MAJOR ARTICLE

Outbreak of *Serratia marcescens* Bloodstream Infections in Patients Receiving Parenteral Nutrition Prepared by a Compounding Pharmacy

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Background. Compounding pharmacies often prepare parenteral nutrition (PN) and must adhere to rigorous standards to avoid contamination of the sterile preparation. In March 2011, *Serratia marcescens* bloodstream infections (BSIs) were identified in 5 patients receiving PN from a single compounding pharmacy. An investigation was conducted to identify potential sources of contamination and prevent further infections.

Methods. Cases were defined as *S. marcescens* BSIs in patients receiving PN from the pharmacy between January and March 2011. We reviewed case patients' clinical records, evaluated pharmacy compounding practices, and obtained epidemiologically directed environmental cultures. Molecular relatedness of available *Serratia* isolates was determined by pulsed-field gel electrophoresis (PFGE).

Results. Nineteen case patients were identified; 9 died. The attack rate for patients receiving PN in March was 35%. No case patients were younger than 18 years. In October 2010, the pharmacy began compounding and filter-sterilizing amino acid solution for adult PN using nonsterile amino acids due to a national manufacturer shortage. Review of this process identified breaches in mixing, filtration, and sterility testing practices. *S. marcescens* was identified from a pharmacy water faucet, mixing container, and opened amino acid powder. These isolates were indistinguishable from the outbreak strain by PFGE.

Conclusions. Compounding of nonsterile amino acid components of PN was initiated due to a manufacturer shortage. Failure to follow recommended compounding standards contributed to an outbreak of *S. marcescens* BSIs. Improved adherence to sterile compounding standards, critical examination of standards for sterile compounding from nonsterile ingredients, and more rigorous oversight of compounding pharmacies is needed to prevent future outbreaks.

Keywords. compounding; contamination; outbreak; nutrition; *Serratia*.

Parenteral nutrition (PN) is widely used in healthcare settings to deliver critical nutrients to patients unable to tolerate enteral feeding. The intravenous formulation is intended to provide all daily nutritional requirements, such as electrolytes, amino acids, dextrose, and lipids, and is considered to be one of the most complex pharmaceuticals to prepare because of the need for careful titration and combination of multiple components [1, 2]. Preparation under rigorous sterile conditions is especially crucial as the nutrient-rich formulation can act as favorable growth media for microorganisms [3, 4] and because the process requires the multistep transfer of several ingredients into a single container, providing opportunities for microbial contamination during the compounding process [5].

In the United States, PN can be compounded in a healthcare facility, outsourced to a compounding

Received 2 December 2013; accepted 23 February 2014.

Presented in part: 49th Annual Meeting of the Infectious Diseases Society of America, Boston, Massachusetts, 20–23 October 2011.

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Clinical Infectious Diseases

DOI: 10.1093/cid/ciu218

pharmacy, or purchased as manufactured, premixed formulations [5]. Healthcare facilities that administer PN to patients often lack the time, expertise, and technology to produce these solutions in their own facilities. As a result, the preparation of PN is frequently outsourced to compounding pharmacies specializing in these practices. In 2011, approximately 43% of 556 US hospitals with >600 beds randomly surveyed reported outsourcing their nutrition support preparations [6]. Compounding pharmacies are expected to adhere to current standards for preparation and handling of compounded sterile preparations (CSPs). One such standard is the United States Pharmacopeia's (USP) General Chapter <797> "Pharmaceutical Compounding—Sterile Preparations," which details conditions and practices that minimize risks of contamination of CSPs, including PN [7]. Additional standards for compounding PN solutions also exist [8, 9]. The adoption of strict standards for sterile compounding have contributed to a decline in the burden of contaminated PN preparations, and US outbreaks related to mishandling of PN during compounding are rare [2]. However, compounding CSPs, especially using nonsterile active pharmaceutical ingredients (APIs), involves challenging and complex processes, and outbreaks associated with improperly compounded preparations are being increasingly reported [10–20].

In March 2011, the Centers for Disease Control and Prevention (CDC) was notified of 5 patients with *Serratia marcescens* bloodstream infection (BSI) in one hospital in Alabama. Receipt of PN from a single compounding pharmacy was identified as a potential common source. The pharmacy was an independent, state-licensed compounding pharmacy in Birmingham that was registered with the Alabama State Board of Pharmacy and subject to the state laws and regulations pertaining to the compounding of parenteral therapy [21]. During the outbreak period, the pharmacy supplied PN to 6 healthcare facilities (5 acute care hospitals and 1 long-term acute care hospital), all located within Alabama. Prescriptions for PN were received daily by the pharmacy, and compounded PN preparations were delivered to hospitals each night.

On 15 March 2011, after being notified of these *S. marcescens* BSIs, the pharmacy voluntarily ceased all compounding activities and subsequently recalled all CSPs as a precautionary measure. An investigation was conducted by the Alabama Department of Public Health and CDC to determine the extent of the outbreak, identify risk factors for infection among PN recipients, and review PN compounding practices to identify potential sources of contamination.

METHODS

Epidemiologic Investigation

Cases were defined as *S. marcescens* BSIs in patients receiving PN from the pharmacy between 1 January 2011 and 15 March 2011. Pharmacy and microbiology records were reviewed at the 6 facilities receiving PN to identify cases and determine the baseline rate of *S. marcescens* BSIs prior to the outbreak. Paper and electronic medical records were reviewed to identify risk factors for infection among PN recipients with *Serratia* bacteremia and describe clinical outcomes. Staff members at each of the 6 hospitals were interviewed about hospital policy for ordering, handling, and dispensing PN from the pharmacy. Because the majority of cases occurred in March 2011, pharmacy PN compounding logs from 1 March–15 March were reviewed to calculate attack rates for this time period.

To ensure that the outbreak was not due to intrinsically contaminated products supplied to other sites and affecting patients outside the pharmacy's distribution area, an inquiry for *S. marcescens* infections related to PN was released on 2 national public health listservs, the Epidemic Information Exchange (Epi-X) and the Emerging Infections Network (EIN). In addition, because the pharmacy also compounded cardioplegia (a CSP for use in cardiothoracic surgery) with the same equipment used for preparing PN ingredients, all 3 facilities in Alabama receiving cardioplegia from the pharmacy during the investigation period were queried for *S. marcescens* infections among cardioplegia recipients.

Pharmacy Investigation

Pharmacy policies for training, quality assurance, aseptic technique, and cleaning and disinfection were assessed. Staff members were directly observed in a mock PN compounding process and were interviewed about the process for compounding and sterilizing PN ingredients. Compounding logs and sterility testing logs were reviewed. PN preparations and individual components (eg, electrolytes, amino acids, and vitamins) were obtained for microbiologic testing. Environmental samples were taken from PN compounding equipment and surrounding surfaces using 3M Sponge-Sticks premoistened with buffer (3M, St Paul, Minnesota) to neutralize residual surface disinfectants before culture.

Microbiologic Methods

All available blood culture *S. marcescens* isolates from case patients were analyzed by the CDC. Environmental surface samples were homogenized in a stomacher and the eluents were cultured on tryptic soy agar plates containing 5% sheep blood and MacConkey II plates. Pulsed-field gel electrophoresis (PFGE) was performed on clinical and environmental *S. marcescens* isolates with a modified PulseNet standard (free) protocol [22]. Molecular chromosomal DNA was digested with the restriction endonuclease *SpeI*. Restriction fragments were separated with CHEF Mapper XA Pulsed Field Electrophoresis System (Bio-Rad Laboratories, Hercules, California). PFGE conditions were switch times of 2 and 40 seconds and total

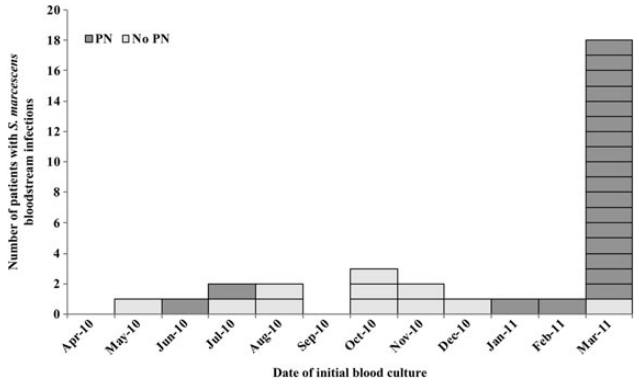

Figure 1. Epidemic curve of *Serratia marcescens* bloodstream infections among patients in hospitals receiving parenteral nutrition (PN) from the pharmacy, by PN exposure, Alabama, April 2010–March 2011. Abbreviation: PN, parenteral nutrition.

run time of 22 hours. *Salmonella* serotype *Braenderup* (H9812 strain) was used as a universal standard. Genetic relatedness of isolates was analyzed by BioNumerics software (Applied Maths, Austin, Texas). Similarity of PFGE patterns was based upon Dice coefficients and a dendrogram was built using the unweighted pairing group method. Isolates were considered genetically related based on previously established criteria [23].

RESULTS

Epidemiologic Investigation

Nineteen case patients were identified from the 6 healthcare facilities receiving PN from the pharmacy from January to March 2011. This number exceeded the baseline number of *S. marcescens* BSIs seen during the prior year at these facilities (Figure 1). Seventeen case patients had an initial positive blood culture for *S. marcescens* between 1 March and 15 March 2011 (attack rate 35% [17/48]); 2 additional cases occurred in January and February. Review of microbiology records from all PN recipients between January and March 2011 revealed no other clusters of pathogens. No additional *S. marcescens* infections were found among the 245 patients in Alabama receiving cardioplegia from the pharmacy in 2011 or reported via the inquiries posted on Epi-X or EIN.

Case patients had a median age of 56 years and 58% were female (Table 1). Neonates also routinely received PN from the pharmacy; however, no case patients were <18 years of age. Case patients had multiple comorbidities at baseline (Table 1). Following infection, 11 (58%) patients had an escalation in their level of clinical care, such as transfer to the intensive care unit or initiation of vasopressor medications. Nine patients died (47% case fatality rate); the median time between the initial *S. marcescens* culture and death was 1 day (range, 0–10).

Table 1. Demographic and Clinical Characteristics of Case Patients (N = 19) Receiving Parenteral Nutrition

Characteristic	No. of Case Patients (%)[a]	
Demographics		
Age, y, median (range)	56	(38–94)
Female sex	11	(58)
White race	14	(74)
Patient location		
Hospital A	1	(5)
Hospital B	5	(26)
Hospital C	7	(37)
Hospital D	3	(16)
Hospital E	1	(5)
Hospital F	2	(11)
Comorbid conditions		
Cerebrovascular disease	3	(16)
Chronic pulmonary disease	4	(21)
Congestive heart failure	2	(11)
Chronic kidney disease	3	(16)
Diabetes	7	(37)
Gastrointestinal disease	16	(84)
Hypertension	13	(68)
Ischemic heart disease	5	(26)
Malignancy	7	(37)
Neutropenia	1	(5)
Obesity	3	(16)
Indication for PN		
Colon cancer	4	(21)
Pancreatitis	2	(11)
Small bowel obstruction	5	(26)
Trauma	1	(5)
Other gastrointestinal pathology	7	(37)
Signs/symptoms of *S. marcescens* infection		
Fever	15	(79)
Hypotension	11	(58)
Leukocytosis	12	(63)
Respiratory distress	12	(63)
Characteristics at time of infection		
In intensive care unit	9	(47)
Duration of hospital stay, d, median (range)	8	(3–92)
Duration of PN use, d, median (range)	5	(1–58)
Outcomes		
Requirement for higher level of care	11	(58)
Deaths	9	(47)

Abbreviation: PN, parenteral nutrition.

[a] Unless otherwise indicated.

Pharmacy Investigation

Staff members at the pharmacy received training in sterile compounding at time of hire and at 6-month intervals. During the

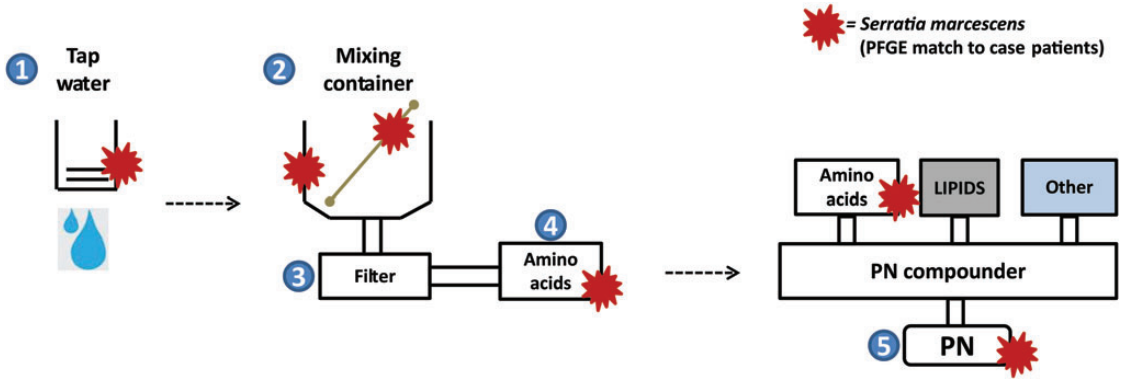

Figure 2. Summary of the parenteral nutrition (PN) compounding process at the pharmacy and breaches in practice that potentially contributed to contamination of amino acids with *Serratia marcescens*. 1, The pharmacy tap water faucet (the postulated source of introduction of *S. marcescens*) was used to clean a large mixing container. 2, Amino acid powders were compounded in sterile water in the mixing container (on occasion up to 48 hours prior to filter-sterilization); failure to filter solution immediately following this process could have allowed for increased bacterial growth and endotoxin production. 3, The solution was passed through a 0.2-µm sterilizing filter into individual sterile bags. A larger upstream filter (prefilter) was not used to reduce the bioburden of bacteria or remove excessive particulate matter visible in solution; this particulate matter could have interfered with efficiency of the sterilizing filter. Also, replacement of the clogged filter during filtration caused a break in the sterile system and could serve as a source for downstream contamination. 4, The filtered amino acid solution was stored in individual sterile bags pending use in PN; suboptimal sampling for sterility testing failed to detect contamination with *S. marcescens*. 5, Contaminated amino acids were eventually incorporated into adult PN preparations and administered to patients at 6 Alabama hospitals. Abbreviations: PFGE, pulsed-field gel electrophoresis; PN, parenteral nutrition.

observational period, appropriate hand hygiene and use of personal protective equipment was observed. A pharmacy technician compounded PN in consultation with a licensed pharmacist using an automated compounding machine. Most PN components were available as sterile ingredients in manufacturer-supplied containers; however, in October 2010, in response to a national manufacturer shortage [24], the pharmacy began compounding and filter-sterilizing 15% amino acid solution from nonsterile powders for adult (but not neonatal) PN preparations (Figure 2). Nonsterile amino acid powders were mixed with 80–100 L of sterile water in a large, nonsterile mixing container. Because amino acid powders were difficult to dissolve in solution, they were occasionally compounded in water and stored for 1-2 days prior to filtration. The amino acid solution was sterilized by passing it through a 0.2-µm capsule filter. During this step, pharmacy staff noted that particulate matter in the prefiltered solution frequently caused a reduction in flow across the filter membrane, necessitating replacement of the filter 1–5 times during the sterilization step. Following filtration, the mixing container was cleaned with detergent and tap water from a non-aerator-containing faucet. Approximately 25 mL of the filtered amino acid solution were set aside for sterility and bacterial endotoxin testing. Although these results were generally reported within 10–14 days, amino acids were routinely added to PN formulations before these results were available.

Four different lots of amino acid solutions were added to PN and administered to case patients in the 1–2 days immediately preceding their infections. The 17 case patients with infections in March 2011 were exposed to at least 1 of 2 different lots. Although these amino acid lots were reported as being sterile at the time of testing, both had detectable endotoxin (one substantially above the established endotoxin limit [25]). Both lots had already been added to PN formulations and administered to patients before the pharmacy became aware of the endotoxin results.

Microbiologic Investigation

Environmental cultures obtained from the pharmacy identified *S. marcescens* from the amino acid mixing container and stirrer, tap water faucet used to clean the mixing container, 15% amino acid solution, and PN preparations from the pharmacy (Table 2, Figure 2). A single colony-forming unit was obtained from the L-valine amino acid powder (an opened, nonsterile product). Clinical *S. marcescens* isolates from 14 of the 19 case patients were available for testing. All *S. marcescens* clinical and environmental isolates had >96% similarity by PFGE (Figure 3).

DISCUSSION

Beginning in January 2011, 19 *S. marcescens* BSIs occurred in patients receiving PN prepared by a compounding pharmacy, including 35% of patients who received PN in March 2011; death occurred in nearly half of these BSI events. Observations from this investigation suggest that the tap water faucet was the likely source of the bacteria and that failure to follow

Table 2. Laboratory Results of Compounded Preparations and Environmental Samples From the Pharmacy

Specimen Description	Culture Result
Compounded preparations	
PN bag, patient 3	*Serratia marcescens*
PN bag, patient 4	No growth
PN bag, patient 5	*S. marcescens*
PN bag, patient 12	*S. marcescens*
PN bag from non–case patient (#1)	No growth
PN bag from non–case patient (#2)	No growth
PN bag from non–case patient (#3)	No growth
15% amino acid solution	*S. marcescens*
Environmental samples	
Sponge-Stick, phone	*Serratia* not found[a]
Sponge-Stick, clock radio	*Serratia* not found[a]
Sponge-Stick, amino acid stirrer	*S. marcescens*
Sponge-Stick, mixing container (interior floor)	*S. marcescens*
Environmental swab, mixing container (spigot)	*Serratia* not found[a]
Environmental swab, tap water faucet	*S. marcescens*
Mixed water from tap	*Serratia* not found[a]
Open sterile water bottle for cleaning	No growth
Open distilled water for cleaning	No growth
Hand soap	No growth
Powder soap (used to clean mixing container)	No growth
L-Valine powdered solid[b]	*S. marcescens*
Sodium hydrosulfite powdered solid	No growth
Sodium chloride granular	*Serratia* not found[a]
Adult multivitamin liquid	No growth
Heparin	No growth

Abbreviation: PN, parenteral nutrition.

[a] Includes coagulase-negative *Staphylococcus* species, *Bacillus* species, and non-*Serratia*, gram-negative bacteria that were not further identified.

[b] *Serratia marcescens* was not found in any of the other 17 amino acid powders tested.

recommended standards for sterile compounding resulted in subsequent contamination of multiple lots of amino acids used in the preparation of adult PN.

Compounding has been defined as the preparation, mixing, packaging, or labeling of a drug in accordance with a licensed prescriber's prescription. This differs from manufacturing, which is the commercial production of US Food and Drug Administration (FDA)–approved drug products that do not require a patient prescription [26]. Although previous investigations have linked serious illnesses and deaths to contaminated CSPs originating from compounding pharmacies [10–20], the point source of contamination is often not identified or reported [11–16, 18–20], which is critical for understanding potential failures in compounding practices to prevent future outbreaks.

The combined epidemiological and laboratory approach in this investigation allowed for a detailed assessment of potential sources of the organism and specific errors in the compounding process that likely led to contamination. The initial investigation revealed an absence of illness in neonates, despite the fact that neonates routinely received PN from the pharmacy, prompting a review of the differences between adult and neonatal PN. After it became known that the pharmacy recently began compounding and sterilizing 15% amino acid solution from nonsterile APIs for use in adult PN, while neonatal PN compounding remained unchanged, targeted environmental samples were taken and identified the tap water faucet and mixing equipment as the likely sources of contamination. The lack of *S. marcescens* infections among recipients of cardioplegia, a solution prepared using the same contaminated equipment, further prompted a review of the differences between the cardioplegia and amino acid solutions; presence of particulate matter in the latter likely contributed to contamination of the final PN solution.

Multiple procedural deficiencies during the amino acid compounding process reflect lack of adherence to established standards for sterile compounding, including USP Chapter <797> (Figure 2). The first deficiency related to the terminal sterilization of the amino acid solution. Current USP standards state that the sterilization of water-containing CSPs should occur within 6 hours of compounding [7]; however, because amino acids were difficult to dissolve into solution, the pharmacy was compounding and allowing amino acids to sit in water for 1–2 days prior to filtration, which may have led to bacterial overgrowth and generation of bacterial endotoxins. In addition, USP recommends a "prefilter" upstream of the sterilizing filter whenever excessive particulate matter is present in solution; however, this additional step was not undertaken. Failure to do so interrupted flow across the 0.2-μm sterilizing filter membrane and likely interfered with the efficiency of the filter. Replacement of the clogged filter caused a break in the sterile filling system and could have served as a potential source for downstream contamination. These deficiencies underscore the importance of implementing a rigorous system to ensure staff competency and adherence to compounding standards. Additionally, adequacy of a 0.2-μm filter for terminal sterilization during compounding warrants further exploration.

According to USP Chapter <797>, all high-risk CSPs, including those compounded from nonsterile APIs, that are prepared in batches of >25 containers must be tested for sterility [7]; however, there is no requirement that CSPs not be released until sterility testing is complete. In this outbreak, the amino acid lots associated with most of the case patients had already been incorporated into PN and administered to patients before the pharmacy became aware of the positive endotoxin results. Moreover, sampling of a small volume (<25 mL) of the amino acid solution was insufficient to detect bacterial growth; testing

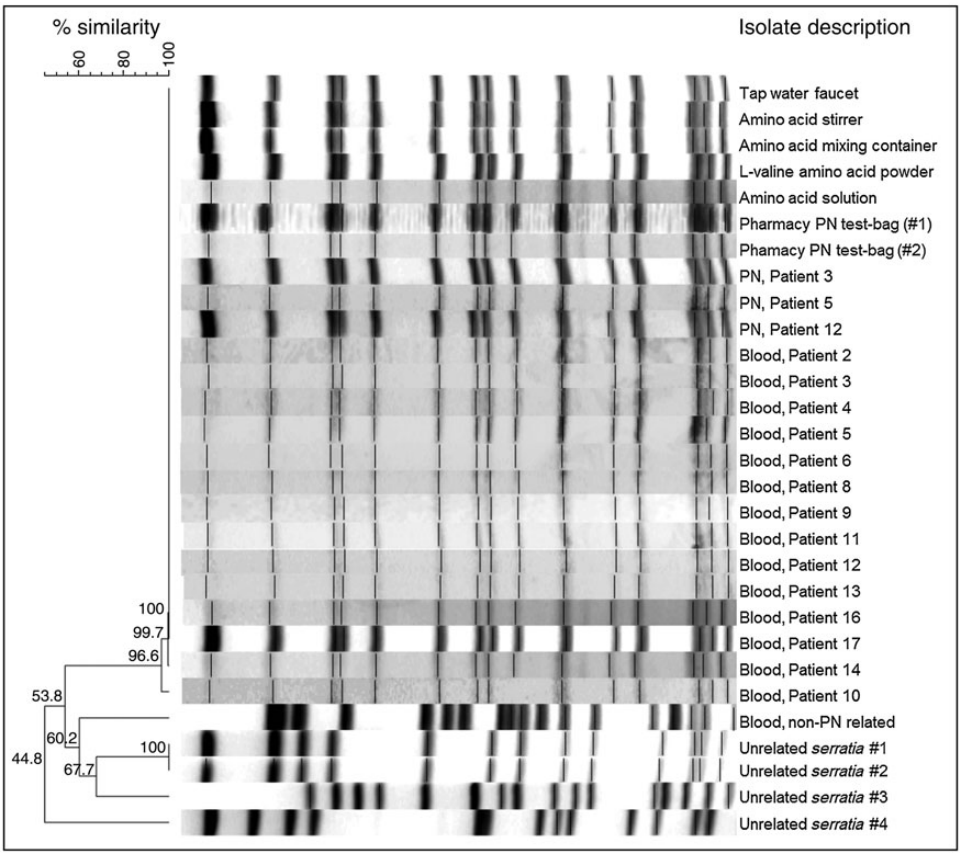

Figure 3. Results of pulsed-field gel electrophoresis (PFGE) of environmental and blood isolates of *Serratia marcescens*. All environmental isolates from the pharmacy were indistinguishable by PFGE. Isolates from 14 of the 19 case patients were available for testing; 13 were indistinguishable to environmental isolates and 1 isolate (patient 10) differed by one band. The "non-PN related" blood specimen was obtained in March 2011 from a patient at hospital B who did not receive parenteral nutrition. Abbreviation: PN, parenteral nutrition.

of larger volumes (on the order of liters), as currently recommended by USP [27], might have led to a higher probability of detecting contamination.

This outbreak occurred in the context of the pharmacy choosing to compound and sterilize their own supply of 15% amino acid solution from nonsterile API in response to a national manufacturer drug shortage [24]. The United States is currently facing an unprecedented number of drug shortages, which significantly impact patient care and healthcare costs [28–30]. Multiple factors contribute to drug shortages, including scarce raw materials, increased demand, and limited production capability [30, 31]. This is amplified in situations where only a small number of companies produce a specific product [31]. As in the case during this outbreak, interruption in supply of amino acids from one manufacturer led to an increase in demand that could not be met by other manufacturers, resulting in a critical national shortage [32]. Despite these challenges, adherence to sterile compounding standards [7, 33] is necessary to ensure the provision of safely prepared CSPs during periods of drug shortages.

According to the FDA, regulatory oversight of pharmacies and enforcement of compounding standards is subject to "gaps and ambiguity" [34] and varies from state to state. Although the National Association of Boards of Pharmacy (NABP) has incorporated USP Chapter <797> as a requirement in the minimum current Good Compounding Practices in the Model State Pharmacy Act and Model Rules [35], NABP has no authority to enforce such standards, and individual states vary with regard to their position on USP Chapter <797>. Different states have adopted the chapter in its entirety, in portions, or not at all [36]. Moreover, because enforcement of the practice of pharmacy, including pharmacy inspections, are primarily the responsibility of the state boards of pharmacy, states must have adequate resources to enforce compliance with these standards. Even when USP Chapter <797> has been incorporated into state pharmacy regulations, states may not have the resources, including trained inspectors, to recognize noncompliance with the highly technical practices outlined in the standards.

Although outsourcing to independent pharmacies is considered to be a potential cost-effective strategy to divert compounding

responsibilities to pharmacies better equipped to comply with USP Chapter <797> [37], failure to adhere to established standards in these pharmacies, as evident in this investigation, can result in adverse events affecting a larger number of patients in multiple facilities. Under new legislation introduced in November 2013 [38], pharmacies will have the option to register as an "outsourcing facility," subjecting them to current good manufacturing practices and increased oversight. The FDA has encouraged hospitals to consider this when choosing pharmacies that supply CSPs to their facilities [39]. Although the new legislation may help clarify federal roles and facilitate more rigorous oversight of compounding pharmacies [38], efforts to improve compounding personnel competency and adoption of rigorous quality assurance processes will continue to be critical in ensuring safely prepared CSPs.

Several factors may underestimate the burden of compounding pharmacy–related outbreaks. These include challenges in associating common healthcare pathogens to contaminated CSPs, lack of mandatory reporting requirements of adverse events from CSPs to FDA, and the distribution of a few contaminated CSPs to multiple healthcare facilities, rendering clusters of disease more difficult to recognize. In this investigation, half of the hospitals reported only 1–2 cases, which might not have been recognized as being above the facility baseline. The staff member who initially identified the cluster of infections during this investigation was critical to the rapid containment of the outbreak. This underscores the importance of heightened clinician awareness about the potential association between clusters of infections and contaminated CSPs and the reporting of adverse events to public health authorities as soon as they are suspected [40].

This investigation was associated with a few limitations. First, the pharmacy was not in operation at the time of the investigation and the full scope of compounding practices could not be directly observed; therefore, observations and interviews may not completely reflect prior practice. Also, because case patients had multiple underlying illnesses, assessing the degree of contribution of *S. marcescens* infection to case patient outcomes, including death, was not possible.

In conclusion, this outbreak investigation demonstrates that failure to comply with established standards for sterile compounding was one of the primary factors allowing for PN contamination and serious patient harm. Improved adherence to sterile compounding standards, critical examination of the adequacy of standards for compounding CSPs from nonsterile ingredients, and more rigorous oversight of compounding pharmacies are needed to mitigate the risks of potential contamination and prevent future outbreaks.

Notes

Acknowledgments. We thank the administration and infection control staff at the participating hospitals for their support during the investigation.

Disclaimer. The findings and conclusions expressed in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Financial support. This work was supported by the CDC and the Alabama Department of Public Health.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. DeLegge MH. Parenteral nutrition therapy over the next 5–10 years: where are we heading? J Parenter Enteral Nutr **2012**; 36(2 suppl):56S–61S.
2. Driscoll DF. Compounding TPN admixtures: then and now. J Parenter Enteral Nutr **2003**; 27:433–8; quiz 9.
3. Kuwahara T, Kaneda S, Shimono K, Inoue Y. Growth of microorganisms in total parenteral nutrition solutions without lipid. Int J Med Sci **2010**; 7:43–7.
4. Kuwahara T, Shimono K, Kaneda S, Tamura T, Ichihara M, Nakashima Y. Growth of microorganisms in total parenteral nutrition solutions containing lipid. Int J Med Sci **2010**; 7:101–9.
5. Turpin RS, Canada T, Rosenthal V, et al. Bloodstream infections associated with parenteral nutrition preparation methods in the United States: a retrospective, large database analysis. J Parenter Enteral Nutr **2012**; 36:169–76.
6. Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: dispensing and administration—2011. Am J Health Syst Pharm **2012**; 69:768–85.
7. United States Pharmacopeial Convention I . In: <797> Pharmaceutical Compounding—Sterile Preparations. United States Pharmacopeia 36—National Formulary 31. Rockville, MD: US Pharmacopeial Convention, **2012**.
8. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. J Parenter Enteral Nutr **2004**; 28:S39–70.
9. Driscoll DP, Giampietro K, Sanborn MD. ASHP guidelines on the safe use of automated compounding devices for the preparation of parenteral nutrition admixtures. Am J Health Syst Pharm **2000**; 57:1343–8.
10. Civen R, Vugia DJ, Alexander R, et al. Outbreak of *Serratia marcescens* infections following injection of betamethasone compounded at a community pharmacy. Clin Infect Dis **2006**; 43:831–7.
11. Centers for Disease Control and Prevention. Exophiala infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July-November 2002. MMWR Morb Mortal Wkly Rep **2002**; 51:1109–12.
12. Held MR, Begier EM, Beardsley DS, et al. Life-threatening sepsis caused by *Burkholderia cepacia* from contaminated intravenous flush solutions prepared by a compounding pharmacy in another state. Pediatrics **2006**; 118:e212–5.
13. Sunenshine RH, Tan ET, Terashita DM, et al. A multistate outbreak of *Serratia marcescens* bloodstream infection associated with contaminated intravenous magnesium sulfate from a compounding pharmacy. Clin Infect Dis **2007**; 45:527–33.
14. 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**; 47:1372–9.
15. Sunenshine R, Schultz M, Lawrence MG, et al. An outbreak of postoperative gram-negative bacterial endophthalmitis associated with contaminated trypan blue ophthalmic solution. Clin Infect Dis **2009**; 48:1580–3.
16. Maragakis LL, Chaiwarith R, Srinivasan A, et al. *Sphingomonas paucimobilis* bloodstream infections associated with contaminated intravenous fentanyl. Emerg Infect Dis **2009**; 15:12–8.

17. Frost BA, Kainer MA. Safe preparation and administration of intravitreal bevacizumab injections. N Engl J Med **2011**; 365:2238.
18. Goldberg RA, Flynn HW Jr, Isom RF, Miller D, Gonzalez S. An outbreak of *Streptococcus* endophthalmitis after intravitreal injection of bevacizumab. Am J Ophthalmol **2012**; 153:204–8. e1.
19. Centers for Disease Control and Prevention. Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy—United States, 2012. MMWR Morb Mortal Wkly Rep **2012**; 61:839–42.
20. US Food and Drug Administration. Main Street Family Pharmacy in Tennessee: FDA alerts health care providers of adverse reactions associated with steroid injections. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm353953.htm?source=govdelivery. Accessed 20 September 2013.
21. Code of Alabama 1975; Rules of Alabama State Board of Pharmacy section 680-X-2.19 parenteral therapy. Available at: http://www.albop.com/act205%20-%20JuLY%202012.pdf. Accessed 20 September 2013.
22. Centers for Disease Control and Prevention. Pulsed-field gel electrophoresis (PFGE). Available at: http://www.cdc.gov/pulsenet/pathogens/pfge.html. Accessed 9 September 2013.
23. 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**; 33:2233–9.
24. American Society for Parenteral and Enteral Nutrition. Information to use in the event of an intravenous amino acids shortage. Available at: http://www.nutritioncare.org/Index.aspx?id=5646. Accessed 20 September 2013.
25. United States Pharmacopeial Convention I. In: <85> Bacterial Endotoxins Test. United States Pharmacopeia 36—National Formulary 31. Rockville, MD: US Pharmacopeial Convention, **2013**.
26. US Food and Drug Administration. Guidance, compliance, and regulatory information: pharmacy compounding. Available at: http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm. Accessed 20 September 2013.
27. Sterility test (general information chapter 71). In: The United States Pharmacopeia, 27th rev, and the national formulary, 22nd ed. Rockville, MD: United States Pharmacopeial Convention, **2004**:2157–62.
28. Institute for Safe Medication Practices, Medication Safety Alert. Drug shortages: National survey reveals high level of frustration, low level of safety. Available at: http://www.ismp.org/newsletters/acutecare/articles/20100923.asp. Accessed 23 September 2013.
29. Kaakeh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. Am J Health Syst Pharm **2011**; 68:1811–9.
30. US Food and Drug Administration. Current drug shortages. Available at: http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm. Accessed 20 September 2013.
31. Jensen V, Kimzey LM, Goldberger MJ. FDA's role in responding to drug shortages. Am J Health Syst Pharm **2002**; 59:1423–5.
32. American Society for Parenteral and Enteral Nutrition. IV amino acids shortage recommendations and update—October 12, 2010. Available at: http://www.nutritioncare.org/Index.aspx?id=5664. Accessed 20 September 2013.
33. Ayers P, Adams S, Boullata J, et al. A.S.P.E.N. parenteral nutrition safety consensus recommendations. J Parenter Enteral Nutr **2014**; 38:296–333.
34. The fungal meningitis outbreak: could it have been prevented? US Food and Drug Administration statement before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce. 112th Congress, 2nd Session, 14 November 2012. Available at: http://www.fda.gov/NewsEvents/Testimony/ucm327664.htm. Accessed 20 September 2013.
35. National Association of Boards of Pharmacy. Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy. Available at: http://www.nabp.net/publications/model-act/. Accessed 20 September 2013.
36. Kastango ES. Compounding USP <797>: inspection, regulation, and oversight of sterile compounding pharmacies. JPEN J Parenter Enteral Nutr **2012**; 36(2 suppl):38S–9S.
37. Sanborn MD. Outsourcing compounding services to meet USP chapter <797> requirements: an overview. Pharmacy Practice News. **2008**. Available at: http://www.pharmacypracticenews.com/download/sr_08018_WM.pdf. Accessed 20 September 2013.
38. Drug Quality and Security Act (PL 113–54, 27 November 2013). Available at: http://www.gpo.gov/fdsys/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf. Accessed 16 January 2014.
39. US Food and Drug Administration. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM380599.pdf. Accessed 17 February 2014.
40. 112th Congress, 2nd Session. The CDC and public health response to the 2012 fungal meningitis and other infections outbreak: US Centers for Disease Control and Prevention Testimony before the Committee on Health, Education, Labor and Pensions. 15 November 2012. Available at: http://www.cdc.gov/washington/testimony/pdf/testimony_20121115.pdf. Accessed 20 September 2013.