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# Central venous catheter related infections: Risk factors and the effect of glycopeptide antibiotics

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## Abstract

**Backround:** We undertook a prospective study of all new central venous catheters inserted into patients in the intensive care units, in order to identify the risk factors and to determine the effect of glycopeptide antibiotics on catheter – related infections.

**Methods:** During the study period 300 patients with central venous catheters were prospectively studied. The catheters used were nontunneled, noncuffed, triple lumen and made of polyurethane material. Catheters were cultured by semiquantitative method and blood cultures done when indicated. Data were obtained on patient age, gender, unit, primary diagnosis on admission, catheter insertion site, duration of catheterization, whether it was the first or a subsequent catheter and glycopeptide antibiotic usage.

**Results:** Ninety-one (30.3%) of the catheters were colonized and infection was found with 50 (16.7%) catheters. Infection was diagnosed with higher rate in catheters inserted via jugular vein in comparison with subclavian vein (95% CI: 1.32–4.81, p = 0.005). The incidence of infection was higher in catheters which were kept in place for more than seven days (95% CI 1.05–3.87, p = 0.03). The incidence of infection was lower in patients who were using glycopeptide antibiotic during catheterization (95% CI: 1.49–5.51, p = 0.005). The rate of infection with Gram positive cocci was significantly lower in glycopeptide antibiotic using patients (p = 0.01). The most commonly isolated organism was *Staphylococcus aureus* (n = 52, 37.1%).

**Conclusion:** Duration of catheterization and catheter insertion site were independent risk factors for catheter related infection. Use of glycopeptide antibiotic during catheterization seems to have protective effect against catheter related infection.

## Background

Central venous catheters (CVCs) are widely used in critically ill patients throughout the developed world. They permit hemodynamic monitoring and allow access for the

administration of fluids, blood products, medications, and total parenteral nutrition (TPN). Estimates of their use in the United States alone suggest that over five million CVCs are inserted annually [1,2]. Although CVCs have significant benefits in many clinical situations, the increase in their use over the last 20 years has been associated with at least a doubling of resultant nosocomial infections [3,4]. A number of factors may contribute to the risk of catheter related infections (CRI) [5–9]. Although a common problem, the descriptive epidemiology, pathophysiology, risk factors and best means of diagnosing CRI have not yet been fully elucidated. We undertook a prospective study of all new CVCs inserted into patients in the intensive care units (ICU), in order to identify the risk factors and to determine the effect of glycopeptide antibiotics on CRI.

## Patients and Methods

Human research ethics committee approval was obtained for the study. As there were no interventions, requirement for written patient consent was waived. All patients admitted to medical, neurosurgical and surgical ICUs of Istanbul Faculty of Medicine between January 2001 and December 2001 who submitted to a CVC were included in the study. The catheters used were nontunneled, noncuffed, triple lumen and made of polyurethane material (Arrow, Erding, Germany). All catheters were inserted via new percutaneous puncture in intensive care units by experienced anaesthetists under strict aseptic techniques. After washing hands and forearms with antiseptic soap, drying with a sterile towel, maximal sterile barrier precautions (sterile gloves, longsleeved sterile gown, mask, cap, and large sterile sheet drape) were observed prior to catheter insertion. Povidone-iodine was used as antiseptic for cleansing the CVC insertion site. After catheter insertion the site was covered with sterile gauze. Every 48 hours the dressing was removed, the site was inspected and cleansed with povidone-iodine, and a new dressing was applied. Catheters were followed for the duration of their insertion and data were obtained daily on inflammation of the catheter sites by a single observer. The catheters were removed at the end of the day seven as scheduled replacement is followed in the ICUs of our hospital. Catheters were removed in less than seven days when the patient had no more need for central line and suspected to have CRI. There was provision for discretionary clinical judgement to leave the catheter longer than seven days. Each CVC was withdrawn aseptically using sterile forceps after the area of insertion was washed with povidone – iodine solution. The distal 5 cm of the catheter was cut off using sterile scissor and sent aseptically to the clinical microbiology laboratory where it was cultured by semiquantitative method [10]. When blood cultures were indicated, 10 mL of venous blood was drawn from catheter and from two peripheral veins following skin preparation with povidone-iodine. Data were also obtained on patients age, gender, unit, primary diagnosis on admission (categorized as cardiorespiratory failure, trauma, postsurgical and others), CVC insertion site, whether it was the first or a subsequent catheter, duration of catheterization and glycopeptide antibiotic usage.

## Definition [1,3]

Colonized catheter: Growth of ≥ 15 colony forming units (cfu) on semiquantitative culture from catheter tip in the absence of accompanying clinical symptoms.

Exit site infection: Erythema, tenderness, induration, or purulence within 2 cm of the skin at the exit site of the catheter.

Definite catheter-related bacteremia (D-CRB): Isolation of the same organism (i.e., identical species, antibiograms) from semiquantative culture of the catheter and from the blood (drawn from a peripheral veins) of a patient with accompanying clinical symptoms of bloodstream infection and no other apparent source of infection.

Possible catheter-related bacteremia (P-CRB): Bacteremia (isolation of the same organism with identical antibiograms from the blood drawn from peripheral veins and CVC), clinical manifestations of sepsis, defervescence after removal of implicated catheter, but no laboratory confirmation of CVC colonization.

## Statistical analysis

The chi-square or the Fisher's test was used to determine the significant differences between categorical variables. Mann-Whitney U test was used for the continuous variables. The variables that were found to be significant ($p \leq 0.05$) in the univariate analysis (catheter insertion site, duration of catheterization and glycopeptide usage) were taken into logistic regression. The software package used for statistical analysis was SPSS for Windows Release 10.0 (SPSS Inc., Chicago, IL., U.S.A.).

## Results

During the study period 300 patients with CVCs were assessed. One hundred and seventy – six (58.6%) of the patients were from the general ICU, 92 (30.7%) were from the surgical ICU and the other 32 (10.7%) were from the neurosurgical ICU. The patients studied were 148 (49.3%) males and 152 (51.7%) females. The mean age was 44 ± 21.1. The primary diagnosis of the patients were as follows; 81 (27%) cardiorespiratory failure, 72 (%24) trauma, 72 (24%) postsurgical and 75 (25%) others. CVCs were inserted either into jugular vein (n = 132, 44%) or into the subclavian vein (n = 168, 56%). Twenty – eight (9.3%) patients were receiving TPN. The mean length of time the catheter was kept in place was 7 ± 2.8

**Table 1: The association between CRI and the risk factors (univariate analysis)**

| Risk groups | Total | | CRI | | RR* | (%95 CI**) | p value |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | | | |
| **Unit** | | | | | | | |
| Surgical ICU | 92 | (30.7) | 20 | (21.7) | 1.53 | (0.90–2.60) | 0.12 |
| Neurosurgical ICU | 32 | (10.7) | 5 | (15.6) | 1.10 | (0.46–2.66) | 0.79 |
| Medical ICU | 176 | (58.6) | 25 | (14.2) | 1.00 | | |
| **Gender** | | | | | | | |
| Male | 148 | (49.3) | 25 | (16.9) | 1.03 | (0.62–1.70) | 0.92 |
| Female | 152 | (50.7) | 25 | (16.4) | 1.00 | | |
| **CVC insertion site** | | | | | | | |
| Jugular vein | 132 | (44) | 30 | (22.7) | 1.91 | (1.14–3.20) | 0.01 |
| Subclavian vein | 168 | (56) | 20 | (11.9) | 1.00 | | |
| **Repeated catheterization** | | | | | | | |
| Subsequent catheters | 197 | (65.7) | 34 | (17.2) | 1.13 | (0.54–2.72) | 0.87 |
| First catheter inserted | 103 | (34.3) | 16 | (15.5) | 1.00 | | |
| **Total parenteral nutrition** | | | | | | | |
| No | 272 | (90.7) | 46 | (16.9) | 1.18 | (0.46–3.05) | 0.99 |
| Yes | 28 | (9.3) | 4 | (14.3) | 1.00 | | |
| **Primary diagnosis** | | | | | | | |
| Cardiorespiratory failure | 81 | (27) | 14 | (19.4) | 0.97 | (0.51–1.87) | 0.93 |
| Trauma | 72 | (24) | 9 | (12.5) | 0.63 | (0.29–1.34) | 0.22 |
| Postsurgical | 72 | (24) | 12 | (14.8) | 0.74 | (0.37–1.48) | 0.39 |
| Others | 75 | (25) | 15 | (20.0) | 1.00 | | |
| **Duration of catheterization** | | | | | | | |
| ≥ 8 day | 99 | (33) | 24 | (24.2) | 1.87 | (1.14–3.09) | 0.01 |
| ≤ 7 day | 201 | (67) | 26 | (12.9) | 1.00 | | |
| **Glycopeptide usage** | | | | | | | |
| No | 187 | (62.4) | 45 | (24.0) | 4.45 | (1.46–3.14) | 0.001 |
| Yes | 113 | (37.6) | 5 | (4.4) | 1.00 | | |

RR*: Risk ratio 95%CI**: 95% confidence interval

days. Two hundred and one (67%) CVCs were kept in place for seven days or less and the other 99 (33%) CVCs were kept in place for more than seven days. Eighty four (28%) of them at the time of catheter insertion, a total of 113 (37.6%) patients were using glycopeptide antibiotic during catheterization. The other 187 (62.4%) patients were not using glycopeptide antibiotic at the time of catheter insertion and for the duration of insertion (Table 1).

Ninety-one (30.3%) of the CVCs were colonized and the CRI was found with 50 (16.7%) catheters. Of the CRIs; 28 (%9.3) D-CRB, 8 (2.7%) P-CRB and 17 (5.6%) exit site infection was diagnosed. Three (1%) patients had both D-CRB and exit site infection. The unadjusted risk ratios of risk factors are given in Table 1. No significant difference were found for age, gender, unit, primary diagnosis, repeated catheterization and TPN use. CRI was diagnosed with higher rate (n = 30, 22.7%) in CVCs inserted via jugular vein in comparison with subclavian vein (n = 20, 11.9%) (p = 0.01). The incidence of CRI (n = 24, 24.2%) was higher in catheters which were kept in place for more than seven days (p = 0.01). The incidence of CRI was also higher in patients who were not using glycopeptide antibiotic (n = 45, 24.0%) than patients who were using glycopeptide antibiotic during catheterization (n = 5, 4.4%) (p = 0.001). The results of the multivariate analysis are broadly in agreement with the univariate analysis (Table 2). Use of a jugular insertion site has an odds ratio of 2.52 (95% CI: 1.32–4.81, p = 0.005) compared with patients with a CVC inserted into the subclavian vein. Catheters kept in place for more than seven days has an odds ratio of 2.02 (95% CI 1.05–3.87, p = 0.03) compared with catheters kept in place for seven days or less. When the patients using glycopeptide antibiotic were taken as the reference category, the patients who were not using these antibiotic during catheterization had an increased risk with an odds ratio of 3.01 (95% CI: 1.49–5.51, p= 0.005).

One hundred and fourty-eight organisms were isolated as the cause of catheter colonization or CRI. Seventy – nine (53.4%) Gram-positive cocci, 66 (44.5%) Gram-negative bacilli and three (2.1%) yeasts were isolated. The most commonly isolated organism was *Staphylococcus aureus* (n = 52, 37.1%) followed by *Pseudomonas aeruginosa* (n = 27, 19.3%), *Staphylococcus epidermidis* (n = 26, %18.6) and *Acinetobacter* spp (n = 21, %15) (Table 3). Of the 50 cases

**Table 2: The association between CRI and the risk factors (multivariate analysis)**

| Risk factors | β coefficient | Standard deviation | OR* | 95% CI | P value |
|---|---|---|---|---|---|
| **CVC insertion site** | | | | | |
| Jugular vein | 0.92 | 0.33 | 2.52 | (1.32–4.81) | 0.005 |
| Subclavian vein | | | 1.00 | | |
| **Duration of catheterization** | | | | | |
| ≥ 8 day | 0.70 | 0.33 | 2.02 | (1.05–3.87) | 0.03 |
| ≤ 7 day | | | 1.00 | | |
| **Glycopeptide usage** | | | | | |
| No | 1.10 | 0.39 | 3.01 | (1.49–5.51) | 0.005 |
| Yes | | | 1.00 | | |

OR*: Odds ratio 95%CI**: 95% confidence interval

**Table 3: Microorganisms isolated from catheter tip and CRI**

| Organisms | Frequency of microorganism isolated from catheter tip | Frequency of microorganism isolated from CRI |
|---|---|---|
| | n (%) | n (%) |
| Gram-positive cocci | 71 (50.7) | 38 (76) |
| *S. aureus* | 47 (33.5) | 32 (64) |
| *S. epidermidis* | 23 (16.4) | 6 (12) |
| *Enterococcus sp.* | 1 (0.7) | - (-) |
| Gram-negative bacilli | 66 (47.1) | 12 (24) |
| *P. aeruginosa* | 27 (19.2) | 3 (6) |
| *Acinetobacter* spp. | 21 (15) | 2 (4) |
| *Enterobacter* spp. | 5 (3.6) | - (-) |
| *K. oxytoca* | 5 (3.6) | 5 (10) |
| *E. coli* | 3 (2.2) | 1 (2) |
| *K. pneumoniae* | 3 (2.2) | 1 (2) |
| *Serratia marcescens* | 2 (1.4) | - (-) |
| *Candida* spp | 3 (2.2) | - (-) |

of CRI, most of the organisms causing infection were Gram-positive cocci (n = 38, 76%), with the most commonly isolated organism being *S. aureus* (n = 32, 64%) (Table 3). All of the *Staphylococcus* spp. were resistant to methicilline.

The etiology of CRI was predominantly Gram-positive cocci (n = 32, 71.1%) in patients who were not using glycopeptide antibiotic during catheterization. In contrast, in patients who were using glycopeptide antibiotic during catheterization Gram-positive cocci was only responsible from one (%20) CRI. This difference was significant (p = 0.01).

## Discussion

Many different risk factors for CRI in intensive care patients have been reported in the literature [3,4,8,9,11–13]. These include insertion site, duration of catheterization, type of dressing, type of catheter, frequent manipulations, improper aseptic techniques, number of catheter lumens, type of topical antiseptic solution used and use of the catheter for TPN. The relative importance of one risk factor over another is diffucult to assess given that in most studies only univariate analysis has been performed and estimates of the risk of each factor has not been attempted. We performed a logistic regression to assess the major determinants of CRI and found that the independent predictors of CRI were catheter insertion site, duration of catheterization and antibiotic (glycopeptide) usage.

In our study infection rates of catheters inserted into jugular vein and subclavian vein were 22.7%, 11.9% respectively (p = 0.005). The CVCs inserted to the jugular vein were associated with approximately two and a half times the risk of infection compared with CVC inserted to subclavian vein in the multivariate analysis. It is also reported in other studies that colonization and infection is more likely in catheters inserted to jugular vein than in catheters inserted to subclavian vein [1,3,14]. Reasons for the higher infection rate in the jugular vein site is thought to be related to difficulty keeping the dressing in place and contamination with oropharyngeal secretions. Therefore, for catheters inserted to jugular vein, the manipulations should be done with more caution and the oropharyngeal secretions should be prevented to contaminate the catheter. Most of the phycians select the jugular vein for catheter insertion because it is easier to insert the catheter and due to low mechanical complication rate. According to our study and other reports, subclavian vein approach has a significant advantage with respect to insertion site colonization and infection [6,15,16]. Therefore, we suggest that the subclavian approach be utilized preferentially for catheterization, provided a serious bleeding diathesis is not present and risk of pneumothorax is not excessive.

In our study the CRI rate was higher for CVCs kept in place for ≥ 8 days (24.2%) in comparison to catheters kept in place for ≤ 7 days (12.9%) (p = 0.03). The CVCs kept in place for ≥ 8 days were associated with approximately two times the risk of infection compared with catheters kept in place for ≤ 7 days. The practise of routinely changing catheters according to some defined time period to reduce the risk of CRI is commonly referred to as "scheduled" replacement [3,7]. There is little or no support from the literature for scheduled replacement, even though it continues to be a common clinical practice. Cook et al looked at the evidence for scheduled replacement using guide-wire exchanges and/or new site replacements[17]. They found no evidence that scheduled replacement, using either of the replacement techniques, at three days or seven days had any advantage over a replacement based on clinical indication. The other studies also failed to prove any reduction of CRI rates by scheduled replacement[18,19]. While catheter tip colonization and CRI may increase with CVC duration controversy still exists regarding scheduled changes.

We found that the incidence and risk of CRI was lower in patients using glycopeptide antibiotic during catheterization in comparison to patients who were not using these antibiotics (p = 0.005). Gram-positive cocci, particularly coagulase-negative Staphylococci (CNS) and *S. aureus*, are responsible for at least two-thirds of the CRI [12,20]. Glycopeptide antibiotics are active against Staphylococci, including methicillin resistant isolates, which was also the most frequently isolated organism in our study. Therefore we searched the effect of these antibiotics against CRI. There is a lack of clarity in the literature about the definition and influence of antimicrobial use. There are only a few reports that, antimicrobials administered at the time of or immediately after insertion of a CVC may reduce the incidence of CRI [21–23]. Other trials demonstrated no benefit of such prophylaxis. [24–26]. According to our results, it seems that their use may prevent catheters from infection especially with Gram – positive cocci. The glycopeptide antibiotics the patients were using during the catheterization seems to have prophylactic effect. This study also concludes that patients using antibiotics effective against Gram – positive cocci during catheterization, Gram – negative organisms should also be suspected as the cause of CRI and antibiotics which are also effective against these pathogens should be started empirically. Further studies are needed to assess the additional benefit afforded by antimicrobials in reducing CRI.

In this prospective study, the rate of CRI was found to be 16.7%. The rate of catheter-related bloodstream infections (CRBIs) and exit site infection was 12% and 5.6% respectively. Of the CRBIs, 28 (77.8%) were diagnosed as D-CRB and the other 8 (22.2%) were diagnosed as P-CRB. P-CRB was diagnosed when bacteremia and clinical manifestations of sepsis resolved after removal of implicated catheter in case of the organism causing bacteremia not identified at any other site that is possible source. As stated in the definition of P-CRB we could not isolate the responsible organisms causing bloodstream infection from the catheter tip in approximately 22% of the CRBI. It is possible for organisms to originate from the internal surface or the hub of the catheters. The method which we used to culture the catheter tip (semiquantative method) has a limitation in that it can take samples only from the external surfaces of catheters and may not retrieve organisms from the internal surfaces of the catheters [10]. Quantitative culture techniques, including the sonication and vortexing methods [27–29], have the advantage of isolating organisms from the external and internal surfaces of the catheters and possibly releasing organisms embedded within the biofilm layer. Other reports comparing semiquantitative catheter segment culture with quantitative culture methods supports the superiority of quantitative culture methods [30]. Thus, although the semiquantitative catheter segment culture is one of the least expensive tests for a clinical microbiology laboratory to perform and the most frequently used method in hospital laboratories, quantitative culture methods should be preferred for catheter tip culture.

A number of investigators have examined the microbiology of CRIs. *S. epidermidis* were the most common organism growing followed by *P. aeruginosa*, yeasts, enterococci, *S. aureus* and *Enterobacter* spp. [29]. In our study the leading organism causing CVC colonization and CRI was *S. aureus* followed by *P. aeruginosa, K. oxytoca, S. epidermidis* and *Acinetobacter* spp. Although the ratio of Gram-positive cocci to Gram-negative rods isolated from all catheters was approximately 1, the ratio increased approximately three fold in CRI. The finding that *Staphylococcus* spp. was the most common positive catheter tip isolate seems to support the current view that infection originates either from the patients own skin flora or that of medical personnel or from hub colonization.

## Conclusion

Duration of catheterization and catheter insertion site were independent risk factors for catheter related infection. We found that the incidence and risk of CRI was lower in patients who were using glycopeptide antibiotics during catheterization in comparison to patients who were not using these antibiotics. It seems that use of glycopeptide antibiotics during catheterization has a protective effect against catheter ralated infection but further studies are needed to assess the benefit. Although the semiquantitative catheter segment culture is one of the least expensive tests for a clinical microbiology laboratory to perform and the most frequently used method in hospital

laboratories, quantitative culture methods should be preferred for catheter tip culture.

## List of abbreviations used

CVC Central venous catheter

CRI Catheter related infection

CFU Colony forming unit

CNS Coagulase negative Staphylococci

TPN Total parenteral nutrition

ICU Intensive care unit

D-CRB Definite catheter related bacteremia

P-CRB Possible catheter related bacteremia

## Authors' contributions

SÖ carried out the study, designed the study, written the manuscript. HO designed the study, supervised its coordination. AY participated in carrying the study. PA performed the statistical analysis. NC participated in design and coordination. HE participated in design and coordination. SC participated in design and coordination.

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