ORIGINAL ARTICLE

Serratia marcescens Bacteremia: Nosocomial Cluster Following Narcotic Diversion

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OBJECTIVE. To describe the investigation and control of a cluster of *Serratia marcescens* bacteremia in a 505-bed tertiary-care center.

METHODS. Cluster cases were defined as all patients with *S. marcescens* bacteremia between March 2 and April 7, 2014, who were found to have identical or related blood isolates determined by molecular typing with pulsed-field gel electrophoresis. Cases were compared using bivariate analysis with controls admitted at the same time and to the same service as the cases, in a 4:1 ratio.

RESULTS. In total, 6 patients developed *S. marcescens* bacteremia within 48 hours after admission within the above period. Of these, 5 patients had identical *Serratia* isolates determined by molecular typing, and were included in a case-control study. Exposure to the post-anesthesia care unit was a risk factor identified in bivariate analysis. Evidence of tampered opioid-containing syringes on several hospital units was discovered soon after the initial cluster case presented, and a full narcotic diversion investigation was conducted. A nurse working in the post-anesthesia care unit was identified as the employee responsible for the drug diversion and was epidemiologically linked to all 5 patients in the cluster. No further cases were identified once the implicated employee's job was terminated.

CONCLUSION. Illicit drug use by healthcare workers remains an important mechanism for the development of bloodstream infections in hospitalized patients. Active mechanisms and systems should remain in place to prevent, detect, and control narcotic drug diversions and associated patient harm in the healthcare setting.

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Serratia marcescens, a gram-negative rod from the *Enterobacteriaceae* family, has been reported at the center of nosocomial outbreaks in various healthcare settings, including neonatal units,[1] maternity wards,[2,3] and medical and surgical units.[4–6] Sources of *S. marcescens* outbreaks included contaminated medications, infusion solutions, disinfectants, medical equipment (eg, bronchoscopes and laryngoscopes), or even healthcare worker hands.[4,7–11] Infections caused by *S. marcescens* can have significant morbidity and mortality.[12] We describe the epidemiological and molecular investigation of a cluster of *S. marcescens* bloodstream infections among adult patients admitted to different medical and surgical floors in a tertiary-care hospital.

METHODS

Setting and Cluster Identification

At the University of Wisconsin Hospital, a 505-bed regional adult referral center, we usually encounter <10 *S. marcescens* bloodstream infections per year. In the 5 weeks from March 1 to April 8, 2014, 6 patients had *S. marcescens* bacteremia, including 1 fatality, suggesting the possibility of a cluster or outbreak. This cluster was confirmed through epidemiological review of before-and-after blood cultures and molecular fingerprinting methods.

Case Definition, Case-Control Study, and Epidemiological Investigation

Cases were defined as patients admitted during the cluster period with blood cultures positive for *S. marcescens* at any time during their hospital stay and whose isolates were considered related or identical by molecular fingerprinting. Controls were randomly selected from patients who did not have positive blood cultures and were admitted at the same time and to the same unit as the case patients, in a 4:1 ratio. We abstracted relevant demographic and clinical variables by retrospective review of medical records. We analyzed categorical variables using the χ^2 test or a 2-tailed Fisher exact test,

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and continuous variables were analyzed using the Student *t* test. Bivariate analyses were performed in Stata 14.1 SE for Windows (StataCorp, College Station, TX).

During the *S. marcescens* cluster period, a separate hospital investigation was started to examine a narcotic diversion that was identified soon after the first *Serratia* bloodstream infection was reported. The hospital epidemiologist was informed of the latter investigation and led the analysis of possible connections between the cluster of bloodstream infections and the narcotic diversion.

Microbiologic and Molecular Assays

Serratia marcescens was identified from patient blood-culture isolates using MALDI-TOF mass spectrometry according to the manufacturer's specifications on a Biotyper system, library v4613 with Compass software (Bruker Daltonik, Billerica, MA). Bacterial and component controls were included in each analysis.[13] Strain relatedness was determined by pulsed-field gel electrophoresis (PFGE). Isolates were prepared using protocols from Alaidan et al[14] with several modifications. We used a 1.8% low-melting agarose for plug preparation and 20 μL proteinase K (20 mg/mL) for proteolysis. The SpeI concentration was 15 U vs 50 U; XbaI concentration was 25 U. We used the following the Centers for Disease Control and Prevention (CDC) parameters for the CHEF Mapper (Bio-Rad, Berkeley, CA): 200 Volts (6 v/cm), 14°C temperature, 2.2 seconds for the initial switch, 54.2 seconds for the final switch, and a run time of 20 hours. Image capture was performed using the Gel Doc XR+ with Image Lab version 5.0 software, build 18 (Bio-Rad). The gel was analyzed using GelComprar II version 6.6 (Applied Maths, bioMérieux SA, Marcy l'Etaile, France). Dendograms were generated using the Dice similarity coefficient and the unweighted-pair group method using arithmetic averages (UPGMA) with 1% optimization and 1% position tolerance. We used the criteria published by Tenover et al[15] to interpret clonal relatedness.

RESULTS

Cluster Case Distribution and Summary

Figure 1 shows the distribution of *Serratia* bacteremia admissions before and after the cluster period. Of the 6 patients admitted within the March–April cluster, a total of 5 patients (83%) met the cluster case definition, as evidenced by molecular typing of their blood isolates. The isolate antibiograms showed susceptibility to all aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole, carbapenems, piperacillin-tazobactam, and third- and fourth-generation cephalosporins. The isolates were resistant to ampicillin-sulbactam, cefoxitin, and cefuroxime. The cluster case patients (identified here as patients 1, 2, 3, 5, and 6) were admitted to 5 different hospital wards and had positive blood cultures on

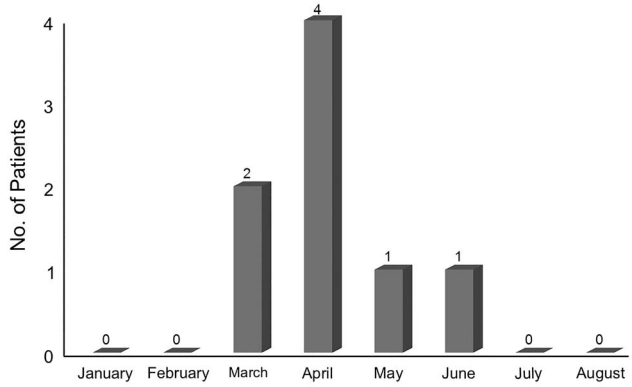

FIGURE 1. Distribution of cases of *Serratia marcescens* bacteremia from January to July 2014. Patients 1–6 were distributed between March and April. The isolates from the subsequent May and June patients had unrelated PFGE patterns by molecular typing.

or within 48 hours after admission. Their clinical presentations are summarized below:

Patient 1, a 58-year-old man with underlying amyotrophic lateral sclerosis (ALS) , was admitted with 2 days of fever, a petechial rash, and right ankle swelling. His admission blood cultures were positive for *S. marcescens*, although a full evaluation of his respiratory, gastrointestinal, and genitourinary systems failed to identify a cause for his bacteremia. The synovial fluid analysis of his right ankle was normal, and the synovial fluid culture was negative. He was treated with piperacillin-tazobactam for 4 days, followed by oral ciprofloxacin to complete a 2-week course. He made a full recovery and was discharged uneventfully in the care of his daughter, although the etiology of his bacteremia remained cryptogenic.

Patient 2, a 53-year-old man with underlying esophageal carcinoma recently treated with chemotherapy was electively admitted for esophageal biopsies and laparoscopic staging. His immediate postoperative course during the night shift was remarkable only for poor pain control, which improved by the next morning on a patient-controlled analgesia (PCA) pump. On his second hospital day, he developed sudden rigors, fevers to 40°C, hypotension, and septic shock, with profound acidosis and disseminated intravascular coagulation. An emergent exploratory laparotomy for suspected intra-abdominal source of sepsis did not identify any bowel abnormalities. Blood cultures from day 2 of hospitalization returned positive for *S. marcescens*. Despite aggressive critical care management and prompt initiation of broad-spectrum intravenous antibiotics, he succumbed by day 3 of his hospital stay. A postmortem examination confirmed sepsis secondary to *Serratia* as the likely cause of death.

Patient 3, an 80-year-old man with underlying adenocarcinoma of the lung was admitted for left upper-lobe resection and mediastinal lymph-node dissection. On postoperative day 2, he developed sepsis with rigors, hypotension, fever,

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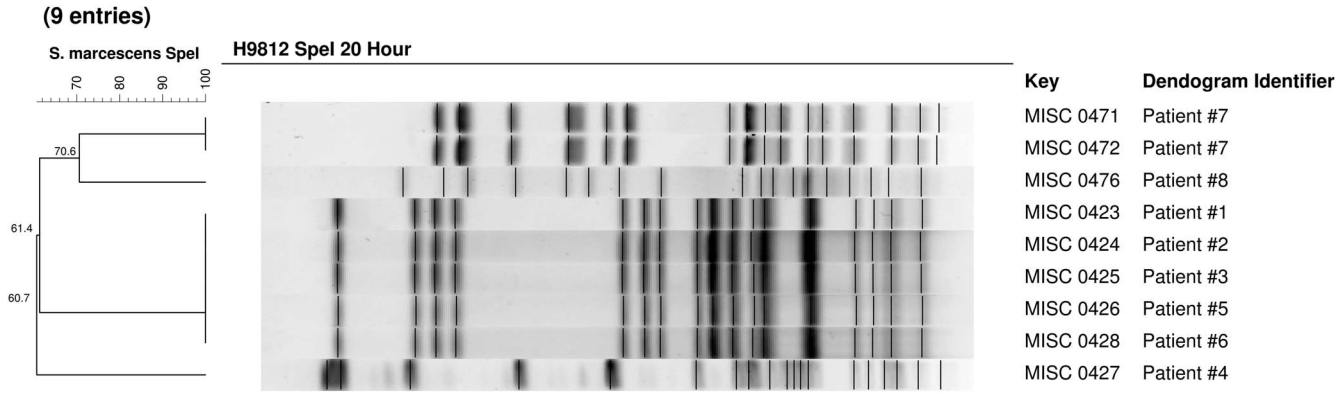

FIGURE 2. Dendrogram comparing banding patterns from PFGE and applying Tenover criteria to all isolates. Of 6 isolates obtained during the outbreak, 5 were indistinguishable, confirming a common source. Unique isolate patterns for *Serratia isolates* discovered in May and June (patients 7 and 8), showing resolution of the outbreak.

altered mental status, and respiratory failure. He was intubated and treated with vasopressors and broad-spectrum antibiotics (ie, vancomycin and piperacillin-tazobactam). Blood cultures drawn during this clinical decompensation returned positive for *S. marcescens*. The source was presumed to be the lung, although confirmatory sputum cultures were not available, and radiology imaging, while positive for a significant pneumothorax, did not conclusively show pneumonia. The patient gradually improved, completed a 2-week antibiotic course with ciprofloxacin, and was discharged after 13 days.

Patient 5 was a 51-year-old woman with colorectal carcinoma who underwent an uneventful laparoscopic resection of a solitary metastatic liver lesion on admission. Her day 1 postoperative course noted difficulty controlling her pain, despite having the maximum allowed opioid dosing on her PCA pump. She began to show a fever on day 2 of her hospital stay, and blood cultures drawn at that time returned positive for *S. marcescens*. She recovered fully after i.v. antibiotics (piperacillin-tazobactam) and was discharged uneventfully on ciprofloxacin after 4 days of hospital stay.

Patient 6 was a 67-year-old man with recurrent prostate cancer and colon cancer, both metastatic, with a recent admission for exploratory laparotomy with lysis of adhesions, appendectomy, sigmoid colectomy with retroperitoneal lymph-node dissection, primary colorectal anastomosis, and left ureteral stent placement. He presented to his scheduled oncology outpatient follow-up 3 weeks postoperatively, and he was noted to be febrile. Blood cultures drawn from his central venous port and peripherally in the office grew *S. marcescens* within 7 and 15 hours, respectively. He improved after port removal and antibiotics (ie, piperacillin-tazobactam followed by ciprofloxacin).

Molecular Analysis of Isolates Identified During the Cluster

Figure 2 shows results of the molecular typing of *Serratia* blood isolates recovered from the patients admitted during the cluster period (patients 1–6) as well as the first subsequent patient identified with *Serratia* bacteremia in May, outside of the cluster period (patient 7), with a different isolate shown by molecular analysis.

Case-Control Study

Patients 1, 2, 3, 5, and 6, with *Serratia* bloodstream isolates molecularly related or identical by PFGE, were included in a case-control study. On bivariate analyses, no significant differences were detected between cases and controls in the frequency of surgical or invasive procedures or in the receipt of opioid-containing medications. Cases were more likely to have had post-anesthesia care unit (PACU) exposure ($P = .01$), however.

Controlled Substance Diversion Investigation

On March 13, a nurse discovered 4 hydromorphone and 6 morphine patient-controlled analgesia (PCA) syringes with the tamper-evident caps no longer intact in the locked automated medication dispensing cabinet on a hospital nursing unit. On internal toxicology lab testing, 7 of 10 syringes were found to have less than detectable levels of drug present. These results triggered a controlled substance diversion investigation (CSDI) by teams from the nursing, pharmacy, compliance, and internal audit departments. A surveillance camera was installed for subsequent review of all medication dispensing activity on the medical floor where the tampered syringes were found.

Almost a month later, on April 9, 3 more hydromorphone PCA syringes were found with tamper-evidence caps no longer intact in the automated dispensing cabinet of a different patient care unit. Our internal toxicology lab showed less than detectable levels of medication in all 3 syringes, and these results were later confirmed by an independent outside lab. A subsequent random sample of 10 morphine and hydromorphone PCA syringes pulled from the NarcVault in Central Pharmacy and a few Accudose cabinets from different patient

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units throughout the hospital showed that 1 of the 10 syringes did not contain the expected drug quantity (3 mcg/mL instead of 200 mcg/mL hydromorphone).

On April 14, the CSDI team instituted new procedures for hospital opioid dispensing, as follows: new morphine and hydromorphone PCA syringes were compounded in the presence of 2 staff members at all times, 1 of whom had a managerial role. All previously stocked morphine and hydromorphone PCA syringes were removed from all storage locations, and 2 staff members, 1 of whom had a managerial role, restocked the new syringes. Additional tamper-evident packaging was implemented, including shrink-wrapping and tamper-evident tape to provide additional control measures. Close monitoring of PCA activity in all operational processes continued. In total, 42 syringes with evidence of narcotic drug diversion were identified over the course of the investigation, and osmolality testing suggested that the syringes were filled with a saline or lactate-ringers–like solution instead of active medication. A nurse was subsequently identified as the diverter, and hospital employment was terminated.

Connecting the Narcotic Diversion and *Serratia* Bacteremia Cluster

On April 16, the pharmacy manager notified the hospital epidemiologist of a potential link between the narcotic diversion and the *Serratia* cluster. The tampered narcotic syringes were no longer available for microbiological analysis at this point.

The results of the case-control study had suggested that a short-term postoperative stay in the PACU was a common exposure for 4 of the 5 cluster patients (patients 2, 3, 5, and 6). At that time, it was recognized that although many of the control patients also had surgery shortly after their hospital admission, not all of them received immediate postoperative care in the PACU. Instead, some were taken directly to the ICU after leaving the operating room, bypassing the potential *Serratia* exposure.

Once the implicated employee responsible for the narcotic diversion was identified, review of her activity from automated medication dispensing cabinet during March and April established that she had indeed accessed the storage pockets of PCA syringes in the PACU Accudose cabinets within a short period before the PCA syringes were administered to patients 2, 3, 5 and 6, respectively. Although patient 1 did not have surgery and did not stay in the PACU during his hospitalization, the connection with the PACU nurse implicated in the narcotic diversion was ultimately established when it was recognized that patient 1 was, in fact, her father, and had lived at her residential address before and after his hospitalization.

Recognition of Cluster Cessation

Review of microbiology blood cultures before and after the cluster period revealed no positive cultures prior to the cluster onset and 2 additional patients with positive blood cultures post cluster, during May–June (Figure 1). Their isolates had a different PFGE molecular pattern than the cluster cases (see patients 7 and 8 in Figure 2). In addition, no further cluster cases were identified after the removal of the implicated healthcare worker, suggesting that the nosocomial *Serratia* cluster has ended.

DISCUSSION

We present a cluster of *S. marcescens* bloodstream infections linked to a hospital employee's narcotic diversion. We hypothesize that the PCA syringes became contaminated as they were tampered with, in the process of withdrawing the opioid medication and refilling the syringes with a saline-like solution. Because testing of i.v. fluids from the PACU and the inpatient pharmacy area did not show evidence of *Serratia* contamination, we suspect that the replacement solution used by the implicated employee was brought in from a source external to the hospital. The fact that patient 1, the employee's father, was already infected at the time of his admission and lived in the employee's home supports this hypothesis, although we had no direct way to test this.

The patients affected experienced significant distress from both the hospital-acquired infection, as well as the lack of pain control in the postoperative setting. One patient died from *Serratia* sepsis, underscoring the importance of promptly recognizing the source of the outbreak and instituting measures to prevent further cases and maintain patient safety.

Unfortunately, in the context of the current US epidemic of opioid addiction, our experience is not isolated. The CDC has reported a total of 9 healthcare-associated bacterial and hepatitis C outbreaks related to drug diversion by healthcare workers within the last 30 years.[16] The common mechanisms of infection were tampering with injectable controlled substances, such as opioids administered by PCA pumps, fentanyl syringes, and vials.[17]

Most of these outbreaks also described the presence of some gaps in the prevention, identification, or response to the narcotic diversion. For example, Ostrowsky et al[11] reported a larger nosocomial *S. marcescens* bacteremia outbreak of 26 patients in a surgical ICU that lasted 9 months before the source was traced to fentanyl diversion by a respiratory therapist. They noted that although the institution had an overall narcotic theft policy, the mechanisms in place to deal with the drug diversion were not entirely adequate at that time.

Interestingly, one of the earliest published reports of nosocomial bacteremia secondary to narcotic drug diversion was also from our institution, reported by Maki et al[18] in 1991. Our institutional procedures related to the safety of narcotic drug administration, monitoring of narcotic use, and investigation of narcotic theft may have been implemented as a result of this initial experience, and they helped us respond to the current cluster before it escalated any further. Easy access to PFGE through our microbiology lab also helped us confirm the suspected *Serratia* bacteremia cluster in a timely manner.

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Institutions where molecular fingerprinting methods are not routinely available during a suspected nosocomial outbreak should contact their local health departments, which can assist with providing epidemiological and molecular expertise during the investigation.

Our investigation was limited by the lack of conclusive evidence of *S. marcescens* on the PCA syringes administered to the cluster patients, as they were no longer available for testing by the time we recognized their potential role in the investigation. However, we felt that the source of the *Serratia* bacteremia cluster was indeed related to the narcotic diversion for the following reasons: (1) We established a direct connection between the employee identified as responsible for the diversion and each of the 5 patients with identical *Serratia* bloodstream isolates comprising the cluster. (2) For most of the 5 cluster patients, bacteremia occurred within 24–48 hours from PCA narcotic administration, which is the expected period when infection occurs by way of infusion contamination. (3) New cluster cases ceased once the employee was removed from duties and the narcotic diversion ended.

In summary, our experience highlights the importance of active monitoring systems to prevent hospital-related drug diversion, and to consider this potential mechanism of infection when investigating nosocomial outbreaks related to gram-negative bacteremia.

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