Sodium bicarbonate catheter lock solution reduces hemodialysis catheter loss due to catheter-related thrombosis and bloodstream infection: an open-label clinical trial

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ABSTRACT

Background. There is no ideal lock solution that prevents hemodialysis (HD) catheter loss due to catheter-related thrombosis (CRT) and catheter-related bloodstream infection (CRBSI). Catheter loss is associated with increased hospitalization and high inpatient costs. Sodium bicarbonate (NaHCO3) demonstrates anti-infective and anticoagulation properties with a good safety profile, making it an ideal lock solution development target.

The objective of this study was to determine the safety and efficacy of using sodium bicarbonate catheter lock solution (SBCLS) as a means of preventing HD catheter loss due to CRT and CRBSI.

Methods. The study took place in a community hospital in Brooklyn, NY, USA. All admitted patients ≥18 years of age who needed HD treatment through CVC were included in the study. 451 patients included in the study were provided SBCLS or NSCLS post-dialysis. Catheter loss due to CRT or CRBSI was evaluated over a period of 546 days.

Results. A total of 452 patients met the criteria; 1 outlier was excluded, 226 were in the NSCLS group and 225 were in the SBCLS group. There were no significant differences between groups in comorbidities at the outset. The NSCLS group had CRT and CRBSI rates of 4.1 and 2.6/1000 catheter days (CD), respectively, compared with 0.17/1000 CD for both outcomes in the SBCLS group. SBCLS patients had a significantly reduced catheter loss rate due to CRT (P < 0.0001) and CRBSI (P = 0.0004). NSCLS patients had higher odds of losing their catheter due to CRT [odds ratio (OR) 26.6 [95% confidence interval (CI) 3.57–198.52]] and CRBSI [OR 15.9 (95% CI 2.09–121.61)] during the study period.

Conclusion. The novel approach of using SBCLS was found to be safe and was statistically superior to normal saline in preventing HD catheter loss due to CRT and CRBSI. NaHCO3 solution is inexpensive, readily available in various settings and holds the potential to decrease hospitalization, length of stay and dialysis-related costs.

Trial registration. Maimonides Medical Center Investigational Review Board, Study IRB 2015-06-25-CIH. ClinicalTrials.gov identifier: NCT03627884.

Keywords: catheter lock, catheter-related bloodstream infection, catheter-related thrombosis, ESRD, sodium bicarbonate

INTRODUCTION

Central venous catheters (CVCs), originally introduced for short-term dialysis, have become an acceptable form of permanent vascular access [1–3]. CVCs evolved as a bridge to optimal management in hemodialysis (HD) patients who await arteriovenous fistula (AVF) maturation as well as a solution for patients who have no alternate access [2, 4]. Despite great advances, two major causes of catheter loss continue to plague sustained effective HD treatment: catheter-related thrombosis (CRT) and catheter-related bloodstream infection (CRBSI) [5, 6].

A report suggests that up to 42% of catheter-related dysfunction is attributable to CRT, and a prospective study suggested that catheter-dependent HD patients have a 35% probability of developing bacteremia within 3 months of catheter insertion [2, 7]. Given the high percentage of dialysis patients who develop CRT and CRBSI, management that mitigates these rates may prove itself invaluable.
Multiple studies have assessed the role of catheter lock solutions for the prevention of CRT and CRBSI. Antibiotic locks demonstrated a reduction in CRBSI; however, there is growing concern that their overuse enables the development of antibiotic resistance [6, 8–13]. Furthermore, Landry and Braden [14] concluded that no ideal catheter lock solution existed that could prevent catheter loss due to CRT and CRBSI.

In reviewing the long history of developing an ideal lock solution, Wong et al. [15] and Wong [16] studied the effects of bicarbonate on blood coagulation. They suggested that removing bicarbonate chelated calcium ions from the coagulation pathway required calcium as a cofactor. In doing so, the bicarbonate-mediated chelation of calcium ions indirectly inhibited the conversion of fibrinogen to fibrin, leading to decreased clotting [15, 16].

Building upon this work, in our previous clinical study we demonstrated the novel approach of using sodium bicarbonate catheter lock solution (SBCLS) as an inexpensive, safe and effective method in preventing HD catheter loss due to clot formation [17]. We also found no CRBSI in the group using SBCLS. However, this finding could not be statistically validated because the sample size was not large enough. Based on the extensive literature review, we hypothesized that sodium bicarbonate (NaHCO3) can play an important role in preventing catheter loss due to CRBSI by multiple anti-infective mechanisms.

NaHCO3 has been shown to inhibit bacterial proliferation by decreasing bacterial adherence and preventing biofilm formation [18, 19]. 'Biofilms are gelatinous masses of microorganisms capable of attaching to virtually any surface. They glom onto medical devices where they are deadly or difficult to eradicate' [20]. According to the National Institutes of Health, they factor into nearly 80% of all bacterial infections and are inherently resistant to antibiotics [21]. Biofilms plague hospitals and contribute greatly to our health care burden, and approaches that minimize biofilm formation are good targets for antimicrobial research [20, 22].

Staphyloccoci are biofilm-forming pathogens commonly associated with serious foreign body and catheter-related infections across settings [20, 23]. Ní Eidhin et al. [24] found a subfamily of adhesins, microbial surface components that recognize adhesive matrix molecules, promoted *Staphylococcus aureus* adherence to HD tubing by targeting extracellular matrix components such as fibrinogen [24]. Adhesins found in similar bacteria were able to confer virulence based on this approach, and it is evident that adhesins contribute greatly to biofilm formation [25]. Alkaline solutions, such as those containing NaHCO3, have been observed to interfere with staphyloccoci adherence and prevent biofilm formation [23].

Additional evidence from other studies suggested that NaHCO3 served as an abundant ionic factor that stimulated global changes in bacterial structure, gene expression and membrane permeability [18, 19, 23, 26–30]. These changes corresponded to the increased susceptibility of microbes to human cationic antimicrobial peptides [18, 19, 23, 26–30]. NaHCO3 was also found to inhibit the growth of bacteria and yeast in agar media [31]. Morphologic examinations by transmission electron microscopy of microorganisms exposed to NaHCO3 solution demonstrated cytoplasmic shrinkage and fibrillar condensation [28]. These cellular changes rendered susceptible bacteria less viable through hindered proliferation [28]. Although these are just a few examples, the evidence of NaHCO3’s antimicrobial properties continues to accumulate.

It is clear that pathogens encountering NaHCO3 must devise facultative qualities to survive an environment that interferes with surface adhesion, biofilm formation and enzymatic processes vital for proliferation [18, 19, 23, 26–30, 32]. In contrast to the inhibitory effects of NaHCO3, equimolar sodium chloride had no effect on growth, ruling out any osmotic or sodium-mediated mechanisms of inhibition [31].

In addition to these antimicrobial properties, an advantage of using SBCLS over other antimicrobial agents is its safety, availability and low cost that is comparable to normal saline catheter lock solution (NSCLS) [28]. The low cost and numerous benefits make NaHCO3 an ideal candidate for development as a locking solution. In this trial we tested the translation of this evidence into the potential clinical use of NaHCO3 as a microbial deterrent for CRBSI in HD patients.

**MATERIALS AND METHODS**

CVCs used in the study varied according to the patient’s needs and consisted of either Mahurkar acute dual lumen catheters, made of polyurethane, or Palindrome chronic catheters, made of urethane. The exposure of polyurethane and urethane catheters to NaHCO3 is considered extremely safe based on the chemical compatibility data and regular clinical use [33, 34].

Mahurkar catheters were not tunneled and Palindrome catheters were tunneled beneath the skin. All CVCs were inserted by an expert operator under strict aseptic protocol. Catheter care was performed by trained dialysis staff according to our hospital’s Administrative Policy and Procedure Manual. At the end of dialysis, all catheters were flushed and locked with one of the two solutions. SBCLS contained 7.5 or 8.4% NaHCO3 at a pH of 7.0–8.5 and was used to lock SBCLS group catheters. An 8.4% SBCLS was used primarily, except for 1 week when our hospital had a shortage of 8.4% SBCLS. During that single week we used 7.5% SBCLS to lock SBCLS group catheters. The NSCLS contained 0.9% sodium chloride at a pH of 4.5–7.0 and was used to lock NSCLS group catheters. All solutions used were sterile nonpyrogenic solutions. Dialysis was performed only on Fresenius model 4008K2 dialysis machines using Advanced Fresenius Polysulfone Optiflux F180NR dialyzers (Fresenius, Bad Homburg vor der Höhe, Germany).

**Study design and patients**

We conducted a prospective cohort, clinical open-label trial at Coney Island Hospital, in Brooklyn, NY, USA. The study period was between 1 October 2016 and 30 March 2018, a total of 546 days. All patients provided written informed consent before enrollment. The trial protocol was approved by the Maimonides Medical Center Investigational Review Board (Study 2015-06-25-CIH). Patients >18 years of age requiring HD via CVCs were eligible. One patient was excluded due to a poor venous system with inadequate blood flow for appropriate HD. No other patient was excluded from the study.
A total of 451 patients undergoing HD with CVCs were included in the study. Patients had tunneled internal jugular vein (IJV) catheters, nontunneled IJV catheters and nontunneled femoral vein catheters. All patients were randomly assigned based on the simple sequential order into one of the two groups: NSCLS (n = 226) and SBCLS (n = 225). NSCLS patients were assigned between 1 October 2016 and 30 June 2017. SBCLS patients were assigned between 1 July 2017 and 30 March 2018. Recruitment ended based on the similar number of enrolled participants between groups. A primary or coinvestigator enrolled the participant into the trial and assigned the participant to the intervention at the time of presentation. Both groups received heparin-free HD treatment. Before each HD treatment, catheters and connections were inspected for leaks, evidence of damage, exit-site infection and tunnel infection. Intraluminal SBCLS or NSCLS lock solution was removed before connecting the HD catheter to a dialysis machine prior to any treatment.

During each treatment, patients were monitored for complications and standard care was provided to every patient. After each treatment, blood was rinsed from the dialysis lines with normal saline solution back to the patient. Upon the conclusion of treatment, each port of all two-port catheters was flushed and locked with 10 mL of NSCLS or SBCLS, respective of the patient’s group. Approximately 2 mL of the injected solution remained locked within the catheter. Catheter exit-site dressing changes occurred after each HD treatment.

We undertook this study for three reasons. First, the US Food and Drug Administration issued an urgent warning to all hospital pharmacies and HD units that citrate-containing tricosatol may cause death when infused into patients [35]. Second, high-concentration (5000 or 10 000 U/mL) heparin-containing catheter locking solution is associated with major bleeding complications after tunneled HD catheter placement [36]. Third, low-concentration (1000 U/mL) heparin catheter lock solution is associated with greater tissue plasmin alaphase use, which further increases bleeding risk and costs [37].

For this last reason, in patients who had clotted catheters, thrombolytic therapy was not instituted. Risk assessment performed by our hospital’s risk management department determined that the net risk of thrombolytic use in their opinion was greater than the net risk of catheter replacement by our qualified operators.

Outcome variables

The primary outcome measured the removal of catheters due to CRBSI, CRT and malfunction. Based on the CDC definitions, CRBSI was diagnosed when clinical sepsis symptoms (clinical manifestations) and empirical evidence of an infection related to the catheter were present [38].

Acceptable empirical evidence of CRBSI was defined as two peripheral venous blood samples drawn from the patient producing positive quantitative (>1000 CFU/segment) culture results. Alternatively, one positive blood culture obtained from a peripheral vein and one catheter culture with a positive semi-quantitative (>15 CFU/segment) result was acceptable. Comparison cultures must have grown the same microorganism, identified by its species and antibiogram, and must have resulted within 2 h of each other. Although this contrasts from practice suggested by Pelletier et al. [39], our institution does not find the evidence compelling to depart from the CDC guidelines at this time.

In concordance with National Kidney Foundation guidelines, catheter dysfunction was defined when extracorporeal blood flow was ≤300 mL/min or the prepump arterial pressure was ≥-250 mmHg [40]. Malfunctioning catheters were recorded when the catheter showed a visible kink or repositioning maneuvers such as ipsilateral arm raising, sitting, standing or rolling the patient onto one side led to catheter dysfunction reversibility. Catheter loss due to CRT was defined as persistent catheter malfunctioning, irreversible difficulty with line aspiration or infusion despite repositioning before or during HD.

Statistical analysis

The assumption of normality for continuous variables was assessed using skewness and kurtosis statistics. Frequency and cross-tabulation statistics were run on categorical variables. The NSCLS and SBCLS groups were compared on baseline demographic and clinical variables using between-group comparisons and all statistical assumptions (normality and homogeneity) were analyzed before interpreting the results. Results are expressed as sample mean (standard deviation) or as a percentage.

Independent sample t-tests were used to compare the groups on normal continuous outcomes. Mann–Whitney U-tests were utilized for between-subject comparisons when statistical assumptions were violated. Chi-square and Fisher’s exact tests were used for testing categorical associations. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were used to compare the rates of catheter adverse events between the NSCLS and SBCLS groups. Statistical significance was assumed at an α-value of 0.05 and all analyses were conducted using SPSS Version 22 (IBM, Armonk, NY, USA).

RESULTS

A total of 451 patients were included in the sample. Of the participants, 226/451 (50.1%) were in the NSCLS group and 225/451 (49.9%) in the SBCLS group. There were no significant differences between groups on onset demographics or exposure, except for serum albumin level (P = 0.006) (Table 1). The NSCLS group patients underwent a combined 2480 treatments corresponding to 5787 catheter days (CD). SBCLS group patients underwent a combined 2474 treatments corresponding to 5773 CD.

Primary outcome variables demonstrated statistically significant between-group differences. In the NSCLS group, 24/226 (10.6%) patients lost catheters due to CRT, 15/226 (6.6%) due to CRBSI and 5/226 (2.2%) due to other malfunctions not attributable to CRT or CRBSI for a total of 44/226 (19.5%) due to all causes. This corresponds to 4.1 CRT and 2.6 CRBSI/1000 CD in the NSCLS group. In the SBCLS group, 1/225 (0.4%) patient lost a catheter due to CRT, 1/225 (0.4%) due to CRBSI and 5/225 (2.2%) due to other malfunctions not attributable to CRT or CRBSI for a total of 7/225 (3.1%) due to all causes. This corresponds to 0.17 CRT and 0.17 CRBSI/1000 CD in the SBCLS group.
group. Malfunction occurred in 0.86/1000 CD in the NSCLS group and 0.87/1000 CD in the SBCLS group (Figure 1).

The SBCLS group was found to have a lower rate of catheter loss due to CRT (P < 0.0001), whereas the NSCLS group had 26.6 times higher odds (95% CI 3.57–198.52) of losing catheters due to CRT (Table 2). SBCLS patients also had a lower rate of catheter loss due to CRBSI (P = 0.0004), whereas NSCLS patients had 15.9 times higher odds (95% CI 2.09–121.61) of losing catheters due to CRBSI (Table 2). No differences between groups were observed for catheter loss due to malfunction (P = 1) (Table 2). Overall, SBCLS patients had reduced catheter loss (P < 0.0001) and NSCLS patients had 7.5 times higher odds (95% CI 3.31–17.12) of losing their catheter. A comparison of the P-values, rates and ORs (95% CIs) for each primary outcome can be found in Table 2.

Table 3 summarizes the post hoc subgroup analysis comparing tunneled and nontunneled catheters used in the internal jugular site. Reductions in catheter loss remained statistically significant for SBCLS patients on primary outcomes, irrespective of catheter type. No deaths or significant adverse events related to HD occurred in any group. Figure 2 visually demonstrates group outcomes via a flow diagram.

DISCUSSION

Infections are common complications among HD patients. Compared with patients with an AVF or graft, HD patients with a CVC have more than double the risk of hospitalization for infection and death [41]. Although nontunneled HD CVCs

| Characteristic          | NSCLS, n (%) | SBCLS, n (%) | P-value | OR (95% CI)* |
|-------------------------|--------------|--------------|---------|--------------|
| Age (years), median (SD)| 69.0 (18.0)  | 69.0 (19.5)  | 0.84    |              |
| Weight (kg), mean (SD)  | 76.5 (23.0)  | 76.4 (22.0)  | 0.96    |              |
| Height (cm), mean (SD)  | 163.3 (7.1)  | 163.9 (8.5)  | 0.44    |              |
| PT, median (SD)         | 11.9 (1.2)   | 12.0 (1.2)   | 0.76    |              |
| INR, median (SD)        | 1.0 (0.2)    | 1.1 (0.2)    | 0.59    |              |
| aPTT, median (SD)       | 30.1 (4.3)   | 30.2 (4.2)   | 0.62    |              |
| Ca, mean (SD)           | 8.6 (0.9)    | 8.5 (0.8)    | 0.42    |              |
| Serum albumin, mean (SD)| 3.3 (0.8)    | 3.4 (1.0)    | 0.006   |              |
| Phos, mean (SD)         | 4.0 (1.5)    | 3.7 (1.4)    | 0.06    |              |
| CO2, mean (SD)          | 23.3 (3.3)   | 23.7 (3.1)   | 0.15    |              |
| Hemoglobin, mean (SD)   | 9.3 (1.5)    | 9.4 (1.4)    | 0.68    |              |
| Gender, n (%)           |              |              |         |              |
| Male                    | 111 (49.1)   | 119 (52.9)   | 0.42    |              |
| Female                  | 115 (50.9)   | 106 (47.1)   |         |              |
| Race, n (%)             |              |              |         |              |
| Caucasian               | 120 (53.1)   | 122 (54.2)   | 0.96    |              |
| African American        | 31 (13.7)    | 34 (15.1)    |         |              |
| Asian                   | 16 (7.1)     | 17 (7.6)     |         |              |
| Hispanic                | 38 (16.8)    | 33 (14.7)    |         |              |
| Other                   | 21 (9.3)     | 19 (8.4)     | 0.96    |              |
| HTN, n (%)              | 196 (86.7)   | 197 (87.6)   | 0.79    |              |
| DM, n (%)               | 122 (54.0)   | 121 (54.3)   | 0.95    |              |
| CAD, n (%)              | 131 (58.0)   | 133 (59.6)   | 0.72    |              |
| IJV tunneled, n (%)     | 160 (71.1)   | 173 (76.9)   | 0.14    |              |
| IJV not tunneled, n (%) | 55 (24.3)    | 45 (20.0)    | 0.27    |              |
| Femoral vein, n (%)     | 11 (4.9)     | 7 (3.1)      | 0.34    |              |
| HD treatments, mean (SD)| 11.01 (8.46) | 11.00 (8.46) | 1.00    |              |

PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; Ca, calcium; Phos, phosphorus; CO2, carbon dioxide; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease.

Table 3. Internal jugular subgroup analysis

Outcome | NSCLS, n (%) | SBCLS, n (%) | P-value | OR (95% CI)* |
---------|--------------|--------------|---------|--------------|
Catheter loss due to CRT | 24 (10.6) | 1 (0.4) | <0.0001* | 26.6 (3.57–198.52) |
Catheter loss due to CRBSI | 15 (6.6) | 1 (0.4) | 0.0004* | 15.9 (2.09–121.61) |
Catheter loss due to malfunction | 5 (2.2) | 5 (2.2) | 1 | 0.996 (0.28–3.49) |
All-cause catheter loss | 44 | 1 | <0.0001* | 7.5 (3.31–17.12) |

*Unadjusted ORs with 95% CIs.

Statistical significance P < 0.05.

Femoral catheter subgroup analysis was not done due to insufficient sample size. All subgroups shown here demonstrated statistical significance at P < 0.05.

*OR was not applied in tunneled catheters, as the sample size did not detect any catheter loss in SBCLS.

Figure 1: NSCLS versus SBCLS catheter loss rate.
remain the preferred means of immediate access, bacteremia is the primary complication that limits their use [42].

Previous studies successfully curbed infection rates using antibiotic lock solutions, but the liberal use of antibiotics entails potential adverse consequences to patients and communities [43, 44]. With an annual incidence of 1 million cases, and 200 000 deaths in the USA alone, the emergence and prevalence of antibiotic-resistant bacteria as an increasing cause of death worldwide should bear significant weight on the choice of a standard lock solution [44]. Antibiotic resistance has resulted in a global ‘call to action’ to avoid receding into an era lacking effective antibiotics [18]. For antibiotic locks, significant costs and catastrophic adverse effects on the community outweigh the benefit of reduced infections for a few patients [26, 43, 44]. Consequently, using antibiotics to regularly reduce CRBSI in a population leads to a poor cost–benefit profile. Antibiotic lock solutions also fail to address catheter loss due to CRT. Exchanging NSCLS, a benign solution, for an antibiotic lock solution is thus impractical and a poor approach to minimize adverse outcomes [31].

In our prior study we challenged the standard NSCLS by demonstrating the effective reduction of CRT using SBCLS, yet the study left us without conclusive results regarding the effects on CRBSIs [17]. Accordingly, the current goal was to evaluate the efficacy of SBCLS in mitigating the CRBSI rate at our community hospital. We considered the known antibacterial properties of NaHCO3 and the favorable cost–benefit profile [18, 27, 43]. The rate of catheter loss due to CRBSI was found to be dramatically lower in the SBCLS group (Figure 1). Only one patient lost a catheter due to CRT, and only one catheter was lost due to CRBSI in the SBCLS group. No patients had any evidence of adverse effects related to the locking solutions, which attests to an equivalent safety profile. Overall, SBCLS patients demonstrated significantly lower catheter loss rates when compared with NSCLS patients for all causes. This is especially striking as the overall 19.5% NSCLS catheter loss rate is below reported average catheter loss rates for similar catheters, 21–46%, implying a strong external validity for our study [45, 46]. Additionally, Napalkov et al. [47] reported that complication by CRBSI had an incidence rate of ’0.46 to 30 per 1000 CD or approximately 4.3% to 26% of placed catheters’ [47]. They also reported that the CRT incidence was between ’0.06 to 21 per 1000 CD or 0.6% to 33% of placed catheters’ [47]. The NSCLS group rates in our study comparatively fall within the lower range of both categories. This suggests that the rates of CRT and CRBSI events in the control group are not exceptionally high. Furthermore, in 2008, Moran et al. [48] described that their rate of ‘flow-related catheter exchange’, almost equivalent to

FIGURE 2: Groups and outcomes.
catheter thrombosis, was 4.1/1000 CD in its heparin lock group. This suggests that the use of heparin may not have significantly decreased the rate of thrombosis compared with NSCLS. The evidence supports our hesitance in using heparin as a strategy to decrease thrombosis at our institution given the limited potential benefit compared with the harms and costs associated with its regular use.

We also considered if the statistically significant difference in mean albumin level between groups could have altered the results, yet a difference of only 0.1 mg/dL is not clinically significant and not consistent with affecting the results pertinent to this study [49].

Despite no statistically significant difference between the groups of catheters used, we considered the potential difference of catheters used within groups, and the collected data were further analyzed. Post hoc subgroup analysis applying the available data continued to demonstrate statistically significant differences between groups even when correcting for catheter type and tunneling as demonstrated in Table 3. These findings suggest that SBCLS is better than NSCLS at CRT and CRBSI prevention, regardless of the type of HD catheter used. SBCLS proved to be a superior lock solution that decreased the likelihood of CRT and CRBSI.

Our findings uphold the growing evidence that NaHCO3 is an overlooked ally of host immunity in the defense against pathogens and may be a solution to some of medicine’s most urgent needs. The unique mechanism of action of bicarbonate has far-reaching effects on the activity of innate immune components and the effectiveness of antibiotics [36]. Furthermore, bicarbonate has remarkable power as an antibiotic adjuvant, suggesting that there is great potential to exploit this activity in the discovery and development of new antibacterial drugs [18, 23].

CONCLUSIONS

Using a standard NaHCO3 solution for locking CVCs will safely lead to a decreased incidence of HD catheter loss due to both CRT and CRBSI. The significance of this finding is self-evident. This solution is readily available in multiple care settings. The implementation of our protocol using SBCLS will be easy among these settings as there is otherwise no change to standard care. All facilities that provide HD and all patients with HD CVCs will greatly benefit from the reduced cost of treatment due to avoidance of expensive thrombolytics, catheter replacements and hospitalizations for CRBSI. This is a step forward in the improvement of HD patient care and possibly the care of patients with other venous catheter types.

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CONFLICT OF INTEREST STATEMENT

Patent number US 9,789,227B1, 17 October 2017, ‘Lock solution for venous catheters using sodium bicarbonate’.

(See related article by Niyyar. Catheter dysfunction and lock solutions: are we there yet? Nephrol Dial Transplant 2019; 34: 1626–1628)

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