Microorganisms isolated from patients on hemodialysis by central venous catheter and related clinical evolution

Microrganismos isolados de pacientes em hemodiálise por cateter venoso central e evolução clínica relacionada

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Abstract

Objective: To identify the microorganisms isolated on the pericatheter skin, catheter tip and blood stream of patients on hemodialysis by central venous catheter, to verify the profile of sensitivity of these microorganisms to antimicrobials and to assess the clinical evolution and mortality related to these microorganisms.

Methods: A cross sectional study. The strains were isolated from the patients on hemodialysis by central venous catheter that, in a previous study, presented pericatheter skin, catheter tip and blood stream infection and were analyzed for microbiological profile and lethality related.

Results: 128 microorganisms were isolated in the bloodstream in the 94 patients studied. There were 35 cases of septicemia and 27 of endocarditis. The mortality in cases of endocarditis due to methicillin-resistant *Staphylococcus aureus* was 100%.

Conclusion: Infection in the bloodstream and endocarditis caused by methicillin-resistant *Staphylococcus aureus* was predictive of mortality and lethality.

Resumo

Objetivo: Identificar os microrganismos isolados da pele pericateter, ponta do cateter e corrente sanguínea de pacientes em hemodiálise por cateter venoso central, verificar o perfil de sensibilidade destes microrganismos aos antimicrobianos e avaliar a evolução clínica e a mortalidade relacionada a estes microrganismos.

Métodos: Estudo transversal. As cepas isoladas de pacientes em hemodiálise por cateter venoso central que em estudo prévio apresentaram infecção na pele pericateter, ponta do cateter e corrente sanguínea foram analisadas quanto ao perfil microbiológico e letalidade relacionada.

Resultados: Foram isolados 128 microrganismos em corrente sanguínea nos 94 pacientes estudados. Ocorreram 35 casos de septicemia e 27 de endocardite. A letalidade nos casos de endocardite por *Staphylococcus aureus* resistente à meticilina foi 100%.

Conclusão: Infecção em corrente sanguínea e endocardite por *Staphylococcus aureus* resistente à meticilina são preditivas de alta mortalidade e letalidade.

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Introduction

Infection is a frequent cause of rehospitalization and the second leading cause of death in chronic renal patients on hemodialysis. The central venous catheter is largely responsible in the majority of cases.[1] Studies have focused primarily on the patient's skin around the insertion site, followed by the the colonization of the catheter insertion site, colonization of the catheter by hematogenous dissemination from elsewhere and/or contamination of the infusion liquid. In addition, dialysis patients are known to suffer from weakened defense mechanisms, attributed in large proportions to the elevated comorbidity of diabetes *mellitus* and malignancies, as well as malnutrition particularly associated with uremia and hemodialysis treatment.[2]

Among the microorganisms, bacteria contribute to approximately 95% of infections, with a considerable percentage of bacterial isolates resistant to antimicrobials. Antimicrobial resistance is a global and growing concern. The transfer of resistant microorganisms among patients, possibly, occurs via the hands and/or the respiratory tract of the health professionals, which can be contaminated at the time of contact with the patient and surfaces.[3]

From the epidemiological point of view, the Gram-positive cocci have emerged as key players, especially *Staphylococcus aureus*, coagulase-negative staphylococci and enterococci.[3,4,5] Although coagulase-negative staphylococci are frequently isolated in blood cultures, they are clinically significant in less than 15.0% of cases. By being part of the skin microbia and submitting a relatively low virulence, they are usually considered contaminants of blood cultures. Although the bacteremia by Gram-negative rods have become less frequent, the associated mortality is higher when compared to Gram-positive cocci.[4]

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased dramatically, becoming responsible for more than half of staphylococcal infections in various healthcare services worldwide. According to the Centers for Disease Control and Prevention, it is estimated that approximately 25-30% of the population is a carrier of the bacteria.[6]

At the end of 1986, in Europe, and 1988, in the United States, clinically significant resistance to vancomycin was identified among the enterococci. At this time, infections caused by *coagulase*-negative *Staphylococcus* with reduced susceptibility to vancomycin have also been described.[7]

The emergence of resistance among the *S. aureus* to the glycopeptides became a constant concern among researchers. The transfer of the vanA gene of the enterococci for *S. aureus* at the experimental level suggested the potential of staphylococci to acquire these genes in vivo, producing clinical resistance.[7] Data from the Canadian Nosocomial Infection Surveillance Program showed that for every thousand hospitalizations in 2007, there were 8.62 new patients infected by MRSA and 1.32 new patients with *S. aureus* resistant to vancomycin per 1000 admissions.[8]

As a function of high morbidity and mortality related to the infectious complications in hemodialysis patients, we were motivated to conduct this study, which had as its objectives: to identify the primary microorganisms isolated on the pericatheter skin, at the tip of the catheter, and in the bloodstream of patients undergoing hemodialysis treatment by central venous catheter; to trace the profile of sensitivity of these microorganisms to antimicrobials; and, to assess the clinical evolution and case fatality related to these microorganisms in these patients.

Methods

This was a cross-sectional study conducted in the University Hospital of the Federal University of São Paulo, in the southeastern region of Brazil, in the period of January to April of 2013.

Records from 156 patient charts in hemodialysis who used central venous catheters as the access route were studied, document analysis was made of the isolated microorganisms, of the variables related to the length of time for catheter permanence, and infectious complications of 94 patients who developed infections in the bloodstream, the pericatheter skin or catheter tip. The catheter removal

occurred in the following situations: malfunctioning of the catheter, presence of local erythema and/or purulent secretion or bacteremia without other identifiable source of infection as recommended by *National Kidney Foundation Kidney Disease Outcomes Quality Initiative (*NKF KDOQI*)*.[9]

The pericatheter skin samples were obtained using a swab - pre-moistened cotton swab - in a solution of calcium alginate (Diagnostic Cefar-Farmaco, São Paulo, Brazil), and were transported to the microbiology laboratory, where they were immediately rolled onto plates containing tryptic soy agar with 5% sheep's blood and agar of mannitol-salt (Difco Laboratories, Detroit, MI). All cultures were incubated at a temperature of 35° C for 48 hours, and examined daily to search for evidence of growth.

The blood samples (20 ml) of the patients were collected in Batec vials and the cultures were processed by means of an automated method for isolating microorganisms (Bactec 9240, Becton Dickinson).

After removing the catheter, approximately 50 mm from its tip was rolled across the plates of Rodac that contained tryptic soy agar with 5% sheep's blood (COMO, Oxoid, Basingstoke Hampshire, United Kingdom), and mannitol salt agar (ASM, Oxoid), which were previously prepared in the laboratory according to the semi-quantitative method. Catheters that presented more than 15 colony forming units were considered significantly colonized.

The disk diffusion method was employed to determine the susceptibility profile, where the culture plates of blood agar were selected for three to five isolated and pure colonies, and further, transferred to a tube containing 5 ml of saline solution. The bacterial suspension had a measured turbidity in the digital turbidimeter (Baxter, Sacramento, USA) and the scale used was a that of 0.5 McFarland, which corresponds to a bacterial concentration of about 1 to 2 x 108 CFU/ml. The sowing was carried out on a Müller-Hinton agar board, as recommended by CLSI M100-S20.[10]

The plates containing the discs impregnated with the clavulanic acid, and antibiotics (amikacin, cefepime, cefoxitin, ceftazidime, ciprofloxacin, clindamycin, erythromycin, gentamicin, imipenem, meropenen, netilmicin, nitrofurantoin, norfloxacin, oxycillin, teicoplanin, tobramycin, and vancomycin) were placed in an oven at ± 35 º C for 24 hours for further reading of the halos. The interpretation of the results was performed according to the criteria established by the CLSI M100-S20. *Staphylococcus aureus* ATCC 25923 *E. faecalis* ATCC 29212, and *Klebsiella pneumoniae* carbapenemase-producing ATCC BAA-1705 strains were used as controls.[10]

A descriptive analysis was performed, and presented in absolute numbers and percentages. We calculated the odds ratios and confidence intervals (95% CIs). The statistical program used was the Statistical Package for the Social Sciences (SPSS), version 14.0.

The study followed the development of national and international standards of ethics in research involving human beings.

Results

In table 1, the 240 microorganisms are presented that were isolated in the cultures of 94 patients in hemodialysis through the central venous catheter that presented blood stream infection.

The gram-positive microorganisms were predominant and among these the *S. aureus* (76%) were

Table 1. Isolated microorganisms

Microorganisms	Skin n(%)	Tip n(%)	Blood n(%)
Gram – positive cocci (119)	522(41)	35(60)	62(49)
Shaphylococcus aureus (91)	311(51)	27(77)	53(85)
Shaplylococcus coagulase – negativo (18)	8(31)	5(14)	5(7)
Enterococcus (10)	2(18)	3(8)	5(8)
Gram – negative cocci (91)	115(28)	18(32)	58(45)
Pseudomonas aeruginosa (38)	106(40)	7(39)	25(43)
Acinetobacter baumanii (32)	4(27)	7(39)	21(35)
Enterobacter (12)	2(13)	2(11)	8(14)
Klebsiella pneumoniae (07)	3(20)	2(11)	4(8)
Fungus (30)	117(31)	5(8)	8(6)
Cândida spp (22)	13(76)	4(80)	5(62)
Others (08)	4(24)	1(20)	3(38)

Legend: Skin – n=54; Tip – n=58; Blood – n=128

isolated more frequently in the three sampling sites, with 51% of the isolates in the skin at the catheter insertion site, 77% of the isolates at the catheter tips, and 85% of isolates in the blood. Among the Gram-negative microorganisms, *Pseudomonas aeruginosa* (40%), and *Acinetobacter baumannii* (34%) were prevalent, being the most frequently isolated in the blood (43% -34%) in the catheter tip (39% -39%) and in the skin at the catheter insertion site (40% -27%), respectively.

The fungi were less prevalent (13%), and Candida spp appeared in 73% of these. Unlike the gram-positive and gram-negative bacteria, fungi were isolated more frequently in the skin at the catheter insertion site (31%), followed by the catheter tip (8%) and less frequently in the blood (6%).

Table 2 shows the analysis of the profile of sensibility of the isolated microorganisms with higher frequency in the blood cultures and the permanence of the central venous catheter.

Table 2. Profile of the sensiblity of the microorganisms and permanence of the central venous catheter

Microorganisms	TC>21days* n(%)	TC=<21days** n(%)	Odds Ratio (IC 95%)
Gram-positive			
S.aureus	40(52)	13(59)	
MRSA	19(48)	4(31)	2.04
MSSA	21(52)	9(69)	(0.54-7.70)
Gram – negative			
Pseudomonas aeruginosa	20(26)	5(23)	
Resistant	10(50)	1(20)	4.00
Sensitive	10(50)	4(80)	(0.37-42.37)
Acinetobacter baumanii	17(22)	4(18)	
			2.75
Resistant	11(47)	2(33)	(0.28-26.60)
Sensitive	6(53)	2(67)	

Legend: TC – Time of catheter; *TC>21days – n=77; ** TC=<21days – n=22

We observed an elevated resistance higher than 70%, of the micro-organisms to the 11 antibiotics tested, and the *S. aureus* was only 100% sensitive to teicoplanin and vancomycin. Among the non-fermenting gram-negative bacilli, *P. aeruginosa* was 100% sensitive only to clavulanic acid and tazobactam, and the *A. Baumanii* presented a highly resistant profile, 80% sensitive only to imipenem.

We found that in the catheters implanted and maintained for a period exceeding 21 days, there were significant increases in the number of microorganisms, and also an increase of resistant strains of virtually all organisms, and that the resistant strains were 80% more isolated with the increased central venous catheter permanence.

After 21 days of implantation of central venous catheter, the risk of isolating strains of *S. aureus* was 50% higher compared to other microorganisms, with strains of *Staphylococcus aureus* resistant to methicillin being two times more isolated than MSSA strains (Odds: 2.04, CI: 0.54 to 7.70). Resistant strains of *Pseudomonas aeruginosa* were isolated four times more (odds: 4.00, CI: 0.37 to 42.3) than the sensitive strains, and resistant strains of *Acinetobacter baumannii* were three times more isolated than the susceptible strains (odds: 2.75, CI: 0.28 to 26.60).

In table 3 we present the clinical evolution of patients and the related lethality to the profile of the microorganisms isolated in the blood stream.

Of the 94 patients previously studied, 62 (66%) developed severe infectious complications, 35 (56%) sepsis, and 27 (44%) endocarditis. Of the patients with endocarditis, 15 (56%) died.

Seventeen strains were isolated from blood cultures of the 12 patients who developed septicemia and died. It was found that strains of *Staphylococcus aureus* were the most prevalent, among which 36.5% were due to strains with 70% resistance to five or more of the 11 antibiotics tested. The risk of death was 50% higher in patients with resistant strains, four times greater (odds: 4.3, CI: 0.80 to 22.90) in patients with septicemia who presented strains of *Staphylococcus aureus* resistant to methicillin, compared to other microorganisms.

Sixteen strains were isolated from the blood cultures of the 15 patients who developed endocarditis and died. The *Staphylococcus aureus* were the most prevalent, among which 60% were of strains with 70% of resistance to five or more antibiotics of the 11 tested. The lethality observed the group of patients with endocarditis due to MRSA was 100% (odds: 11.0; IC :1,16-103, 94). We emphasize that 52% of the patients with a confirmed diagnosis of

Table 3. Clinical evolution and lethality related to the profile of microorganisms isloated in the blood stream

Microrganisms	Septicemia n(%)	Death* n(%)	Odds (IC 95%	Endocarditis n(%)	Death** n(%)	Odds (IC 95%)
MRSA	7(13)	5(28)	4.3 (0.80-22.90)	9(27)	9(45)	11.0 (1.16-103.94)
MSSA	18(33)	3(17)		11(33)	1(5)	
P. aeruginosa MR	8(18)	3(17)	2.3 (0.18-27.37)	3(15)	2(15%)	1.3 (0.06-26.61)
P. aeruginosa S/I	6(11)	1(6)		2(3)	1(5)	
A. baumanii MR	6(13)	4(28)	2.0 (0.14-26.73)	2(12)	2(15%)	2.0 (0.10-44.35)
A. baumanii S/I	3(6)	1(6)		2(3)	1(5)	

Legend: Septicemia – n=35; *Death – n=12; Endocarditis – n=27; **Death – n=15

endocarditis presented concomitantly the same microorganism isolated from the blood and the catheter tip.

Discussion

The occurrence of infections caused by resistent microorganisms constitutes a worldwide public health problem. Resistent bacterias, such as *Acinetobacter baumannii*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Enterococcus* spp, have become increasingly common in health care institutions.[4]

The infections caused by gram-positive pathogens are still shown to be predominant, characterized by a reduced sensitivity profile to different antimicrobials, which contributes to reducing the therapeutic options and the high rates of mortality.[11]

The high rates of catheter-related blood stream infection (CRBSI) associated with the increased growth in the rates of resistence have made these infections particularly worrisome. Various conditions have been identified as risk factors for the development of CRBSI, such as the duration of catheter placement, skin colonization at the catheter insertion site, and the frequent manipulation of the venous line.[1]

The skin is the principal source for colonization and infection of the short-dwelling catheter. The bacteria that are in the skin of the patient migrate along the surface, colonizing the distal end, resulting in infection. However, these micro-organisms can also colonize the inner surface of the catheter, where they adhere and can become incorporated into a biofilm which enables the sustenance of the local infection and hematogenous dissemination. When catheters are used for long periods, intraluminal colonization is greater than extraluminal.[2]

The contamination of the connection was the possible origin of colonization in long-term indwelling catheters (greater than 30 days), responsible for infection related to the central venous catheter, while pericatheter skin contamination determined the beginning of colonization of the short-term catheter (less than 10 days).[12] Given these results, researchers concluded that the permanence of the central venous catheter is considered a major cause of infection.[1,2,12] In the USA about five million central venous catheters are introduced annually. In this context, data from the CDC indicate bloodstream infection rates related to the catheters of 5.3 per 1000 catheter-days, with a rate of colonization in 50% of cases.[13]

In the present study we found that in the catheters implanted and maintained for a period exceeding 21 days, there were significant increases in the number of microorganisms isolated, with an increase in resistant strains of virtually all microorganisms. After 21 days of implantation of the central venous catheter, the risk of isolating strains of *S. aureus* increased by two times, methicillin resistant *Staphylococcus aureus* was isolated five times more in catheters with a permanence time greater than 21 days. The risk of isolating strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* after 21

days of implantation of the central venous catheter doubled, and the multiresistant strains were 90% more isolated with increasing permanence of central venous catheters.

The discovery of the antimicrobials revolutionized the treatment of infections, but their indiscriminate use has led to the rapid emergence of bacterial resistance, which shows increasing prevalence in healthcare facilities.[3] Currently, in the USA, 55% of infections caused by *Staphylococcus aureus* are related to MRSA. In France, isolation of resistant bacteria ranges from 30% to 40%, reaching a percentage of up to 78% of the units.[14]

According to SENTRY (the Program of Antimicrobial Surveillance) results from Latin America and Brazil, the non-fermenting Gram negative rods (*Acinetobacter* spp. and *Pseudomonas aeruginosa*) multidrug-resistance, and the *Enterobacteriaceae* (*Escherichia coli*, *Salmonella* spp, *Shigella* spp and *Proteus mirabilis*), producers of the extended spectrum beta-lactamase (ESBL) constitute the main problem in pharmaceutical resistence in these countries. We observed high rates of resistant isolates, except the polymyxins, since the program's inception, in 1997.[14] Of the Gram-positive cocci, oxycillin resistance among staphylococci represents an important problem in Latin America and the United States. However, rates vary significantly between hospitals and countries, although the percentage of isolates of *Staphylococcus aureus* sensitive to oxacillin originatimg from cases of bacteremia in Brazil, in comparison to Latin America, has been approached: 68.2% and 68.5%, respectively.[14]

The prevalence of MRSA increased dramatically, becoming responsible for more than half of the staphylococcal infections in various healthcare services worldwide. At the end of the 1980s, clinically significant resistance to vancomycin became identified among enterococci (VRE). At this time, infections caused by coagulase-negative staphylococci (CNS), with reduced susceptibility to vancomycin have also been described. The emergence of resistance among *S. aureus* to glycopeptides has become a constant concern among researchers. The transfer of the vanA enterococci gene for *S. aureus* at the experimental level suggested the potential of staphylococci to acquire these genes in vivo, producing clinical resistance. In addition, laboratory studies with coagulase-negative *Staphylococcus* and *S. aureus* exposed to progressively higher levels of glycopeptides demonstrated the ability of these agents to select resistant subpopulations.[8]

In our study we observed an elevated resistance, greater than 70%, of the microorganisms to the antimicrobials tested, and *S. aureus* was only 100% sensitive to teicoplanin and vancomycin. Among the non-fermenting gram-negative bacilli, *P. aeruginosa* was 100% sensitive only to the clavulanic acid and tazobactam and the *A. Baumanii* presented a highly resistant profile, 80% sensitive only to the Imipenem.

Patients hospitalized with infecction by *S. aureus* have a five times higher risk of mortality.[13] Mortality associated with bacteremia, caused by *S. aureus*, varies from 11.9 to 46.5% per year.[15]

Although the protocols recommended by the Centers for Disease Control and Prevention (CDC) are adopted in our service, the blood stream infection (BSI) mortality and the lethality related to the use of central venous catheters for dialysis is elevated, as well as the prevalence of the resistant microorganisms. In this study, 62 patients developed severe infectious complications, 37% with septicemia, 29% with endocarditis - 56% of these resulted in death. The risk of death was higher than 50% in patients with resistant strains, four times higher in patients with septicemia who presented strains of MRSA, compared to other microorganisms. The lethality rate was 100% in the group of patients with endocarditis due to MRSA.

This study is in line with the current literature, complementing the results of the previously published studies in this journal, reinforcing that *S. aureus* are responsible for most infections and that their control proposes a challenge. Since the possibility of the emergence of bacteria resistant to all available antimicrobials in clinical practice is a current reality, health professionals should be aware of precautions, including staff education on proper techniques for insertion and maintenance of the

central venous catheter and instituting more effective and efficient quality control measures, aimed at reducing horizontal transmission of these pathogens in hospital environments.

Further studies are suggested that correlate cross-infection to be harnessed to analyze the colonization of patients with chronic renal failure before starting dialysis therapy, thereby enabling the evaluation of the issues involved in cross-transmission of microorganisms and the development of ICS, preventing the emergence of these pathogens, thus reducing the high lethality observed in these patients.

Conclusion

Among the main microorganisms isolated in cultures of hemodialysis patients by central venous catheter, the *S. aureus* were predominant in the three collection locations. We found that in the catheters implanted and maintained for a period exceeding 21 days, there were significant increases in the number of microorganisms isolated, with an increase of resistant strains of virtually all microorganisms. We observed an elevated resistance exceeding 70%, of the microorganisms to the antibiotics tested. Patients who presented resistant strains had a 50% increased risk of death compared to the other microorganisms. The observed mortality was 100% in the group of patients with endocarditis due to methicillin-resistant *Staphylococcus aureus* (MRSA).

Collaborations

Esmanhoto CG participated in the project design, planning, interpretation of data, drafting of the article and critical revision of the content. Taminato M and Fram DS contributed in the design and planning steps the project. Belasco AGS contributed in data interpretation and critical review of the content. Barbosa DA collaborated with the project design, planning, interpretation of data, drafting the article, critical revision of the content and final approval of the version to be published.

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