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Original Article

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Prevention of dialysis catheter-related sepsis with a citrate–taurolidine-containing lock solution

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Abstract

Background. The use of haemodialysis catheters is complicated by catheter-related sepsis. Intraluminal colonization of the catheter with bacteria is important in the pathogenesis of catheter-related sepsis. The use of a catheter lock solution containing the antimicrobial taurolidine might prevent bacterial colonization, thereby reducing the incidence of catheter-related sepsis.

Methods. In a randomized prospective trial, patients receiving a dialysis catheter were included and catheters were locked with either heparin or a citrate–taurolidine-containing solution. Blood cultures drawn from the catheter lumen were routinely taken every 2 weeks and at time of removal of the catheter to detect bacterial colonization. Catheter-related sepsis and exit-site infections were registered for both groups.

Results. A total of 76 catheters were inserted in 58 patients. The incidence of catheter colonization progressed slowly over time with no differences between dialysis catheters filled with heparin or citrate–taurolidine-containing solution. The number of exit-site infections was also similar between both groups. In the heparin group, four cases of catheter-related sepsis occurred as opposed to no sepsis episodes in the patients with catheters locked with the citrate–taurolidine-containing solution ($P < 0.5$). No side effects with the use of citrate–taurolidine catheter lock solution were noted.

Conclusions. This study shows that catheter filling with a solution containing the antimicrobial taurolidine may significantly reduce the incidence of catheter-related sepsis. Taurolidine appears to be effective and safe and does not carry the risk for side effects that have been reported for other antimicrobial lock solutions containing gentamicin or high concentrations of citrate.

Keywords: catheter; haemodialysis; lock; sepsis; taurolidine

Introduction

The use of central venous catheters for haemodialysis is restricted by complications like thrombosis and infection. The catheter-related sepsis (CRS) incidence varies per dialysis unit, type of catheter used and site of insertion. An average CRS incidence of 2–3 episodes per 1000 catheter days is considered good, but most studies report a CRS incidence of 4–6 episodes per 1000 catheter days [1,2]. About half of all infections in haemodialysis patients are related to central venous catheters and CRS is causing significant morbidity and mortality [3].

Bacterial colonization of the intraluminal surface of the catheter with biofilm formation occurs in a high percentage of catheters and precedes peripheral bacteraemia and septic symptoms [4]. Several catheter fillings, such as highly concentrated citrate solutions and gentamicin, have been tested for their efficacy in reducing bacterial colonization and thereby lowering the incidence of CRS. Although effective, their use is restricted by undesirable side effects, such as the risk for hypocalcaemia and high trough levels of gentamicin [5,6].

Taurolidine, a derivative of the amino acid taurine, is an antimicrobial agent that inhibits and kills a broad range of micro-organisms [7,8]. The high concentrations that are needed to exert its antibacterial effect limits the use of taurolidine for parenteral use, but can be easily achieved intraluminal in a dialysis catheter. A catheter lock solution containing citrate and taurolidine has been developed and a low CRS incidence was observed when this lock solution was used in

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combination with subcutaneous catheter devices and tunnelled catheters [9–11]. In a single centre open label randomized trial, we tested the efficacy of citrate–taurolidine lock solution compared with heparin in the prevention of CRS.

Subjects and methods

The study design was a single centre randomized controlled trial comparing the efficacy of citrate–taurolidine lock solution *vs* the standard heparin catheter filling in the prevention of CRS. All patients were recruited in a teaching hospital between May 2002 and June 2003. Patients were eligible for the study if they needed a haemodialysis catheter for starting or continuing haemodialysis treatment. Patients were excluded if the dialysis catheter was used on the intensive care unit or for reasons other than haemodialysis. Patients using antibiotics were also excluded.

Experienced nephrologists inserted all catheters and catheter placement was controlled for by a radiograph of the thorax. The choice of catheter was guided by the expected duration for the catheter to be in use. A non-tunnelled pre-curved single lumen catheter (Medcomp, Harleysville, PA, USA) was placed in the right jugular vein if the expected duration of use was <4 weeks and a double or single lumen tunnelled catheter was inserted for prolonged use (Tesio Cath and Ash Split Cath; Medcomp, Harleysville, PA, USA). The femoral vein was only used for catheters expected to be in place for <1 week.

Catheters were placed under strict aseptic conditions and the exit site was covered with a transparent, oxygen-permeable dressing. Patients were administered nasal mupirocin on a weekly basis, because this may reduce the number of catheter-related infections [5]. Exit-site care involved inspection of the catheter exit site at each dialysis, cleaning with chlorhexidine or iodine and covering with a new transparent dressing. Connecting and disconnecting of the dialysis catheter to the bloodlines was done under strict aseptic conditions, with nurses wearing facial masks, sterile gloves and a sterile gown. Before the catheter was opened, the catheter hub was wrapped for 5 min in gauzes soaked in iodine or chlorhexidine.

Patients were allocated to receive either heparin (5000 U/ml) or citrate–taurolidine (1.35% taurolidine and 4% sodium citrate; Neutrolin™, Biolink, Norwell, MA, USA) as a catheter lock solution using a computer-generated table of random numbers. The randomization procedure was done independent of type of catheter or place of insertion. The lock solution was withdrawn before each dialysis and the catheter was locked after dialysis with a volume equivalent to the lumen volume plus 0.1 ml. Patients' clinical characteristics are shown in Table 1.

Catheter-related infection

Blood cultures were taken every 2 weeks until positive for bacteria and at the time of removal of the catheter. From each catheter lumen, the first 5 ml of aspirated blood was discarded and then 10 ml of blood was aspirated and inoculated in culture bottles for anaerobic and aerobic culture.

The primary end-point was CRS. This was defined as a symptomatic patient with a positive bacterial blood culture drawn from the dialysis catheter with no other apparent source of infection.

Clinical exit-site infection was defined according to the Centers for Disease Control criteria [12]: erythema, tenderness and/or induration within 2 cm of the exit site with or without a purulent exudate or microbiological exit-site infection where the exudate yields a micro-organism on culture.

As a secondary end-point, bacterial colonization of the catheter was chosen. Bacterial colonization was defined as a positive bacterial culture in blood drawn routinely every 2 weeks and at the time of removal from the catheter lumen before starting dialysis.

CRS or bacterial colonization-free survival was defined as the number of days from catheter insertion to diagnosis of CRS or positive bacterial blood culture during routine

Table 1. Clinical characteristics of patients

	Heparin	Citrate–taurolidine	*P*-value
Age (years)[a]	50.3 ± 20.4	58.3 ± 16.3	> 0.1
Male gender (%)	61.5	56.8	> 0.1
Underlying renal disease (*n*)			
Diabetic nephropathy	11	6	> 0.1
Renovascular disease	8	11	> 0.1
Glomerulonephritis	11	5	> 0.1
Polycystic kidney disease	0	3	> 0.1
Other/unknown	9	12	> 0.1
Diabetes mellitus	33%	22%	> 0.1
Serum haemoglobin (mmol/l)	6.0 ± 14	5.9 ± 11	> 0.1
Serum albumin (g/l)	30.6 ± 6.0	30.9 ± 5.6	> 0.1
Serum ferritin (μg/l)	497 ± 406	509 ± 574	> 0.1
Number of catheter days	1885	1519	
Type of catheter inserted (*n*)			
Tunnelled catheter	10	8	> 0.1
Non-tunnelled catheter			
Jugular/subclavian position	22	22	> 0.1
Femoral position	7	7	

[a]Values are means ± SE.

control. Exit from the study for any event other than CRS was treated as a censored observation for the purposes of survival analysis. Catheter use was defined as the number of days from catheter insertion to CRS or censored observation.

Statistical analysis

Based on the observed CRS incidence of 3.5 CRS episodes per 1000 catheter days in our dialysis unit, the power analysis revealed that at least 35 catheters per group were required to demonstrate an effect size of $>80\%$ with an α-value of 0.05 and 80% power.

The effect size of 80% was chosen on the basis of results with taurolidine as a catheter filling in previous reports [10,11]. All statistical analyses were performed using SPSS (version 10.0; SPSS Inc., Chicago, IL, USA). Independent *t*-tests were used to compare continuous variables between groups and skewed variables were analysed with the Mann–Whitney *U*-test. Cumulative infection-free catheter survival was analysed by the Kaplan–Meier method and log-rank test.

Results

Seventy-six catheters were placed in 58 patients, of which 39 catheters were randomized to heparin and 37 catheters to the citrate–taurolidine group. In Table 1 the clinical characteristics of both groups are shown, with no statistically significant differences for underlying disease and laboratory parameters. Four patients died during the study period, with cardiovascular disease as the cause of death.

Three catheters were removed because of catheter malfunction, probably caused by thrombus formation (two in the heparin group and one in the citrate–taurolidine group). Median catheter use was 158 days (range: 14–169 days) for tunnelled catheters, 28 days (range: 7–119 days) for non-tunnelled catheters in the jugular or subclavian vein and 7 days (range: 1–21 days) for catheters inserted in the femoral vein. Groups did not differ in the type of catheter inserted or median catheter use (Table 1).

Figure 1 shows the result of the primary end-point CRS. A total of four CRS episodes were registered in four different patients. Three CRS episodes were caused by *Staphylococcus aureus* (two pre-curved catheters in the jugular vein and one catheter in the femoral vein) and one by *S.epidermidis* (in a tunnelled catheter). All these cases were registered in the heparin-filling group (Table 2). The CRS incidence in this group was 2.1 per 1000 catheter days and the sepsis-free survival was significantly lower in patients allocated to the heparin catheter lock compared with the citrate–taurolidine-filling group ($P=0.047$; Figure 1). The CRS incidence was 1.7 per 1000 catheter days for tunnelled catheters and 2.6 per 1000 catheter days for non-tunnelled catheters. When non-tunnelled catheters in the femoral vein were excluded, the CRS incidence for non-tunnelled catheters was 1.8 per 1000 catheter days. Analysed separately, the sepsis-free survival for non-tunnelled catheters was lower in patients allocated to the heparin catheter lock compared with the citrate–taurolidine-filling group, but this difference did not reach statistical significance ($P=0.066$). When CRS with *S.aureus* was diagnosed, the catheter was removed and vancomycin given intravenously for 3 weeks. CRS with *S.epidermidis* was treated with vancomycin intravenously for 2 weeks.

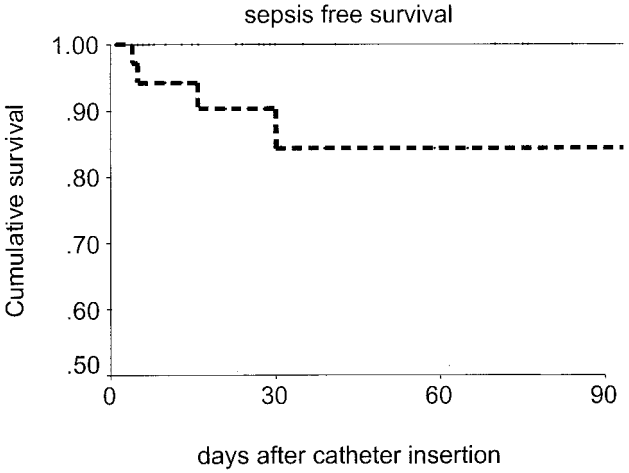

Fig. 1. Sepsis-free survival curves for patients with dialysis catheters locked with heparin (broken line) or citrate–taurolidine-containing lock solution (solid line). Survival curves differ significantly when analysed with the log-rank test ($P=0.047$).

Table 2. Pathogens isolated from exit site and blood cultures

CRS ($n=4$, all randomized to heparin)
Staphylococcus aureus ($n=3$)
Staphylococcus epidermidis ($n=1$)
Positive blood cultures in asymptomatic patients ($n=9$)
Corynebacterium species and *Micrococcus luteus* ($n=1$ heparin)
Staphylococcus epidermidis ($n=2$ heparin, $n=3$ citrate–taurolidine)
Staphylococcus epidermidis, *Streptococcus salivarius* and *Streptococcus* species ($n=1$ heparin)
Acinetobacter species ($n=1$ citrate–taurolidine, $n=1$ heparin)
Exit-site cultures ($n=6$)
Staphylococcus aureus ($n=1$ heparin, $n=1$ citrate–taurolidine)
Serratia marcescens and *Enterobacter cloacae* ($n=1$ heparin)
Enterobacter cloacae ($n=1$ citrate–taurolidine)
Citrobacter freundii and *Pseudomonas aeroginosa* ($n=1$ heparin)
Culture negative ($n=1$ heparin)

Standard blood culture from the catheter lumen yielded a variety of different bacteria, with *S.epidermidis* being isolated most frequently. The incidence of a positive blood culture (excluding CRS) 30 days after catheter placement was 7% for the citrate–taurolidine group and 9% for the heparin group and the positive blood culture-free survival curves were similar (Figure 2). The sepsis episode caused by *S.epidermidis* was not preceded by a routine positive blood culture and a positive blood culture with *S.aureus* was not observed in any asymptomatic patient. Positive bacterial blood culture in asymptomatic patients did not lead to treatment with antibiotics, change of catheter or removal of the catheter.

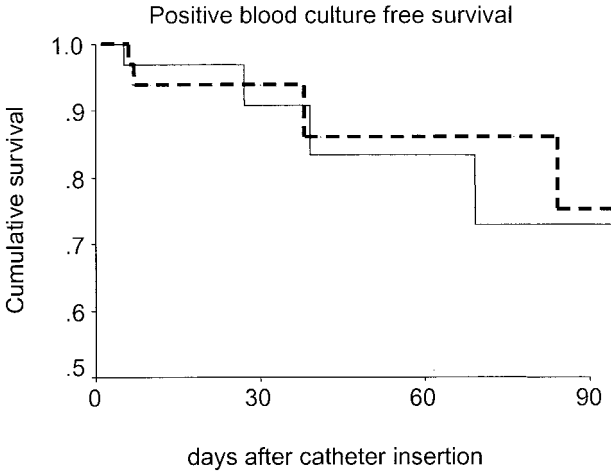

Fig. 2. Bacterial colonization-free survival curves of dialysis catheters locked with heparin (broken line) or citrate–taurolidine-containing lock solution. The survival curves were not significantly different.

Exit-site infections were seen at a similar frequency in both groups (Table 2). In one patient, the CRS episode caused by *S.aureus* was preceded by an exit-site infection with *S.aureus*. Exit-site infections were treated with antibiotics given orally for 7 days.

There were no adverse events reported with the use of citrate–taurolidine solution as a catheter filling.

Discussion

In this randomized study, a significant decrease in CRS incidence was observed when citrate–taurolidine solution was used as a catheter filling. The CRS incidence in the heparin group was already relatively low, with 2.1 cases per 1000 catheter days compared with an average CRS incidence of 4–6 cases per 1000 catheter days reported by many other dialysis centres using tunnelled catheters exclusively [1,2,9]. The power analysis underlying this study was based on a higher CRS incidence than observed in the study period. In retrospect, this might be caused by a relatively higher percentage of catheters in the femoral vein in the years before. However, the difference in CRS incidence between the heparin and citrate–taurolidine groups was such that even at a lower CRS incidence than predicted, a significant difference in sepsis-free catheter survival between the two groups could be found. Our results are in accordance with two recently published studies. In the study by Soderman *et al.* [10], citrate–taurolidine solution was used in combination with a subcutaneous catheter device (Dialock system). They observed a CRS incidence of 0.29 per 1000 catheter days of use, but the study design was uncontrolled. However, another study observed at least a 3-fold higher CRS incidence of this new device with heparin filling [13].

The other recently published study by Allon [9] includes 20 patients with tunnelled dialysis catheters that were studied for 90 days using citrate–taurolidine lock solution. The CRS incidence in this period was compared with the historical CRS incidence on heparin in this group as well as a non-randomized control group using heparin filling. A 90% reduction in the CRS incidence of 5.6 cases per 1000 catheter days was observed in the citrate–taurolidine group, in which only one case of CRS (*Enterococcus*) was observed in 1679 catheter days. The total number of catheter days was similar to our study and the majority of micro-organisms isolated in the heparin-filling group were also *Staphylococcus* species.

Of interest to note is that in the current study a clinically relevant case-mix of catheters was prospectively included and the majority of catheters were non-tunnelled as opposed to the selected cases of tunnelled catheters and subcutaneous devices in the studies by Soderman *et al.* and Allon [9,10]. In our centre, the choice between insertion of a tunnelled or non-tunnelled catheter is primarily based on the expected duration of catheter use (see 'Subjects and methods'), because, in our own experience and that of others [14], the non-cuffed pre-curved catheters have an almost identical CRS incidence as the tunnelled catheters. Using non-tunnelled catheters filled with heparin lock, the CRS incidence was acceptable in our dialysis centre but could be substantially reduced with the use of citrate–taurolidine catheter lock solution, confirming the data obtained in previous studies. The antimicrobial effect of the citrate–taurolidine catheter lock is most likely related to the presence of taurolidine, because a 4% citrate concentration *in vitro* has little to no antibacterial effect [6].

Allon [9] found an increased requirement for thrombolytic interventions to maintain catheter patency among patients receiving citrate–taurolidine solution, indicating a less effective anticoagulant activity of 4% sodium citrate compared with heparin. In our study, we did not observe such a difference and only three catheters (two with heparin lock) were replaced because of persistent flow problems. Others also reported an equally effective anticoagulant activity for heparin and citrate-containing catheter locks at concentrations similar to those used in the current study [15].

Most central vein catheters develop a bacterial biofilm on their surface that can already occur within 24 h after placement [4,16]. Bacteria gain access to the circulation via this biofilm and by embolization during dialysis, thereby causing CRS. In *in vitro* studies, taurolidine has a broad antibacterial activity and can prevent biofilm formation on dialysis catheters. Surveillance of biofilm formation by weekly blood cultures from the catheter has been advocated for early detection and treatment of bacterial colonization [4]. In a prospective study it was shown that 68% of dialysis catheters became colonized (defined as a positive bacterial blood culture from the catheter lumen) after a mean time of 27 days after placement [4]. *Staphylococcus epidermidis* was the colonizing micro-organism in the majority of cases. In our study, the

rate of bacterial colonization of the dialysis catheters was much lower. This difference might be caused by differences in culture technique or, more likely, is related to our meticulous nursing techniques. Optimal catheter care by an experienced nursing team may reduce the rate of CRS up to eight times [3]. We were unable to show a difference in bacterial colonization incidence for catheters filled with citrate–taurolidine or heparin. It is conceivable that more sensitive methods to detect catheter bacterial colonization (e.g. catheter flushing with broth) could have shown such a difference. However, these techniques are, in general, not applicable with catheters *in situ* and also not clinically relevant since the risk for bacteraemia is closely related to the presence of a high count of colony forming units per ml [4,17]. We could not identify a relationship between intraluminal bacterial colonization and a CRS episode. A possible explanation might be that *S.aureus*, which was isolated in the majority of CRS episodes, is rapidly causing CRS after colonization of the catheter lumen, thereby preventing its detection by routine blood culture once every 2 weeks.

Exit-site infections may also contribute to the pathogenesis of CRS [3]. In our group of patients, a low incidence of exit-site infections was observed with, as expected, no difference between the heparin- and citrate–taurolidine-filling groups. The micro-organisms cultured from the exit site were predominantly Gram-negative organisms and the culture results did not correlate with the bacterial blood culture results. Therefore, in our population, exit-site infections are, in general, not predisposing for intraluminal bacterial colonization and CRS. A similar observation was made in a recent study evaluating the relation between exit-site inflammation, catheter bacterial colonization and CRS in 1263 non-cuffed central venous catheters [18].

CRS is a potential serious complication of the use dialysis catheters and may lead to septic emboli and even death [3]. The frequent administration of antibiotics for the treatment of CRS can give rise to multiple antibiotic-resistant bacteria [19]. Catheter filling with taurolidine seems an effective and safe way to achieve a substantial reduction in CRS incidence. Taurolidine has a simple and general antimicrobial action and *in vitro* assays using sub-inhibitory concentrations of taurolidine did not show the emergence of resistance [7,20]. Therefore, it seems unlikely that prolonged intraluminal instillation of taurolidine in the dialysis catheter will give rise to drug-resistant bacterial infection. No adverse effects of taurolidine have been observed so far. It is rapidly metabolized to the final harmless products taurine and carbon dioxide and large daily quantities of taurolidine can be given daily without apparent toxicity [21]. Antibacterial lock solutions containing taurolidine, therefore, seem safe to administer over a prolonged period of time.

In conclusion, this study shows that citrate–taurolidine catheter filling is effective and safe for the prevention of CRS. It may lead to a sizeable reduction in CRS incidence, even in a dialysis centre where CRS incidence is already low using heparin filling.

Conflict of interest statement. None declared.

References

1. Krishnasami Z, Carlton D, Bimbo L *et al*. Management of hemodialysis catheter related bacteremia with an adjunctive antibiotic lock solution. *Kidney Int* 2002; 61: 1136–1142
2. Saad TF. Bacteremia associated with tunnelled-cuffed hemodialysis catheters. *Am J Kidney Dis* 1999; 34: 1114–11124
3. Raad I. Intravascular-catheter-related infections. *Lancet* 1998; 351: 893–898
4. Dittmer ID, Sharp D, McNulty CAM, Williams AJ, Banks BA. A prospective study of central venous hemodialysis catheter colonisation and peripheral bacteremia. *Clin Nephrol* 1999; 51: 34–39
5. Dogra GK, Herson H, Hutchison B *et al*. Prevention of tunnelled hemodialysis catheter-related infections using catheter-restricted filling with gentamycin and citrate: a randomised controlled study. *J Am Soc Nephrol* 2002; 13: 2133–2139
6. Weijmer MC, Debets-Ossenkopp YJ, van de Vondervoort FJ, ter Wee PM. Superior antimicrobial activity of trisodium citrate over heparin for catheter locking. *Nephrol Dial Transplant* 2002; 17: 2189–2195
7. Torres-Viera C, Thauvin-Eliopoulos C, Souli M *et al*. Activities of taurolidine *in vitro* and in experimental enterococcal endocarditis. *Antimicrob Agents Chemother* 2000; 44: 1720–1724
8. Shah CB, Mittelman MW, Costerton JW *et al*. Antimicrobial activity of a novel catheter lock solution. *Antimicrob Agents Chemother* 2002; 46: 1674–1679
9. Allon M. Prophylaxis against dialysis catheter-related bacteremia with a novel antimicrobial lock solution. *Clin Infect Dis* 2003; 36: 1539–1544
10. Soderman K, Polaschegg HD, Feldmer B. Two years' experience with Dialock and CLS. *Blood Purif* 2001; 19: 251–254
11. Jurewitsch B, Lee T, Park J, Jeejeehoy K. Taurolidine 2% as an antimicrobial lock solution for prevention of recurrent catheter related bloodstream infections. *J Parenter Enter Nutr* 1998; 22: 242–244
12. Mermel LA, Farr BM, Sherertz RJ *et al*. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001; 32: 1249–1272
13. Qaurello F, Forneris G. Prevention of hemodialysis catheter-related bloodstream infections using an antimicrobial lock. *Blood Purif* 2002; 20: 87–92
14. Weijmer MC. Prospective follow-up of a novel design hemodialysis catheter for the jugular site; lower infection-rate and improved survival. *J Am Soc Nephrol* 2001; 12: 306A
15. Buturovic J, Ponikva R, Kandus A *et al*. Filling hemodialysis catheters in the interdialytic period. Heparin versus citrate versus polygeline: a prospective randomised study. *Artif Organs* 1998; 22: 945–947
16. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science* 1999; 284: 1318–1322
17. Sherertz RJ, Raad I, Balani A, Koo L, Rand K. Three-year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. *J Clin Microbiol* 1990; 28: 76–82
18. Safdar N, Maki DG. Inflammation at the insertion site is not predictive of catheter related bloodstream infection with short-term, noncuffed central venous catheters. *Crit Care Med* 2002; 30: 2632–2635

19. Beathard GA. Management of bacteremia associated with tunneled-cuffed hemodialysis catheters. *J Am Soc Nephrol* 1999; 10: 1045–1049
20. Blenkharn JI. Antibacterial and related properties of taurolin: a survey. In: Redin R, Verlag TM, eds. *Chirurgische Gastroenterologie mit Interdisciplinaren Gesprachen*. International Communications and Translations (ICA) no. 30871, Philadelphia: 1991; 143–151
21. Blenkharn JI. Prevention of septic complications associated with TPN. *J Parenter Enter Nutr* 1986; 10: 436–437

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