International Journal of Infectious Diseases 17 (2013) e718–e722

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Outbreak of *Serratia marcescens* postsurgical bloodstream infection due to contaminated intravenous pain control fluids

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ARTICLE INFO

Article history:
Received 18 June 2012
Received in revised form 11 February 2013
Accepted 12 February 2013

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Serratia marcescens
Bloodstream infection
Postsurgical infection
Contaminated intravenous fluids
Fentanyl

SUMMARY

Background: Serratia marcescens is an important nosocomial pathogen causing significant outbreaks. Here we report an outbreak of bloodstream infection caused by *S. marcescens* at a 3500-bed hospital in Taiwan. The effective cooperative efforts of both laboratory personnel and infection control practitioners (ICPs) jointly contributed to the total control of the outbreak.
Methods: A sudden increase in the isolation of *S. marcescens* from blood cultures was noted in the Clinical Microbiology Laboratory. The information was passed to the ICPs and an investigation was initiated. Pulsed-field gel electrophoresis was used to study the relationships among the isolates.
Results: Pulsotype A was identified in 43 (82.7%) of the 52 blood isolates studied. They were isolated from 52 patients distributed across 22 wards that were surveyed by seven ICPs. All patients had undergone surgery before the infection, and fentanyl-containing intravenous fluids were used for pain control in 43 of them. Isolates from 42 belonged to pulsotype A. Three *S. marcescens* isolates, all from fentanyl-containing fluids and demonstrating pulsotype A, were identified from 251 environmental cultures. All fentanyl-containing fluids that were in use were withdrawn and the outbreak was stopped.
Conclusions: The outbreak of *S. marcescens* bloodstream infection apparently occurred through the use of fentanyl-containing fluids contaminated by a pulsotype A *S. marcescens*.

1. Introduction

Serratia marcescens is a Gram-negative bacillus belonging to the family *Enterobacteriaceae*. Its role in human infection was first noted in 1913.[1] However, the organism did not attract much attention until the first outbreak of nosocomial infections was reported in 1951.[2] *S. marcescens* is now recognized as a prominent opportunistic pathogen associated with significant outbreaks of various healthcare-associated infections (HAIs), including bacteremia, central nervous system infection, pneumonia, and urinary tract infection.[3–15] Sources of the infection may include contaminated equipment,[3] injected medications or fluids,[4–13] and cleansers/disinfectants.[14]

Outbreaks of HAIs are usually identified by hospital infection control practitioners (ICPs) through the established surveillance system. A significant increase in the number of HAI cases caused by certain microorganisms in a defined hospital area usually indicates the possibility of an existing outbreak. In order to fulfill the workload of total infection control management, an optimal staffing of at least one ICP per 250 beds has been recommended and used in the USA and many international healthcare facilities since 1985. Hence, for larger hospitals, several ICPs would be equipped to form an infection control team and serve the duty of hospital-wide infection control. Consequently, each ICP may be assigned to certain departments and may become more familiar with the situations in the area under his/her responsibility than other areas. Therefore, weekly or at least monthly team meetings to report and discuss the situation in their areas are necessary so that every ICP updates their understanding of the HAI situation in the hospital as a whole. However, if an outbreak of HAIs is caused by factors across multiple departments that are covered by several ICPs, the outbreak may not be discovered until the affected areas or patient numbers exceed a certain amount, or may even become a hospital-wide epidemic.[15]

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1201-9712/$36.00 – see front matter
http://dx.doi.org/10.1016/j.ijid.2013.02.012

Here we report an overwhelming outbreak of bloodstream infection (BSI) caused by *S. marcescens* at a 3500-bed university hospital in Taiwan. The majority of the patients had undergone various surgical procedures in which fentanyl-containing intravenous fluids were used for postsurgical pain control management, prior to the development of the *S. marcescens* BSI. The patients were widely distributed across 22 wards, and a total of seven ICPs were responsible for the routine surveillance of these areas. The supervisor of the Clinical Microbiology Laboratory in the hospital raised the alert due to an unusual increase in *S. marcescens* blood isolates, and the investigation was started. The effective cooperative efforts of both laboratory and clinical personnel jointly contributed to the total control of the outbreak.

2. Methods

2.1. Setting

Chang Gung Memorial Hospital (CGMH) is a 3500-bed university-affiliated medical center located in northern Taiwan. The hospital serves patients with different clinical needs and consists of 13 disease-orientated departments, including 26 intensive care units (ICUs) and 73 ordinary wards. For patients with surgical needs, the hospital is also equipped with a surgical center with 68 operating theatres. The Clinical Microbiology Laboratory in the Department of Laboratory Medicine provides routine services for the isolation/identification and antimicrobial susceptibility testing of microbiological pathogens for the whole hospital.

Active hospital-wide surveillance for HAIs has been conducted by ICPs of the infection control team at CGMH since 1976.[16] From 1995, a case of HAI was defined according to the updated criteria suggested by the US Centers for Disease Control and Prevention (CDC).[17] The infection control team consisted of 14 ICPs. Each ICP was responsible for the HAI surveillance in different departments or ward units.

2.2. Epidemiological investigation

A healthcare-associated BSI was defined in a patient with blood cultures positive for a microorganism that was obtained more than 48 h after being admitted to the hospital. In the present study, to assess the potential risk factors, the medical records of patients with *S. marcescens* BSI were reviewed and compared, including demographic characteristics, underlying diseases, recent surgery, and the associated medications. Evaluation of the practices in the associated operating theatres was performed. To identify the possible reservoirs, environmental cultures were conducted in the surgical center and its pharmacy unit. In accordance with the antibiogram of the *S. marcescens* isolates, 32 μg/ml of cefuroxime was added to the culture media to improve the efficiency of isolation.

2.3. Microbiological examination

All clinical isolates of *S. marcescens* were cultured and identified by standard methods.[18] Antimicrobial susceptibility was tested by a standard disk diffusion method.[19] Susceptible and resistant isolates were defined according to the criteria suggested by the Clinical and Laboratory Standards Institute.[19] To determine the relationships among *S. marcescens* isolates, molecular typing by pulsed-field gel electrophoresis (PFGE) was performed using the method described previously.[20] The criteria suggested by Tenover et al. were used to analyze the results.[21]

2.4. Statistical analysis

Epi Info software (version 6.04, CDC, Stone Mountain, GA, USA) was used for the statistical analysis. The Chi-square test or Fisher's exact test, when appropriate, was used. A difference was considered statistically significant with a two-tailed p-value of less than 0.05.

3. Results

3.1. Epidemiological investigation

During the last week of October 2003, the supervisor of the Clinical Microbiology Laboratory noticed that the incidence of *S. marcescens* identified from routine blood cultures had increased dramatically from less than one isolate per week to several isolates per day (Figure 1). The majority of the isolates were resistant to ampicillin/cefazolin/cefuroxime and susceptible to the other antimicrobial agents. This unusual event was immediately communicated to the ICPs. An initial investigation revealed that the patients were distributed across 22 different wards that were surveyed by seven ICPs. At the same time, the 52 blood isolates of *S. marcescens* identified during October and November 2003 were analyzed by PFGE. A predominant pattern, named pulsotype A, was identified in 43 (82.7%) of the isolates. The emergence of the pulsotype A isolates also coincided with the upsurge in *S. marcescens* infections (Figure 1).

A comparison of clinical features between patients infected with the pulsotype A strain and the patients with other pulsotypes was performed by the ICPs (Table 1). No significant difference was found regarding the demographic characteristics or underlying diseases. Recent surgery and the associated medications, such as intravenous fluids (0.9% saline) and preventive antibiotics (cefazolin), were significantly associated with the pulsotype A infection ($p < 0.000005$). The use of fentanyl for pain control after surgery was also significantly associated with the pulsotype A group ($p < 0.000005$).

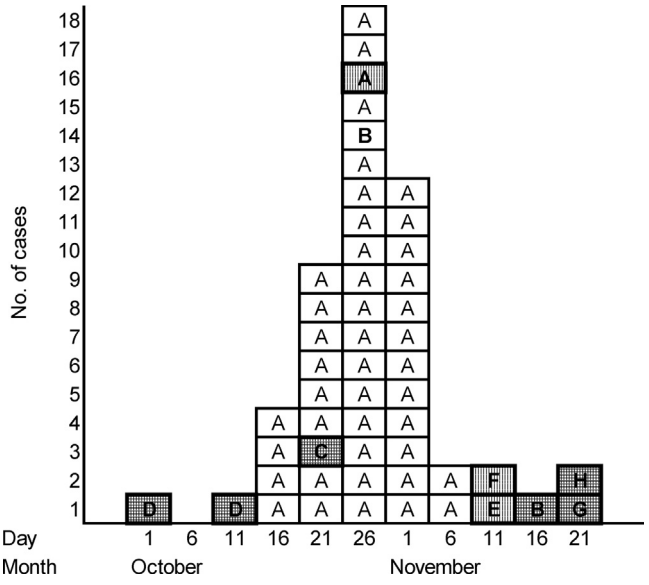

Figure 1. Epidemic curve of the outbreak of bloodstream infection caused by *Serratia marcescens*. Each cell represents a case with the infection. Blank cells are cases with surgery and the use of fentanyl-containing pain control fluids. Cells with vertical lines are cases with surgery but without the use of the pain control fluids. Cells with small squares are cases with neither surgery nor the use of the pain control fluids. Pulsotypes of the isolates are indicated as A to H.

Table 1
Comparison of clinical features between patients with *Serratia marcescens* bloodstream infections caused by the pulsotype A strain and strains of other pulsotypes

Characteristic	Mean ± SD (range), or number (%) of patients		*p*-Value[a]	Odds ratio (95% CI)
	Pulsotype A (n = 43)	Other pulsotypes (n = 9)		
Male sex	22 (51.2%)	6 (66.7%)	NS	0.52 (0.09–2.83)
Age (years)	51.3 ± 15.1 (17–80)	58.1 ± 13.8 (35–76)	NS	N/A
Underlying disease				
Burn	2 (4.7%)	0 (0%)	NS	N/A
Diabetes mellitus	2 (4.7%)	1 (11.1%)	NS	0.39 (0.02–12.35)
Liver cirrhosis	0 (0%)	1 (11.1%)	NS	0.00 (0.00–3.66)
Malignancy	3 (7.0%)	5 (55.6%)	<0.005	0.06 (0.01–0.45)
Stone	1 (2.3%)	0 (0%)	NS	N/A
Trauma	10 (23.3%)	0 (0%)	NS	N/A
None	25 (58.1%)	2 (22.2%)	NS	4.86 (0.77–38.74)
Recent surgery				
Cardiovascular	3 (7.0%)	0 (0%)	NS	N/A
Central nervous system	0 (0%)	1 (11.1%)	NS	0.00 (0.00–3.66)
Chest	3 (7.0%)	0 (0%)	NS	N/A
General	2 (4.7%)	2 (22.2%)	NS	0.17 (0.01–2.09)
Orthopedic	25 (58.1%)	0 (0%)	<0.005	N/A
Plastic	8 (18.6%)	0 (0%)	NS	N/A
Urogenital	2 (4.7%)	0 (0%)	NS	N/A
Any	43 (100.0%)	3 (33.3%)	<0.000005	N/A
Intravenous fluids/medication				
Saline, 0.9%	43 (100.0%)	3 (33.3%)	<0.000005	N/A
Cefazolin	43 (100.0%)	3 (33.3%)	<0.000005	N/A
Fentanyl	42 (97.7%)	1 (11.1%)	<0.0000005	336.0 (14.47–48651.47)
Antibiogram				
Resistant to ampicillin, cefazolin, and cefuroxime	43 (100.0%)	3 (33.3%)	<0.000005	N/A

SD, standard deviation; CI, confidence interval; NS, not statistically significant; N/A, not applicable.
[a] The Chi-square test (or Fisher's exact test, when appropriate) and two-tailed Student's *t*-test were used for statistical analysis of the difference. A difference was considered statistically significant with $p < 0.05$.

All 43 patients infected with the pulsotype A strain had undergone various surgical procedures 1 to 6 days prior to the infection. All the significant factors (use of intravenous fluids, fentanyl-containing pain control fluids, and preventive antibiotics) were also associated with the surgery. The surgical center was therefore suspected to be the major source of the infection. Further investigations revealed that the surgical procedures were performed in different operating theatres by different surgeons and nurses. However, an on-site inspection of the associated operating theatres and procedures could not identify any lapse in the associated sterile/aseptic techniques.

3.2. Environmental culture of the surgical center

To identify the possible reservoirs, environmental cultures were conducted in the surgical center. A total of 251 specimens were collected, including various intravenous fluids containing fentanyl (six unopened and 39 left-over after use) or others (seven unopened and 18 left-over after use), detergents/antiseptics (four unopened and 160 in use), surface swabs of surgical instruments and any other suspected objects (n = 17).

Despite this effort, only three isolates of *S. marcescens* were identified. They were recovered from three bags of left-over intravenous fluids that contained fentanyl for pain control. Only one of the patients who used these fluids was retrievable; he had a fever after surgery and had been empirically prescribed gentamicin without any bacterial culture. PFGE analysis indicated that the three isolates also belonged to the pulsotype A observed in the majority of the clinical isolates from patients.

After finding that the contaminated fentanyl-containing intravenous fluids might be the reservoir of the outbreak, an on-site inspection was conducted in the pharmacy unit where the pain control fluids were prepared in the surgical center. Standard operation procedures were executed by the personnel and all fulfilled the infection control policies. To identify the source of the contamination, a second environmental culture was performed in the pharmacy unit. A total of 112 specimens were collected, including hand cultures of the pharmacy personnel (n = 7), swabs of the associated environment surfaces (n = 11), detergents/antiseptics (n = 4), empty vials of narcotic agents, including fentanyl (n = 65), and others (n = 25). Only one isolate of *S. marcescens* was recovered from the surface of a tap in the preparation room. PFGE analysis indicated that the strain was not pulsotype A and thus may not be related to the outbreak. Reinforcement of infection control policies and re-education of the pharmacy personnel regarding hand-washing, aseptic preparation, and environmental cleansing, were conducted. Weekly surveillance cultures of intravenous medication prepared in-house were performed continuously to monitor the sterility of the products. No further contamination by *S. marcescens* or other bacteria has been identified since the outbreak.

3.3. Termination of the outbreak

Immediately after the identification of the *S. marcescens* in the left-over fentanyl-containing fluids, the superior authorities of the hospital immediately decided to withdraw all of the in-use fentanyl-containing fluids to prevent any further infection. Also, to prevent any possible misuse, the withdrawn fluids were destroyed on site immediately. None of the removed fluids was available for further examination. The outbreak subsided very quickly without any mortality (Figure 1). Only sporadic isolates of *S. marcescens* with different pulsotypes were identified from the blood cultures (Figure 1). During the 9-year period after the outbreak, up to the present, no similar outbreak of infection has occurred at this hospital.

4. Discussion

Outbreaks of healthcare-associated bloodstream infections associated with extrinsic contamination of narcotic agents have been described in many previous reports.[5–8,22–25] Interestingly, *S.*

marcescens or other species are frequently involved in such events.[5–8] In the present study, *S. marcescens* was also isolated from some fentanyl-containing fluids and was genetically indistinguishable from the outbreak strain isolated from the majority of the patients, indicating that the outbreak was associated with the contaminated fentanyl-containing fluids.

Previous reports have indicated some of the possible causes that may be related to such contaminations, including lapses in the aseptic technique, use of single-use medication vials on multiple patients, use of a common syringe for multiple medications/patients, and even illicit use by healthcare personnel.[4–8,22–25] However, despite the efforts to reveal the possible route of contamination, none of these conditions could be found in the present study. As *S. marcescens* was found in only three of the left-over fentanyl-containing fluids, the contamination might have been introduced accidentally during the preparation procedure. The problem might also have been overcome by education and continuous monitoring during the investigation and thereafter. Consequently, after the complete withdrawal of all the in-use fentanyl-containing fluids, no similar infection cases were reported.

Although only three contaminated fentanyl-containing fluids were identified, one patient was traceable and was found to have developed fever after surgery. The patient had recovered with empirical antibiotics without any culture evidence. Similar situations have been reported previously; patients who received contaminated fluids may not have developed illnesses and therefore remained unaware before any investigation was started.[22,23] This situation implies that the outbreak may have involved more patients than we identified. Moreover, the hidden patients may have deterred or delayed the investigation until more patients were affected and the outbreak became more obvious. Positive bacterial culture results are usually used by ICPs to screen for the existence of HAI cases. However, manual surveillance is not only time-consuming but may also miss some HAI cases, such as the one we identified herein. Recently, an automated detection system incorporating data from multiple sources, including microbiology and other laboratory results, as well as medication data, was developed to predict drain-related meningitis.[26] A similar design may also be feasible in detecting the hidden cases who develop postsurgery infections and are given empirical antimicrobial agents without any microbiological evidence.

It is disappointing that no further contaminated fentanyl-containing fluids could be identified. However, it is generally accepted that outbreak investigations should first solve the problem to prevent any further risk to patients. The immediate withdrawal of all the in-use fentanyl-containing fluids was a must once the possible source of contamination was revealed. To prevent any misuse, all the withdrawn bags were also destroyed immediately and therefore no further evidence could be retrieved. Judging from the fact that no new cases were identified, the immediate act of withdrawal and destroying of the fluids definitely played an important role in stopping the outbreak.

It has long been recognized that the microbiology laboratory has the earliest opportunity to detect the emergence or clusters of specific organisms or antimicrobial resistance patterns, as a result of continuous monitoring and analysis of the extensive data accumulated from routine cultures. With the close communication with ICPs, laboratory personnel can therefore help to detect and eliminate potential outbreaks of HAIs.[27–29] The present report is another good example, demonstrating how microbiology laboratory personnel can assist in infection control. Because the infected patients were distributed across 22 different wards that were surveyed by seven ICPs, the sudden increase in *S. marcescens* infections would not have been so obvious to each of the seven ICPs in the initial stages. The excellent professional awareness of the Clinical Microbiology Laboratory personnel, as well as the good communication between the laboratory and the ICPs jointly contributed to the early detection of this unusual outbreak, leading to an efficient investigation and prompt termination of the outbreak. Recently, several computer-assisted surveillance systems using microbiology data to detect potential outbreaks of HAIs have been reported.[30,31] Integration of such information technology should further extend the value of microbiology data and contribute more efficiently to hospital-wide infection control and outbreak detection.

In conclusion, an unusual and overwhelming outbreak of *S. marcescens* BSIs was reported. Contamination of fentanyl-containing fluids was found to be associated with the outbreak. Continuous education on infection control policies and monitoring of the aseptic preparation procedures are necessary for personnel responsible for the preparation of intravenous fluids with or without other medications. Until the implementation of any automated detection systems, close communication among ICPs, as well as between ICPs and laboratory personnel, is important for the rapid identification and termination of such outbreaks.

Acknowledgements

The authors thank all their colleagues on the infection control team and the Clinical Microbiology Laboratory for their outstanding professional performance and cooperation. There was no other funding source provided.

Ethical approval: The study was conducted as part of the healthcare quality improvement program of the Chang Gung Memorial Hospital, Linkou, Taiwan. Ethical approval was not required.

Conflict of interest: No competing interest declared.

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