European Review for Medical and Pharmacological Sciences 2015; 19: 2440-2445

Catheter-related bloodstream infections by opportunistic pathogens in immunocompromised hosts

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Abstract. **Catheter-related bloodstream infections (CRBI) represent a frequent complication of immune-compromised hosts with a high mortality rate. In this setting, opportunistic pathogens can create a biofilm on implanted devices, being the source of infection.**

We provide a mini-review of the literature, starting from the description of two cases of CRBI by opportunistic pathogens in poly-morbid patients, successfully treated by antibiotic lock-therapy.

Key Words:
Sepsi, Opportunistic pathogens, Central venous catheter, Biofilm.

Introduction

Catheter-related bloodstream infections (CRBI) represent a significant cause of morbidity and mortality in patients treated with long-term vascular access devices[1]. As well as other types of medical implants, venous devices are associated with the development of biofilm on the internal lumen[2]. Consequently, CRBI represent a typology of sepsis in which the vascular device acts as source and reservoir of infection[3].

As general rule, the treatment of bloodstream infections is based on the removal of the source of sepsis and on the administration of intravenous antibiotics[1,3]. When CRBI is diagnosed, the most effective therapeutic strategy is to remove the catheter, in order to remove the source of infection and to collect microbiological samples for culture[1]. On the other hand, for certain patients, catheter removal could represent a high-risk procedure since the lack of venous access and the potential for coagulation disorders[4]. Moreover, when clinical situation allows, the cost of a new procedure supports catheter salvage[1,4].

Antibiotic lock therapy (ALT) consists in the infusion of a concentrated antibiotic solution in a small volume, in order to completely fill the lumen of the catheter. The rationale of this technique is to expose the interior walls of the catheter to high antibiotic concentrations, in order to penetrate the biofilm, and to achieve bacterial eradication[5]. ALT at present represents an approved indication for coagulase-negative staphylococci and Gram-negative bacilli[6]. In case of Gram-positive bacteria vancomycin represents the antibiotic of choice, while, in case of Gram-negative bacilli, ciprofloxacin represents the most used treatment[7]. It has been demonstrated that the use of ALT in addition to intravenously administered antibiotics reduces the failure rate to cure the CRBI, although the optimal ALT regimens are still matter of research[8], in particular in the treatment of opportunistic-germ related infections.

Here we provide a mini-review of the literature, starting from the description of two cases of catheter-related bloodstream infections by opportunistic pathogens in immunocompromised hosts successfully treated by ALT in combination to systemic treatment.

Case One

A 47-year-old woman was admitted to our Internal Medicine inpatient Unit because of a 10-days fever (peak 38°C) resistant to ceftriaxone treatment. The patient was affected by Systemic Lupus Erythematous (SLE) with end-stage renal disease treated by hemodialysis via a silicone, double-lumen, tunneled, right subclavian central

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venous catheter (CVC) due to a previous thrombosis of the artero-venous fistula. At physical examination patient's clinical condition were discrete: blood pressure, pulse and respiratory rate and peripheral oxygen saturation were normal (Table I). A complete blood count showed mild thrombocytopenia without leukocytosis. Chest X-ray was normal. At the first febrile peak, peripheral and CVC blood cultures were collected and an empirical antibiotic treatment with meropenem was started. Procalcitonin (PCT) [Thermo Fischer Scientific (B-R-A-H-M-S PCT-Q)] levels were high, beta-D-glucane was negative (Table II). Trans-thoracic echocardiography (TTE) did not show signs of endocarditis. Blood cultures were positive for *Ralstonia pickettii* (*Burkholderia pickettii*) with a differential time to positivity of 12 h (6h from CVC vs. 18h from peripheral blood). *Ralstonia pickettii* is a non-fermenting gram-negative bacillus known to have a relatively low virulence and to be often associated with pseudobacteremia or asymptomatic colonization of patients[9]. However, it has been reported to create a biofilm on implanted devices[9]. Antibiotics' susceptibility is shown in Table I. Treatment with meropenem was continued for 10 days, until PCT normalization. Antibiotic lock therapy with ciprofloxacin was prescribed for 14 days. The patient showed a complete recovery. Blood cultures from CVC collected 15 days after ciprofloxacin discontinuation were negative.

Case Two

An 81-year-old man was admitted to our Internal Medicine inpatient Unit because of the rapid onset of fever, dyspnea and blood-traced cough after chemotherapy infusion. He had been treated with left hemicolectomy because of colon adenocarcinoma, and he was now on adjuvant chemotherapy because of lung and liver metastases. A few hours after the infusion of chemotherapy through the CVC (Port-a-Cath), the patient showed nausea, vomiting, chills, fever, dyspnea and blood-traced cough and came to the emergency department. Chest X-ray showed the presence of multiple bilateral pulmonary hypodiaphanias, associated to bilateral pleural effusion. Blood analysis showed elevated serum creatinine, anemia and neutrophilic

Table I. Clinical characteristics and blood tests of case 1.

VITAL PARAMETERS			
Blood pressure	130/70 mmHg	Normal	
Pulse rate	90 beats/min	Normal	
Respiratory rate	18 breaths/min	Normal	
Peripheral oxygen saturation	97% in 0.21 FiO_2	Normal	
LABORATORY TESTS			
Blood count:			
• HB 12.5 g/dl (n.v. 12.0; 16.0 g/dl)			
• WBC 4.05 x 10^9/l (n.v. 4.10; 9.80 x 10^9/l)			
• PLT 138,000/mm^3; (n.v. 140,000; 450,000/mm^3)			
OTHER EXAM			
Procalcitonin PTC	4.97 ng/ml	(n.v. 0.00; 0.05 ng/ml)	
B-D-glucane	negative		
Antibiotics' susceptibility	***Pseudomonas spp Ralstonia pickettii***		**MIC (mcg/ml)**
Piperacillin/tazobatam	Sensitivity		< =4
Ciprofloxacin	Sensitivity		< =0.2
Cefepime	Sensitivity		< =1
Meropenem	Sensitivity		1
Gentamicin	Resistance		> =16
Ceftazidime	Resistance		16
Amoxicillin/clavulanic acid	Resistance		16
Amikacin	Resistance		

Table II. Clinical characteristics and blood tests of case 2.

VITAL PARAMETERS			
Blood pressure	90/60 mmHg	Low	
Pulse rate	95 beats/min regular	High	
Respiratory rate	24 breaths/min	High	
Peripheral oxygen saturation	85% in 0.5 FiO_2	Low	
LABORATORY TESTS			
Blood gas:			
• pH 7.414, pO_2 85.9 mmHg (pO_2/FiO_2 170),			
• pCO_2 35.5 mmHg,			
• HCO_3- 22.0 mEq/l.			
Blood count:			
• HB 11.0 g/dl (n.v. 12.5;16 g/dl)			
• WBC 11.28 x 10^9/l (n.v. 4.10; 9.80 x 10^9/l)			
• NG 9.64 x 10^9/l (n.v. 1.90; 7.00 x 10^9/l)			
• PLT 142,000/mm^3; (n.v. 140,000; 450,000/mm^3)			
OTHER EXAM			
Serum creatinine	1.64 mg/dl	(n.v. 0.67; 1.17)	
Clcr Cockroft-Gault	39.00 mL/min		
NT-Pro BNP	9753 pg/ml	(n.v. 0; 450)	
Procalcitonin	2.55 ng/ml	(n.v. 0.00; 0.00)	
C-Reactive Protein	81.5 mg/mL	(n.v < 3)	
B-D-glucane	Negative		
Antibiotics' susceptibility	***Agrobacterium radiobacter Rhizobium radiobacter***		**MIC (mcg/ml)**
Imipenem	Sensitivity		< = 0.25
Ciprofloxacin	Sensitivity		< = 0.25
Meropenem	Sensitivity		< = 0.5
Gentamicin	Resistance		4

leukocytosis (Table II). Patient's clinical conditions at admission were poor: hypotension, tachycardia and tachypnea were present (Table II). Fluid therapy was started via CVC. After few minutes of infusion, the patient presented shaking chills. Therefore, peripheral and CVC blood cultures were collected and an empirical antibiotic treatment with piperacillin/tazobactam, teicoplanin and levofloxacin was started, together to fluid therapy via a peripheral venous access. PCT levels were high [Thermo Fischer Scientific (B-R-A-H-M-S PCT-Q)], beta-D-glucane was negative (Table II). Transthoracic echocardiography (TTE) did not show signs of endocarditis. Blood cultures were positive for *Rhizobium radiobacter* with a differential time to positivity of 20h (19h from CVC vs. 39h from peripheral blood). *Rhizobium radiobacter* is a Gram-negative bacillus infrequently recognized in clinical setting but emerging as an opportunistic human pathogen[10]. However, it has been reported to create a biofilm on implanted devices[11]. Antibiotics' susceptibility is shown in Table I. Treatment with piperacillin/tazobactam was continued for 10 days, until PCT normalization. Antibiotic lock therapy with ciprofloxacin was prescribed for 14 days. The patient showed a complete recovery. Blood cultures from CVC and collected 15 days after ciprofloxacin discontinuation were negative.

Discussion

Patients admitted to Internal Medicine Inpatient units are typically affected by multiple comorbidities, taking poly-pharmacotherapy and often needing chronic treatments. Both of the described patients were immune-compromised, the first one because of autoimmune disease, the second one because of chemotherapy. Both were needing a long-term CVC, one because of haemodialysis, the other because of chemotherapy.

Ralstonia pickettii, generally considered of minor clinical significance, has been frequently found in dialysis water treatment systems and has been shown to be associated to CRBI[12,13]. *Rhizobium radiobacter*, also called *agrobacterium radiobacter*, represents a phytopathogenic organism widely distributed in soil, being recognized as rare human pathogen affecting mostly immune-compromised hosts[14], in particular oncologic patients[15]. Not much is known about the antibiotic resistance of these bacteria and about the optimal treatment strategy. The majority of *Ralstonia pickettii* isolates showed susceptibility to most of tested antibiotics. However, the most effective were found to be the quinolones and sulfamethoxazole-trimethoprim[12].

Catheter-related bloodstream infections represent a significant cause of morbidity and mortality[16], being also a major cause of premature catheter removal and increased treatment costs[3]. As well as other infections related to almost every temporary or permanent medical implant, such as orthopedic prosthesis and cardiac and neurological devices, venous device infections are associated with biofilm development on the surface of the foreign body[17]. Most of the infections originate from the skin microbiota surrounding the insertion site of the catheter. Micro-organisms reach the subcutaneous catheter tract at the moment of venous catheter implantation. This event is often related to external colonization of short-term catheters[1,18], while catheter manipulation is implicated with intraluminal colonization of long-term catheters[18,19]. Repeated access to ports often leads to formation of intraluminal biofilm[20]. The first step in biofilm development is the attachment of bacterial cells to an artificial or native surface. Micro-organisms will form a community that will encase itself in a self-produced polymeric matrix[21,22]. This matrix is a hydrated polyanionic complex of exopolysaccharides of bacterial origin, but can also be formed by proteins and DNA. As the polymeric matrix grows and matures, it builds a sophisticated system of water channels resembling a circulatory system for biofilm support[17,21]. It has been estimated that biofilms are associated with more than 70% of nosocomial infections, and that the treatment of these biofilm-related infections costs more than a billion dollars annually[1,16].

Antibiotic treatment represents the traditional approach to eradicate biofilm-producing bacteria. However, since the deepest layers of biofilm are inaccessible to most of antibiotics, N-acetilcysteine and acetylsalylic acid have been proposed as an alternative pharmacological approach to control bacterial biofilm growth in human diseases[23,24].

Gram-positive bacteria are most frequently responsible for CVC infections. However, other pathogens, such as Gram-negative bacilli, fungi and *corynebacteria* can be found, particularly in neutropenic patients[18].

Risk factors for catheter-related infection are associated with the time of catheterization and handling of the venous catheter[1,18], the variables related to the type of tunneled catheter[25], catheter insertion technique[26], hematological malignancies[25], patient age[27], parenteral nutrition administration[22,25], immunosuppression[28], and prolonged neutropenia[29,30].

There are two methods for *in situ* diagnosis of CRB: quantitative culture of paired blood samples, and differential time to positivity of catheter blood sample compared to peripheral vein blood culture. Quantitative culture of paired blood samples looks for the correlation between a positive differential quantitative blood culture threefold greater than identical bacterial colony count in peripheral vein blood specimen. In differential time to positivity of catheter blood sample compared to peripheral vein blood culture, a cut-off differential time to positivity value of 120 minutes has 91% specificity and 94% sensitivity for the diagnosis of CRB[16,18].

When CRBI is diagnosed, the most effective therapeutic strategy is to remove the device, since catheter retention is associated with a high risk of bacteremia recurrence. Withdrawing the catheter removes the source of infection and enables microbiological analysis of the catheter, but the decision to remove a catheter should take into consideration at least three factors: the type of the catheter; the micro-organism involved in the infection; and clinical status of the patient. Usually adopted criteria for CVC removal are signs of subcutaneous tunnel infection, suppurative phlebitis, pulmonary embolization, clinical suggestion of infective endocarditis, persistent bacteremia, recurrent infection despite medical treatment, or infection sustained by *Staphylococcus (S.) aureus*, *Candida* spp., or *Mycobacterium spp*[3,18]. When patient's hemodynamic is stable, CVC was surgically implanted and may not be easily replaced, catheter removal as first step of treatment should be avoided[4,18]. In these cases, CVC should not be used for infusion and ALT can be started in adjunction to systemic treatment for a duration of 10 to 14 days[4,5,18]. ALT consists of the infusion of a

concentrated antibiotic solution in a small volume to fill the lumen catheter. The rationality of this technique is to expose the interior walls of the catheter to high concentrations of an antibiotic that may penetrate the biofilm, and therefore to achieve bacterial eradication[31,32] . The antimicrobial lock has also been studied as a prophylactic measure to prevent catheter-related bacteremia[33]. According to the Infectious Diseases Society of America (IDSA) guidelines, when the involved micro-organism is a coagulase negative Staphylococcus or a Gram-negative bacillus, with positive catheter-blood cultures but negative from peripheral vein, ALT has to be considered from 10 to 14 days, without systemic antibiotic treatment[34,35]. Systemic treatment has to be administered in case of criteria of sepsis[34].

As discussed, the decision to remove a catheter should consider at least three factors: the type of CVC, the micro-organism involved in the infection and clinical status of the patient[18,34]. Both of the described patients were affected by CRBI of a long-term implanted CVC, both showed a Gram-negative opportunistic pathogen, and both were immune-compromised. Considered the lack of a standardized treatment for both pathogens, CVC-removal had been hypothesized in both cases. However, ALT seemed to be the most safe decision. Since the presence of clinical and laboratory signs of sepsis, empiric systemic antibiotic treatment was started after collecting blood cultures. In both cases, the differential time to positivity was > 120 min, allowing us to diagnose CRBI[34,36,37]. On this connection, antibiotic lock-therapy was started with the resolution of catheter infection, as documented by the negativity of the cultures after ALT discontinuation. The use of ALT strategy led us to save the CVC, avoiding surgical procedures (CVC removal and implant of a new CVC) with the relative infective risks and costs.

Conclusions

This report highlights on a common situation in clinical practice: the need to use the best treatment strategy with the safest solution and the less resource-expending choice. Antibiotic lock-therapy seems to be effective in the treatment of CRBI and should be considered in the therapeutic workup of Internal Medicine patients affected by CRBI since it has lowers costs compared to CVC-removal and re-implantation.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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