



HAL
open science

Cost-effectiveness of taurolidine locks to prevent recurrent catheter-related blood stream infections in adult patients receiving home parenteral nutrition: a 2-year mirror-image study

Damien Lannoy, Alexia Janes, Xavier Lenne, Sebastien Neuville, Julien Bourry, Pascal Odou, Amelie Bruandet, David Seguy

► To cite this version:

Damien Lannoy, Alexia Janes, Xavier Lenne, Sebastien Neuville, Julien Bourry, et al.. Cost-effectiveness of taurolidine locks to prevent recurrent catheter-related blood stream infections in adult patients receiving home parenteral nutrition: a 2-year mirror-image study. *Clinical Nutrition*, 2021, *Clinical Nutrition*, 10.1016/j.clnu.2021.01.017 . hal-04490116

HAL Id: hal-04490116

<https://hal.univ-lille.fr/hal-04490116>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Cost-effectiveness of taurolidine locks to prevent recurrent**
2 **catheter-related bloodstream infections in adult patients receiving**
3 **home parenteral nutrition: a 2-year mirror-image study**

4
5 Damien Lannoy, PharmD, PhD^{1,2}, Alexia Janes, PharmD¹, Xavier Lenne, MSc³, Sebastien
6 Neuville, PharmD¹, Julien Bourry, MD, MSc⁴, Pascal Odou, PharmD, PhD^{1,2}, Amélie
7 Bruandet, MD, PhD³, David Seguy, MD, PhD^{5,6,4}.

8
9 1- CHU Lille, Institut de Pharmacie, F-59000 Lille, France

10 2- Univ. Lille, ULR7365 – GRITA – Groupe de Recherche sur les formes injectables et les
11 Technologies Associées, F-59000 Lille, France

12 3- CHU Lille, Département d'Information Médicale, F-59000 Lille, France

13 4- CHU Lille, Service Endocrinologie Diabétologie Maladies Métaboliques et Nutrition, F-
14 59000 Lille, France

15 5- Univ. Lille, U1286 – Infinite – Institute for Translational Research in Inflammation, F-
16 59000 Lille, France

17 6- Inserm, U1286, F-59000 Lille, France

18
19 Corresponding author: Pr. David Seguy, MD-PhD.

20 Univ. Lille, Inserm, CHU Lille, U1286 – Infinite – Institute for Translational Research in
21 Inflammation, F-59000 Lille, France

22 david.seguy@univ-lille.fr

23 Phone : +33 (0)3 20 44 53 06

24 Fax : +33 (0)3 20 44 45 65

25
26 Short Title: Cost effectiveness of taurolidine locks in HPN patients

27 Key words: home parenteral nutrition, taurolidine, cost effectiveness

1 **Background & Aims:** The use of long-term taurolidine locks (LTTL) seems to be effective in
2 preventing catheter-related bloodstream infections (CRBSI), especially in patients on home
3 parenteral nutrition (HPN). This work targets the cost-effectiveness of LTTL in a cohort of
4 adult HPN patients.

5 **Methods:** A monocentric mirror-image design study was conducted in our referral centre
6 among long-term HPN patients experiencing recurrent CRBSI. From 7th January 2011, LTTL
7 were started after the third CRBSI episode within 12 months. CRBSI data was prospectively
8 collected until 7th January 2013, in the same way as it had retrospectively been done before
9 initiating LTTL. A cost-effective analysis was conducted to estimate the incremental costs
10 and effects on CRBSI with LTTL. The efficacy of LTTL on CRBSI rate was assessed over
11 1,000 days of catheter use.

12 **Results:** A total of 31,100 catheter days were analysed in 37 patients (median [interquartile
13 range (IQR)] aged 58 [42 - 68] years. The mean \pm SD proven CRBSI rate was 3.18 ± 3.51
14 per 1,000 catheter days before the introduction of LTTL and 0.39 ± 1.50 per 1,000 catheter
15 days after its introduction ($p < 0.0001$). Considering both proven and probable CRBSI
16 requiring hospital management, LTTL reduced (mean [bootstrap CI 95%]) $-2.63 [-3.26 \text{ to } -$
17 $2.06]$ infections per patient (from $2.89 [2.31 \text{ to } 3.49]$ before to $0.26 [0.13 \text{ to } 0.41]$ after) as well
18 as incremental costs by $-7,258 [-10,450 \text{ to } -4,016]$ € (from $11,176 [8,004 \text{ to } 14,968]$ € before
19 to $3,918 [2,390 \text{ to } 5,445]$ € after).

20 **Conclusion:** Implementing LTTL to prevent recurrent CRBSI is cost-effective by dramatically
21 decreasing their incidence.

1 **1. Introduction:**

2 Catheter-related blood stream infections (CRBSI) are the main complication in patients on
3 long-term home parenteral nutrition (HPN) [1]. According to the systematic review by
4 Dreesen et al., the incidence of CRBSI (where is defined as isolation of the same organism
5 in paired blood cultures from peripheral vein and catheter lumen associated with clinical
6 symptoms) varies from 0.38 to 4.58 episodes per 1,000 catheter days in adults and reaches
7 10.6 in the retrospective Walshe et al. study [2, 3]. CRBSI require hospitalisation and
8 treatment with intravenous (IV) antibiotics combined or not with catheter locks; they
9 complicate or limit the venous access and occasionally justify the replacement of the central
10 venous access (CVA). Iterative replacements may lead to suspending HPN and making
11 intestinal transplantation surgery necessary for patients at greater risk of death [4]. HPN
12 patients fear CRBSI because they are aware of the impact on their quality of life [5].

13 While patient and nurse awareness is an essential aspect of CRBSI prevention, there is
14 currently no consensus about the type and use of CVA locks for prophylaxis or treatment.
15 Transient antibiotic locks should be adequate to salvage the CVA in uncomplicated
16 infections, but this strategy has to be challenged, because of the induced risk of resistance
17 and the limited effect on the biofilm that shelters bacteria [6-8]. Ethanol lock therapy,
18 assessed in various adult cohorts has also been proposed to reduce CRBSI rate, but no
19 licensed and ready-to-use product is available in Europe [9-11]. Currently, the ESPEN does
20 not recommend locking with 70% ethanol because of the risk of systemic toxicity and
21 catheter damage leading to reaspiration which increases the number of catheter
22 manipulations [8].

23 Among the different types of locks tried, taurolidine, whose efficacy was first shown in
24 hemodialysis, appears to be a promising candidate [8, 12]. Taurolidine is an antiseptic agent
25 with bactericidal and fungicidal properties which attacks irreversibly the cell wall of both
26 Gram positive and negative bacteria, as well as fungi via the methylol taurinamide, its
27 hydrolysed form. Thanks to its action mechanism, it could also be effective on biofilm

1 eradication [13]. To date, no resistance has been described with taurolidine [14]. Different
2 studies have shown its efficacy in preventing both CRBSI and their recurrences and in
3 improving catheter salvage [14-24]. Unfortunately, there is little data about the cost-
4 effectiveness of this strategy.

5 The aim of this work was to evaluate the cost-effectiveness of long-term taurolidine locks
6 (LTTL) in preventing recurrent CRBSI in a cohort of adult patients receiving HPN.

1 **2. Materials and methods:**

2 **2. 1. Patients**

3 Patients recruited in the study were all followed by the referral centre for HPN patients at Lille
4 University Hospital and were aged ≥ 18 years.

5 Patients included in the study were those receiving LTTL between 1st July 2011 and 1st July
6 2013, following a monocentric mirror-image design. Data prospectively collected during the
7 LTTL period was compared for each patient to data collected in a similar retrospective period
8 before LTTL (mirror period). Patients with fewer than 60 days' LTTL were not considered for
9 the analysis. Non-compliant patients, patients who changed for another HPN centre or were
10 hospitalised for a period longer than their home-stay during the 2-year study were excluded.
11 In France, Ethical approval was not required for cohort monitoring before the Jardé law of
12 16th November 2016. A declaration to the National Commission on computer technology and
13 freedom (CNIL) permitting data treatment and anonymity was made (ref Lille 18-12-2014
14 12:53).

15

16 **2.2. Methods:**

17 *Management of CRBSI*

18 Among patients receiving HPN, CRBSI were suspected when patients experienced
19 hyperthermia ($> 38^{\circ}\text{C}$), hypothermia ($< 36^{\circ}\text{C}$) or chills during HPN infusion; patients were
20 then admitted to the referral centre for exploratory tests (biological sampling) and hospital
21 management.

22 Before 1st July 2011, apart from CRBSI episodes, the CVA was flushed with saline at the end
23 of HPN infusion. Patients with suspected CRBSI were hospitalised. During both mirror and
24 LTTL periods, the same procedure was applied to diagnose CRBSI. According to the ESPEN
25 Guidelines, CRBSI was proven by a positive culture from the lumen of the CVA (when it was
26 removed), or by paired qualitative blood cultures from a peripheral vein and from the CVA of
27 the same microorganism, the delay for positivity being more than 2 hours shorter for the CVA

1 [8, 25]. In practice, patients with clinical signs suggesting septicemia with a pathogen
2 identified from at least one catheter blood sample and not related to an infection at another
3 site were also treated as probable CRBSI cases [8].

4 Treatment consisted in a 14-day period of intra-venous (IV) discontinuous or continuous
5 (when vancomycin was required) anti-infectious treatment, according to the spectra of
6 isolated bacteria or fungi. Treatment initiated at the hospital was pursued at home. Antibiotic
7 CVA locks were empirically used daily for one month (25 mg/mL amikacin, 40 mg/mL
8 gentamicine or 12.5 mg/mL vancomycin). These locks were initiated simultaneously or
9 delayed by 14 days, depending on whether the anti-infective treatment was discontinuous or
10 continuous. CVAs infected with *Staphylococcus aureus*, *Pseudomonas aeruginosa* or
11 *Candida spp.*, were systematically removed immediately and replaced. CVA sterility was
12 systematically checked by blood culture within the 2 weeks following the restart of saline
13 locks.

14 Since 1st July 2011, the use of anti-infective systemic treatment has remained unchanged
15 but thanks to the results of the Bisseling et al. study we decided to switch from short-term
16 antibiotics followed by long-term saline CVA locks to LTTL [16]. Consequently, LTTL became
17 part of the first 14 days of systemic treatment and were used for prophylaxis thereafter.

18

19 *Long-term taurolidine locks*

20 A formulation of 5 mL TauroLock[®] containing heparin (1.35% taurolidine, 4% citrate, 500
21 IU/mL heparin) was the only one available in France, although other formulations with
22 various concentrations of taurolidine, heparin and citrate exist worldwide. This product
23 (provided by Theradial, France) is considered as a medical device in Europe (CE marked,
24 class IIb). According to the supplier's instructions, the lock must be removed by aspiration
25 before using the catheter. Tolerance issues have been noted.

26

27 *HPN characteristics*

1 Patients received individualised all-in-one PN mixtures compounded by Baxter Fasonut, a
2 pharmaceutical laboratory, according to their nutritional needs. HPN duration, type of CVA
3 (implantable chamber or central catheter), number of HPN infusions per week were noted.

4 The data collected was: demographic (gender, age), duration of HPN, underlying disease,
5 associated comorbidities and treatment with infection risk, type of CVA devices, laboratory
6 values and blood cultures. Bacterial strains were collected in all cases of infection, once
7 isolated and identified. Matrix-Assisted Laser Desorption/ionisation-time-of-flight mass
8 spectrometry (MALDI-TOF MS) identification was performed using a Microflex mass
9 spectrometer (Bruker Daltonics, Wissembourg, France). An accurate identification score to
10 species level was assessed by a score value ≥ 2.0 according to manufacturer's
11 recommended cutoff.

12 The dates of the onset of HPN and of LTTL therapy were noted; if required, the date and the
13 cause of LTTL discontinuation (death, PN weaning, intolerance) also.

14 Retrospective CRBSI data collection included patient medical charts and mail, from original
15 paper information, data in medical software, data in software from the microbiology
16 laboratory, placing the hour, minute and date of positivity of microbial growth and encoding
17 software from medical information departments, with keywords containing: catheter
18 infection; infection following therapeutic injection, infusion or transfusion; infection and
19 inflammatory reaction due to prosthesis, implants or cardiac and valvular grafts.

20 The number of catheter changes was sought in clinical charts, in notebooks from operating
21 rooms, and in the software used for the traceability of implanted devices. When the catheter
22 was set up the first time for PN it was not taken into account.

23

24 *Cost effectiveness of LTTL*

25 The economic evaluation was a cost-effective analysis in which we estimated the
26 incremental costs (ΔC) and incremental effects (ΔE) attributable to the introduction of LTTL
27 considering both proven and probable CRBSI cases requiring hospital management.

1 In line with current French recommendations for technology appraisal, the economic
2 evaluation adopted the societal perspective [26]. The time horizon for the economic
3 evaluation was equivalent to that of the data collection.
4 Unit cost estimation followed recent guidelines on pricing healthcare services as part of an
5 economic evaluation [26]. Only the direct costs (medical and non-medical) at a single time
6 point (2011) were considered [27]. A 4% discounting was applied to costs and health effects,
7 as the time horizon for the economic evaluation was above one year in some patients [26].
8 Collected data provided the costs linked to primary outcomes/endpoints of the study.
9 Hospital costs were evaluated according to diagnosis-related code-groups using the French
10 National scale of costs [27]. Mean values for each item (acquisition of drugs, radiological and
11 biological tests, physician and nurse work, logistics, etc.) were listed for every diagnosis-
12 related code-group [27]. The diagnosis-related code-groups corresponding to hospitalisation
13 for each patient due to a prior infection or any related event were indexed. Costs were
14 modified in the case of hospitalisation in an intensive care unit. The cost of expensive
15 antibiotics and replaced catheters not included in the standard costs of hospitalisation were
16 added, as well as ambulatory antibiotic drugs and cost of delivery materials, taurolidine vials
17 and patient transportation from home to the hospital.

18

19 *End points*

20 The main criterion of this mirror-image study was the cost-effectiveness of the LTTL strategy.
21 However, we also studied the effect on the following parameters: efficacy on proven CRBSI
22 rates per 1,000 catheter days according to ESPEN Guidelines, effectiveness on CRBSI
23 management considering both proven and probable cases, the number, mean and total
24 duration of hospital stays due to CRBSI management or any related event such as side
25 effects caused by treatment or complications, the number of total CVA removals related to
26 CRBSI.

27

28 *Statistical analysis*

1 Qualitative variables were expressed in frequencies and percentages. Quantitative variables
2 were expressed by median [interquartile range (IQR)] and/or mean \pm SD. For quantitative
3 variables, the Wilcoxon's signed rank test was adopted to test the hypothesis that
4 distributions for each variable were the same between the two periods. Due to multiple
5 comparisons, the statistical significance threshold was defined at 0.01. The Kaplan-Meier
6 method was used to estimate the cumulative incidence curves according to the ESPEN
7 definition of CRBSI. The comparison of curves was made using the Log-rank test considering
8 the mirror-period of each patient.

9 In common with economic evaluations, cost distribution was skewed. Consequently, a non-
10 parametric estimation using the bootstrap method was adopted to obtain the 95% CI for
11 mean effectiveness, costs and differences between the two strategies. Each of the
12 confidence intervals was calculated using 1,000 bias-corrected bootstrap replications. Non-
13 parametric bootstrap simulation was also performed to generate 1,000 replications of the
14 cost effect pairs; these were subsequently represented graphically on a four-quadrant cost-
15 effectiveness plane [28]. Mean hospital costs were expected to follow a lognormal
16 distribution, reflecting the long right tail and leaning towards positive values according to cost
17 data in the French diagnosis-related code-groups. Statistical analyses were performed with
18 Stata software (Texas, USA, version 14.0).

19

20 **3. Results:**

21 Among the 48 patients who received at least one taurolidine lock between July 2011 and July
22 2013, 11 were excluded: 7 for LTTL use $<$ 60 days, 2 for hospital stays longer than home
23 stays and 2 for lack of data as indicated in the flow chart (figure 1). Among the 7 patients
24 aged 48.5 ± 13.5 years excluded due to an LTTL duration $<$ 60 days (43.7 ± 11.6 days) with
25 newly initiated HPN (HPN duration of 53 ± 27 days), none had suspected or proven CRBSI
26 or hospitalisation during the LTTL period. Two patients were not considered as receiving

1 HPN as they died in hospital because of an underlying disease. Finally, 37 patients were
2 considered for analysis.

3 After LTTL implementation, 33 patients (89%) were free of CRBSI. After 2011, four patients
4 were weaned from HPN thanks to surgery and 3 died from causes independent of CRBSI
5 (cirrhosis and hepatic failure for a 58-year-old, palliative care after end of treatment for an 85-
6 year-old, renal failure for a 65-year-old).

7 The study was therefore performed on 37 patients with recurrent CRBSI using a mirror-study
8 period of 367 [226-700]; 420 ± 239 days, representing a total of 31,100 catheter days. The
9 characteristics of patients at LTTL initiation are defined in Table 1. Six patients had balanced
10 insulin-dependent diabetes: 2 apparent before HPN and 4 consecutive to HPN initiation.
11 Seven patients with Crohn's disease received immunosuppressant treatment: 3 remained
12 unchanged before and after LTTL; on LTTL initiation 1 switched from certolizumab to
13 adalimumab and the other from budesonide and azathioprine to ustekinumab, 2 began
14 adalimumab and intermittent corticotherapy during the ITTL period. Two other patients
15 received treatment for cancer: 1 initiated imatinib before the mirror period and 1 received
16 chemotherapy (paclitaxel and carboplatin) during the LTTL period. Body weights of patients
17 were comparable at the beginning of mirror and at the start and end of LTTL periods (54
18 [47.4-61] kg and 55 [52-66] kg and 58 [52-67] kg; not significant), respectively. The number
19 and duration of overall hospitalisations (including those not related to CRBSI) during mirror
20 vs. LTTL periods were (4 [2-7] vs. 1 [0-2]; $p < 0.001$ and 7 [4-13] days vs. 3 [0-10] days; not
21 significant), respectively. During the overall study, patients kept the same home and HPN
22 referral centre healthcare givers; practices in prevention and management of CRBSI were
23 unchanged except for LTTL introduction.

24 The rate of proven CRBSI according to the ESPEN definition was 3.18 ± 3.51 per 1,000
25 catheter days before the introduction of LTTL and 0.39 ± 1.50 per 1,000 catheter days after,
26 $p < 0.0001$. The cumulative incidence curves for proven infections are presented in Figure 2.

27 The overall rate of both proven and probable CRBSI requiring hospital management
28 decreased in the same proportion from 8.21 ± 3.95 per 1,000 catheter days beforehand to

1 0.74 ± 1.79 per 1,000 catheter days after, $p < 0.0001$. Table 2 indicates patient outcomes
2 before and after the introduction of LTTL. Cumulative hospital stays were 677 and 133 days,
3 before and after the introduction of LTTL, respectively.

4 Effectiveness and costs are reported in Table 3. After versus before the introduction of LTTL,
5 we observed a decrease in the number of infections per patient which required hospital
6 management (mean [bootstrap CI 95%]) (-2.63 [-3.26 to -2.06]). This corresponds to an
7 average reduction in total cost per patient of (mean [bootstrap CI 95%]) -7,258 [-10,450 to -
8 4,016] €. Figure 3 indicates the variability around the estimate of cost-effectiveness. The fact
9 that the totality of the bootstrapped replications of the cost-effect pairs was traced in the
10 south-east quadrant of the cost-effectiveness plane indicated that the LTTL strategy was
11 significantly more effective and less expensive.

12

13 **4. Discussion**

14 Our study shows LTTL cost-effectiveness to prevent recurrent CRBSI, the incidence of which
15 dramatically decreased in our HPN adult cohort of patients. The 65% cost reduction we
16 observed can be largely accounted for as previous hospitalisation and ambulatory
17 medication costs were superior and not balanced by LTTL incremental cost.

18 Little published data has concerned infection management and their costs in HPN patients. A
19 retrospective Spanish study including 13 patients reported a lower accumulated cost before
20 and during a taurolidine period, but this difference has not been statistically tested. The
21 randomised study by Tribler S et al. reported as a secondary objective a total cost divided by
22 2 in the LTTL group compared with the control group [21]. In this study fixed prices were
23 used to determine costs while we determined individual costs per patient. To our knowledge,
24 the present study is the first designed and conducted to assess the cost-effectiveness of
25 LTTL in HPN patients. It is significant and can reach 19.8 euros per vial, but should appear
26 even more cost-effective as, since we performed this work, the cost per vial has decreased
27 from 7 to 5 euros [21]. Moreover, another recent randomised study (after excluding one non-

1 conform patient) confirmed a similar cost saving with LTTL because of an even lower price
2 per vial of 3 USD [23]. However, it should be noted that taurolidine or saline locks were used
3 with new catheters on 70% of the 102 enrolled patients.

4 Our results confirm that LTTL is successful in dramatically decreasing the recurrence of
5 CRBSI as already reported by others in both randomised [16, 21, 23, 29] and cohort studies
6 [14, 15, 17-20, 22, 24] and the rate of CRBSI before LTTL onset was also consistent with
7 that reported in other research [15, 17-21, 24]. However, the accepted (grade A) ESPEN
8 definition of CRBSI underestimates incidence today. In the present study, the CRBSI rate
9 does not reflect incidence in our whole cohort of HPN patients as the 35 excluded patients
10 did not experience any CRBSI till July 2011. In spite of LTTL efficacy, maintaining low sepsis
11 rates requires careful catheter protocols, as well as a multidisciplinary nutrition support team
12 and patient awareness. The patient is the key to minimising the CRBSI rate at home.

13 In practice, the decision to treat a patient is independent of the proven ESPEN CRBSI
14 definition. Indeed, patients suffering from the clinical symptoms of CRBSI require
15 hospitalisation and proper management of the suspected infection. This explains why we
16 have also considered probable CRBSI when calculating cost effectiveness.

17 Nowadays, no data recommends LTTL use in primary prevention. This strategy has been
18 assessed only in a cohort of 3 patients at high risk for vascular access [20]. In a randomised
19 trial focusing on patients with a low infection rate (0.3 per 1,000 catheter days), taurolidine
20 was no better than saline locks [29]. Consequently, in this case, the cost of taurolidine was
21 significantly higher than the cost of saline. In our cohort, LTTL remains cost-effective when
22 adding the cost estimated for its use in primary prevention over two years for the 42%
23 (35/83) of patients who did not have CRBSI, but this was not the aim of the present study.

24 The sample size and duration of the lock period were shorter than those published by Olthof
25 *et al* [19]. They compared two independent samples of patients before and after taurolidine
26 lock introduction. This prevented a possible paired analysis as opposed to our study, i.e. a
27 comparison for each patient liable to benefit from LTTL over a retrospective mirror-image

1 period. Our monocentric restricted cohort was larger in size than the prospective randomised
2 study by Bisseling *et al* [16] in which HPN indications were more heterogeneous.

3 Our work has some important limitations that have to be discussed. Respecting the design of
4 the first randomised study published by Bisseling *et al.* in 2010 involving patients who had
5 developed an episode of CRBSI, we chose to exclude the 35 patients who had not
6 experienced CRBSI during the prospective period corresponding to LTTL implementation
7 [16]. The decrease in CRBSI rate after versus before LTTL should have been influenced by
8 the phenomenon of regression to the mean in our high prevalence CRBSI cohort. It should
9 be noted we did not select any patient a priori among our cohort as we considered only
10 patients with CRBSI within a prospective period of 2 years to define a posteriori the
11 retrospective mirror period. In the absence of blinding or control group, it cannot be excluded
12 that both patients and healthcare workers may have experienced the Hawthorne effect
13 modifying their behaviour and motivation in response to LTTL implementation. Although this
14 was the only change made to our patient management, an awareness of being observed
15 could introduce a bias in favour of the LTTL period since it did not exist during the
16 retrospective mirror period. Conversely, it cannot be ignored that some caregivers may be
17 tempted to think that with LTTL they can be less rigorous with catheter management.
18 Because of an average participation of about 2.5 years, patient status may have changed
19 between the retrospective and prospective periods and influenced our results. However,
20 considering an overall average length of hospital stay (including those not related to CRBSI)
21 of approximately 10 days for these two periods, we can consider that patients were relatively
22 clinically stable at home, since their mean HPN duration was three times as long as their
23 mean participation in the study. Their body weight and use of immunosuppressive or
24 cytotoxic drugs were comparable during these two periods. Obviously, during the prospective
25 period, patients were older, had a longer history of HPN and chronic diseases such as
26 diabetes, but these factors worked against a reduction in CRBSI under LTTL. Moreover, both
27 home and hospital HPN caregivers and CRBSI management were similar, except for LTTL
28 implementation.

1 These promising results have to be confirmed by a larger, prospective, multicentre study
2 which should evaluate direct benefits in terms of quality of life for HPN patients. It may also
3 concern patients requiring parenteral nutrition during their hospital stay in surgery or in
4 oncology.

1 **Acknowledgements**

2 The authors thank Alexandra Tavernier, M.A. (University of Glasgow U.K.), Professeur
3 Agrégée, France, for her assistance in correcting and editing the text.

4

5 **Statement of Authorship**

6 Damien Lannoy is the guarantor of the article.

7 Damien Lannoy, Alexia Janes, Xavier Lenne, Sebastien Neuville, Pascal Odou, Amélie
8 Bruandet and David Seguy performed the research.

9 Damien Lannoy, Alexia Janes and Julien Bourry acquired the data.

10 Damien Lannoy, Alexia Janes, Xavier Lenne, Pascal Odou, Amélie Bruandet and David
11 Seguy analysed and interpreted the data.

12 Damien Lannoy, Alexia Janes, Xavier Lenne and David Seguy conceived and designed the
13 research study and wrote the article. Sebastien Neuville, Pascal Odou and Amélie Bruandet
14 contributed to the design of the study and critically revised the article for important intellectual
15 content.

16 Damien Lannoy, Alexia Janes, Xavier Lenne, Sebastien Neuville, Julien Bourry, Pascal
17 Odou, Amélie Bruandet and David Seguy all state that they approve the final version of the
18 article.

19

20 **Conflict of Interest Statement**

21 The authors declare that they have no conflict of interest concerning this article.

22

23 **Funding Sources**

24 This research did not receive any specific grant from funding agencies in the public,
25 commercial, or not-for-profit sectors.

26

1 **References**

- 2 [1] Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-
3 term parenteral nutrition. *Aliment Pharmacol Ther.* 2013;37:587-603.
- 4 [2] Dreesen M, Foulon V, Spriet I, Goossens GA, Hiele M, De PL, et al. Epidemiology of
5 catheter-related infections in adult patients receiving home parenteral nutrition: a systematic
6 review. *Clin Nutr.* 2013;32:16-26.
- 7 [3] Walshe CM, Boner KS, Bourke J, Hone R, Phelan D. Diagnosis of catheter-related
8 bloodstream infection in a total parenteral nutrition population: inclusion of sepsis
9 defervescence after removal of culture-positive central venous catheter. *J Hosp Infect.*
10 2010;76:119-23.
- 11 [4] Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, et al. Long-term follow-
12 up of patients on home parenteral nutrition in Europe: implications for intestinal
13 transplantation. *Gut.* 2011;60:17-25.
- 14 [5] Dreesen M, Pironi L, Wanten G, Szczepanek K, Foulon V, Willems L, et al. Outcome
15 Indicators for Home Parenteral Nutrition Care: Point of View From Adult Patients With
16 Benign Disease. *JPEN J Parenter Enteral Nutr.* 2015;39:828-36.
- 17 [6] Longuet P, Douard MC, Arlet G, Molina JM, Benoit C, Leport C. Venous access port--
18 related bacteremia in patients with acquired immunodeficiency syndrome or cancer: the
19 reservoir as a diagnostic and therapeutic tool. *Clin Infect Dis.* 2001;32:1776-83.
- 20 [7] Messing B, Man F, Colimon R, Thuillier F, Beliah M. Antibiotic-lock technique is an
21 effective treatment of bacterial catheter-related sepsis during parenteral nutrition. *Clin Nutr.*
22 1990;9:220-5.
- 23 [8] Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN
24 guidelines on chronic intestinal failure in adults. *Clin Nutr.* 2016;35:247-307.
- 25 [9] Salonen BR, Bonnes SL, Vallumsetla N, Varayil JE, Mundi MS, Hurt RT. A prospective
26 double blind randomized controlled study on the use of ethanol locks in HPN patients. *Clin*
27 *Nutr.* 2017.
- 28 [10] Davidson JB, Edakkanambeth Varayil J, Okano A, Whitaker JA, Bonnes SL, Kelly DG,
29 et al. Prevention of Subsequent Catheter-Related Bloodstream Infection Using Catheter Locks
30 in High-Risk Patients Receiving Home Parenteral Nutrition. *JPEN J Parenter Enteral Nutr.*
31 2017;41:685-90.
- 32 [11] John BK, Khan MA, Speerhas R, Rhoda K, Hamilton C, Dechicco R, et al. Ethanol lock
33 therapy in reducing catheter-related bloodstream infections in adult home parenteral nutrition
34 patients: results of a retrospective study. *JPEN J Parenter Enteral Nutr.* 2012;36:603-10.
- 35 [12] Liu Y, Zhang AQ, Cao L, Xia HT, Ma JJ. Taurolidine lock solutions for the prevention
36 of catheter-related bloodstream infections: a systematic review and meta-analysis of
37 randomized controlled trials. *PLoS One.* 2013;8:e79417.
- 38 [13] Shah CB, Mittelman MW, Costerton JW, Parenteau S, Pelak M, Arsenault R, et al.
39 Antimicrobial activity of a novel catheter lock solution. *Antimicrob Agents Chemother.*
40 2002;46:1674-9.
- 41 [14] Olthof ED, Rentenaar RJ, Rijs AJ, Wanten GJ. Absence of microbial adaptation to
42 taurolidine in patients on home parenteral nutrition who develop catheter related bloodstream
43 infections and use taurolidine locks. *Clin Nutr.* 2013;32:538-42.

- 1 [15] Al-Amin AH, Sarveswaran J, Wood JM, Burke DA, Donnellan CF. Efficacy of
2 taurolidine on the prevention of catheter-related bloodstream infections in patients on home
3 parenteral nutrition. *J Vasc Access*. 2013;14:379-82.
- 4 [16] Bisseling TM, Willems MC, Versleijen MW, Hendriks JC, Vissers RK, Wanten GJ.
5 Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in
6 patients on home parenteral nutrition: a heparin-controlled prospective trial. *Clin Nutr*.
7 2010;29:464-8.
- 8 [17] Cullis PS, McKee RF. Taurolidine lock - experience from the West of Scotland. *Clin*
9 *Nutr*. 2011;30:399-400; author reply 1.
- 10 [18] Jurewitsch B, Jeejeebhoy KN. Taurolidine lock: the key to prevention of recurrent
11 catheter-related bloodstream infections. *Clin Nutr*. 2005;24:462-5.
- 12 [19] Olthof ED, Versleijen MW, Huisman-de Waal G, Feuth T, Kievit W, Wanten GJ.
13 Taurolidine lock is superior to heparin lock in the prevention of catheter related bloodstream
14 infections and occlusions. *PLoS One*. 2014;9:e111216.
- 15 [20] Saunders J, Naghibi M, Leach Z, Parsons C, King A, Smith T, et al. Taurolidine locks
16 significantly reduce the incidence of catheter-related blood stream infections in high-risk
17 patients on home parenteral nutrition. *Eur J Clin Nutr*. 2015;69:282-4.
- 18 [21] Tribler S, Brandt CF, Petersen AH, Petersen JH, Fuglsang KA, Staun M, et al.
19 Taurolidine-citrate-heparin lock reduces catheter-related bloodstream infections in intestinal
20 failure patients dependent on home parenteral support: a randomized, placebo-controlled trial.
21 *Am J Clin Nutr*. 2017;106:839-48.
- 22 [22] Wouters Y, Roosenboom B, Causevic E, Kievit W, Groenewoud H, Wanten GJA.
23 Clinical outcomes of home parenteral nutrition patients using taurolidine as catheter lock: A
24 long-term cohort study. *Clin Nutr*. 2018.
- 25 [23] Wouters Y, Theilla M, Singer P, Tribler S, Jeppesen PB, Pironi L, et al. Randomised
26 clinical trial: 2% taurolidine versus 0.9% saline locking in patients on home parenteral
27 nutrition. *Aliment Pharmacol Ther*. 2018;48:410-22.
- 28 [24] Arnoriaga Rodriguez M, Perez de Ciriza Cordeu M, Camblor Alvarez M, Breton Lesmes
29 I, Motilla de la Camara M, Velasco Gimeno C, et al. Clinical and economic impact of the
30 taurolidine lock on home parenteral nutrition. *Nutr Hosp*. 2018;35:761-6.
- 31 [25] Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on
32 Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of
33 complications). *Clin Nutr*. 2009;28:365-77.
- 34 [26] Haute Autorité de Santé. Choices in methods for economic evaluation. 2011;
35 [http://www.has-sante.fr/portail/jcms/r_1499251/fr/choix-methodologiques-pour-l-evaluation-](http://www.has-sante.fr/portail/jcms/r_1499251/fr/choix-methodologiques-pour-l-evaluation-economique-a-la-has)
36 [economique-a-la-has](http://www.has-sante.fr/portail/jcms/r_1499251/fr/choix-methodologiques-pour-l-evaluation-economique-a-la-has)
- 37 [27] Agence Technique de l'information sur l'hospitalisation. Référentiel de coût MCO 2011
38 2011.
- 39 [28] Black WC. The CE plane: a graphic representation of cost-effectiveness. *Med Decis*
40 *Making*. 1990;10:212-4.
- 41 [29] Klek S, Szczepanek K, Hermanowicz A, Galas A. Taurolidine lock in home parenteral
42 nutrition in adults: results from an open-label randomized controlled clinical trial. *JPEN J*
43 *Parenter Enteral Nutr*. 2015;39:331-5.

1 **List of figures:**

2 **Figure 1.** Flowchart describing the selection of patients who received long-term taurolidine
3 locks (LTTL).

4

5 **Figure 2.** Kaplan-Meier analysis before (continuous line) and after (dotted line) the
6 introduction of LTTL. Log rank test for equality of the cumulative incidence curves for proven
7 CRBSI, $p < 0.0001$.

8

9 **Figure 3.** Cost-effectiveness plane after 1,000 replications considering proven and probable
10 CRBSI requiring hospital management. LTTL avoided -2.63 [-3.26 to -2.06] infections per
11 patient and reduced incremental costs by -7,258 [-10,450 to -4,016] € per patient (mean
12 [bootstrap CI 95%]).

13

1 **Table 1.** Characteristics of patients at LTTL initiation

2

	(n=37)
Gender, F/M	25/12
Age (yr), mean \pm SD; median [IQR]	55.5 \pm 17.0; 58.1 [42.6-68.6]
	Short bowel syndrome 35 (95)
	Crohn's disease 12 (32)
	Mesenteric infarction 10 (27)
Indication for HPN n (%)	Cancer 5 (14)
	Surgery complications 7 (19)
	Radiation enteritis 1 (3)
	Motility disorders 2 (5)
	Cancer and Cytotoxic drugs 2 (5)
Associated comorbidities n (%)	Diabetes 6 (16)
	Immunosuppressants 7 (19)
	None 22 (60)
Type of central venous access n (%)	CVA 26 (70)
	Port-a-cath 11 (30)
HPN use in days, mean \pm SD; median [IQR]	1 996 \pm 1 939; 1 388 [579-2 648]
LTTL use in days, mean \pm SD; median [IQR]	422 \pm 238; 369 [226-700]

3

1 **Table 2.** Patient outcomes before and after the introduction of LTTL for overall proven and
 2 probable CRBSI requiring hospital management (Wilcoxon's signed rank test)

3

	Before (n=37)	After (n=37)	p value
Overall CRBSI rate per 1,000 catheter days, mean \pm SD; median [IQR]	8.21 \pm 3.95; 7.94 [5.56-10.94]	0.74 \pm 1.79; 0 [0-0]	< 0.0001
Catheter replacement rate per 1,000 catheter days, mean \pm SD; median [IQR]	1.79 \pm 2.75; 1.37 [0-2.74]	0.15 \pm 0.55; 0 [0-0]	< 0.0001
Number of hospitalisations per patient, mean \pm SD; median [IQR]	1.92 \pm 1.80; 1 [1-3]	0.22 \pm 0.49; 0 [0-0]	< 0.0001
Length of hospital stays per patient, mean \pm SD; median [IQR]	8.27 \pm 7.96; 6.66 [4-11]	3.26 \pm 8.41; 0 [0-0]	= 0.0047

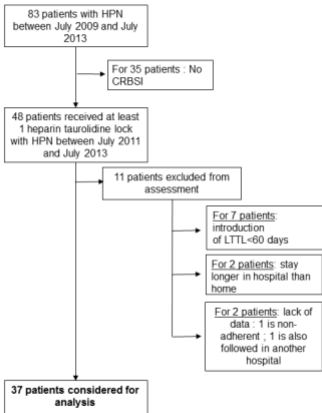
4

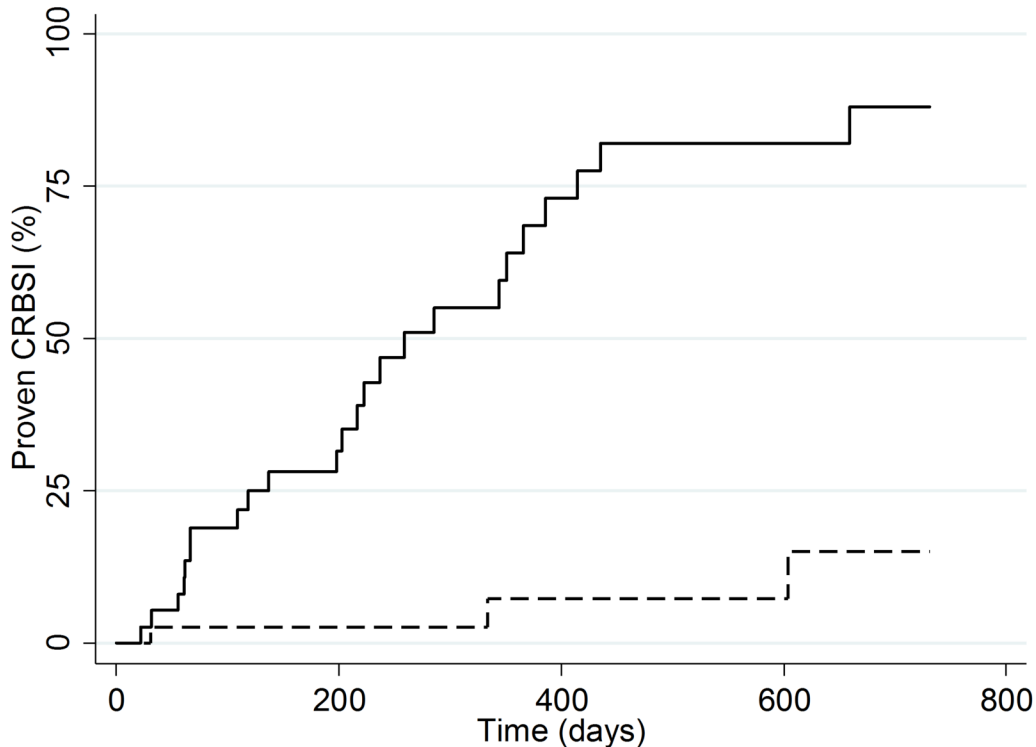
1 **Table 3.** Results of effectiveness and costs before and after the introduction of LTTL per
 2 patient considering proven and probable CRBSI requiring hospital management (mean [95%
 3 CI] non-parametric bootstrap)

	Before (n=37)	After (n=37)	Δ
Number of infections	2.89 [2.31 to 3.49]	0.26 [0.13 to 0.41]	-2.63 [-3.26 to -2.06]
Hospitalisation costs	9,625 [6,629 to 12,934] €	1,687 [448 to 3,170] €	-7,939 [-11,382 to - 5,053] €
Ambulatory medication costs	1,234 [757 to 1,802] €	57 [11 to 119] €	-1,177 [-1,739 to -697] €
Transportation costs	200 [137 to 275] €	23 [5 to 46] €	-178 [-253 to -118] €
Long term LTTL costs	-	2,151 [1,734 to 2,573] €	2,151 [2,573 to 1,734] €
Total costs	11,176 [8,004 to 14,968] €	3,918 [2,390 to 5,445] €	-7,258 [-10,450 to - 4,016] €

4

5





Number at risk

After	37	30	18	12	0
Before	37	20	6	3	0

