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**Commentary to the article by Yu.V. Zhirkova, R.F. Tepaev and Yu.I. Kucherov  
“Prevention of catheter-related infection in neonates”**

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Dear colleagues, we would like to call attention to an article dedicated to one of the most important sections of intensive care – prevention of catheter-related infectious complications. Infection is one of the most widespread causes of complications associated with central venous catheters (CVC); it is associated with the reduction in survival rate values at resuscitation and intensive care units (RICU). Observance of guidelines of aseptics and antiseptics is the basis of prevention of infectious complications. It is well known that the “horizontal” infection transmission route is the primary for the development of purulent-septic complications. Therefore, solutions for infusion therapy, assembly and connection of infusion lines to CVC must be conducted in aseptic conditions using sterile gloves. Symptoms of catheter-related sepsis must be daily checked in the event of parenteral feeding. In the event of development of such clinical symptoms as fever (body temperature over 38.0 °C), metabolic acidosis, thrombocytopenia, unstable blood glucose level and hyperlactatemia in a child, infectious process shall be suspected. It is necessary to inoculate CVC blood immediately upon detection of the listed symptoms. In compliance with the recommendations of international organization “The Surviving Sepsis Campaign” (SSC), cultural trials require sampling of CVC and peripheral vein blood and other biological fluids, which may serve as a source of infection before an anti-infection therapy has begun. Fungal CVC infections and stable hyperthermia with positive blood culture inoculations are indications for CVC removal. CVC-related infection must be monitored regularly. Operative measures must be taken upon slightest suspicion as one hour of delayed anti-infection therapy in patients with sepsis is associated with a 9% lethality increase.

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**Prevention of catheter-related infection in neonates**

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*The article is dedicated to an urgent issue of intensive therapy in neonatology – prevention of catheter-related blood flow infections. The article dwells upon etiological factors, formation mechanisms and modern methods of preventing colonization of central venous catheters and catheter-related infections.*

**Keywords:** neonates, catheter-related blood flow infections.

Hospital-acquired infections are one of the main causes of morbidity and mortality at neonatal resuscitation and intensive care units (NRICU) – they result in prolonged hospitalization and require additional treatment costs. Neonates, especially premature neonates, are especially vulnerable to hospital-acquired infections due to immature immune system, abundant invasive procedures in the course of treatment and frequent contacts with medical personnel required throughout inpatient stay [1].

Vein catheterization is widely applied during intensive care and management of neonates with various therapeutic and surgical diseases. Several variants of venous access are used in practice depending on indications: catheterization of peripheral veins, use of cuffless central catheters and peripherally inserted central catheters (PICC), insertion of long-functioning catheters with a subcutaneous cuff (Broviac) and implantable port. Infection of central venous catheters with development of catheter-related bloodstream infections (CRBSI) is the most frequent hospital-acquired infection at NRICU – 45-55% of all the infectious complications (device-associated healthcare-associated infections, DA-HAI) [2-4]. Mortality in the event of CRBSI may be up to 38% (RR – 3.09; 2.17-4.42;  $p=0.0001$ ) in comparison with lethality of neonates at NRICU without DA-HAI – 12.3% [5]. CRBSI development risk is higher in neonatology. A multicenter study conducted by J.A. Navoa-Ng et al. showed that CRBSI rate in adults patients at intensive care units is 4.6 per 1,000 catheter-days (number of catheter use days), in children – 8.23, in neonates – 9.6, respectively [6].

Standardized diagnostic criteria, classification and terminology developed for DA-HAI hospital-acquired infections are in use in world practice at the moment [7, 8].

- Catheter colonization –  $10^3$  or more colony-forming cultures at quantitative method or growth of more than 15 colony-forming units at semiquantitative method of microbial study of the removed catheter's distal segment with no clinical symptoms present.
- Catheter-related bloodstream infection (CRBSI) – isolation of the catheter-colonizing microbe from peripheral blood within 48 hours before or after removal of the catheter and clinical manifestation of the infection with no other causes of the infection present.

The most widespread clinical symptoms of CRBSI in neonates are fever (49%) and respiratory disorders (30%); slightly less widespread symptoms are erythema and purulent discharge in the catheter insertion site (20%) [9].

There are 3 pathogenetic ways of CRBSI development [10, 11]:

- intraluminal (infection of drugs for infusion therapy and parenteral feeding or directly of catheter's cannula);
- extraluminal (skin infection in the catheter insertion site, due to contacts with infected medical personnel or contaminated antiseptics);
- hematogenic (remote, unrelated infection nidus).

The most widespread CRBSI causative agent in neonates at NRICU are coagulase-negative staphylococcus (25-83%); *Staphylococcus aureus* (6.0-24.6%), *Pseudomonas spp.* (12.5%), *Escherichia spp.* (12.5%), *Enterobacteriaceae* (5.0%) and *Candida* varieties (13.0-37.5%) are less widespread [2, 5, 9, 12-15]. Ca. 35% of *S. aureus* are methicillin-resistant [14].

Detection of risk factors and reduction of their effect with various preventive methods is the basis of CRBSI preventive measures. It ought to be mentioned that CRBSI prevention is of high importance due to high efficacy. Numerous techniques aimed at CRBSI risk reduction have been studied in the recent decades; most of the studies involved adult patients as participants. Several recommendations for use among children, including neonates, have been taken from the studies conducted among adult patients [16-18].

There are 3 groups of CRBSI development risk factors:

- 1) patient-related risk factors due to a child's peculiarities (gestational age and body weight, immune suppression, skin affection, condition severity);

- 2) health service (care) – factors related to setup and use of a central catheter (provision of aseptics during insertion of a catheter, catheter maintenance, vascular access method, catheterization duration);
- 3) catheter-related factors (material and construction of a catheter) [19].

It has also been observed that CRBSI rate at NRICU depends on socioeconomic status of the country and the medical establishment. According to a multicenter trial, CRBSI risk in neonates is considerably higher in countries with low average income of population than in countries with high average income of population (37.0 and 17.6 per 1,000 catheter-days, respectively;  $p < 0.05$ ); the rate of infectious complications also correlates with the type of the healthcare establishment (public, academic or private inpatient hospital; 14.6, 14.3 and 10.8 per 1,000 catheter-days, respectively) [20].

CRBSI rate in neonates is in reverse proportion to **birth weight**: 13.6 in children with body weight less than 750 g; 12.6 – with body weight of 751-1,000 g; 7.7. – with body weight of 1,001-1,500; 3.2. – with body weight of 1,501-2,500 g and 1.6 – in neonates with body weight over 2,500 g (per 1,000 catheter-days) [9, 13, 14, 21]. Several researchers did not reveal correlation of low birth weight and gestational age with CRBSI development risk [2]. It has been observe that the more the rated gestational age at the time of catheter insertion, the lower the CRBSI development risk ( $p < 0.0013$ ); an extremely low body weight (ELBW;  $< 1,000$  g) at the time of catheter insertion is a factor independently connected with an infection (OR=5.13; 95% confidence interval – 2.1-12.5) [9, 22]. Other patient-related risk factors include transfusion of blood products (8/15 against 3/34;  $p < 0.01$ ), administration of corticosteroids (7/15 against 3/34;  $p < 0.01$ ), prolongation of respiratory therapy with positive continuous pressure in respiratory tract (13.6 against 2 days;  $p < 0.01$ ) [23]. In their prospective study conducted at NRICU, L.M. Mahieu et al. mention parenteral feeding duration (OR=1.04; 95% CI – 1.0-1.08) and catheter insertion at the age of 8 or more days of life (OR-2.7; 95% CI – 1.1-6.7) among the CRBSI-related factors [22].

**Duration of use of a central catheter** is the second most important risk factor of infectious complications in neonates ( $p < 0.001$ ) [2, 9]. A retrospective study by M. Butler-O'Hara et al. shows that the CRBSI rate in the event of use of umbilical catheters for  $\leq 7$  days is 1.0/1,000 days, for more than 7 days – 4.0/1,000 days ( $p < 0.001$ ); therefore, the infection development risk is higher (OR=5.48) [24]. That is why it is advisable to remove a central venous catheter from a neonate *as soon as it is no longer required* [2].

**Insertion site of a central venous catheter** and the technique employed (percutaneous catheterization, classic Seldinger catheterization etc.) affect the risk of infectious complications; however, the data for neonates are contradictory. In the study by F. L'Hériveau et al., the CRBSI rate was lower in the event of umbilical catheterization (2.9/1,000 days; 95% CI – 1.9-3.8) in comparison with central access (11.2/1,000 days; 95% CI – 10.0-12.5) [15]. S.N. Hocevar et al showed that the CRBSI rate is lower in the event of umbilical catheterization only in premature infants with body weight  $> 750$  g (3.94/1,000 days); the CRBSI rate in children with body weight  $\leq 750$  g is 4.52/1,000 days [14]. M. Butler-O'Hara et al. report that the CRBSI rate increases faster in the event of umbilical vein catheterization that when PICC is employed and recommend replacing a umbilical catheter with PICC if central venous access is required for more than 7 days [24]. However, a different trial showed that the infection rate in neonates is higher when PICC is employed in comparison with other central venous catheters ( $p < 0.01$ ) [13].

M.E. Fallat et al. did not reveal significant differences in the CRBSI rate in neonates depending on localization and type of catheter [9]. Several studies shows that insertion of a central venous catheter through femoral veins is characterized by a higher risk of infection in comparison with insertion through the jugular or the subclavian vein (1.76; 95% CI – 1.01-3.07;  $p = 0.045$ ) [2, 25]. On the other hand, a retrospective study by R.K. Vegunta shows that the highest rate of infectious complications in the event of insertion of a silicone Broviac catheter was observed at catheterization of the subclavian vein and cervical veins (12.5%) (in comparison with the inguinal region (2.04%)) [26].

**Thorough antiseptic treatment of skin** before catheter insertion and during bandage replacement is of key importance to prevention of infectious complications. The practice in adult patients and older children shows that the most widely employed antiseptic is chlorhexidine; it has advantages with regard to prevention of infectious complications in comparison with other solutions [16]. Studies of neonates revealed advantage of chlorhexidine use for working with central catheters to reduce catheter colonization in comparison with 10% povidone iodine solutions [27]. However, the later study of these authors did not reveal significant difference in the catheter colonization rate and CRBSI [19, 28]. A prospective study of 373 neonates (40% - children with ELBW) conducted by American researchers showed that CRBSI in children with umbilical arterial or venous catheter reduced from 15 to 10 per 1,000 catheter days after treating cannula with 2% chlorhexidine (OR=0.47; 95% CI – 0.17-0.91), in children with PICC – from 23 to 10 per 1,000 catheterization days (OR=0.33; 95% CI – 0.12-0.91) [29].

Skin reactions to 2% chlorhexidine were observed only in premature infants with ELBW (11%) [30]. However, M. Visscher et al. reported that skin reddening and dryness in the treatment site cannot be associated only with an antiseptic. It has been observed that dermatitis development risk increases in premature infants when chlorhexidine is combined with adhesive bandage. To prevent dermatitis, it is necessary to thoroughly wash antiseptic away with a sterile saline before applying a bandage [31].

**Application of a special antimicrobial bandage or sponge (impregnated with chlorhexidine or silver) in the catheter insertion site** reduces the risk of catheter colonization, but not of CRBSI. However, dermatitis developed in 15% of children with ELBW and 1.5% of children with body weight >1,000 g in the chlorhexidine-impregnated sponge application site; this restricts use of this technique in premature infants [32]. Application of a bandage with alginate silver did not reveal any skin reactions in neonates at PICC insertion [33].

Benefits of systemic **administration of antibiotics at insertion and/or use of central venous catheters** have yet to be determined. Recommendations for adult and pediatric patients do not support routine antibiotic prevention for central vein catheterization; however, it may be indicated to certain groups of patients with high risk of infectious complications [16]. Studies of neonates showed that CRBSI rate is significantly reducing at administration of vancomycin during catheter setup ( $p<0.0057$ ) [9]. Administration of 25 mcg/ml of vancomycin with parenteral feeding preparations reduces catheter colonization with coagulase-negative staphylococcus (40 against 22%;  $p=0.03$ ) and CRBSI rate from 15 to 0% ( $p=0.004$ ); neonates also recover their body weight faster (13.4 and 17.1 days;  $p=0.014$ ) [34]. Meta-analysis conducted by A. Lodha et al. showed that application of vancomycin at the use of a central catheter results in reduction in CRBSI rate from 23 to 2.4% in premature neonates ( $p=0.0001$ ), though it does not affect mortality and duration of central access use [35]. However, wide spread of this technique is not advisable due to the risk of development of vancomycin-resistant microbes.

**Periodical application of a “lock” with antibiotic solutions** is seen as a possible method of reducing infectious complications, though it is not recommended for routine application in patients with central venous catheters [16, 36]. In their study of neonates, J.S. Garland et al. compared efficacy of “lock” vancomycin (25 mcg/ml) + heparin BID-TID for 20-60 minutes at PICC to efficacy of heparin. The work proved higher efficacy of such a “lock” for reducing CRBSI: relative risk – 0.16 (95% CI – 0.04-0.66;  $p=0.002$ ). The study of microbes from skin surface and rectum did not reveal vancomycin-resistant strains. Theoretically, application of an antibiotic “lock” prevents formation of a microbial biofilm on the cannula and in the lumen of the catheter; this reduces risk of an infection [37].

Additional **antimicrobial and antifungal central venous injection catheter properties** presuppose reduction in the risk of infectious complications: the catheters are impregnated with heparin, chlorhexidine-silver complex, antibiotics (most often – rifampicin and minocycline), silver and 5-fluorouracil. Silicone catheters for long-term operations may contain a silver-impregnated subcutaneous cuff. The studies conducted mainly among adult patients show that

use of heparin-coated and antibiotic-impregnated central venous catheters results in considerable CRBSI reduction, though it affects catheter colonization to a lesser extent [16, 25]. The only study conducted among neonates involving silver-impregnated (AgION technology) umbilical catheters proved their advantage for reducing infectious complications (CRBSI – 2 against 22%;  $p=0.005$ ). Use of catheters did not reveal any specific side effects related to the toxic effect of silver [38]. Due to the lack of small catheters with antimicrobial impregnation for neonates under 3 kg of body weight, there have been no studies among neonates.

Strict **observation of aseptic and antiseptic** rules during injection and maintenance of central venous catheters in neonates, primarily, thorough performance of scrubbing by medical personnel is a foundation stone of prevention of all nosocomial infections (DA-HAI). Analysis of NRICU operation revealed that only 60.3% of medical personnel observe correct scrubbing procedures (95% CI – 55.5-64.9) [5, 39]. In their work, A. Maas et al. showed that compulsory use of sterile gowns and gloves, medical caps and masks during operation of central venous catheters according to the developed regulations at NRICU results in CRBSI reduction from 42 to 12% (RR – 0.27; 95% CI – 0.15-0.51;  $p<0.001$ ) [40]. Maintenance of central venous catheters ought to be performed in sterile environment, replacement of infusion systems – in conformity with the recommended intervals; it is also advisable to reduce disconnection rate of the catheter and the infusion system. It is important to regularly perform examination and evaluation of catheter condition and the area around it and timely change dressing. Data of multiple studies show that simple action may minimize risk of development of infectious complications. Clearly defined code of good practice for the medical personnel injecting and performing maintenance of the catheter must be strictly performed and controlled. Development of patient safety culture and guaranteed availability of the consumables required for maintaining strict aseptics in the process of catheter injection, dressing change and manipulations with catheter cannulas and results in observation of optimal practice by medical personnel and reduces risk of CRBSI 3 times [7, 16, 39, 41-43].

Introduction of **specifically trained crews for operation of central venous catheters** to the NRICU department structure reduced CRBSI rate by 65% (11.6 against 4.0 per 1,000 catheter-days;  $p<0.001$ ) [24, 44]. The study by T. Taylor et al. showed that risk reduction is especially significant in the neonates who had had a functioning central venous catheter for more than 30 days [45].

**Continuous training of medical personnel** using audiovisual techniques, performance analysis, data of the latest studies and control of knowledge and skills improves qualification of medical personnel and plays an important role in prevention of nosocomial infections [29, 42, 44].

Medical personnel's understanding that CRBSI is a preventable to a large extent complication related to developmental care is the first and the most important step in prevention of CRBSI at NRICU. Other important conditions of preventive measures are:

- professional training of medical personnel;
- hand hygiene;
- observation of sanitary standards of children placement (avoid overcrowding);
- fully staffed departments;
- use of breast milk for enteral feeding of neonates;
- common effort of child's parents and medical personnel in order to prevent an infection.

It is also advisable to perform microbiological monitoring and analysis of the infectious complications related to central venous catheters, which will help to reveal and dispose of shortcomings of medical personnel's performance and to improve preventive methods [42, 46].

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