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COSMOS Study Microbiological Results: Bacterial Colonization and Infection of Long-Term Peripheral Catheters

Juan Luis González López[1], Paloma Ruiz Hernández[1] and Kenneth W Strauss[2]*

[1]*Nursing Department of Universidad Complutense de Madrid (UCM), Instituto de Investigación Sanitaria 'San Carlos' (IdISSC), Madrid, Spain*
[2]*Global Medical Director, Director of Safety in Medicine, European Medical Association, Brussels, Belgium*

Abstract

Background: Peripheral venous catheters (PVC) have a lower risk of the infection than central venous catheters (CVC), however, their high frequency of use makes PVC a major problem.

Nowadays, there is no consensus regarding the diagnosis of PVC infections and current recommendations are not only utopian but can lead to an underestimation of infection rates.

Objectives: To compare the incidence of bacterial colonization and CRI.

To identify the significant bacterial colonization in CRI, as well as the main pathogens causing bacterial colonization and CRI in long-term PVC.

Material and methods: Nurse-driven, randomized controlled trial to compare closed system (COS) versus open system (MOS), where catheters were removal only by clinical-indication and were inserted and maintained in accordance with CDC guidelines, except those that apply to routine replacement recommendations. The blinded Maki's semiquantitative culture technique was used. *ClinicalTrials.gov* (NCT00665886).

Results: A total of 1183 catheters (631 patients) were randomized, 584 in the COS group (54,173 catheter-hours recorded), and 599 in the MOS group (50,296). 283 PVC were cultured, i.e. 24% of the sample.

The mean in-dwell time to onset of event of COS was 239.5 hours compared to 171.9 with MOS.

No significant difference in cumulative incidence or incidence density rates per 1000 catheter-days for bacterial colonization, and no statistical significance were found between rates of CRI (COS, 2.2%; MOS, 2.5%). However, we observed a 22% relative risk reduction (RRR) in CRI with COS.

Of the 283 cultures, 21.9% were positive, of which the 46.8% were in COS and 53.2% in MOS. There were no significant differences between microorganisms isolated, number of colonies or type of germ. *Staphylococcus* was responsible for 80.3% of the colonization, and 85.7% of CRI. *S. epidermidis* was responsible for 48.8% of colonization and 52.4% of CRI. *S. aureus* was isolated in two cases (9.5%), one in each group.

Discussion: As in previous studies, despite a reduction in the incidence of CRI in closed system, the difference did not reach statistical significance.

Nine CRI registered in COS were caused by Gram + (100%), while in MOS 9 CRI were recorded by Gram + (75%), 2 by Gram - (16.7%) and one by Candida (8.3%). Our data seems to confirm that bacteria isolated from closed systems are less virulent and/or that these systems may offer protection against CRI.

Conclusion: International guidelines for best clinical practice should differentiate CRI from CRBSI in the management of peripheral lines-related infections.

No statistical differences exist between rates of CRI. However, there is a RRR of CRI with closed systems.

A total of 29% of the catheter cultured were associated with CRI (26.5% in COS, 31.3% in MOS), suggesting less virulence of the bacteria isolated in closed systems or greater protection offered by such systems.

In long-term PVC, staphylococci causes 80% of colonizations, and 100% of CRI in closed systems and while only 75% in open.

There were no significant differences between isolated bacteria, the number of colonies or the type of pathogen.

Keywords: Catheter colonization; Catheter-Related Bloodstream Infection (CRBSI); Catheter-Related Infection (CRI); Clinically indicated; Germs; Safety peripheral venous catheter

Background

As the use of intravenous devices (IVD) has risen so have the number of serious complications, mainly infectious, associated with its use. In fact, IVD are currently the most important independent cause of nosocomial infection in the health care sector [1,2]. Catheter-related infections (CRI) are the leading cause of primary septicemia with a high prevalence leading to increased hospital stays and costs. Furthermore they carry a 3% mortality [3].

Catheter-related infection in peripheral catheters

Spanish data from the program of surveillance of infections in patients admitted to critical care units (ICU) shows 6-8 bacteremias/1000 catheter days, of which 10% of cases were attributable to peripheral venous catheters (PVC).

***Corresponding author:** Ken Strauss, Global Medical Director, BD, Director of Safety in Medicine, European Medical Association, Brussels, Belgium, Tel: +32475380454; E-mail: kenneth_strauss@europe.bd.com

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According to data from the Spanish Society of Infectious Diseases and Clinical Microbiology there were 10,000 bacteremias in spanish patients admitted to ICU. The attributable mortality varies from 14% to 28%, the average additional hospital stay is 7 days with an additional cost estimated to be $29,000 (USA) per episode [4].

While the vast majority of catheter-related bloodstream infection (CRBSI) is associated with central venous catheters (CVC), nosocomial infection has also been linked to many invasive procedures and to the use of devices such as short peripheral catheters, especially in infants [5,6].

However, not all intravenous devices have equal rates of infection. Although the onset of infection and/or phlebitis are maximum-quality indicators of IV therapy with peripheral catheters, in his review of 200 prospective studies, Maki et al. [2] confirmed that only 0.5 cases of CRBSI occurred per 1000 PVC-days (95% CI: 0.2-0.7). This is similar to data reported for PICC catheters (0.8 cases per 1000 catheter-days) and for tunneled central catheters (0.9 cases). These figures are far-removed from the 2.9 cases per 1000 catheter days reported with non-tunneled CVC.

Peripheral catheters cause fewer infections, with the risk of CRBSI being less than 0.2% [7-9]. In prospective studies, the risk of a catheter-related infection is 2 to 855 times higher with a CVC than with a PVC [10]. However, the sheer number of peripheral catheters used makes them a major health risk and cost.

Recently several authors [11-13] have warned about an increase in the number of infections and bacteremias caused by PVC. These were associated with significant morbidity, mortality and complication rates. What is surprising, but little-known, is that the 87% primary bacteremias reported were with PVC, according to the National Nosocomial Infection Surveillance System (NNIS) for the 112 medical ICU surveyed in the United States [14].

PVCs have also been recognized as a source of *Staphylococcus aureus* bacteremia in 12-50% of all CRBSI [11,15]. They are the cause of considerable morbidity and mortality, prolonged hospital stays and an increased cost [16,17] of up to € 3,700 per episode [2].

Despite the central role that PVC has in catheter infections, there is no consensus regarding diagnosis of these infections. The Infectious Diseases Society of America (IDSA) identifies and defines various infectious entities in its current 'Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection' [18]. However, the IDSA gives purely microbiological definitions. There is no mention of infectious entities of primary importance in PVC. These may be diagnosed clinically and microbiologically by a combination of the following manifestations: pain, suppuration, phlebitis, fever of unknown origin, etc.; and colonization of the catheter (significant isolation of ≥15 colony-forming units {CFU} of a same microorganism on semiquantitative culture of the tip of the catheter), according to the technique described in 1977 by Maki [19].

These local CRI can become systemic without adequate intervention, but cannot be linked to a CRBSI without a positive blood culture with an identical organism. Nevertheless it is common knowledge that CRI is often a precursor to many CRBSI.

Identifying the bacterial genotype in order to confirm a PVC-related infection is like killing flies with a cannon: it is a procedure with a high cost and low efficiency and its results are usually irrelevant in practice. In this sense the current IDSA recommendations are not only utopian but can also lead to an underestimation of infection rates and the existing health hazard. In fact, despite the multiplicity of existing alternatives, the Maki technique [19] remains the reference standard in clinical microbiology laboratories for its speed and simplicity [20]. It is considered the 'gold standard' for the diagnosis of CRI in PVC, though not in CVC. In fact, since it is a semiquantitative culture it has poor positive predictive value (PPV) for CRBSI [21-23].

Pathogens causing IRC

Electron microscopy studies show that the majority of catheters, even those with negative cultures, are colonized by microorganisms. It is estimated that between 30-45% of catheters have contamination of their tips by a variety of hospital bacteria (>75% Gram-positive cocci such as staphylococci, streptococci and enterococci), without the patient showing any signs of sepsis and with negative blood cultures [24].

The microorganisms that produce catheter infection most frequently are those whose natural habitat is the skin. In fact it has been reported that the *Staphylococus epidermidis* coagulase-negative group, present ubiquitously on skin, causes more than 50% of the CRI. Hence handwashing and disinfection insertion sites are critical preventative procedures. The second leading cause of nosocomial infection of PVC (44.7% of cases) is Methicillin-resistant *Staphylococcus aureus* (MRSA) according to an epidemiological study published in 2000 [25]. Patients infected with a strain of MRSA in the United States were admitted to the hospital for an average of 12 days longer, corresponding to an additional cost of $ 27,082. Anyway, infections caused by all species of *S. aureus* non-resistant to methicillin extended hospital stay by 4 days on average, and increasing hospital costs by $ 9,661 [26].

Gram-positive skin organisms represent the most commonly reported causative microorganisms of CRBSI [27-30]. Data from SCOPE, a nationwide surveillance study in the United States [24] found that coagulase-negative staphylococci and *Staphylococcus aureus* account for 31% and 20%, respectively, of all CRBSI. *Enterococcus* and *Candida* species ranked third and fourth, at 9% each [29]. One quarter of the infections were caused by Gram-negative organisms, with *Escherichia coli* (6%) and *Klebsiella* species being the most common (Table 1 [29,31]). Gram-negative organisms, however, have been found to be a more important cause of CRBSI in some areas of the world [32].

Although the risk of bacteremia is lower in peripheral than in central catheters, the sheer number of the former tends to equate the absolute number of episodes. In addition, various authors highlight the greater relative preponderance of episodes due to *S. aureus* in PVC in

	Percentage of BSIs		
Pathogen	**Total**	**ICU**	**Non-ICU**
Coaqgulase-negative satphylococci	31.3	35.9	26.6
Staphylococcus aureus	20.2	16.8	23.7
Enterococcus spp.	9.4	9.8	9
Candida spp.	9	10.1	7.9
Gram-negative rods			
Escherichia coli	5.6	3.7	7.6
Klebsiella spp.	4.8	4	5.5
Enterobacter spp.	4.3	4.7	3.8
Pseudomonas aeruginosa	3.9	4.7	3.1
Acinetobacter baumannii	1.7	2.1	1.3
Serratia spp.	1.3	1.6	0.9

Table 1: Most common pathogens isolated from nosocomial bloodstream infections, SCOPE [22,23].

contrast to CVC, with consequent increase in morbidity, mortality and health care costs from *S. epidermidis* [8,9,11,15,33,34].

Most Fungal-Related Catheter (FRC) infections are due to *Candida*. In the SCOPE study *Candida* species ranked fourth among CRBSI-causing microorganisms [9]. A majority of these infections (51%) were observed in ICUs [29].

Objectives and Definitions

This secondary analysis of the results of the COSMOS study [35] has as its main objective the presentation of microbiological analyses for:

1. Comparing the incidence in a random sample of catheters of bacterial colonization in both study groups.

Colonization is defined as the presence of ≥ 15 CFU/ml of a single species of microorganism on semiquantitative culture of the tip of the catheter after it has been removed from the patient and cut using a sterile technique (Figure 1).

2. Comparing the incidence of CRI, defined by the presence of >15 CFU/ml of a single species of microorganism in the semiquantitative culture of the catheter withdrawn as a result of phlebitis, pain or fever, or for the disappearance of fever within 24 hours of the withdrawal of the catheter.

Whenever this occurred in the study, the tip of the catheter was cultured.

3. Identify the significant bacterial colonization for CRI in catheters with culture growth.

4. Identifying pathogens that cause bacterial colonization and CRI in PVC that remain in the vein for long periods of time.

Material and Methods

The COSMOS Study was a nurse-driven, Phase IV, prospective, open label, randomized controlled trial to comparatively evaluation the performance, efficacy, security and costs of safety peripheral integrated closed system BD Nexiva™ (manufactured by BD, Franklin Lakes, NJ, USA). This interventional group was named COS for 'compact' closed system. It used an all-in-one system consisting of a polyurethane catheter with an integrated Y extension tubing and a needleless connector split septum named Q-Syte™. The COS group was compared to an open PVC system using the safety catheter Vasocan™ Safety (manufactured by B. Braun, Melsungen, Germany). This group was called MOS for 'mounted' open system. The system consisted of a polytetrafluoroethylene catheter with a three-way tap ('stopcock') and an added 10 cm extension tubing BD Connecta™). In both groups catheters were removal only by clinical-indication in a real world evaluation on 3 hospital wards [36].

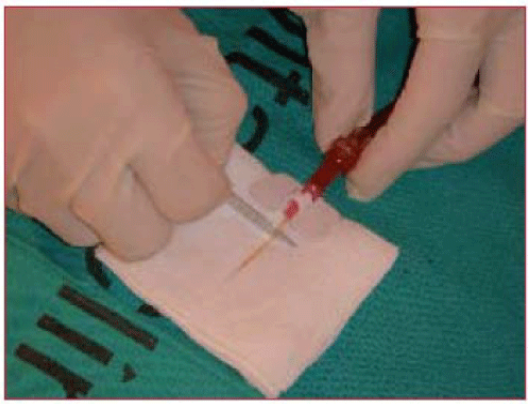


Figure 1: Example of the sterile technique for obtaining catheter tip culture.

This pioneering study was the first to investigate, in a prospective and randomized way, the time that PVC remain in place without complications. The study was performed on three medical (61 beds) and surgical (154 beds) wards at the Hospital Clínico San Carlos (HCSC), a 1000-beds tertiary care university hospital in Madrid, Spain. The trial lasted 108 days and took place between March and July 2008.

The 3M Tegaderm™ 1633 intravenous dressing (3M Healthcare, St. Paul, MN, USA) was used for both groups. Following manufacturer recommendations, dressings were changed every seven days, or sooner if necessary. Seventy-percent alcohol was used for skin antisepsis and disinfection of access ports. The needleless connector was replaced routinely every eight days (after up to 64 activations), which is less than the 70 activation-limit reported by Adams [37].

PVCs were inserted and maintained in accordance with the guidelines of the US Centers for Disease Control and Prevention (CDC), except that the CDC routine replacement recommendations were not followed. Catheter replacement was performed only if clinically indicated instead of every 72-96 hours as recommended by the CDC [17].

At least 141 catheters from each group were selected at random and cultured to determine baseline colonization rates. Catheters were evaluated using Maki's semiquantitative culture technique [19]. Laboratory technicians and microbiologists who cultured the catheter tips were blinded as to the study group assignment.

Randomization was computer-generated [38]. The study design, sample size, inclusion and exclusion criteria, and variables with their definitions have been described elsewhere [35,36].

In all analyses, the level of statistical significance was assumed to be $p<0.05$. The post-hoc power of the study was 97% (Granmo 7.11. Consortion URLEC, Institut Hospital del Mar d'Investigacions Médiques, Barcelona, Spain).

The trial protocol was in accordance with the CONSORT 2010 statement [39], and was registered on the *ClinicalTrials.gov*, web of the US National Institutes of Health (identifier: NCT00665886). All subjects gave informed consent for the study and it was conducted according to GCP and the guidelines of the Helsinki Protocol.

All statistical analyses were undertaken using Statistical Package for Social Sciences (SPSS for Windows Version 15.0, SPSS Inc., Chicago, IL, USA) and Data Analysis and Statistical Software Version 9.0 (Stata Corp., College Station, TX, USA).

Definition of colonization and infection of peripheral venous catheters in the COSMOS Study

The COSMOS study, which analyzes the performance of safety PVC, uses the following definitions for colonization and infection:

- Bacterial colonization: growth of ≥ 15 CFU/ml of the same microorganism on semiquantitative culture of the catheter tip, in the absence of signs of local or systemic infection [9,19,40,41].
- Catheter-Related Infection (CRI): the growth of ≥ 15 CFU/ml of the same species in semiquantitative culture of catheter tips removed as a result of phlebitis, pain or the suspicion of

infection due to unexplained fever, or by defervescence within 24 hours of removal catheter [17,19,42,43]. A yield of ≥ 15 CFU/ml from a catheter, by means of semiquantitative culture, or a yield of ≥ 10^3 CFU/ml from a catheter, by quantitative culture, is considered indicative of catheter-related infection [19,42].

- Catheter-Related Bloodstream Infection (CRBSI) comprises positive semiquantitative culture and blood culture specimens growing the same species without another apparent source for septicemia [19,40,41,44].
- Significant catheter colonization: Growth of ≥ 15 CFU/ml of the same microorganism on semiquantitative culture of the catheter tip removed as a result of phlebitis, pain or the suspicion of infection due to unexplained fever. Expresses the proportion of culture-positive catheters who presented CRI.

CRI rates were expressed as cases per 1000 PVC days to facilitate the comparison with international data (Category B) [45,46].

Results

Of 1294 catheters evaluated in 694 patients, 1183 catheters in 631 patients were randomized, 584 in COS group with 54,173 catheter-hours recorded, and 599 in MOS group with 50,296 catheter-hours.

Excluding lost catheters, catheter tips were cultured in a randomized fashion. From a total of 364 PVC randomized, 290 were cultured and 283 of these were included in the analysis (128 from MOS and 155 from COS), i.e. 24% of the total sample.

Demographic data and results of the study variables were recently published [35].

Since catheters were replaced only by clinical indication, many had long indwell times, ranging up to 40.5 days, with a mean of 206,4 hours (95% CI: 176.1-236.6) and a median of 114.3 hours (95% CI: 102.6-126.0).

In the population evaluated by Intention to Treat (ITT; n=1183), mean time till the appearance of a closed systems (COS) event was 239.5 hours (95% CI: 189.5-289.5), or 10 days, as opposed to 171.9 hours (95% CI: 149.3-194.5) or 7 days for open systems (MOS). The median time till the appearance of an event was 137 hours (95% CI: 120.1-154.0) or 6 days for COS and 96 hours (95% CI: 87.5-104.5) or 4 days for MOS (*p<0.003*).

We observed a significant reduction in the rate of phlebitis (36%), complications (25%) and infiltration (24%) in the COS group, and this was associated with RRR for painful haematoma (49%), occlusion (24%), pain (22%) and CRI (20%).

Nevertheless, in ITT population, there was no significant difference in the cumulative incidence (22.6% COS vs 21.3% MOS), or in the incidence density rates per 1,000 catheter-days (51.1 COS vs 54.1 MOS) for bacterial colonization, and no statistical significance could be found between the rates of CRI of COS (2.2 per 100 catheters and 5.76 cases/1000 catheter-days) and MOS (2.5 per 100 catheters and 6.65 cases/1000 catheter-days). However, observed a 22% of relative risk reduction (RRR) in CRI with closed system (HR 0.78 CI 95%: 0.37-1.64; p=0.514), as shown in Figure 2.

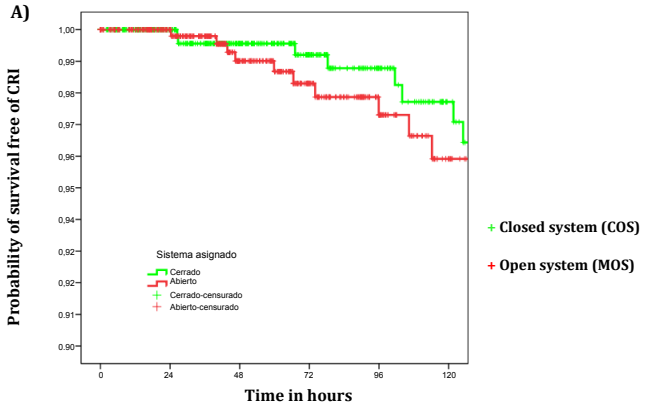
Although more cases of bacterial colonization were detected in the COS group (n=37) than in the MOS group (n=33), only nine cases of CRI were confirmed in the COS group, compared with 12 cases in the MOS group.

Of the 283 catheters randomized to tip culture and cultivated, 20.5% (58 catheters) were positive (>15 CFU of the same pathogen), of which 26 (44.8%) were closed systems (COS) and 32 (55.2%) open systems (MOS). These differences did not reach statistical significance. In catheters randomized to tip culture, there are no significant differences in rates of microbial colonization of closed systems (18.75%, 42.3 cases per 1000 catheter/days) and open systems (16.12%, 41.2 cases/1000 catheter/days), p=0.923 (Table 2).

Nor are there statistical difference between rates of CRI of closed systems (1.56%, 3.5 cases/1000 catheter/days) and open systems (4.51%, 11.5 cases/1000 catheter/days), p=0.132. However, we observed a 69% RRR in CRI in closed systems randomized to tip culture and cultured (HR 0.31; 95% CI: 0.03-1.61 (Table 2)).

There were no significant differences between microorganisms isolated, the number of colonies or the type of bacteria between the two groups in terms of catheters randomized to culture. In this study, *Staphylococcus* was responsible for 80.3% of catheter colonization, 85.7% of total CRI, and 100% of CRI in the COS group. *S. epidermidis*

A)



B)

	p	HR	95,0% CI for HR	
			Lower	Upper
System	0.514	0.781	0.371	1.643

CRI, catheter-related infection; p, statistical significance; HR, hazard ratio; CI, confidence interval.

Figure 2: Kaplan-Meier survival curve to the onset of CRI (ITT population).

	Closed			Open					
	N=128	Rate/1000 hours	Rate/1000 days	N=155	Rate/1000 hours	Rate/1000 days	Rate ratio*	95% CI	p-value
Catheter/hours	13,618			14,571					
Catheter/days	567			607					
Colonization	24	1.762	42.328	25	1.716	41.186	1.03	0.56-1.87	0.923
CRI	2	0.147	3.527	7	0.48	11.532	0.31	0.03-1.61	0.132

CRI, catheter related ifection; CI, confidence interval

Table 2: Bacterial colonization and CRI rates in catheters randomized to tip culture and cultivated.

Germ type	Germ	Colonization		CRI	
		COS	MOS	COS	MOS
Gram + Cocci	*Staphylococcus epidermidis*	17	15	5	6
	Staphylococcus hominis	8	5	2	2
	Staphylococcus haemolyticus	0	3	1	0
	Staphylococcus warneri	1	1	0	0
	S. Coagulasa Negativo	2	0	0	0
	Subtotal	**28 (77.8%)**	**24 (80%)**	**8 (88.9%)**	**8 (66.7%)**
	Staphylococcus aureus	1	0	1	1
	Subtotal	**1 (2.8%)**	**0 (0%)**	**1 (11.1%)**	**1 (8.3%)**
	Total	**29 (80.5%)**	**24 (80%)**	**9 (100%)**	**9 (75%)**
Bacilli	*Corynebacterium afermentans*	0	0	0	1
	Eschericha coli	0	0	0	1
	Otros bacilos	2	1	0	0
	Total	**2 (5.5%)**	**1 (3.3%)**	**0**	**2 (16.6%)**
Fungi	*Candida sp*	0	1	0	1
	Total	**0 (0%)**	**1 (3.3%)**	**0 (0%)**	**1 (8.3%)**
Mixed	*Various germs*	5	4	0	0
	Total	**5 (13.8%)**	**4 (13.3%)**	**0**	**0**
	TOTAL GROUPS (100%)	**36 (54.5%)**	**30 (45.5%)**	**9 (43%)**	**12 (57%)**

*Compare rates per 1000 catheter-hours.

Table 3: Colonization and germs causing of CRI in the COSMOS study.

was responsible for 48.8% of the PVC colonization and the 52.4% of cases of CRI. *S. aureus* was isolated in two of 21 cases (9.5% of total CRI), one case in each of the study groups (Table 3).

Discussion

Catheter tip colonization

Maki noted that catheters with less than 15 CFU did not produce bacteremia, unlike those with higher counts. This cutoff had a specificity of 76% as compared to the gold standard, quantitive culture, and allows us to reduce the number of false positives. However the absolute value of a count of 15 CFU has been questioned [47-50]. Nevertheless we believe that its sensitivity and specificity in catheters removed for suspected infection remain acceptable [47,51]. Given its simplicity it has emerged as the technique of choice in daily clinical practice for the diagnosis of CRI in PVC.

Even with its limitations the Maki technique remains the only viable procedure for the diagnosis and management of infections associated with PVC.

An important limitation of our study was that the protocol required 380 cultures of randomized catheters, as well as cultures of those catheters removed for phlebitis, pain and/or fever of unknown origin (222 cases). However, for various reasons, of the 602 potential cultures only 283 (47%) were performed.

Nevertheless, with the data obtained, the study micorbiologist conducted a blinded classification of pathogens based on diagnostic costs associated with colonization by certain bacteria, e.g. *Staphylococcus aureus*. These costs were base don the need for blood analysis, echocardiography, increased stay, etc. Subsequently, the study epidemiologist compared this classification by study groups and found no differences in colonization or microbiological behavior between open and closed systems or between costs attributable to each one.

Our overall findings show a lower rate of colonization of the catheter tip to that reported by Bouza et al. [49] for a closed system with a needleless connector, CLAVE™ (52.6/1000 catheters/days in COSMOS study vs 59.2/1000 catheter/days in Bouza study).

The same occurs if we compare colonization rates of closed system in our study (51.1/1.000 catheter/days), representing a reduction of 8 cases per 1000 catheter/days with respect to the results shown by the closed system CLAVE™, despite it was found to be an independent protective against colonization in the Bouza study [49].

This may be due to the fact that catheters were manipulated in COSMOS in a regulated and aseptic fashion and only by nurses. Colonization rates of accesses properly disinfected with 70% alcohol did not show significant differences in infection rates [50], despite reports in the literature to the contrary [51].

The same occurs if we compare colonization rates of closed system in our study (51.1/1000 catheter/days), representing a reduction of 8 cases per 1000 catheter/days, to results reported with the closed system CLAVE™, despite it was found to be an independent protective against colonization in the Bouza study [49].

Our rates of bacterial colonization however remain high compared to those reported in 2014 by Mansur et al. [52]. That study put colonization rates in underdeveloped countries at 42.1%. But it must be remembered that the PVC studied in COSMOS had a long indwell time (>206 hours), a duration unmatched in any other published study.

Our data on randomized catheter tip culture and cultivated (Table 2) put the cumulative incidence of colonization at 18.75% and the rate of incidence density at 42.3/1000 catheter/days. This is in line with data by Mansur et al. [52] and was achieved despite the increased indwell time of the catheters used in COSMOS.

Bacterial colonization and phlebitis

An association was found between those patients with greater than 15 CFU isolated from catheter tips and with the presence of phlebitis *(p=0,022)* [53]. Many studies have shown an association between signs of local inflammation and positive catheter culture [19,54-58]. However, COSMOS found a bacterial phlebitis rate of 3.7% corresponding to 10.1

cases per 1000 catheter/days for the total sample, significantly lower than that reported in a similar study (9.5%) [44].

The incidence rate of bacterial phlebitis in our study is 4.3% and 11.1 cases per 1000 catheter/days with the closed system and 3.2% and 9.1 cases per 1000 catheter/days in the open system (no statistical difference). This suggests that the higher rates of phlebitis seen in the open systems (101 cases, 17%, 45 cases/1000 catheter/days, versus 70 cases, 12%, 31 cases/1000 catheter/days in the closed system) are more likely due to mechanical phlebitis than bacterial phlebitis [35].

Catheter-related infection

In ITT analysis, COSMOS has found a CRI rate of 2.36%, with a median in-dwell time of 114.3 hours and a mean of 206.3 hours. Although this rate is well above the rates of CRBSI in peripheral lines reported by Maki et al. [2], who studied systemic infections in contrast to our study, they are surprisingly and significantly lower than those reported in similar studies (6.9% [44], 3.4% [49] and 14% [52]).

In addition, we found a RRR in CRI of closed systems, with a Vialon™ catheter, which goes against the suggestion by Maki and Ringer [9] that higher CRBSI rates are associated with Vialon™ than with Teflon. However, as occurred in the study of Bouza et al. [49] and despite a reduction in the incidence of CRBSI in closed system, these differences did not reach statistical significance.

Significant colonization, predictive of CRI

CRBSI clinically is highly variable and can be confused with other intercurrent processes [58]. It can provoke the removal of catheters on the basis of suspicion. These catheters are culture-negative in up to 80% of cases [59,60]. In a study of 109 cases of catheters removed for suspected infection, only 40 were confirmed by culture to be infected. There is rarely clinical or laboratory assistance *a priori* to determine if a catheter is the source of the fever [60].

As in other major issues in IV therapy, there is no agreement on whether bacterial colonization should be considered a recognized forerunner of CRI. Some authors are in favor [61] and some, against [9,44,62]. However, Aygun et al. [41] found that 9.5% of PVC cultures showed significant growth, and even when significant growth was detected from PVCs, this growth was predictive of a CRBSI in only 43% of cases.

Significant bacterial colonization among randomized catheters in our study was 17.31%, and was predictive of CRI in 31% of cases. Only 13 of the 49 culture-positive COS led to CRI as opposed to 15 of the 48 MOS. Our data seems to confirm that bacteria isolated from closed systems are less virulent and that these systems may offer protection against CRI.

Germs causing CRI

The microbial species most frequently responsible for CVC-related infection are Gram-positive cocci, of which Staphylococci (*S. aureus*, *S. epidermidis*) are most frequent. The prevalence of these have remained unchanged over the years (remaining around 75%). Gram-negative bacteria, especially *Enterobacteriaceae* and *Pseudomonaceae*, caused the remaining 25% of cases [63].

Among Gram-positive bacteria, CNS were the most common isolates. This shows the primary role played by these opportunistic microorganisms in CVC infections [64]. The reason seems to be that for the insertion of the device, an incision must first made for venous access and then the CVC is inserted [65,66]. Passage through the skin as well as the manipulation by the medical staff, cause CVC bacterial contamination, and the pathogens are usually normal bacterial flora [63].

In our study, 9 CRI in closed systems were caused by Gram-positives bacteria (100%), while in open systems 9 CRI were from Gram-positives (75%), 2 from Gram-negatives (16.7%) and one from Candida (8.3%). Thus, there was a greater diversity of CRI-causing pathogens in open systems, and this more closely corresponds to the bacterial distribution reported with CVC [63].

Conclusions

1. It is necessary that international agencies and their guidelines for best clinical practice differentiate as distinct entities the CRI (which requires the presence of symptoms and positive semiquantitative culture for diagnosis) and the CRBSI (which also requires positive blood cultures for the same species of germ for diagnosis), to facilitate the prevention, diagnosis and control of infections associated with peripheral lines.
2. In catheters cultured there are no significant differences in the rates of microbial colonization between open and closed systems, p=0.923.
3. However, despite their longer in-dwell times, catheters used in COSMOS had lower bacterial colonization rates than those reported by other authors for closed and open systems.
4. Colonization rates of accesses properly disinfected with 70% alcohol did not show significant differences.
5. The rate of significant bacterial colonization in catheters cultured was 17.31% and was predictive of CRI in 31% cases.
6. There are no statistical differences between the rates of CRI between closed and open systems, p=0.132.
7. However, there is a RRR of CRI of 22% with closed systems. As in the case of Bouza et al. [50] and despite the reduction in the incidence of CRI in closed systems, this difference did not reach statistical significance.
8. Overall 28.9% of the catheter tips cultured were associated with CRI, 26.5% in closed systems and 31.3% in open systems, suggesting a reduced virulence of bacteria isolated in closed systems or greater protection offered by such systems against CRI. This represents a 15.2% decrease of CRI in closed systems compared with open systems.
9. In long-term peripheral catheters, staphylococci cause 80% of colonizations for entire sample, and 100% of CRI in the closed systems and 75% in open systems.
10. There is no significant difference between the isolated bacteria, the number of colonies or the type of pathogen in both groups.
11. Our data call into question the suggestion of Maki and Ringer [55] that there is more CRBSI associated with Vialon catheters than Teflon ones.

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Conflict of Interest Statement

One of the authors (KWS) is an employee of BD, a manufacturer of several components used in the COSMOS study. No other conflicts of interest to declare.

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