REVIEW

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CURRENT ASPECTS IN THE DIAGNOSIS AND MANAGEMENT OF CATHETER-RELATED SEPSIS, OBSERVED IN PATIENTS UNDERGOING HEMODIALYSIS WITH A TUNNELED CATHETER

B. Borisov[1], D. Borisov[2]

[1]Department of Nephrology and Dialysis, Medical University – Pleven, Bulgaria
[2]Department of Vascular Surgery, Medical University – Sofia, Bulgaria

Abstract. *Tunnelled catheters have become established as a common vascular access in the last few decades. Besides the convenience associated with their use, we also reap the bitter fruits of their complications. Catheter-associated infections are part of daily life in dialysis units and we must know them well – early diagnosis, adequate behaviour and prevention. The aim of this short review is to highlight some modern aspects of diagnosis and treatment of catheter-associated infections, while also sharing our modest experience.*

Key words: *hemodialysis, tunneled catheter, catheter-related bloodstream infection, catheter-related sepsis, diagnosis and management*

Corresponding author: *Biser Borisov, MD, PhD, Department of Nephrology and Dialysis, Medical University – Pleven, George Kochev str. 8A, 5800, Pleven, Bulgaria; tel: +359 898313029; e-mail: biserugo@abv.bg*

https://orcid.org/0000-0002-6828-3890

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INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem affecting many people and engaging a huge financial resource [1]. Estimates show that by 2017, the number of people suffering from kidney disease exceeded 850 million people [2], and expectations are that by 2040, CKD "from the third fastest growing cause of death worldwide, will become the fifth most common cause of death" [3].

The life expectancy in patients treated with hemodialysis is severely reduced compared to the rest of the population. According to the United States Renal Data System, the life expectancy of men and women without dialysis from 40 years of age to age 45 is about 40 years longer, while for dialysis patients – life expectancy is reduced to no more than 10 years [4].

Almost 1/3 of hospitalizations of patients undergoing hemodialysis, are about vascular access problems. Central venous catheter (CVC) – related problems are usually the leading causes of hospitalizations [5]. According to data cited by H. Htay et al., usage of CVC is most often in countries with medium economic development, compared to countries with developed and those with a developing economy [6].

Epidemiological studies show the frequency of vascular access-related infections from 0.57/100 patient-months for Canada to 34.5/100 patient-months for Iran. These data show economic, ethnic, social, household and religious differences in these countries [3].

In the majority of articles comparing the complications of various vascular accesses for hemodialysis, insufficient critical commentary is offered related to the various difficulties in creating hemodialysis vascu-

lar access. The latter include the increasing number of patients with compromised venous vessels in the pre-dialysis period, the age and comorbidity structure of patients starting hemodialysis, and probably the consistently high share of late referral patients.

CATHETER-ASSOCIATED BLOODSTREAM INFECTION

Catheter-related bloodstream infection (CRBSI) can be defined as bacterial colonization of the blood with a primary source – a central venous catheter [7]. Its frequency is determined between 0.5 to 5.5 episodes per 1000 catheter-days (CD). The usage of the left jugular vein for catheters insertion and the diagnosis of diabetes mellitus were reported as independent risk factors for catheter infection. Substantially less infections have been established in ex-smokers, a finding that has no clear scientific explanation [9].

When the infection becomes clinically manifested, it is correct to call it catheter-related sepsis (CRS).

Etiological spectrum: CRBSIs are most commonly associated with gram-positive skin flora, especially staphylococci [10]. The most common groups of microorganisms causing CRBSI are coagulase-negative staphylococci (CoNS), Staphylococcus aureus, enteric gram-negative bacilli and fungi. Some of these agents have a particular affinity for the formation of a multilayered biofilm, which is perhaps 100 times larger than the microorganisms and is a frequent cause of therapeutic failures [11].

Bacterial biofilm formation was first described for Staphylococcus epidermidis in 1982 [12]. It is a microbial consortium, bound to a surface and embedded in an extracellular matrix. Microbial contamination and colonization on catheter surfaces can occur as early as the first 24 hours after its insertion. This process involves several specific steps: attachment of bacteria to the catheter surface and formation of bacterial aggregates; cellular signaling, known as quorum sensing, resulting in the production of exopolysaccharides. As a result of these three steps, the biofilm begins its maturation, acquiring a spongy shape. The last step is called “biofilm dispersion” - a process of dispersal, spreading of the biofilm to new surfaces, caused by the impact of unfavorable conditions such as meeting with antibiotics, antiseptics, etc. This process is well described by Janine Treter and Aleksandre Macedo [13].

Clinical manifestation. The diagnosis of CRS is often suspected clinically in a patient with an available CVC who has chills or fever, unexplained hypotension during or immediately after a dialysis session, and no evidence of other infectious foci [14]. Mild symptoms include malaise and nausea, while severe include: high fever with chills, hypotension, vomiting, and mental status changes, with a lack of problems of the catheter exit site and tunnel [15].

Catheter sepsis is actually quite different from infection, because it often involves multiple organ dysfunction due to a compromised patient’s immune response to a bacterial agent.

The incidence of catheter-associated sepsis in the UK is estimated to be around 123,000 cases with 37,000 deaths annually, according to data from 2017 [16].

In daily practice, it is noticeable that the severity of clinical manifestations is more pronounced in infections caused by gram-negative microorganisms than in those with a gram-positive causative agent. Although the organs damaged by Gram-positive sepsis are clinically indistinguishable from Gram-negative sepsis, there is increasing evidence that differences in host response exist. The initiating factor of gram-negative bacterial sepsis is endotoxin, while gram-positive bacterial sepsis relies on exotoxin production. Gram-negative sepsis also differs from Gram-positive in that the microorganisms often originate from intestinal or genitourinary sources rather than from skin, wounds, and catheter sites [17, 18].

In our opinion, any infectious symptomatology developing during the dialysis session should be suspected to be related to catheter sepsis, until proven otherwise, with all diagnostic and therapeutic measures resulting from this assumption.

CURRENT DIAGNOSTICS

Laboratory indicators

Procalcitonin (PCT). In today’s clinical practice, procalcitonin (PCT) has become a promising biomarker for the early diagnosis of systemic bacterial infections. It is a precursor of the hormone calcitonin, with 116-amino acid residues, on which Le Moullec et al. [19, 20] in 1984 paid attention for the first time. Almost 10 years later, M. Assicot et al. found a correlation between its serum levels and proven bacterial infections and sepsis [21]. Procalcitonin can also be synthesized in the liver, kidneys, pancreas, leukocytes, etc., but its levels usually increase mainly under the influence of proinflammatory cytokines, such as IL-6, tumor necrosis factor (TNF) -alpha, and viral infections reduce its production [22]. Besides its high specificity regarding the bacterial etiology of inflammation, procalcitonin is a very convenient indicator for monitoring the effect of antibiotic treatment [23].

C-reactive protein (CRP). CRP is an acute-phase protein synthesized in the liver in response to infection or inflammation and is often studied to monitor response to therapy in patients with acute and chronic inflammatory conditions. Because of its wide availability, good reproducibility, and low cost, serum CRP levels are a convenient marker for the diagnosis of sepsis. C-reactive protein was discovered by Tillett and Francis in 1930. The name CRP arose because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the "C"-carbohydrate antigen of the pneumococcal capsule. Its production is mainly induced by the action of IL-6 on the gene responsible for its transcription during the acute phase of an infectious process. There are many causes of elevated C-reactive protein. These include acute and chronic conditions, and may be infectious or non-infectious in etiology. However, markedly elevated CRP levels are most often associated with an infectious cause [19, 24].

J. Li et al. accept that simultaneous testing of CRP and procalcitonin has sufficient sensitivity and specificity in sepsis [25].

Interleukins (IL). Cytokines are chemokines produced by the host immune system in response to infection or injury that play a role in the complex pathophysiology of sepsis. Interleukin-6 (IL-6), IL-8, and IL-10 are the most widely studied cytokines for the diagnosis of sepsis, as well as for the assessment of the inflammatory response, and help determine patient prognosis. IL-6 is a proto-inflammatory cytokine, IL-8 is a major chemokine, and IL-10 is an important anti-inflammatory cytokine [19].

None of the cytokine markers has been shown to be more sensitive or specific than PCT or CRP [26].

Ryuzo Abe et al. (2010) found in their study that blood levels of CRP and IL-6 were significantly higher in cases of Gram-negative sepsis. They draw attention to the fact that despite the considerable amount of our knowledge, related to the immune response to bacterial invasion, the exact mechanisms, explaining the differences in the clinical course in different patients and agents, remain unclear [27].

In another study, it was found that serum levels of TNF-α, IL-8, IFN-γ were significantly increased in cases of gram-negative sepsis, compared to those with gram-positive causative agents. This increase correlates directly with the adverse outcome of the condition [28].

Other, less commonly used laboratory indicators are the serum lactate level [29], D-dimer and others [19]. Given the relationship of lactate mainly with hypoxia and hypoperfusion of the body, its examination has more of a prognostic value in relation to the outcome of severe multiple organ damage [30].

Microbiological studies. Taking a blood culture is the most important laboratory test to confirm blood infections, including sepsis, and to determine adequate antibiotic treatment [31]. According to the American Association for Microbiology, the proportion of contaminated samples is about 3%, but it varies widely, with up to 26% of contaminated samples reported in pediatric units. Blood collection from a peripheral vein is associated with the lowest risk of contamination, but it also impairs the assessment of potential catheter colonization [32].

The reference value for blood contamination level is < 3% as suggested by the Clinical Laboratory Standard Institute (CLSI) [33].

When taking blood from a peripheral vein, the following protocol must be followed: the personnel involved in the venipuncture wear sterile gloves and a mask, the venipuncture site is disinfected with a 70% ethanol solution - inside-out, then wait for about 30 sec until some of the alcohol evaporates. 5.0 ml of blood is taken, which is placed in a blood culture medium, the cap of which has also been previously cleaned with a 70% ethanol solution. The ratio of blood to nutrient medium, quantitatively, is 1:10. Culture bottles are incubated at 37°C for 24 hours and then inoculated onto blood agar and McConkey agar.

R Gunvanti et al. found in their study that the rate of contamination in adults correlated with male gender and advanced age [34].

In 2009, the Infectious Diseases Society of America (IDSA) published updated guidelines for the prevention and diagnosis of catheter-related bloodstream infections (CRBSI), and for the first time hemodialysis catheters were recognized as a separate entity [43]. In these guidelines, the basis for diagnosis is the obtaining of results from peripheral blood cultures that are compared with those obtained from: (1) the arterial or venous end of the catheter meeting quantitative criteria (three times the number of CFU per milliliter of the catheter end, compared to those from peripheral venous blood); (2) arterial or venous catheter hub, meeting criteria for different time to positivity of blood cultures (DTTP: catheter tip blood culture becomes positive at least 2 hours before peripheral blood culture), or (3) hemodialysis catheter tip developed the same microorganism as peripheral venous culture (requiring catheter removal for diagnosis) [35].

Conventional practice is to collect blood samples at or around the time of the rise in body temperature. This practice is based on the principle that the presence of microorganisms in the intravascular space leads

to the production of cytokines, which in turn leads to an increase in body temperature [36]. Patients on hemodialysis usually get a feeling of chills, most often after the second hour of the dialysis session, and only 1-1.5 hours later they get a raise in temperature. Blood sampling during chills is less likely to identify the causative agent than during fever [37, 38, 39].

These rules are reasonable and logical, as long as, of course, they do not apply to hemodialysis patients. In addition to the possibility of errors related to the time of transport and the labeling of the different blood samples, it is good to take into account that tunneled catheters are usually used to treat patients who lack accessible peripheral veins for the construction of an arterio-venous anastomosis. These are also outpatients who demonstrate clinical symptoms after completion of the dialysis session and are located outside of a healthcare facility. In these cases, our practice shows that a good alternative is to take blood for blood culture directly from the tunneled catheter before starting the next dialysis session. We draw blood before flushing the catheter, thereby aspirating the contents of the catheter lumen. In our opinion, this method sharply increases the probability of obtaining a positive blood culture - containing the cause of the septic condition and the preparation of an antibiogram.

Similar arguments are also discussed in the recently published good clinical practice guidelines from the Kidney Disease Outcomes Quality Initiative (KDOQI) [40].

F. Pelletier et al. found in their study that taking blood for blood culture from a peripheral vein did not improve either the sensitivity, or the specificity of the method in hemodialysis patients. According to them, taking blood for blood culture directly from the dialysis catheter or blood lines is sufficient for daily practice and has high specificity [35].

BEHAVIOR

Antibiotic treatment

In our opinion, antibiotic treatment should be started as soon as possible after diagnosis, without waiting for the results of blood cultures taken, especially in patients in severe general condition. We usually start treatment with an aminoglycoside antibiotic (gentamycin or amikacin) in patients with mild clinical manifestations or with the combination of vancomycin+ceftazidime – in severely ill patients who present with hemodynamic instability or cerebral manifestations [41, 42]. The doses for gentamycin that we use are: 0.8 mg/kg – after dialysis only but no more than 100 mg; vancomycin – 20-35 mg/kg – loading dose and then – 1.0 g after every second dialysis session; ceftazidime – 1.0 g/daily.

Treatment lasts a minimum of 2 to 4 weeks in the absence of metastatic foci. In case metastatic foci are present – treatment can last up to 8-12 weeks [43].

Management of the catheter

In the recent past, most clinical practice guidelines recommended strong consideration of immediate removal of the tunneled catheter [43, 44].

Nowadays, to soften the tone of this imperative rule, guidelines have changed even with regard to temporary hemodialysis catheters [40, 45].

Our behavior is guided by the general condition of the patient and our desire to save the catheter if possible. If the condition is serious, we remove the catheter under antibiotic protection, but it is not obligatory. If this one is the last chance for inserting a catheter and there is no local infection of the tunnel or the exit hole, we exchange the catheter over the guidewire.

Otherwise, we consider as ideal the option to remove the infected catheter, for the patient to continue their dialysis treatment with a temporary catheter until negative blood cultures and no clinical manifestations, then to insert a new tunneled catheter [46].

Prevention

With the presumption of an increasing frequency of patients with a single vascular access central venous catheter, we use antibiotic prophylaxis on all catheters where we expect a stay of more than 90 days. The use of different solutions mainly in high-risk patients (>3.5 episodes/1,000 days) and a history of previous infectious episodes is justified and should be considered in daily practice [40].

CONCLUSION

The increasing use of tunneled catheters for hemodialysis requires us to face the most common problems associated with this vascular access. We expect prevention, timely diagnosis and sufficient (such as drug selection and duration) antibiotic treatment to reduce the financial burden on the healthcare system, shortening patients' hospital stay and improving their quality of life.

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