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Catheter related blood stream infections in critically ill patients with continuous haemo(dia)filtration and temporary non-tunnelled vascular access

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Summary

This prospective, single centre, observational study analysed the rate of catheter related blood stream infections in critically ill patients in intensive care units treated with haemo(dia)filtration. The infection rate was 3.8 per 1000 patient days. All infections were caused by coagulase negative staphylococci.

BACKGROUND: Temporary central venous catheters in patients undergoing continuous veno-venous haemo(dia)filtration contribute to serious infectious complications. The goal of this study was to assess the incidence of catheter related blood stream infections in critically ill patients treated with continuous veno-venous haemo(dia)filtration.

METHODS: Prospective observational study of all intensive care unit patients treated with continuous veno-venous haemo(dia)filtration by a central venous catheter at the University Hospital Basel. All patients underwent a standardised anti-infective protocol including screening for nasal colonisation with *S. aureus* on the day of catheter insertion, antiseptic catheter placement technique and daily disinfection of the insertion site followed by local mupirocin application. Catheter related blood stream infection was diagnosed according to standard guidelines of the Center of Disease Control and Prevention. Primary end point was the incidence of catheter related blood stream infection in all intensive care unit patients treated with continuous veno-venous haemo(dia)filtration.

RESULTS: From 2003 to 2007 a total of 194 consecutive critically ill patients treated with continuous veno-venous haemo(dia)filtration were investigated. 173 patients (63% men) were suitable for final analysis. Median age was 68.6 years (18.9–87.8). Eight patients (4.6%) had positive blood cultures, six of them had a catheter related blood stream infection (incidence 3.8/1000 catheter days). All infections were caused by coagulase negative staphylococci. The duration of catheter use ($p = 0.02$) and pre-existing chronic skin disease ($p = 0.042$) were identified as potential risk factors for catheter related blood stream infection.

CONCLUSIONS: The incidence of catheter related blood stream infection in critically ill patients on intensive care units treated with continuous veno-venous haemo(dia)filtration was 3.8 per 1000 catheter days. All catheter related blood stream infections were caused by coagulase negative staphylococci.

Key words: *blood stream infection; catheter related infection; haemodiafiltration; intensive care medicine; acute renal failure*

Introduction

Continuous veno-venous haemo(dia)filtration is the modality of choice for patients in intensive care units suffering from acute renal failure. For this procedure, short term central venous catheters are required to access the bloodstream. Central venous catheters set the patient at risk for serious complications such as catheter malfunction, thrombosis and infections. A prospective analysis of health care associated bloodstream infections showed that a temporary vascular access is the most important predisposing factor [1]. In this study 72% of the patients with positive blood cultures had a central venous catheter. Risk factors associated with catheter related bloodstream infections are age, malnutrition, hospitalisation or recent operation, iron substitution and skin or nasal colonisation with *Staphylococcus aureus* [2, 3]. Catheter related bloodstream infections cause substantial mortality and excess cost [4]. Therefore the Center of Disease Control and Prevention established guidelines to prevent catheter related blood stream infection [5]. These guidelines include training of health care providers, maximal barrier precautions at insertion, and use of chlorhexidine for care of the insertion site.

At present no data exist on the incidence and prevention of catheter related blood stream infection in intensive care

unit patients undergoing continuous veno-venous haemo(dia)filtration with a temporary non-tunnelled central venous catheter. Only few data on catheter related blood stream infection in dialysis patients are available [6]. A meta-analysis of dialysis patients with temporary, tunnelled and non-tunnelled catheters (16 studies, 51840 catheter days) revealed a rate of 4.8 catheter related blood stream infections per 1000 catheter days [7]. There is also evidence that local antibiotic ointment can reduce catheter related blood stream infection [8, 9]. However none of these results can be extrapolated to the specific population of severely ill patients in intensive care units.

Therefore, the goal of our study was to assess the incidence of catheter related blood stream infection in the specific population of intensive care unit patients undergoing continuous veno-venous haemo(dia)filtration and treated with a standardised anti-infective prophylactic regimen.

Methods

All patients treated with continuous veno-venous haemo(dia)filtration in the medical and surgical intensive care units at the University Hospital Basel from March 1st 2003 to May 1st 2007 were included in this prospective observational study. Ethical approval for data analysis was given by the local ethics committee.

Data on patients, catheter site and duration, and potential risk factors for the development of a catheter related bloodstream infection were prospectively collected in a case report form. Central venous catheters were placed using the Seldinger technique according to a written standard operating procedure by an intensive care staff physician. Maximal sterile-barrier precautions, including large sterile drape, sterile gown, mask, gloves and cap to reduce infectious complications were used. Ultrasound guided insertion was needed only in case of difficult placement. Uncoated, 3-lumen dialysis catheters (Arrow-Howes®, Arrow Int. Inc., Reading PA, USA) were used for all patients. The two 16 gauge catheter lumens were used for continuous veno-venous haemo(dia)filtration only and not accessed for other purposes.

From March 1st 2003 to September 30th 2006 all patients were treated by continuous veno-venous haemo(dia)filtration at a standard ultrafiltration rate of 2000ml per hour and blood flow of 150 ml per minute using a Prisma haemofilter device (Gambro, Stockholm, Sweden). Anticoagulation was performed with unfractionated heparin, using a bolus injection of 2500 units, followed by 500 to 1000 units of heparin per hour. From October 1st till the end of the study treatment was switched to a Prismaflex haemodiafiltration device (Gambro, Stockholm, Sweden). Continuous veno-venous haemo(dia)filtration was then performed with 2100 ml ultrafiltration per hour, 1000 ml dialysate volume per hour and a blood flow of 180 ml per minute. Anticoagulation was administered with heparin as described above. The setup of the haemo(dia)filter device and the filter changes were implemented by the nursing staff of the Clinic for Transplantation Immunology and Nephrology. The setting of the removal rate and the replacement of the substitute was done by the staff physicians of the intensive care units.

All patients underwent a screening for nasal colonisation with *S. aureus* at the time of central venous catheter placement. Exit site swabs were obtained using dry sterile swabs, enriched in a selective medium for 24 hours, then streaked in tubes containing Agar. Results were available after 48 hours. Positive cases were decolonised with 2% calcium mupirocin ointment (Bactroban®, Smith Kline Beecham Pharmaceuticals, Australia). Mupirocin ointment was placed in each nostril in the morning and in the evening for five days. Bactroban ointment application was repeated monthly until the catheter was removed. A mupirocin resistance test was performed on any positive probe. The site of central venous catheter insertion was disinfected daily with Octenidindihydrochloid/Phenoxyethanol (Octenisept®, Schülke and Mayr AG, Zurich, Switzerland), followed by local mupirocin application and finally covered by a non woven fabric mull dressing. Patients with suspected bacteraemia (fever higher than 38.5 °C and chills or other signs of ongoing infections were investigated with at least two sets of blood cultures, one by venepuncture and one by catheter (BacT/ALERT FA®, Biomérieux, Inc., Durham NC, USA). All cultures were incubated at 35 °C for at least 144 hours and analysed for growth daily. Blood stream infections were diagnosed according to standard guidelines established by the Center for Disease Control [10]. A catheter related blood stream infection must fulfil the criteria for *laboratory diagnosis of infection* and *clinical signs of sepsis*. Laboratory diagnosis of infection was defined as a positive blood culture with a strain not descending from a different site of infection. Bacteria that colonise the skin had to be detected in at least two blood cultures. Clinical signs of sepsis were fever (>38.5 °C), tachycardia, hypotonia and increased fluid requirement. Catheter associated blood stream infection was defined as a positive blood culture with a known source of infection in the presence of a catheter at least 48 hours in position.

Primary end point was the incidence of catheter related blood stream infection according to the laboratory and clinical definition of the Center for Disease Control in all intensive care unit patients treated with continuous veno-venous haemo(dia)filtration.

We used JMP software version 7.0 (SAS Institute Inc., Cary, NC) for statistical analysis. For categorical data, Fisher's exact test or Pearson's chi-square test were used. Parametric continuous data were analysed by Student's t-tests. For nonparametric continuous data, the Wilcoxon rank-sum test was used. A p-value <0.05 was considered to indicate statistical significance.

Results

A total of 194 consecutive patients treated with continuous veno-venous haemo(dia)filtration were enrolled in the study. Twenty one patients had to be excluded because of lack of screening for nasal colonisation with *S. aureus* leaving 173 patients with complete data collection for final analysis. The median age was 68.6 years. Sixty four (37%) patients were female, 109 (63%) were male (summary of demographic data see table 1). Fifty two (30%) of the patients were diabetic. One hundred and thirty two (76%) patients had a concomitant antibiotic treatment, and 35 (20%)

an immunosuppressive treatment mostly due to solid organ transplantation. Other reasons were pulmonary disease, adrenal insufficiency, Crohn's disease, multiple sclerosis, vasculitis, bullous pemphigoid and amyloidosis. Four (2.3%) patients suffered from chronic skin affections, 13 (7.5%) patients had skin ulcers. Four (2.3%) patients were treated with iron supplementation whilst they underwent continuous veno-venous haemo(dia)filtration. Most central venous catheters were inserted in the subclavian vein (47%), followed by the jugular (39%) and the femoral vein (11%). The indication for renal replacement therapy was acute renal failure (75.3%), acute on chronic renal failure (20.1%), lactate acidosis (3.1%), lithium intoxication (1%) and metabolic acidosis (0.5%). Screening for nasal colonisation with *S. aureus* was positive in 50 patients (29%). All patients screened positive received topical local treatment with mupirocin ointment. No mupirocin resistance was observed. No local or systemic adverse reactions to mupirocin ointment were noted during the study. In eight (4.6%) of the 173 patients positive blood cultures were found. Six patients had a catheter related blood stream infection according to the definition mentioned above. All

Table 1: Patient characteristics.

Number of patients, n	**173**	
Age (years)		
Median	68.6	
Range	18.9 to 87.8	
Men / women, n (%)	109/64	*(63/37)*
Patients on intensive care unit, n (%)	173	*(100)*
Medical intensive care unit	69	*(39.9)*
Surgical intensive care unit	104	*(60.1)*
Risk factors for development of catheter related bloodstream infection		
Diabetes mellitus, n (%)	52	*(30.1)*
Immunosuppression, n (%)	35	*(20.2)*
only corticosteroids	13	*(7.5)*
only calcineurin inhibitors	8	*(4.6)*
only antimetabolites	2	*(1.2)*
corticosteroids and calcineurin inhibitors	3	*(1.7)*
corticosteroids and calcineurin inhibitors and antimetabolites	6	*(3.5)*
corticosteroids and antimetabolites	3	*(1.7)*
Positive blood cultures during hospitalisation in the past, n (%)	19	*(11)*
Antibiotics, n (%)	132	*(76.3)*
Chronic skin disease, n (%)	4	*(2.3)*
Skin ulcers, n (%)	13	*(7.5)*
Hospitalisation within the month before continuous veno-venous haemo(dia)filtration, n (%)	98	*(56.6)*
Interval at home	18	*(10.4)*
Transfer directly to ICU	80	*(46.2)*
Iron substitution while central venous catheter in use, n (%)	4	*(2.3)*
Duration of central venous catheter use (days)		
Mean	9.2	
Median	6.0	
Range	1 to 60	
Total catheter days	1595	
Insertion site, n (%)		
Subclavian vein	81	*(46.8)*
Jugular vein	67	*(38.7)*
Femoral vein	19	*(11)*
Unknown	6	*(3.5)*

observed catheter related blood stream infections in this study were caused by coagulase-negative staphylococci, in one case a co-infection with *Klebsiella pneumoniae* was diagnosed. Two patients had catheter associated bloodstream infections; one with coagulase-negative staphylococcus (ventilator associated pneumonia), the other with Streptococcus oralis (tracheobronchitis). The cumulative incidence of catheter related blood stream infection in this study was 3.8 per 1000 catheter days. Eighty six (49.7%) patients died whilst being treated with continuous veno-venous haemo(dia)filtration. There was, however, no fatal event directly related to central venous catheter infection.

Table 3 compares the risk factors in the six patients (3.5%) with catheter related blood stream infection and the group without catheter related blood stream infection. The duration of central venous catheter use ($p = 0.02$) and pre-existing chronic skin disease ($p = 0.042$) were the only significant risk factors for catheter related blood stream infection found in this analysis.

Discussion

To the best of our knowledge this is the first study that evaluates the incidence of catheter related blood stream infection in severely ill patients in intensive care units treated with continuous veno-venous haemo(dia)filtration, a population with a high risk for catheter related blood stream infection. The risk of catheter related blood stream infection in the study group was 3.8 per 1000 catheter days. The number is similar to other studies on catheter related blood stream infection including intensive care unit patients [11] in general and comparable with the results of a meta-analysis that included stable haemodialysis patients temporarily treated with non-tunnelled catheters [12]. However, the number is higher than in our own population of stable haemodialysis patients treated with the same prophylactic protocol (0.8 catheter related blood stream infection per 1000 catheter days; data not shown), and as shown in a clinical trial using topical medicinal barriers at exit site [13]. Therefore, the result may in part reflect the additional risk of this critically ill study population underlined by a mortality rate of 50%, which corresponds to the experience of other studies including patients with renal replacement therapy in intensive care units [14, 15].

All catheter related blood stream infection in this study were caused by coagulase negative staphylococci, which are known to be the most frequently encountered pathogens in this setting [16]. There was no catheter related blood stream infection involving *S. aureus*. The applied standardised prophylactic regimen that included screening for and prophylaxis of *S. aureus* colonisation may have been of benefit. A position statement recently published by European Renal Best Practice is consistent with the prophylactic procedure applied in this study [17]. It is known that the application of mupirocin ointment in haemodialysis patients leads to a fourfold reduction of *S. aureus* bloodstream infection as compared to historical controls [18]. In addition, treatment of *S. aureus* carriers prior to surgery cut postoperative infections by half, also supporting the use of mupirocin to prevent *S. aureus* infections [19]. No conclusion on the efficacy of the applied regimen can be drawn as the study had an observational character only and lacked a control group.

Risk analysis for catheter related blood stream infection revealed two potential risk factors (table 3): (i) the duration of central venous catheter use and (ii) pre-existing chronic skin lesions. Both are well known risk factors for catheter related blood stream infection as already shown in the literature [1]. However, the number of events is too low to draw any conclusions.

The strength of the present study is its prospective character that included a case-mix of medical and surgical patients and a standardised protocol of catheter handling. Its significance is weakened by the observational setting and therefore the lack of comparison to an intervention with a control group. There is very limited significance on potential risk factors of catheter related blood stream infection due to the low number of events. The applied protocol of catheter handling can also be questioned. Mupiriocin resistance among *S. aureus* is a concern, however there is no case reported in a dialysis population [20]. The workload induced by daily dressing and the associated risk of con-

Table 2: Outcome data.

Nasal screening *(S. aureus)*, n (%)	**173**	
Positive	50	*(28.9)*
Negative	123	*(71.1)*
Positive blood culture while central venous catheter in use, n (%)	**8**	*(4.6)*
Catheter related bloodstream infection	6	*(75)*
Catheter associated bloodstream infection	2	*(25)*
Catheter related bloodstream infection/1000 catheter days	3.8	
Bacteria, n (%)		
Catheter related bloodstream infection	**6**	
Coagulase negative staphylococci	5	*(83.3)*
Coagulase negative staphylococci + *Klebsiella pneumonia*	1	*(16.7)*
Catheter associated bloodstream infection	**2**	
Streptococcus oralis	1	*(50)*
Coagulase negative staphylococci	1	
Death, n (%)	86	*(49.7)*
Death catheter associated, n (%)	0	

tamination with other class of micro-organisms must be mentioned.

Nevertheless, for the first time this study provides an idea of the risk of catheter related blood stream infection in this specific population. Future prospective interventional studies should focus on prophylactic regimens to minimise the risk of catheter related blood stream infection with coagulase negative staphylococci.

Conclusion: The incidence of catheter related blood stream infection in critically ill patients in our intensive care units treated with continuous veno-venous haemo(dia)filtration was 3.8 per 1000 catheter days. In this study all catheter related blood stream infections were caused by coagulase negative staphylococci.

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Table 3: Risk factors.

	Patients with CR-BSI (= 6)		**Patients without CR-BSI (= 167)**		***P***
Age					
Median	66.2		68.6		*0.49*
ICU, n (%)	6	(100)	167	(100)	*1.00*
mICU	1		68		
sICU	5		99		
Diabetes mellitus, n (%)	1	(16.7)	51	(30.5)	*0.47*
Positive blood cultures in the past, n (%)	1	(16.7)	18	(10.8)	*0.65*
Immunosuppression, n (%)	1	(16.7)	34	(20.4)	*0.83*
Antibiotics, n (%)	6	(100)	126	(75.4)	*0.16*
Chronic skin disease, n (%)	1	(16.7)	3	(1.8)	***0.042***
Skin ulcers, n (%)	0		13	(7.8)	*0.48*
Hospitalisation within the last month Before CVVH(D)F, n (%)	4	(66.7)	94	(56.3)	*0.41*
Iron substitution while CVC in use, n (%)	0		4	(2.4)	*0.70*
Days of CVC use (median)	25		6.0		***0.02***
Insertion, n (%)					*0.88*
jugular vein	3	(50)	64	(38.3)	
subclavian vein	1	(16.7)	80	(47.9)	
femoral vein	1	(16.7)	18	(10.8)	
unknown	1	(16.7)	5	(3)	
Nostril screening positive *(S. aureus)*, n (%)	1	*(16.7)*	*49*	*(29)*	*0.50*

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