American Journal of Infection Control 000 (2019) 1−6

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Connectors as a risk factor for blood-associated infections (3-way stopcock and needleless connector): A randomized-experimental study

Tuba Sengul RN, CWON, PhD [a,*], Betul Guven RN, PhD [b], Ayse Ferda Ocakci RN, PhD [a], Nurten Kaya PhD, BSN [c]

[a] *Department of Fundamental Nursing, Koç University School of Nursing, İstanbul, Turkey*
[b] *Department of Surgical Nursing, Bilim University, İstanbul, Turkey*
[c] *Department of Midwifery, Health Sciences Faculty, Istanbul University, İstanbul, Turkey*

Key Words:
Three-way stopcock
Colonization
Catheter-related bloodstream infections

Background: Microorganisms causing catheter-related bloodstream infections colonize to intravenous catheters (IVC)—particularly to connectors mounted to catheters. The aim of this study was to examine the colonization in 3-way stopcock (TWS) connectors and needleless connectors (NCs) that integrated into central, port, and peripheral venous catheters.

Methods: This random, experimental study consisted of 180 connectors that were inserted into the IVCs of patients in general surgery, reanimation intensive care, and daily chemotherapy units. Cultures of the connectors were obtained at least 48 hours after connecting to IVCs.

Results: This study showed that gram-negative, gram-positive, and other pathogens reproduced, although their colonization level was not high enough to develop an infection. When the results of colonization for patients using TWS and NC were compared, the peripheral venous catheters (using a TWS) resulted in a significantly higher increase in reproduction than in patients using NC ($P \leq .01$) and no significant difference in the level of colonization in other types of connectors or catheters ($P > .05$).

Conclusions: The study's results indicated no significant difference between NC and TWSs in terms of reproduction. It should also be noted that connectors integrated into IVC pose a risk in the development of catheter-related bloodstream infections.

The use of intravenous catheters (IVCs) for hospitalized patients is one of the main causes of catheter-related bloodstream infections (CRBSIs). CRBSIs are increasingly becoming one of the more common health care−associated infections and increase patient rates of mortality and morbidity.[1-6] Approximately 75% of all health care−associated bloodstream infections are owing to CRBSIs around the world. According to the Centers for Disease Control and Prevention (CDC) data, 1.7 million people are admitted to hospitals every year owing to health care−associated infections.[7] According to studies,[8,9] 648,000 of 721,000 people with health care−associated infections in the United States in 2011 suffered from CRBSIs, and intensive care unit (ICU) treatment expenses per patient were reported as reasonably high. In Turkey, however, CRBSI vary according to unit types, and each hospital conducts its own surveillance studies, with the results not reported to the public.

Microorganisms causing CRBSI may infiltrate IVCs in various ways, such as by the skin near the entrance of the catheter, by a contaminated infusion set, by the staff's own microflora, or by contaminated catheters.[10] Though microorganisms colonise around the lumen of the catheter, colonization usually occurs at the entrance of the catheter and its juncture with the skin.[11] For such colonization to generate an infection, the culture, taken from catheter tip and juncture point with semiquantitive and quantitive methods before infection-related symptoms, must include a significant number of [semiquantitive culture >15 colonies; quantitive culture >10^3 colonies] colonies.[6,12] To ensure that multiple intravenous (IV) implementations to the entrance points of catheters as well as to maintain vascular access, the use of inserted connectors is dramatically increasing.[2,13]

Needleless connectors are standard luer-lock-linked, compact 2-way devices. Three-way stopcocks (TWSs), however, are negative fluid displacement devices without standard-lidded internal mechanisms.[2] Studies on the topic have reported that connectors protected patients from CRBSI.[14] However, under some conditions (eg, misuse of the product and inadequate education for staff), it was reported that connector-related bloodstream infections tended to occur in

* Address correspondence to Tuba Sengul, RN, CWON, PhD
E-mail address: tsengul@ku.edu.tr (T. Sengul).

Funding/support: This research was supported by Koç University Semahat Arsel Nursing Education and Research Center (SANERC) in Turkey.

Conflicts of interest: None to report.

https://doi.org/10.1016/j.ajic.2019.08.020
0196-6553/

ICUs and homecare settings.[3,15] One study[16] suggests that when the aseptic technique is not implemented, connectors may be a potential source of microbial contamination.

Although different types of connectors are available in clinical settings, it is still unknown whether this affects patient safety or the development of CRBSI.[17] This may be owing to the fact that TWSs and NCs are still the most commonly used connectors in clinical settings. Although the number of studies on TWS and NC is increasing, studies on the effect of connector type on colonization rate are limited. Many studies have been conducted on the effect of colonization on the development of CRBSI, but few studies show whether the colonization rate in connectors affects CRBSI.[7,11,14,15,17-23] In some of the following studies, it has been stated that colonization in hub and intraluminal progression especially in central venous catheters (CVCs) poses a potential risk for CRBSIs.[11,15,24] In other studies, it was emphasized that colonization on the interior surface of the valved connectors increases the risk of CRBSIs by creating biofilm formation.[14,18,19,21,22] In another study, the direct correlation of colonization in both catheters and connectors with CRBSIs was demonstrated.[25]

Because of the inadequate examination of colonization occuring in connectors during culture collecting and the lack of systematic analysis, further study in this area is necessary.

METHODS

Study purpose and design

This random, experimental study design was used to examine the colonization rate in connectors (TWS and NC) that connected to peripheral, central, and port catheters.

Study selection

The eligibility criteria for this study required adult patients to catheterize with peripheral, central, and port catheters; have received 2 IVCs for at least 48 hours, have no infections, and volunteered for the study. Before the study, patients were clinically examined to record body temperature (<37°C), C-reactive protein levels (< .9 mg/L), and white blood cell levels(<11.00 mm^3).

Study site and population

This study was conducted between January 2016 and December 2017 in the general surgery, reanimation intensive care, and daily chemotheraphy units of a training and research hospital in Istanbul, Turkey. Our study was conducted in 3 different clinics. According to the general policy of the hospital, there are 2 different connectors in all 3 clinics; TWS and NC. These connectors are generally used according to the preferences of nurses. The general surgery department where the research was conducted was the place where various surgical diseases such as thyroidectomy, appendectomy, cholecystectomy, and breast surgery were treated. In the surgical ward, peripheral venous catheters are placed into the in-patient's pre-operative area by the nurse by aseptic technique. In the intensive care unit, CVCs are placed in the pre-operative or intraoperative area by the doctors by using a sterile technique. The patient population consists of trauma patients and patients requiring long-term follow-up. Similarly, daily chemotheraphy units are placed in an outpatient unit for various cancer patients (breast, lung, prostate, and colorectal) and port catheters are placed under sterile conditions in the operating theater. All catheters and connectors were inserted and used with the same procedures outlined by the catheter-related bloodstream infections prevention strategy. In all of the catheters with connectors, an IV line was utilized for feeding and IV treatment. Patients with catheters were not given any antibiotics during their treatment.

Approximately 1,200 connectors were used in this hospital during the course of the study. The study included 180 connectors with the significance level at 5%, effect size at 0.5, and power of the study at (1-β) 80%. Both TWSs and NCs were used in the general surgery, reanimation intensive care, and daily chemotheraphy units. Peripheral catheters were commonly used in general surgery, reanimation intensive care units, and port catheters in daily chemotheraphy units. Data were collected on a total of 180 connectors using 30 NCs and 30 TWSs for each type of catheter.

Data tools and randomization

Connectors were classified according to a selection of sample patient groups admitted to the hospital who met the eligibility criteria. Web-based randomization was used to assign NC and TWS to the patient groups. Patient information and IV catheter and connector follow-up forms were used to collect data for this study.

The patient information form consisted of 7 questions concerning patient demographic characteristics (including age, gender, and body mass index), medical diagnosis, type of catheter used, and type of clinic in which the patient was treated. The IV catheter and connector follow-up form included information about catheter area, insertion date, type of connector, and colonization status after culture. The connector follow-up form included information about catheter area, medical diagnosis of the disease, age, gender, catheter insertion date and location, type of connector and catheter, and colonization status after culture. Figure 1 shows after this form was completed, any changes were recorded every 24 hours.

Definitions

Patients participating in the study were catheterized with central, port, and peripheral catheters using 2 different types of connectors. The connectors were removed from the catheter according to the asepsis rules. Nonsterile gloves were used because the outer surfaces of the connector and the catheter were not sterile. However, the connector was removed without contacting the catheter access site. During the infection transfer of connectors, the infection more likely can come from internal/intraluminal region than outer surface of the connector. In microbiological investigations, methods were used to determine colonization of intraluminal bacteria. Therefore, contact with the outer surface with a nonsterile glove was not considered as risky; the transfer in a sterile environment is also intended to prevent intraluminal contamination until the procedure, which is applied in the laboratory. The samples were sent to the laboratory in a sterile box according to asepsis rules. Ensuring contamination did not occur on the untouchable points, connectors were then placed into an empty sterile container and then sent to the microbiology lab within 20 minutes. The study was conducted by specialized biologists in a microbiology laboratory of a private hospital. Samples were analyzed by using test methods in accordance with the standards that are determined by national and international organizations. In the microbiology laboratory, semiquantitive and quantitive methods were used to assess colonization of bacteria in the TWS and needleless connectors. Using the semiquantitive (roll-plate) catheter culture method (defined by Maki et al), the connector's distal 3- to5-cm tip point was held with sterile forceps and, without contaminating the tip, placed into a 5% sheep blood agar and MacConkey agar culture. Bacteria growth was evaluated in a 37°C aerobe environment following 48-72 hours of incubation. Units containing 15+ colonies were evaluated. Using the quantitive method, the flushing technique was used to pass 1 mL of bouillon through the connector, after which 1/10 and 1/100 dilutions of the liquid, respectively, were prepared. Following flushing, 100 μL of liquid

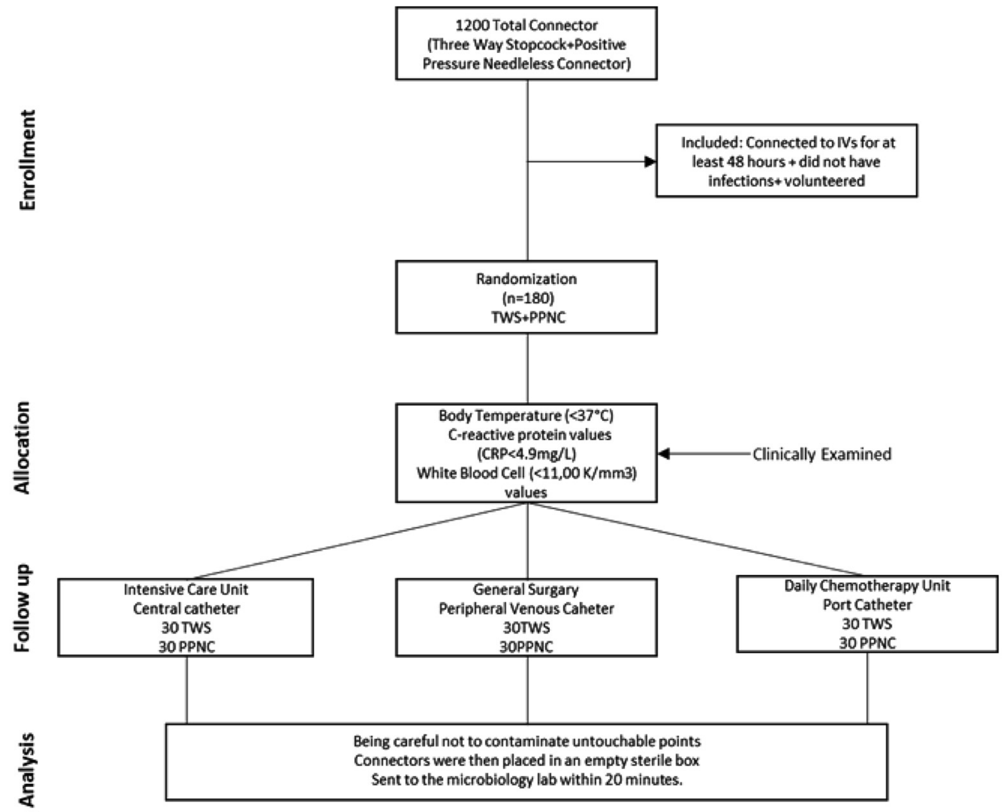

Fig. 1. Example flow diagram adapted from Pandis N, Chung B, Scherer RW, Elbourne D, Altman DG. CONSORT 2010 statement: extension checklist for reporting within person randomised trials. BMJ 2017;357.

was taken from each dilution using a sterile micropipette and added to a 5% sheep blood agar and MacConkey agar culture. The cultures were assessed after 48-72 hours of incubation at 37°C.

Ethical consideration

Approval for this study was obtained from the Koc University Research Ethical (2013.254.IRB2.95) and the Institutional Review Board of Hospitals, Istanbul, Turkey. Prior to gathering data, written permission from relevant institutions was obtained by submitting an information form, including the purpose and scope of the study. The objective and benefits of the study, as well as patient roles, were carefully explained to those patients included in the study's sample. Verbal informed consent was obtained from each of the participants.

Statistical analysis

The SPSS software version 22.0 for Windows (IBM Corporation, Armonk, NY) was used to analyze the data. Descriptive statistics (ie, frequency, percentages, means, and SDs) were also calculated. The Pearson X^2 and Fisher exact tests were used to compare categorical data. The study included 180 connectors, number of groups with the significance level at 0.05, effect size at 0.53, and power of the study at (1-β) 95% (F test: 1-way analysis of variance test:Fixed effects, and omnibus,).

RESULTS

Table 1 shows the patient characteristics in this study. Of the patients catheterized using TWS, 60% (n = 54) were diagnosed with cancer, and of the patients catheterized using NC, 47.8% (n = 43) were

Table 1
Patient characteristics (N = 180)

Patient characteristic		Mean ± SD		Min-Max		
Age		56.16 ± 12.29		(27-80)		
BMI		32.71 ± 4.53		(25-43)		
		TWS		NC		
		n	%	n	%	*P* value
Gender	Female	40	44.4	43	47.8	X^2 = 0.201
	Male	50	55.6	47	52.2	*P* = .383
Medical diagnosis	Surgical diseases	25	27.8	35	38.9	X^2 = 3.247
	Cancer	54	60.0	43	47.8	*P* = .355
	Chronic diseases	1	1.1	2	2.2	
	Trauma	10	11.1	10	11.1	

BMI, body mass index; *NC*, needleless connector; *TWC*, 3-way stopcock.

diagnosed with cancer. There was no statistically significant difference between each connector group with regard to gender and medical diagnosis (Table 1).

The average duration of catheter with TWS stay was 48 hours (53.3%,n = 48), whereas the average duration of stay for the catheter with NC was 46.7% (n = 42). The rate of TWS and NC insertion in the jugular catheter area was 14.4% (n = 13), whereas it was 18.9% (n = 17) in the subclavian catheter area. The rate was equal for port (33.3%, n = 30) and peripheral catheters (33.3%, n = 30). No significant difference was detected in terms of those variables (Table 2).

Table 3 lists the colonization rates regarding to type of catheter used, showing gram-negative, gram-positive, and other pathogens reproduced. As shown in the Table 3, colonization rates for connectors integrated to central venous catheters, number of remain sterile were lower than those for other types of catheters.

When colonization status regarding connector types were compared, the use of the TWS in peripheral venous catheters caused significantly more colonization than in the use of NC ($P \leq .01$). This study found no significant difference between bacterial colonization rates for other types of connectors and catheters ($P > .05$) (Table 4). In our study, the mandatory instructions of the manufacturer were fulfilled for CRBSI prevention strategies during catheter and connector use. During the application of the TWS connectors, the ends of the connectors are kept closed. The ends were wiped with 70% ETOH before various applications to the NC entrance place, with a 1-minute wait to allow for drying time. The integrated connectors of all catheters in our study were used with IV line. The catheters that were used (central, port, peripheral) did not contain antibiotic-containing/impregnated type of catheters, and biopatch and catheter securement devices were not used.

Table 2
Catheter characteristics (N = 180)

		TWS		NC		
		n	%	n	%	*P* value
Duration of stay	48 h	48	53.3	42	46.7	$X^2 = 2.094$
	60 h	18	20.0	15	16.7	$P = .351$
	72 h	24	26.7	33	36.7	
Catheter area	Juguler	13	14.4	13	14.4	$X^2 = 0.046$
	Subclavian	17	18.9	17	18.9	$P = .997$
	Port	30	33.3	30	33.3	
	Peripheral	30	33.3	30	33.3	

NC, needleless connector; *TWS*, 3-way stopcock.

DISCUSSION

Factors causing CRBSI include a series of interactions between the catheter, the patient, and various microorganisms, as well as interactions between the type of catheter being used, its location of placement, and the condition of the patient.[1,15] Risk factors leading to the development of IVC infections include the age of the patient, the presence of disease, the use of immunosuppressive therapy, the integrity of the skin, and the presence of other infections.[1,15] This study revealed no significant difference detected between groups using TWS and NC in terms of age, gender, health status, and BMI. Thus, the effects of these confounding variables were minimized, which may be a risk factor in the development of infection.

According to previously published studies, risk factors leading to the development of IVC infections include the type of vascular catheter used, the function of the catheter, location of catheter insertion, duration of catheter use, catheter placement and maintenance procedures, and the presence of catheter connections.[1] There is no need to replace peripheral catheters more frequently than every 72-96 hours to reduce risk of infection and phlebitis in adults (Category IB), and central venous and port catheters should not be changed regularly (Category IB).[7,24] The results of our study revealed no significant difference between the duration of stay for catheters used with TWSs and for those used with NCs. Duration of stay for each of the connectors varied between 48 and 72 hours. According to the 2011 Centers for Disease Control and Prevention guidelines, replacing IV sets and connectors before 72 hours had no effect in reducing the risk of infection.[7,24] However, the use of IV sets and connectors for >72 hours may pose a risk for infection. In this study, both of the connectors' duration of stay was similar, indicating that colonization in connectors is not related to duration of stay.

In our study, 70% alcohol was applied during the use of NCs, as dictated by hospital protocol and the catheter-related bloodstream infections protection strategy. Various studies show that effective precautions in reducing the risk of catheter-related bloodstream infections include protection from infection and skin antisepsis.[25-26] Some studies suggest that to reduce the risk of contamination to a minimal level, 70% alcohol/chlorhexidine/povidone iodine should be applied at the category 1A level.[20] One study reports that the use of NC with a 5-econd application of 70% alcohol ensures disinfection in clinical or lab settings.[22] Other studies show that traditional disinfection methods using 70% alcohol do not hinder contamination.[13] According to Tsuchida et al,[26] applying asepesis procedures before

Table 3
Colonization rate regarding type of catheter and connector

	Intensive care (Central catheter)				Daily chemotherapy (Port catheter)				General surgery (Peripheral catheter)			
	TWS		NC		TWS		NC		TWS		NC	
Pathogens	n	CFU/mL*** (Avg)	n	CFU/mL*** (Avg)	n	CFU/mL*** (Avg)	n	CFU/mL*** (Avg)	n	CFU/mL*** (Avg)	n	CFU/mL*** (Avg)
Coagulase negative staphylococcal	8	26.417	7	11,500	—	—		1,500	5	10,167	1	1,500
Leuconostoc sp	—	—	—	—	1	5,000	—	—	—	—	—	—
Acinetobacter baumannii	—	—	2	11,250	1	25,000	1	20,000	—	—	—	—
Pseudomonas aeruginosa	2	12,500	1	20,000	—	—	—	—	1	5,000	—	—
Acinetobacter lwoffii	—	—	—	—	—	—	—	—	2	425,000	—	—
Stenotrophomonas maltophilia	—	—	—	10,000	—	—	—	—	—	—	—	—
Enterococcus faecalis	—	—	2	3,500	—	—	—	—	—	—	—	—
Candida sp.	—	—	1	1,500	—	—	—	—	—	—	—	—
Klebsiella pneumoniae	1	15,000	—	—	—	—	—	—	—	—	—	—
Total no. of bacteria	11		13		8		1		2		1	—
Sterile	19		17		22		29		28		29	—
Total	30		30		30		30		30		30	—

CFU, colony-forming unit; *TWS*, 3-way stopcock; *NC*, needless connector.

Table 4
Colonization rates regarding to type of catheter and connector

	Central catheter		Port catheter		Peripheral catheter		Total	
	TWS (n = 30) %	NC (n = 30) %	TWS (n = 30) %	NC (n = 30) %	TWS (n = 30) %	NC (n = 30) %	TWS (n = 90) %	NC (n = 90) %
With colonization	36.7	46.7	6.7	3.3	26.7	3.3	23.3	16.7
Without colonization	63.3	53.3	93.3	96.7	73.3	96.7	79.7	83.3
x^2; *P* value	x^2 = 0.61; *P* = .43		x^2 = 0.35; *P* = .55		x^2 = 6.40; *P* = .011		x^2 = 1.25; *P* = .18	

NC, needleless connector; *TWC*, 3-way stopcock.

operation hinders the development of catheter-related bloodstream infection. In this study, we used similar aseptic procedures in the maintenance of both catheters and connectors. In the discussion, we stated that, under aseptic technical conditions, we have fulfilled the procedures that became mandatory to apply in both connectors by the manufacturer. The 3-way tap of the connectors placed in the patients was used under aseptic technical conditions and the ends were always kept closed. Needle-free vein valve was used by wiping with 70% alcohol before application.

In the present study, gram-positive coagulase negative *Staphylococcus* (*Epidermidis, hominis, warneri, intermedius, haemolyticus*); gram-negative (*Acinetobacter baumannii, Acinetobacter lwoffii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia*); and other pathogens (*Enterococcus faecalis, Candida* sp, and *Leuconostoc* sp) revealed that pathogens can reproduce, but that their colonization levels were not high enough to result in the development of infection. Similarly, the Perez-granda et al study[27] showed that *Staphylococcus* (*epidermidis, haemolyticus, chromogenes, hominis, aureus,* and *saprophyeticus*) and *Moraxella osloensis* were identified in colonizations of NC inserted in CVCs. Another study confirmed that in 372 of 504 health-associated infections, a total of 481 pathogens were present. Those respective pathogens—*Clostridium difficile* 12.1%, *S aureus* 10.7%, *Klebsiella pneumonia, Klebsiella oxytoca* 9.9%, and *Escherichia coli* 9.3% were also found to cause health care−associated infections.[8]

Because the literature suggests that CVCs cause CRBSI,[1,4,6,21,22,27] studies generally focus on the use of CVC. Studies comparing the effect of NC and TWSs inserted in peripheral venous catheters on the development of infection are limited. In their examination of the effect of NC and TWS on the development of CRBSI, Luna et al. (2000)[28], and Oto et al. (2007)[15] determined that there was no difference between both types of connectors. However, studies conducted by Bouza et al,[11] Niel Weise et al,[29] and Casey et al[20] showed that NC proved much safer in reducing the risk for infection. Conversely, Maki et al[14] reported that NC increase the development rate of CRBSI. Likewise, Moureau et al (2015)[16] indicated that unless strict aseptic techniques were used, needleless systems might be a possible source of contamination. Results of our study showed that though there was no difference between colonization rates of TWS and NC in total, the colonization rates of TWSs inserted in peripheral catheters were higher than those of NC. These results may indicate that the use of NC more reliable in preventing CRBSI for peripheral catheters. In order to determine why this is the case, further studies should be conducted in this study's same general surgery unit. Health care professionals are generally aware that many factors (including environmental conditions and the hygiene of the skin of patients) affect the bacterial contamination. Although the nurses participating in this study may have carefully disinfected the NC, however, they may not have strictly followed the guide outlining the appropriate disinfection of TWSs.

Although this study's results found no statistically significant difference in the colonization rates of both types of connectors inserted in central vein and port catheters, colonization rates in both connectors inserted in CVCs were identified as significantly high. In addition, rates of infection may be significantly higher in intensive care units. The relation between connectors inserted in catheters and CRBSI is still not entirely clear; however, abiding by the guidelines concerning asepsis and the disinfection of NC for 15 seconds with 70% alcohol was found to be successful at the prevention of colonization of surfaces.[6,13,25]

Limitations

This study's sample included patients receiving treatment in general surgery, reanimation intensive care, and daily chemotherapy units of a training and education hospital in Turkey. Therefore, we recommend that future studies be conducted in different clinical settings using different connector types.

CONCLUSIONS

Results of this study found no significant difference between rates of colonization in NCs and TWSs. The rate of colonization was significantly high in both types of connectors integrated into central vein catheters. Thus, connectors used to connect IV catheters might increase the risk for catheter colonization and CRBSI. Under the condition that they are carefully cleaned before insertion, the use of NC for peripheral venous catheters might be recommended. Health care professionals should keep in mind that the lids of TWSs should always be kept closed, and implementation protocols regarding the maintenance of IV catheters should be carefully followed.

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