

# Quotidian dialysis – update 2005

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## Purpose of review

The interest in quotidian hemodialysis has increased further after the HEMO study reported that high-dose thrice-weekly hemodialysis failed to improve clinical outcomes. This, in combination with a significant volume of newly published data, made a review of the topic of quotidian hemodialysis timely.

## Recent findings

The published research has revealed further evidence of cardiovascular and quality-of-life improvements as well as financial benefits with quotidian hemodialysis. Accrued worldwide experience has confirmed the previously published benefits of quotidian hemodialysis. There has been a significant effort by industry to produce patient-friendly machines for home hemodialysis. Reports on the use of daily hemodialysis and hemodiafiltration in children have appeared. An international registry of patients on quotidian hemodialysis has been created. The need for modification of the funding mechanisms and the lack of prospective randomized controlled studies on quotidian hemodialysis led to the funding of such studies by the National Institutes of Health in collaboration with Centers for Medicare and Medicaid services to be completed by 2008. The proper funding for daily home hemodialysis was secured in the province of British Columbia, Canada, and is under consideration elsewhere.

## Summary

There is increasing evidence confirming that quotidian hemodialysis improves clinical outcomes in a cost-efficient manner. Provided that the reimbursement issues are resolved these modalities may be utilized extensively at home as well as in the in-center facilities. The revitalization of home hemodialysis will compensate for the decline in utilization of continuous ambulatory peritoneal dialysis and the nursing shortage encountered in most countries.

## Keywords

daily hemodialysis, home hemodialysis, nocturnal hemodialysis

## Abbreviation

**ESRD** end-stage renal disease

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## Introduction

Since the HEMO study demonstrated that modest increases in dialysis dose did not reduce mortality in people receiving conventional thrice-weekly hemodialysis treatments [1], interest in intensive dialysis regimens including long intermittent hemodialysis, short quotidian hemodialysis and quotidian nocturnal hemodialysis has intensified [2]. The interest in convection techniques such as hemofiltration and hemodiafiltration has also increased [3<sup>•</sup>,4<sup>•</sup>]. In this review we will focus on recent clinical trial results that have studied the various forms of quotidian hemodialysis. Older references can be found in our previous review in this journal [5].

## Technique advancements

The method of delivery of quotidian dialysis has been described previously [5]. Industry efforts have led to new hemodialysis machines that are simpler to operate. Some have unique features that are useful for short or long home hemodialysis [6–12], such as mobile flat screens, fewer alarms and easier setup. New capabilities include low dialysate flow, ultrapure dialysate, in-situ dialyzer reuse, hemoperfusion techniques, batch dialysate or sorbent cartridges. The need for remote monitoring for nocturnal hemodialysis is still debated, and not all units perform remote monitoring unless required by local regulatory bodies. The quality of monitoring is improving by extending it to include biological parameters [13<sup>•</sup>,14<sup>•</sup>]. Monitoring of a wide geographical area by a single center has been tried successfully.

## Patient selection and training

Quotidian hemodialysis can be initiated by patients in order to improve quality of life or to have free time to work. Alternatively, patients start quotidian dialysis as a 'rescue' therapy. Ability and willingness to be trained as well as adequate housing are the only prerequisites for home techniques. Interestingly, a recent study suggests that only about half of patients would agree to come to the dialysis facility daily even if the benefits of quotidian hemodialysis were established [15]. In the current reimbursement structure the main indication for in-center quotidian hemodialysis is the presence of significant co-morbidities, hemodynamic instability or severe

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malnutrition [16<sup>••</sup>]. Although the length of training for home hemodialysis for untrained patients is usually 5–8 weeks, attempts to increase training efficiency have been made.

### Blood access

Although the use of native arteriovenous fistulae is encouraged for quotidian hemodialysis, synthetic grafts and central venous catheters can be used. Some centers use the buttonhole technique, where cannulation occurs repeatedly at the same site, often using non-cutting needles, which are guided by the tract into the fistula. The single-needle system may increase safety, patient comfort and improve access survival but can be utilized only for nocturnal hemodialysis, in which low blood flow rates are acceptable. Infectious and thrombotic access complications on quotidian hemodialysis are reported to be similar to, or less frequent than, conventional hemodialysis, but prospective studies are missing [17,18<sup>•</sup>,19<sup>•</sup>].

### Results

The published outcomes of quotidian nocturnal hemodialysis will be discussed below.

### Kinetics and solute removal

The solute-removal measure correlating best to clinical outcomes remains unclear. Potential candidates include the peak urea concentration, the equivalent kidney urea clearance (EKR) based on the average urea concentration (TAC), standard Kt/V (stdKt/V; where K is dialyzer clearance, t is dialysis time and V is urea volume of distribution) based on the average predialysis urea concentration [20<sup>••</sup>], and the normalized Kt/V based on the average concentration of a theoretical solute diffusing slowly across intercompartmental barriers and therefore better representing larger molecules [21<sup>•</sup>]. In order to explain the benefits of quotidian hemodialysis, these techniques have been extended to the comparison of larger molecule removal [22<sup>•</sup>]. stdKt/V based on the average predialysis urea, and therefore favoring the high-frequency regimens, has been the most popular method in the field [23<sup>•</sup>] and is advocated by some authorities [20<sup>••</sup>]. While conventional hemodialysis and peritoneal dialysis typically yield a stdKt/V of 2.0, the values for quotidian short hemodialysis and nocturnal hemodialysis are about 3 and 5 respectively [16<sup>••</sup>,23<sup>•</sup>,24<sup>•</sup>]. A weekly stdKt/V of 2 would be equivalent to a daily equilibrated Kt/V of 0.38 (six times a week). Convective techniques including hemofiltration and hemodiafiltration offer higher removal of higher-molecular-weight solutes and therefore measures of urea kinetics likely underestimate dialysis adequacy [22<sup>•</sup>,25]. The use of about 15 l of replacement solution for daily hemofiltration 6 days a week in an average-sized patient provides a stdKt/V of about 2.0 per week, which is similar to conventional hemodialysis but lower than short daily

hemodialysis of equal weekly duration [25]. Use of short daily hemodiafiltration has been associated with lower  $\beta_2$ -microglobulin levels [3<sup>•</sup>]. Long hemodialysis is associated with increased middle-molecule removal and quotidian nocturnal hemodialysis offers a 4-fold increase in  $\beta_2$ -microglobulin removal [5]. Advanced glycated end products and protein-bound molecules have been reported to decrease upon conversion from conventional to short daily hemodialysis [5]. While short daily hemodialysis reduces homocysteine levels, quotidian nocturnal hemodialysis appears to reduce these levels further [5,26<sup>•</sup>].

### Quality of life

When quality of life was measured, quotidian dialysis was associated with a reduction in the number and severity of dialysis-related symptoms, as well as a reduction in time to recover from dialysis [27<sup>•</sup>]. Quality-of-life instruments such as the Kidney Disease Quality of Life (KDQOL), the Sickness Impact Profile (SIP), the Beck Depression Index, the RAND-36 and the SF-36 method have all reported higher global quality of life in quotidian-dialysis patients [16<sup>••</sup>,28<sup>••</sup>,29,30<sup>••</sup>,31,32<sup>•</sup>]. Utility scores assess a patient's preference for health states and are graded on a scale between 0 (a quality of life equivalent to death) and 1 (the best quality of life imaginable) [33<sup>••</sup>]. Patients receiving conventional hemodialysis typically report utility scores of about 0.5, which represents a quality of life worse than in patients who suffer from blindness or paraplegia. Mean utility scores for patients receiving home quotidian hemodialysis were about 0.7, similar to historically reported values following kidney transplant [27<sup>•</sup>,33<sup>••</sup>].

### Calcium, phosphorus metabolism and bone disease

Disorders of mineral metabolism contribute to cardiovascular disease in dialysis patients. Phosphate is removed by hemodialysis less efficiently than urea, due to its slow mobilization from the deep tissues. Consequently, an early decrease in serum phosphate during hemodialysis is followed by rebound prior to and after the end of dialysis [34]. High dialysis frequency increases phosphate removal by allowing daily equilibration of the serum levels and restoring the blood to dialysate gradient. However, the main determinant of phosphate removal is the duration of dialysis. A quantitative approach to phosphate removal has been recently described [35]. The effect of the two forms of quotidian dialysis on mineral metabolism is as follows.

#### Short daily hemodialysis

Unless dialysis time is longer than 2 h, short daily hemodialysis results in a minimal decrease in serum phosphate or phosphate binders, and no effect on parathyroid hormone [5]. Measurement of phosphate in dialysate suggests that phosphate removal increases on short daily

hemodialysis, but patients typically increase their protein intake, which minimizes the net effect on serum phosphate levels [36•].

#### *Quotidian nocturnal hemodialysis*

Quotidian nocturnal hemodialysis doubles phosphate removal when compared to conventional hemodialysis, allowing discontinuation of phosphate binders despite increased dietary phosphate intake. Typically phosphate must be added to the dialysate to avoid hypophosphatemia [5]. Normalization of serum phosphate typically results in normalization of the calcium phosphorus product [28••], and allows the safe increase in the dialysate calcium, which can result in higher serum calcium and lower parathyroid hormone levels without the use of vitamin D analogues. Tumoral calcinosis resolved in one patient after conversion to quotidian nocturnal hemodialysis [37].

Higher dialysate calcium losses and the discontinuation of phosphate binders can result in a negative calcium balance in patients performing quotidian nocturnal hemodialysis dictating high dialysate calcium [30••,38]. Dialysate calcium and phosphorus can be adjusted by the patients through the addition of powdered calcium chloride or sodium phosphate, the latter being added into either the acid or bicarbonate concentrate.

#### **Nutrition**

Most patients who convert to quotidian hemodialysis experience improved appetite. Reports on the short and long-term effects of quotidian nocturnal hemodialysis on serum albumin and weight are variable, with improvements seen in most [39•,40], but not all studies [16••]. High baseline co-morbidity appears to blunt the nutritional benefits of quotidian hemodialysis and this may explain the differences in serum albumin between patients on short and nocturnal quotidian hemodialysis reported in a recent study [26•]. The use of nocturnal hemodialysis or daily hemodiafiltration in children has led to improved nutritional status and accelerated growth [41,42].

#### **Cardiovascular disease**

Improvement in blood-pressure control without or with minimal use of medications has consistently been reported in both quotidian short and nocturnal hemodialysis [5]. Current understanding of the mechanism by which blood pressure is lowered by frequent dialysis suggest that quotidian short hemodialysis lowers blood pressure primarily via enhanced extracellular fluid volume control [43•,44•]. In contrast, quotidian nocturnal hemodialysis lowers blood pressure by a selective decrease in total peripheral resistance [45••]. Both forms of intensive hemodialysis have been suggested to regress left-ventricular hypertrophy not seen on intermittent

long hemodialysis [43•,46]. Other cardiovascular effects unique to nocturnal hemodialysis include restoration of impaired left-ventricular systolic ejection fraction [47], correction of sleep apnea and restoration of cardiac autonomic balance during sleep [48•,49], improvement in flow-mediated dilation and endothelium-independent vasodilation [48•], restoration of impaired peripheral vascular flow [50] and an increase in serum high-density lipoprotein levels [51]. Further evidence for the vasodilatory effect of nocturnal hemodialysis has been an observed increase in blood pressure after transplantation. Conversely a decrease in blood pressure was observed after the transplantation of patients previously on conventional hemodialysis [52].

The difference in phosphate control between the two quotidian regimens may explain the dissimilar cardiovascular effects of the two regimens. The vascular responsiveness in patients before and after conversion to nocturnal hemodialysis was compared in patients with either high or normal baseline plasma phosphate levels. There was delay in the restoration of vascular responsiveness in the hyperphosphatemic cohort suggesting that phosphate control is related to the cardiovascular homeostasis [53••]. Coronary calcification, quantified using spiral computed tomography scan, was unchanged 1 year after conversion to nocturnal hemodialysis, suggesting a beneficial effect of the improved uremic control and normalization of serum phosphate [54••].

Patients on conventional hemoialysis have a 3–4-fold decrease in endothelial progenitor cell number and function, which are new cardiovascular prognostic indicators in the non-end-stage renal disease (ESRD) population, as compared to matched control [55•]. In contrast, patients on nocturnal hemodialysis have normal endothelial progenitor cell number and function, suggesting that improved uremic control may restore the balance between cardiovascular injury and repair [56••].

#### **Erythropoietin dose and anemia control**

There have been conflicting reports of the impact of quotidian hemodialysis on anemia management. Most groups described an increase in hemoglobin concentrations and a fall in erythropoietin requirements of as much as 45% [16••]. However, negative results have also been reported [29,57]. Some of the negative results were ascribed to insufficient iron supplementation. Similarly, despite the lack of improvement in erythropoiesis in the early reports on nocturnal hemodialysis [58], a significant increase in hemoglobin levels and a decrease in erythropoietin requirements were reported recently [59]. Red-cell survival did not improve on quotidian hemodialysis [60]. Further prospective studies are needed to delineate the mechanisms and clinical impact of intensive hemodialysis on anemia control and erythropoietin responsiveness.

**Sleep**

Sleep disorders such as sleep apnea, periodic limb movements and daytime sleepiness are highly prevalent in ESRD. Quotidian nocturnal hemodialysis has been demonstrated to normalize the sleep pattern in patients with prior sleep apnea [49]. However, the prevalence of daytime sleepiness did not change after conversion to quotidian nocturnal hemodialysis, and nor did the frequency of periodic limb movements [61<sup>\*</sup>]. There are no data on the effect of short daily hemodialysis on sleep disorders.

**Patient survival: hospitalization**

An 80% 5-year patient survival on short daily hemodialysis has been described [62]. Similar results of 81% survival over 5 years were reported on quotidian nocturnal hemodialysis [30<sup>\*\*</sup>]. Improved survival was reported using quotidian hemodialysis in acute renal failure [63]. Multicenter data on mortality from the quotidian hemodialysis registry [30<sup>\*\*</sup>,64], as well as randomized prospective studies [65], are needed. Retrospective as well as prospective data suggest decreased hospitalization rates of patients on quotidian hemodialysis but more data are needed [16<sup>\*\*</sup>,66,67].

**Daily hemofiltration**

There is only limited use of quotidian hemodiafiltration in-center for both adults and children or hemofiltration at home using pre-prepared sterile replacement solutions [3<sup>\*</sup>,4<sup>\*</sup>,42]. Lower predialysis serum  $\beta$ 2-microglobulin has been reported with quotidian hemodiafiltration [3<sup>\*</sup>]. Early clinical results from the use of the short daily hemofiltration are encouraging [4<sup>\*</sup>].

**Modality choices**

There are no adequate studies comparing the forms of intensive hemodialysis. The advantages of quotidian nocturnal hemodialysis must be weighed against the requirement for long and frequent treatments, the potential for deficiency syndromes, long exposure to dialysis membranes and safety concerns at night. It is the preferred modality for increased dialysis requirements as with large body size, or in pregnancy [68<sup>\*</sup>].

A prospective non-randomized study of 11 short daily, 12 nocturnal hemodialysis and matched controls receiving conventional hemodialysis for 5–36 months was published recently [14<sup>\*</sup>,57,69<sup>\*\*</sup>,70<sup>\*</sup>,71]. The study confirmed improvements in quality of life and blood-pressure control for both quotidian modalities [27<sup>\*</sup>,44<sup>\*</sup>] and better phosphate control with nocturnal hemodialysis [23<sup>\*</sup>,72<sup>\*\*</sup>].

The main advantage of long intermittent hemodialysis is the favorable financial profile, the known improved hemodynamic benefits and the increased middle-molecule removal [2]. Hemofiltration has the added

advantage of better removal of middle molecules which may lead to better outcomes.

**Health economics: the costs of dialysis**

In-center hemodialysis is one of the most expensive medical undertakings to ever be approved for widespread use. It is unclear if any therapy that adds to the cost of dialysis would be acceptable [33<sup>\*\*</sup>]. However, quotidian dialysis is not only cost-effective, but also potentially cost saving.

The cost of in-center hemodialysis is estimated to be between \$50 000 and \$100 000 per patient-year (2003 US dollars) [72<sup>\*\*</sup>]. Savings from quotidian dialysis must offset the expected rise in costs associated with higher treatment frequencies and, in the case of home hemodialysis, capital costs for water treatment and dialysis machines. Material costs more than double with quotidian dialysis, typically by about \$8000 per patient-year [33<sup>\*\*</sup>,66,69<sup>\*\*</sup>]. Capital costs are about six times higher for home quotidian methods, typically increasing costs by about \$5000 per patient-year [33<sup>\*\*</sup>,66,69<sup>\*\*</sup>].

The savings from decreased hospitalization associated with quotidian hemodialysis have varied from \$1000 to \$5000 per patient-year. Reduced medication use (primarily erythropoietin, cardiovascular medications and phosphate binders) has led to savings of between \$2500 and \$7000 per patient-year [33<sup>\*\*</sup>,66,69<sup>\*\*</sup>]. These savings may be enough to compensate for the higher material costs. Staffing costs of home hemodialysis have been reported to be between \$8000 and \$24 000 less per patient-year [72<sup>\*\*</sup>]. Most studies report a reduction in overhead and support costs of about \$5000 per year [72<sup>\*\*</sup>].

These savings make quotidian dialysis cost-effective, with home modalities typically saving over \$10 000 per patient-year over conventional hemodialysis [33<sup>\*\*</sup>,66,69<sup>\*\*</sup>]. When combined with the expected improvements in quality of life, these savings make quotidian hemodialysis the economically dominant option, both reducing costs and improving outcomes.

**Current utilization of quotidian hemodialysis and obstacles**

More than 1000 patients perform quotidian hemodialysis, with reports published from North and South America, Europe and Australia [16<sup>\*\*</sup>,24<sup>\*</sup>,28<sup>\*\*</sup>,29,39<sup>\*</sup>,40,58,62,73]. The main obstacle to the utilization of quotidian hemodialysis is the unfavorable reimbursement structure. Patient willingness and ability to perform home hemodialysis is a second barrier, as eligibility decreases with advancing age and co-morbidity.

Clinical as well as costing data from randomized controlled studies are needed [65]. The National Institutes

of Health (NIH) and the Centers for Medicare and Medicaid services (CMS) have funded such studies aiming to compare short and quotidian nocturnal with conventional hemodialysis. The results of these studies are expected in 2008. An international quotidian hemodialysis registry already in operation will be useful in collecting data from many centers and provide pilot data for further studies [64].

### Conclusion

Existing studies consistently demonstrate that quotidian hemodialysis provides improvement in quality of life, biochemical and cardiovascular parameters, and likely anemia and nutrition. Provided that a solution to the reimbursement problem is found, quotidian dialysis is expected to become a prevalent choice in the treatment of ESRD. The role of hemofiltration may also grow. These methods will provide revitalization of home hemodialysis, bringing social and vocational rehabilitation to more patients, while also providing a solution to the nursing shortage prevalent in many countries. Further studies of all aspects of quotidian hemodialysis are necessary to increase our understanding of the methods and also provide the data necessary for their appropriate reimbursement.

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