Incidence of bloodstream infection in multicenter inception cohorts of hemodialysis patients

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Objective: To assess incidence of and identify risk factors for bloodstream infection in patients starting hemodialysis or starting a new means of vascular access for hemodialysis.

Method: Two cohorts of patients, 1 initiating hemodialysis (new patients) and a 1:1 matching group of patients continuing hemodialysis but starting a new vascular access (continuing patients), were enrolled from 9 Canadian hemodialysis units and followed for 6 months. Bloodstream infection was defined using established criteria. A nested case-control study was carried out, using as cases those cohort patients diagnosed with infection. Each case was matched with a control having the same means of access and new or continuing status.

Results: A total of 527 patients (258 new, 269 continuing), were recruited and underwent 31,268 hemodialysis procedures during this 6-month follow-up. There were 96 bloodstream infections in 93 patients (11.97/10,000 days, 28.81/10,000 hemodialysis procedures), yielding a relative risk of infection of 3.33 (95% CI, 2.12-5.24) for patients with a previous bloodstream infection and 1.56 (95% CI, 1.02-2.38) for patients continuing hemodialysis by a new means of access. Survival analysis revealed that compared to arteriovenous fistula vascular access, the relative risk of bloodstream infection in patients was 1.47 (95% CI, 0.36-5.96) for arteriovenous grafts, 8.49 (95% CI, 3.03-23.78) for cuffed central venous catheters, and 9.87 (95% CI, 3.46-28.20) for uncuffed central venous catheters. The regression model of the case-control study identified earlier bloodstream infection (OR, 6.58), poor patient hygiene (OR, 3.48), and superficial access-site infection (OR, 4.36) as additional risk factors.

Conclusion: During the first 6 months there is a high rate of bloodstream infection in patients starting hemodialysis either for the first time or by a new means of vascular access. Previous hemodialysis bloodstream infection and continuing hemodialysis by a new means of vascular access are markers for an increased risk of infection, as is poor patient hygiene. Central venous catheter vascular access, whether cuffed or uncuffed, has a much higher infection risk. In this study, there was no difference in infection rate between cuffed and uncuffed central catheters. (Am J Infect Control 2004;32:155-60.)

Hemodialysis continues to be an important treatment option for persons with end-stage renal disease. Infection is a serious complication of hemodialysis, and infection arising from the percutaneous vascular access necessary to accomplish hemodialysis is the most common source of infection occurring in these patients.[1,2] Previous studies have established that infection risk is lowest when vascular access occurs through ateriovenous graft and highest through central venous catheter (CVC).[2-9] Other identified risk factors for infection include diabetes, *Staphylococcus aureus* nasal carriage, patient hygiene, iron overload, hypoalbuminenia, and use of bioincompatible membranes.[10-13]

Although previous studies have identified type of vascular access as a determinant in the risk of bloodstream infection, quantitation of risk has been variable. The objective of this study was to determine the relative risk (RR) of infection and identify potentially modifiable risk factors for hemodialysis access-related bloodstream infection by prospectively following an inception cohort of hemodialysis patients either starting hemodialysis or continuing hemodialysis by a new means of vascular access.

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METHODS

The Canadian Nosocomial Infection Surveillance Program is a network of largely university-affiliated Canadian hospitals that carries out surveillance

examining the frequency and risk factors for the occurrence of hospital-acquired infections. In this project, 9 hospitals from the Canadian Nosocomial Infection Surveillance Program network participated in recruiting patients starting hemodialysis to examine the frequency and risk factors for hemodialysis-associated bloodstream infection. Patients with chronic renal failure requiring hemodialysis for at least 1 month were prospectively followed. Two patient groups were identified. The first consisted of patients receiving hemodialysis for the first time (new patients). For each new hemodialysis patient, the next hemodialysis patient recruited was admitted to that hospital unit for continuing hemodialysis using a new vascular access (continuing patients). A CVC exchanged over a guide wire was considered a new vascular access, but a surgical revision of a previous arteriovenous graft or fistula was not. Such exchanges, if carried out during an infection episode, were not considered definitive therapy, and subsequent positive blood culture for the same species was not considered to represent a new infection.

Patients were enrolled over a 6-month period from December 1998 to May 1999. Each patient was then followed for 6 months regardless of where hemodialysis was received, or until the patient died, recovered renal function, received a successful renal transplant, started peritoneal dialysis, or moved to another Canadian province or country.

Cohort patient data collected included demographic information, cause of renal failure, presence of diabetes, and mode of vascular access. Access-associated bloodstream infections were defined by previously published criteria for definite or probable infections.[13] Specifically, a microorganism recovered from a blood culture was considered to represent a definite bloodstream infection if there was histologic evidence of septic thrombopheblitis in an excised vessel or if the intravascular device surface or skin surface site was culture positive for the same organism as a blood culture. The recovery of a microorganism from a blood culture was considered to represent a probable bloodstream infection if 2 positive blood cultures yielded the same organisms when drawn from different sites, if *S aureus* or *Candida* species (spp) grew in 1 blood culture, or if coagulase-negative staphylococci, *Bacillus* spp, *Corynebacterium* spp, or *Enterococcus* spp were recovered in 1 or more blood cultures from an immunocompromised patient. End-stage renal disease was not itself considered an immunocompromising condition. After clinical review, an isolate was considered vascular-access related if no alternative source or organ system infection could be implicated. Possible vascular-access bloodstream infection (ie, isolation of a common skin contaminant from a single blood culture specimen), without other concordant microbiologic evidence of infection such as positive CVC tip culture or culture of pus from a vascular-access site, was excluded, as was any bloodstream infection secondary to an infection source at a nonvascular-access body site. A patient was considered to have developed a second infection episode if a blood culture meeting the case definition grew a different bacterial species or, if the same species, on a case-by-case basis if sufficient time had elapsed without antimicrobial therapy, usually more than 2 weeks, for a relapse of the previous infection to be unlikely.

A nested case-control study was carried out from patients in the cohort. Patients with a bloodstream infection were considered cases. Control subjects who had not experienced an infection during the study period (1 per case) were patients randomly taken from the same cohort. Patient hygiene status (good or poor) was determined subjectively on the basis of clinical and Infection Control Service staff assessment of the patient. Malignancy was considered to be present if currently active. Medication use was as of time of enrollment. Contiguous infection at access site was determined on the basis of clinical signs, with or without microbiologic confirmation.

Statistical methods

PC SAS (Version 8.1, SAS Institute; Cary, NC) was used to conduct statistical analyses. Cox proportional hazards model was used to evaluate the association between variables and risk of infection, adjusted for patient age and the relationship between variables and the occurrence of bloodstream infection. A model was fitted to examine occurrence of bloodstream infection by type of access involving all accesses used. In this model, acquisition of infection is considered to be independent for each means of access. For the nested case-control study, factors identified as potentially associated with infection in univariate analysis were included in a stepwise multivariate logistic regression model. All risk estimates were adjusted for the age of the patient at the time of enrollment.

RESULTS

Cohort study

The cohort consisted of 527 patients; 258 had never undergone hemodialysis (new), whereas 269 were continuing hemodialysis by a new vascular access (continuing). Diabetes (181, 34.3%) and hypertension (99, 18.8%) were the most common known causes of end-stage renal disease. Of the 527 patients, 395 (75%) completed 6 months of follow-up. During the follow-up period, 13 (2.5%) underwent successful renal transplantation, 26 (4.9%) started peritoneal dialysis, 14 (2.7%) discontinued dialysis, 5 (0.9%) had return of

Table 1. Risk of bloodstream infection using the Cox proportional hazards model

Variable	Patients	Observed infections*	Relative risk† and 95% confidence interval
Patient group			
Patient starting new access	256	58	1.56 (1.02-2.38)
New hemodialysis patients	266	35	1.0
Diabetes	189	38	1.27 (0.84-1.93)
Previous bloodstream infection	56	30	3.33 (2.12-5.24)
Status before enrollment in study			
Never dialyzed	232	53	1.0
Hemodialysis	249	2	1.20 (0.78-1.85)
Peritoneal dialysis	31	3	0.45 (0.11-1.86)
Renal transplant	10	35	1.33 (0.40-4.45)
Cause of renal failure			
Diabetes	180	34	1.0
Glomeruloneophritis	39	5	0.48 (0.18-1.26)
Hypertension	98	21	1.31 (0.76-2.27)
Other	205	33	0.81 (0.50-1.31)

*Patients were censored at the end of the access where an infection occurred; it was assumed that the infection occurred at the end of the access treatment.
†Adjusted for age of the patient at baseline.

Table 2. Risk of a bloodstream infection according to the type of vascular access using Cox proportional hazards model

Type of access	Number of infections*	Treatments	Relative risk† and 95% confidence interval	Relative risk‡ and 95% confidence interval
Noncuffed CVC	32	302	10.54 (3.69-30.10)	9.87 (3.46-28.20)
Cuffed CVC	53	297	9.78 (3.53-27.11)	8.49 (3.03-2378)
AV graft	4	107	1.69 (0.42-6.79)	1.47 (0.36-5.96)
AV fistula	4	223	1.0	1.0

CVC, Central venous catheter; *AV*, arteriovenous.
*This model assumes that the occurrence of infection are independent across individual patient treatment accesses.
†Adjusted for age of the patient at baseline.
‡Adjusted for age at baseline, previous bloodstream infection, and new dialysis patient vs patient on hemodialysis starting a new vascular access.

renal function, and 54 (10.2%) died. Of the 54 deaths, 10 (18.5%) were attributed directly to bloodstream infections. The cohort underwent 33,316 hemodialysis procedures by 929 different means of vascular access. The number of accesses per patient ranged from 1 to 7.

Ninety-three of the 527 patients (17.6%) developed 96 instances of bloodstream infection (11.97/10,000 patient-days and 28.81/10,000 hemodialysis procedures). Access-specific infection rates per 10,000 procedures were 40.26 for uncuffed and 45.26 for cuffed CVC, 7.97 for arteriovenous grafts, and 5.02 for arteriovenous fistula. Starting hemodialysis by new access (RR, 1.56; 95% CI 1.02-2.38) and having experienced a previous bloodstream infection (RR, 3.33; 95% CI, 2.12-5.24) were significantly associated with risk of bloodstream infection (Table 1). The microbial etiology of these infections were coagulase-negative staphylococci 45%, *S aureus* 28.1%, *Enterococcus* 8.8%, aerobic gram negative bacilli 8.6%, other 8.8%.

The Cox proportional hazards model analyzed the 929 accesses to construct a hierarchy of bloodstream infection RR by means of access (Table 2). Survival curves (Fig 1) show a progressive occurrence of infection throughout the follow-up period. Although there was clear separation of infection rates between arteriovenous fistula or graft and CVC access, there was no difference in the 2 forms of CVC access.

Case-control study

There were 186 patients enrolled in the case-control study. Univariable analysis identified patient hygiene (OR, 2.4) and contiguous infection at the access site (OR, 2.8) as independently associated with bloodstream infection (Table 3). In the multivariable logistic regression model, prior bloodstream infection (OR, 6.56; $P = .004$), poor patient hygiene (OR, 3.48; $P = .001$), and contiguous infection (OR, 4.36; $P = .002$) were all independently associated with occurrence of a bloodstream infection (Table 4).

DISCUSSION

This study of a large multicenter cohort of patients starting hemodialysis documents the very high short-term risk of access-related bloodstream infection and confirms the importance of means of access as the major determinant of risk for bloodstream infection,

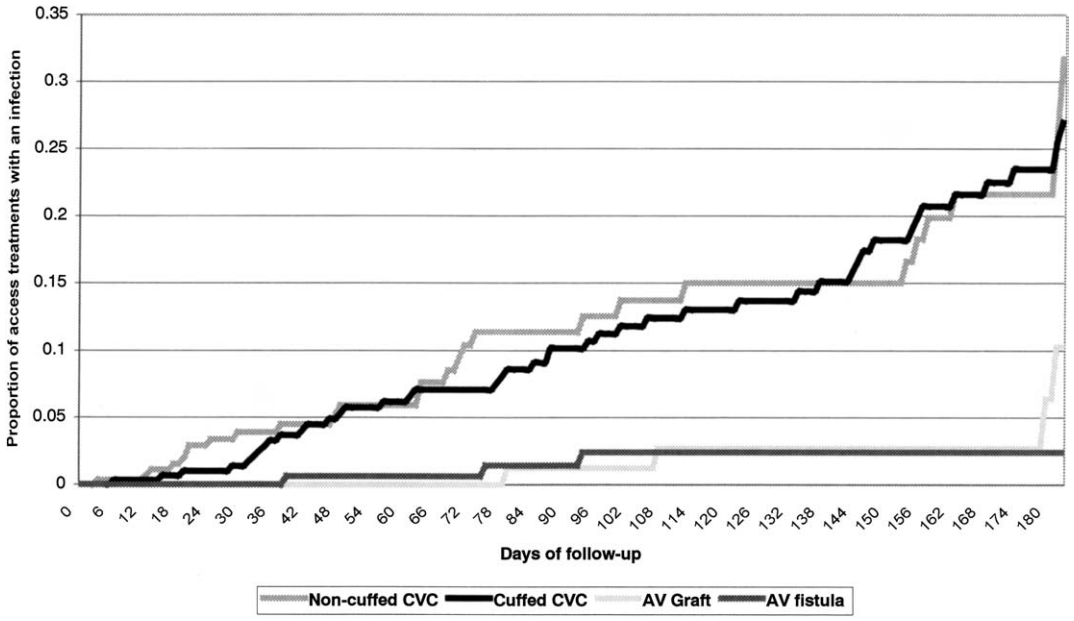

Fig 1. Proportion of access treatments with bloodstream infections, by type of vascular access. (Cumulative hazard function estimated using the Cox proportional hazards with adjustment for group differences in age, previous bloodstream infection, and patient status.)

whether the patient is starting dialysis for the first time or continuing dialysis by a new vascular access. This is the first study to use survival analyses to demonstrate this relationship.

The population impact of CVCs as an infection risk is reflected by the fact that almost all (92%) episodes of infection were acquired during this form of access. Recently,[2] CVC access (cuffed and uncuffed) has also been shown to increase risk of death in hemodialysis patients. For patients in whom arteriovenous graft and fistula access are not an option, there is an urgent need to find safer means of access. Impregnating hemodialysis catheters with antimicrobial agents has not been shown to reduce infection rates.[15]

Another attempt to find a safer means of access was the development in the 1980s of cuffed and subcutaneous tunneled CVCs. Theoretically, the cuff and long subcutaneous track provide a barrier to microorganisms accessing the bloodstream down the catheter. These catheters have become increasingly popular in hemodialysis units and have been recommended for use in 2 guidelines.[16-18] No randomized trial comparing the 2 forms of CVC access has been carried out. Some population studies, including our own, have suggested cuffed catheters may have a lower infection risk,[5,6,19] though Pastan[2] was unable to show a mortality difference between cuffed and noncuffed catheters. The current study differs from others in that we recruited cohorts of patients starting hemodialysis, either for the first time or by a new means of access, which may give a more accurate assessment of infection risk. We were unable to show a difference in infectious outcome between cuffed and tunneled CVCs and traditional catheters, nor did the survival curves suggest a trend to earlier acquisition of infection by the noncuffed catheters in the 6-month study period. Our study did not involve random assignment of catheter type. Type of CVC used was established by unit policy, but it is possible that at the few sites where both forms of CVC were used, patients who were at higher infection risk were assigned to dialysis through cuffed catheters. Nevertheless, given the difficulty and expense of inserting cuffed catheters, and the absence of any randomized trials demonstrating superiority, a randomized comparison of the 2 types of CVC is justifiable.

The surveillance definition used in this study is the Canadian, which has been used previously for published reports of hemodialysis-related bloodstream infection.[19] It differs slightly from the Centers for Disease Control and Prevention (CDC) definition in that common skin contaminants rowing in blood culture are considered significant in the CDC definition if the attending physician prescribes therapy, and in the Canadian definition if the organism is repetitively isolated, if the patient is receiving total parenteral nutrition (rarely the case in hemodialysis patients), or if the patient is immuncompromised for reasons other than renal failure itself. Although no direct comparisons of the 2 definitions have been published, we

Table 3. Characteristics of the patients enrolled in the case-control study

	Cases, N = 93	Control, N = 93		
Variable	**No. (%)**	**No. (%)**	**OR (95% CI)**	***P* value**
Age in years	57	57		1.00
Median (range)	59 (17-89)	59 (22-91)		
Patient group				
Patient starting new access	58 (62.4)	52 (48.1)	1.3 (0.7-2.5)	.37*
New dialysis patient	35 (37.6)	41 (51.9)	1.0	
Type of vascular access				
Uncuffed CVC	32 (34.4)	36 (38.7)	2.7 (0.8-9.1)	.11*
Cuffed CVC	53 (57.0)	31 (33.3)	5.1 (1.4-20.9)	.004*
AV graft	4 (4.3)	14 (15.1)	0.9 (0.1-3.7)	.84*
AV fistula	4 (4.3)	12 (12.9)	1.0	
Diabetes	38 (40.8)	35 (37.6)	1.1 (0.6-2.2)	.65
Previous transplant	10 (10.9)	9 (9.7)	1.1 (0.4-3.2)	.81
Prior bloodstream infection	30 (32.3)	4 (4.4)	10.5 (3.3-37.0)	<.001*
Single-use membrane	73 (78.5)	68 (73.1)	1.3 (0.7-2.6)	.39
Poor patient hygiene	63 (67.7)	43 (46.2)	2.4 (1.3-4.6)	.003*
Total parental nutrition	3 (3.2)	2 (2.2)	1.5 (0.2-13.3)	.65
Malignancy	7 (7.5)	4 (4.3)	1.8 (0.5-7.7)	.35*
No desferioxamine	6 (6.4)	11 (11.8)	1.9 (0.7-5.5)	.20*
Erythropoietin	69 (74.2)	70 (75.3)	0.9 (0.7-5.5)	.87
Immunosuppressive agents	4 (4.3)	5 (5.3)	0.8 (0.2-3.5)	.98
Urokinase	13 (14.0)	14 (15.1)	0.9 (0.4-2.2)	.85
Corticosteroids	5 (5.4)	3 (3.2)	1.7 (0.3-9.3)	.72
Contiguous skin infection	25 (26.9)	11 (11.8)	2.8 (1.2-6.4)	.009*

AV, Arteriovenous; *CI*, confidence interval; *CVC*, central venous catheter; *OR*, unadjusted odds ratio.
*Included in the multivariable analysis.

Table 4. Risk factors associated with bloodstream infections in a multivariate logistic regression model, N = 186

	Coefficient estimate	SE	Adjusted OR	95% CI	*P* value
Intercept	−1.8698	0.6027			
Type of vascular access					
Uncuffed CVC	0.5867	0.6144	1.79	0.54-5.99	0.3397
Cuffed CVC	1.1228	0.6175	3.07	0.92-10.31	0.0690
AV-graft	−0.4287	0.7886	0.65	0.14-3.06	0.5867
AV-fistula	0		1.0		
Prior bloodstream infection	1.8078	0.6204	6.56	1.81-20.56	0.0036
Poor patient hygiene	1.2739	0.3361	3.48	1.74-7.33	0.0005
Contiguous skin infection	1.5019	0.4698	4.36	1.78-11.28	0.0018
Age over 57 years	0.1260	0.3354	1.13	0.59-2.19	0.7075

AV, Arteriovenous; *CI*, confidence interval; *CVC*, central venous catheter; *OR*, odds ratio; *SE*, standard error.

believe the impact on infection rates of these differences is slight.

The burden of infection risk appears to be disproportionately carried by hemodialysis patients. Even when means of access is controlled, having experienced a previous infection increased the probability of another infection by more than 6-fold in the rather short 6-month follow-up of this study. Although other studies have identified diabetes, carriage of *S aureus,* and use of urokinase as infection risks,[9,12,14] we were able to identify surprisingly few other factors so associated. Again, it is possible that our study design, following incident rather than prevalent dialysis patients, is responsible for these different results from other studies. Only poor patient hygiene, as perceived by the clinical staff caring for the patient, was identified in the multivariable model, associated at 2.4 times infection risk. This factor has previously been identified as an infection hazard in hemodialysis patients[14] and is potentially remediable, suggesting that at the onset of hemodialysis, patients should be given education in the importance of hygiene.

In summary, this study of incident patients confirms the high short-term infection risk of hemodialysis patients and the hierarchy of risk by access type but

fails to demonstrate a significant difference between cuffed and uncuffed CVC access.

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