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Cathasept Line Lock and Microbial Colonization of Tunneled Hemodialysis Catheters: A Multicenter Randomized Controlled Trial

Authors:

1. Dr Muhammad Kanaa, MD (Corresponding author)

   Consultant Nephrologist

   Doncaster & Bassetlaw Hospitals NHS Foundation Trust

   Doncaster Royal Infirmary

   Armthorpe Road

   Doncaster, South Yorkshire

   DN2 5LT

   UK

   Tel: 0044-1302 366666 Ext: 4750

   Email: Muhammad.kanaa@dbh.nhs.uk

2. Dr Mark J Wright, MD

   Consultant Nephrologist

   Leeds Teaching Hospitals NHS Trust

3. Dr Habib Akbani, FRCP

   Consultant Nephrologist

   Bradford Teaching Hospitals NHS Foundation Trust

4. Dr Paul Laboi, MD

   Consultant Nephrologist

   York Teaching Hospital NHS Foundation Trust

5. Professor Sunil Bhandari, PhD

   Consultant Nephrologist/ Honorary Clinical Professor

   Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School

6. Professor Jonathan A T Sandoe, PhD

Consultant Microbiologist/ Associate Clinical Professor

Leeds Teaching Hospitals NHS Trust and University of Leeds

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Abstract

Background

Catheter-related bloodstream infections (CRBSI) are associated with increased morbidity and mortality in hemodialysis patients (HD). Cathasept (Tetra-sodium EDTA) solution has antimicrobial and anticoagulant activities.

Study Design

Multi-center, prospective, randomized, and controlled study.

Setting & Participants

117 maintenance HD patients with confirmed uncolonised tunneled hemodialysis catheters (t-HDC) were recruited from four hemodialysis centers.

Intervention

Patients were randomly assigned to remain on heparin 5000 units/ml locks (Heparin Group - HG) or to receive Cathasept 4% locks (Cathasept Group - CG) thrice weekly according to the catheter lumen volume and were followed up until their catheter was removed or for a maximum of 8 months.

Outcomes

Primary outcome was the incidence rate of clinically significant microbial colonization of t-HDC defined as through-catheter quantitative blood culture (TCQBC) yielding ≥1000 CFU/ml of bacteria or yeast. Secondary outcomes included CRBSI rate, catheter patency, and biomarkers of inflammation and anemia.

Measurements

Weekly TCQBC. hs-CRP was measured fortnightly, and FBC and Ferritin monthly.

Results

Catheter colonization rate was 0.14/1000 catheter-days in the CG and 1.08/1000 catheter-days in the HG [Incidence rate ratio (IRR) 0.13; 95% CI, 0.003- 0.94; p=0.02]. CRBSI rate was 0.28/1000 catheter-days in the CG and 0.68/1000 catheter

days in the HG [IRR 0.40; 95% CI, 0.08- 2.09; p=0.3]. The proportion of dialysis sessions with achieved prescribed blood flow rate was significantly lower in the CG (66.8% vs 75.3%; p<0.001), with more patients required thrombolytic locks or infusion to maintain catheter patency (22 vs 9; p=0.01). On average, hs-CRP was 11.6 (SE ±5.3) mg/l lower for patients in the HG (p=0.03). Anemia markers were comparable in both groups.

Limitations

The study was underpowered to assess the effect on CRBSI, was terminated early due to slow recruitment, and was not double-blinded.

Conclusion

Cathasept significantly reduced t-HDC colonization but the reduction in CRBSI was not statistically significant, and it was associated with more thrombotic complications. Its safety profile was comparable to heparin lock solution.

Introduction

Infection is the second most common cause of death in the dialysis population in the UK and the western world, accounting for 18%of deaths in the prevalent dialysis population in the UK alone[1]. Patients receiving hemodialysis (HD) have a higher incidence of bloodstream infections (BSI) compared to patients on peritoneal dialysis (PD) [2-4], with central venous catheters (CVCs) being a major and independent risk factor for developing BSI [3, 5-8]. Although discouraged as a permanent form of vascular access, the use of tunneled HD catheters (t-HDC) has remained steady and even increased in most countries participating in the Dialysis Outcomes and Practice Patterns (DOPPS) study [9-11]. BSI are associated with a significant cardiovascular morbidity [4] and intra-luminal colonization of catheters which usually precedes BSI[12] is reported to cause subclinical inflammation in the HD population [3, 13-17] contributing to anemia [18-20], malnutrition and atherosclerosis [3, 21-23]. Heparin, which is commonly used to maintain catheter patency, has been implicated in the growth of biofilms on abiotic surfaces [24, 25] and is associated with an increased risk of bleeding, episodes of hyperkalemia, hair loss and heparin-induced thrombocytopenia [26, 27]. Alternative catheter lock solutions have been used to prevent intravascular catheter related bloodstream infection (CRBSI) and avoid complications associated with heparin. Several meta-analyses of randomized controlled studies (RCTs) have demonstrated significant reduction in CRBSI rates when various antimicrobial lock solutions were used to prevent CRBSI in HD patients, but there was a significant heterogeneity between the studies [28-34]. Concerns remain over the risk of bacterial resistance developing when antibiotic solutions are used and the potential side effects of some antibiotics [35]. One randomized controlled study in 110 HD patients showed that taurolidine (1.35%)/citrate lock (4%) solution did not reduce bacteremia rates from

any cause with t-HDC [36]. A randomized trial of a novel catheter lock containing sodium citrate 7%, methylene blue 0.15%, methylparaben 0.15%, and propylparabe 0.015%, showed a significant reduction in CRBSI compared to heparin locks[37].

Cathasept is composed of 4% tetra-sodium ethylene diamine tetra-acetic acid (EDTA) and has both anticoagulant [38, 39] and antimicrobial effects [40] and is therefore a potentially useful line lock solution.

Methods

Study Design

Multi-center, prospective, randomized (1:1), controlled, part-blinded (laboratory personnel were blinded), comparative study. The study was approved by the Leeds (West) Medical Research Ethics Committee, UK (Reference: 05/Q1205/241) and was registered and regulated by the Medicines and Healthcare Products Regulatory Agency (MHRA, UK; Reference: CI/2006/0003).

The study was conducted at four hemodialysis centers in the Yorkshire region in the UK between August 2006 and October 2008.

Study Participants

Eligible participants were adult HD patients aged 18 to 85 years who met all inclusion and had no exclusion criteria.

Inclusion criteria

Participants had to be able to provide informed consent, with a history of established renal failure (ERF) and were starting or undergoing hemodialysis using a t-HDC in an internal jugular or subclavian vein.

Exclusion criteria

- Any medical, social or psychological condition that would compromise participation and follow-up in study.
- Females who were pregnant or lactating.
- Patients who had a tunneled catheter with an expected duration of placement or use of less than 60 days.
- Patients enrolled in another clinical study, or had participated in the study.
- Life expectancy of less than three months.
- Patients with existing tunneled central venous catheters who had positive blood cultures or received antimicrobial therapy, including antibiotic lock solution and/or antimicrobial catheters, for documented or suspected CRBSI within 14 days prior to enrolment.
- Evidence of systemic infection or catheter exit site infection at the time of enrolment.
- Patients with colonized catheters (screening quantitative through catheter blood cultures (QTCBC) yielding >20 cfu/ml bacteria or yeasts).
- Patients whose catheters demonstrated signs of dysfunction in two or more dialysis sessions during the last two weeks prior to enrolment. These signs were defined as:

  a) Blood flow rate < 200 ml/min, or prescribed blood flow rate was not achieved, **OR**

  b) Elevated venous pressure (>250 mmHg), or negative arterial pressure of greater than (-250 mmHg),

  OR

  c) Line reversal (using the arterial port to aspirate and the venous port to return blood)

- A known sensitivity to heparin, disodium EDTA, or natural rubber latex.

Outcomes

Primary outcome:

Incidence rate of clinically significant microbial colonization of t-HDC per 1000 catheter-days, defined as TCQBC yielding ≥1000 CFU/ml of bacteria or yeast.

Secondary outcomes:

Incidence rate of CRBSI; number of dialysis sessions where the prescribed blood flow was achieved; incidence rate of interventions to improve catheter patency including intra-catheter lock or infusion of thrombolytic agents; and difference between both groups for hemoglobin, hs-CRP, serum ferritin, Kt/V, and iron and erythropoietin-stimulating requirements. Kt/V is a measurement used to quantify dialysis treatment adequacy (K is the dialyzer clearance of urea, t is the time spent on dialysis that day and not the prescribed time on dialysis, and V is the volume of distribution of urea which is approximately equal to total body water). The Kt/V was calculated monthly using the following formula from the national Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines:

$Kt/V = -Ln(R-0.008t) + (4 – 3.5R) (\Delta \text{ body weight / end dialysis body weight})$

where R is the post-dialysis urea to pre-dialysis urea ratio, and Δ denotes the change in body weight before and after dialysis.

Interventions

Eligible patients underwent a through-catheter quantitative blood culture (TCQBC) to determine the colonization status of their catheter. After discarding the existing lock solution, 1 ml of blood was obtained from each catheter lumen and cultured for bacteria and yeast as described below. Clinically significant colonization was defined

as blood culture from one or both lumens yielding ≥1000 colony forming units (CFU)/mL bacteria or yeasts. Patients with TCQBC yielded ≤20 CFU/ml were randomized to either continue heparin lock solution 5000 units/ml (Control Group) or to receive Cathasept 4% (Intervention Group). The amount of lock solution was determined by the catheter lumen volume. Participants were followed up until their catheter was removed or for eight months if the catheter was not removed.

Measurements

Baseline characteristics:

The following demographic, clinical and laboratory data were collected: age**,** gender**,** height**,** weight**,** Davies comorbidity score [41]**,** drug history (including erythropoietin stimulating agents and iron supplements)**,** allergies, cause of ERF**,** start of hemodialysis treatment**,** site of central venous catheter insertion**,** type and brand of catheter used**,** date of catheter insertion**,** current prescribed blood flow rate in ml/minute, dialysis adequacy as measured using Kt/V, Full blood count (FBC), high sensitive C-reactive protein (hs-CRP), and albumin.

Study Data:

All episodes of CRBSI; episodes of catheter exit-site infections; maximum blood flow rate achieved during every dialysis session; catheter interventions aimed at improving blood flow rate (for example, treatment with thrombolytic agents, flushing with 0.9% saline, reversal of lumens, or catheter replacement); monthly Kt/V, and the monthly iron and erythropoietin requirements.

Treatment Evaluations

Clinical assessment

At the start of each dialysis session tympanic body temperature was taken and patients were screened for symptoms and signs of infection by the dialysis staff. Patients who

had clinical signs of a possible exit site infection, or presented with (or developed) fever ≥ 38°C during dialysis, or had rigors, were assessed by their medical teams for a source of infection and appropriate investigations including blood culture, exit site swab, urine culture and chest x-ray if clinically indicated were performed.

Laboratory assessments

Catheter colonization was assessed by weekly TCQBC from each catheter lumen. hs-CRP was performed every two weeks to check for sub-clinical inflammation. Monthly blood samples were obtained for FBC and serum ferritin levels.

Catheter care procedure

Catheters had been inserted by the nephrology team responsible for the patient's care at each participating center. The Patient's skin was cleaned with 2% chlorhexidine gluconate and 70% isopropyl alcohol solution in all centers. Heparin 5000 units/ml had been instilled into each catheter lumen, according to the lumen volume, after catheter insertion and after each dialysis session until enrolment onto the study. The exit site was covered with a transparent polyurethane dressing and was inspected for signs of infection and loss of dressing integrity at each dialysis session. The exit site was cleaned with sterile 0.9% saline followed by using 2% chlorhexidine gluconate and 70% isopropyl alcohol solution, and dressings were changed every week unless inspection revealed loss of the dressing integrity, which resulted in an earlier dressing change. Catheter hubs were cleaned with 2% chlorhexidine gluconate and 70% isopropyl alcohol solution.

Microbiology Methods

TCQBC for the diagnosis of microbial colonization

TCQBC has been previously used for detecting microbial colonization of central venous catheters [42] , and for the diagnosis of CRBSI without catheter removal [43-45].

Once a week, at the start of a dialysis session, the lock solution in each catheter lumen (arterial and venous) was aspirated and discarded using aseptic technique. Subsequently, 1ml of blood was aspirated from each catheter lumen, collected into a 1.3ml pediatric heparin tube (UK-Greiner Bio-one Ltd, Ref. LH/1.3 Greiner), and sent for quantitative culture of bacteria and yeasts as follows. Three 50 microliter samples of blood were plated on three separate pre-poured Cystine-Lactose-Electrolyte-Deficient (CLED) agar plates (E&O Laboratories Ltd, UK) using the Whitley Automated Spiral Plater (WASP) (Don Whitley Scientific Ltd, UK) to make a 3-fold log dilution across the plate. After overnight (18-24 hrs) incubation at 37°C, each plate was read using the ProtoCol counter (Don Whitley Scientific Ltd, UK) to calculate the colony counts per ml. The average colony count of the three samples was calculated and used to determine the catheter colonization status. Catheters with an average colony count of ≥ 1000 CFU/ml from one or both lumens on at least one occasion were considered to have reached clinically significant colonization. Standard microbiological methods were applied to identify the cultured organism.

Diagnosis of intravascular catheter-related bloodstream infection (CRBSI)

Patients with clinical signs suggestive of CRBSI had 10ml of blood obtained from each catheter lumen and, where possible, from a peripheral vein, and all samples were split equally between the anaerobic and aerobic blood collection bottles. Qualitative blood culture with differential time to positivity (DTP) was performed according to the local microbiology protocol[46, 47]. The criteria outlined by the Centres for Disease Control and Prevention (http://www.cdc.gov/) for the definite diagnosis of CRBSI were used. "Definite" diagnosis of CRBSI was made if a growth of microbes from blood aspirated through the catheter hub was detected at least 2 hours before it was detected from a blood sample obtained from a peripheral vein; or if the same microbe was cultured from a peripheral blood culture and the catheter tip if it was removed

(≥15 CFU by semi-quantitative, roll-plate culture); or if the same microbe was cultured from a peripheral blood culture and exit site swab when signs of exit site infection were present [48-50]. Where the above criteria could not be satisfied, the diagnosis of CRBSI was regarded as "Probable" when: 1) pyrexia resolved after removal of the catheter and appropriate antibiotic treatment AND blood cultures or catheter tip cultures were positive, but microbiological criteria for definite CRBSI were not met; or 2) after appropriate antibiotic treatment when only blood cultures were positive in a symptomatic patient with no other apparent source of infection. Episodes were regarded as "Possible" CRBSI when pyrexia resolved after removal of catheter with or without antibiotic treatment in the absence of laboratory confirmation of bloodstream infection in a symptomatic patient with no other apparent source of infection[51, 52].

Statistical Methods

Sample size

A previous eight month audit by the Yorkshire Research Group who performed fortnightly QTCBC on HD patients with tunneled catheters estimated the prevalence of catheter colonization to be of the order of 25% [53]. It was hypothesized that a reduction in colonization rate of 75% would be clinically significant. A two-tailed chi-squared test with a 0.05 significance level and a power of 80% would require two groups of 70 catheters (140 total), allowing 10% for dropouts.

Randomization

Randomization was performed using a random number table and blocking factor of 10 in a 1:1 ratio. Treatment allocation was concealed in a sealed opaque envelope.

Blinding

Only microbiology laboratory personnel were blinded to the study lock solution used. Medical teams treating study subjects were not informed of the randomized lock solution unless it was specifically requested for patient care purposes.

Analysis

Baseline characteristics were summarized with descriptive statistics using SPSS version 14. Normally distributed data were reported as means (± SD) and non-normally distributed data as medians and range. Categorical data were compared using Chi-square test or Fisher's exact test. Numerical data were compared using Mann-Whitney U for non-parametric data and independent samples t test for parametric data. To compare incidence rates in the HG and CG, we calculated the incidence rate ratio (IRR) and 95% Confidence Intervals (CI)[54]. Time to first colonization was assessed by Kaplan-Meier curves with the log-rank test used for comparison between groups. Odds ratio was used to compare catheter blood flow rates. All other secondary outcomes were assessed for change over time by the repeated measures (random-effects) regression model using Stata 9 software and were expressed as means ± SE. All analyses were performed on an intention-to-treat basis.

Results

A total of 308 patients with t-HDC were assessed for eligibility to participate in the study, of whom, 117 patients were randomized to either continue heparin lock solution [Heparin Group (HG); 58 patients] or Cathasept lock solution [Cathasept Group (CG); 59 patients). Two patients randomized into the HG died before they received the first dose on the study and therefore were excluded from the intention-to-treat analysis. Enrolment and allocation procedures and reasons for withdrawal from study are outlined in figure 1. The study was terminated early by the sponsors due to slow recruitment which was attributed to a regional improvement in the vascular

access service and consequent reduction in the number of patients receiving HD by t-HDC.

There was a total of 14693 catheter days (7306 in the CG and 7387 in the HG,). The median number of catheter days was 91 (7- 248 days) in the CG and 117 (range 1-249) in the HG (p=0.5). Patients and catheter baseline characteristics are summarized in table 1.

Primary outcome

Clinically significant catheter colonization occurred in nine catheters (1 in the CG and 8 in the HG and). The catheter colonization rate was statistically significantly different in the two study groups: 0.14 per 1000 catheter-days in the CG and 1.08 per 1000 catheter-days in the HG (IRR 0.13; 95% CI, 0.003-0.94; p=0.02). Time to colonization (catheter survival without microbial colonization) was also statistically significantly longer in the CG (Figure 2).

Five catheters became colonized with coagulase negative staphylococci and four catheters were colonized with gram-negative bacteria [one grew multiple organisms (Serratia liquefaciens, Pseudomonas aeruginosa, Pseudomonas luteola, and Serratia marcescens); one was colonized with an Acinetobacter species; one was colonized with a coliform and one with a Pseudomonas species.].

Secondary outcomes

CRBSI

Four episodes (1 in the CG and 3 in the HG) met the criteria for “definite” CRBSI, and further three episodes (1 in the CG and 2 in the HG) met the criteria for “probable” CRBSI. Incidence rates and IRR for CRSI are reported in table 2.

Responsible organisms were methicillin-sensitive Staphylococcus aureus (3), coagulase negative staphylococci (2), methicillin-resistant Staphylococcus aureus (1) and Proteus species (1).

Weekly TCQBC were positive in only one case of CRBSI in the heparin group. Two cases of CRBSI had a positive culture for the same organism by endoluminal brushing and blood culture, one of which also showed endoluminal bacteria by SEM imaging (Results reported elsewhere) [55].

Catheter patency

Data on blood flow rate were available for 114 patients (59 in the CG and 55 in the HG). Prescribed blood flow rate was achieved in 1861 out of 2788 (66.8%) dialysis sessions in the CG compared to 2178 out of 2893 (75.3%) of dialysis sessions in the HG (odds ratio 1.94; 95% CI, 1.03 to 3.6; p=0.04), indicating that blood flow rate was almost twice as likely to be achieved in the HG.

The number of patients who required any intervention to improve catheter patency was not statistically different in the two groups (CG, 44 patients vs HG, 34; p=0.2). However, the number of patients who received thrombolytic locks or infusions was significantly higher in the CG (22 vs 9 patients; p=0.01).

Interventions used to improve catheter patency are summarized in table 3.

Laboratory data

Monthly hemoglobin remained stable during the study in both groups and was 0.4 (SE ± 0.23) g/dl higher in the HG but this was not statistically significant (p=0.09). Ferritin level was on average 87.8 (SE±79.8) ng/ml lower in the HG but with no statistically significant difference (p= 0.3). Fortnightly hs-CRP was significantly lower in the HG. On average, hs-CRP was 11.6 (SE ±5.3) mg/l lower for patients in

the HG (p=0.03). Monthly Kt/V measurements were similar in both groups with patients in the HG achieving slightly higher Kt/V values at 0.08 (SE±0.07) per month (p=0.3).

Darbepoetin and iron saccharate dose

There was no significant difference in the monthly requirements of darbepoetin alfa or iron saccharate between both groups. Patients in the CG received on average 16.2 (SE±21.2) mcg of darbepoetin alfa per month more than patients in the HG (p=0.4). Monthly iron requirements were on average 27 (SE±34.7) mg lower in the CG (p=0.4).

Adverse/Serious adverse events

The number of reported adverse events was 224 in the HG and 233 in the CG (Independent sample t-test; p=0.9). The number of reported serious adverse events was 79 in the HG and 66 in the CG (Independent sample t-test; p=0.9) and the number of reported serious adverse device effects was four in the HG and six in the CG (Independent sample t-test; p=0.8). There were no safety concerns and in particular there were no episodes of hypocalcaemia.

Discussion

In this randomized controlled study, Cathasept reduced clinically significant microbial colonization of t-HDC by 87% (p=0.02) compared to heparin. Although this reduction was statistically significant, it should be pointed out that the 95% confidence interval was wide (0.003- 0.94) indicating reduced precision when estimating the risk reduction. Despite fewer episodes of CRBSI in the Cathasept group, this was not statistically significant. This may represent a type 2 error as the sample size may not have been large enough to show a significant difference in CRBSI rates. The catheter

colonization rate in our institution before 2006, which was used to calculate the sample size, was much higher than that observed in this study (25% vs 7.8%). The observed reduction in CRBSI rates may have been the result of the "saving lives" campaign and other UK-wide to reduce methicillin-resistant Staphylococcus aureus (MRSA) bacteremia and healthcare associated infection.

Cathasept was not as effective as heparin in maintaining catheter patency. Prescribed blood flow rate was more likely to be achieved in the HG than in the CG group (Odds ratio 1.94; p=0.04) and the number of patients who required thrombolytic locks or infusions was also significantly lower in the HG group (9 vs 22 patients; p=0.01). However, the number of catheters removed because of clotting or luminal occlusion was similar in both groups (3 in each group). This suggests that catheter dysfunction may have been due to extra-luminal formation of fibrin sheaths or non-occlusive clots, rather than luminal problems. Due to a significant leakage of the instilled lock solution over time, as evident from experimental work and the well documented systemic anticoagulation effect of heparin locks [27, 56-58], it is possible that catheters locked with heparin are less likely to develop extra-luminal occlusion. This might explain the differences seen between catheters locked with Cathasept and heparin in this study, but confirmatory work would be required.

High-sensitive CRP was significantly higher in the CG despite having lower catheter colonization rate and this finding might be explained by the higher number of infections unrelated to the catheter lumen occurring in the CG. There were 68 infective complications (including Exit site infection, respiratory infections, and others) in the CG, and 48 infections in the HG, with corresponding incidence rates of 9.3 and 6.5 episodes/1000 patient-days (IRR, 1.43; 95% CI, 0.99- 2.07; p=0.06).

Although it did not reach statistical significance, this difference in infection events might be high enough to account for CRP differences.

Haemoglobin level, serum ferritin concentration, and Darbepoetin and iron requirements were similar for both groups despite the differences in hs-CRP.

There are several limitations to this study. Firstly, it was stopped earlier than planned (as explained earlier) with 117 patients recruited, when the recruitment target was 140. This did not impact on the primary outcome of this study, which reached statistical significance in favor of the Cathasept lock solution. Secondly, the study was not double-blinded which could have introduced bias. Double blinding was not possible because Cathasept could not be manufactured in glass vials like heparin due to its high pH at around 10.5. Thirdly, the study was not powered to show a significant effect on CRBSI rate or other secondary outcomes as discussed above. The incidence of "Definite" and "Probable" CRBSI was 8.9% in the HG and 3.4% in the CG. A sample size of 300 patients in each group would be required to detect a significant difference with a 0.05 significance and a power of 80%.

This study has confirmed the effectiveness of Cathasept in reducing microbial colonization of t-HDC and would be applicable to other hemodialysis populations as well as other CVC applications in non-dialysis patients. However, a larger study with enough power to assess catheter dysfunction and CRBSI rate is recommended.

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Contributions: research idea and study design: MK, MJW, PL, SB, JATS; data acquisition: MJW, SB, HA, PL; data analysis: MK; results interpretation: MK, MJW, JATS; supervision or mentorship: MJW, JATS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. MK takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and registered) have been explained.

References

1. Ansell D, Roderick P, Hodsman A, Ford D, Steenkamp R, Tomson C. Survival and causes of death of UK adult patients on Renal Replacement Therapy in 2007: national and centre-specific analyses: UK Renal Registry, 2008 report, Chapter 7; 2008.

2. Aslam N, Bernardini J, Fried L, Burr R, Piraino B. Comparison of Infectious Complications between Incident Hemodialysis and Peritoneal Dialysis Patients. Clin J Am Soc Nephrol. November 1, 2006 2006;1(6):1226-1233.

3. Ishani A, Collins AJ, Herzog CA, Foley RN. Septicemia, access and cardiovascular disease in dialysis patients: The USRDS Wave 2 Study. Kidney International. Jul 2005;68(1):311-318.

4. Foley RN, Guo H, Snyder JJ, Gilbertson DT, Collins AJ. Septicemia in the United States Dialysis Population, 1991 to 1999. J Am Soc Nephrol. April 1, 2004 2004;15(4):1038-1045.

5. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. Journal of the American Society of Nephrology. May 1998;9(5):869-876.

6. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W. Septicemia in dialysis patients: Incidence, risk factors, and prognosis. Kidney International. Mar 1999;55(3):1081-1090.

7. Tokars JI, Miller ER, Stein G. New national surveillance system for hemodialysis-associated infections: Initial results. American Journal of Infection Control. Aug 2002;30(5):288-295.

8. Astor BC, Eustace JA, Powe NR, et al. Type of vascular access and survival among incident hemodialysis patients: The choices for healthy outcomes in caring for ESRD (CHOICE) study. Journal of the American Society of Nephrology. May 2005;16(5):1449-1455.

9. Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: Results from the DOPPS. Kidney International. Jan 2002;61(1):305-316.

10. Rayner HC, Besarab A, Brown WW, Disney A, Saito A, Pisoni RL. Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): Performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines. American Journal of Kidney Diseases. Nov 2004;44(5):S22-S26.

11. Ethier J, Mendelssohn DC, Elder SJ, et al. Vascular access use and outcomes: an international perspective from the dialysis outcomes and practice patterns study. Nephrology Dialysis Transplantation. Oct 2008;23(10):3219-3226.

12. Sherertz RJ. Pathogenesis of Vascular Catheter Infection. In: Waldvogel FA, Bisno AL, eds. Infections Associated with Indwelling Medical Devices. Third ed. Washington, D. C.: ASM Press; 2000:111- 125.

13. Costerton JW, Stewart, P.S., Greenberg, E.P. Bacterial biofilms: A common cause of persistent infections. Science. 1999(284):1318- 1322.

14. Cappelli G, Ballestri M, Perrone S, Ciuffreda A, Inguaggiato P, Albertazzi A. Biofilms invade nephrology: Effects in hemodialysis. Blood Purification. 2000;18(3):224-230.

15. Schindler R. Causes and therapy of microinflammation in renal failure. Nephrol. Dial. Transplant. August 1, 2004 2004;19(suppl_5):v34-40.

16. Tsirpanlis G, Chatzipanagiotou S, Nicolaou C. Microinflammation versus inflammation in chronic renal failure patients. Kidney International. Nov 2004;66(5):2093-2094.

17. Cappelli G, Tetta C, Canaud B. Is biofilm a cause of silent chronic inflammation in haemodialysis patients? A fascinating working hypothesis. Nephrol. Dial. Transplant. February 1, 2005 2005;20(2):266-270.

18. Macdougall IC, Cooper AC. Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines. Nephrology Dialysis Transplantation. 2002;17:39-43.

19. Stenvinkel P, Barany P. Anaemia, rHuEPO resistance, and cardiovascular disease in end-stage renal failure: links to inflammation and oxidative stress. Nephrology Dialysis Transplantation. 2002;17:32-37.

20. Horl WH, Vanrenterghem Y. Optimal Treatment of Renal Anaemia (OPTA): improving the efficacy and efficiency of renal anaemia therapy in haemodialysis patients receiving intravenous epoetin. Nephrology Dialysis Transplantation. May 2005;20:III25-III32.

21. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: Sources, consequences, and therapy. Seminars in Dialysis. Sep-Oct 2002;15(5):329-337.

22. Phanish MK, Marcora SM, Lemmey AB. Malnutrition, chronic inflammation and atherosclerosis in dialysis patients. Nephrology Dialysis Transplantation. Feb 2003;18(2):446-446.

23. Wanner C, Metzger T. C-reactive protein a marker for all-cause and cardiovascular mortality in haemodialysis patients. Nephrology Dialysis Transplantation. 2002;17:29-32.

24. Shanks RMQ, Donegan NP, Graber ML, et al. Heparin stimulates Staphylococcus aureus biofilm formation. Infection and Immunity. Aug 2005;73(8):4596-4606.

25. Shanks RMQ, Sargent JL, Martinez RM, Graber ML, O'Toole GA. Catheter lock solutions influence staphylococcal biofilm formation on abiotic surfaces. Nephrol. Dial. Transplant. August 1, 2006 2006;21(8):2247-2255.

26. Karaaslan H, Peyronnet P, Benevent D, Lagarde C, Rince M, Leroux-Robert C. Risk of heparin lock-related bleeding when using indwelling venous catheter in haemodialysis. Nephrol. Dial. Transplant. October 1, 2001 2001;16(10):2072-2074.

27. Agharazii M, Plamondon I, Lebel M, Douville P, Desmeules S. Estimation of heparin leak into the systemic circulation after central venous catheter heparin lock. Nephrol. Dial. Transplant. June 1, 2005 2005;20(6):1238-1240.

28. James MT, Conley J, Tonelli M, et al. Meta-analysis: Antibiotics for prophylaxis against hemodialysis catheter-related infections. Annals of Internal Medicine. 2008;148(8):596-605.

29. Jaffer Y, Selby NM, Taal MW, Fluck RJ, McIntyre CW. A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. American Journal of Kidney Diseases. Feb 2008;51(2):233-241.

30. Labriola L, Crott R, Jadoul M. Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: a meta-analysis of prospective randomized trials. Nephrol. Dial. Transplant. May 1, 2008 2008;23(5):1666-1672.

31. 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. Clinical Infectious Diseases. 2008;47(1):83-93.

32. Rabindranath KS, Bansal T, Adams J, et al. Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections. Nephrol. Dial. Transplant. December 1, 2009 2009;24(12):3763-3774.

33. Snaterse M, Rüger W, Scholte op Reimer WJM, Lucas C. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. Journal of Hospital Infection. 2010;75(1):1-11.

34. Zhao Y, Li Z, Zhang L, et al. Citrate Versus Heparin Lock for Hemodialysis Catheters: A Systematic Review and Meta-analysis of Randomized Controlled Trials. American Journal of Kidney Diseases. 2015/03/04 2014;63(3):479-490.

35. Landry DL, Braden GL, Gobeille SL, Haessler SD, Vaidya CK, Sweet SJ. Emergence of Gentamicin-Resistant Bacteremia in Hemodialysis Patients Receiving Gentamicin Lock Catheter Prophylaxis. Clinical Journal of the American Society of Nephrology. Oct 2010;5(10):1799-1804.

36. Solomon LR, Cheesbrough JS, Ebah L, et al. A Randomized Double-Blind Controlled Trial of Taurolidine-Citrate Catheter Locks for the Prevention of Bacteremia in Patients Treated With Hemodialysis. American Journal of Kidney Diseases. 2010;55(6):1060-1068.

37. Maki DG, Ash SR, Winger RK, Lavin P, for the ATI. A novel antimicrobial and antithrombotic lock solution for hemodialysis catheters: A multi-center, controlled, randomized trial*. Critical Care Medicine. 2011;39(4):613-620.

38. Zucker M, B., . Divalent cations in blood clotting. In: Seve M, J., Johnson, L.,A., ed. Metal-Binding in Medicine. Philadelphia: PA: J B Lippincott; 1960:137-142.

39. Godal H, C., Brosstad, F., Kierulf, P. Influence of Na2-EDTA and some compounds used for dissolution of fibrin clots on the physiochemical properties of fibrinogen and fibrin. Biblthca Haemat. 1978;44:151- 155.

40. Kite P, Eastwood K, Sugden S, Percival SL. Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro. Journal of Clinical Microbiology. Jul 2004;42(7):3073-3076.

41. Davies SJ, Phillips L, Naish PF, Russell GI. Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival. Nephrol. Dial. Transplant. June 1, 2002 2002;17(6):1085-1092.

42. Kite P, Eastwood K, Sugden S, et al. Prevalence of Intravascular Catheter Colonisation in Haemodialysis Patients by Serial In Vivo Luminal Blood Sampling.

Interscience Conference of Antimicrobial Agents and Chemotherapy. San Diego, California: National Library of Medicine; 2002.

43. Kite P, Dobbins BM, Wilcox MH, McMahon MJ. Rapid diagnosis of central-venous-catheter-related bloodstream infection without catheter removal. Lancet. 10/30/ 1999;354(9189):1504-1507.

44. Catton J, Wood J., Dobbins, B. M., Burke, D., Kite, P., Eastwood, K., Sugden, S.A., Wilcox, M.H. & McMahon, M.J. Quantitative culture of through line blood is an accurate method for the diagnosis of central venous catheter-related-bloodstream-infection(CRBSI) without catheter removal. Nutrition in Clinical Practice. 2002;17:71.

45. Catton JA, Dobbins BM, Kite P, et al. In situ diagnosis of intravascular catheter-related bloodstream infection: a comparison of quantitative culture, differential time to positivity, and endoluminal brushing. Crit Care Med. 04 2005;33(4):787-791.

46. Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential Time to Positivity: A Useful Method for Diagnosing Catheter-Related Bloodstream Infections. Annals of Internal Medicine. 01/06/ 2004;140(1):18-25.

47. Safdar N, Fine JP, Maki DG. Meta-Analysis: Methods for Diagnosing Intravascular Device-Related Bloodstream Infection. Annals of Internal Medicine. 03/15/ 2005;142(6):451-466.

48. Pearson ML. Guideline for Prevention of Intravascular-Device-Related Infections. Infection Control and Hospital Epidemiology. 1996;17(7):438-473.

49. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the Prevention of Intravascular Catheter-related Infections. Morbidity and Mortality Weekly Report. Centers for Disease Control and Prevention. http://www.cdc.gov/mmwr/PDF/rr/rr5110.pdf. Vol 51 (RR-10); 2002:1-29.

50. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of Intra-vascular catheter-related infections. Clinical Infectious Diseases. 2001 2001;32:1249- 1272.

51. Little MA, O'Riordan A, Lucey B, et al. A prospective study of complications associated with cuffed, tunnelled haemodialysis catheters. Nephrology Dialysis Transplantation. Nov 2001;16(11):2194-2200.

52. Dogra GK, Herson H, Hutchison B, et al. Prevention of tunneled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: a randomized controlled study. Journal of the American Society of Nephrology. Aug 2002;13(8):2133-2139.

53. Wheatley RE, Higginbotham, M., Jones, C., Laboi, P.,Taylor, G.,Than, N. &Turney,J. An audit on the use of chlorhexidine gluconate in the prevention of dialysis catheter colonisation and infection. Paper presented at: British Renal Society Conference 20- 22 May, 2004; Harrogate, UK, May 20-22.

54. Kirkwood B, R. & Sterne, J.,A.,C. Comparing rates. Essential Medical Statistics. Massachusetts, USA: Blackwell Science; 2003:240-248.

55. Kanaa M, Wright MJ, Sandoe JAT. Examination of tunnelled haemodialysis catheters using scanning electron microscopy. Clinical Microbiology and Infection. Jun 2010;16(6):780-786.

56. Besarab A, Pandey R. Catheter Management in Hemodialysis Patients: Delivering Adequate Flow. Clinical Journal of the American Society of Nephrology. January 1, 2011 2011;6(1):227-234.

57. Yevzlin AS, Sanchez RJ, Hiatt JG, et al. Concentrated Heparin Lock Is Associated with Major Bleeding Complications after Tunneled Hemodialysis Catheter Placement. Seminars in Dialysis. 2007;20(4):351-354.

58. Pepper RJ, Gale DP, Wajed J, et al. Inadvertent postdialysis anticoagulation due to heparin line locks. Hemodialysis International. 2007;11(4):430-434.

Table 1: Baseline characteristics
(+: Davies Co-morbidity score: grade 0 (No Co-morbidity), grade 1 (1-2), grade 2 (≥3)

	Heparin n=58	**Cathasept** n= 59	**p value**
Gender			
Male (%)	38 (65.5%)	44 (74.6%)	0.3
Female (%)	20 (34.4%)	15 (25.4%)	
Age (Years)			
Median (Range)	60 (21-84)	61 (24-83)	0.7
Duration on HD (month) Median (Range)	4 (0- 102)	4 (1- 155)	0.7
Catheter type			0.2
Tesio ® (%)	48 (82.8%)	53 (89.8%)	
Arrow ® (%)	7 (12.1%)	5 (8.5%)	
Others (%)	3 (5.1%)	1 (1.7%)	
Number of catheter days prior to randomization			
Median (Range)	54 (5- 1857)	44 (5- 1795)	0.5
Number of incident catheters (%) [In situ for ≤30 days]	16 (27.6%)	13 (22%)	0.5
Number of prevalent catheters (%) [In situ for >30 days]	42 (72.4%)	46 (78%)	0.5
Co-morbidity grade +			0.9
0 (Low risk)	13 (22.4%)	13 (22%)	
1 (Medium risk)	32 (55.2%)	30 (50.9%)	
2 (High risk)	13 (22.4%)	16 (27.1%)	

Table 2: Incidence rates for "definite" and "probable" catheter-related blood stream infections (CRBSI) in the Cathasept Group (CG) and Heparin Group (HG) [N, number of episodes; IR, Incidence Rate/1000 catheter-days; IRR, Incidence Rate Ratio (HG is the reference group)]

CRBSI	Cathasept		Heparin			
	N	IR	N	IR	**IRR** (95% CI)	**P value**
Definite	1	0.14	3	0.41	0.34 (0.035- 3.24)	0.3
Probable	1	0.14	2	0.27	0.51 (0.046- 5.58)	0.6
Total	2	0.28	5	0.68	0.40 (0.078- 2.09)	0.3

Table 3: Number of interventions required to improve catheter patency [N, number of episodes; IR, Incidence Rate/1000 catheter-days; IRR, Incidence Rate Ratio (HG is the reference group)]

(+: Saline flushes and reversal of dialysis circuit connection to the catheter)

	N	IR	IRR	p value
Thrombolytic locks				
Cathasept	64	8.76		
Heparin	23	3.11	2.8 (1.7- 4.7)	<0.001
Thrombolytic infusions				
Cathasept	16	2.19		
Heparin	5	0.68	3.2 (1.13- 11.29)	0.02
Other [+]				
Cathasept	495	67.7		
Heparin	279	37.8	1.79 (1.54- 2.08)	<0.001

Figure 1: Screening, randomization, and follow-up flow chart (ITT; Intention-to-treat)

Figure 2: Survival (Kaplan-Meier) plot showing the colonization-free catheter survival for the HG (dashed line) and CG (solid line) [Log rank, p= 0.02]