Intensified Hemodialysis in Adults, and in Children and Adolescents

Julia Thumfart, Wolfgang Pommer, Uwe Querfeld, Dominik Müller

SUMMARY

Background: There are now almost 70,000 dialysis patients in Germany. Conventional hemodialysis does not adequately compensate for malnutrition, arterial hypertension, renal osteopathy, and diminished performance ability. Various strategies for intensified hemodialysis have been implemented in an attempt to lower the considerable morbidity and mortality of end-stage renal failure.

Methods: We selectively review the literature on intensified dialysis in adults, children, and adolescents.

Results: In a randomized, controlled trial (RCT), a group of patients undergoing conventional dialysis was compared to a group undergoing brief, daily dialysis. Daily dialysis significantly improved the combined endpoint of left-ventricular hypertrophy or death (hazard ratio [HR] 0.61). In contrast, another, retrospective study found daily dialysis to be associated with higher mortality (15.6 vs. 10.9 deaths, HR 1.6). A prospective case-control study found nocturnal intermittent hemodialysis to be associated with lower mortality than conventional dialysis (1.77 vs. 6.23 per 100 patient-years); this result was confirmed in a further, retrospective study. An RCT on nocturnal dialysis performed every night revealed a significant regression of left-ventricular mass, yet the patients’ quality of life improved only in individual domains specifically related to renal function. Small-scale studies of intensified hemodialysis in children and adolescents have found that it leads to a higher growth rate and weight gain.

Conclusion: Intensified hemodialysis techniques improve arterial blood pressure, uremia-associated variables, and psychosocial variables. They also lower the necessary doses of antihypertensive drugs and phosphate binders. Dietary restrictions need not be as stringent. Further prospective trials are needed for a reliable assessment of the effect of intensified hemodialysis on mortality and quality of life.

Cite this as:
When two figures are given, the first refers to the intensified technique in question, the second to conventional hemodialysis. The difference incorporating both left ventricular mass and quality of life; ConvHD, conventional hemodialysis; SF-36, short form of the test for health-related quality of life; py, patient-years; ns, not studied.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of pts</th>
<th>Type of study, type of analysis</th>
<th>BP control</th>
<th>Left ventricular hypertrophy</th>
<th>Phosphate (mg/dL)</th>
<th>Quality of life</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short daily hemodialysis</td>
<td>FNIH Trial Group et al. (16)</td>
<td>125</td>
<td>RCT, per protocol</td>
<td>improved</td>
<td>∆−10.1 g in left ventricular mass</td>
<td>∆−0.56</td>
<td>+ 2 points on RAND-36</td>
</tr>
<tr>
<td>Intermittent nocturnal hemodialysis</td>
<td>Ok et al. (18)</td>
<td>247</td>
<td>case-control study, per protocol</td>
<td>improved</td>
<td>left ventricular mass index: 116 g/m² for NHHD vs. 139 g/m² for ConvHD</td>
<td>3.87 vs. 4.96</td>
<td>constant (worse under ConvHD on SF-36</td>
</tr>
<tr>
<td>Nocturnal hemodialysis every night</td>
<td>Rocco et al. (17)</td>
<td>45</td>
<td>RCT, per protocol</td>
<td>no effect</td>
<td>∆−1.4</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>Cullen et al. (31)</td>
<td>52</td>
<td>RCT, per protocol</td>
<td>improved</td>
<td>∆−15.3 g in left ventricular mass</td>
<td>∆−1.5</td>
<td>no effect on overall quality of life; improvement in specific areas of SF-36 related to renal function</td>
<td>ns</td>
</tr>
</tbody>
</table>

In this article, we present the current evidence (based on a selective literature review) regarding the effects of intensified hemodialysis on the following variables:

- arterial blood pressure
- left ventricular hypertrophy
- dietary restrictions
- pharmacotherapy
- quality of life
- overall mortality.

To this end, we searched the PubMed database, using the search terms “intensified dialysis,” “frequent hemodialysis,” “short daily hemodialysis (SDHD),” “nocturnal intermittent hemodialysis (NIHD),” and “nocturnal home hemodialysis (NHHD).” In our analysis, we considered all prospective randomized trials (Table 1) and observational studies (Table 2) on adults that were published after 1998 and involved at least 30 patients, and all relevant publications on children and adolescents.

### Intensified hemodialysis techniques

The first publications on intensified hemodialysis appeared 30 years ago. In Tassin, France, patients were treated with dialysis at low blood flow rates for 24 to 30 hours per week (15). All of them were normotensive, none received antihypertensive medication, and none had a myocardial infarction during the period of the study. The 10-year survival rate was 85%.

Currently, intensified hemodialysis is generally performed by one of the following three techniques:

- short daily hemodialysis (2–3 hours, 5–7 days a week)
- nocturnal intermittent hemodialysis (6–8 hours, 3 days a week)
- nocturnal hemodialysis every night (6–8 hours, 5–7 days a week).

All of these techniques can be performed either at home or in a dialysis center (Table 3).

All three techniques improve urea elimination and increase the clearance of intermediate-sized molecules (16–18). They enable lowering of the ultrafiltration rate; higher ultrafiltration rates in conventional hemodialysis are associated with higher mortality (19). Movilli et al. showed that patients who died within 5 years of starting dialysis had higher ultrafiltration rates than those who were still alive at 5 years (14.1 vs. 11.4 mL/kg/h) (19).

The International Quotidian Dialysis Register contains data on patients treated with different types of intensified hemodialysis (20). This initiative was also the origin of the Frequent Hemodialysis Network Trial Group, which has published 2 of the 4 prospective controlled trials on intensified hemodialysis that have been carried out to date (16, 17). The other studies provide evidence of a low level (Table 2).

### Short daily hemodialysis

This type of dialysis is characterized by a high frequency of treatment (5–7 days a week for 2–3 hours), usually with no more than a slight increase in the number of hours spent undergoing dialysis per week. It is carried out either at home or in a dialysis center.

Kjellstrand et al. reported retrospectively on 415 patients who were treated with short daily hemodialysis for 29 (± 31) months, either at home or in a dialysis center.
center, and compared their survival rates with those of patients undergoing conventional dialysis (21). Short daily hemodialysis was found to prolong the predicted median survival time by 2.3 to 10.9 years. Woods et al. reported that patients who were switched to short daily hemodialysis experienced a lowering of arterial blood pressure by 7 mmHg (systolic) and 4 mmHg (diastolic), despite concomitant reduction of antihypertensive medication (22).

No distinction was drawn between home and center-based dialysis in these two studies (21, 22). This may have led to misinterpretation of the data, as home dialysis is associated with longer survival regardless of the dialysis technique (conventional vs. intensified), probably because of selection of suitable patients (23). Patients with fewer comorbidities, higher motivation, and a more stable social environment are more likely to opt for home dialysis.

In two further studies, both short daily dialysis and conventional dialysis were performed exclusively in a dialysis center (16, 24). One of these was the single prospective, randomized trial of short daily vs. conventional dialysis that has been performed to date: it included 125 patients in the former group, who underwent dialysis six times a week, and 120 in the latter group (16). Patients under age 18 were also included in this study. Short daily dialysis was found to be associated with improvement in both of the combined end-points studied, i.e., regression of left ventricular hypertrophy or reduction of death rate (median difference of left ventricular mass, 10.1 g; hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.46–0.82) and improved health-related quality of life or reduction of death rate (median difference in health-related quality of life, 2 points; HR, 0.70; 95% CI, 0.53–0.92). These combined endpoints were chosen because of the brief duration of the study (12 months) and the small number of patients. Short daily dialysis did not lower mortality; rather, the endpoints were reached by regression of left ventricular hypertrophy and by an improved health-related quality of life, respectively.

The patients treated with short daily dialysis experienced an improvement in blood pressure control and normalization of hyperphosphatemia. They did, however, need intervention for vascular access more frequently than patients treated with conventional

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**TABLE 2**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of pts.</th>
<th>Type of study</th>
<th>BP control</th>
<th>Left ventricular hypertrophy</th>
<th>Phosphate (mg/dL)</th>
<th>Quality of life</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short daily hemodialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kjellstrand et al.</td>
<td>415</td>
<td>retrospective observation</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Median survival time prolonged by 2.3–10.9 years</td>
</tr>
<tr>
<td>Woods et al.</td>
<td>72</td>
<td>retrospective observation</td>
<td>improved</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Suri et al.</td>
<td>318</td>
<td>retrospective case-control study</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>15.6 vs. 10.9 deaths per 100 py</td>
</tr>
<tr>
<td>Fischbach et al.</td>
<td>5</td>
<td>prospective observation</td>
<td>improved</td>
<td>improved</td>
<td>1.28 vs. 1.87</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Nocturnal intermittent hemodialysis</td>
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<td></td>
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</tr>
<tr>
<td>Lacson et al.</td>
<td>746</td>
<td>retrospective case-control study</td>
<td>improved</td>
<td>ns</td>
<td>5 vs. 5.73</td>
<td>ns</td>
<td>2-year mortality 19% vs. 27%</td>
</tr>
<tr>
<td>Bugeja et al.</td>
<td>39</td>
<td>retrospective observation</td>
<td>improved</td>
<td>ns</td>
<td>4.4 vs. 5.3</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Hoppe et al.</td>
<td>16</td>
<td>prospective observation of intervention</td>
<td>improved</td>
<td>improved</td>
<td>1.37 vs. 2.14</td>
<td>ns</td>
<td></td>
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<td>Nocturnal hemodialysis every night</td>
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<td></td>
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</tr>
<tr>
<td>Bergman et al.</td>
<td>32</td>
<td>retrospective case-control study</td>
<td>ns</td>
<td>ns</td>
<td>1.3 vs. 1.7</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Geary et al.</td>
<td>4</td>
<td>case series</td>
<td>no effect</td>
<td>improved</td>
<td>improved</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

When two figures are given, the first refers to the intensified technique in question, the second to conventional hemodialysis. The difference ∆ is the value for the intensified technique minus the value for conventional dialysis. When only qualitative results are quoted, this is because very different variables were measured, making direct comparison impossible, or because no concrete figures were given at all. The number of patients listed is the number treated with intensified hemodialysis in the study in question. BP, blood pressure; ns, not studied; py, patient-years.

* pediatric studies; SF-36, short form of test for health-related quality of life
dialysis (16). Only 78% of the patients undergoing intensified dialysis had more than 5 sessions a week.

In the second study that exclusively involved patients undergoing center-based dialysis, by Suri et al. (24), propensity score–based matching was used for a retrospective comparison of the mortality of conventional hemodialysis and short daily hemodialysis (in 575 and 318 patients, respectively). This is probably the most methodologically sound large-scale study of comparative mortality that has been performed to date. Patients who underwent short daily dialysis had a higher mortality (15.6 vs. 10.9 deaths; HR, 1.6; 95% CI 1.1–2.3). Possible causes include a more pronounced inflammatory reaction induced by longer exposure to dialysate and the increased physical and emotional stress associated with daily dialysis (24).

The first report on short daily dialysis in children and adolescents was that of Fischbach et al. in 2004 (25). Hemodiafiltration was carried out 6 days a week in a pediatric center (specifically pediatric data) (Table 4). The patients undergoing short daily dialysis no longer needed to restrict their diet, grew more rapidly, and required less antihypertensive medication (26). Their quality of life was not studied. The clear disadvantage of this technique is that the patients, in general, can no longer attend school regularly (27).

### Nocturnal intermittent hemodialysis

Nocturnal intermittent hemodialysis (NIHD) is performed 3 nights a week for 6–8 hours, either in a dialysis center or at home. This method increases the overall time spent in dialysis without increasing the frequency of sessions. Performing dialysis at night makes its long duration less bothersome for the patient.

There has been only one prospective case-control study comparing center-based NIHD to conventional dialysis (247 patients each) (18). NIHD was associated with significantly lower mortality (1.77 vs. 6.23 per 100 patient-years, HR 0.28, 95% CI 0.09–0.85) after a mean follow-up of 11.3 (± 4.7) months.

Blood-pressure values were the same in both groups, but the patients undergoing NIHD took less antihypertensive medication than those undergoing conventional dialysis (8% vs. 22% required antihypertensive drugs). Left-ventricular mass was significantly lower in the NIHD group (116 [± 34] vs. 139 [± 45] g/m²). Likewise, fewer NIHD patients required phosphate binders (22% vs. 83%). Over the period of observation, the patients undergoing conventional dialysis experienced a significant deterioration of their quality of life with respect to physical pain, mental health, and vitality, while the quality of life of the NIHD patients was unchanged. 19% of the patients initially treated with NIHD abandoned this form of treatment because they found center-based NIHD to be too cumbersome (18).

In a second, large-scale study (746 patients undergoing exclusively center-based NIHD), propensity score–based matching was used for a retrospective comparison of mortality in patients undergoing NIHD versus those undergoing conventional hemodialysis (28). The mortality at 2 years was significantly lower under NIHD (19% vs. 27%, HR 0.69, 95% CI 0.58–0.84). Switching from conventional dialysis to NIHD lowered the serum phosphate level significantly (from 5.73 to 5 mg/dL) (28).

Similarly, in a retrospective observational study, Bugeja et al. reported that switching to NIHD lowered the phosphate level (median 4.4 vs. 5.3 mg/dL, range 3.8–6.7 vs. 4.3–7.5 mg/dL) (29). The average number of tablets of antihypertensive medication taken daily was lowered from 2 to 1.5, while the average number of phosphate binder tablets taken daily was lowered from 6.2 to 4.9. Quality of life improved during NIHD (29).

The authors established the concept of center-based NIHD for children and adolescents in their own dialysis center in 2005 (30). Twenty-one children and adolescents have been followed to date in an observational study. Switching from conventional hemodialysis to NIHD lowered these patients’ requirement for phosphate binders while also lowering their serum phosphate levels. The mortality at 2 years was significantly lower under NIHD (19% vs. 27%, HR 0.69, 95% CI 0.58–0.84). Switching from conventional dialysis to NIHD lowered the serum phosphate level significantly (from 5.73 to 5 mg/dL) (28).

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patients being treated with intensified hemodialysis experienced a significant regression of left ventricular mass (15.3 g, 95% CI 1.0–29.6 g) (31). Their overall quality of life did not improve, but improvement was seen in certain specific domains (stress due to renal disease). They used less antihypertensive medication and less phosphate-binding medication than patients undergoing conventional hemodialysis (31).

Bergman et al. reported that, in a group of patients who were switched from conventional dialysis to nocturnal dialysis every night, the rate of hospitalization dropped from 0.5 (± 0.15) to 0.17 (± 0.06) admissions per person-year (32). The patients' mean serum phosphate level dropped from 1.7 (± 0.1) to 1.3 (± 0.1) mg/dL.

In 2002, Geary et al. established a program for nocturnal dialysis every night at home for children and adolescents (33, 34). After the switch from conventional hemodialysis, these patients were no longer under fluid or dietary restrictions. Their serum phosphate and PTH levels were markedly lower. These encouraging results are not very informative, however, as only 4 patients were studied (33, 34).

Evaluation of the individual techniques
It is difficult to compare the various techniques of intensified hemodialysis with each other because of the heterogeneity of patient groups and clinical endpoints in the studies performed to date.

The dietary restrictions that are necessary for patients undergoing conventional hemodialysis can often be eliminated with intensified hemodialysis; this is true both for adults and for children and adolescents. Studies in which phosphate homeostasis was investigated revealed an improvement of hyperphosphatemia and/or a lesser need for phosphate binders.
Hyperphosphatemia is a major risk factor for cardiovascular complications. Arterial blood pressure and/or the need for antihypertensive medication was lowered in all studies in which these variables were investigated (16–18, 22, 28–30, 35). Left ventricular hypertrophy, a surrogate parameter for the risk of cardiovascular death, regressed in 4 of the 5 relevant case series and clinical studies (16–18, 30, 31). The available studies do not tell us definitively whether intensified hemodialysis improves quality of life. Health-related quality of life improved in only one of the four prospective controlled trials performed to date (16). In the study on NIHD, quality of life remained the same under NIHD, but deteriorated under conventional hemodialysis (18). In one of the studies on nocturnal hemodialysis every night, some domains of quality of life were found to have improved (31); in another, no such difference was detected (17).

Notably, many of the patients undergoing high-frequency intensified dialysis (either short daily hemodialysis or nocturnal hemodialysis every night) switched over to conventional dialysis, or else underwent dialysis at a lower frequency than intended (16, 17, 31). Patients being treated with these methods also had more complications involving vascular access (technical failures) (16, 17). Thus, the high-frequency intensified dialysis techniques may be less useful for many patients over the long term. The available studies do not definitively answer the question whether intensified dialysis lowers mortality. There was, indeed, a drop in mortality in two of the four prospective controlled trials (16, 18), but one trial showed no effect at all (17). When large retrospective studies are considered in addition, the overall evidence appears inconsistent. Mortality under NIHD was lower than under conventional hemodialysis (28). Short daily dialysis was associated with lower mortality in the study of Kjellstrand et al. (21), but with higher mortality in that of Suri et al. (24).

### Overview

For patients with end-stage renal failure, intensified dialysis techniques are an option to be considered. Realistically, these techniques can only be carried out at home or else in a specialized center offering nocturnal hemodialysis. Certain psychosocial aspects of intensified hemodialysis may improve patients’ prospects for rehabilitation, e.g., improved drug compliance and the opportunity for young patients under nocturnal dialysis to have a normal everyday life at school and at work.

### Conflict of interest statement

Prof. Pommer has received reimbursement of scientific meeting participation fees from the Amgen company as well as lecture fees from the Baxter, Fresenius, and Amgen companies. He is a member of the German Dialysis and Renal Transplantation Board (Kuratorium für Dialyse und Nierentransplantation). Dr. Thumfart, Prof. Querfeld, and Prof. Müller state that they have no conflicts of interest.

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### REFERENCES


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