# $m{B}$ ulletin de la $m{D}$ ialyse à $m{D}$ omicile

# Advantages and limitations of long nocturnal hemodialysis

(According to the presentation given at the home dialysis day (DIADOM) during the congress Seminars of Nephrology which was held in Paris in January 2022)

(Intérêts et limites de l'Hémodialyse Longue Nocturne)

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# Summary

Intermittent long nocturnal hemodialysis (LNHD) combines dialysis and sleep. Its clinical advantages are a reduced ultrafiltration rate, better control of blood volume with improved tolerance of the sessions and cardiac performance, better clearance of phosphates and middle molecules, and better survival in cohort studies. Quality of life is not impaired by the length of the sessions and, when not optimal, improves when transferring from standard hemodialysis (HD) to LNHD. The quality of sleep is sometimes disturbed, but it is not an important cause of exit from the program. The sustainability of an LNHD program depends on the joint medical and managerial will, the selection of stable patients, respect for schedules, and the duration of sessions, which is essential for sleep dialysis. The health authorities must play a role in allowing this modality under acceptable financial conditions. Informing the patient of the existence of LNHD before the dialysis stage is essential, helped by the testimony of peers. Learned societies should support research and the provision of information to nephrologists. Finally, architectural conditions that promote privacy and sleep are key to the success of the program.

#### Résumé

L'hémodialyse (HD) Longue Nocturne intermittente permet de combiner dialyse et sommeil. Ses avantages cliniques sont une vitesse d'ultrafiltration réduite, un meilleur contrôle de la volémie avec amélioration de la tolérance des séances et des performances cardiaques, une phosphatémie et des moyennes molécules mieux épurées et une meilleure survie dans les études de cohortes. La qualité de vie n'est pas altérée par la longueur des séances et elle s'améliore quand elle n'est pas optimale lors du transfert de l'HD standard vers l'HDLN. La qualité du sommeil n'est parfois perturbée mais elle n'est pas une cause importante de sortie du programme. La pérennité d'un programme d'HDLN passe par les volontés conjointes médicales et managériales, la sélection des patients stables, le respect des horaires et de la durée de séances, indispensable à la dialyse de sommeil. Les autorités de santé doivent jouer un rôle pour permettre cette modalité dans des conditions financières acceptables. L'information au patient de l'existence de l'HDLN avant le stade de la dialyse est essentielle, aidée par le témoignage des pairs. Les sociétés savantes doivent soutenir la recherche et l'information aux néphrologues. Enfin les conditions architecturales favorisant l'intimité et le sommeil sont une clé de réussite du programme.

**Keywords**: Long nocturnal hemodialysis, ultrafiltration, quality of life,  $\beta$ 2-microglobulin, phosphatemia, mortality.

Mots clés : hémodialyse longue nocturne, ultrafiltration, qualité de vie,  $\beta 2$ -microglobuline, phosphatémie, mortalité.

# INTRODUCTION

Long nocturnal hemodialysis (LNHD) is a dialysis modality that has been prescribed since the 1960s. The length of the sessions at that time (between 8 and 12 hours, 2 to 3 times a week) favored its emergence to allow the combination of dialysis and sleep in young patients returning to work. In the last decade, there has been some confusion in the definition of LNHD. Indeed, the daily practice of chronic hemodialysis (HD) has been highlighted by Frequent Hemodialysis Network (FHN) studies. One of them failed to show a beneficial effect of daily home HDLN on the primary endpoint (combined endpoint of death/ventricular mass or death/physical activity score), mainly caused by the lack of recruitment and inclusion of incident patients [1]. LNHD 3 times a week, which has been practiced for decades, has not been the subject of randomized controlled trials. However, solid observational studies have shed light on their value [2]. Some programs have been developed over the past few years and have been acclaimed by patients and their feedback [3], but others have been discontinued, showing both undeniable clinical interest and operational difficulties. This contribution will highlight the interests and limitations of LNHD at 3 sessions per week (intermittent LNHD).

#### ADVANTAGES OF INTERMITTENT LONG NIGHT HEMODIALYSIS

Intermittent LNHD was favored by patients during the Etats généraux du Rein in 2013. The Centre de Rein Artificiel de Tassin (CRAT) (Tassin Artificial Kidney Center) has offered this modality since its creation in 1969. A survey with a control group of 59 patients (37 responses) treated with intermittent LNHD is summarized in *Table I*. Around 73% of the patients had chosen CRAT because of this modality, while 65% of them had already experienced standard HD. No patient wanted to return to daytime dialysis, and 75% liked the length of the sessions, 25% asked for one hour less, and none were willing to dialyze with a standard 4 hours [4]. Clinically, no randomized controlled trial has been conducted on this dialysis modality, and it has been "forgotten" in FHN trials. However, solid data has demonstrated the expected benefits.

◆ Table 1. Investigation of intermittent HDLN at the Tassin Artificial Kidney Center [4]

	nittent	Reasons for choosing intermittent	HDLN
LNHD*			
Choice of CRAT** for LNHD	73%	Professional activity	21%
Standard HD experience	65%	Social and family life	73%
Satisfaction with the length of the sessions	75%	Quality of treatment	70%
Wish for one hour less	25%	Sleep/dialysis combination	73%
Wish to return to standard HD	0%		
Overall satisfaction with LNHD	89%		
Desire for daytime dialysis	2%		

<sup>\*:</sup> long night hemodialysis; \*\*: Tassin Artificial Kidney Center

# 1- Ultrafiltration rate and clinical tolerance of the session

In a cohort study, Lacson et al. [5] compared 746 patients who switched from standard HD to LNHD in a dialysis center and 2,062 patients who remained on standard HD. The hourly ultrafiltration rate (UF) decreased from 11 to 6 ml/h/kg in the LNHD group, remaining constant at 12 ml/h/kg in the standard HD group. This result is all the more interesting given that the speed of

UF is currently recognized as a risk factor for mortality [6] and that the patients who had switched to LNHD showed a significant increase in interdialytic weight gain of 0.5 kg on average. Interdialytic weight gain is associated with the risk of arterial hypotension during the session [7]. The study of Lacson et al. does not mention this complication in their standard LNHD–HD comparative study. However, Ok et al. [8] reported that 247 patients switched from standard HD to LNHD in a dialysis unit compared to 247 patients who remained in standard HD, matched on 45 criteria and followed for 1 year. The incidence of in-session hypotension requiring saline infusion was comparable at the baseline—60.4 and 67.0 episodes per 1,000 sessions, respectively, decreasing in the LNHD group to 21.2 episodes (p < 0.0001) and increasing to 80.3 episodes/1,000 sessions in the standard HD group (p = 0.15).

# 2 - Phosphatemia

While phosphatemia quickly reaches a plateau during the session, phosphate clearance is prolonged throughout the dialysis session, as shown by Gutzwiller et al. [9] with 5-hour sessions. In the "case control" study by Ok et al. [8], the mean phosphatemia over 1 year was significantly lower in the LNHD group  $(3.87 \pm 1.20 \text{ mg/dl})$  than in the standard HD group  $(4.96 \pm 1.14 \text{ mg/dl})$ , whereas it was comparable at the beginning of the study  $(4.63 \pm 1.32 \text{ and } 4.82 \pm 1.26)$ . The prescription of phosphate binders, stable over 1 year in conventional HD (82.9% of patients treated at the end of 1 year), fell from 83.0% to 22.4% among patients in LNHD. These results confirmed the cohort study by Lacson et al. [10], which found a significant decrease in blood phosphorus levels in LNHD (5.73 to 5.02 mg/dl (p < 0.001)), whereas it increased in standard HD (5.75 to 5.85 mg/dl (p = 0.01)).

# 3 - Cardio-vascular parameters

In the Turkish case control study [8], 91 and 85 patients, respectively, were analyzed by echocardiography at the beginning and end of the study. Cardiac parameters (atrial volume, ejection fraction, ventricular end-diastolic diameter, and ventricular mass index) were identical at the baseline between the two groups and did not change in standard HD. In LNHD, atrial and ventricular end-diastolic volume and ventricular mass index decreased, and ejection fraction increased significantly. After 1 year, atrial and ventricular end-diastolic volume and ventricular mass index were significantly lower in LNHD than in standard HD. However, the ejection fraction did not differ between the two groups at 1 year. Blood pressure did not vary significantly in both groups during the follow-up year, but the prescription of antihypertensive drugs, stable in the standard HD group, decreased from 22% to 8% of patients in the LNHD group. In their study of an equivalent duration (1 year), Karur et al. [11] covered right ventricular remodeling by switching 30 patients from standard HD to LNHD compared to 37 patients who remained in standard HD. The right ventricular telesystolic and telediastolic volume indices and the right ventricular mass index decreased in the LNHD patients with a stable ejection fraction, but only the right ventricular end-diastolic volume index significantly decreased in the LNHD group compared to the standard HD group after 1 year. In a non-randomized controlled study evaluating cardiac parameters 6 months after the transfer of 13 patients to LNHD compared to 12 patients who remained in standard HD, the data was in favor of a significant reduction in cardiac fibrosis [12].

# 4 - β2-microgobuline (β2M)

In the HEMO study, the plasma  $\beta 2M$  level above which an increased risk of mortality is associated is 27.5 mg/l [13]. In a crossover study, Chazot et al. [14] showed that long HD (average of 6.4 hours thrice per week) with low-permeability membranes did not result in a significant decrease in  $\beta 2M$  (43.3 mg/l), whereas with a high-permeability membrane under the same dialysis conditions,  $\beta 2M$  decreased to 27.5 mg/L. With the same high permeability dialyzer (polysulfone), Eloot et al. [15] showed that over sessions of 4, 6, and 8 hours, increasing the session length increases the mass of  $\beta 2M$  extracted, the plasma volume cleared of  $\beta 2M$ , and the  $\beta 2M$  extraction ratio (ratio of dialyzer clearance to blood flow), confirming a beneficial effect of session length regarding the clearance of medium molecules. In hemodiafiltration (HDF), for equal duration in long dialysis (7–8 hours/session), Maduell et al. [16] showed that a high convective volume (35–50 vs. 20–30 liters/session) still optimizes the  $\beta 2M$  reduction rate.

#### **5 - Anemia treatment**

The use of erythropoiesis-stimulating agents (ESAs) was studied in the Turkish case control study [8]. After 1 year of follow-up, the percentage of patients on ESA and the weekly dose of ESA remained stable (53.7% and 2,819 IU/week), while both parameters decreased significantly in LNHD (patients on ESA: 55.5% to 24.7%; weekly EPO dose in LNHD decreased from 3,026 to 1,697 IU/week).

# 6 - Quality of life, sleep, and employability

The first two aspects grouped in this paragraph are critical elements of the sustainability of an LNHD program, especially sleep, as highlighted by Laruelle et al. [17]. Ok et al. [8] studied the evolution in standard HD after the transfer to LNHD of memory capacities, cognitive functions and mental health, perceived pain, vital momentum, and anxiety and depression scores. In the standard HD group, an increase in perceived pain and a decrease in vitality and mental health were noted after 1 year. These parameters remained stable in the LNHD patients, who saw an improvement in memory abilities. More recently, Dumaine et al. [18] showed among 36 patients transferred to LNHD that patients whose baseline quality of life scores were below the group median showed significant improvement at 12 months in mental, physical, and chronic kidney disease—related symptoms and impact. It is notable that the duration of dialysis did not impact the quality of life and even appeared to improve it.

In our experience in Tassin with regard to sleep, in a cohort of 36 patients [4], 86% of the patients declared that they had slept at least 4 hours during the session, 30% of the patients finished their night at the center after disconnection, and 81% slept again after returning home (but not those who left for work, who were few in number). A quarter of the patients considered their sleep to be of poor quality and took hypnotics both on dialysis and at home. Recently, Hull et al. [19] evaluated sleep in 36 patients in an anonymized fashion: 24 continued the LNHD program, and 12 left the program. The ability to fall asleep was found to be impaired in 71% and 86% (LNHD continuation and LNHD discontinuation, respectively) of the cases. The ability to stay asleep was unchanged in 42% and 8% of the patients, respectively, whereas the deterioration of sleep and/ or the feeling of "restless legs" increased during the sessions in 54% and 92% of the patients, respectively. The overall quality of sleep among patients who remained in LNHD was judged to be unchanged (37.5%), improved (4%), and slightly (33%) or significantly (21%) worse. Patients

who left the LNHD program were judged to fare significantly worse overall in 83% of the cases, slightly affected and unchanged in 8% of the cases. In the Tassin's experience, poorer sleep during the session is not a frequent cause of discontinuation of LNHD, which is also reported by Lacson et al. [10]. Hull et al. [19] emphasized the value of a "sleep kit" with a mask and earplugs to help patients adapt to LNHD. It is also important to emphasize the logistical setup with, where possible, individual rooms or cubicles that promote sleep, as illustrated *in Figure 1*.



♠ Figure 1. Dialysis box at the Kamome Minatomirai Clinic in Yokohama, Japan, courtesy of Dr. Hiroshi Kaneda.

One of the reasons for choosing LNHD is to increase daytime availability for working people, among others. There is little data on this subject. Li et al [20] compared incident patients on LNHD (20 patients) and peritoneal dialysis (80 patients). After one year, the percentage of employed LNHD patients remained stable (from 75% to 80%, mean age 47 years), whereas it dropped in peritoneal dialysis from 60% to 33% (mean age 52 years).

# 7-Morbi-mortality

As mentioned above, no randomized controlled trials confirm reduced hospitalizations and mortality in patients treated with LNHD compared to standard dialysis—but cohort data exists. Lacson et al. [10] showed a 25% reduced risk of mortality at 2 years with in-center LNHD compared to standard in-center HD (746 vs. 2,062 propensity score matched patients; p = 0.004). In the study by Ok et al. (242 patients transferred to LNHD vs. 242 patients remaining in standard HD matched on 35 criteria [8]), the 1-year hospitalization rate was 5.4 versus 18.8 days per 100 patients/month (p = 0.002), and 1-year mortality was reduced by 72% (p = 0.02). Another U.S. study compared survival in 1,206 patients treated with LNHD and 111,707 patients treated with standard HD, with a 33% survival advantage in LNHD [21]. More recently, the ERA-EDTA registry confirmed this 27% survival advantage in favor of LNHD [22].

In conclusion, this data, even with scientific limitations, shows that LNHD has many clinical advantages on known criteria associated with mortality (UF rate, phosphatemia; cardiac conditions), and the mortality data is convergent. The patient's quality of life is not impacted by session length. The main obstacle is sleep, which is not optimal. In spite of this, the surveys show a large adherence of the patients to the modality.

# BARRIERS AND OBSTACLES TO LONG NIGHTLY HEMODIALYSIS (LNHD)

1 - Example of the closure at the former Tassin Artificial Kidney Centre (CRAT)

In this facility, LNHD started from its opening on August 4, 1969, at a time when patients were young and active. The LNHD program closed permanently on February 8, 2021. This closure represents a good summary of the practices to be avoided for the sustainability of the LNHD program (*Table II*).

♣ Table II. Factors that contributed to the end of the HDLN program at the former Tassin Artificial Kidney Center and measures to perpetuate an LNHD program.

Factors for failure	Sustainability factor
Lack of managerial will	Management commitment to determine the clinical benefits of LNHD
Lack of specific funding	Recognition by health authorities of the specificity of LNHD
"À la carte" schedules Duration of "à la carte" session	Strict schedules and non-negotiable session lengths to avoid activity and disturbance during sleep periods
Premises without privacy	Adjustement, if possible, of the current premises (e.g., an adapted architecture in case of moving)
Loss of patient autonomy	Evaluating the inconvenience caused to the proper functioning of LNHD and recommending, if necessary, the return to dialysis during the day

# a. Lack of managerial will to maintain the modality

Since its arrival in 2009, the operational management of the group that owns the CRAT has expressed and repeated its wish to see the LNHD program disappear for financial and organizational reasons. The financial difficulties are concrete with the absence of adequate pricing for the additional costs of the modality (night work, deficit patient/ID ratio, increased expenses). The additional cost of the modality has been calculated at 42€ per session [17]. The decrease in the in-center tariffs made it impossible to compensate for the LNHD deficit when the two modalities coexist. The Regional HealthCare Authorities in 2018 was sollicitated, without success, to expose the difficulties and the risk of disappearance of LNHD to find a solution. The messages remained "dead letter."

In addition, there are recurrent human resource difficulties in recruiting night staff. These difficulties, combined with a lack of vision and managerial interest in the quality of treatment and a lack of knowledge of medical results, have maintained a deleterious environment for the future of LNHD in the facility for over 10 years. The medical, nursing, and management teams were destabilized by these recurrent assaults, which were a source of demotivation. The conclusion of this observation is that proactive leadership on the part of the management teams is essential for the sustainability of the LNHD program.

# b. Prescription drift and organizational problems

"À la carte" dialysis was gradually implemented on the CRAT, facilitated by a large number of stations and a culture of long dialysis with a dedicated area for non-standard dialysis, in contrast to the uniform industrial model of "one size fits all" prescribing denounced by one of the pioneers of dialysis, Lee W. Henderson [23]. This flexibility was also necessary to respond to numerous requests from patients to reduce their session length. The individualized prescription of the duration was also applied in nocturnal dialysis, resulting in durations varying from 5 to 8 hours per session with, as a consequence, permanent activity in the dialysis room, bringing light and noise incompatible with sleep. This was also favored by late afternoon connection times and the end

of sessions after 11:00 p.m. In addition, some patients who had been dialyzed for many years in LNHD and who were attached to this modality progressively lost part of their autonomy, complicating the management with a need for stretchering that was incompatible with sleeping LNHD.

Another consequence of the variable duration of sessions was an extremely low patient/caregiver ratio at the end of the night, with inactivity that was deleterious to the organization of work. Finally, the premises used for LNHD were the same as those used during the day, with no particular arrangements to promote relative privacy, whereas the CRAT had moved to new premises in 2011. No thought had been given to the subject, and this was a mistake.

In practice, LNHD must be prescribed to selected patients in self-care or low-medicalized units modality, performed in premises that favor relative privacy, with a specific time frame that does not overlap with evening dialysis, and with uniform non-negotiable session lengths. It can be practiced at home, but scant data exists on this particular aspect. The expected clinical benefits are the same.

#### 2 - Other brakes and barriers

Patients are not easy to convince for LNHD despite its undeniable clinical advantages because of the length of dialysis, the wish for many patients to spend the night "in their own bed," the difficulty to leave the spouse alone for the night, and the fear of not sleeping. It is important to ensure that in the preparation phase for dialysis ("CKD 5 pathway"), patients are informed about this modality if it is available and about its clinical and socio-professional advantages. Moreover, the "sleep kits" mentioned above represent a measure that can improve adherence if the fear of sleep disturbance is the main obstacle [19]. Moreover, access to transversal functions such as dietary, psychological, or social care is more complicated as patients often refuse to return to the dialysis center during the day and outside of the sessions. The development of telephone or video interviews can provide solutions that were well tested during the COVID-19 pandemic. Finally, patients' associations or testimonies, such as those of Fabrice Huré [3], are crucial. Given the refusal of the ARS to discuss LNHD within the former CRAT, the mobilization of patient associations could have changed the situation.

Caregivers may not commit to LNHD for fear of the lack of vigilance with night work and the absence of a doctor on site in the event of a serious event linked to care, such as accidents involving the disconnection of the vascular approach. The programs designed with only one caregiver (1 nurse for 6 patients in a selfcare unit) are not necessarily adapted, posing the problem of isolation in the event of an incident and of the "isolated worker" for the caregiver, which is subject to strict regulations.

**Nephrologists** are not always convinced of the relevance of LNHD in the absence of randomized controlled trials. They are the linchpin of patient education, which is crucial. It is the job of our learned societies to promote this modality and to convince them because the data and feedback are abundant and positive.

**Management** must be convinced that this care is optimal and beneficial for patients. Collaboration with nephrologists is essential to make or keep the project or program durable. They must explore all possibilities of financing projects proposed by regional agencies to finally make LNHD

emerge as an innovative modality, even if it has existed almost since the beginning of dialysis.

**♣** Table III. Other barriers and obstacles to LNHD and how to overcome them.

Brakes/Obstacles	Solutions
Patient	
Refusal to extend dialysis time	Stage 4 and 5 education on dialysis modalities
	Specific education on the benefits of LNHD
	Contact with patient associations
Disseminating feedback [3]	Kit sommeil
	Préserver le calme et la pénombre dans la salle de dialyse
Fear of not sleeping	Sleep kit
	Keeping the dialysis room quiet and dark
Limitations on access to cross-cutting functions	Organizing telephone or video interviews
Caregivers	
Concern about the absence of a doctor	Using experienced nurses
Worry about being alone	Preferring programs requiring at least 2 nurses
Lack of motivation to work at night	Financial incentives
Nephrologist	
Lack of belief in the benefits of LNHD	Highlighting LNHD by learned societies
	Reading patient testimonials
Management	
Lack of awareness of the benefits of LNHD	Dialogue and training with and by nephrologists
Financial constraints	Exploring potential funding from regional health agencies

# **CONCLUSIONS**

Even if LNHD has disappeared in some institutions, it has developed in recent years. According to the REIN registry in June 2022 (data provided by Cecile Couchoud), 208 patients are currently being treated with LNHD for 6 to 8 hours per session, mainly in low-medicalized units. The most important centers (at least 10 patients in LNHD) are in Rennes, Hyères, Montpellier, Angers, Paris, Nouméa, and St Malo. This modality allows optimal dialysis with increased time for personal or professional life. It must be addressed to stabilized patients within a defined and stable time frame and session duration. Everything must be done to respect the patient's sleep as much as possible. Access to transversal functions must be organized. Experiences must be published to show the relevance of LNHD in terms of clinical results, quality of life, and patient satisfaction. Finally, lobbying work carried out by patients and their associations, caregivers, and nephrologists as well as their learned societies and institutions and their representative organizations must be done with the supervisory authorities to have LNHD recognized as a specific modality requiring fair and appropriate funding.

# **CONFLICT OF INTEREST**

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