Review

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Clinical impact of needle-free connector design: A systematic review of literature

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Abstract

The objective of this systematic review is to analyze types of needle-free connectors and open systems and their effects on central line–associated bloodstream infection rates and other adverse outcomes through a research protocol consistent with the Preferred Reporting Items for Systematic Reviews' recommendations. MEDLINE and Cochrane databases of systematic reviews were searched for relevant comparative studies published from January 2000 to September 2017. Eighteen studies compared central line–associated bloodstream infection (according to the Centers for Disease Control and Prevention/National Healthcare Safety Network definition), internal microbial contamination, occlusions, phlebitis, and other outcomes associated with needle-free connectors with a positive displacement device, negative displacement device, neutral displacement device, or three-way stopcock. Ten studies reported central line–associated bloodstream infection rates, which were lower with positive displacement devices versus negative displacement devices/neutral displacement devices (one study) and with negative displacement devices versus three-way stopcocks (three studies), but varied with different positive displacement device and negative displacement device/neutral displacement device designs (four studies). Seven studies reported internal microbial contamination rates, which were higher with three-way stopcocks versus negative displacement devices (two studies) and positive displacement devices (two studies), lower when positive displacement devices were used versus neutral displacement devices (one study), and varied with different types of negative displacement device (one study). Central line–associated bloodstream infection rates and most other outcomes analyzed were statistically significantly higher with three-way stopcocks (open devices) versus positive displacement device, negative displacement devices, and neutral displacement devices, but varied among closed device designs.

Keywords

Mechanical valve, split septum, needleless connector, needle-free connector, open-system connectors, three-way stopcock, bloodstream infections, central venous catheter-associated infections, contamination

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Introduction

Needles have traditionally been used to connect intravenous (IV) tubing to intravascular catheters and to inject or infuse medications and fluids into the catheter injection port. Needlestick and percutaneous injuries from sharp devices occur in approximately 384,000 healthcare workers (HCWs) in US hospitals annually, with approximately 61% of needlestick injuries caused by hollow-bore needles and 8% of injuries caused by accessing the intravascular catheters.[1] The risk of occupational exposures to blood-borne infections such as hepatitis B and C, and HIV, brought the issue of preventing needlestick injuries to the forefront in the early 1980s.[2] In 1991, the Occupational Safety and Health Administration (OSHA) issued a final ruling on the Bloodborne Pathogen Standard that regulates occupational exposure to blood-borne pathogens (BBPs) and needlestick and sharps injuries among HCWs.[3] The standard was revised 10 years later to incorporate the Needlestick Safety and Prevention Act.

Since the enactment of these standards, needle-free connectors (NFCs) were introduced on the market to

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eliminate needle use with intravascular catheters.[3] However, since the introduction of NFCs into clinical practice, reports have emerged of sudden and significant increase of central line–associated bloodstream infection (CLABSI) rates with the mechanical valves.[3]

Today's NFCs evolved from the industry's initial efforts to make devices that comply with these OSHA regulations. They were designed primarily for HCW safety, to prevent accidental needlestick injury and BBP infection. With the initial introduction of split septum NFCs, outbreaks of CLABSIs occurred.[4] With the re-emphasis on the importance of infection control practices with these devices (e.g. septum disinfection and cap changes), infection risk was lowered.[4] To further decrease the risk of needle use with such devices, negative displacement mechanical NFCs were introduced. Then, with the purpose of reducing the risk of occlusions, positive displacement NFCs were introduced. This led to a few CLABSI outbreaks associated with some of these NFCs.[4,5] Ultimately, this led to the Food and Drug Administration (FDA)'s "522 Postmarket Surveillance (PS) Studies Program," which required that US manufacturers of positive displacement NFCs provided data that their devices were associated with risk of CLABSI at or below the level associated with negative displacement NFCs.[6] This program aimed at ensuring that well-designed 522 PS studies were conducted effectively and efficiently. In May 2008, its oversight responsibility was transferred to the Division of Epidemiology of the Office of Surveillance and Biometrics/Center for Devices and Radiological Health, which launched a publicly available webpage to inform the progress and status of each of the 522 PS studies.[7] In this regard, Carefusion & B Braun responded to this FDA request by showing the absence of a higher risk of CLABSI when using positive versus negative displacement NFCs, given comparable patient populations.[7]

Newer generations of NFCs have been designed to improve patient safety and specifically reduce CLABSI risk. These design features include the following: a visible fluid path so that clinicians can assess the efficacy of their flush technique; a solid, flat, smooth access surface that can be effectively disinfected; a one-part activation of the fluid path for effective flush; an open fluid pathway to provide a high flow rate and avoid hemolysis; and other desired safety features (e.g. tight septum seal, minimal internal complexity, ability to flush with saline alone).[8,9]

The aim of this study was to review the types of NFCs and open systems and their effects on CLABSI rates and other adverse outcomes.

NFCs and open systems

NFCs provide needle-free access at the hub end of the catheter for IV medication administration, fluid infusion, withdrawal of blood samples, or connecting administration sets to the intravascular catheters. NFCs include the split septum connectors and the luer-activated mechanical valves.[10] The standard split septum connectors or negative reflux caps do not have internal mechanisms and are pre-pierced to allow access by a blunt cannula to open the fluid pathway for IV fluid infusion or medication administration.

On the basis of their internal membrane function, mechanical valves are classified as negative, neutral, or positive displacement types.[10] Mechanical valves have an internal membrane or valve and require a mating luer connector when flushing or administering IV fluids or medications.

The syringe tip or the tip of the IV tubing is directly inserted into the cap without the need for a blunt needle.[10] The design of positive pressure valves (PPVs) is aimed at limiting the retrograde blood flow inside the catheter at the moment of luer syringe disconnection.[11]

Methods

Definitions

Anti-reflux NFCs: incorporate a bidirectional fluid control valve designed to restrict fluid movement on connection and prevent unplanned reflux into the intravascular catheter during infusion, connection, disconnection, and patient changes in intrathoracic pressure.[12]

Fluid displacement: the volume, movement, and direction of fluid during connector and/or disconnection.

Negative displacement (negative displacement device) NFCs: allow blood reflux into vascular access device (VAD) lumen upon disconnection due to movement of valve mechanism or removal of syringe/set.

Positive displacement (positive displacement device) NFCs: allow a small amount of fluid to be held in the device. On disconnection, this fluid is pushed through the catheter lumen to clear any blood that refluxed into the lumen.

Neutral displacement (neutral displacement device) NFCs: designed to limit blood reflux into the catheter lumen upon connection or disconnection; although some may contain an internal mechanism/valve to limit reflux, most neutral displacement devices (NEDDs) do not have an anti-reflux valve. Some fluid reflux has been reported in the literature.[13]

Reflux: a negative displacement of fluid or blood.

Three-way stopcock: a form of valve that includes a body having three ports therein or turning plugs that control the flow of fluid from a container through a tube. A three-way stopcock (3WSC) can be used on IV tubing to turn off one solution and turn on another. It is open to

the air without a membrane when the cover is not in place and, thus, is considered an open IV system.

Data sources

A systematic review (SR) was conducted through a research protocol consistent with the Preferred Reporting Items for SRs' recommendations.[14] MEDLINE and Cochrane databases of SRs were searched for relevant studies published from January 2000 to September 2017.

Study selection and data extraction

Study inclusion criteria were randomized controlled trials or observational comparative studies that reported the CLABSI, colonization, phlebitis, occlusion, bending, kinking, blockage, displacements, loosening, and extravasation rates in patients with positive, negative, and neutral displacement and open-system connectors compared with other devices. The following Medical Subject Headings and keywords were used for the search: "mechanical valve, split septum, needleless connector, needle-less connector, needlefree connector, needle-free connector, open-system connectors, three-way stop cock, bending, blockage, bloodstream infections, central venous catheter-associated infections, contamination, displacement, extravasation, flushing, kinking, loosening, occlusion, phlebitis."

Process

- An Internet search was conducted, and all abstracts identified were read independently.
- Data were extracted on standardized forms including study design, setting, patient population, facility location, number of CLABSIs (numerator), number of central line (CL) days (denominator), bending, blockage, contamination, displacement, extravasations, flushing, kinking, loosening, occlusion, and phlebitis during the study, plus NFC device versus comparator device periods for the studies included.
- CLABSI incidence density (infections per 1000 CL days) was recorded at each site and percentage of bending, blockage, contamination, displacement, extravasation, flushing, kinking, loosening, occlusion, and phlebitis.

Results

Published studies

Our search strategies produced 18 prospective studies that compared CLABSI, contamination, displacement, kinking or loosening, occlusion, or phlebitis rates associated with NFCs with that of positive displacement devices (PDDs), negative displacement devices (NDDs), NEDDs, and 3WSCs. Among them, 11 were randomized studies, 6 were sequential studies, and 1 was a meta-analysis. All 18 studies used Centers for Disease Control and Prevention (CDC)'s National Healthcare Safety Network (NHSN) definition of CLABSI for outcome measures.

Description of the studies

The characteristics of the reviewed studies are shown in Table 1, and the comparison among the studies' main outcomes by type of device used is shown in Table 2.

- Two studies compared PDDs against other designs of PDDs.[18,23]
- One study compared PDDs against NDDs.[24] However, it did not attain statistically significant results.
- One study compared PDDs against NEDDs.[29]
- One study compared PDDs against NDDs or NEDDs.[19]
- Two studies compared PDDs against 3WSC open connectors.[17,25] However, one of them[17] did not attain statistically significant results.
- Seven studies compared NDDs against 3WSC open connectors.[15,16,20,22,26,27,30]
- One study compared NEDDs against NEDDs.[31]
- One study compared NEDDs against NDDs.[21]
- Two studies compared NDDs against other designs of NDDs[5,28]

Discussion

In this SR, 18 studies comparing CLABSI rates (according to the CDC/NHSN definition), IMC, occlusions, phlebitis, or other adverse outcomes associated with NFCs with PDD, NDD, or NEDD, or 3WSC. Ten studies reported CLABSI rates, but in two of them, there were not any difference between the groups studied.[16,17] From the remaining eight studies with statistically significant CLABSI rate outcomes, CLABSI rates were lower if using NDDs was compared with using 3WSC open devices as shown in two studies,[16,22] with the exception of one study conducted in which "SmartSite" NDD showed a higher CLABSI rate compared with 3WSC.[15] In one study, CLABSI rates were lower if PDD was used in comparison with the use of NDDs and NEDDs.[19] On the other hand, in three studies, CLABSI rates varied when different designs of PDDs[18,23] and NDDs were compared.[5]

The outcomes concerning internal microbial contamination (IMC) were reported in seven studies. In two of them, there were no differences in the groups compared.[20,24] In three of them, contamination percentages were higher when using 3WSC was compared with using NDD.[20,26,27] Similarly, in one study, microbial contamination was higher if 3WSC was used in comparison with

Table 1. Studies' characteristics.

Study	Controlled	Prospective	Trial	In vivo	Outcome(s)	Level of evidence
Yebenes et al.[15]	Yes	Yes	Randomized	Yes	Central line–associated bloodstream infection	High
Esteve et al.[16]	Yes	Yes	Randomized	Yes	Central line–associated bloodstream infection	High
Field et al.[5]	No	No	Sequential	Yes	Central line–associated bloodstream infection	Moderate
Khalidi et al.[17]	No	Yes	Randomized	Yes	Bloodstream infection,[a] occlusion[a]	High
Royer[18]	No	Yes	Sequential	Yes	Central line–associated bloodstream infection	Moderate
Tabak et al.[19]	Yes	Yes	Meta Analysis	Not applicable	Central line–associated bloodstream infection	High
González López et al.[20]	Yes	Yes	Randomized	Yes	Central line–associated bloodstream infection, phlebitis	High
Wheeler et al.[21]	No	Yes	Sequential	Yes	Central line–associated bloodstream infection	Moderate
Rosenthal et al.[22]	Yes	Yes	Randomized	Yes	Central line–associated bloodstream infection	High
Wallace and Macy[23]	No	Yes	Sequential	Yes	Central line–associated bloodstream infection	Moderate
Casey et al.[24]	Yes	Yes	Randomized	Yes	Internal microbial contamination	Moderate
Casey et al.[25]	Yes	Yes	Randomized	Yes	Internal microbial contamination	High
Casey et al. [26]	Yes	Yes	Randomized	Yes	Internal microbial contamination	High
Yebenes et al.[27]	Yes	Yes	Randomized	Yes	Internal microbial contamination	High
Casey et al.[28]	Yes	Yes	Randomized	Yes	Internal microbial contamination	High
Casey et al.[29]	No	Yes	Sequential	Yes	Internal microbial contamination	Moderate
Tamura et al.[30]	Yes	Yes	Randomized	Yes	Bending/kinking, blockage, displacement/loosening, extravasation, phlebitis	High
Holt and Lawrence[31]	No	Yes	Sequential	Yes	Occlusion	Moderate

[a]No statistical significance.

PDD.[25] In turn, contamination percentages varied when PDDs were used instead of NDDs according to two studies.[24,29] Microbial contamination varied when different types of NDDs were compared in one study in which "ClearLink" NDD showed a higher percentage of contamination than "V-LINK" NDD.[28]

Central line occlusion was analyzed in two studies.[17,31] Phlebitis percentages were analyzed in two studies.[20,30] Rates were similar or lower with NDDs versus 3WSCs.[20,30]

Finally, regarding other adverse outcomes, one study showed the use of 3WSC resulted in higher percentages of bending/kinking (0 vs 5.5), blockage (2.1 vs 4.6), displacements/loosening (0 vs 5.5), extravasations (9.1 vs 24.8), and occlusions (3.7 vs 11.9) than the use of NDDs (split septum).[30] The same percentages were reported for phlebitis.[30]

Study limitations

The main limitation of this study is that most of the studies included in the analysis present a strong bias: the fact that the incidence of CLABSI is mainly associated with the way NFCs are used (which type/time of disinfection, use or not use of port protectors, etc.) as much as the incidence of occlusion is mainly related to the policies of catheter flushing and locking.

Conclusion

This review showed that in most of the studies analyzed, CLABSI rates and most of the adverse outcomes' rates were statistically significantly higher when 3WSC (open device) was compared to PDD, NDDs and NEDD, but these results varied among closed device designs. From the study of the publications available on the different design variations of NFCs, it is clear that adequate cleaning, use, and disinfection processes are crucial for successful infection prevention; however, further research is needed to generate sufficient evidence for HCWs to make informed choices and allow safe and optimal practices. To have confidence in the type of NFC design to be used, it becomes necessary to conduct more studies analyzing standardized testing of microbial ingress, anti-septic methods, and biofilm formation in the different types of NFC designs.

Table 2. Comparison among studies' main outcomes by the type of device used.

Study	Device type: product name	CLABSIs per 1000 CL days	Device type: product name	CLABSIs per 1000 CL days
CLABSI				
Rosenthal et al.[22]	NDD: Q-Syte	2.2	Open device: 3WSC	6.4 ($p = .006$)
Yebenes et al.[15]	NDD: SmartSite™	0.7	Open device: 3WSC	5.0 ($p = .03$)
González López et al.[20]	NDD: Q-Syte™	5.76	Open device: 3WSC	6.65[a]
Esteve et al.[16]	NDD: SmartSite	4.26	Open device: 3WSC	5.27[a]
Khalidi et al.[17]	PDD: Posiflow™	2.32	Open device: 3WSC	0[a]
Field et al.[5]	NDD: INTERLINK split septum	2.6	NDD: Clave™ mechanical valve	5.8 ($p = .031$)
Royer[18]	PDD: MaxPlus clear	0.84	PDD: other NFC	1.73 ($p < .05$)
Wheeler et al.[21]	NEDD: MicroClave™	0.9	NDD: Spiros™	1.8 ($p < .05$)
Tabak et al.[19]	PDD: MaxPlus	0.5	NDD or NEDD NFC	1.5 ($p = .0004$)
Wallace and Macy[23]	PDD: MaxPlus clear	0.8	PDD: Non-swabable NFC	2.9 ($p < .05$)
Internal microbial contamination	Device type: product name	Rate/percentage	Device type: product name	Rate/percentage
Casey et al.[26]	NDD: ClearLink	0.5% (1 of 193 internal surfaces contaminated)	Open device: 3WSC	10% (20 of 200 internal surfaces contaminated; $p < .0001$)
González López et al.[20]	NDD: Q-Syte	51.1 colonization per 1000 CL days	Open device: 3WSC	54.1 colonization per 1000 CL days[a]
Casey et al.[25]	PDD: Posiflow	6.6% (18 of 274 internal surfaces contaminated)	Open device: 3WSC	18% (55 of 306 internal surfaces contaminated; $p < .05$)
Yebenes et al.[27]	PDD: SmartSite™Plus Positive Bolus	2.4% (catheter hubs colonized in 1 of 41 cases)	Open device: 3WSC	20.5% (catheter hubs colonized in 8 of 39 cases; $p = .03$)
Casey et al.[24]	NDD: Clave™	4% internal microbial contamination	PDD: Posiflow™	5.5% internal microbial contamination[a]
Casey et al.[28]	NDD: V-LINK	26.1% of connectors had microorganisms present within the internal fluid pathway	NDD: ClearLink	47% of connectors had microorganisms within internal fluid pathway ($p = .001$)
Casey et al.[29]	PDD: MaxPlus clear	4% internal microbial contamination	NEDD: MicroClave	13% internal microbial contamination ($p \leqslant .0001$)
Occlusion	Device type: product name	Rate/percentage	Device type: product name	Rate/percentage
Khalidi et al.[17]	PDD: Posiflow	6.95	Open device: 3WSC	1.30[a]
Holt and Lawrence[31]	NEDD: Neutron™	0.98	NEDD: MicroClave	3.93 (*Not available*)
Phlebitis				
González López et al.[20]	NDD: Q-Syte	31 cases per 1000 CL days; 96-h phlebitis dwell time	Open device: 3WSC	45 cases per 1000 CL days; 137-h phlebitis dwell time ($p = .004$)
Tamura et al.[30]	NDD: Nexiva™ peripheral catheter with split septum	2.8% (4 of 143 cases)	Open device: peripheral catheter with 3WSC	2.8% (3 of 109 cases)[a]
Other adverse outcomes	Device type: product name	No. of adverse outcomes	Device type: product name	No. of adverse outcomes
Tamura et al.[30]	NDD: Nexiva peripheral catheter with split septum	Bending/kinking: 0 (0%) Blockage: 3 (2.1%) Displacement/loosening: 0 (0%) Extravasation: 13 (9.1%)	Open device: peripheral catheter with 3WSC	Bending/kinking: 6 (5.5%; $p = .0060$) Blockage: 5 (4.6%) Displacement/loosening: 6 (5.5%; $p = .0060$) Extravasation: 27 (24.8%; $p = .0009$)

CLABSI: central line–associated bloodstream infection; CL: central line; NDD: negative displacement device; 3WSC: three-way stopcock; PDD: positive displacement device; NEDD: neutral displacement device; NFC: needle-free connector.

[a]No statistical significance.

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References

1. Panlilio AL, Orelien JG, Srivastava PU, et al. Estimate of the annual number of percutaneous injuries among hospital-based healthcare workers in the United States, 1997-1998. *Infect Control Hosp Epidemiol* 2004; 25(7): 556–562.
2. Marcus R, Kay K and Mann JM. Transmission of human immunodeficiency virus (HIV) in health-care settings worldwide. *Bull World Health Organ* 1989; 67(5): 577–582.
3. United States Department of Labor. Revision to OSHA's Bloodborne Pathogens standard: technical background and summary, https://www.osha.gov/needlesticks/needlefact.html (2001, accessed 17 April 2018).
4. Salgado CD, Chinnes L, Paczesny TH, et al. Increased rate of catheter-related bloodstream infection associated with use of a needleless mechanical valve device at a long-term acute care hospital. *Infect Control Hosp Epidemiol* 2007; 28(6): 684–688.
5. Field K, McFarlane C, Cheng AC, et al. Incidence of catheter-related bloodstream infection among patients with a needleless, mechanical valve-based intravenous connector in an Australian hematology-oncology unit. *Infect Control Hosp Epidemiol* 2007; 28(5): 610–613.
6. Empaire GD, Guzman Siritt ME, Rosenthal VD, et al. Multicenter prospective study on device-associated infection rates and bacterial resistance in intensive care units of Venezuela: International Nosocomial Infection Control Consortium (INICC) findings. *Int Health* 2017; 9(1): 44–49.
7. Al-Abdely HM, Alshehri AD, Rosenthal VD, et al. Prospective multicentre study in intensive care units in five cities from the Kingdom of Saudi Arabia: impact of the International Nosocomial Infection Control Consortium (INICC) multidimensional approach on rates of central line-associated bloodstream infection. *J Infect Prev* 2017; 18(1): 25–34.
8. Jarvis WR. Choosing the best design for intravenous needleless connectors to prevent bloodstream infections, http://www.infectioncontroltoday.com/infusion-vascular-access/choosing-best-design-intravenous-needleless-connectors-prevent-bloodstream (2010, accessed 4 August 2017).
9. Bowers L, Speroni KG, Jones L, et al. Comparison of occlusion rates by flushing solutions for peripherally inserted central catheters with positive pressure Luer-activated devices. *J Infus Nurs* 2008; 31(1): 22–27.
10. Hadaway L and Richardson D. Needleless connectors: a primer on terminology. *J Infus Nurs* 2010; 33(1): 22–31.
11. Yebenes JC and Serra-Prat M. Clinical use of disinfectable needle-free connectors. *Am J Infect Control* 2008; 36(10): S175.e171–S175.e174.
12. Casey AL, Karpanen TJ, Nightingale P, et al. The risk of microbial contamination associated with six different needle-free connectors. *Br J Nurs* 2018; 27(2): S18–S26.
13. Hull GJ, Moureau NL and Sengupta S. Quantitative assessment of reflux in commercially available needle-free IV connectors. *J Vasc Access* 2018; 19: 12–22.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151: W65–W94.
15. Yebenes JC, Vidaur L, Serra-Prat M, et al. Prevention of catheter-related bloodstream infection in critically ill patients using a disinfectable, needle-free connector: a randomized controlled trial. *Am J Infect Control* 2004; 32(5): 291–295.
16. Esteve F, Pujol M, Limon E, et al. Bloodstream infection related to catheter connections: a prospective trial of two connection systems. *J Hosp Infect* 2007; 67(1): 30–34.
17. Khalidi N, Kovacevich DS, Papke-O'Donnell LF, et al. Impact of the positive pressure valve on vascular access device occlusions and bloodstream infections. *J Assoc Vasc Access* 2009; 14: 84–91.
18. Royer T. Implementing a better bundle to achieve and sustain a zero central line-associated bloodstream infection rate. *J Infus Nurs* 2010; 33(6): 398–406.
19. Tabak YP, Jarvis WR, Sun X, et al. Meta-analysis on central line-associated bloodstream infections associated with a needleless intravenous connector with a new engineering design. *Am J Infect Control* 2014; 42(12): 1278–1284.
20. González López JL, Arribi Vilela A, Fernández del Palacio E, et al. Indwell times, complications and costs of open vs closed safety peripheral intravenous catheters: a randomized study. *J Hosp Infect* 2014; 86(2): 117–126.
21. Wheeler DS, Giaccone M, Hutchinson N, et al. An unexpected increase in catheter-associated bloodstream infections at a children's hospital following introduction of the Spiros closed male connector. *Am J Infect Control* 2012; 40(1): 48–50.
22. Rosenthal VD, Udwadia FE, Kumar S, et al. Clinical impact and cost-effectiveness of split-septum and single-use prefilled flushing device vs 3-way stopcock on central line-associated bloodstream infection rates in India: a randomized clinical trial conducted by the International Nosocomial Infection Control Consortium (INICC). *Am J Infect Control* 2015; 43(10): 1040–1045.

23. Wallace MC and Macy DL. Reduction of central line-associated bloodstream infection rates in patients in the adult intensive care unit. *J Infus Nurs* 2016; 39(1): 47–55.
24. Casey AL, Spare MK, Worthington T, et al. Needleless connectors—the way forward in the prevention of catheter-related infections? *J Hosp Infect* 2002; 50(1): 77–79.
25. Casey AL, Worthington T, Lambert PA, et al. A randomized, prospective clinical trial to assess the potential infection risk associated with the PosiFlow needleless connector. *J Hosp Infect* 2003; 54(4): 288–293.
26. Casey AL, Burnell S, Whinn H, et al. A prospective clinical trial to evaluate the microbial barrier of a needleless connector. *J Hosp Infect* 2007; 65(3): 212–218.
27. Yebenes JC, Sauca G, Solsona M, et al. Safety of positive-pressure valve connectors in arterial catheters inserted into critically ill patients. *J Hosp Infect* 2008; 70(4): 341–345.
28. Casey AL, Karpanen TJ, Nightingale P, et al. Microbiological comparison of a silver-coated and a non-coated needleless intravascular connector in clinical use. *J Hosp Infect* 2012; 80(4): 299–303.
29. Casey AL, Karpanen TJ, Nightingale P, et al. Microbiologic contamination of a positive- and a neutral- displacement needleless intravenous access device in clinical use. *Am J Infect Control* 2016; 44(12): 1678–1680.
30. Tamura N, Abe S, Hagimoto K, et al. Unfavorable peripheral intravenous catheter replacements can be reduced using an integrated closed intravenous catheter system. *J Vasc Access* 2014; 15(4): 257–263.
31. Holt D and Lawrence S. The influence of a novel needleless valve on central venous catheter occlusions in pediatric patients. *J Assoc Vasc Access* 2015; 20: 214–220.e2.