

Tunneled Catheters with Taurolidine-Citrate-Heparin Lock Solution Significantly Improve the Inflammatory Profile of Hemodialysis Patients

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Mortality and morbidity are significantly higher among patients with dialysis catheters, which has been associated with chronic activation of the immune system. We hypothesized that bacteria colonizing the catheter lumen trigger an inflammatory response. We aimed to evaluate the inflammatory profile of hemodialysis patients before and after locking catheters with an antimicrobial lock solution. High-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), IL-10, and tumor necrosis factor alpha (TNF- α) were measured in serum, and levels of mRNA gene expression of IL-6, IL-10, and TNF- α were analyzed in peripheral blood mononuclear cells (PBMC). Samples were obtained at baseline and again after 3 months' use of taurolidine-citrate-heparin lock solution (TCHLS) in 31 hemodialysis patients. The rate of catheter-related bloodstream infections (CRBSI) was 1.08 per 1,000 catheter-days in the heparin period and 0.04 in the TCHLS period ($P = 0.023$). Compared with the baseline data, serum levels of hs-CRP and IL-6 showed median percent reductions of 18.1% and 25.2%, respectively ($P < 0.01$), without significant changes in TNF- α or IL-10 levels. Regarding cytokine gene expression in PBMC, the median mRNA expression levels of TNF- α and IL-6 decreased by 20% ($P < 0.05$) and 19.7% ($P = 0.01$), respectively, without changes in IL-10 expression levels. The use of TCHLS to maintain the catheter lumen sterility significantly reduces the incidence of CRBSI and improves the inflammatory profile in hemodialysis patients with tunneled catheters. Further studies are needed to evaluate the potential beneficial effects on clinical outcomes.

During the last few years, switching from a catheter to an arteriovenous fistula has been shown to be associated with a substantial decrease in mortality risk (1). Some authors have demonstrated that, even in the absence of catheter-related infection, patients receiving hemodialysis through a catheter had significantly higher serum concentrations of C-reactive protein, suggesting that chronic inflammation could be the reason for their significantly higher mortality rate (2–4). However, some patients are unable to have an arteriovenous fistula and it is therefore highly important to identify the mechanism through which catheters trigger a chronic inflammatory response even in the absence of clinically evident infection.

The catheter lumen is colonized by microorganisms during its insertion or as a result of manipulating the hub (5). Once the microorganisms are attached to the intraluminal surface of the catheter, they embed themselves in a matrix of extracellular polymeric substances, thereby creating a biofilm (6). The maturation of this complex structure is a dynamic process that requires a chemically controlled detachment of biofilm fragments that starts after the third day of biofilm formation (7). Dittmer et al. (8) grew blood cultures from the catheter weekly after insertion in 31 patients with a central venous hemodialysis catheter. When the central cultures became positive, indicating catheter colonization, peripheral venous blood cultures were taken during dialysis to detect peripheral bacteremia. Twenty-one catheters (68%) became colonized, and 11 patients (35%) developed peripheral bacteremia with the same organism. However, peripheral bacteremia occurred only when blood drawn from the catheter cultured more than 3,000 CFU per ml, suggesting that lower inoculums are

cleared by the host immune system, potentially triggering a chronic inflammatory response.

These observations prompted us to hypothesize that, if the chronic inflammation in patients with catheters is due to transient or persistent low-inoculum bacteria released from the catheter, maintaining efforts to reduce the bacterial colonization of the catheter lumen would be associated with a significant reduction in the inflammatory markers. To test this hypothesis, we obtained samples from patients enrolled in a study protocol performed in our institution to evaluate the efficacy of taurolidine-citrate-heparin lock solution (Taurolock, TauroPharm GmbH, Waldbüttelbrunn, Germany) in preventing catheter-related bacteremia, in order to analyze its potential beneficial effects on the inflammatory serum and gene expression profile.

MATERIALS AND METHODS

Patients. Thirty-one patients in a stable hemodialysis program using tunneled cuffed catheters with standard 5% heparin lock during the previous

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6 months (heparin phase) were enrolled in a study to prospectively evaluate the efficacy of taurolidine-citrate-heparin lock solution (TCHLS; 13,500 mg/liter of taurolidine, 4% citrate, and 500 IU of heparin) after each dialysis session for the following 6 months (TCHLS phase). Arterial and venous lines of each catheter were locked with 1.8 and 1.9 ml of TCHSL, respectively, and the solution was maintained for the entire period between hemodialysis sessions. The lock solution was always aspirated after it was used. All the catheters were placed under sterile conditions in the interventional vascular radiology department, and hemodialysis nurses used the same protocol for catheter manipulation during both heparin and TCHLS periods. All patients included in the study provided written informed consent in our institution and were undergoing hemodialysis with a 5008S Fresenius Medical Care machine and routine hemodialysis parameters: dialysis buffer with bicarbonate and 1.5-m² or 1.8-m² high-flux polysulfone or helixone filters. The variables gathered from each patient were age, sex, comorbidity, rate of catheter-related infections, tunnel infections, and bloodstream infections (CRBSI), hemodialysis dose, and the need for thrombolytic treatment with urokinase.

CRBSI were defined as growth of microbes from a blood sample drawn from a catheter at least 2 h before microbial growth was detected in a blood sample obtained from a peripheral vein (differential time to positivity), following the recommendations in the latest consensus statement of the Infectious Diseases Society of America (9). We also included paired blood cultures showing a recognized pathogen in the blood sample drawn from the catheter but without microorganisms in the blood sample obtained from a peripheral vein.

Inflammatory parameters. In all patients enrolled in the study, a 10-ml blood sample from a peripheral vein was obtained at baseline (before the start of TCHLS) and after 3 months of TCHLS use. Samples were always obtained after confirmation that the patient was clinically stable and had no documented infections at the moment of sampling or within the previous months. Serum was obtained and frozen at -80°C for biochemical analysis and measurement of inflammatory parameters. High-sensitivity C-reactive protein (hs-CRP) was measured by a high-sensitivity particle-enhanced immunoturbidimetric fully automated assay (Roche Diagnostics GmbH, Mannheim, Germany) in a Cobas 6000 analyzer from the same manufacturer (the functional sensitivity was 0.3 mg/liter, and the intra-assay precision and interassay precision were 1.6 and 8.4, respectively). Levels of tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), and IL-10 were measured by a high-sensitivity immunoenzymatic enzyme-linked immunosorbent assay (ELISA) method (Quantikine Human; R&D Systems, Minneapolis, MN) in a DSXTM 4-plate ELISA processor (Vitro SA, Spain). Minimum detectable concentrations were 0.10 pg/ml, 0.70 pg/ml, and 0.50 pg/ml, respectively. Intra- and interassay coefficients of variability were <10.8%.

Gene expression analysis. For analysis of gene expression in peripheral blood mononuclear cells (PBMC), whole-blood samples (2.5 ml) from the patients included in the study were collected in PAXgene blood RNA tubes (BD, Franklin Lakes, NJ) at the same time as serum samples. Total RNA was isolated using a PAXgene blood RNA kit (Qiagen, Valencia, CA) and was stored at -80°C. The quality of extracted RNA was tested using an Experion automated electrophoresis system (Bio-Rad Laboratories, Hercules, CA) to ensure that 28S and 18S rRNA bands were clearly evident. RNA was quantified using a Thermo Scientific NanoDrop 2000 spectrophotometer. The cDNA was obtained using a High Capacity RNA-to-cDNA kit (Applied Biosystems, Foster City, CA) to be used in reverse transcription-PCR (RT-PCR) and in quantitative RT-PCR (qRT-PCR).

Transcripts of TNF- α , IL-6, IL-10, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as constitutive genes were measured by real-time TaqMan quantitative PCR (qRT-PCR) with TaqMan Fast Universal PCR master mix (Applied Biosystems). TaqMan gene expression assays for each transcript [Hs00174128_m1 [TNF- α], Hs00985639_m1 [IL-6], Hs0961622_m1 [IL-10], and Hs99999905_m1 [GAPDH]] were analyzed in a 7500 Fast real-time PCR system (Applied Biosystems). The level of target mRNA was estimated by relative quantification using the compar-

ative threshold cycle (C_T) method ($2^{-\Delta\Delta C_T}$) by normalizing to GAPDH expression. Quantification of each cDNA sample was tested in triplicate, and a corresponding non-reverse transcriptase reaction was included as a control for DNA contamination.

Statistical analysis. The results are expressed as means and standard deviations (SD), except for hs-CRP and inflammatory cytokines, whose results are presented as geometric means and interquartile ranges and percentages. The Shapiro-Wilk W test was used to test for normality. Due to nonnormal distribution, serum concentrations of inflammatory parameters and gene expression ratios were logarithmically transformed for analyses and were then back-transformed to their natural units for presentation in tables and figures. Continuous variables were compared using Student's *t* test and categorical variables using the χ^2 test or Fisher's exact test when necessary. A *P* value < 0.05 was considered statistically significant. The statistical analysis was performed using the PASW 19.0 package (SPSS, Inc., Chicago, IL).

RESULTS

A total of 31 patients were included in the study, with a mean (SD) age of 73.9 (15.1) years (range, 32 to 92 years); 18 were male (58%). Underlying kidney diseases (KDs) consisted of chronic glomerulonephritis in 5 patients, nephroangiosclerosis in 6 patients, diabetic nephropathy in 8 patients, chronic tubulointerstitial disease in 2 patients, polycystic kidney disease in 1 patient, and undiagnosed kidney disease in 9 patients. The most common comorbidities were hypertension in 24 patients (77%), diabetes mellitus in 10 (32%), dyslipidemia in 11 (35%), ischemic heart disease in 9 (29%), peripheral vascular disease in 6 (19%), and previous stroke in 6 (19%). The mean (SD) time on hemodialysis was 60.8 (64.2) months, with a range of 12 to 336 months. The tunneled catheter was placed in the jugular vein in 29 patients (93.5%) and in the femoral vein in 2 (6.5%). The dialysis dose measured with on-line dialysance (Kt) was 52.3 \pm 10.5 liters during the heparin phase and 55.8 \pm 9.8 liters during the TCHL phase, without significant differences.

A total of eight episodes of CRBSI were identified, seven during the heparin lock solution phase and one during the TCHLS phase. The species of microbial isolates collected during the study period consisted of three cases of coagulase-negative *Staphylococcus* spp., two of *Enterobacter cloacae*, one of *Klebsiella oxytoca*, one of *Pseudomonas aeruginosa*, and one of *Streptococcus haemolyticus*. The incidence of CRBSI was 1.08 per 1,000 catheter-days during the heparin phase and was 0.04 during the TCHLS phase (*P* = 0.023). During the TCHLS phase, the mean cost due to the use of thrombolytic treatment with urokinase decreased (251.6 \pm 471.1 Euros versus 460.8 \pm 1,004.1 Euros; *P* = 0.653).

Analysis of changes in the inflammatory profile showed that, after 3 months of TCHLS, serum levels of IL-10 and TNF- α were unchanged, whereas serum concentrations of hs-CRP and IL-6 were significantly reduced compared with the baseline levels: 1.0 (0.4 to 2.6) pg/ml and 9.3 (5.3 to 14.8) pg/ml versus 0.8 (0.5 to 1.0) pg/ml and 7.0 (3.9 to 10.6) pg/ml, respectively (*P* = 0.01) (Table 1). Compared with the baseline values, the median percent variations for serum hs-CRP and IL-6 were, respectively, -18.1% (-33.3 to 25.0) and -25.2% (-44.9 to 27.0) (*P* < 0.01) (Fig. 1). Hs-CRP levels increased in 9 of 31 patients and IL-6 levels in 8 of 31 patients; interestingly, levels of both cytokines increased in the patient who had had bacteremia during TCHLS. The balance between pro- and anti-inflammatory forces was evaluated by changes in the ratios between TNF- α and IL-6 and the anti-inflammatory cytokine IL-10. The TNF- α /IL-10 and IL-6/IL-10 ra-

TABLE 1 Changes in serum concentrations of inflammatory parameters and mRNA expression levels in peripheral blood mononuclear cells after the use of TCHLS

Parameter ^a	Values ^b		P value
	Baseline	3 mos	
Serum concn			
hs-CRP (mg/liter)	1.0 (0.4–2.6)	0.8 (0.5–1.0)	0.015
IL-6 (pg/ml)	9.3 (5.3–14.8)	7.0 (3.9–10.6)	0.01
IL-10 (pg/ml)	0.8 (0.3–2.1)	1.0 (0.5–2)	0.23
TNF- α (pg/ml)	3.1 (0.5–9.4)	3.1 (1.5–8.9)	0.37
mRNA expression level (fold increase)			
TNF- α	2.2 (1.4–3.0)	1.6 (1.4–2.1)	0.02
IL-6	2.5 (2.2–3.5)	1.9 (1.1–3.5)	0.01
IL-10	0.6 (0.4–1.5)	0.4 (0.2–1.1)	0.07

^a hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; TCHLS, taurolidine-citrate-heparin lock solution; TNF- α , tumor necrosis factor alpha.

^b Data are expressed as geometric means and interquartile ranges (IQR).

tios after TCHLS showed a reducing trend with respect to the baseline values, with median decreases of 16.5% ($P = 0.1$) and 40.6% ($P = 0.06$), respectively.

Changes in mRNA expression levels of the proinflammatory cytokine genes in PBMC are shown in Fig. 1. After 3 months of TCHLS, pretreatment mRNA expression levels of TNF- α and IL-6 significantly decreased, with median percent reductions of 20% for TNF- α ($P < 0.05$) and 19.7% for IL-6 ($P = 0.01$), without changes in IL-10 expression levels. The median values of the TNF- α /IL-10 and IL-6/IL-10 mRNA expression ratios decreased by 29.1% and 15.6%, although these changes did not reach statistical significance ($P = 0.1$ and $P = 0.09$, respectively).

DISCUSSION

The main aim of this study was to evaluate the potential beneficial effect of TCHLS in preventing CRBSI through analysis of the inflammatory profile of hemodialysis patients with tunneled catheters. Our results show that the use of TCHLS as a maintenance treatment lock significantly reduces the rate of CRBSI and decreases the cost of the use of thrombolytic treatment with urokinase without requiring changes in the dialysis dose. This study characterized the effects of TCHLS on the inflammatory profile of these patients, demonstrating a reduction in the serum concentration of the main inflammatory cytokines, as well as the effects on levels of mRNA gene expression of these molecules in PBMC.

Inflammation is a highly prevalent condition in patients with chronic kidney disease (CKD) which has been related to important complications, including accelerated atherosclerosis and elevated cardiovascular morbidity and mortality (10). In patients with end-stage renal disease under treatment with hemodialysis, an inflammatory reaction may originate from several factors, including vascular access (central venous catheters and grafts) (11). Hemodialysis through a tunneled cuffed catheter is associated with a 1.4-fold-higher risk of all-cause mortality and a 3-fold-higher risk of death due to an infection (12). This risk is significantly reduced after catheter removal (1). It has been recently reported that patients with tunneled catheters, even in the absence of infection, have a higher serum CRP concentration, suggesting the development of a chronic inflammatory response (2, 3). Cytokines are crucial molecules in the inflammatory process, with

key roles in critical pathways resulting in cardiovascular injury, including vascular calcification and atherosclerosis (13, 14). The Cardiovascular Health Study reported that patients with renal failure had significantly higher levels of CRP and IL-6 than subjects with normal renal function (15). More importantly, these inflammatory parameters were independently associated with cardiovascular and all-cause mortality in hemodialysis patients, with a better prognostic value than that of other inflammatory parameters (16, 17). Therefore, identifying the mechanism that triggers the inflammatory response in this population is of great interest.

Previous studies have reported a high rate of catheter lumen colonization in hemodialysis (8), a reduction in erythropoietin use, and an increase in hemoglobin levels in patients receiving gentamicin lock solution compared with those receiving heparin lock solution—a benefit that was maintained after removing patients with CRBSI from the analysis (18)—and have indicated that bacterial products are able to induce immune activation in the absence of clinical bacteremia (19, 20). On the basis of these findings, we hypothesized that bacterial colonization of the catheter lumen is an inflammatory stimulus and, therefore, that the use of an antimicrobial lock solution would be associated with a modulation of inflammation in these patients. To support our hypothesis, we evaluated the serum inflammatory profile and mRNA expression levels of PBMC inflammatory cytokines in 31 patients with hemodialysis using tunneled catheters after 3 months of TCHLS. After this period, we found that the serum concentrations of hs-CRP and IL-6 were significantly decreased, representing median percent reductions of 18.1% and 25.2% versus baseline values, respectively. To the best of our knowledge, this is the first study to have evaluated inflammatory serum and gene expression profiles after the use of an antimicrobial lock solution.

Taurolidine has activity against Gram-positive and Gram-negative bacteria and *Candida* spp. and has been commercialized combined with citrate and heparin to avoid occlusion. A study by Solomon et al. (21) observed that the addition of 500 U/ml heparin and 4% citrate to taurolidine reduces the need for thrombolytic agents without increasing the bacteremia rate. In the present study, the use of TCHLS was not associated with any change in the dialysis dose measured with on-line dialysance (Kt). However, the mean cost of the use of thrombolytic treatment with urokinase decreased by 45% during the TCHLS phase compared with the

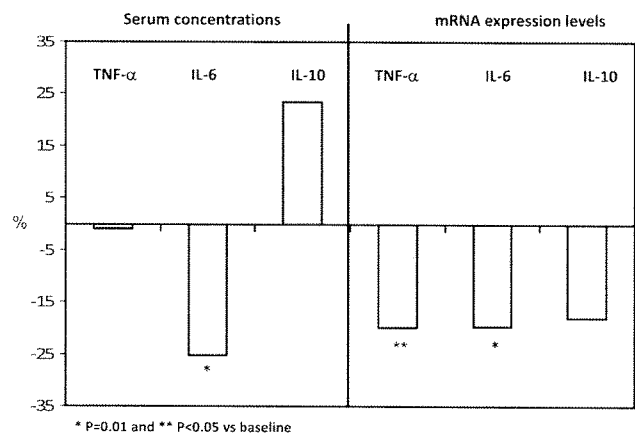


FIG 1 Median percent variations in serum concentrations and mRNA expression levels of inflammatory cytokines after the use of TCHLS.

previous phase of heparin lock. Regarding CRBSI, several studies have shown the efficacy of TCHLS in preventing this complication in patients with cancer and in those receiving home parenteral nutrition or hemodialysis (22–24), with a low risk of resistance development (25). Handrup et al. (26) showed that taurolidine significantly reduced the incidence of CRBSI compared with heparin lock but that there was no statistically significant difference in biofilm formation measured by scanning electron microscopy. In that interesting study, the authors found that biofilm was often present in catheters without the patients experiencing any symptoms and was also often present without growth of microbes when the catheters were cultured. A possible explanation for these results is that bacteria in a biofilm are capable of transforming into a slow-growing phase (27) and that, consequently, this phenomenon inhibits the migration of live bacteria into the bloodstream. According to the results of our study, maintaining the catheter lumen sterility with TCHLS is associated with a significant reduction in serum concentrations of inflammatory parameters and mRNA expression in PBMC. Although these results are not confirmatory, they strongly support our hypothesis to explain the beneficial effects of TCHLS on chronic immune activation in hemodialysis patients with tunneled catheters. These findings are of particular interest, since the use of central venous catheters for permanent vascular access has increased in the last few years (28). Indeed, according to the last published report in 2011, among 3,194 patients on hemodialysis in Catalonia, 727 (20.2%) had a tunneled catheter (29).

The major limitations of our study were the small number of patients, the randomized design, and the relatively short period of analysis (only 3 months), which did not allow us to evaluate the potential impact of our findings on other important clinical aspects such as hemoglobin levels, epoetin consumption, cardiovascular disease, and the mortality rate. Another limitation is that we did not confirm the sterility of the catheter lumen using TCHLS (e.g., doing surveillance blood cultures through the catheter); however, the significant reduction of the CRBSI rate is a good surrogate marker for lumen sterilization.

Conclusions. In adult patients with end-stage renal disease under treatment with hemodialysis with cuffed tunneled catheters, the use of TCHLS after each hemodialysis session is associated with a significant improvement in the inflammatory serum and cytokine gene expression profile in PBMC, as well as a significant reduction in the rate of CRBSI. Future studies are required to confirm our results and to evaluate the long-term consequences of maintaining the sterility of the catheter lumen.

REFERENCES

- Allon M, Daugirdas J, Depner TA, Greene T, Ornt D, Schwab SJ. 2006. Effect of change in vascular access on patient mortality in hemodialysis patients. *Am. J. Kidney Dis.* 47:469–477. <http://dx.doi.org/10.1053/j.ajkd.2005.11.023>.
- Goldstein SL, Ikizler TA, Zappitelli M, Silverstein DM, Ayus JC. 2009. Non-infected hemodialysis catheters are associated with increased inflammation compared to arteriovenous fistulas. *Kidney Int.* 76:1063–1069. <http://dx.doi.org/10.1038/ki.2009.303>.
- Al Saran K, Sabry A, Shalaby M, Al Sherbeiny S, Abdelkader M. 2013. Level of C-reactive protein in chronic hemodialysis patients: a comparative study between patients with non-infected catheters and arteriovenous fistula in a large Saudi hemodialysis center. *Ther. Apher. Dial.* 17:35–39. <http://dx.doi.org/10.1111/j.1744-9987.2012.01116.x>.
- Yeun JY, Levine RA, Mantadilok V, Kaysen GA. 2000. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am. J. Kidney Dis.* 35:469–476. [http://dx.doi.org/10.1016/S0272-6386\(00\)70200-9](http://dx.doi.org/10.1016/S0272-6386(00)70200-9).
- Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP. 1993. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. *J. Infect. Dis.* 168:400–407. <http://dx.doi.org/10.1093/infdis/168.2.400>.
- Costerton JW, Stewart PS, Greenberg EP. 1999. Bacterial biofilms: a common cause of persistent infections. *Science* 284:1318–1322. <http://dx.doi.org/10.1126/science.284.5418.1318>.
- Periasamy S, Joo HS, Duong AC, Bach TH, Tan VY, Chatterjee SS, Cheung GY, Otto M. 2012. How *Staphylococcus aureus* biofilms develop their characteristic structure. *Proc. Natl. Acad. Sci. U. S. A.* 109:1281–1286. <http://dx.doi.org/10.1073/pnas.1115006109>.
- Dittmer ID, Sharp D, McNulty CA, Williams AJ, Banks RA. 1999. A prospective study of central venous hemodialysis catheter colonization and peripheral bacteremia. *Clin. Nephrol.* 51:34–39.
- Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad I, Rijnders BJ, Sherertz RJ, Warren DK. 2009. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* 49:1–45. <http://dx.doi.org/10.1086/599376>.
- Foley RN, Parfrey PS, Sarnak MJ. 1998. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am. J. Kidney Dis.* 32:S112–S119. <http://dx.doi.org/10.1053/ajkd.1998.v32.pm9820470>.
- Nadsem M, Stephen L, Schubert C, Davids MR. 2009. Association between periodontitis and systemic inflammation in patients with end-stage renal disease. *SADJ* 64:470–473.
- Pastan S, Soucie JM, McClellan WM. 2002. Vascular access and increased risk of death among hemodialysis patients. *Kidney Int.* 62:620–626. <http://dx.doi.org/10.1046/j.1523-1755.2002.00460.x>.
- Swaminathan S, Shah SV. 2011. Novel inflammatory mechanisms of accelerated atherosclerosis in kidney disease. *Kidney Int.* 80:453–463. <http://dx.doi.org/10.1038/ki.2011.178>.
- Tedgui A, Mallat Z. 2006. Cytokines in atherosclerosis: pathogenic and regulatory pathways. *Physiol. Rev.* 86:515–581. <http://dx.doi.org/10.1152/physrev.00024.2005>.
- Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM. 2003. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107:87–92. <http://dx.doi.org/10.1161/01.CIR.0000042700.48769.59>.
- Zoccali C, Tripepi G, Mallamaci F. 2006. Dissecting inflammation in ESRD: do cytokines and C-reactive protein have a complementary prognostic value for mortality in dialysis patients? *J. Am. Soc. Nephrol.* 17(Suppl 3):S169–S173. <http://dx.doi.org/10.1681/ASN.2006080910>.
- Barreto DV, Barreto FC, Liabeuf S, Temnar M, Lemke HD, Tribouilloy C, Choukroun G, Vanholder R, Massy ZA, European Uremic Toxin Work Group (EUTox). 2010. Plasma interleukin-6 is independently associated with mortality in both hemodialysis and predialysis patients with chronic kidney disease. *Kidney Int.* 77:550–556.
- McIntyre CW, Hulme LJ, Taal M, Fluck RJ. 2004. Locking of tunneled hemodialysis catheters with gentamicin and heparin. *Kidney Int.* 66:801–805. <http://dx.doi.org/10.1111/j.1523-1755.2004.00806.x>.
- Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC. 2006. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat. Med.* 12:1365–1371. <http://dx.doi.org/10.1038/nm1511>.
- Jiang W, Lederman MM, Hunt P, Sieg SF, Haley K, Rodriguez B, Landay A, Martin J, Sinclair E, Asher AI, Deeks SG, Douek DC, Brenchley JM. 2009. Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection. *J. Infect. Dis.* 199:1177–1185. <http://dx.doi.org/10.1086/597476>.
- Solomon LR, Cheesbrough JS, Bhargava R, Mitsides N, Heap M, Green G, Diggle P. 2012. Observational study of need for thrombolytic therapy and incidence of bacteremia using taurolidine-citrate-heparin, taurolidine-citrate and heparin catheter locks in patients treated with hemodialysis. *Semin. Dial.* 25:233–238. <http://dx.doi.org/10.1111/j.1525-139X.2011.00951.x>.
- Betjes MG, van Agteren M. 2004. Prevention of dialysis catheter-related

- sepsis with a citrate-taurolidine-containing lock solution. *Nephrol. Dial. Transplant.* 19:1546–1551. <http://dx.doi.org/10.1093/ndt/gfh014>.
23. Al-Amin AH, Sarveswaran J, Wood JM, Burke DA, Donnellan CF. 1 July 2013. Efficacy of taurolidine on the prevention of catheter-related bloodstream infections in patients on home parenteral nutrition. *J. Vasc. Access* <http://dx.doi.org/10.5301/jva.5000168>.
 24. Handrup MM, Møller JK, Schröder H. 2013. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of taurolidine versus heparin. *Pediatr. Blood Cancer* 60:1292–1298. <http://dx.doi.org/10.1002/pbc.24482>.
 25. Olthof ED, Rentenaar RJ, Rijs AJ, Wanten GJ. 2013. Absence of microbial adaptation to taurolidine in patients on home parenteral nutrition who develop catheter related bloodstream infections and use taurolidine locks. *Clin. Nutr.* 32:538–542. <http://dx.doi.org/10.1016/j.clnu.2012.11.014>.
 26. Handrup MM, Fuursted K, Funch P, Møller JK, Schröder H. 2012. Biofilm formation in long-term central venous catheters in children with cancer: a randomized controlled open-labelled trial of taurolidine versus heparin. *APMIS* 120:794–801. <http://dx.doi.org/10.1111/j.1600-0463.2012.02910.x>.
 27. Beenken KE, Dunman PM, McAleese F, Macapagal D, Murphy E, Projan SJ, Blevins JS, Smeltzer MS. 2004. Global gene expression in *Staphylococcus aureus* biofilms. *J. Bacteriol.* 186:4665–4684. <http://dx.doi.org/10.1128/JB.186.14.4665-4684.2004>.
 28. Robinson BM, Bieber B, Pisoni RL, Port FK. 2012. Dialysis Outcomes and Practice Patterns Study (DOPPS): its strengths, limitations, and role in informing practices and policies. *Clin. J. Am. Soc. Nephrol.* 7:1897–1905. <http://dx.doi.org/10.2215/CJN.04940512>.
 29. Department of Public Health: Catalonia registry. 2011. Statistical report 2011. OCAT. <http://www20.gencat.cat>.