Q J Med 2014; **107**:995–1000
doi:10.1093/qjmed/hcu128 Advance Access Publication 17 June 2014

Taurolidine–citrate–heparin catheter lock solution reduces staphylococcal bacteraemia rates in haemodialysis patients

E.C. MURRAY, C. DEIGHAN, C. GEDDES and P.C. THOMSON

From the Glasgow Renal and Transplant Unit, Western Infirmary, Glasgow G11 6NT, UK

Address correspondence to Dr E.C. Murray, Glasgow Renal and Transplant Unit, Western Infirmary, Dumbarton Road, 1/1 173 Kenmure St, Glasgow G41 2LE, UK. email: eleanormurray@doctors.org.uk

Received 3 April 2014 and in revised form 16 May 2014

Summary

Background: Infection is second only to cardiovascular disease as a cause of death in the haemodialysis (HD) population.
Aim: To assess the effect of introducing catheter lock solution taurolidine–citrate–heparin to all tunnelled central venous catheters (TCVCs) on staphylococcal bloodstream infection rates in patients on chronic HD.
Design: Observational, prospective analysis of the incidence rates of staphylococcal bacteraemic events in National Health Service (NHS) Greater Glasgow & Clyde and NHS Forth Valley between April 2011 and June 2013, with taurolidine–citrate–heparin catheter lock solution introduced July 2012.
Methods: Data were collected each calendar quarter through a structured query language interrogation of the renal unit electronic patient record, with staphylococcal bacteraemic events expressed per 1000 vascular access exposed days. Comparison between pre- and post-intervention periods was made by student's *t*-testing.
Results: Two hundred and thirty-nine staphylococcal bacteraemic events occurred over a total of 424 835 HD days in 565 patients; 81 events in 289 389 arterio-venous fistula or graft (AVF/AVG) HD days and 158 events in 135 446 TCVC HD days. Following the introduction of taurolidine–citrate–heparin, bacteraemic events in patients dialysing via a TCVC fell from 1.59/1000 HD days to 0.69/1000 HD days, $P = 0.004$. The staphylococcal bacteraemia rate in AVF/AVGs remained unchanged; 0.30 vs. 0.26/1000 HD days, $P = 0.52$.
Conclusions: Replacing heparin 5000 IU with Taurolidine–citrate–heparin as catheter lock solution was associated with a statistically significant 56% reduction in staphylococcal bloodstream infection rates in our TCVC HD population.

Introduction

Patients on renal replacement therapy (RRT) experience significantly higher rates of morbidity and mortality compared with the general population.[1] Infection is the second-highest cause of death and accounts for ~20% of RRT patient mortality.[1] As such, infection continues to represent a preventable and treatable therapeutic target. Several studies have reported on the use of antibiotic or antimicrobial lock solutions to prevent haemodialysis (HD) catheter-related bacteraemia.[2–4] Concerns persist with regard to the impact antibiotic catheter-lock solutions may have on the development of antibiotic resistance, although some recent studies have reported encouraging results on the use of taurolidine–citrate-based solutions.[4,5] Taurolidine is an antimicrobial agent in which antibiotic resistance is felt to be less of a concern, whilst the combination of taurolidine–citrate with heparin 500 IU/ml has been demonstrated as comparable to heparin 5000 IU/ml in maintaining catheter patency.[4]

In this study, we report our experience of replacing heparin 5000 IU/ml as standard tunnelled central venous catheter (TCVC) lock solution with

1.35% Taurolidine, 4% citrate and 500 IU/ml heparin, and the impact of such on staphylococcal bloodstream infection rates in a large HD cohort.

Methods

An analysis of prospectively recorded data was conducted by a structured query language interrogation of the National Health Service (NHS) Greater Glasgow & Clyde and NHS Forth Valley Renal Unit Electronic Patient Record (EPR). Haemodialysis of the Greater Glasgow & Clyde and Forth Valley population is distributed over seven outpatient dialysis units. Policies and protocols are standardized throughout the units; including intention to achieve vascular access via an arterio-venous fistula (AVF) or graft (AVG) for both incident and prevalent patients; if a TCVC is required, this is generally sited in the internal jugular vein. The EPR database includes all patients attending renal services, and in real time imports all West of Scotland microbiology results from any source. The EPR also includes complete individual patient histories on RRT and vascular access.

Data on all incident staphylococcal-positive blood cultures and the HD vascular access used by each patient in our HD population were collected for every calendar quarter between 1 April 2011 and 30 June 2013. A total of five calendar quarters of observation was undertaken before TCVC locking with Heparin 5000 IU was replaced by locking with Taurolidine–citrate–heparin (TauroHep500) catheter lock solution on 1 July 2012. A further four calendar quarters of observation was then undertaken to monitor the impact on staphylococcal bacteraemia event rates.

Aside from the change in catheter lock solution from heparin 5000 IU to taurolidine–citrate–heparin on 1 July 2012, standard NHS Scotland catheter care and dialysis protocols were otherwise consistent throughout the period of observation; specifically, the maintenance of standard sterile technique during catheter insertion and on each subsequent occasion when manipulating the catheter hubs thereafter. Chlorhexidine-impregnated exit site patches are not part of this care bundle.

Consecutive blood culture results more than 14 days apart were regarded as separate events. Staphylococcal-positive blood cultures were classified as coagulase-negative, methicillin-sensitive (MSSA) or methicillin-resistant (MRSA) in order to assess if any observed effect was restricted by virulence factors.

With many patients undergoing a change in vascular access method during the observation period, data on the precise number of exposed days on each vascular access type for each patient were determined electronically and then cross-checked manually. AVF and AVG numbers were combined, as the number dialysing via AVGs was very small. Haemodialysis days where the access was a temporary, non-tunnelled CVC were excluded from either group, due to the low number of cumulative days and the intrinsic differences associated with this group. Event rates for each calendar quarter were expressed as events per 1000 HD-exposed days for both TCVCs and AVF/AVG vascular access types. Number needed to treat (NNT) was similarly calculated as per 1000 HD days. Rate ratios with 95% confidence intervals were calculated comparing the pre- and post-intervention periods for both the TCVC group and the AVF/AVG group. Comparisons between pre- and post-intervention periods were made by student's *t*-testing with a significance level set at *P*-value <0.05.

Results

Over the observation period a total of 239 staphylococcal bacteraemic events occurred over a cumulative 424 835 HD exposed days in 565 patients; 81 events in 289 389 AVF/AVG HD days and 158 events in 135 446 TCVC HD days (Table 1). The rate ratio of staphylococcal bacteraemic events in the TCVC group was 0.42 (95% CI 0.35, 0.50, $P < 0.01$) following the conversion to Taurolidine–citrate–heparin. The rate ratio of staphylococcal bacteraemic events in the AVF group was 0.86 (95% CI 0.72, 1.03, $P = 0.11$) over the same time periods.

Comparing the staphylococcal bacteraemia rate before and after the introduction of taurolidine–citrate–heparin in TCVCs demonstrated a 56% relative risk reduction (RRR) from 1.59 per 1000 HD days (95% confidence interval [CI] 1.16, 2.02) to 0.69 per 1000 HD days (95% CI 0.25, 1.13), $P = 0.004$. The staphylococcal bacteraemia rate in AVF/AVGs remained unchanged; 0.30 per 1000 HD days pre-July 2012 (95% CI 0.17, 0.42) vs. 0.26 per 1000 HD days post-July 2012 (95% CI 0.18, 0.33), $P = 0.52$ (Table 1 and Figure 1A). For TCVC-access patients, this equates to an absolute risk reduction (ARR) of 0.90 staphylococcal bacteraemia events per 1000 HD days, and a NNT of 1.11 over 1000 HD days (NNT 3.04 per patient year).

The reduction in bacteraemias was demonstrated across the spectrum of methicillin-sensitive, methicillin-resistant and coagulase negative staphylococci, as Table 1 and Figure 1B illustrate; TCVC coagulase negative bacteraemia fell from 1.09 to

Table 1 Rates of staphylococcal bacteraemia by dialysis access type and catheter-lock solution

	Heparin catheter-lock	Taurolidine–citrate–heparin catheter lock	Total	*P* value
AVF/AVG				
HD days	164 861	124 528	289 389	
Bacteraemias				
Coagulase negative	36	25	61	
Rate (95% CI)	0.22 (0.09, 0.34)	0.20 (0.14, 0.26)		0.77
MSSA	13	6	19	
Rate (95% CI)	0.08 (0.04, 0.12)	0.05 (0.02, 0.08)		0.17
MRSA	0	1	1	
Rate (95% CI)	0 (N/A)	0.01 (N/A)		N/A
All *S. aureus*	13	7	20	
Rate (95% CI)	0.08 (0.04, 0.12)	0.06 (0.01, 0.11)		0.36
All Staph	**49**	**32**	**81**	
Rate (95% CI)	**0.3 (0.17, 0.42)**	**0.26 (0.18, 0.33)**		**0.52**
TCVC				
HD days	72 280	63 166	135 446	
Bacteraemias				
Coagulase negative	79	30	109	
Rate (95% CI)	1.09 (0.70, 1.50)	0.49 (0.14, 0.83)		0.01
MSSA	32	13	45	
Rate (95% CI)	0.44 (0.24, 0.64)	0.21 (0.09, 0.33)		0.03
MRSA	4	0	4	
Rate (95% CI)	0.06 (N/A)	0 (N/A)		N/A
All *S. aureus*	36	13	49	
Rate (95% CI)	0.50 (0.27, 0.72)	0.21 (0.10, 0.36)		0.02
All Staph	**115**	**43**	**158**	
Rate (95% CI)	**1.59 (1.16, 2.02)**	**0.69 (0.25, 1.13)**		**0.004**
Combined				
HD days	237 141	187 724	424 865	
Bacteraemias				
Coagulase negative	115	55	170	
Rate (95% CI)	0.48 (0.31, 0.66)	0.29 (0.17, 0.42)		0.05
MSSA	45	19	64	
Rate (95% CI)	0.19 (0.11, 0.27)	0.10 (0.08, 0.12)		0.35
MRSA	4	1	5	
Rate (95% CI)	0.02 (N/A)	0.01 (N/A)		N/A
All *S. aureus*	49	20	69	
Rate (95% CI)	0.21 (0.12, 0.30)	0.11 (0.08, 0.13)		0.03
All Staph	**164**	**75**	**239**	
Rate (95% CI)	**0.69 (0.51, 0.87)**	**0.4 (0.25, 0.54)**		**0.01**

'Rate', per 1000 HD days; 'All *S. aureus*', MSSA and MRSA; 'All Staph', coagulase negative, MSSA and MRSA.

0.49/1000 HD days (56.6% RRR, 0.62 per 1000 HD days ARR); TCVC MSSA bacteraemias from 0.44 to 0.21/1000 HD days (53.5% RRR, 0.24 per 1000 HD days ARR) and TCVC MRSA 0.06 to 0.00/1000 HD days (100% RRR, 0.06 per 1000 HD days ARR). Taking the *Staphylococcus aureus* infections in isolation (i.e. excluding coagulase negative bacteraemia) and the HD population in its entirety (i.e. including AVF- and AVG-access patients), the bacteraemia rate fell from 0.21 to 0.11 per 1000 HD days following the intervention ($P = 0.03$).

Discussion

One limitation of the study is the lack of data on possible sources of infection other than vascular access, and data regarding other pathogens, particularly Gram negative organisms. This is partly pragmatic due to the variable text strings used within microbiology reports that makes automated searching for these infections challenging. Nevertheless, concentrating on staphylococcal bacteraemia when monitoring and auditing HD-related infection rates is a

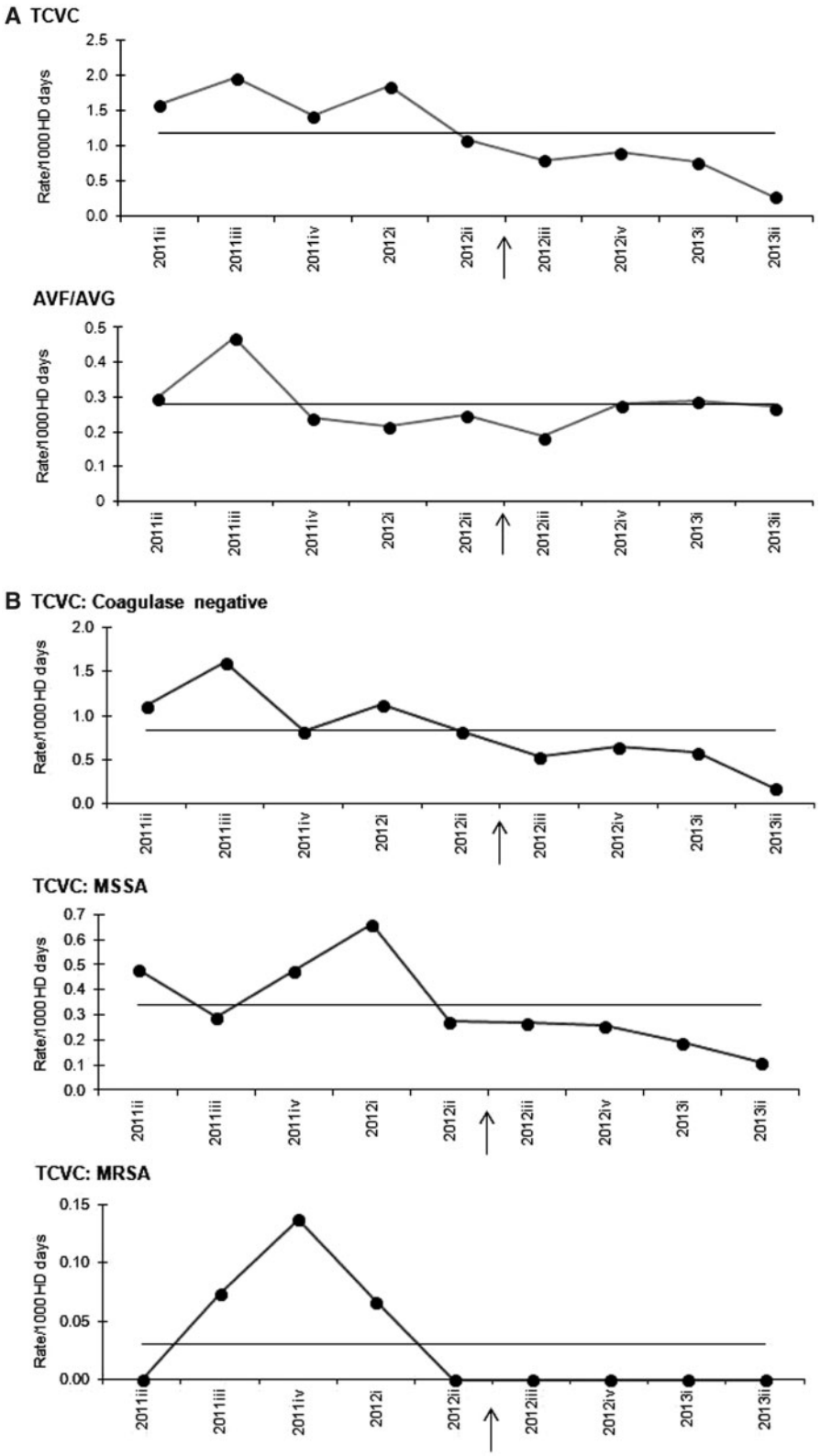

Figure 1. (A) Rate of staphylococcal bacteraemic events (per 1000 HD days) by dialysis access type in each of the year quarters of the study period. TCVC, tunnelled central venous catheter; AVF, arteriovenous fistula; AVG, arteriovenous graft. The arrow indicates the replacement of heparin locking solution with taurolidine–citrate–heparin locking solution in all TCVCs. The solid line represents the median for the whole period. (B) Rate of TCVC staphylococcal bacteraemic events (per 1000 HD days) by staphylococcal subgroups in each of the year quarters of the study period. TCVC, tunnelled central venous catheter. The arrow indicates the replacement of heparin locking solution with taurolidine–citrate–heparin locking solution in all TCVCs. The solid line represents the median for the whole period.

valid approach, as it has been established that up to 90% of bacteraemic events in our HD population are staphylococcal.[6] We expect this to be typical of many other renal units. As staphylococci are ubiquitous skin commensals, this also suggests that vascular access is the primary source of such infections, an assumption supported by observational data demonstrating that catheter-related HD access is associated with significantly higher infection rates than AVF or AVG, which does appear to translate to higher mortality even adjusting for other variables.[6–8] Likewise, both intravascular access devices and HD have been identified as independent risk factors for developing complications of staphylococcal bacteraemia through haematogenous seeding, such as infective endocarditis, septic arthritis or vertebral osteomyelitis.[9]

Preventing infection-related deaths on HD therefore requires two things: first, maximizing the proportion of the population dialysing via AVF or AVG, as opposed to tunnelled or non-tunnelled central venous catheter (TCVC/NTCVC); and second, reducing the prevailing bacteraemia rate for all patients, irrespective of vascular access modality. Focusing here on the prevailing bacteraemia rate in TCVCs, the catheter has various components with distinct infection risks associated: the exit site, where organisms can breach the skin 'barrier'; and within the lumen, relatively protected from blood flow where microbial organisms exist either 'free', or in a biofilm, aggregated in a nutrient-rich matrix. Most antibiotics have poor activity against biofilms,[10] though taurolidine has been demonstrated to reduce biofilm formation through anti-lipopolysaccharide activity, and macrophage and neutrophil activation.[10,11] It has a broad spectrum of activity and has so far not been associated with resistance; manufacturers of TauroHep500 (taurolidine–citrate–heparin) claim infection rates can be reduced over 90%.[12]

The majority of studies on the effectiveness of antibiotic and antimicrobial-based catheter lock solutions have reported on small patient numbers. A 2008 meta-analysis by Bradshaw and Puntis concluded that there was insufficient evidence to support routine use of taurolidine catheter lock solution in long-term catheters.[3] In contrast, Solomon *et al.* endorse the use of taurolidine, and the addition of heparin to maintain catheter patency, reporting bacteraemia rates from any causative organism of 1.33 per 1000 HD days with taurolidine–citrate–heparin; 1.22 per 1000 HD days with taurolidine–citrate; and 3.25 per 1000 HD days with heparin alone ($P < 0.001$). A subgroup analysis of only *S. aureus* infections demonstrated rates of 0.50, 0.52 and 1.39 per 1000 days in the respective groups ($P = 0.002$), somewhat higher than our own measure of 0.21 *S. aureus* bacteraemias per 1000 days. Finally, they conclude that the need for thrombolysis is reduced by addition of heparin (hazard ratio, 0.2; 95% CI: 0.06, 0.5; $P < 0.001$).[4]

Our methodology was limited by its observational nature; whilst we had a natural control group with the AVF/AVG cohort in whom no significant change in the staphylococcal bacteraemia rate was demonstrated, we cannot exclude the possibility that there could be other unmeasured confounding factors that impacted on the staphylococcal bacteraemia rates in the TCVC group over the course of the observation period. We also acknowledge our inclusive definition of bacteraemia which simply required a single positive staphylococcal blood culture result to register as an event. We took the view that it is better to risk over-counting such events than to potentially miss clinically significant infections through the application of additional criteria such as a concurrent fever or laboratory measures of systemic inflammatory response. Previous work would support our definition with the increasing recognition that any staphylococcal growth on blood culture is significant and associated with heightened risk of clinical complications.[9] Furthermore, the subgroup analysis of coagulase negative, MSSA and MRSA staphylococci demonstrated similar effect size of taurolidine–citrate–heparin, supporting our ongoing integrated monitoring of all staphylococcal bacteraemic events to allow early identification of emerging infection-related issues.

A further feature to note is that the switch from heparin 5000 IU to taurolidine–citrate–heparin locks occurred in all prevalent catheters on 1 July 2012. The majority of prevalent TCVCs at that time would be expected to have some degree of biofilm, the underlying substrate behind many catheter-related bloodstream infections. The effect size of taurolidine–citrate–heparin locking on the bacteraemia rate may therefore have been blunted over the initial months after its introduction, as has been demonstrated elsewhere;[5] the full impact of its implementation on our HD population bacteraemia rate will only become apparent in newly inserted incident catheters without the presence of existing biofilm.

The UK Renal Association (UKRA) and European Renal Best Practice recommend that an antimicrobial agent should be included in catheter locks,[13, 14] and the UKRA state as an audit measure that the annual *S. aureus* bacteraemia rate should be <2.5 episodes per 100 HD patients (<0.07 events per 1000 HD-exposed days).[13] Although our overall *S. aureus* bacteraemia rates fell from 0.21 to 0.11 per 1000 HD days, we remain above this UKRA target; though as prevalent catheters with

pre-existing biofilm are replaced, this will hopefully be achieved.

With such ambitious national and international targets, continuing efforts must be made to reduce further the morbidity and mortality associated with infection in the HD population; in particular we must (i) ensure all eligible patients obtain functioning arteriovenous access through an AVF or AVG where possible; (ii) reduce prevailing bacteraemia rates for each of the HD access types through impeccable infection control measures and continued use of catheter lock solutions such as taurolidine–citrate–heparin and (iii) continue research into the consequences of bacteraemias on morbidity and mortality and on service provision, as well as research into novel preventative and treatment options. Critical to achieving both of these goals is the presence of a supportive information technology infrastructure that facilities the ongoing monitoring and auditing of these variables within the HD population in real time.

Conflict of interest: None declared.

References

1. Caskey F, Dawnay A, Farrington K, Feest T, Fogarty D, Inward C, *et al.* UK Renal Registry 2010 Report. 13th Annual Report of the Renal Association. *Nephron Clin Pract* 2011; **119(Suppl. 2)**:c135–40.
2. Yahav D, Rozen-Zvi B, Gafter-Gvili A, Leibovici L, Gafter U, Paul M. Antimicrobial lock solutions for the prevention of infections associated with intravascular catheters in patients undergoing hemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Clin Infect Dis* 2008; **47**:83–93.
3. Bradshaw JH, Puntis JWL. Taurolidine and catheter-related bloodstream infection: a systematic review of the literature. *J Pediatr Gastroenterol Nutr* 2008; **47**:179–86.
4. Solomon LR, Cheesbrough JS, Bhargava R, Mitsides N, Heap M, Green G, *et al.* Observational study of need for thrombolytic therapy and incidence of bacteremia using taurolidine-citrate-heparin, taurolidine-citrate and heparin catheter locks in patients treated with hemodialysis. *Semin Dial* 2012; **25**:233–8.
5. Dumichen MJ, Seeger K, Lode HN, Kuhl JS, Ebell W, Degenhardt P, *et al.* Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies. *J Hosp Infect* 2012; **80**:304–9.
6. Thomson PC, Stirling CM, Geddes CC, Morris ST, Mactier RA. Vascular access in haemodialysis patients: a modifiable risk factor for bacteraemia and death. *QJM* 2007; **100**:415–22.
7. Pisoni RL, Arrington CJ, Albert JM, Ethier J, Kimata N, Krishnan M, *et al.* Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. *Am J Kidney Dis* 2009; **53**:475–91.
8. Stevenson KB, Hannah EL, Lowder CA, Adcox MJ, Davidson RL, Mallea MC, *et al.* Epidemiology of hemodialysis vascular access infections from longitudinal infection surveillance data: predicting the impact of NKF-DOQI clinical practice guidelines for vascular access. *Am J kidney Dis* 2002; **39**:549–55.
9. Fowler VG, Justice A, Moore C, Benjamin DK, Woods CW, Campbell S, *et al.* Risk factors for hematogenous complications of intravascular catheter-associated *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2005; **40**:695–703.
10. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *Lancet* 2001; **358**:135–8.
11. Watson R, Redmond H, Mc Carthy J, Bouchier-Hayes D. Taurolidine, an antilipopolysaccharide agent, has immunoregulatory properties that are mediated by the amino acid taurine. *J Leukoc Biol* 1995; **58**:299–306.
12. TauroPharm GmbH. Antimicrobial Catheter Lock System To Provide Patency and Infection Control. 2012; http://www.tauropharm.de/GB/home.html (1 December 2013, date last accessed).
13. Fluck R, Kumwenda M. Clinical Practice Guidelines Vascular Access for Haemodialysis. UK Renal Association, 2011. www.renal.org/guidelines (10 January 2014, date last accessed).
14. Vanholder R, Canaud B, Fluck R, Jadoul M, Labriola L, Marti-Monros A, *et al.* Diagnosis, prevention and treatment of haemodialysis catheter-related bloodstream infections (CRBSI): a position statement of European Renal Best Practice (ERBP). *NDT Plus* 2010; **3**:234–46.