

Infections Associated with the Central Venous Catheters

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SUMMARY

Central venous catheters are of an essential importance to critically ill patients who require long-term venous access for various purposes. Their use made the treatment much easier, but still they are not harmless and are prone to numerous complications. Catheter infections represent the most significant complication in their use. The frequency of infections varies in different patient care settings, but their appearance mostly depends on the patient's health condition, catheter insertion time, localization of the catheter and type of the used catheter. Since they are one of the leading causes of nosocomial infections and related to significant number of morbidity and mortality in intensive care units, it is very important that maximal aseptic precautions are taken during the insertion and the maintenance period. Prevention of infection of the central venous catheters demands several measures that should be applied routinely.

Keywords: infectious disease; central venous catheter; catheter-related infection

INTRODUCTION

Central venous catheters (CVC) are used in critically ill patients around the world and are essential in the treatment of infants and adults requiring hemodynamic monitoring, hemodialysis, tissue and organ transplantation, administration of liquids, blood products, chemotherapy, antibiotics and parenteral nutrition [1-5]. Infections are the most common complications that develop in the use of CVC [6, 7]. Incidence of infections varies with the patient's health status, duration of insertion time and localization, as well as with the type of catheter and asepsis precautions [8].

In US, more than 5 million patients require prolonged central venous access. Even though it is often avoidable, the risk of infection is very high and in US it ranges between 80.000 cases annually [7]. CVC infection-related mortality and morbidity rates are not negligible and range from 0% to 35%. It is certain that these infections are the cause of prolonged stay in hospitals and increased medical care costs [7, 9, 10]. It is estimated that additional costs of medical care due to bloodstream infections vary between 34.000 to 56.000 USD [11].

TYPES OF INFECTIONS ASSOCIATED WITH THE CENTRAL VENOUS CATHETERS

Infections associated with the CVC are manifested as local and systemic infections.

Local infections developed around the insertion site are often manifested by erythema, edema, and purulent exudate in diameter of 2 cm, with or without the bloodstream infection and pus [8]. This should be distinguished from the clear exudates, which commonly occur after catheter insertion. They may also involve

thrombophlebitis within the cannulated blood vessel or subcutaneous sepsis, which are associated with tunneled devices [12] or as tunnel infection in the form of erythema, induration or pain in diameter of 2 cm from the exit place of the catheter and along the tunnel projection, with or without the Catheter Related Blood Stream Infection (CRBSI) [8]. Cellulitis can occasionally spread from the catheter exit site, particularly in *Streptococcus pyogenes* or *Staphylococcus aureus* infections. Colonization of the central venous catheter implies the growth of more than 15 bacterial colonies (semi-quantitative method) in the absence of other clinical signs of infection [1, 12].

Patients with systemic manifestation of CVC-related infection can develop pyrexia of 38°C without any other clear signs of infection. Transient pyrexia or rigor can develop during the regular flushing of the catheter [12]. Catheter Related Blood Stream Infection (CRBSI) is either a bacteremia or fungemia documented with at least one peripherally obtained blood culture, which can lead to the development of sepsis. Sepsis is one of the most complex challenges in the treatment of critically ill patients, despite implementation of new resuscitating protocols. Definition of catheter associated bloodstream infections (CABI) is less strict and it implies the presence of vascular catheter as a solitary cause in patients who either have an indwelling catheter or have had one within 48 hours of the positive blood culture [11, 13, 14].

ORIGIN OF THE MICROORGANISMS CAUSING THE CENTRAL VENOUS CATHETER RELATED INFECTIONS

The most common etiological factors are the conditions under which CVC is inserted, ex-

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perience of the operator, choice of the place for insertion, care of the catheter and many more. There are five different ways that microorganisms use to reach the tip of the CVC and cause the consequent CRBSI [11].

1. Extra luminal: The most common infection of the short-term catheters in the Intensive Care Unit (ICU) is caused by the migration of the microorganisms from the patient's skin micro flora from the outer side of the catheter up to its tip and finally to the bloodstream [6, 8]. This source of infection is primarily related to the inability of skin antiseptics to sterilize the skin at the site of catheter insertion. Once the catheter is colonized it becomes a permanent cause of bacteremia [12].

2. Intra luminal: It has been proven that microorganisms colonize the inner components of the catheter hub and its luer connector via intraluminal migration from infusates [12]. This is considered the most common way of infection of long-term CVCs.

3. Hematogenous: Dissemination of microorganisms through the blood from distant sites can result in colonization of the catheter. This is a less common way of infection [12], which predominantly depends on the catheter material and antibiotic coating.

4. Contamination through medicaments and infusion: Infusates may be contaminated during manufacturing or manipulation with sets for intravenous infusion or even during the preparation of fluids for injection. This way of contamination is very rare in the USA but may occur in developing countries [11].

5. Impaction during insertion: Frequently neglected way of infection. It occurs by entering of bacteria from the patient's skin to the catheter hub during the placement of catheter and is a direct indicator of inadequate asepsis of the skin prior to insertion.

When microorganisms reach the surface of the catheter they directly bind to the polymers on its outer surface and form a biofilm called glycocalyx which consists of various polysaccharides. The biofilm protects the microorganisms from the effect of neutrophils and antibiotics and thus makes these infections very difficult to treat. During the insertion of catheter, a large number of platelets and proteins gets attached to its surface, and in a period of 3 hours forms a layer consisting mainly of fibronectin, which may later on represent a potential binding place for microorganisms, especially *Staphylococcus* [7, 12].

Most of the microorganisms causing catheter infection originate from the patient's own microflora. Gram-positive cocci, including the *Staphylococcus aureus* and coagulase-negative *Staphylococcus* – such as *Staphylococcus epidermidis* are the leading cause of infections associated with catheters [1, 7, 11]. Infections caused by gram negative bacillus and most commonly the coli form bacteria (*Enterobacteriaceae*) are usually found in highly risk units like the ICU. Infections with coli form bacteria are common in patients with tracheostomy on mechanical ventilation [12].

Candida species has become a significant pathogen in the ICUs, especially in patients on total parenteral nutrition (TPN) and patients on corticosteroid and other immunosuppressive therapy [3, 7, 11, 12].

Table 1. Most common bacteria in CVC infections in pediatric patients

Bacteria	Frequency (%)
Coagulase-negative <i>Staphylococcus</i>	20–50
<i>Staphylococcus aureus</i>	10
<i>Candida species</i>	10
<i>Enterococcus</i>	8.5–9.4
<i>Klebsiella spp</i>	7.5

Infections of the catheter in pediatric patients are caused by the similar spectrum of microorganisms. Most common is coagulase-negative *Staphylococcus* in 20%-50%. Gram-negative bacteria cause 25% of nosocomial infections and *Staphylococcus aureus* and *Candida spp.* are responsible for about 10% of these infections. Other microorganisms vary in relation to patient's age, so β Hemolytic *Streptococcus* has larger prevalence in neonatal population and accounts for 8.5%, *Enterococcus* has bimodal peak so it is most common in neonatal population and in patients of 13-65 years, with frequency of 8.5–9.4%. *Klebsiella spp.* makes 7.5% of CVC-related infections in pediatric patients and together with coagulase-negative *staphylococcus* and *Staphylococcus aureus* it is on the third place of causes of CVC-related infections in pediatric population (Table 1) [11].

CLINICAL AND BACTERIOLOGICAL DIAGNOSIS AND TREATMENT OF THE CENTRAL VENOUS CATHETER RELATED INFECTIONS

The basis for making diagnose of CRBSI is an identification of the microorganism from the tip of the catheter and from the blood. Accordingly, definite diagnosis usually means that the catheter must be extracted. The diagnosis or high degree of suspicion on CRBSI must lead to urgent reaction in order to avoid complications of persistent bacteremia such as septic shock, endocarditis or septic metastasis [8].

Clinical manifestations typical for CRBSI are unspecific, and they can manifest with high temperature, rigor and shivering. Because of relatively low specificity, catheter should not be removed only because of the presence of high temperature. Pus and inflammation signs on the output of the catheter and positive hemoculture have a higher specificity but no sensibility, which is why the extraction of catheter in such cases should be recommended only for clinically well-justified doubt on CRBSI.

CV-related infection most possibly occurs when the hemocultures are positive for common causes of nosocomial infection, such as coagulase-negative *Staphylococcus*, *Staphylococcus aureus* and *Candida spp.* [11]. If the catheter was tunneled, tunnel infection would develop which might affect a wide area of the anterior chest wall, especially in patients with neutropenia and in immunocompromised patients. In the ICU patients, CRBSI can manifest as inexplicable hypotension, tachycardia and metabolic acidosis.

A diagnostic procedure that includes blood sampling for bacterial culture should be applied only when there is an adequate clinical doubt on CRBSI. If there is such doubt, two sets of samples are taken for the culture [7, 15].

Hemoculture taken by aspiration from the catheter is more commonly associated with false positive results and because of that it is important that one peripheral blood sample is taken. For the confirmation of CRBSI, microbiological profile of the sample taken from the lumen of the catheter should be the same with the hemoculture obtained from the peripheral veins. Colonies obtained from the CVC should be 5 times numerous than those obtained from the peripheral veins and antibiogram taken from the CVC should be positive two hours before the result of the sample from the peripheral veins [11, 16].

Routine extraction of the suspicious catheter results in the loss of a large number of "innocent" catheters which could have been saved. Catheters should always be extracted if there were clear signs of venous thrombosis, if septic shock was developing or if pus appeared around the site of catheter insertion. Saving of the catheter depends on the localization of the infection, cause of infection, and the immune status of the host. Short-term catheters are usually extracted, while long-term catheters should be considered for treatment. Infections of the tunnel or port demand extraction because the mechanism of infection includes the creating of biofilm around the internal surface that cannot be efficiently treated with antibiotics.

Fungal infections cannot be treated successfully in this way. In order to prevent the development of sepsis, systematic antifungal therapy is necessary for the infection with *Candida spp.* Because of the small number of successfully cured fungal CRBSI (30%) and the direct increase of morbidity, it is recommended that the catheter should be removed as soon as fungal infection is diagnosed. Assumption that the catheter is the source of fungal infection is supported by the isolated *Candida Parapsilosis*, moreover if the patient is on parenteral nutrition. The ratio of culture taken from the suspiciously infected catheter in comparison to the one taken from the skin should be 5:1, confirmation of the cause is two blood samples taken more than 2 hours apart, or if the patient has neutropenia without other clear causes of infection [8, 17].

In patients without persistent infection of the bloodstream and with positive culture on coagulase-negative *Staphylococcus*, but without local or metastatic infective complications, the catheter should not necessarily be removed and antibiotic therapy should be applied [11]. Data collected from several studies showed that *Staphylococcus Aureus* infection was the most common ($\frac{2}{3}$ CRBSI), during the first two weeks after the catheter was inserted. This resulted in studies wherein prophylactic vancomycin therapy was applied in duration of 10-14 days. For milder forms of infection, vancomycin solution 100-1000 times more concentrated compared to the standard dosage for parenteral usage was placed in the lumen of the catheter, and then the catheter was closed for 12 hours. However, this method is not recommended for routine use, while the prophylactic use of vancomycin lock solution of 25 $\mu\text{g}/\text{mL}$ represents the unique factor of risk of the vancomycin resistant *Enterococcus* infection [7, 18].

If, however, it was decided that the catheter should be removed, the tip of the catheter should be sent for the

microbiological analysis. Surface of the skin around the place of the catheter's extraction must be adequately disinfected, catheter is removed with pean, the tip is then placed in a sterile test tube, and sent for bacteriological analysis. For patients with mild and moderate signs of infection suspected for possible CVC-related infection, the replacement of the catheter may be an option while waiting for the microbiological results taken from the tip of the catheter. If the result from the tip was positive for bacteria, the newly placed catheter would be removed and placed on some other position. The catheter exchange through a guide wire reduces mechanical risks of placing the catheter in an unwanted place, but does not eliminate the risk of infection. In case of persistent bacteremia when there is no clinical improvement in 3 days after the removal, there is a possibility of infective endocarditis, septic thrombosis or the infection expansion to distant places [11].

RISK FACTORS AND PREVENTION OF DEVELOPMENT OF THE CENTRAL VENOUS CATHETER INFECTION

Logical approach to prevention of infections associated with CVC is an observation of this problem through two aspects: the aspect of the catheter and the aspect of the medical staff.

The catheter

The risk of CRBSI is much higher for CVCs than for peripheral vein cannulas and Swan-Ganz catheters [12]. One of the main reasons is that CVCs, especially those used for parenteral nutrition, reside in the blood vessel for longer time, which is in hospital conditions the most significant factor of risk of CVC-related infection [7].

The material, from which the catheter is made of, has high effect on development of CRBSI. It is very important that the catheter is biocompatible, hemocompatible, biostable, chemically neutral and inert to the influence of other medicaments. It must be flexible but at the same time resistant, X-ray opaque, with a thin wall resistant to sterilization and with a safe lock system. From all available catheters on market, the CVC made of Teflon and polyurethane has proved to be the safest in terms of complications resulting from the infections, whereas the catheters made of polyethylene and polyvinyl chloride have been withdrawn from the market due to their numerous disadvantages.

When considering infections associated with CVC, the circumstances under which the catheter is inserted cannot be ignored. Urgent catheter placement carries a much higher risk of CVC-related infection, and these catheters must be replaced as soon as the general condition of the patient is stabilized [19].

The requirements of every individual patient will determine the type of catheter, but for the administration of parenteral nutrition and other solutions containing lipids,

there should always be a separate lumen that will be used only for this purpose [20].

Catheters coated with antibiotics, working preventively in relation to adhesion and colonization of microorganisms, have been developed. Most commonly used and tested catheters impregnated with antibiotics are:

- Catheters coated with Minocycline/rifampin: Efficiency of these catheters in prevention of infections has been confirmed in many studies; it has been proven that they are associated with a small degree of colonization and incidence of CVC-related infection. The comparison of catheters coated with Minocycline/rifampin and those coated with Chlorhexidine-Silver Sulfadiazine has confirmed that the former ones are three times more efficient in their protective function [21]. These catheters keep their antimicrobial feature for 2 weeks after the insertion, and their use is cost-effective if they are used for more than one week [22].
- Catheters coated with Chlorhexidine-Silver Sulfadiazine: the catheters coated with these substances, both externally and internally are currently available. Antiseptics are released from its surface for the period of 15 days after the insertion, which makes them effective in the struggle against the colonization of bacteria and infections associated with CVC. So far, there have been no data on development of resistance of any of these substances, but there have been some case reports in Japan and UK on anaphylactic reactions that had appeared after the insertion of these catheters [7, 23]. This is a very rare side effect but it certainly must be taken in consideration. It is advised for catheters coated with Minocycline/Rifampin and Chlorhexidine-Silver Sulfadiazine to be used when there is a need for them from 1 to 3 weeks as well as in case of higher risk of infection [24].
- Silver-platinum and carbon catheters: This type of coating is relatively new, and together with Minocycline-rifampin and Chlorhexidine-Silver Sulfadiazine catheters, represents an equally good instrument for the prevention of colonization and development of CVC-related infection when the central venous access is needed for more than 5 days.
- 5-fluorouracil: catheters coated with this substance are also new generation catheters and are very efficient in prevention of infections associated with catheters; these catheters are even more efficient than those impregnated with the Chlorhexidine-Silver Sulfadiazine [25].

Numerous studies have proved that the use of anticoagulant medication reduces the incidence of thrombosis of catheter and consequential CRBSI. This approach reduces the amount of deposited fibronectin on the surface of the catheter which may later on favor the adhesion of staphylococcus [7, 12].

Insertion of CVC in the femoral vein is associated with higher risk of infection than the insertion in the internal jugular vein, and the insertion into the subclavian vein carries the lowest risk of infection. From the aspect of the infection control, subclavian vein is the place where the

catheter should be inserted, but when choosing the right place for insertion of CVC, mechanical complications, subclavian vein stenosis and the experience of the operator must be taken into consideration. One study has shown that the colonization, in case of the internal jugular vein is increased with the body mass index (BMI) lower than 24.2 and in case of the femoral vein with BMI higher than 28.4. In case of the catheter insertion in the contraindicated subclavian route, the patient's BMI and the risk of thrombophlebitis, which is higher for femoral vein, have a great effect [7, 26].

There is different percentage of aqueous and alcoholic solutions of chlorhexidine and povidone iodine available on the market. The disinfection of the CVC insertion site with 2% alcohol chlorhexidine lessens the risk of infection by 50% compared to 10% povidone iodine and 70% alcohol and is crucially important for the prevention of CVC infection. The solution of 2% chlorhexidine with 70% alcohol is very efficient in the elimination of the biofilm and proteins from the tip of the catheter [7, 25]. Even today, this solution is recommended as useful for disinfection [27, 28].

Two most common instruments for the coverage of the insertion site are transparent sticking plaster and standard gauze and plaster. Transparent plaster has many advantages when compared to conventional bandages because it gives the clear view on the condition of the skin around the catheter and consequently contributes to prompt recognition of possible local complications. It also helps the patient keep his/her personal hygiene by showering, demands less frequent replacement and saves time for medical staff.

Despite the abovementioned advantages, the use of standard gauze is recommended in cases of heavy bleeding [7, 12].

The use of ultrasound during the placement of CVC is considered the method of choice for the reduction of incidence of CVC infections, but only in cases when operator has an adequate experience in placement of catheter using this method [7].

Medical staff

Experience of operator, and the time and technique of insertion have effect on the risk of infection of CVC. During the insertion, optimal conditions of asepsis should be provided by routine use of sterile gloves, compresses, masks, caps and medical coats. Best way to insert catheter is using the Seldinger technique [7].

Blood, blood products and lipid emulsions increase the infection incidence of CVC, which is why the routine replacement of all catheter connectors, systems and extensions of CVC for infusion immediately or in the first 24 hours after the administration of one of the abovementioned solutions is recommended. Before any manipulation with the catheter, one's hands should be cleaned with alcohol or disinfectant. External parts of the catheter are treated before every use with antiseptic solutions based on chlorhexidine. Application of antibiotic ointments around the catheter exit has been proven to be inefficient in the

attempt to prevent CVC infection, therefore its use is not recommended. It has been confirmed that antibiotic coating helps the development of resistance to local microorganisms [7, 12].

The programs of education for young doctors on the CVC insertion in the ICU and training of nurses and technicians about the proper care of the catheters and an optimal number of medical staff for the care of a single patient significantly contribute to reduction of CVC infections [7, 29, 30].

CONCLUSION AND RECOMMENDATIONS

Central venous catheters are of an essential importance in the therapeutic approach to a critically ill patient. Infections of the catheter are very serious and very common complications in the establishment of the venous route and the leading cause of nosocomial infections in the ICU [13]. Prevention of CVC infection implies several methods

that should be the routine. Most important are the implementation of well-defined protocols about the placement and care of CVC, and the education of doctors and other medical staff about proper handling with the equipment. During the insertion and care of CVC, the most important rules of asepsis and antisepsis must be respected, related primarily to disinfection of the insertion site with 2% chlorhexidine solution, disinfection of operator's hands, and the use of sterile gloves and compresses. Choice of the vein for the elective placement of CVC is the subclavian vein whenever possible. If there was an increased risk of infection, catheter coated with antibiotics would be recommended. Prophylactic use of antibiotics should be avoided along with the use of antibiotic cream around the place of catheter exit site. Transparent hydro permeable plasters should be used and replaced more often than every 7 days. Catheters should not be changed unless indicated and should be withdrawn only when they are no longer needed. Always consider enteral nutrition and peripheral veins prior to the use of CVCs [7, 12].

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Инфекције повезане са централним венским катетерима

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КРАТАК САДРЖАЈ

Централни венски катетери су од пресудног значаја за болесника којима је потребан дуготрајан и безбедан венски приступ у различите сврхе. Иако је њихова употреба допринела унапређењу лечења критично оболелих особа, она је повезана с великим бројем могућих компликација. Учесталост инфекција зависи од услова лечења, здравственог стања болесника, трајања постављања катетера, његове локализације и врсте. С обзиром на то да су инфекције централ-

них венских катетера водећи узрок болничких инфекција и узрок морбидитета и морталитета у јединицама интензивне неге, веома је важно водити рачуна о максималној асепси приликом њиховог пласирања и одржавања. Превенција инфекција које су повезане са централним венским катетерима подразумева неколико мера које је потребно рутински примењивати.

Кључне речи: заразна обољења; централни венски катетери; инфекције повезане са централним венским катетерима

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