median length of stay...
of 6 days (range, 2-19 days). Twenty-one (78%) case patients were women, and the median age was 65 years (range, 37-77 years). The median time between date of last infusion and date of onset of symptoms for these case patients was 5 days (range, 3-14 days). Ten (37%) case patients had at least 1 systolic blood pressure reading of 90 mm Hg or lower while hospitalized, but no one died as a result of a BSI associated with this outbreak.

Among the 55 Clinic A attendees who had had at least 1 infusion through a CVC between February 17 and March 3, 2004, 27 (49%) were confirmed cases, compared to 0 cases among the 48 Clinic A attendees who had not received infusion through a CVC during that period (relative risk undefined, \( P < .001 \)). Among the 27 case patients, 23 had implanted central catheters, and 4 had peripherally inserted central catheters.

ENVIRONMENTAL INVESTIGATION: CLINIC PROCEDURE

Most patients seen at Clinic A were receiving chemotherapy regimens that required multiple visits to the facility during a period of months. Clinic A was staffed by 2 or 3 nurses who delivered intravenous and intramuscular chemotherapy to 20 to 30 patients per day. There were no pharmacists based at the clinic, and nurses were responsible for preparing some chemotherapy drugs.

Six patient chairs were used for infusion treatments. A bathroom located adjacent to the infusion area was used by clinic patients, staff, and patients being seen at the adjoining gastroenterology clinic. There were 2 conveniently located sinks in the clinic available for use by staff; soap was available but alcohol-based hand rub was not. Before and after each infusion or intravenous medication, the CVC was flushed with either dextrose or isotonic sodium chloride solution, depending on the type of chemotherapy being infused. Formal infection-control resources were not present at the clinic at the time of the outbreak.

Interviews with Clinic A staff revealed that at the start of each day, clinic nurses prefilled multiple 10- and 20-mL sterile syringes used to flush CVCs. The syringes were filled from a 500-mL bag of isotonic sodium chloride solution or a 100-mL bag of dextrose. The isotonic sodium chloride solution was drawn from the bag through a dispensing valve set containing a 2-way valve, while the dextrose was drawn directly from the bag. Although the bags of isotonic sodium chloride solution were typically changed each day, clinic staff reported that the dispensing valve sets generally were not discarded after 1 use. According to clinic staff, the set in place at the time of the clinic closure had been in use for approximately 1 week. Leftover prefilled syringes were typically discarded at the end of each day.

ENVIRONMENTAL SPECIMENS

Of the 21 prefilled isotonic sodium chloride solution syringes cultured, all demonstrated growth of bacterial organisms; 4 were positive for *K. oxytoca*, 3 for *E. cloacae*, and 14 for both organisms. No dextrose-containing syringes were available for culture. The bag of isotonic sodium chloride solution and administration set in use at the time of clinic closing were also positive for both organisms. None of the other materials tested, including the artificial fingernails, and none of the environmental cultures revealed *K. oxytoca* or *E. cloacae*.

LABORATORY ANALYSIS

The PFGE patterns of the *K. oxytoca* and *E. cloacae* isolates from the blood cultures of the 27 case patients were indistinguishable from those of the isolates from the prefilled isotonic sodium chloride solution syringes and the bag of isotonic sodium chloride solution in use at the time of clinic closure (Figure).

We report a large outbreak of catheter-associated gram-negative BSIs among patients in an oncology chemotherapy center. The case patient blood culture isolates were indistinguishable from isolates cultured from the isotonic sodium chloride solution used for injection at the chemotherapy clinic. The injection of contaminated isotonic sodium chloride solution through the CVCs of attendees at the clinic from February 17 to March 3, 2004, likely provided the opportunity for BSI in these 27 case patients.

Studies of intravenous systems by the CDC have demonstrated a 6% or higher prevalence of bacterial contamination within intravenous tubing or bottles after the systems have been in use. The risk of contamination increases significantly if the administration apparatus remains unchanged for more than 48 hours.10 Current recommendations are that intravenous administration sets be replaced every 72 hours.12 Staff of Clinic A indicated that the set sent for culture had been in continuous use for the week leading up to the clinic’s closure. The 16-day epidemic suggests that the contaminated dispensing setup may have been in place longer than 1 week. The implicated pathogens, *K. oxytoca* and *E. cloacae*, are fecal organisms, and the investigation identified several hygiene concerns. In addition, no infection-control personnel were located on site at the time of the outbreak. The initial source of contamination in this outbreak, however, is unknown.

This large outbreak, which occurred in an outpatient setting, highlights yet another challenge to efforts to prevent nosocomial BSIs. Invasive procedures and infusion treatments increasingly are performed in the outpatient setting. Not unexpectedly, the severity of illness being managed in the outpatient setting has also increased, especially in the oncology population. There is little surveillance for infections occurring among outpatients, despite the demonstration of increased risk of CVC-related BSI among patients receiving outpatient treatment. One reason might be that patients who become acutely ill often will go to hospital emergency departments or other clinical settings that may or may not be affiliated with the exposure setting, thus making surveillance for outpatient-associated BSIs a challenge. Currently, available information about infection rates in ambulatory settings is limited, and the identification of outbreaks is often delayed.7
This investigation has limitations. We attempted to obtain as much information as possible from clinic records to establish risk factors for BSI, but information on risk factors other than presence of a CVC could not be analyzed. For our case definition, we used the CDC NNIS System definitions for laboratory-confirmed BSI. In our investigation, blood cultures were obtained from CVCs to determine presence of bacteria. Therefore, the case count could include patients with both bacteremia and colonization. For the patients with symptoms, the explanation of the 5 days between last infusion and clinical symptoms is unknown, but contributing factors may have included any type of manipulation of the CVC, host factors related to the chemotherapy cycle, and the number of organisms that were present in the particular isotonic sodium chloride solution flush used. Our case count also includes 9 case patients who did not report symptoms consistent with sepsis who were identified through blood culture surveillance of attendees seen during the epidemic. Whether these patients with colonized CVCs would have developed infections with symptoms is unknown. However, it is important to note that two thirds of the patients in this outbreak had symptoms.

Bloodstream infections remain a major cause of morbidity and mortality. Studies of inpatient BSIs have estimated the attributable mortality of catheter-related BSI to be 12% to 25%, with a cost to the health care system of $25 000 per episode. Although similar studies have not been performed for outpatients, our investigation clearly demonstrates that morbidity and increased costs are associated with outpatient BSIs. All 27 patients involved were hospitalized as a direct result of their BSIs, with a median length of hospitalization of 6 days. Prevention of BSIs, in both inpatient and outpatient settings, must remain a priority. Current guidelines from the Hospital Infection Control Practices Advisory Committee provide evidenced-based recommendations for the prevention of catheter-associated BSIs in both inpatient and outpatient settings. To ensure the quality and safety of care delivered, these guidelines should be followed in all health care settings. In addition, creating policies that ensure appropriate infection control in the outpatient setting requires attention and further discussion by the medical community. Understanding the unique environment of today’s outpatient health care setting is necessary to structure effective BSI surveillance methods and infection-control policies.

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Correspondence: Susan I. Gerber, MD, Chicago Department of Public Health, Westside Center for Disease Control, 2160 W Ogden, Chicago, IL 60612 (Gerber_Sue@cdph.org).

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Figure. Pulsed-field gel electrophoresis patterns after XbaI digestion of isolates of Klebsiella oxytoca (A) and Enterobacter cloacae (B) obtained from patient blood cultures and prefilled syringes taken from the oncology clinic. Lanes 1 and 8 (A) and lanes 1 and 10 (B) are molecular weight standards.
REFERENCES