24. Richardson CJ, Magee EAM, Cummings JH. A new method for the determination of sulphide in gastrointestinal contents and whole blood by microdistillation and ion chromatography. *Clin Chim Acta* 2000; 293: 115–125
25. Stenvinkel P, Carrero JJ, Axelsson J *et al*. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? *Clin J Am Soc Nephrol* 2008; 3: 505–521
26. Ingrosso D, Cimmino A, Perna AF *et al*. Folate treatment and unbalanced methylation and changes of allelic expression induced by hyperhomocysteinaemia in patients with uraemia. *Lancet* 2003; 361: 1693–1699
27. Perna AF, Ingrosso D, De Santo NG *et al*. Mechanism of erythrocyte accumulation of methylation inhibitor S-adenosylhomocysteine in uremia. *Kidney Int* 1995; 47: 247–253
28. Van Guldener C, Stehouwer CD. Homocysteine and methionine metabolism in renal failure. *Semin Vasc Med* 2005; 5: 201–208
29. Massy ZA, Borderie D, Nguyen-Khoa T *et al*. Increased plasma S-nitrosothiol levels in chronic haemodialysis patients. *Nephrol Dial Transplant* 2003; 18: 153–157
30. Nakanishi T, Hasuike Y, Otaki Y *et al*. Free cysteine is increased in plasma from hemodialysis patients. *Kidney Int* 2003; 63: 1137–1140
31. Kamoun P, Belardinelli M, Chabli A *et al*. Endogenous hydrogen sulfide overproduction in Down syndrome. *Am J Med Genet* 2003; 116A: 310–311
32. Łowicka E, Bełtowski J. Hydrogen sulfide (H2S)—the third gas of interest for pharmacologists. *Pharmacol Rep* 2007; 1: 4–24.
33. Casas JP, Bautista L, Smeeth L *et al*. Homocysteine and stroke: evidence on a causal link from Mendelian randomization. *Lancet* 2005; 365: 224–232
34. Chunyu Z, Junbao D, Dingfang B *et al*. The regulatory effect of hydrogen sulfide on hypoxic pulmonary hypertension in rats. *Biochem Biophys Res Commun* 2003; 302: 810–816
35. Siggaard-Andersen O, Nørgaard-Pedersen B, Rem J. Hemoglobin pigments, spectrophotometric determination of oxy-, carboxy-, met-, and sulfhemoglobin in capillary blood. *Clin Chim Acta* 1972; 42: 85–100
36. Perna AF, Satta E, Acanfora F *et al*. Increased plasma protein homocysteinylation in hemodialysis patients. *Kidney Int* 2006; 69: 869–876
37. Ponchel F, Toomes C, Bransfield K *et al*. Real- time PCR based on SYBR-Green I fluorescence: an alternative to the TaqMan assay for a relative quantification of gene rearrangements, gene amplifications and micro gene deletion. *BMC Biotechnol* 2003; 13: 3–18
38. Dawson-Saunders B, Trapp RG. *Basic and Clinical Biostatistics*. Norwalk: Appleton & Lange, 1990
39. Prudova A, Bauman Z, Braun A *et al*. S-adenosylmethionine stabilizes cystathionine ß-synthase and modulates redox capacity. *Proc Natl Acad Sci USA* 2006; 103: 6489–6494
40. Perna AF, Ingrosso D, De Santo NG. MTHFR C677T polymorphism and skin color: the white man's blackness. *Kidney Int* 2004; 65: 2444
41. Singh S, Padovani D, Leslie RA *et al*. The relative contributions of cystathionine beta-synthase and gamma-cystathionase to H_2S biogenesis via alternative transsulfuration reactions. *J Biol Chem* 2009; in press (doi:10.1074/jbc.M109.010868)
42. Chiku T, Padovani D, Zhu W *et al*. H_2S biogenesis by human cystathionine gamma-lyase leads to the novel sulfur metabolites lanthionine and homolanthionine and is responsive to the grade of hyperhomocysteinemia. *J Biol Chem* 2009; 284: 11601–11612
43. Sun Q, Collins R, Huang S *et al*. Structural basis for the inhibition mechanism of human cystathionine-γ-lyase: an enzyme responsible for the production of H_2S. *J Biol Chem* 2009; 284: 3076–3085
44. Hasuike Y, Nakanishi T, Moriguchi R *et al*. Accumulation of cyanide and thiocyanate in hemodialysis patients. *Nephrol Dial Transplant* 2004; 19: 1474–1479
45. Vanholder R, Argiles A, Baurmeister U *et al*. Uremic toxicity: present state of the art. *Int J Artif Org* 2001; 24: 695–725
46. Sen U, Basu P, Abe OA *et al*. Hydrogen sulfide ameliorates hyperhomocysteinemia associated chronic renal failure. *Am J Physiol Ren Physiol* 2009; (May 27). doi: 10.1152/ajprenal.00145.2009
47. Zoccali C, Catalano C, Rastelli S. Blood pressure control: hydrogen sulfide, a new gasotransmitter, takes stage. *Nephrol Dial Transplant* 2009; 24: 1396–1396

Received for publication: 4.6.09; Accepted in revised form: 6.7.09

Nephrol Dial Transplant (2009) 24: 3763–3774
doi: 10.1093/ndt/gfp327
Advance Access publication 10 July 2009

Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections

Kannaiyan S. Rabindranath[1], Tarun Bansal[2], James Adams[3], Ruma Das[4], Ranjit Shail[5], Alison M. MacLeod[6], Carol Moore[7] and Anatole Besarab[7]

[1]Renal Unit, Churchill Hospital, Oxford, [2]Renal Unit, North Middlesex Hospital, [3]Renal Unit, Kings College Hospital, London, [4]Renal Unit, Royal Berkshire Hospital, Reading, [5]Renal Unit, Royal London Hospital, London, [6]Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, UK and [7]Department of Nephrology and Hypertension, Henry Ford Health System, Detroit USA

Correspondence and offprint requests to: Kannaiyan S. Rabindranath; E-mail: ksrabi@yahoo.co.uk

Abstract

Background. Almost 30% of chronic haemodialysis (HD) patients are dependent on central venous catheters (CVCs) for their vascular access, and catheter-related bacteraemia (CRB) is the major reason for catheter loss and has been associated with substantial morbidity, including meta-static infections. This systematic review evaluates the benefits and harms of antimicrobial

interventions for the prevention of catheter-related infections (CRIs).

Methods. MEDLINE (1950–May 2009), EMBASE (1980–May 2009) CENTRAL (up to May 2009) and bibliographies of retrieved articles were searched for relevant RCTs. Analysis was by a random effects model and results expressed as rate ratio, relative risk (RR) and weighted mean difference (WMD) with 95% confidence intervals (CI).

Results. A total of 29 trials with 2886 patients and 3005 catheters were included. Antimicrobial catheter locks (AMLs) significantly reduced the rates of CRBs (rate ratio, 0.33, 95% CI 0.24–0.45) and exit-site infections (ESIs) (rate ratio 0.67, 95% CI 0.47–0.96). Exit-site antimicrobial application also significantly reduced the rates of CRBs (rate ratio 0.21, 95% CI 0.12–0.36) and ESIs (rate ratio 0.22, 95% CI 0.10–0.47). Antimicrobial coating of HD catheters and the use of peri-operative antimicrobials did not result in significant reduction in rates of CRBs and ESIs.

Conclusion. The use of AMLs and exit-site antimicrobials are useful measures in the reduction of CRIs, whereas antimicrobial impregnated catheters and peri-operative systemic antimicrobial administration have not been found to be beneficial. Further head-to-head trials of various AMLs and exit-site antimicrobials are needed to know about their comparative clinical efficacy.

Keywords: antimicrobial locks; antimicrobials; bacteraemia; catheter; haemodialysis

Introduction

Central venous catheters (CVCs) continue to be used in a significant proportion of chronic haemodialysis (HD) patients for vascular access despite recommendations by several national and international guidelines to minimize their usage as much as possible. It has been estimated that almost 30% of chronic HD patients are dependent on CVCs for their vascular access [1,2]. CVCs are responsible for almost half of all infections in HD patients even though they represent the smallest fraction of accesses [3].

CVCs have significantly higher rates of infections when compared with grafts and fistulae. It has been estimated that the relative risk (RR) for infection in tunnelled cuffed catheters (TCC) and uncuffed catheters (UCs) when compared with native arteriovenous fistulae (AVF) is 15.5 and 25.5, respectively [4]. The infection rate in TCCs have been reported to range from 1.6 to 5.5 episodes per 1000 catheter-days and in UCs from 3.8 to 6.6 episodes per 1000 catheter days [5,6]. The most important risk factors for catheter-related infections (CRIs) include the presence of diabetes, peripheral atherosclerosis, a previous history of bacteraemia, nasal carriage of *Staphylococcus aureus*, longer duration of catheter use and local infection [7,8]. Infection is the leading cause of catheter removal and morbidity in dialysis patients [9,10]. Catheter-related bacteraemia (CRB) is the major reason for catheter loss and has been associated with substantial morbidity, including meta-static infection [11,12]. The costs to the health care system are also substantial. It has been estimated from the United States Renal Data System and Medicare reimbursement data that there are approximately 100 000 episodes of CRB per year in the US and at an average cost of $22 000 per episode of CRB, the total cost of these infections may well approach dollar 1 billion [13,14].

Several techniques have been used to decrease the incidence of CRB. These include the use of systemic (usually by intravenous route) antibiotics around the time of catheter implantation, antimicrobial locks (AMLs) instilled into the catheter lumen, antimicrobial impregnated catheters, exit-site antimicrobials (ESAs) and agents used to reduce nasal colonization [15–19]. The main health risks associated with antimicrobial interventions include side effects such as ototoxicity with gentamicin, and hypocalcaemia and metallic taste with citrate, and the possible emergence of resistant organisms [20,21]. These interventions also entail additional costs to the health care provider. Currently, none of the renal societies have guidelines regarding the use of antimicrobial interventions to prevent CRI.

Methods

Guidelines from the Cochrane Renal Group and the QUOROM statement for undertaking and reporting systematic reviews were followed [22].

Inclusion criteria

We included any randomized controlled trial (RCT) of antimicrobial agents used to prevent CRIs in HD patients, regardless of whether the antimicrobials were tested between themselves (head-to-head) or against placebo/control intervention such as heparin. Trials of the following agents were included: peri-operative systemic antimicrobials (defined as antimicrobials given just a few hours before or after insertion of the HD catheter), AMLs, exit-site antimicrobial application (ESAs), treatment of nasal *S. aureus* carriage before or after catheter insertion, antimicrobial coating of catheters or catheter components such as catheter cuffs. The trials exclusively assessing the effectiveness of catheter type and insertion technique were excluded.

Search strategy

Electronic searches were performed using MEDLINE (1966 to May 2009), EMBASE (1980 to May 2009) and the Cochrane Central Register of Controlled Trials (CENTRAL) (up to May 2009) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) (up to September 2008) by using optimally sensitive search strategies for identification of RCTs developed by the Cochrane Collaboration. The following medical subject heading terms and text words were used: HD, catheters and antibacterial agents. Additionally, relevant text words relating to all investigated interventions were used. Based on standard systematic review methods, titles and abstracts identified by these searches were screened initially by two of the authors (K.S.R and R.D). No language restrictions were applied. Studies that clearly did not meet inclusion criteria (i.e. animal studies, non-RCTs and RCTs of interventions that were not stated a priori in inclusion criteria for this review) were not considered further. The full text (if published or otherwise available) of all other studies was assessed by two independent reviewers (K.S.R. and R.D.) for eligibility criteria. Disputes were solved in consultation with a third investigator (C.M.).

Data extraction

From all included RCTs, data were extracted by at least two of four authors (K.S.R., T.B., J.A., R.S.) independently on the following outcomes when they were reported: CRB (no. of patients with CRB, CRB episodes per 1000 catheter-days), exit-site infections (ESI) (no. of patients with ESI, ESI episodes per 1000 catheter-days), catheter thrombosis (no. of patients with catheter thrombosis), loss of catheter due to any complication, hospitalization (no. of patients hospitalized, no. of hospitalization days), all-cause mortality and mortality due to CRIs.

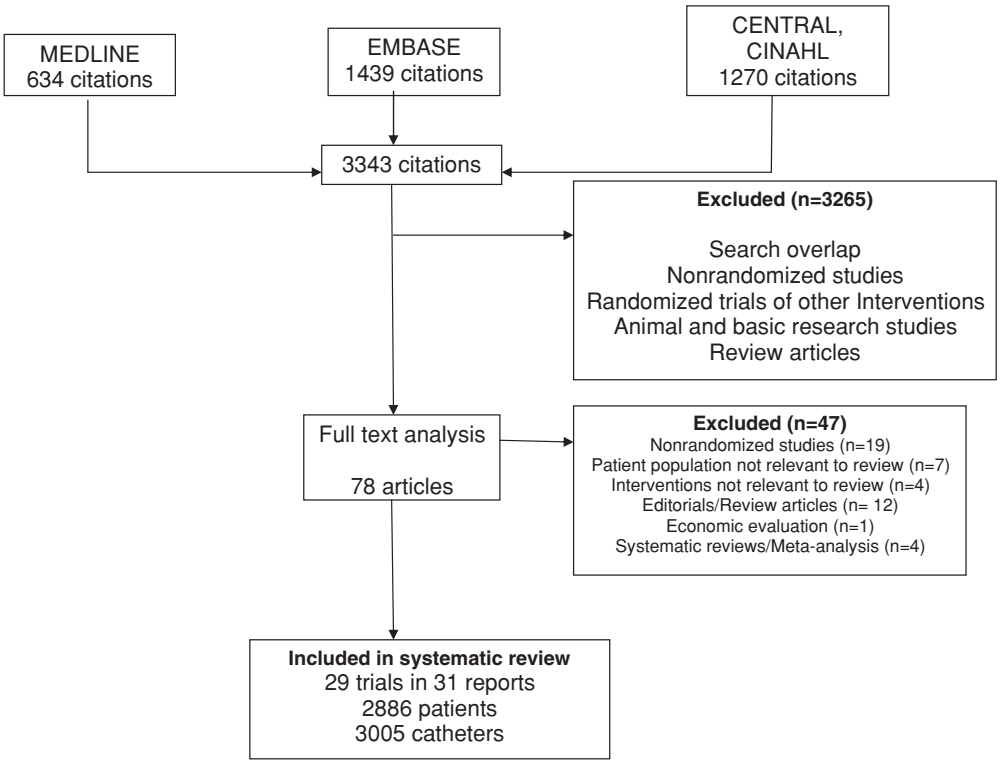

Fig. 1. Flow chart indicting the number of citations retrieved by individual searches and the final number of included trials; reasons for exclusions are provided.

Quality assessment

The quality of included randomized trials was assessed using standard criteria (allocation concealment, intention-to-treat analysis, loss to follow-up and blinding). Any differences in data extraction were resolved by discussion among authors. When data were missing or incomplete, investigators of the trials were contacted by written correspondence for clarification.

Statistical analysis

Treatment effects were summarized with the RR measure and its 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean difference (WMD) and its 95% CIs for continuous outcomes. Estimates from individual RCTs were pooled using the DerSimonian and Laird random-effects model, when appropriate. The Mantel–Haenszel fixed-effect model was also computed to evaluate robustness and susceptibility to outliers. Where data on the number of episodes were available, the rate ratio was calculated as the ratio of the rate of the outcome (e.g. the CRB rate) in the experimental treatment group (given by number of episodes of the outcome over unit time) over the rate in the control group. The generic inverse variance method was used to calculate rate ratios and their 95% CIs. The rate ratio shows the reduction in the incidence rate in the experimental intervention group compared to that in the control intervention group. For example, a rate ratio of 0.6 indicates a 40% reduction in events in the experimental intervention group compared to those on the control intervention. Heterogeneity of treatment effects between studies was formally tested using the Q (heterogeneity chi-square) and I^2 statistics. Subgroup analysis was planned to explore how possible sources of heterogeneity (type of catheter, catheter vintage) might have influenced treatment effect when these data were reported in the trials or provided by the investigators on request. All analyses were undertaken using RevMan 4.2.10 (2006; The Cochrane Collaboration, Oxford, UK).

Results

Literature search

The combined search identified 3343 articles, of which 3265 articles were excluded initially (see Figure 1). Major reasons for exclusion were (1) duplicate references, (2) non-RCTs, (3) RCTs of other interventions not stated in the inclusion criteria and (4) animal and basic research studies. Full-text assessment of 78 potentially eligible reports identified 29 eligible RCTs [15–21,23–44], with 2886 patients and 3005 catheters published in 31 reports.

Trial characteristics

The trial characteristics are summarized in Table 1. A total of 19 trials evaluated the efficacy of AMLs [17,21,23–26,28–30,32,35–38,40–44]. ESAs were evaluated in six trials [15,18,31,33,34,39]. There were three trials of antimicrobial coating of catheter or catheter components such as catheter cuff [19,27,29] and one of peri-operative systemic antibiotics [16]. Two studies were published only in a conference abstract format [23,28].

There were four trials that had head-to-head comparison of antimicrobial interventions [15,17,36,39]. In the trial by Nori *et al*., patients were divided into three groups [17]. One group was allocated to receive gentamicin lock, the other to minocycline-EDTA lock and the third to heparin lock. The trial by Johnson *et al*. compared exit-site application

Table 1. Study characteristics

Study ID	Country	Time period of study	No. of patients	Mean age (years)	Diabetics (%)	Tunnelled or non-tunnelled catheter	Catheter vintage	Experiment intervention (s)	Control Intervention	Co-interventions
Antimicrobial locks										
Al-Hwiesh (2007) [23]	Saudi Arabia	February 2005–January 2006	63	46.50	20.63	Tunnelled	New	Vancomycin 25 mg/ml, gentamicin 40 mg/ml and heparin	Heparin	None mentioned
Betjes 2004 [24]	Netherlands	May 2002–June 2003	58	50.3	27.50	Both	New	Citrate–taurolidine (1.35% taurolidine and 4% citrate)	Heparin	Weekly nasal mupirocin application and exit-site application of chlorhexidine and iodine
Bleyer 2005 [25]	USA	August 1998–November 1999	60	54.40	38.85	Both	New	Minocycline-EDTA	Heparin	None mentioned
Buturovic 1998 [26]	USA/Slovenia	Not stated	20	63	NK	Non-tunnelled	New	4% Sodium citrate	Heparin	None mentioned
Cooper 1999 [28]	USA	Not stated	36	NK	NK	Tunnelled	NA	Gentamicin (40 mg/lumen)	Heparin	None mentioned
Dogra 2002 [20]	Australia	May 1999–June 2001	83	57.50	35.00	Tunnelled	New	Gentamicin and citrate (2 ml of 40 mg/ml gentamicin and 1 ml of 3.13% tri-sodium citrate in a 3 ml syringe)	Heparin	Cephalothin 1 g prior to insertion. Weekly nasal Mupirocin application
Hendrickx 2001 [30]	Belgium	April 2000–October 2000	19	73	NK	Tunnelled	New	5% tri-sodium citrate	Heparin	None mentioned
Kim 2006 [32]	South Korea	March 2001–February 2003	120	54.93	52.50	Non-tunnelled	New	Cefazolin 10 mg/ml with gentamicin 5 mg/ml and heparin	Heparin	Skin disinfection, using either chlorhexidine or povidone iodine solution, followed by povidone–iodine ointment or mupirocin ointment at the catheter exit
McIntyre 2004 [35]	UK	March 2002–April 2003	50	60.70	26.00	Tunnelled	New	Gentamicin and heparin (gentamicin 5 mg/ml, heparin 5000 IU/ml)	Heparin	None
Meeus 2005 [36]	Belgium	March 2002–August 2002	28	75	32.14	Tunnelled	New	10% citrate	5% citrate	None mentioned
Nori 2006 [17]	USA	October 2003–April 2004	61	58.40	56.66	Tunnelled	Old and new	Gentamicin (4 mg/ml) and 3.13% tri-sodium citrate Minocycline (3 mg/ml) and EDTA (30 mg/ml)	Heparin	None mentioned
Pervez 2002 [37]	USA	January 1999–April 2000	55	49.63	38.18	Tunnelled	New	Gentamicin (40 mg/ml) and tri-sodium citrate 46.70%	Heparin	Covering the exposed part of the catheter with thin layer of povidone–iodine solution
Power 2009 [38]	UK	Not stated	232	62.50	43.10	Tunnelled	Old	46.70% Sodium citrate	Heparin	Cleansing with 4% chlorhexidine with each dialysis session

(*Continued*)

Table 1. (Continued)

Study ID	Country	Time period of study	No. of patients	Mean age (years)	Diabetics (%)	Tunnelled or non-tunnelled catheter	Catheter vintage	Experiment intervention (s)	Control Intervention	Co-interventions
Saxena 2005 [40]	Saudi Arabia	July 2002–June 2003	208	48.35	28.35	Non-tunnelled	New	Cefotaxime (10 mg/ml) and heparin	Heparin	None mentioned
Saxena 2006 [41]	Saudi Arabia	March 2002–February 2003	96	58.60	100	Tunnelled	New	Cefotaxime (10 mg/ml) and heparin	Heparin	None mentioned
Saxena 2006a [42]	Saudi Arabia	March 2002–February 2003	113	76.80	37.10	Tunnelled	New	Cefotaxime (10 mg/ml) and heparin	Heparin	None mentioned
Weijmer 2005 [21]	Amsterdam	August 01–September 2002	291	61.10	29.50	Both	New	Tri-sodium citrate 30%	Heparin	Exit-site application of polyantibiotic ointment
Zhang 2006 [43]	China	October 2004–May 2006	101	NK	NK	Tunnelled	NA	Gentamicin (concentration not mentioned) and heparin	Heparin	None mentioned
Zhang 2009 [44]	China	January 2005–June 2007	140	52.00	13.60	Tunnelled	New	Gentamicin (4 mg/ml) and heparin	Heparin	Exit-site application of povidone–iodine ointment
Exit-site antibiotic ointment application										
Johnson 2002 [31]	Australia	August 1999–May 2001	50	55.20	40.00	Tunnelled	New	2% Mupirocin ointment	None	Exit-site cleaning with povidone–iodine solution
Johnson 2005 [15]	Australia	February 2002–July 2004	101	57.60	34.50	Tunnelled	New	Medihoney	2% Mupirocin	Exit-site cleaning with povidone–iodine solution
Levin 1991 [33]	Canada	Not mentioned	129	51.40	8.52	Non-tunnelled	New	10% Povidone–iodine ointment	None	Exit-site cleaning with povidone–iodine solution
Lok 2003 [34]	USA/Canada	November 1999–November 2000	169	NA	62.30	Tunnelled	New	Polysporin ointment	None	Exit-site cleaning with chlorhexidine solution
Quadri 1998 [39]	Saudi Arabia	Not mentioned	34	NA	NA	Non-tunnelled	New	Manuka honey	Povidone–iodine	None
Sesso 1998 [18]	Brazil	June 1994–December 1996	136	46.50	18.40	Non-tunnelled	New	2% Mupirocin	None	Cleansing with povidone–iodine solution
Antimicrobial-coated catheters or catheter components										
Chatzinikolou 2005 [27]	USA	May 2000–March 2002	130	56.50	NA	Non-tunnelled	New	Minocycline–rifampicin impregnated catheters	None	Exit-site application of povidone–iodine
Dahlberg 1995 [29]	USA	Not mentioned	101	63.40	32.70	Tunnelled	New	Silver impregnated cuff over catheter	None	Exit-site application of Polyantibiotic ointment
Trerotola 1998 [19]	USA	Not mentioned	91	51.50	NA	Non-tunnelled	New	Silver-coated catheters	None	Application of povidone–iodine ointment
Peri-operative antimicrobials										
Mavromatidis 1999 [16]	Greece	Not mentioned	110	NA	NA	Non-tunnelled	New	Intravenous vancomycin 1 g, 1–2 h after catheter insertion in one arm and vancomycin 1–2 h after insertion and repeat vancomycin dose and then repeated every 6th day in another arm	None	Exit-site cleaning with povidone–iodine solution

NA, data not available from trial report.

of Medihoney with mupirocin [15], and the trial by Quadri *et al*. compared exit-site application of Manuka honey with povidone–iodine [39]. In one trial [36], a 5% citrate locking solution was compared with a 10% citrate locking solution.

Seventeen of the 29 trials assessed tunnelled catheters only [15,17,20,23,28–31,34–38,41–44], 9 assessed non-tunnelled catheters only [16,18,19,26,27,32,33,39,40] and 3 assessed both types of catheters [21,24,25]. The catheter vintage was unclear in two study reports [28,43], included both old and new catheters in one study [17], old catheters alone in two studies [38,44] and all the other studies (24 of 29) only assessed newly inserted HD catheters [15,16,18–21,23–27,28–37,39–42].

Skin cleaning with povidone–iodine or chlorhexidine solutions or the application of povidone–iodine ointment after each dialysis session appeared to be the most common co-interventions. Only one trial [36] was a crossover study, and all the rest had a parallel study design.

Trial quality

Twenty-two out of 29 included trials [15–21,24,25,27,31–35,37,38,39,40–42,44] had an adequate allocation concealment method. The method of allocation was unclear in seven trial reports [23,26,28–30,42]. Eight trials had blinding of patient, heath care provider and outcome assessors [20,21,25,27,34,40–42]. The patients and health care providers alone were blinded in two trials [32,36], and one trial had blinding of patients alone [18]. The results were analysed on an intention-to-treat basis in 26 trials [15–17,19–21,23,24,26, 28–44]. A total of 20 patients out of 2886 (0.69%) were lost to follow-up.

Effectiveness of interventions

The details of the total number of catheter days and the number of CRB episodes per 1000 catheter-days are given in Table 2.

AMLs. AMLs were found to have significantly reduced rates of CRB (15 trials, rate ratio, 0.33, 95% CI 0.24–0.45) and ESI (10 trials, rate ratio 0.67, 95% CI 0.47–0.96) (see Figure 2). Similarly, AMLs significantly reduced the risk of CRB (12 trials, 1047 patients, RR 0.22, 95% 0.13 to 0.35) and ESI (five trials, 498 patients, RR 0.33, 95% CI 0.19–0.58) and catheter loss due to all complications (three trials, 399 patients, RR 0.61, 95% CI 0.45–0.83). There was no significant heterogeneity between the studies for the outcomes mentioned above.

Exit-site antimicrobial application. ESAs significantly reduced rates of CRB (four trials, rate ratio 0.21, 95% CI 0.12–0.36) and ESI (three trials, rate ratio 0.22, 95% CI 0.10–0.47) (see Figure 3). Similarly, ESAs significantly reduced the risk of CRB (four trials, 477 patients, RR 0.35, 95% CI 0.23–0.52), ESI (two trials, 179 patients, RR 0.22, 95% CI 0.07–0.66) and catheter loss due to all complications (two trials, 298 patients, RR 0.54, 95% CI 0.29–0.99). There was no significant heterogeneity between the studies for the outcomes mentioned above.

Antimicrobial coating of catheters or catheter components. This antimicrobial intervention did not result in a significant reduction in the rates of CRB (two trials, rate ratio 0.17, 95% CI 1.05–1.38) or ESI (two trials, rate ratio 0.55, 95% CI 2.23–1.12). It also did not significantly reduce risk with respect to CRB (three trials, 322 patients, RR 0.81, 95% CI 0.31–2.08), ESI (two trials, 192 patients, RR 0.36, 95% CI 0.06–2.22) and catheter loss due to all complications (three trials, 322 patients, RR 1.29, 95% CI 0.87–1.91). There was no significant heterogeneity between the studies for the outcomes mentioned above.

Peri-operative systemic antimicrobial administration. Peri-operative antimicrobial administration (intravenous vancomycin 1–2 h post-insertion of catheter) was not found to significantly reduce rates of CRB (one trial, rate ratio 0.66, 95% CI 0.27–1.63) or ESI (one trial, rate ratio 0.87, 95% CI 0.45–1.65). Similarly, peri-operative antimicrobials also did not result in a significant reduction in risk with respect to CRB (one trial, 110 patients, RR 0.78, 95% CI 0.34–1.76) or ESI (one trial, 110 patients, RR 1.02, 95% CI 0.60–1.72). It must be noted that this study was performed in patients with non-tunnelled HD catheters alone.

Head-to-head comparison of antimicrobials. The patients on mupirocin and Medihoney were found to have similar risk of CRB (one trial, 101 patients, RR 1.18, 95% CI 0.38–3.61) and ESI (effect measures not estimable as this outcome did not occur during the trial period). Honey when compared to mupirocin or povidone–iodine did not significantly reduce the rates of CRB (two trials, rate ratio 0.86, 95% CI 0.35–2.12) and ESI (two trials, rate ratio 0.81, 95% CI 0.16–4.12). In the study by Nori *et al*. comparing gentamicin and micocycline-EDTA AMLs, no difference was found between patients in either group for the risk of CRB (one trial, 41 patients, RR 0.35, 95% CI 0.02–8.10) [17]. One study [34] compared 5% citrate and 10% citrate AMLs. The results were not in a meta-analysable format, but this study did not report any difference between either intervention for the risk of CRIs or thrombosis.

Complications relating to antimicrobial agent used. Four patients were found to have dizziness in the gentamicin/citrate group in the study by Dogra *et al*. [20]. In another study, nine patients in the tri-sodium citrate group and four in the heparin group had perioral or peripheral paraesthesia or metallic taste [21]. Symptoms disappeared within 1 min of lock instillation and did not return.

Emergence of resistant organisms. One patient had reported MRSA infection in studies by Chatzinoklaou *et al*. and McIntyre *et al*. [26,33]. In the study by Dogra *et al*., one candida ESI was reported [20].

Other outcomes. The data regarding other outcomes such as catheter thrombosis and mortalities (all-cause and CRB related) when reported have been presented in Table 3.

Subgroup analysis. Sufficient numbers of studies were available only for effect of AMLs on CRB rates according to the type of catheter (tunnelled or non-tunnelled). From the

Table 2. Details of total catheter-days and CRB events per 1000 catheter-days in the included studies

Study ID	No. of patients	Experiment intervention (s)	Control intervention	No. of catheter days		No. of CRB events per 1000 catheter-days	
				Experimental intervention	Control intervention	Experimental intervention	Control intervention
Antimicrobial locks							
Al-Hwiesh 2007 [23]	63	Vancomycin 25 mg/ml, gentamicin 40 mg/ml and heparin	Heparin	7212	7656	0.28	2.09
Betjes 2004 [24]	58	Citrate–taurolidine (1.35% taurolidine and 4% citrate)	Heparin	1519	1885	0	2.12
Bleyer 2005 [25]	60	Minocycline-EDTA	Heparin	2336	2118	0	0.47
Buturovic 1998 [26]	20	4% Sodium citrate	Heparin	NA	NA	NA	NA
Cooper 1999 [28]	36	Gentamicin (40 mg/lumen)	Heparin	1485	1610	0	3.11
Dogra 2002 [20]	83	Gentamicin and citrate (2 ml of 40 mg/ml gentamicin and 1 ml of 3.13% tri-sodium citrate in a 3 ml syringe)	Heparin	3280	2643	0	2.65
Hendrickx 2001 [28]	19	5% Trisodium citrate	Heparin	NA	NA	NA	NA
Kim 2006 [32]	120	Cefazolin 10 mg/ml with gentamicin 5 mg/ml and heparin	Heparin	2272	2243	0.44	3.12
McIntyre 2004 [35]	50	Gentamicin and heparin (gentamicin 5 mg/ml, heparin 5000 IU/ml)	Heparin	3252	2470	0.31	4.05
Meeus 2005 [36]	28	10% citrate	5% citrate	NA	NA	NA	NA
Nori 2006 [17]	61	Gentamicin (4 mg/ml) and 3.13% tri-sodium citrate Minocycline (3 mg/ml) and EDTA (30 mg/ml)	Heparin	3937	1700	0.25	4.12
Pervez 2002 [37]	55	Gentamicin (40 mg/ml) and tri-sodium citrate 46.70%	Heparin	1612	3206	0.62	2.50
Power 2009 [38]	232	46.70% Sodium citrate	Heparin	NA	NA	0.7	0.7
Saxena 2005 [40]	208	Cefotaxime (10 mg/ml) and heparin	Heparin	58 038	17 885	1.65	3.13
Saxena 2006 [41]	96	Cefotaxime (10 mg/ml) and heparin	Heparin	18 615	21 170	1.56	3.68
Saxena 2006a [42]	113	Cefotaxime (10 mg/ml) and heparin	Heparin	21 535	21 900	1.67	3.61
Weijmer 2005 [21]	291	Tri-sodium citrate 30%	Heparin	8431	8116	1.07	4.07
Zhang 2006 [43]	101	Gentamicin (concentration not mentioned) and heparin	Heparin	5635	3665	0	0.89
Zhang 2009 [44]	140	Gentamicin (4 mg/ml) and heparin	Heparin	17 781	16 299	0.06	0.67
Exit-site antibiotic ointment application							
Johnson 2002 [31]	50	2% Mupirocin ointment	None	1250	761	1.60	10.51
Johnson 2005 [15]	101	Medihoney	2% Mupirocin	6185	5882	0.97	0.85
Levin 1991 [33]	129	10% Povidone–iodine ointment	None	2437	2397	0.41	4.59
Lok 2003 [34]	169	Polypsporin ointment	None	12 745	10 487	0.63	2.48
Quadri 1998 [38]	34	Manuka honey	Povidone–iodine	331	308	9.06	15.46
Sesso 1998 [18]	136	2% Mupirocin	None	2836	1682	1.76	8.32
Antimicrobial-coated catheters or catheter components							
Chatzinikolou 2005 [27]	130	Minocycline–rifampicin impregnated catheters	None	528	512	0	5.86
Dahlberg 1995 [29]	101	Silver impregnated cuff over catheter	None	1639	2241	1.22	0.89
Trerotola 1998 [19]	91	Silver-coated catheters	None	2846	5507	1.76	0.91
Peri-operative antimicrobials							
Mavromatidis 1999 [16]	110	Intravenous vancomycin 1 g, 1–2 h after catheter insertion in one arm and vancomycin 1–2 h after insertion and repeat vancomycin dose and then repeated every 6th day in another arm	None	1549	1139	5.81	8.78

NA, data not available from trial report

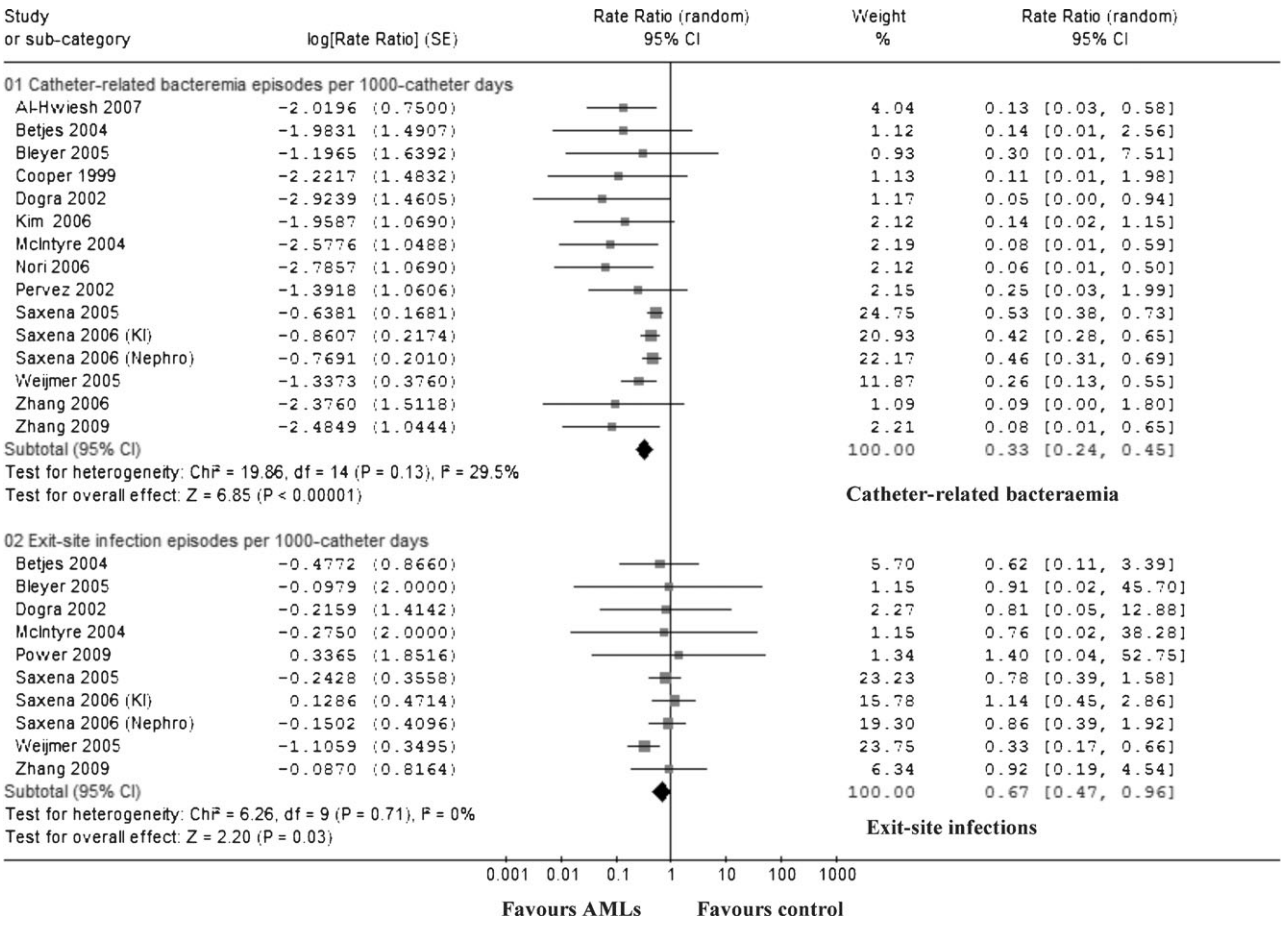

Fig. 2. Effect of AMLS on catheter-related bacteraemia and exit-site infections expressed as episodes per 1000 catheter-days.

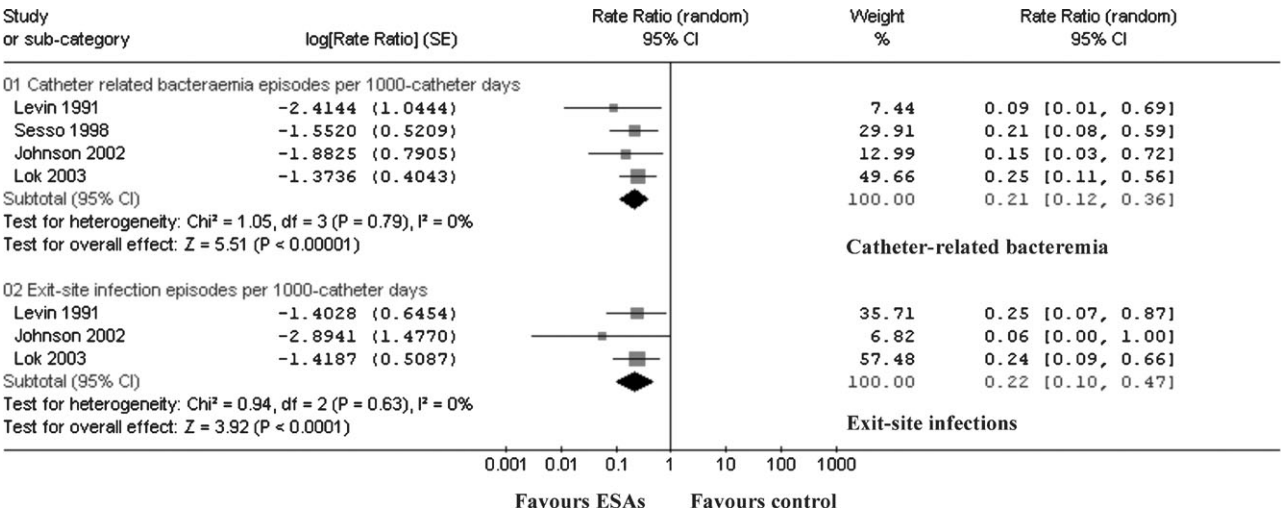

Fig. 3. Effect of exit-site antibiotic applications on rates of CRB and ESI expressed as episodes per 1000 catheter-days.

studies that used both types of catheters [21,24,25], separate data for both types of catheter were available only from the Weijmer *et al*. study to be used in this analysis [21]. AMLs significantly reduced CRB rates both for tunnelled (rate ratio 0.28, 95% CI 0.18–0.43) and non-tunnelled catheters (rate ratio 0.50, 95% CI 0.36–0.68).

Discussion

This systematic review of antimicrobial interventions for the prevention of HD CRIs shows a number of key findings. The use of AMLs and ESAs significantly reduces the risk and rate of CRB and ESI, and the risk of catheter loss due

Table 3. Other outcomes

Outcome analysed	Number of studies	Number of patients	Results	
			Relative risk[a]	95% CIs
Antimicrobial locks				
Number of patients with catheter thrombosis	1	33	0.90	0.31–2.61
All-cause mortality	1	291	0.70	0.36–1.37
Mortality due to catheter-related infection	1	291	0.09	0.00–1.57
Exit-site antibiotic application				
Risk of hospitalization	2	298	0.54	0.16–1.86
Mortality due to catheter-related infection	1	162	0.14	0.01–2.59
Antimicrobial coating of catheter or catheter components				
All-cause mortality	1	130	1.03	0.56–1.91

[a]Relative risk <1 favours experimental intervention (i.e. antimicrobial usage); relative risk >1 favours control intervention.

to any complication. Currently, we do not have sufficient evidence to draw conclusions regarding the effectiveness of antimicrobial coating or impregnation of HD catheters or peri-operative systemic administration of antibiotics in the form of intravenous vancomycin for the reduction of HD-CRI. There were very limited data to compare the relative clinical efficacy of various antimicrobial interventions in head-to-head clinical trials. One multi-arm study that compared gentamicin and minocycline-EDTA AMLs did not find any difference between them in their clinical efficacy [17]. Similarly, exit-site application of honey compared to other antimicrobials (mupirocin and povidone–iodine) was found to be of similar efficacy in the prevention of CRI.

The rate of CRB in the control arms of the included studies varied greatly ranging from 0.47 to 15.46 per 1000 catheter-days. The presence of a dialysis catheter has been shown to be a major risk factor for bacteraemia and can result in life-threatening complications, including septic shock, endocarditis, septic arthritis, osteomyelitis or epidural abscess [45]. One study has calculated that there are 2750–5500 deaths due to CRB in the HD population in the USA assuming that the mortality rate due to CRB is 5–10% and that there are two CRB events per 1000 patient-days for patients with tunnelled catheters [46]. Thus, CRB in the HD population can have an enormous adverse impact on patient outcomes and can translate into increased consumption of health care resources.

The efficacy of AMLs in the prevention of CRB is striking. The use of AMLs has been shown in our analysis to result in the reduction of risk of CRB by 75%. With regard to effect of AMLs on ESI, the meta-analysis shows that only the study by Weijmer *et al*. [21] showed a significant reduction in both the rate and risk for this outcome, whilst the others did not. However, due to the size of this study, it influenced the summary outcome as well showing a difference in favour of AMLs in terms of ESI prevention. None of the studies showed the emergence of resistant organisms; however, the studies were not designed to answer this question. Although the use of AMLs has demonstrated effectiveness at reducing the incidence of CRB, there continues to be a hesitance to their overall use, likely due to the concern for the potential for development of drug resistance. It has been known from previous studies that the use of antimicrobials can cause the emergence of drug-resistant organisms [47]. The studies included in this review were of relatively short duration, with most of them lasting <1 year, and the patient numbers were relatively small. It is therefore not possible to state that the use of AMLs in the long term will be risk-free from a drug resistance point of view. Almost 10% of the patients in the Dogra *et al*. study experienced ototoxicity; however, the authors used a higher concentration of gentamicin (40 mg/ml) [20]. This systemic exposure was not seen in the McIntyre *et al*. study, which used a concentration of 5 mg/ml [33]. It must be noted that none of the studies performed formal audiometry to assess ototoxicity. Citrate locks possibly provide a fairly wider therapeutic window than other AMLs in that the major side effect reported was metallic taste. No major trials have been reported so far in the literature showing evidence of emergence of drug resistant organisms with this agent.

None of the current guidelines relating to the use of intravascular devices provide consistent guidelines with regard to the use of antimicrobial interventions apart from the use of chlorhexidine skin cleansing (Table 4).

Several meta-analysis and reviews have been published on the use of antimicrobials for the prevention of infections relating to the use of CVCs. A meta-analysis published in 2002 assessed studies that compared the risk for CRB in patients with CVCs following insertion-site skin care with either any type of chlorhexidine gluconate solution versus povidone–iodine (PI) solution [53]. This analysis indicated that the use of chlorhexidine solution rather than povidone–iodine can reduce the risk for CRB by ∼49% (RR 0.51, CI 0.27–0.97) in hospitalized patients who require short-term catheterization. One meta-analysis reported that the use of CVCs impregnated with chlorhexidine and silver sulfadiazine significantly reduced the odds of CRB (Odds ratio 0.44, 95% CI 0.36–0.54) [54].

The main drawback with the meta-analyses reported above is that none of them included trials in the HD population. It may well be that interventions that are useful with central vascular access devices in other settings (total parenteral nutrition, central lines for chemotherapy administration, etc.) may not be effective in the HD population as the nature of the dialysis catheter, i.e. its chemical composition, the frequency of their usage and the nature of their usage are

Table 4. Current guidelines with regard to antimicrobial use for the prevention of HD catheter-related infections

Guideline	Recommendation
National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) [48]	Chlorhexidine solutions to be used as first-line agents for exit-site cleaning, with povidone–iodine as an alternative in those unable to tolerate chlorhexidine. Advocates the adherence to Centers for Disease Control guidelines [49] for the prevention of central venous catheter infections, which were published in 2002. The CDC guidelines recommend the use of AMLs in patients who have recurrent bacteraemia and in whom maximum adherence to sterile technique has been determined.
Renal Association (UK) [50]	Recommends the use of dry gauze instead of transparent dressings, disinfection with chlorhexidine solutions instead of povidone–iodine, the use of topical mupirocin or Medihoney or antiseptic at the catheter exit-site and the use of citrate and/or antibiotics with heparin as a catheter locking solution.
European Renal Association (ERA-EDTA) [51]	Recommends strict protocols for handling catheters based on aseptic manipulation and mentions that the regular and pre-emptive use of locking solutions (citrate) with both antithrombotic and/or antiseptic properties is effective in preventing catheter infection.
The Evidence-Based Practice in Infection Control (EPIC) [52]	Recommends the use of alcoholic chlorhexidine solution (2% chlorhexidine gluconate in 70% isopropyl alcohol) for skin cleansing prior to insertion of central venous catheters and also during handling of such catheters. The EPIC guidelines advocate against the use of AMLs and ESAs.

considerably different to other CVCs. Therefore, the results from the trials involving other types of CVCs should not automatically be considered applicable to HD catheters. Our literature search did not reveal any study that was a head-to-head comparison of various skin cleansing antimicrobial solutions (chlorhexidine, povidone–iodine) for HD catheter care.

Several renal units in the UK administer intravenous antibiotics, especially flucloxacillin or vancomycin prior to the insertion of tunnelled catheters (author's personal experience). The only trial that evaluated intravenous antibiotics in the peri-operative setting assessed its use in patients with non-tunnelled catheters alone. The use of peri-operative intravenous antibiotics for the prevention of CRI in patients with tunnelled catheters is therefore not currently supported by trial evidence.

S. aureus carriage has received attention in the literature as a possible source of infection in HD patients. A recently published trial looked at the carriage of MRSA and subsequent infection among dialysis patients, healthcare workers and their families within a single dialysis centre [55]. The investigators found that 36% of colonized subjects went on to develop MRSA infection with the same molecular phenotype as the colonizing strain. Two trials [56,57] have reported a decrease in incidence of *S. aureus*-related infections with eradication of *S. aureus* carriage. However, neither of these trials included patients with HD catheters and therefore we currently do not have evidence regarding the effectiveness of eradicating *S. aureus* carriage on the reduction of HD CRI.

Whilst antimicrobials in the form of AMLs and exit-site applications have been impressively effective in the reductions of CRI, one should be mindful of addressing basic aspects effectively such as the use of masks and sterile gloves and the use of non-touch techniques. One study has shown that the adoption of a strict aseptic protocol alone significantly reduced the incidence of CRB [58]. The NKF-KDOQI guidelines recommend following the CDC guidelines with respect to aseptic handling of catheters, and the EPIC guidelines in the UK make similar recommendations [48,49,52].

We feel that the judicious use of antimicrobials, especially in the form of AMLs and exit-site antibiotics, along with scrupulous attention to aseptic techniques during the handling of HD catheters, can lead to significant reductions in CRI and consequently reduce patient morbidity and mortality, and also reduce the financial burden incurred by the health care providers on account of such infections. However, we need to continue to be vigilant about emergence of a drug-resistant organism and continue to evaluate alternative antimicrobials agents (non-antibiotics) against which resistance is not possible (e.g. calcium chelators). Further, adequately powered and well-designed studies assessing the effectiveness of antimicrobial-coated catheters, peri-operative systemic antibiotic usage and head-to-head trial of various antimicrobials are recommended to inform us regarding their relative effectiveness.

Acknowledgements. The authors wish to thank Drs Betjes, Buturovic, Dogra, Saxena, Weijmer, for responding to our queries and providing details about their trials.

Conflict of interest statement. I declare that the results presented in this paper have not been published previously in whole or part, except in abstract format Kannaiyan S. Rabindranath (corresponding author).

References

1. Pisoni RL, Young EW, Dysktra DM *et al*. Vascular access use in Europe and the United States: results from the DOPPS. *Kidney Int* 2002; 61: 305–316
2. Rayner HC, Besarab A, Brown WW *et al*. Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): performance against Kidney Diseases Outcomes Quality Initiative (K-DOQI) Clinical Practice Guidelines. *Am J Kidney Dis* 2004; 44(Suppl 2): S22–S26
3. Dittmer ID, Sharp D, McNulty CAM *et al*. A prospective study of central venous haemodialysis catheter colonization and peripheral bacteraemia. *Clin Nephrol* 1999; 51: 34–39
4. Taylor G, Gravel D, Johnston L *et al*. Prospective surveillance for primary bloodstream infections occurring in Canadian haemodialysis units. *Infect Control Hosp Epidemiol* 2002; 23: 716–720

5. Hannah EL, Stevenson KB, Lowder CA *et al*. Outbreak of haemodialysis vascular access site infections related to malfunctioning permanent tunneled catheters: making the case for active infection surveillance. *Infect Control Hosp Epidemiol* 2002; 23: 538–541
6. Saxena AK, Panhorota BR, Al-Mulhim AS. Vascular access-related infections in haemodialysis patients. *Saudi J Kidney Dis Transplant* 2005; 16: 46–71
7. Jean G, Charra B, Chazot C *et al*. Risk factor analysis for long-term tunneled dialysis catheter-related bacteraemias. *Nephron* 2002; 91: 399–405
8. Saeed Abdulrahman I, Al-Mueilo SH, Bokhary HA *et al*. A prospective study of haemodialysis access-related bacterial infections. *J Infect Chemother* 2002; 8: 242–246
9. Butterly DW, Schwab SJ. Dialysis access infections. *Curr Opin Nephrol Hyp* 2000; 209: 631–635
10. Marr KA, Sexton DJ, Conlon PJ *et al*. Catheter-related bacteraemia and outcome of attempted catheter salvage in patients undergoing haemodialysis. *Ann Intern Med* 1997; 127: 275–280
11. Kovalik EC, Raymond JR, Albers FJ *et al*. A clustering of epidural abscesses in chronic haemodialysis patients: risks of salvaging access catheters in cases of infection. *J Am Soc Nephrol* 1996; 7: 2264–2267
12. Suhocki PV, Conlon PJ Jr, Knelson MH *et al*. Silastic cuffed catheters for haemodialysis vascular access: thrombolytic and mechanical correction of malfunction. *Am J Kidney Dis* 1996; 28: 379–386
13. Engemann JJ, Friedman JY, Reed SD *et al*. Clinical outcomes and costs due to *Staphylococcus aureus* bacteraemia among patients receiving long-term haemodialysis. *Infect Control Hosp Epidemiol* 2005; 26: 534–539
14. Manierski C, Besarab A. Antimicrobial locks: putting the lock on catheter infections. *Adv Chronic Kidney Dis* 2006; 13: 245–258
15. Johnson DW, van Eps C, Mudge DW *et al*. Randomised, controlled trial of topical exit-site application of honey (Medihoney) versus mupirocin for the prevention of catheter-associated infections in haemodialysis patients. *J Am Soc Nephrol* 2005; 16: 1456–1462
16. Mavromatidis K, Kontodemou A, Tsoulfa S *et al*. The impact of vancomycin administration on prevention of haemodialysis catheter-related infections. *Dial Transplant* 1999; 28: 727–733
17. Nori US, Manoharan A, Yee J *et al*. Comparison of low-dose gentamicin with minocycline as catheter lock solutions in the prevention of catheter-related bacteraemia. *Am J Kidney Dis* 2006; 48: 596–605
18. Sesso R, Barbosa D, Leme IL *et al*. *Staphylococcus aureus* prophylaxis in haemodialysis patients using central venous catheter: effect of mupirocin ointment. *J Am Soc Nephrol* 1998; 9: 1085–1092
19. Trerotola SO, Johnson MS, Shah H *et al*. Tunneled haemodialysis catheters: use of a silver-coated catheter for prevention of infection—a randomised study. *Radiology* 1998; 207: 491–496
20. Dogra GK, Herson H, Hutchison B *et al*. Prevention of tunneled haemodialysis catheter-related infections using catheter-restricted gentamicin and citrate: a randomised controlled study. *J Am Soc Nephrol* 2002; 12: 2133–2139
21. Weijmer MC, Van Den Dorpel MA, Van de Ven PJG *et al*. Randomised, clinical trial comparison of Trisodium Citrate 30% and Heparin as catheter-locking solution in haemodialysis patients. *J Am Soc Nephrol* 2005; 16: 2769–2777
22. Moher D, Cook JC, Eastwood S *et al*. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999; 354: 1896–1900
23. Al-Hwiesh AK, Abdul-Rahman ISA. Successful prevention of tunneled, central catheter infection by antibiotic lock therapy using vancomycin and gentamycin. *Saudi J Kidney Dis Transplant* 2007; 18: 239–247
24. Betjes MG, van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate–taurolidine-containing lock solution. *Nephrol Dial Transplant* 2004; 19: 1546–1551
25. Bleyer AJ, Mason L, Russell G *et al*. A randomised, controlled trial of a new vascular catheter flush solution (minocycline-EDTA) in temporary haemodialysis access. *Infect Control Hosp Epidemiol* 2005; 26: 520–524
26. Buturovic J, Ponikvar R, Kandus A *et al*. Filling haemodialysis catheters in the interdialytic period: heparin versus citrate versus polygeline: a prospective randomised study. *Artif Organs* 1998; 22: 945–947
27. Chatzinikolaou I, Finkel K, Hanna H *et al*. Antibiotic-coated haemodialysis catheters for the prevention of vascular catheter-related infections: a prospective, randomised study. *Am J Med* 2003; 115: 352–357
28. Cooper RI, Saad TF. Prevention of bacteremia in patients with tunneled cuffed 'permanent' hemodialysis catheters using gentamicin catheter packing. *J Am Soc Nephrol* 1999; 10: 203A
29. Dahlberg PJ, Agger WA, Singer JR *et al*. Subclavian haemodialysis catheter infection: a prospective, randomised trial of an attachable silver-impregnanted cuff for prevention of catheter-related infections. *Infect Control Hosp Epidemiol* 1995; 18: 506–511
30. Hendrickx L, Kuypers D, Evenpoel P *et al*. A comparative prospective study on the use of low concentrate citrate lock versus heparin lock in permanent dialysis catheters. *Int J Artif Organs* 2001; 24: 208–211
31. Johnson DW, MacGinley R, Kay TD *et al*. A randomised controlled trial of topical exit-site mupirocin application in patients with tunneled, cuffed haemodialysis catheters. *Nephrol Dial Transplant* 2002; 17: 1802–1807
32. Kim SH, Song KI, Chang JW *et al*. Prevention of uncuffed haemodialysis catheter-related bacteraemia using an antibiotic lock technique: a prospective, randomised clinical trial. *Kidney Int* 2006; 69: 161–164
33. Levin A, Mason AJ, Jindal KK *et al*. Prevention of haemodialysis subclavian vein catheter infections by topical povidone–iodine. *Kidney Int* 1991; 40: 934–938
34. Lok CE, Stanley KE, Hux JE *et al*. Haemodialysis infection prevention with polysporin ointment. *J Am Soc Nephrol* 2003; 14: 169–179
35. McIntyre CW, Hulme LJ, Taal M *et al*. Locking of tunneled haemodialysis catheters with gentamicin and heparin. *Kidney Int* 2004; 66: 801–805
36. Meeus G, Kuypers DR, Claes K *et al*. A prospective, randomised, double-blind crossover study on the use of 5% citrate lock versus 10% citrate lock in permanent haemodialysis catheters. *Blood Purificat* 2005; 23: 101–105
37. Pervez A, Ahmed M, Ram S *et al*. Antibiotic lock technique for prevention of cuffed tunnel catheter associated bacteraemia. *J Vascular Access* 2002; 3: 108–113
38. Power A, Duncan N, Singh SK *et al*. Sodium citrate versus heparin catheter locks for cuffed central venous catheters: a single-center randomized controlled trial. *Am J Kidney Dis* 2009; 53: 1034–1041
39. Quadri KHM, Tanimu DZ, Iqbal A *et al*. A prospective randomised controlled trial of topical honey versus povidone iodine in the prevention of haemodialysis catheter related sepsis. *J Am Soc Nephrol* 1998; 9: 180A–181A
40. Saxena AK, Panhotra BR. The impact of catheter-restricted filling with cefotaxime and heparin on the lifespan of temporary haemodialysis catheters: a case controlled study. *J Nephrol* 2005; 18: 755–763
41. Saxena AK, Panhotra BR, Sundaram DS *et al*. Tunneled catheters' outcome optimization among diabetics on dialysis through antibiotic-lock placement. *Kidney Int* 2006; 70: 1629–1635
42. Saxena AK, Panhotra BR, Sundaram DS *et al*. Enhancing the survival of tunneled haemodialysis catheters using an antibiotic lock in the elderly: a randomised, double-blind clinical trial. *Nephrol* 2006; 11: 299–305
43. Zhang P, Zhang A, Qiang H *et al*. A randomized controlled study on the prevention of cuff-tunneled catheter related bacteremia with gentamicin-heparin licked solution (abstract). *J Am Soc Nephrol* 2006; 17: 592A
44. Zhang P, Yuan J, Tan H *et al*. Successful prevention of cuffed hemodialysis catheter-related infection using an antibiotic lock technique by strictly catheter-restricted antibiotic lock solution method. *Blood Purif* 2009; 27: 206–211
45. Allon M. Dialysis catheter-related bacteraemia: treatment and prophylaxis. *Am J Kidney Dis* 2004; 44: 779–791

46. Bleyer AJ. Use of antimicrobial catheter lock solutions to prevent catheter-related bacteraemia. *Clin J Am Soc Nephrol* 2007; 2: 1073–1078
47. Bergman M, Huikko S, Huovinen P *et al*. Finnish Study Group for Antimicrobial Resistance (FiRe Network). Macrolide and azithromycin use are linked to increased macrolide resistance in Streptococcus pneumoniae. *Antimicrob Agents Chemother* 2006; 50: 3646–3650
48. Vascular Access Work Group. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006; 48(Suppl 1): S248–S273
49. O'Grady NP, Alexander M, Dellinger EP *et al*. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2002; 35: 1281–1307
50. Renal Association (UK). Clinical guidelines—module 3a—haemodialysis. 2007. Available at: http://www.renal.org/guidelines/module3a.html#VascularAccess (Accessed on 14 December 2007)
51. Tordoir J, Canaud B, Haage P *et al*. EBPG on vascular access. *Nephrol Dial Transplant* 2007; 22(Suppl 2): ii88–ii117
52. Pratt RJ, Pellowe CM, Wilson JA *et al*. EPIC 2: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2007; 65S: S1–S64
53. Chaiyakunapruk N, Veenstra DL, Lipsky BA *et al*. Chlorhexidine compared with povidone–iodine solution for vascular catheter-site care: a meta-analysis. *Ann Inter Med* 2002; 136: 792–801
54. Walder B, Pittet D, Tramer M. Prevention of bloodstream infections with central venous catheters treated with anti-infective agents depends on catheter type and insertion time: evidence from a meta-analysis. *Infect Control Hosp Epidemiol* 2002; 23: 748–756.
55. Lu PL, Tsai JC, Chiu YW *et al*. Methicillin-resistant *Staphylococcus aureus* carriage, infection and transmission in dialysis patients, healthcare workers and their family members. *Nephrol Dial Transplant* 2008; 23: 1659–1665
56. Yu VL, Goetz A, Wagener M. *Staphylococcus aureus* carriage and infection in patients on haemodialysis. Efficacy of antibiotic prophylaxis. *N Engl J Med* 1986; 315: 91–96
57. Boelaert JR, De Smedt RA, De Baere YA *et al*. Nasal mupirocin ointment decreases the incidence of *Staphylococcus aureus* bacteraemias in haemodialysis patients. *Nephrol Dial Transplant* 1989; 4: 278–281
58. Beathard GA. Catheter management protocol for catheter-related bacteraemia prophylaxis. *Semin Dial* 2003; 16: 403–405

Received for publication: 8.3.08; Accepted in revised form: 12.6.09

Nephrol Dial Transplant (2009) 24: 3774–3782
doi: 10.1093/ndt/gfp348
Advance Access publication 21 July 2009

Survival of patients from South Asian and Black populations starting renal replacement therapy in England and Wales

Paul Roderick[1], Catherine Byrne[2], Anna Casula[3], Retha Steenkamp[3], David Ansell[3], Richard Burden[2], Dorothea Nitsch[4] and Terry Feest[3]

[1]Public Health Sciences and Medical Statistics, University of Southampton, C floor, South Academic Block, Southampton General Hospital, Southampton SO166YD, [2]Renal Unit, Nottingham City Hospital, Hucknall Road, Nottingham, NG51PB, [3]Renal Association UK Renal Registry, Southmead Hospital, Southmead Road, Bristol BS10 5NB and [4]Non-communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Correspondence and offprint requests to: Paul Roderick; E-mail: pjr@soton.ac.uk

Abstract

Background. South Asian and Black ethnic minorities in the UK have higher rates of acceptance onto renal replacement therapy (RRT) than Caucasians. Registry studies in the USA and Canada show better survival; there are few data in the UK.

Methods. Renal Association UK Renal Registry data were used to compare the characteristics and survival of patients starting RRT from both groups with those of Caucasians, using incident cases accepted between 1997 and 2006. Survival was analysed by multivariate Cox's proportional hazards regression split by haemodialysis and peritoneal dialysis (PD) due to non-proportionality, and without censoring at transplantation.

Results. A total of 2495 (8.2%) were South Asian and 1218 (4.0%) were Black. They were younger and had more diabetic nephropathy. The age-adjusted prevalence of vascular co-morbidity was higher in South Asians and lower in Blacks; other co-morbidities were generally common in Caucasians. Late referral did not differ. They were less likely to receive a transplant or to start PD. South Asians and Blacks had significantly better survival than Caucasians both from RRT start to Day 90 and after Day 90, and for those on HD or PD at Day 90. Fully adjusted hazard ratios after Day 90 on haemodialysis were 0.70 (0.55–0.89) for South Asians and 0.56 (0.41–0.75) for Blacks.

Conclusion. South Asian and Black minorities have better survival on dialysis. An understanding of the mechanisms may provide general insights for all patients on RRT.

Keywords: ethnic minorities; haemodialysis; peritoneal dialysis; survival