The effects of needleless connectors on catheter-related bloodstream infections

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Needleless connectors, including the standard split septum and the luer-activated mechanical valve connectors, have been introduced into clinical practice to eliminate the risk of needlestick injuries by avoiding the use of needles when accessing the intravascular catheters. Negative and positive displacement mechanical valves have been associated with increased rates of catheter-related bloodstream infections as compared with split septum connectors. Based on available data, split septum connectors should be preferentially used instead of mechanical valves. Adequate disinfection by scrubbing the access port preferably with chlorhexidine is recommended to minimize the risk of catheter microbial contamination along with proper infection control practices. Large prospective randomized clinical trials are needed to evaluate further the possible causes and effects of different types of mechanical valve needleless connectors on bloodstream infections.

Key Words: Needleless connectors; mechanical valves; catheters; contamination; infection.

Needles have traditionally been used to connect intravenous 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 health care workers in US hospitals annually, with approximately 61% of needlestick injuries caused by hollow-bore needles and 8% of injuries when accessing the intravascular catheters.[1,2] The risk of occupational exposures to bloodborne infections such as hepatitis B and C and HIV further brought the issue of preventing needlestick injuries to the forefront in the early 1980s. In 1991, the Occupational Safety and Health Administration (OSHA) issued a final rule on the Bloodborne Pathogen Standard that regulates occupational exposure to bloodborne pathogens and needlestick and sharps injuries among health care workers.[3] The standard was revised 10 years later to incorporate the Needlestick Safety and Prevention Act. Since the enactment of these standards, the needleless connectors were introduced on the market to eliminate the use of needles on intravascular catheters. However, since the introduction of needleless connectors into clinical practice, reports have emerged of sudden and significant increase of catheter-related bloodstream infection (CRBSI) rates with the mechanical valves. This paper reviews the types of needleless connectors and their effects on CRBSIs.

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NEEDLELESS CONNECTORS

Needleless connectors provide needleless access at the hub end of the catheter for intravenous medication administration, fluid infusion, or withdrawal of blood samples or to connect administration sets to the intravascular catheters. Needleless connectors include the split septum connectors and the luer-activated mechanical valves. The standard split septum connectors or negative reflux caps do not have internal mechanisms and are prepierced to allow access by a blunt cannula to open the fluid pathway for intravenous fluid infusion or medication administration. Based on their internal membrane function, mechanical valves are classified as negative, neutral, or positive displacement types. Mechanical valves have an internal membrane or valve and require a mating leur connector when flushing or administering intravenous fluids or medications. The syringe tip or the tip of the intravenous tubing is directly inserted into the cap without the need for a blunt needle.[4] With the negative displacement mechanical valves, the leur caps must be clamped prior to removing the syringe or tubing set to prevent blood from backing up into the catheter. For the neutral

displacement valves, there is no displacement of fluid into the catheter when connecting or disconnecting the syringe or tubing and require no change in clamping practices. The positive displacement valves, also called positive pressure valves (PPVs), have a fluid reservoir that creates a positive displacement movement or pressure and should not be clamped when disconnecting the syringe or intravenous administration sets. The design of PPVs is aimed at preventing retrograde blood flow inside the catheter after the luer is disconnected to prevent thrombotic occlusions and also to avoid catheter hub and endoluminal microbial contamination, assuming that aseptic techniques are followed.[5]

Mechanical valve needleless connectors have been adopted for use by health care institutions not only to avoid the use of needles and needlestick injuries but also because of the compatibility of some valves with specific infusion systems and pumps, the ability to visualize the inside of some transparent valves (eg, Clearlink; Baxter, Deerfield, IL), the ease of infusion and tubing disconnection and nursing satisfaction, and the possible reduction of catheter-related thrombotic occlusions.[6-8] Reducing catheter occlusions maintains catheter patency, avoids the interruption of intravenous therapies and the need for antithrombotics for unclogging the catheters, and reduces the risk of CRBSIs.[9] However, there is no convincing evidence that mechanical valves reduce thrombotic catheter occlusions.[10-13]

The effects of mechanical valves on CRBSI rates have been the subject of experimental and clinical investigations. Approximately 250,000 to 500,000 CRBSIs occur annually in US hospitals,[14] with approximately 80,000 cases of central venous catheter (CVC)-related bloodstream infections reported in US intensive care units alone.[15] CRBSIs increase patient morbidity and mortality, prolong hospital stay, and increase health care costs.[16-18] Considering the impact that the mechanical valves may have on CRBSI rates, it is of clinical and epidemiologic importance to use the safest needleless connectors that do not expose patients to the risk of CRBSIs.

STUDIES OF THE EFFECTS OF DISINFECTANTS AND MECHANICAL VALVES ON MICROBIAL CONTAMINATION

Experimental studies

In laboratory simulation models, mechanical valves have shown to decrease catheter microbial contamination and endoluminal microbial transmission provided that proper disinfection is followed.[19,20-23] In some studies, disinfection with 70% alcohol did not reliably prevent microbial transmission inside the connectors or microbial growth on the external surfaces of the mechanical valves.[24-26] Significantly higher external microbial contaminants remained following disinfection with isopropyl alcohol as compared with chlorhexidine or povidone-iodine (69.2% vs 30.8% and 25%, respectively; $P < .0001$).[26] However, the superiority of disinfection with chlorhexidine as compared with alcohol in reducing microbial contamination was challenged by a study of 300 different mechanical valves that showed vigorous scrubbing of the catheter access port for 15 seconds with alcohol or chlorhexidine before use and entry of the connector's membrane septum was equally effective in sterilizing the mechanical valve ports.[27]

Novel technologies

Experimental studies have reported a reduction in microbial contamination with the use of antimicrobial-impregnated connectors. An experimental antiseptic barrier cap containing chlorhexidine gluconate 2% was shown to significantly reduce microbial transmission on 3 different types of negative (Clearlink), positive (Posiflow; BD Medical, Franklin Lakes, NJ), and neutral (Micro CLAVE; ICU Medical, Inc, San Clemente, CA) displacement mechanical valves.[25,28] A novel leur-activated needleless connector with an internal coating of controlled-release bactericidal silver nanoparticles (V-Link; Baxter) has become available on the market. An in vitro simulation study of the antimicrobial connector showed a significant and sustained suppression over 96 hours of the growth of 6 common microorganisms known to cause CRBSIs and prevented the formation of an intraluminal microbial biofilm along the infused fluid path.[29]

In summary, conventional disinfection of the connector's septum membrane and the catheter's access port may fail in total prevention of microbial contamination and entry into the catheter. Chlorhexidine should be preferentially used as a disinfectant, with a vigorous scrubbing of the membranous septum of the connector for at least 15 seconds before actuation and entry. The role of antiseptic barrier caps and silver-coated needleless connectors in reducing microbial contamination is promising, and their role in preventing CRBSIs requires further evaluation in prospective randomized clinical trials.

Clinical studies

Microbial contamination of the catheter insertion site and/or hub are the most likely sources of CRBSIs.[30] Although microbial contamination does not necessarily lead to bloodstream infections,[19,21,26,31-33] most microorganisms incriminated in CRBSIs originate from outside the catheter,[34] and the addition of an antiseptic

barrier cap has shown to significantly reduce catheter microbial contamination.[25,28] The use of PPVs has also shown to reduce the catheter hub microbial contamination. When a PPV (SmartSite Plus; Alaris Medical Systems, San Diego, CA) was used on 100 radial arterial catheters in critically ill patients, catheters' hub contamination rate was significantly decreased as compared with conventional caps (11.1% vs 56.3%, respectively; $P = .01$). Decreased contamination rates were thought however to be related to good infection control practices rather than the use of the PPV.[35] Similarly, when a different PPV (Posiflow) (n = 274) was compared with a standard cap (n = 306) in critically ill patients, there was a lower percentage of contaminated hubs with the PPV as compared with the standard cap (6.6% vs 18%, respectively; $P < .0001$).[26]

In summary, the role of mechanical valve needleless connectors alone in reducing catheter microbial contamination is debatable. Microbial contamination was greatly enhanced when antiseptic caps were used and proper disinfection techniques were followed.

CLINICAL TRIALS THAT REPORTED DECREASED CRBSIs WITH MECHANICAL VALVES

Only 1 trial reported decreased CRBSIs with the use of a negative displacement valve. This was a prospective randomized controlled trial that compared the effects of a negative displacement mechanical valve (SmartSite; Alaris Medical Systems, San Diego, CA) to a standard 3-way stopcock open system on 278 multilumen CVCs in 243 medical and surgical critically ill patients. There were significantly lower rates of CRBSIs with the mechanical valve as compared with standard caps (0.7 vs 5 CRBSIs per 1,000 catheter-days, respectively; $P = .03$).[36] Although this was a well-designed trial, results cannot be generalized because the trial was limited to single center intensive care units.

CLINICAL TRIALS THAT REPORTED NO SIGNIFICANT EFFECTS OF MECHANICAL VALVES ON CRBSIs

Four clinical trials reported no significant difference on CRBSI rates between the mechanical valves and standard connectors.[7,13,37,38] An early trial that compared a reflux mechanical valve (SafSite; B Braun Medical Inc, Bethlehem, PA) to a conventional heparin-lock system on peripheral catheters reported 1 CRBSI with the needleless connector and 3 CRBSIs with the conventional device, but the difference was not statistically significant.[7] When a negative displacement mechanical valve (SmartSite) was compared prospectively with a 3-way stopcock connector in 799 critically ill patients, there was also no difference in CRBSI rates, although there was a trend toward increased CRBSIs with the mechanical valve on arterial catheters.[38] However, the observed trend in increased CRBSIs with arterial catheters may not have been necessarily associated with the mechanical valve but rather with the arterial catheters that are known to have higher infection rates.[14]

When a PPV (Posiflow) was compared with a standard cap in a prospective randomized trial of 160 medical and surgical patients, there were 2 CRBSIs in the PPV group and none with the standard cap. The difference was not however statistically significant. Because infections occurred only with double-lumen peripherally inserted central catheters the investigators speculated that the higher infection rate in the PPV group could have been related to the higher risk of CRBSIs with multilumen catheters, rather than the use of PPV.[13] In a similar prospective controlled trial that included 312 CVCs in pediatric patients, there was a trend toward increased CRBSI rates with the PPV (CLC2000; ICU Medical, Inc, San Clemente, CA) as compared with the standard cap (15.5 vs 8.8 infections per 1,000 catheter-days, respectively), although the difference was also not significant. However, catheters with PPVs were flushed with saline, whereas heparin was used to flush the catheters with standard connectors.[10] Heparin flushes contain preservatives with antimicrobial properties, and their use on PPVs may have impacted the results.[37]

In summary, clinical trials have reported a trend toward increased CRBSI rates with the use of negative displacement valves and PPVs alike. Although there was a lack of statistically significant difference on CRBSIs between the mechanical valves and standard caps, a clinical difference on CRBSI rates, however, cannot be excluded.

CLINICAL STUDIES THAT REPORTED INCREASED CRBSIs WITH MECHANICAL VALVES

Home and long-term care patients

Home care data have shown increased CRBSIs with the use of mechanical valves.[39-41] In 1 study, fluid collected from the injection caps of needleless connectors grew significantly more microorganisms as compared with the fluid from the protected-needle device ($P = .04$). Because parenteral nutrition and lipid emulsion infusions are commonly used therapies in home care, they were independent risk factors for CRBSIs ($P < .001$) because they make a favorable milieu for microbial growth.[39] In another study of 182 home care hematology/oncology patients with 243 CVCs (75,085 CVC-days), there were significant increases in CRBSIs from 0.8 to 1.4 CRBSI per 1,000 catheter days ($P < .02$) following the introduction of a mechanical valve (SafSite) that replaced the injection port device.[40] Similarly,

the introduction of a negative displacement mechanical valve (SmartSite) in a long-term care facility was also associated with significant increases in CRBSI rates as compared with the earlier period when a split septum connector was used (5.95 vs 1.79 CRBSIs per 1,000 catheter-days, respectively; $P < .001$).[41]

Acute care patients

Positive displacement mechanical valves versus split septum connector. A significant increase in CRBSIs was reported following the introduction of a PPV into critical care, transplantation, and inpatient adult care units. There was a 2.7-fold increase in CRBSI rates following the change from a split septum connector (Interlink; Becton Dickinson and Company, Franklin Lakes, NJ) to a PPV (SmartSite Plus). In critical care units, CRBSI rates significantly increased from 3.87 to 10.64 infections per 1,000 catheter-days following the introduction of the PPV ($P < .001$). CRBSI rates significantly increased from 3.47 to 7.3 infections per 1,000 catheter-days ($P = .02$) in other inpatient units and from 5.3 to 15.2 infections per 1,000 catheter-days in the transplantation step-down care units ($P < .001$). After changing back to using the split septum connector, overall CRBSI rates decreased significantly to 5.59 infections per 1,000 catheter-days in critical care and transplantation units ($P = .02$).[42]

Positive versus negative displacement mechanical valves. A clinical study in pediatric patients reported a significant increase in CRBSIs following the replacement of a negative displacement mechanical valve (CLAVE) with a PPV (SmartSite Plus). There was a significant increase in CRBSIs in pediatric intensive care patients from 1.5 to 2.5 infections per 1,000 catheter-days ($P = .003$). In other pediatric care units, CRBSI rates also significantly increased from 1.55 to 2.79 per 1,000 catheter-days ($P = .01$).[43] The study however reported missing data about the exact dates when the PPV was introduced, which may have influenced the accuracy of the results.

Positive and negative displacement mechanical valves versus split septum connector. Similar to PPVs, negative displacement mechanical valves have also been associated with increased CRBSIs. In a small study of needleless connectors on single- and double-lumen tunneled catheters in 25 hematology/oncology patients, CRBSI rates significantly increased following the introduction of a negative displacement mechanical valve (CLAVE) and a PPV (CLC2000), as compared with the time when a split septum connector (Interlink) was used (5.8 vs 2.6 CRBSIs per 1,000 catheter-days, respectively; $P = .031$). CRBSI rates reverted to baseline following the reintroduction of the split septum connector and stopping the use of mechanical valves. The study however did not distinguish between infection rates with either group of valves separately. Similar to other studies, the investigators mentioned possible differences in flushing techniques that may have confounded the results.[44]

A large, multination, multicenter study evaluated the CRBSI rates in 1 entire hospital, 16 intensive care units, and 1 oncology unit in 5 different hospitals (2 in Australia and 3 in the United States) following the replacement of needles and a split septum connector (Interlink) with a PPV (Ultrasite; B Braun Medical Inc) or negative displacement mechanical valves (Clearlink or SmartSite). All infection surveillance data had been collected prospectively. The CDC definitions were used in all hospitals for CRBSI surveillance. Data on CRBSI rates and prevention practices were collected and compared with before (average, 15.6 months; range, 6-24 months), during (average, 18.8 months; range, 11-39 months), and after (average, 10.3 months; range, 5-18 months; data missing from 2 hospitals) the introduction of the mechanical valves. CRBSI prevention practices were similar at all times. Positive and negative displacement mechanical valves were associated with significant increase in CRBSIs despite adequate infection control practices. In intensive care units, CRBSI rates significantly increased when mechanical valves replaced the needles or split septum connector (9.49 vs 6.15 CRBSIs per 1,000 CVC-days, respectively; $P < .001$). After reverting to the split septum connector, there was a significant reduction in CRBSI rates in intensive care units (5.77 vs 9.49 CRBSIs per 1,000 CVC-days, respectively; $P < .001$).[6] Compared with other studies, this was the largest and only multicenter clinical study with the longest duration that linked negative and positive displacement mechanical valves to increased CRBSIs. Another point that distinguishes this study was the description of infection surveillance methods and prevention practices that other studies did not include.

In summary, outbreaks of CRBSIs occurred in acute and home care patients following the use of positive and negative mechanical valves that replaced the split septum connectors. Cumulative clinical evidence indicates that negative and positive displacement mechanical valves alike are associated with rapid and significant increase in CRBSI rates.

DISCUSSION

CRBSIs independently prolong hospitalization and increase health care costs.[16-18] Catheter hubs, injection ports, and needleless connectors are the main sites for microbial contamination and provide a port of entry for microorganisms inside the catheter. Microorganisms may migrate inside the catheter lumen from extraluminal contamination or from intraluminal contaminants

to form a biofilm that may ultimately disseminate into the bloodstream.[34,45-47]

When the mechanical valves were first introduced into practice, increased CRBSI rates with their use were partly blamed to the unfamiliarity of health care workers with the new devices and the lack of strict adherence to the manufacturers use guidelines.[48,49] Repeated educational programs to comply with the manufacturers recommendations for the proper use of mechanical valves did not however result in reduced CRBSIs.[41] It was later recognized that other factors may have also contributed to increased CRBSIs with the mechanical valves, including a possible inherent flow in the connectors' design, improper disinfection, frequent actuation and accessing of the valve, and infrequent cap replacement.[5,49] In contrast to the split septum connectors that do not have an internal valve and are open to the fluid path that allows easy flushing, it is postulated that the possible flaw in the mechanical valves design makes it difficult to properly disinfect the space between the valve and the hub. This allows blood reflux in the catheter lumen that causes irregularity in fluid flow and also creates a favorable milieu for microbial growth. This ultimately may increase the risk of microbial contamination and possibly leads to systemic microbial transmission.[8,42-44] Although the PPV is by design aimed at avoiding catheter hub and endoluminal microbial contamination,[5] surprisingly higher CRBSI rates have been reported with PPVs in comparison to split septum connectors.[6,42,44] Only 1 study compared the effects of PPVs on CRBSIs to negative displacement valves and reported higher CRBSI rates with PPVs. However, this study had its limitations and suffered from a design flaw.[43] To differentiate better the effects of PPVs and negative displacement valves on CRBSIs, these deserve to be compared in head-to-head prospective randomized clinical trials.

There is no consensus on the best disinfection methods of injection ports and connectors to prevent CRBSIs because prospective randomized clinical trials of the effects of different disinfectants and disinfection techniques of connectors on the prevention of CRBSIs are lacking.[29] Proper disinfection and more frequent replacements of caps have shown to reduce microbial contamination but had little effects on reducing CRBSIs.[39,50,51] Despite the differences in manufacturers' disinfection recommendations whereby negative displacement valves are disinfected after the intravenous access is clamped and PPVs are disinfected before clamping, both negative and positive mechanical valves have been linked to increased CRBSI rates.[6] Based on available clinical data, catheter contamination risk is minimized by vigorously scrubbing the access port with an antiseptic, preferably chlorhexidine, for at least 15 seconds. Using proper aseptic technique at the intravenous insertion site further reduces extraluminal contamination.

The frequency of caps replacement remains a subject of debate because of the lack of scientific evidence to support any specific recommendations. Caps are typically replaced according to the manufacturers' recommendations and professional practice experiences. In clinical studies, changing the caps every 24 to 72 hours instead of 6 to 7 days along with proper disinfection decreased microbial contamination without having a substantial effect on preventing CRBSIs.[39,50,51] To date, the optimal frequency for caps replacement remains unknown. According to the 2002 CDC guidelines for the prevention of intravascular catheter-related infections, caps should be changed no more frequently than every 72 hours.[52] In practice, the frequency of replacing caps varies between 1 and 7 days, and caps are changed at any time of malfunction or if blood leaks into the cap.

Although the 2002 CDC guidelines on the prevention of CRBSIs state that needleless connectors do not substantially affect the incidence of CRBSIs when used according to manufacturers' recommendations,[52] these guidelines are outdated. The more recent 2008 Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America guidelines recommend against the routine use of PPVs before a comprehensive assessment of the risks and benefits and staff education of their proper use.[53,54] Although the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America guidelines refer only to PPVs, the data referenced in the guidelines included studies of both positive and negative displacement mechanical valves.[41-44]

Differences in patient populations, types of connectors, infection control practices, types of infusions, blood draws through the device, duration of catheterization, flushing practices, and study designs may have contributed to the mixed results on CRBSI rates.[35,38,41] The largest clinical study to date showed significant increase in CRBSIs when negative and positive mechanical valves are used.[6] Because the luer-activated mechanical valves have been associated with significant increases in CRBSIs, split septum connectors should be preferentially used until more data from higher quality studies with the mechanical valves become available.

Antimicrobial- or antiseptic-impregnated or coated CVCs have been found to decrease the risk of catheter microbial contamination and CRBSIs.[55,56] Similarly, the introduction of the novel silver-coated antibacterial leur connecting connectors has the premise of reducing CRBSI rates especially for its sustained antimicrobial effects and its prevention of formation of an intraluminal biofilm, which is a major cause of CRBSIs. The clinical merits of the silver-coated needleless

connectors still need to be confirmed in prospective randomized clinical trials.

Although institutional choices of connectors may vary, involving infection control personnel in the choice of connectors, adherence to infection control practice recommendations, and continuous monitoring and surveillance of infectious trends and outcomes remain the essential steps in preventing CRBSIs.

CONCLUSION

Needleless connectors reduce needlestick injuries and facilitate nursing care and catheter management. There is clinical evidence of significant increase of CRBSI rates with the use of negative and positive displacement mechanical valves as compared with split septum connectors. Split septum connectors should be preferably used until more safety data on mechanical valves become available. Adherence to infection control practices and continuous surveillance of infection rates should be followed especially when new needleless connectors are introduced into practice. The effects of mechanical valves on CRBSI rates and patient outcomes deserve to be further evaluated in well-designed prospective randomized clinical trials.

References

1. United States General Accounting Office. Occupational safety: selected cost and benefit implication of needlestick prevention devices for hospitals. GAO-01–06R; November 17, 2000.
2. Centers for Disease Control and Prevention. Workbook for designing, implementing, and evaluating a sharps injury prevention program. February 12, 2004. Available at: http://www.cdc.gov/sharpssafety/. Accessed August 12, 2009.
3. Occupational Safety and Health Administration: final rule on occupational exposure to bloodborne pathogens. Federal Register 1991;56: 48250.
4. Hadaway L, Richardson D. Needleless connectors: a primer on terminology. J Infus Nurs 2010;33:22-31.
5. Yebenes JC, Serra-Prat M. Clinical use of disinfectable needle-free connectors. Am J Infect Control 2008;36(Suppl 175):e1-4.
6. Jarvis WR, Murphy C, Hall KK, Fogle PJ, Karchmer TB, Harrington G, et al. Health care-associated bloodstream infections associated with negative- or positive-pressure or displacement mechanical valve needleless connectors. Clin Infect Dis 2009;49:1821-7.
7. Mendelson MH, Short LJ, Schechter CB, Meyers BR, Rodriguez M, Cohen S, et al. Study of a needleless intermittent intravenous-access system for peripheral infusions: analysis of staff, patient, and institutional outcomes. Infect Control Hosp Epidemiol 1998;19:401-6.
8. Schilling S, Doellman D, Hutchinson N, Jacobs BR. The impact of needleless connector device design on central venous catheter occlusion in children: a prospective, controlled trial. JPEN J Parenter Enteral Nutr 2006;30:85-90.
9. Krzywda EA. Predisposing factors, prevention, and management of central venous catheter occlusions. J Intraven Nurs 1999;22(Suppl 6):S11-7.
10. Jacobs BR, Schilling S, Doellman D, Hutchinson N, Rickey M, Nelson S. Central venous catheter occlusion: a prospective, controlled trial examining the impact of a positive pressure valve device. JPEN J Parenter Enteral Nutr 2004;28:113-8.
11. Rummel MA, Donnelly PJ, Fortenbaugh CC. Clinical evaluation of a positive pressure device to prevent central venous catheter occlusion: results of a pilot study. Clin J Oncol Nurs 2001;5:261-5.
12. Berger L. The effects of positive pressure devices on catheter occlusions. JVAD Winter 2000;1-4.
13. Khalidi N, Kovacevich D, Papke-O'Donnell L, Btaiche I. Impact of the positive pressure valve on vascular access device occlusions and bloodstream infections. JAVA 2009;14:84-91.
14. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc 2006;81:1159-71.
15. Mermel LA. Prevention of intravascular catheter-related infections. Ann Intern Med 2000;132:391-402.
16. Renaud B, Brun-Buisson C. Outcomes of primary and catheter-related bacteremia: a cohort and case-control study in critically ill patients. Am J Respir Crit Care Med 2001;163:1584-90.
17. Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis 2005;41: 1591-8.
18. Warren DK, Quadir WW, Hollenbeak CS, Elward AM, Cox MJ, Fraser VJ. Attributable cost of catheter-associated bloodstream infections among intensive care patients in a non teaching hospital. Crit Care Med 2006; 34:2084-9.
19. Yebenes JC, Martinez R, Serra-Prat M, Sauca G, Capdevila JA, Balanzó X, et al. Resistance to the migration of microorganisms of a needle-free disinfectable connector. Am J Infect Control 2003;31:462-4.
20. Trautmann M, Moosbauer S, Schmitz FJ. Experimental study on the safety of a new connecting device. Am J Infect Control 2004;32:296-300.
21. Yebenes JC, Delgado M, Sauca G, Serra-Prat M, Solsona M, Almirall J, et al. Efficacy of three different valve systems of needle-free closed connectors in avoiding access of microorganisms to endovascular catheters after incorrect handling. Crit Care Med 2008;36:2558-61.
22. Arduino MJ, Bland LA, Danzig LE, McAllister SK, Aguero SM. Microbiologic evaluation of needleless and needle-access devices. Am J Infect Control 1997;25:377-80.
23. Luebke MA, Arduino MJ, Duda DL, Dudar TE, McAllister SK, Bland LA, et al. Comparison of the microbial barrier properties of a needleless and a conventional needle-based intravenous access system. Am J Infect Control 1998;26:437-41.
24. Brown JD, Moss HA, Elliot TSJ. The potential for catheter microbial contamination from a needleless connector. J Hosp Infect 1997;36:181-9.
25. Menyhay SZ, Maki DG. Preventing central venous catheter-associated bloodstream infections: development of an antiseptic barrier cap for needleless connectors. Am J Infect Control 2008;36(Suppl 174):e1-5.
26. Casey AL, Worthington T, Lambert PA, Quinn D, Faroqui MH, Elliott TS. A randomized, prospective clinical trial to assess the potential infection risk associated with the PosiFlow needleless connector. J Hosp Infect 2003;54:288-93.
27. Kaler W, Chin R. Successful disinfection of needleless access ports: a matter of time and friction. JAVA 2007;12:3-9.
28. Menyhay SZ, Maki DG. Disinfection of needleless catheter connectors and access ports with alcohol may not prevent microbial entry: the promise of a novel antiseptic-barrier cap. Infect Control Hosp Epidemiol 2006;27:23-7.
29. Maki DG. In vitro studies of a novel antimicrobial luer-activated needleless connector for prevention of catheter-related bloodstream infection. Clin Infect Dis 2010;50:1580-7.
30. Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. Ann Intern Med 1997;127:257-66.
31. Seymour VM, Dhallu TS, Moss HA, Tebbs SE, Elliot TSJ. A prospective clinical study to investigate the microbial contamination of a needleless connector. J Hosp Infect 2000;45:165-8.

32. Bouza E, Munoz P, Lopez-Rodrıguez J, Jesús Pérez M, Rincón C, Martín Rabadán P, et al. A needleless closed system device (CLAVE) protects from intravascular catheter tip and hub colonization: a prospective randomized study. J Hosp Infect 2003;54:279-87.
33. Casey AL, Burnell S, Whinn H, Worthington T, Faroqui MH, Elliott TS. A prospective clinical trial to evaluate the microbial barrier of a needleless connector. J Hosp Infect 2007;65:212-8.
34. Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. Intensive Care Med 2004;30:62-7.
35. Yebenes JC, Sauca G, Solsona M, Martinez R, Serra-Prat M, Gil P, et al. Safety of positive-pressure valve connectors in arterial catheters inserted into critically ill patients. J Hosp Infect 2008;70:341-5.
36. Yebenes JC, Vidaur L, Serra-Prat M, Sirvent JM, Batlle J, Motje 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;32:291-5.
37. Elliott TS, Curran A. Effects of heparin and chlorbutol on bacterial colonisation of intravascular cannulae in an in vitro model. J Hosp Infect 1989;14:193-200.
38. Esteve F, Pujol M, Limon E, Saballs M, Argerich MJ, Verdaguer R, et al. Bloodstream infection related to catheter connections: a prospective trial of two connection systems. J Hosp Infect 2007;67:30-4.
39. Danzig LE, Short LJ, Collins K, Mahoney M, Sepe S, Bland L, et al. Bloodstream infections associated with a needleless intravenous infusion system in patients receiving home infusion therapy. JAMA 1995; 273:1862-4.
40. Kellerman S, Shay DK, Howard J, Goes C, Feusner J, Rosenberg J, et al. Bloodstream infections in home infusion patients: the influence of race and needleless intravascular access devices. J Pediatr 1996; 129:711-7.
41. Salgado CD, Chinnes L, Paczesny TH, Cantey JR. 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;28:684-8.
42. Rupp ME, Sholtz LA, Jourdan DR, Marion ND, Tyner LK, Fey PD, et al. Outbreak of bloodstream infection temporally associated with the use of an intravascular needleless valve. Clin Infect Dis 2007;44: 1408-14.
43. Maragakis LL, Bradley KL, Song X, Beers C, Miller MR, Cosgrove SE, et al. Increased catheter-related bloodstream infection rates after the introduction of a new mechanical valve intravenous access port. Infect Control Hosp Epidemiol 2006;27:67-70.
44. Field K, McFarlane C, Cheng AC, Hughes AJ, Jacobs E, Styles K, 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;28:610-3.
45. Murga R, Miller JM, Donlan RM. Biofilm formation by gram-negative bacteria on central venouscatheter connectors: effect of conditioning films in a laboratory model. J Clin Microbiol 2001;39:2294-7.
46. Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. J Infect Dis 1993;168:400-7.
47. Garland JS, Alex CP, Sevallius JM, Murphy DM, Good MJ, Volberding AM, et al. Cohort study of the pathogenesis and molecular epidemiology of catheter-related bloodstream infection in neonates with peripherally inserted central venous catheters. Infect Control Hosp Epidemiol 2008;29:243-9.
48. Cookson ST, Ihrig M, O'Mara EM, Denny M, Volk H, Banerjee SN, et al. Increased bloodstream infection rates in surgical patients associated with variation from recommended use and care following implementation of a needleless device. Infect Control Hosp Epidemiol 1998; 19:23-7.
49. Blake M. Update: catheter-related bloodstream infection rates in relation to clinical practice and needleless device type. Can J Infect Control 2008;23:156-60.
50. McDonald LC, Banerjee SN, Jarvis WR. Line-associated bloodstream infections in pediatric intensive-care-unit patients associated with a needleless device and intermittent intravenous therapy. Infect Control Hosp Epidemiol 1998;19:772-7.
51. Do AN, Ray BJ, Banerjee SN, Illian AF, Barnett BJ, Pham MH, et al. Bloodstream infection associated with needleless device use and the importance of infection control practices in the home health care setting. J Infect Dis 1999;179:442-8.
52. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Centers for Disease Control and Prevention. Guidelines for the prevention of intravascular catheter-related infections. MMWR Recomm Rep 2002;51(RR-10):1-29.
53. Marschall J, Mermel LA, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. Infect Control Hosp Epidemiol 2008; 29(Suppl 1):S22-30.
54. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1-45.
55. Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. JAMA 1999; 281:261-7.
56. Ramritu P, Halton K, Collignon P, Cook D, Fraenkel D, Battistutta D, et al. A systematic review comparing the relative effectiveness of antimicrobial-coated catheters in intensive care units. Am J Infect Control 2008;36:104-17.