

Outbreak of Bloodstream Infection Temporally Associated with the Use of an Intravascular Needleless Valve

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Background. Needleless intravascular catheter connector valves have been introduced into clinical practice to minimize the risk of needlestick injury. However, infection-control risks associated with these valves may be underappreciated. In March 2005, a dramatic increase in bloodstream infections was noted in multiple patient care units of a hospital in temporal association with the introduction of a needleless valve into use.

Methods. Surveillance for primary bloodstream infection was conducted using standard methods throughout the hospital. Blood culture contamination rates were monitored. Cultures were performed using samples obtained from intravascular catheter connector valves.

Results. The relative risk of bloodstream infection for the time period in which the suspect connector valve was in use, compared with baseline, was 2.79 (95% confidence interval, 2.27–3.43). In critical care units, the rate of primary bloodstream infection increased with the introduction of the valve from 3.87 infections per 1000 catheter-days to 10.64 infections per 1000 catheter-days ($P < .001$), and it decreased to 5.59 infections per 1000 catheter-days ($P = .02$) in the 6 months following removal of the device from use. Similarly, in inpatient nursing units, the rate of bloodstream infection increased from 3.47 infections per 1000 catheter-days to 7.3 infections per 1000 catheter-days ($P = .02$) following introduction of the device, and it decreased to 2.88 infections per 1000 catheter-days ($P = .57$) following removal of the device from use. Similar events occurred in the cooperative care units. The rate of blood culture contamination did not substantially change over the course of the study. Of 37 valves that were subjected to microbiological sample testing, 24.3% yielded microbes, predominantly coagulase-negative staphylococci.

Conclusion. A significant association between primary bloodstream infection and a needleless connector valve was observed. Evaluation of needleless connector valves should include a thorough assessment of infection risks in prospective randomized trials prior to their introduction to the market.

Needleless intravascular access systems are mandated to reduce the risk of needlestick injuries in health care workers [1, 2]. There are 3 basic design types of needleless access systems: split-septum connectors; luer-activated valves; and positive-displacement, luer-activated valves. There are numerous commercially available products within each basic design type. Many

of these needleless access systems are introduced into clinical use without thorough evaluation of associated infection control risks. Recently, concerns have been expressed regarding increased rates of bloodstream infection associated with the use of newer needleless mechanical valve systems [3–5].

Intravascular catheter-related bacteremia is a substantial clinical problem that results in an attributable mortality of ~3% and an attributable cost-per-incident of ~\$25,000 among the estimated 250,000 patients annually who experience this complication in the United States [6–9]. Therefore, if any portion of the intravascular access system increases the risk of bloodstream infection, it must be thoroughly evaluated, and clinicians should be appropriately alerted.

A dramatic increase in the rate of primary blood-

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stream infection in multiple inpatient units was observed in our institution in temporal association with the introduction of a positive-displacement, luer-activated, needleless connector valve. Similarly, upon removal of the putative offending device, the rate of bloodstream infection decreased. Herein, we report these findings and other observations supporting the causative role of the intravascular needleless connector valve in the outbreak.

METHODS

Location and surveillance methods. The Nebraska Medical Center (Omaha) is a 689-bed academic medical center. Continuous active surveillance for bloodstream infections in critical care units and cooperative care units (step-down care facilities for bone marrow and solid-organ transplant recipients in which a patient and a care partner [a spouse or family member] are housed together in a home-like environment) has been conducted for years using Centers for Disease Control and Prevention methods and definitions [10]. Surveillance for device-associated bloodstream infections was implemented in other nursing units in November 2004. Initially, surveillance was conducted every third month; in May 2005, continuous surveillance was instituted. Bloodstream infection rates were monitored in 3 types of patient care areas: critical care and transplantation units (8 patient care units consisting of 132 beds), inpatient nursing units (9 patient care units consisting of 312 beds), and transplantation cooperative care units (2 inpatient care units consisting of 22 beds). A primary bloodstream infection was defined as occurring when ≥ 1 blood culture of samples obtained from a patient yielded a pathogen that was not present because of an infection at another site. Common skin contaminants (e.g., diptheroids or coagulase-negative staphylococci) were disregarded, unless they were recovered from ≥ 2 blood samples that were obtained separately or from a patient who had a central venous catheter and for whom the physician instituted appropriate antimicrobial therapy. Infections manifesting within 48 h after admission to the hospital were regarded as non-hospital acquired. Primary bloodstream infection rates were expressed in infections per 1000 central venous catheter-days. In the cooperative care units, accurate intravascular catheter census data were not reliably available, and the infection rates were expressed in infections per 1000 patient-days.

Devices and timing of clinical use. Prior to February of 2005, a split-septum intravascular access connector valve (Interlink IV Access System; Baxter) was in use in our hospital. During the last week of February 2005, a luer-activated, positive-displacement, intravascular access valve (SmartSite Plus; Alaris Medical Systems) was introduced into clinical practice throughout the hospital. Education on the proper use of the intravascular access valve was conducted on all units by nurse

educators and manufacturer's representatives. No changes were instituted in catheter insertion or care protocol during the observation periods. The intravenous administration set and connector valves were changed every 7 days, or more frequently if the connector valve or tubing appeared to be damaged, showed signs of leakage, or was visibly contaminated with blood [9]. Administration sets were changed more frequently when blood products, lipids, or parenteral nutrition formulations were infused [9]. Intravenous access ports were cleaned with a swab containing 70% isopropyl alcohol before accessing the port. Following an observed increase in the rate of bloodstream infections, efforts to replace the positive-displacement intravascular access valve were initiated in late June 2005, and the previously used split-septum valve was returned to use throughout the hospital by 1 September 2005. Although there was widespread institutional recognition of the outbreak and increased vigilance with regard to compliance with vascular access insertion and care protocol, a formal, system-wide reeducation effort was not conducted during the period when the positive-displacement intravascular access valve was in use.

Blood culture contamination. The clinical microbiology laboratory routinely monitored the rate of blood culture contamination using a laboratory definition of contamination. Blood cultures were considered to be most likely contaminated when single blood cultures (1 of 1 blood culture) yielded *Bacillus* species, aerobic and anaerobic diptheroids (including *Corynebacterium* species and *Propionibacterium acnes*), or *Micrococcus* species. If a single blood culture among multiple blood cultures performed using samples obtained from the same patient yielded coagulase-negative staphylococci, it was regarded as being a likely contaminated specimen.

Catheter connector valve cultures. Intravascular access valves were removed from the central venous catheters of 12 adult critical care unit patients and replaced with new valves. The used valves were transported to the laboratory in individual sterile containers. The diaphragms of the used valves were disinfected with 70% isopropyl alcohol wipes (Kendall), and 1 mL of trypticase soy broth (Bacto; Difco Laboratories) was injected through the valves and collected in sterile 5-mL plastic test tubes. A 0.1 mL aliquot of the broth was inoculated onto trypticase soy agar plates (Difco Laboratories), and the plates and remaining broth were incubated at 37°C for 48 h. Standard microbiological testing techniques were used to identify recovered microbes.

Statistical analysis. Primary bloodstream infection rates were modeled over the 3 time periods (baseline [before March 2005], outbreak [March 2005–August 2005], and follow-up [September 2005–February 2006]) for the 3 types of patient care units (critical care and transplantation units [8 areas], inpatient nursing units [9 areas], and transplantation cooperative care units [2 areas]). The number of bloodstream infec-

tions that were observed was modeled using Poisson regression, with the rates assumed to be constant for each of the 6 patient-care-unit-time-period combinations. SAS GENMOD software, version 9.1.3 (SAS) was used for modeling. Comparisons of patient care units and time periods were expressed as relative risks.

RESULTS

As is illustrated in figure 1, the rate of bloodstream infection increased dramatically in all types of patient care areas in conjunction with the introduction of the positive-displacement connector valve. In the 8 critical care and transplantation units, the baseline bloodstream infection rate, which was calculated on the basis of 38,250 central venous catheter-days over a 26-month period, was 3.87 infections per 1000 central venous catheter-days. During the 6-month period when the positive-displacement connector valve was in clinical use in our facility (accounting for 10,340 days of central venous catheter use), the rate of bloodstream infection increased 2.82-fold (95% CI, 2.21-fold to 3.61-fold) to 10.64 infections per 1000 central venous catheter-days ($P < .001$). In the 6 months following the discontinuation of use and the removal of the positive-displacement connector valves, the bloodstream infection rate decreased to 5.59 infections per 1000 central venous catheter-days ($P = .02$, compared with baseline). In the 9 inpatient nursing units, the baseline rate of catheter-associated bloodstream infection, which was calculated on the basis of 2 one-month-long observation periods (November 2004 and February 2005) that involved 3745 central venous catheter-days, was 3.47 infections per 1000 central venous catheter-days. During the outbreak period, the rate of bloodstream infection increased 2.1-fold (95% CI, 1.15-fold to 3.86-fold) to 7.3 infections per 1000 central venous catheter-days ($P = .02$). During the postintervention period, the rate of bloodstream infection decreased to 2.88 infections per 1000 central venous catheter-days during 11,475 days of central venous catheter use, which is a similar rate to that observed at baseline ($P = .57$). Finally, in the 2 cooperative care transplantation populations, the baseline rate of bloodstream infection of 5.31 infections per 1000 patient-days that was demonstrated during 7535 patient-days of observation over 26 months of time increased 2.86-fold (95% CI, 1.69-fold to 4.85-fold) to 15.18 infections per 1000 patient-days during 1383 days of patient observation ($P < .001$). This rate decreased to 3.82 infections per 1000 patient-days over 1047 patient-days of observation in the postintervention period, which is a similar rate to that observed at baseline ($P = .53$). There was no statistical evidence that the increased risk differed across the 3 patient care units. The estimated relative risk of bloodstream infection for the 6-month period in which the positive-displacement connector valve was used in our facility,

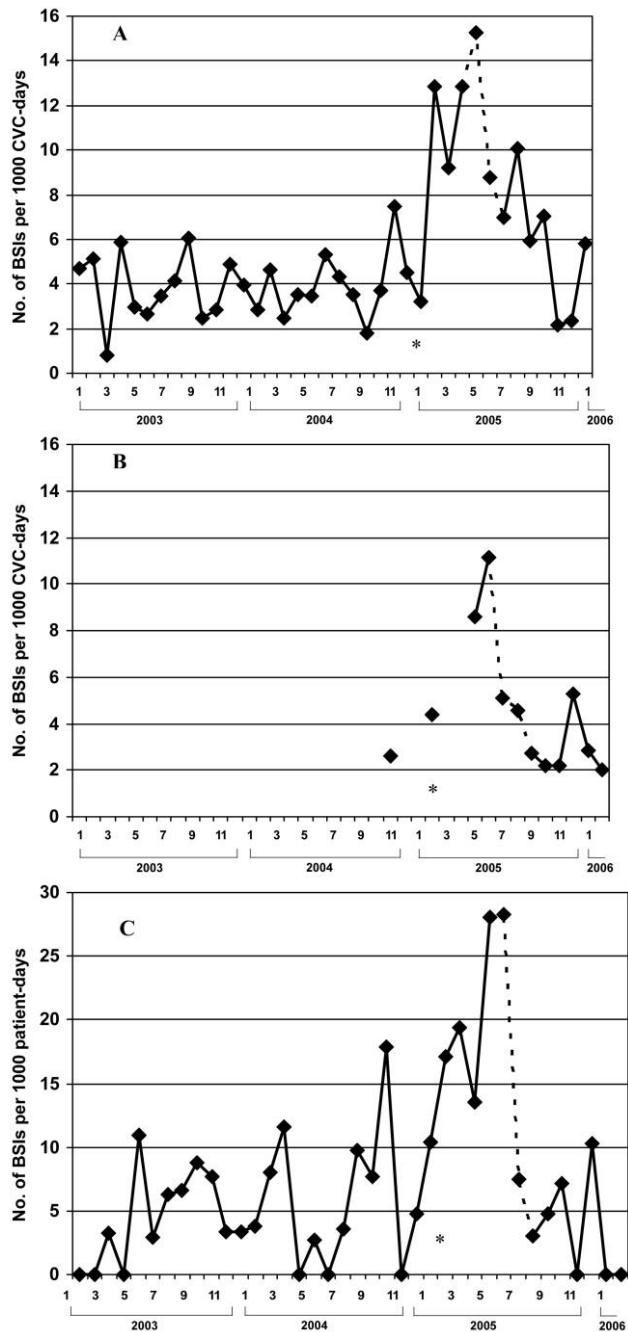


Figure 1. Rate of bloodstream infection versus time, January 2003 to February 2006. Numbers 1–12 in the x-axis refer to consecutive months (from January to December) of the year indicated. Bloodstream infections in critical care units (A), in inpatient nursing units (B), and in cooperative care units (C). Infections are expressed as bloodstream infections (BSI) per 1000 central venous catheter (CVC)-days in panels A and B and as bloodstream infections per 1000 patient-days in panel C. Asterisk, when the positive-pressure displacement valve was introduced; dotted trend line, the transition period as the valves were removed from clinical use. In panel B, the first 2 data points indicate separate observation months in November 2004 and February 2005; continuous surveillance was instituted in May 2005. The connector valve was introduced in late February 2005 and was completely removed from clinical use by September 2005.

compared with the baseline period, was 2.79 (95% CI, 2.27–3.43).

Table 1 documents the microbiological characteristics of the bloodstream infections that were observed during the overall investigation period. In the 26-month preoutbreak period, 201 bloodstream infections were defined, of which 24 (11.9%) were polymicrobial. Sixty-four percent of the infections were due to gram-positive cocci, and 33% were due to coagulase-negative staphylococci. Microbiological characteristics during the outbreak period were quite similar to those in the preoutbreak period. A total of 189 bloodstream infections were observed, of which 16 (8.5%) were polymicrobial. Sixty-four percent of the infections were due to gram-positive cocci and 34% were due to coagulase-negative staphylococci. In the postoutbreak period, 98 bloodstream infections were observed, of which 5 (5.1%) were polymicrobial. The proportion of bloodstream infections due to gram-positive cocci increased to 76%, and coagulase-negative staphylococci caused 45% of the infections. There was no substantial difference in the proportion of polymicrobial bloodstream infections during the observation periods ($P = .15$, by Fisher's exact test). The proportion of infections due to *Candida* species remained fairly constant throughout the periods of observation, at 6%, 6%, and 7% during the preoutbreak, outbreak, and postoutbreak periods, respectively.

The rate of blood culture contamination remained relatively constant over the course of the outbreak. In the 14 months prior to the outbreak, the rate of blood culture contamination was 3.00% (816 contaminated cultures of 27,172 blood samples obtained). During the 6-month outbreak period, the contam-

ination rate was 3.02% (415 contaminated cultures of 13,742 blood samples obtained); during the 6-month follow-up period, the contamination rate was 3.13% (407 contaminated cultures of 12,994 blood samples obtained). The number of blood samples obtained per month increased by 18%, from 1941 samples per month during the preoutbreak period to 2290 samples per month during the outbreak period. In the 6 months following the outbreak, the number of samples obtained per month decreased modestly to 2166 samples per month.

Samples obtained from 9 (24.3%) of 37 positive-displacement intravascular catheter access valves in 7 (58.3%) of the 12 patients yielded positive results when cultured; all valves from multilumen catheters were sampled. The catheters had been inserted an average of 8 days before sampling (median, 5 days; range, 1–27 days). As previously noted, connector valves were routinely changed at 7-day intervals. All positive sample cultures yielded typical skin flora (e.g., coagulase-negative staphylococci or diptheroids) ranging in quantity from 10 to 1500 colony forming units/mL of broth flush solution. No gram-negative bacilli or yeast were recovered from the connector valves. In 1 instance, it was noted that the broth was bloody after being flushed through the connector valve.

DISCUSSION

Needleless vascular connectors have been widely introduced throughout the health care system in response to mandates for improvement in health care worker safety and avoidance of bloodborne pathogen exposure [1, 2]. Split-septum devices were the first needleless devices to be introduced to the market,

Table 1. Microbiological characteristics of central venous catheter-associated bloodstream infections (BSIs).

Pathogen	Percentage of total BSIs caused by specific pathogen		
	Preoutbreak period (<i>n</i> = 201)	Outbreak period (<i>n</i> = 189)	Postoutbreak period (<i>n</i> = 98)
Gram-positive cocci	64	64	76
Coagulase-negative staphylococci	33	34	45
<i>Enterococcus</i> species	19	19	19
<i>Staphylococcus aureus</i>	7	7	8
Other gram-positive cocci	5	4	4
Gram-negative bacilli	25	27	16
<i>Enterobacter</i> species	6	3	1
<i>Klebsiella</i> species	7	6	4
<i>Escherichia coli</i>	2	5	3
<i>Pseudomonas</i> species	2	8	4
<i>Serratia</i> species	2	2	1
Other gram-negative bacilli	6	3	3
<i>Candida</i> species	6	7	6
Other	5	2	2

and consist of a prepierced diaphragm that is accessed via a blunt cannula. Luer-activated devices control an antireflux valve and are compatible with standard twist-lock connector tubing or syringes. Most recently, to minimize catheter occlusion, positive-displacement devices have been introduced that expel a small volume of flush solution back into the catheter when the device is disconnected. Although needleless connectors have been shown to reduce the risk of needlestick injury [11, 12], the benefit of early-generation needleless connectors was questioned after reports of increased rates of primary bloodstream infections associated with their use [13–16]. Investigation of these outbreaks revealed that the risk of infection was increased when connectors were changed less frequently than is recommended, when specific infusates (such as total parenteral nutrition or lipids) were administered, and when other independent factors were considered (such as patient race and education, multilumen catheter use, or recent hematopoietic stem cell transplantation) [13–17]. In 2002, the Centers for Disease Control and Prevention reported that needleless connectors do not substantially affect the incidence of bloodstream infection when they are used according to manufacturer's recommendations [9]. More recently, increasingly sophisticated mechanical valve connectors have been introduced into clinical practice. Limited data are available regarding the risk of bloodstream infection that is associated with these devices. In studies comparing luer-activated valves with simple caps, rates of contamination and bloodstream infection were reduced with the use of the mechanical valves [18–20]. In 2004, Hall et al. [3] first reported infection-related concerns regarding the newer devices; reports from other institutions followed [4–5, 21, 22]. The device implicated in the outbreak described by Maragakis et al. [5] is the same brand of device temporally associated with the increase in rate of bloodstream infection described in this report. In addition, Shilling et al. [23] noted higher catheter occlusion rates associated with the use of a positive displacement needleless valve, compared with a simpler mechanical valve, as well as a trend toward higher infection rates when saline was used to flush the device.

The present report adds to the increasing attribution of unintended consequences to the introduction of various mechanical needleless catheter connectors into use. Several features of our study merit emphasis. There was a striking temporal relationship between introduction of the connector valve and a ~2.7-fold increase in primary bloodstream infection. Similarly, when the connector valve was removed from clinical use in our facility, the rate of bloodstream infection decreased toward baseline. The increase in bloodstream infection was quickly detected and was observed in all areas and in all patient groups where the device was used. The rapid detection of this outbreak emphasizes the value of well-functioning systems of surveillance for health care-associated infection. The wide-

spread nature of the outbreak indicated a generalized problem, not one associated with a small group of health care workers or a limited point-source outbreak. As illustrated in table 1, the microbiologic etiology of the bloodstream infections was relatively constant and was most consistent with inoculation of the intravascular catheter system with skin flora. The variety of microbial species that were isolated and the lack of reports of similar outbreaks in the region argues against a generalized contamination of infusate as the causative factor. Likewise, no change in the protocol of intravascular catheter insertion or care occurred that could explain a generalized outbreak. Finally, additional support for the causative role of the connector valve came from the results of microbiological testing of samples obtained from the connector valves in clinical use. Microbes were recovered from 24.3% of the sampled connector valves. In comparison, 2 clinical studies examining the risk of microbial colonization of connector valves [18, 20] reported rates of colonization of 4.3% of patients and 6.6% of devices, whereas Danzig et al. [15] related a connector device colonization rate of 21.7% associated with a bloodstream infection outbreak.

Limitations of this study must also be emphasized. First, this was not a prospective, randomized trial. These data are retrospective, observational, and uncontrolled. In addition, our report details experience at a single institution. Although the connector valve was introduced into clinical use in conjunction with an extensive educational program, it is not known whether further education regarding catheter insertion and care would have ameliorated the outbreak. Although earlier studies [13, 14, 16] have indicated that lapses in intravascular catheter care could explain increased infection rates associated with the introduction of new connector valves, other investigators have found repeated educational efforts regarding proper use of the devices to be unrewarding [4].

Although speculative, we believe that the design of the connector valve introduced in our hospital in March 2005 may have promoted microbial contamination and colonization. Upon close inspection of the valve (figure 2), one can observe a shallow depression and rim between the diaphragm and the plastic housing. It is possible that microbes and debris could collect in this area, which would be relatively resistant to cleansing or disinfection. The internal mechanism of the valve contains moving parts, which introduces irregularities in the fluid flow and may promote areas of stagnation and create potential reservoirs for microbial growth. Also, the plastic housing is opaque, which prohibits visual inspection of the connector valve. Therefore, it is possible that blood or infusion products could collect within the valve and, because of its opaque nature, go unnoticed by health care workers. Last, because of stiffness or “memory” of plastic intravenous tubing, if the luer connection mechanism is not fully engaged, the tubing can untwist, resulting in disconnection and possible contamination.



Figure 2. The 2 vascular catheter connector valves described in this study. The valve on the left is the split-septum valve used before and after the outbreak of primary bloodstream infection. The valve on the right is the luer-activated, positive-displacement connector valve that was temporally associated with an increase in the rate of bloodstream infection.

This study also demonstrated the complexities of health care system supply lines. A multitude of persons and viewpoints are involved in decisions regarding supply purchases; potential infection control concerns are only one, albeit a very important, consideration. In heavily bureaucratized and outsourced hospital supply systems, decisions regarding device distribution are not easily communicated throughout. In addition, end users of supplies may have personal stockpiles of supplies that are not officially sanctioned. We encountered obstacles at various levels of the supply chain in attempting to remove the connector valve from clinical use. Although efforts to remove the new connector valve and replace it with the original valve were initiated in June, we continued to find the putative offending device in sporadic clinical use throughout the summer. This may explain why bloodstream infection rates did not decrease as steeply when the device was removed as they had increased when the device was introduced. Only through repeated, thorough searches of supply rooms, bedside cabinets, and nursing units and repeated communication along the supply line did we finally achieve a complete exchange of devices by September.

In conclusion, a strong temporal relationship was observed between the introduction of a positive-displacement intravascular catheter connector valve and an increase in the rate of primary bloodstream infection that resolved when the connector valve was removed from clinical use. Although causation can not be concluded from these data, clinicians and persons responsible for institutional medical device purchase and use should be aware of the association between this particular connector valve and an increased risk for bloodstream infection. Because of significant morbidity, mortality, and economic cost associated with bloodstream infection, any change in the design

of intravascular catheter devices or the procedures used in their insertion or care should be thoroughly investigated in adequately sized and well-designed studies to ascertain unanticipated infectious complications before they are approved and introduced to the market. Finally, the value of surveillance systems for the detection of health care-associated adverse events and well-functioning infection-control programs is once again demonstrated.

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