TITLE: Positive versus Negative Needleless Connectors for Central Venous Lines and Peripheral Lines: A Review of the Clinical Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES:

In response to an increased emphasis on preventing needlestick injuries, infusion technology has developed specific types of needleless connectors.1 These devices allow connection of catheters, administration sets and syringes. They are categorized as simple or complex based on the complexity of the internal mechanisms.2

The blunt cannula access devices (BCADs), also known as split-septum devices, are simple devices with no internal mechanism, allowing the fluid to move straight through the device lumen.1 BCADs are negative fluid displacement (NFD) devices, meaning that a small amount of blood will be pulled back into the catheter lumen upon disconnection of the administration set or syringe from the device.1 All simple devices that include a three-way stopcock are NFD connectors.

Complex needleless connectors contain an internal mechanism called a mechanical valve.2 Luer activated devices (LADs) are complex needleless connectors that incorporate a valve to prevent fluid flow through the device until a male luer is inserted. Four designs of LADs are currently available:1

- Capped NFD LADs - NFD devices that must be capped with a new sterile cap after each use.
- Noncapped NFD LADs – NFD devices that do not need a cap, but must be swabbed with antiseptic before use.
- Noncapped positive fluid displacement (PFD) LADs – PFD LAD devices that produce a positive fluid displacement upon disconnection of the administration set or syringe from the device, since the valve has a reservoir for holding a small amount of fluid. This reduces the potential for reflux of blood into the catheter lumen.
- Noncapped neutral fluid displacement LADs – LAD devices that also reduce the potential reflux of blood into the catheter lumen upon connection and disconnection.
The major difference in the use of the NFD and the PFD devices is that the NFD device is clamped before the syringe is disconnected, whereas the PFD device is not clamped until after the syringe is disconnected.\textsuperscript{2}

There has been concern about the risk of catheter-related bloodstream infections (CR-BSIs) and vascular access device occlusions with complex needleless connectors, since the mechanical valve products were introduced.\textsuperscript{3,4} This report reviews the evidence for clinical effectiveness of PFD versus NFD needleless connectors on central and peripheral venous catheters. The clinical outcomes are catheter-related occlusions and bloodstream infections.

**RESEARCH QUESTIONS:**

1. What is the clinical effectiveness of positive fluid displacement needleless connectors versus negative fluid displacement needleless connectors for adults with central venous lines?
2. What is the clinical effectiveness of positive fluid displacement needleless connectors versus negative fluid displacement needleless connectors for adults with peripheral venous lines?
3. What are the guidelines for the use of positive fluid displacement and negative fluid displacement needleless connectors for patients with central venous lines or peripheral venous lines?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including OVID Medline, EBSCOhost CINAHL, The Cochrane Library (Issue 3, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and March 30, 2010. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Systematic reviews are presented first, followed by randomized controlled trials and observational studies.

**SUMMARY OF FINDINGS:**

One systematic review,\textsuperscript{5} three randomized controlled trials (RCTs),\textsuperscript{6-8} and five observational studies\textsuperscript{9-13} were included. No clinical guidelines for the use of PFD and NFD needleless connectors for patients having central or peripheral catheters were found.

Seven\textsuperscript{6-12} of the studies (three RCTs and four observational studies) compared the rates of catheter-related bloodstream infections (CR-BSI) between the complex needleless connectors containing a mechanical valve (luer-activated PFD or NFD type) and the simple needleless connectors without the internal mechanism. One observational study\textsuperscript{13} compared the efficacy between PFD and NFD mechanical valve connectors. The luer-activated PFD type of internal mechanical valves were Posiflow\textsuperscript{6} (BD Medical), CLC2000\textsuperscript{10} (Abbott Laboratories), SmartSite Plus\textsuperscript{11,13} (Alaris Medical Systems). The luer-activated NFD type of internal mechanical valves were Clearlink\textsuperscript{7} (Baxter), SmartSite\textsuperscript{8,12} (Alaris Medical Systems) and CLAVE\textsuperscript{13} (ICU Medical). The simple needleless connectors were the standard capped connector,\textsuperscript{6} three-way stopcock with cap attached,\textsuperscript{7,8} and Interlink split septum\textsuperscript{10-12} (Baxter).
Systematic reviews and meta-analyses

Niel-Weise et al., 2006⁵ performed a systematic review to determine the efficacy of needleless connector devices in terms of prevention of catheter-related infections. The review included five RCTs, four of which compared needleless closed systems with conventional open systems and one RCT compared the needleless closed systems with conventional closed systems. The needleless closed systems are complex devices containing mechanical valves of either negative or positive fluid displacement types. Those used in the studies were CLAVE (ICU Medical), PosiFlow (Becton Dickinson), MultiFlow hub (Clave), Multilumen Smartsite DNFC (Alaris Medical Systems), and Interlink (Baxter). The conventional open systems included standard luer caps with and without hub protection boxes, while the conventional closed system was the PRN Luer slip adaptor. Study populations were intensive care patients with diverse underlying diseases, receiving different types of intravascular lines. Although combining of data was not possible due to substantial heterogeneity, the authors suggested that needleless closed systems might provide an advantage in reducing catheter-related infections. However, they stated that the evidence was insufficient to recommend the use of needleless closed vascular devices.

Randomized controlled trials

Appendix 1 shows the characteristics and outcomes of the included RCTs.

**PFD mechanical valve device versus NFD simple device**

Khalidi et al., 2009⁶ conducted an RCT to assess the impact of using positive pressure valves on occlusion and CR-BSI for both peripheral and central venous lines. The Posiflow® (BD Medical), a luer-activated PFD type of mechanical valve was compared with a standard capped connector. Eighty adult patients receiving parental therapy from a tertiary care hospital were randomized to each arm of treatment. The source of study funding was not reported. There was no significant difference between the luer-activated PFD type of mechanical valve and the standard capped connector in the rates of catheter occlusions (6.95 versus 1.30 occlusion per 1,000 catheter days, \( p=0.43 \)) or CR-BSI (2.32 versus 0 infections per 1,000 catheter days, \( p=0.497 \)).

**NFD mechanical valve device versus NFD simple device**

Casey et al., 2007⁷ conducted an RCT to study the microbial contamination rate associated with NFD luer-activated Clearlink® (Baxter) needleless connectors and three-way stopcock luers with standard caps in central venous catheters. Each arm contained 25 adult patients admitted for elective cardiothoracic surgery. The study was sponsored by Baxter. Following 72 hours in situ, the connectors were removed from the central venous catheters and transported to the laboratory for microbiological culture. It was found that internal microbial contamination was 0.5% for the Clearlink® connectors and 10% for the three-way stopcock connectors (\( p<0.0001 \)). CR-BSI or catheter occlusions were not assessed in this study. The authors concluded that the use of the Clearlink® device with a dedicated disinfection regimen reduces the internal microbial contamination rate of central venous catheter luers compared with standard caps.

Esteve et al., 2007⁸ conducted an RCT to assess the efficacy of a needleless valve connection system in the prevention of CR-BSI. A luer-activated NFD type of mechanical valve connector (Smartsite®, Alaris Medical Systems) was compared with a three-way stopcock connector. A total of 799 adult patients (404 patients in the Smartsite group and 395 patients in the three-way...
stopcock group) who required central venous catheter and arterial catheter placement for a duration of greater than 48 hours during their ICU stay at a university hospital were included. The study received public funding. It was found that the rates of CR-BRI were similar in both groups (4.61 in the n the Smartsite group versus 4.11 in the three-way stopcock group for infections per 1,000 catheter days). The authors concluded that the use of a needleless valve connection system does not reduce the incidence of catheter-related bacteremia.

**Observational studies**

Appendix 2 shows the characteristics and outcomes of the included observational studies.

**Any mechanical valve device versus NFD simple device**

Jarvis et al., 2009\(^9\) retrospectively analyzed multicenter data to compare the health care-associated bloodstream infection rates on wards or intensive care units at five hospitals that had been converted from split septum connectors or needles to mechanical valve needleless connectors. The mechanical valve needleless connectors, either NFD or PFD type (UltraSite®, Clearlink®, SmartSite®), were compared with split septum connectors (Interlink®). Adult patients from 16 intensive care units who received central venous catheters were included. Patient numbers and characteristics were not reported. The study was sponsored by Becton-Dickinson. The rate of infection per 1,000 catheter days during the period of split septum connector or needle use in the 16 intensive care units was 6.15 versus 9.49 with mechanical valves during the period when connector use was switched to mechanical valves. The relative risk (95% CI) of infection was 1.54 (1.37-1.74), \(p<0.001\) (an OR greater than 1.0 indicates that the risk of infection was greater with mechanical valves). When the hospitals (14 intensive care units) switched back to split septum needleless connectors, the rate of infection dropped from 9.49 to 5.77 per 1,000 catheter days. The relative risk (95% CI) of infection was 1.65 (1.38-1.96), \(p<0.001\). The authors concluded that the use of mechanical valve needleless connectors was associated with increased health care-associated bloodstream infections rates, despite CR-BSI surveillance, definitions, and prevention strategies.

**PFD mechanical valve device versus NFD simple device**

Field et al., 2007\(^10\) conducted a retrospective analysis to audit the CR-BSI rates in response to a perceived increase in incidence that was coincident with a change from split septum connector to a mechanical valve connector. A luer-activated PFD type of mechanical valve connector (CLC2000®, Abbott Laboratories) was compared with Interlink split septum (Baxter), NFD simple device without internal mechanism. The type of venous access device (i.e., central or peripheral) was not specified. Source of funding was not reported. A 12-month period was analyzed, including the first split septum period (July 2004 to November 2004), the mechanical valve period (November 2004 to April 2006) and the second split septum period (April 2006 to July 2006). Patients were from a regional public hospital and were those with Hickman catheters inserted during the 12-month period, of which 62 patients were in the period of mechanical valve and 83 patients were in the period of split septum. The CR-BSI rate increased from 2.6 infections per 1,000 catheter days in the split septum periods to 5.8 infections per 1,000 catheter days in the mechanical valve period (\(p=0.031\)). Thus, a significant increase in the incidence of CR-BSI with the introduction of a mechanical valve intravenous connector was observed.

Rupp et al., 2007\(^11\) retrospectively investigated an outbreak of bloodstream infections that was temporally associated with the use of an intravascular needleless valve connector. A luer-
activated PFD type of mechanical valve connector (Smartsite® Plus, Alaris Medical Systems) was compared with Interlink split septum (Baxter), a NFD simple device without an internal mechanism. A total of 488 patients received central venous catheters within a 3-year period, of which 201 patients were in the preoutbreak period (use of split septum), 189 patients were in the outbreak period (use of SmartSite Plus), and 98 were in the postoutbreak period (removal of the PFD connector valves). The source of funding was not reported. It was found that the rates of infection (per 1,000 catheter days) increased from 3.87 in the period where split septum connector was used to 10.64 during the introduction period of Smartsite® Plus connector. The relative risk of infection was 2.79 (95% CI: 2.27-3.43), \( p < 0.001 \). The rate dropped back to 5.59 in the six months following removal of the PFD device. The authors concluded that there was a strong temporal relationship between the introduction of a PFD 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.

**PFD mechanical valve device versus NFD mechanical device**

Maragakis et al., 2006\(^{13}\) retrospectively evaluated the correlation between CR-BSI rates and switching from a NFD mechanical valve device to a PFD mechanical valve device within the past 3-year period. A luer-activated PFD type of mechanical valve connector (Smartsite® Plus, Alaris Medical systems) was compared with CLAVE® needless connector (ICU medical), a NFD type of mechanical valve device. The study received public funding. Patients were both adults and children who received central venous catheters at the intensive care units. The numbers of patients and their characteristics were not reported. The results showed that the CR-BSI rates increased from 1.5 (in the period before the new PFD device was introduced) to 2.4 infections per 1,000 catheter days (in the period of introduction of PFD mechanical valve). The relative risk of infection was 1.60 (95% CI: 1.04-2.48), \( p = 0.03 \). The authors concluded that a significant increase in CR-BSI was observed after the introduction of a needle-free positive-pressure mechanical valve intravenous access port.

**NFD mechanical valve device versus NFD simple device**

Salgado et al., 2007\(^{12}\) retrospectively investigated whether the introduction of a needleless mechanical valve device at a long-term acute care hospital was associated with an increased frequency of CR-BSI. A luer-activated NFD type of mechanical valve connector (Smartsite®, Alaris Medical Systems) was compared with a split septum connector, a NFD simple device without an internal mechanism. Patients were those with complex medical needs receiving central venous catheters at a long-term acute care hospital. The number of patients and their characteristics were not reported. Source of funding was not reported. It was found that the rate of infection per 1,000 catheter days during 24-month introduction of a NFD mechanical valve connector was 5.95 compared to 1.79 during the use of split septum device period. The relative risk was 3.32 (95% CI: 2.88-3.83), \( p < 0.001 \). The authors concluded that an increased CR-BSI rate was temporally associated with the use of a needleless mechanical valve device at the study hospital, despite several educational sessions regarding proper use of the mechanical device.

**Limitations**

The evidence from the included studies did not directly answer the questions asked in this review with respect to the type of needleless connector to use for central venous lines or peripheral venous lines. Most studies compared the mechanical valve devices to the simple
open devices in terms of catheter-related infections. With the exception of one study, comparisons between the current types of mechanical valve connectors (i.e. NFD versus PFD) were not found. The included systematic review was not updated with the current literature. The study durations in RCTs were relatively short and, therefore, may not capture the differences in CR-BSI rates as shown in the observational studies using retrospective approach. No guidelines were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In the comparison between the mechanical valve devices (either NFD of PFD type) versus simple devices (NFD type), evidence from the RCTs showed no differences in terms of catheter-related infections, while evidence from the observational studies showed that the introduction of mechanical valve devices was associated with significant increase in CR-BSI rates. One observational study showed that a PFD mechanical valve device was associated with more CR-BSI than a NFD mechanical valve device used for central venous catheters. Taken together, the clinical effectiveness of PFD needleless connectors versus NFD needleless connectors for adult patients receiving central venous lines or peripheral venous lines is inconclusive based on the current evidence. There were no guidelines to indicate which type of mechanical devices (NFD or PFD) should be used for venous access devices (central or peripheral).

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REFERENCES


## APPENDIX 1: Characteristics and outcomes of randomized controlled trials

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<th>Patients / settings</th>
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</table>
| Khalidi et al., 2009<sup>6</sup> | Intervention: Posiflow®, BD Medical; a luer-activated PFD type of mechanical valve  
Control: Standard capped connector; NFD type  
VAD: Both peripheral and central venous lines  
Duration: about 10 catheter days | Patients: Adults receiving parental therapy  
Total: 160; 80 patients in each arm  
Setting: tertiary care hospital | (Rate per 1,000 catheter days)  
Occlusion: 6.95 in intervention versus 1.30 in control, \( p = 0.43 \)  
CR-BSI: 2.32 in intervention versus 0 in control, \( p = 0.497 \) | There was no difference in the rate of catheter occlusions or CR-BSI when using PFD connector valves or standard caps |
| Casey et al., 2007<sup>7</sup> | Intervention: Clearlink®, Baxter; a luer-activated NFD type of mechanical valve  
Control: 3-way stopcock luers with caps attached  
VAD: Central venous catheter  
Duration: 72 hours in situ | Patients: Adult (31-77 years) admitted for elective cardiothoracic surgery.  
Total: 50; 25 patients in each arm  
Setting: University hospital | Internal microbial contamination: 0.5% with intervention versus 10% with control, \( p < 0.0001 \) | The use of the Clearlink® device with a dedicated disinfection regimen reduces the internal microbial contamination rate of central venous catheter luers compared with standard caps |
| Esteve et al., 2007<sup>8</sup> | Intervention: SmartSite®, Alaris Medical Systems; a luer-activated NFD type of | Patients: adult required central venous catheter and arterial catheter | (Rate per 1,000 catheter days)  
CR-BSI: 4.61 in | The use of needleless valve connection system does not reduce the |
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<tr>
<td>parallel, two arms</td>
<td>mechanical valve Control: 3-way stopcock connection with caps VAD: Central venous catheter Duration: &gt;48 hours</td>
<td>placement for a duration ≥ 48 h during their ICU stay Total: 799; 404 in intervention and 395 in control Setting: ICU of a university hospital</td>
<td>intervention versus 4.11 in control</td>
<td>incidence of catheter-related bacteraemia</td>
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</tbody>
</table>

CI: confidence interval; CR-BSI: catheter-related bloodstream infection; ICUs: intensive care units; PFD: positive fluid displacement; NFD: negative fluid displacement; NR: not reported; RCT: randomized controlled trial; VAD: venous access devices
## APPENDIX 2: Characteristics and outcomes of observational studies

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<tr>
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<tbody>
<tr>
<td>Jarvis et al., 2009&lt;sup&gt;9&lt;/sup&gt;</td>
<td><strong>Intervention</strong>: Any mechanical valve (NFD or PFD) needleless connectors (UltraSite®, Clearlink®, SmartSite®) <strong>Control</strong>: Split septum (Interlink®, Baxter) connectors or needles <strong>VAD</strong>: Central venous catheter <strong>Duration</strong>: All study periods (11 to 39 months)</td>
<td><strong>Patients</strong>: Adults from 16 intensive care units of 5 hospitals <strong>Patient numbers and characteristics not reported</strong> <strong>Settings</strong>: Academic hospitals, 3 from US and 2 from Australia</td>
<td>(Rate per 1,000 catheter days) CR-BSI: - Switching from split septum or needles to mechanical valve connectors (16 ICUs): 6.15 versus 9.49 Relative risk (95% CI): 1.54 (1.37-1.74), ( p &lt; 0.001 ) - Switching back to split septum connectors (14 ICUs): 9.49 versus 5.77 Relative risk (95% CI): 1.65 (1.38-1.96), ( p &lt; 0.001 )</td>
<td>The use of mechanical valve needleless connectors was associated with increased health care-associated bloodstream infections rates, despite CR-BSI surveillance, definitions, and prevention strategies.</td>
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<td>Field et al., 2007&lt;sup&gt;10&lt;/sup&gt;</td>
<td><strong>Intervention</strong>: CLC2000®, Abbott Laboratories; a luer-activated PFD type of mechanical valve <strong>Control</strong>: Interlink split septum, Baxter; a NFD type of simple connector with no internal mechanism <strong>VAD</strong>: not specified <strong>Duration</strong>: 12-month period</td>
<td><strong>Patients</strong>: Those with Hickman catheters inserted between July 1, 2004 and June 30, 2005 Total: 145; 62 in intervention period and 83 in control period. <strong>Setting</strong>: Regional public hospital, hematology-oncology unit</td>
<td>(Rate per 1,000 catheter days) CR-BSI: 5.8 in intervention (during introduction of a mechanical valve connector) versus 2.6 in control (during the use of split septum connector), ( p = 0.031 )</td>
<td>There was a significant increase in the incidence of CR-BSI with the introduction of a mechanical valve intravenous connector.</td>
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<td>Rupp et al., 2007&lt;sup&gt;11&lt;/sup&gt;</td>
<td><strong>Intervention</strong>: SmartSite Plus, Alaris Medical Systems; a luer-activated</td>
<td><strong>Patients</strong>: Those in the three types of care areas: 1) critical care and</td>
<td>(Rate per 1,000 catheter days) CR-BSI in critical care</td>
<td>There was a strong temporal relationship between the introduction of</td>
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<td>retrospective</td>
<td>PFD type of mechanical valve</td>
<td>transplant units, 2) inpatient nursing units, 3) transplantation cooperative care units</td>
<td>units: 10.64 in intervention (during introduction of a PFD mechanical valve connector) versus 3.87 in control (during the use of split septum connector)</td>
<td>a PFD intravascular catheter connector valve and an increased in the rate of primary bloodstream infection that resolved when the connector valve was removed from clinical use.</td>
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<td>Sponsor: not reported</td>
<td>Control: Interlink split septum, Baxter; a NFD type of simple connector with no internal mechanism</td>
<td>Total: 488; 201 in the preoutbreak period (use of split septum), 189 in the outbreak (use of SmartSite Plus), 98 in the postoutbreak (removal of PFD connector valves) Setting: The Nebraska Medical Center</td>
<td>The rate dropped to 5.59 in 6 months following removal of the PFD device Similar patterns were observed for inpatient nursing units and cooperative care units</td>
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<tr>
<td>Salgado et al., 2007</td>
<td>Intervention: SmartSite, Alaris Medical Systems; a luer-activated NFD type of mechanical valve</td>
<td>Patients: Those with complex medical needs Patient numbers and characteristics not reported Setting: Long-term acute care hospital</td>
<td>Relative risk (95% CI): 2.79 (2.27-3.43), ( p &lt; 0.001 )</td>
<td>An increased CR-BSI rate was temporally associated with the use of a needleless mechanical valve device at the study hospital, despite several educational sessions regarding proper use of the mechanical device</td>
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<td>Observational, retrospective</td>
<td>Control: Needleless split septum device; a NFD type of simple connector with no internal mechanism</td>
<td>(Rate per 1,000 catheter days) CR-BSI: 5.95 in intervention (during 24-month introduction of a NFD mechanical valve connector) versus 1.79 in control (during the use of split septum device)</td>
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<tr>
<td>Sponsor: not reported</td>
<td>VAD: Central venous catheter Duration: 4-year period</td>
<td>Relative risk (95% CI): 3.32 (2.88-3.83), ( p &lt; 0.001 )</td>
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<td>Maragakis et al., 2006</td>
<td>Intervention: SmartSite Plus, Alaris Medical</td>
<td>Patients: both adults and children at the intensive</td>
<td>(Rate per 1,000 catheter days)</td>
<td>A significant CR-BSI was observed after the</td>
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<td>Observational, retrospective</td>
<td>Systems; a luer-activated PFD type of mechanical valve &lt;br&gt; <strong>Control:</strong> CLAVE® needlefree connector, ICU Medical; a NFD type of mechanical valve &lt;br&gt; <strong>VAD:</strong> Central venous catheter &lt;br&gt; <strong>Duration:</strong> 3-year period</td>
<td>care units &lt;br&gt; Patient numbers and characteristics not reported &lt;br&gt; <strong>Setting:</strong> Tertiary care academic medical center</td>
<td><strong>CR-BSI:</strong> 2.4 in intervention (in the period of introduction of PFD mechanical valve) versus 1.5 in control (in the period before the new PFD device was introduced) &lt;br&gt; Relative risk (95% CI): 1.60 (1.04-2.48), <em>p</em>=0.03 &lt;br&gt; After PFD device was removed, the CR-BSI rate dropped to 1.43.</td>
<td>introduction of a needle-free positive-pressure mechanical valve intravenous access port.</td>
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CI: confidence interval; CR-BSI: catheter-related bloodstream infection; ICUs: intensive care units; PFD: positive fluid displacement; NFD: negative fluid displacement; NR: not reported; RCT: randomized controlled trial; VAD: venous access devices