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EBPG guideline on dialysis strategies

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Outline

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1. Time and frequency

Guideline 1.1

Dialysis should be delivered at least 3 times per week and the total duration should be at least 12 h per week, unless supported by significant renal function. See also Guideline 4.1. (Evidence level III)

Guideline 1.2

An increase in treatment time and/or frequency should be considered in patients with haemodynamic or cardiovascular instability. (Evidence level II)

Guideline 1.3

Dialysis treatment time and/or frequency should be increased in patients who remain hypertensive despite maximum possible fluid removal. (Evidence level III)

Guideline 1.4

An increase of treatment time and/or frequency should be considered in patients with impaired phosphate control. (Evidence level III)

Guideline 1.5

An increase of dialysis time and/or frequency should be considered in malnourished patients. (Opinion)

Rationale

Definitions of dialysis schedules

Due to high mortality and morbidity rates and, inter and intradialytic symptoms associated with conventional intermittent HD three times a week, different modalities of HD treatment based on variations in dialysis time and frequency have been developed in the last years:

- Intermittent conventional haemodialysis (HD):
  - A HD session of 3–5 h three times a week.
  - Long intermittent HD: A HD session of more than 5.5 h three times a week.
  - Conventional haemodiafiltration (HDF): A HDF session of 3–5 h three times a week.
- Extended HD > 3 times/week
- Daily (Quotidian) dialysis (at least 6 times/week)
  - Short daily HD 2–3 h/6–7 times a week.
  - Long nocturnal daily HD 6–10 h/6–7 nights a week.
  - Daily haemodiafiltration: 2–2.5 h/6 times a week.

Are there specific indications for increasing the duration of HD?

The ideal length of dialysis is still controversial [1–5]. The length of the dialysis should be individualized according to the requirements of each patient [6]. Adequate randomized controlled trials comparing increased dialysis time with conventional HD are lacking, however, some recommendations may be made:

A dialysis session of 8 h three times a week increases both the dialysis dose and time [7]. Uncontrolled study suggests that it results in better blood pressure control with a significant reduction in antihypertensive drugs, fewer intradialytic complications, improvement of nutritional status and an increased survival [1,8]

Increased treatment time reduces the ultrafiltration rate and may benefit patients with haemodynamic or cardiovascular instability [4]. The incidence of hypotension is significantly reduced in older patients when the length of the dialysis session is increased [6,9].

Increasing treatment time makes it easier to meet the body weight target in unstable haemodialysis patients with high comorbidity [7,9] and may help control blood pressure.

A randomized crossover study reported a significantly lower incidence of hypotension and post-dialysis orthostatic hypotension in 5 h than in 4 h HD sessions, especially in patients over 65 years [9], although some intradialytic symptoms such as headache, nausea, chills, back pain and pruritus were higher with 5 h HD. The main limitation of this trial is the short follow-up of only 2 weeks for each dialysis period.

A randomized study comparing long HD (6–8 h) at home with conventional HD (3.5–4.5 h) in-centre suggests that additional factors to extra-cellular volume may contribute to the superior blood control produced by long HD [10]. On the other hand, a prospective randomized study reported that an increase in the dialysis treatment time without a change in the dry body weight appeared to have a beneficial effect on the blood pressure control in dialysis patients [11]. In addition, preliminary data suggests that an increase of dialysis time *per se* might have an independent effect on blood pressure control [1,7,8,10–13]. In general, an increase in the length of the dialysis session makes it easier to achieve dry body weight target, improves the tolerance of the dialysis session and allows better control of blood pressure with a marked reduction in the need for antihypertensive therapy [7,12,14]. In summary, longer dialysis is associated with improved fluid volume management [1,15].

An increase in the treatment time improves solute removal [7,16]. This is particularly true for the clearance of middle molecules such as beta 2-microglobulin β2m in comparison with less time and similar Kt/V. Some studies have shown an inverse relationship between weekly treatment duration and pre-dialysis (β2m) concentration [17,18].

Treatment time should be increased in patients with poor phosphate control [7]. The effect of increasing the session length on clearance of diffusible small molecular weight solutes (e.g. urea) is minimal. In contrast, the duration of session length is very important for the clearance of small solutes (e.g. phosphorus) that are mainly located in the intracellular compartment [16,19]. Increasing the dialysis time has been reported to increase phosphate removal [19]. Increasing dialysis time and/or frequency are practical and effective options for increasing phosphate removal by HD.

Increasing dialysis time does not seem to improve endothelial function [20]. However, further long-term studies are required.

Impact on mortality. The effect of length of the dialysis sessions on patient mortality is controversial [1,3,4]. Some indirect evidence suggests that a longer dialysis improves the survival of dialysis patients [7,21,22]. Long slow HD 3×8 h a week has been associated with a high survival rate and a reduced cardiovascular mortality, mainly attributed to the adequate control of blood pressure [7]. Increased morbidity and mortality have been associated with shorter HD sessions [3,21–24]. Observational studies of HD session length yielded controversial results [22]. Shorter dialysis seems to be associated with an increased risk of death independent of the adequacy of the dose of dialysis delivered [7,15,21,22]. Difficulties in determining the dialysis time actually delivered, rather than prescribed, limits the value of these retrospective studies [4,22]. Analysis of the Japanese Renal Registry with more than 71 000 patients showed that increased patient survival was associated with the length of treatment sessions up to 5.5 h after accounting for Kt/V [21]. There is no evidence in three times weekly dialysis that session length can be reduced to <4 h without compromising outcome [21].

In summary, results on the effects of haemodialysis length and mortality are inconclusive. Future trials should evaluate haemodialysis length independent of dialysis dose and efficiency.

Can the effects of increased time be separated from increased dose?

Treatment time is probably an independent factor in patient outcome [4,7]. However, it is very difficult to separate the effect of treatment time and dose of dialysis [5]. One study has suggested that an increase in dialysis time, without increasing dialysis dose is associated with improved blood pressure control [10].

An additional problem is that the treatment time actually delivered may not be the same as the time prescribed. In a prospective randomized study, the reduction of the dialysis length (240 *vs* 150 min) maintaining a constant solute removal, did not show differences in biochemical and haematological measurements, nutritional assessment, nerve conduction studies and morbidity rate. This trial [2] was a short-term study (36 months) with a small number of patients (n=14).

The role of time as an independent determinant factor of dialysis adequacy requires further study.

Are there specific indications for increasing frequency?

Increased dialysis frequency constitutes a potential alternative to conventional HD [26–30]. However, it is very difficult to perform randomized trials with a large number of patients during a long period of time to compare three times HD a week with more frequent dialysis sessions [31]. Therefore, there is no available evidence of the potential benefits of these modalities in the treatment of stage 5 renal disease patients [5,18,29]. The majority of reports on frequent HD are based on studies with a small number of selected patients [26,32,33].

Increasing the frequency has theoretical potential advantages that have to be confirmed with adequate trials [29,30,34,35]. The question of what constitutes an adequate dialysis schedule remains unanswered [36]. However, it is interesting to stress that there are several publications reporting the potential benefits of more frequent dialysis treatments and none indicating that this modality is harmful.

An increase in frequency of dialysis results in lower interdialytic weight gains and should benefit patients with haemodynamic instability or large fluid weight gains. An increased frequency has been shown to facilitate the achievement of body weight target in unstable haemodialysis patients with high comorbidity [37,38]. Improved tolerance to dialysis (fewer muscle cramps, headaches and dizziness) and haemodynamic stability with a marked reduction in the number and severity of intra-dialysis hypotensive episodes has been reported [39–42].

High blood pressure is common and difficult to control in HD patients. Daily HD decreases both systolic and diastolic blood pressure with a reduction in the dose and number of anti-hypertensive drugs [32,37,43–50]. This effect is probably due to better fluid volume control [45,46].

The prevalence of left ventricular hypertrophy is greater in HD patients than in the general population and is considered a powerful predictor of poor outcome in maintenance HD. Daily HD has been associated with improved cardiac performance and a reduction in left ventricular hypertrophy [46,49]. This is probably related to a decrease of body fluid volume and better fluid management [44,46]. A prospective crossover study with a small number of patients showed that increased dialysis frequency allows better control of blood pressure with a reduction of left ventricular hypertrophy [49]. These effects seem to be related in part to a reduction of extracellular volume [46]. However, another prospective controlled study reported that the reduction in left ventricular hypertrophy in short daily dialysis occurred even in the absence of blood pressure control [44].

Daily HD seems to improve nutritional status [32,42,51,52]. After switching to daily HD, appetite and nutritional biochemical parameters improve, such as albumin and pre-albumin [52,53]. An increase of dry body weight and lean body mass has also been observed in the majority of patients treated with daily dialysis [32,54]. Daily protein intake [55] and energy intake increased after switching patients from conventional to daily HD [52]. This higher dietary intake was associated with an increase in serum albumin, pre-albumin and total cholesterol [56]. Dry body weight and lean body mass also increased [37,52,53]. Probably increased frequency is more effective than increased dialysis dose to improve nutritional status in HD patients [56].

Daily HD has been considered more physiological than conventional three times a week, with lower peak values of uraemic toxins [17,36,57–62]. Mean pre-dialysis BUN levels are significantly lower in daily HD as compared with conventional HD [40,63].

Improved phosphate control has been reported with nocturnal daily haemodialysis with a reduction in the administration of phosphate-binders [64]. Other studies comparing intermittent conventional and daily dialysis reported conflicting effects on phosphate control [44,65,66]. It is likely that patients on daily HD have more appetite with higher phosphate intake [30], which may counterbalance the higher phosphate removal [53]. Phosphate removal is closely related to the length of the HD session in daily HD [44], a dialysis time longer than 2 h is required to obtain a decrease in phosphorus plasma levels [30].

Daily HD has also been shown to be associated with a decrease in homocysteine levels with daily HD [45]. Non-randomized studies have reported a reduction of C-reactive protein [44] and oxidative stress with daily dialysis [67], however, these findings have not been confirmed in other trials. On the other hand, a better control of circulating AGE protein-bound molecules has been observed on short daily dialysis treatment [46,68,69]. A decrease in the concentration of glycation parameters, both in diabetic and non-diabetic patients, was observed after shifting from conventional HD to daily HD [69].

There is no clear relationship between correction of anaemia and increases of dialysis frequency [29,37,70]. An increase in the haemoglobin concentration and a decrease in the mean erythropoietin dosage have been reported with quotidian HD [38,71]. However, it is important to note that quotidian dialysis patients received a higher dose of dialysis, even when the weekly dialysis time was unchanged [70,71]. Therefore, it is not possible to differentiate clearly the effects of the dose of dialysis from the increased dialysis frequency. A rise in the haematocrit among patients not treated with erythropoietin after increasing the HD frequency from three to six times per week has been reported [32]. On the other hand, daily dialysis has been associated with a greater quantity of blood loss [70].

An evident improved well-being of the patients is reported with daily HD [58,72–74]. A few studies have evaluated the quality of life of HD patients with different dialysis modalities. The majority of these showed a significant improvement of quality of life on daily HD [42,44]. Once treated by daily HD, patients chose to return to conventional HD three times a week only rarely [39,75]. However, many patients on conventional thrice weekly HD declined to be included in a daily dialysis regimen regardless of the potential benefits of this dialysis modality [76].

Improvement in hospitalization rate has been reported with daily HD compared with conventional HD [38]. More data are needed to corroborate these results. The London Daily/Nocturnal Haemodialysis study [77], a non-randomized prospective trial, did not find significant differences between short daily dialysis ($n = 11$), long nocturnal HD ($n = 12$) and a control group on conventional HD ($n = 22$) in total number of hospital admissions, hospital days or number of emergency visits per patient-year.

There is a high patient survival rate after switching to daily HD, which has been attributed to patient selection [32]. However, daily HD showed potential benefits even when a negative selection of patients was made [38]. In a prospective study, 42 patients with high comorbidity were shifted from conventional HD to short daily HD, maintaining the same total weekly time. There was a significant improvement in the quality of life, blood pressure control and anaemia, a decreased hospitalization rate and no vascular access problems, with a cumulative survival of 35% in patients who remained in daily dialysis for more than 1 year.

Technique survival in daily HD is higher for patients who dialysed at home and lower in patients dialysed in a dialysis unit. Fewer machine alarms and nursing interventions have been reported in daily HD [42].

Potential disadvantages

Potential disadvantages of more frequent HD are related to organization, cost [78,79] and repeated vascular access punctures [80]. Another problem is that most patients did not accept this kind of treatment regardless of the documented benefits [76]. A daily HD programme requires an appropriate infrastructure and very important logistic changes [79]. Daily HD has an increased cost of disposable materials, treatment preparation time and patient transportation [72,74]. However, the cost analysis should include potential cost reductions, such as less consumption of medications (erythropoietin, anti-hypertensive drugs, phosphate binders, etc.) and a reduction in the hospitalization rate [74,79–82]. An important drawback for the in-centre haemodialysis patient is the time spent in more frequent trips to the dialysis unit [82].

It has been reported that the repeated vascular punctures have no deleterious effect on vascular access survival [32,77,83,84]. However, prospective studies are lacking, and vascular access loss may constitute a late complication of quotidian dialysis [83].

Summary. In summary, it seems that increasing the dialysis frequency improves patient outcome with a favourable effect on blood pressure control, nutrition status, hospitalization rate and quality of life, without influencing anaemia. There is no data on mortality rate. Adequate clinical trials to compare quotidian dialysis regimens with conventional thrice-weekly haemodialysis are required.

Particular advantages of daily long nocturnal HD. Quotidian dialysis schedules, short daily dialysis and long nocturnal HD, have been reported to be more effective than conventional HD in increasing weekly urea clearance measured by single-pool Kt/V, standard Kt/V and equilibrated Kt/V [85]. Increased clearance of middle molecular weight solutes has been also reported with long nocturnal HD. The mass of β2m removed was significantly higher with long-nocturnal HD [27]. Pre-dialysis serum β2m levels declined progressively at initiation of long-nocturnal HD and remained stable along the follow-up period [27,86]. Total homocysteine levels in patients undergoing nocturnal HD are significantly lower when compared with conventional HD [45,87].

Improved phosphate control has been reported in nocturnal daily haemodialysis with a marked reduction in the dose of phosphate binders [30,59,88], despite an increase in the dietary phosphate intake [64]. In some patients, phosphate was added to the dialysate to correct hypophosphataemia [89].

Regarding the well-being of patients, a marked decrease of intra-dialysis hypotension episodes and cardiovascular complications has been shown when patients on conventional HD were switched to nocturnal HD [90]. An excellent control of blood pressure with a marked reduction in anti-hypertensive drugs has been reported [29,91]. In observational studies, reductions in blood pressure with nocturnal HD were accompanied by regression of left ventricular hypertrophy [91] and improvement in ejection fraction [90]. It has been suggested that there are several factors involved in the blood pressure control [92]. Recent data suggest that nocturnal HD reduces peripheral vascular resistance and increases baroreflex sensitivity via greater afferent baroreceptor responsiveness to pulsatile pressure [93].

In a prospective cohort study of 11 patients, triglyceride levels decreased significantly with an increase of high-density lipoprotein, with no changes in total cholesterol and low-density lipoprotein after conversion from conventional to nocturnal HD [94].

In patients with sleep apnoea syndrome, oxygen saturation has been reported to improve with long nocturnal daily dialysis in comparison with conventional three times a week HD [95]. Nocturnal HD decreases the frequency of apnoea, hypopnoea and duration of nocturnal hypoxaemia. The increased heart rate and impaired vagal and augmented sympathetic heart rate modulation during sleep observed in conventional HD is normalized [96,97].

Particular limitations of daily long nocturnal HD

Calcium and phosphate depletion has been reported in long nocturnal HD, due to a high removal [88]. In a study with a small number of patients pre-dialysis phosphate was better controlled with long nocturnal HD than by short daily or conventional HD. In long nocturnal HD patients all phosphate binders were discontinued. However, a decrease in serum calcium levels associated with an increase in PTH was observed. This required an elevated dialysate calcium concentration [88].

A systematic review of the effect of nocturnal HD has been recently published [98]. The main results of this analysis was that of 270 papers identified only 14 were considered relevant, no studies examining the impact of this dialysis modality on mortality were identified, and all reports showed an improved blood pressure control after switching to nocturnal HD. Data regarding left ventricular hypertrophy, anaemia, mineral metabolism and health-related quality of life revealed mixed results. The main conclusion of this analysis is that further randomized clinical trials are required to evaluate the potential benefit of this dialysis regimen on mortality and cardiovascular morbidity.

Daily haemodiafiltration

Daily haemodiafiltration (2–2.5 h with an exchange volume of 13–14 l) six times a week compared with on-line haemodiafiltration (4–5 h) three times a week results in a significant decrease of plasma levels of urea, creatinine, uric acid, β2m and homocysteine [99,100]. A reduction in the dose of phosphate binders, better blood pressure control without anti-hypertensive medications, disappearance of post-dialysis fatigue, improvement of nutritional status and a marked decrease of left ventricular mass were also reported [99].

Can the effects of increased frequency be separated from increasing time?

In daily HD, it is difficult to separate the effects of increased frequency from increasing time due to the high dose of dialysis delivered in most cases of daily HD. Regarding the positive effects of long nocturnal daily dialysis the effect of increased dialysis frequency cannot be separated from increased dose of dialysis.

References

1. Laurent G, Charra B. The results of an 8 h thrice weekly haemodialysis schedule. *Nephrol Dial Transplant* 1998; 13 [Suppl 6]: 125–131
2. Hartley GH, Goodship TH, Hoenich NA *et al*. Is decreased treatment time in hemodialysis patients harmful if solute clearance is maintained? *Int J Artif Organs* 2002; 25: 844–851
3. Innes A, Charra B, Burden RP, Morgan AG, Laurent G. The effect of long, slow haemodialysis on patient survival. *Nephrol Dial Transplant* 1999; 14: 919–922
4. Kurella M, Chertow GM. Dialysis session length ('t') as a determinant of the adequacy of dialysis. *Semin Nephrol* 2005; 25: 90–95
5. Locatelli F, Buoncristiani U, Canaud B, Kohler H, Petitclerc T, Zucchelli P. Dialysis dose and frequency. *Nephrol Dial Transplant* 2005; 20: 285–296.
6. Locatelli F, Manzoni C. Duration of dialysis sessions–was Hegel right? *Nephrol Dial Transplant* 1999; 14: 560–563
7. Charra B, Chazot C, Jean G *et al*. Long 3×8 hr dialysis: a three-decade summary. *J Nephrol* 2003; 16 [Suppl 7]: S64–S69
8. Charra B, Calemard E, Ruffet M *et al*. Survival as an index of adequacy of dialysis. *Kidney Int* 1992; 41: 1286–1291
9. Brunet P, Saingra Y, Leonetti F, Vacher-Coponat H, Ramananarivo P, Berland Y. Tolerance of haemodialysis: a randomized cross-over trial of 5-h versus 4-h treatment time. *Nephrol Dial Transplant* 1996; 11 [Suppl 8]: 46–51
10. McGregor DO, Buttimore AL, Lynn KL, Nicholls MG, Jardine DL. A comparative study of blood pressure control with short in-center versus long home hemodialysis. *Blood Purif* 2001; 19: 293–300
11. Luik AJ, Sande FM, Weideman P, Cheriex E, Kooman JP, Leunissen KM. The influence of increasing dialysis treatment time and reducing dry weight on blood pressure control in hemodialysis patients: a prospective study. *Am J Nephrol* 2001; 21: 471–478
12. Chazot C, Charra B, Laurent G *et al*. Interdialysis blood pressure control by long haemodialysis sessions. *Nephrol Dial Transplant* 1995; 10: 831–837
13. Luik AJ, Charra B, Katzarski K *et al*. Blood pressure control and hemodynamic changes in patients on long time dialysis treatment. *Blood Purif* 1998; 16: 197–209
14. Katzarski KS, Charra B, Luik AJ *et al*. Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrol Dial Transplant* 1999; 14: 369–375
15. Charra B, Chazot C, Jean G, Laurent G. Long, slow dialysis. *Miner Electrolyte Metab* 1999; 25: 391–396
16. Leypoldt JK. Kinetics of beta2-microglobulin and phosphate during hemodialysis: effects of treatment frequency and duration. *Semin Dial* 2005; 18: 401–408
17. Skroeder NR, Jacobson SH, Holmquist B, Kjellstrand P, Kjellstrand CM. Beta 2-microglobulin generation and removal in long slow and short fast hemodialysis. *Am J Kidney Dis* 1993; 21: 519–526
18. Raj DS, Ouwendyk M, Francoeur R, Pierratos A. beta(2)-microglobulin kinetics in nocturnal haemodialysis. *Nephrol Dial Transplant* 2000; 15: 58–64
19. Vaithilingam I, Polkinghorne KR, Atkins RC, Kerr PG. Time and exercise improve phosphate removal in hemodialysis patients. *Am J Kidney Dis* 2004; 43: 85–89
20. McGregor DO, Buttimore AL, Lynn KL, Yandle T, Nicholls MG. Effects of long and short hemodialysis on endothelial function: a short-term study. *Kidney Int* 2003; 63: 709–715

21. Shinzato T, Nakai S, Akiba T *et al*. Survival in long-term haemodialysis patients: results from the annual survey of the Japanese Society for Dialysis Therapy. *Nephrol Dial Transplant* 1997; 12: 884–888
22. Held PJ, Levin NW, Bovbjerg RR, Pauly MV, Diamond LH. Mortality and duration of hemodialysis treatment. *JAMA* 1991; 265: 871–875
23. Hakim RM, Breyer J, Ismail N, Schulman G. Effects of dose of dialysis on morbidity and mortality. *Am J Kidney Dis* 1994; 23: 661–669
24. Charra B, Calemard M, Laurent G. Importance of treatment time and blood pressure control in achieving long-term survival on dialysis. *Am J Nephrol* 1996; 16: 35–44
25. Charra B, Terrat JC, Vanel T *et al*. Long thrice weekly hemodialysis: the Tassin experience. *Int J Artif Organs* 2004; 27: 265–283
26. Traeger J, Sibai-Galland R, Delawari E, Arkouche W. Daily versus standard hemodialysis: one year experience. *Artif Organs* 1998; 22: 558–563
27. Raj DS, Charra B, Pierratos A, Work J. In search of ideal hemodialysis: is prolonged frequent dialysis the answer? *Am J Kidney Dis* 1999; 34: 597–610
28. Depner TA. Why daily hemodialysis is better: Solute kinetics. *Semin Dial* 1999; 12: 462–471
29. Lindsay RM. Daily hemodialysis: the time has come?–*Pro Am J Kidney Dis* 2005; 45: 793–797
30. Pierratos A, McFarlane P, Chan CT. Quotidian dialysis–update 2005. *Curr Opin Nephrol Hypertens* 2005; 14: 119–124
31. Lacson E Jr, az-Buxo JA. Daily and nocturnal hemodialysis: how do they stack up? *Am J Kidney Dis* 2001; 38: 225–239
32. Woods JD, Port FK, Orzol S *et al*. Clinical and biochemical correlates of starting 'daily' hemodialysis. *Kidney Int* 1999; 55: 2467–2476
33. Lugon JR, Andre MB. Initial Brazilian experience with short-duration in-center daily hemodialysis. *Hemodial Int* 2005; 9: 3–6
34. Ting GO. Future role of short daily hemodialysis, an opinion based on a California studt. *Semin Dial* 1999; 12: 448–450
35. Mastrangelo F, Alfonso L, Napoli M *et al*. Dialysis with increased frequency of sessions (Lecce dialysis). *Nephrol Dial Transplant* 1998; 13: 139–147
36. Suri R, Depner TA, Blake PG, Heidenheim AP, Lindsay RM. Adequacy of quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [Suppl 1]: 42–48
37. Kooistra MP, Vos J, Koomans HA, Vos PF. Daily home haemodialysis in The Netherlands: effects on metabolic control, haemodynamics, and quality of life. *Nephrol Dial Transplant* 1998; 13: 2853–2860
38. Ting GO, Kjellstrand C, Freitas T, Carrie BJ, Zarghamee S. Long-term study of high-comorbidity ESRD patients converted from conventional to short daily hemodialysis. *Am J Kidney Dis* 2003; 42: 1020–1035
39. Heidenheim AP, Muirhead N, Moist L, Lindsay RM. Patient quality of life on quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [Suppl 1]: 36–41
40. Andre MB, Rembold SM, Pereira CM, Lugon JR. Prospective evaluation of an in-center daily hemodialysis program: results of two years of treatment. *Am J Nephrol* 2002; 22: 473–479
41. Okada K, Abe M, Hagi C *et al*. Prolonged protective effect of short daily hemodialysis against dialysis-induced hypotension. *Kidney Blood Press Res* 2005; 28: 68–76
42. Williams AW, Chebrolu SB, Ing TS *et al*. Early clinical, quality-of-life, and biochemical changes of 'daily hemodialysis' (6 dialyses per week). *Am J Kidney Dis* 2004; 43: 90–102
43. Fagugli RM, Reboldi G, Quintaliani G *et al*. Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis* 2001; 38: 371–376
44. Ayus JC, Mizani MR, Achinger SG, *et al*. Effects of short daily versus conventional hemodialyis on left ventricular hypertrophy and inflammatory markers: A prospective, controlled study. *J Am Soc Nephrol* 2005; 16: 2778–2788
45. Nesrallah G, Suri R, Moist L, Kortas C, Lindsay J. Volume control and blood pressure management in patients undergoing quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [Suppl 1]: S13–S17
46. Fagugli RM, Buoncristiani U, Ciao G. Anemia and blood pressure correction obtained by daily hemodialysis induce a reduction of left ventricular hypertrophy in dialysed patients. *Int J Artif Organs* 1998; 21: 429–431
47. Williams AB, O'Sullivan AJ, McCarthy JT. Slow nocturnal and short daily hemodialysis: A comparisson. *Semin Dial* 1999; 12: 431–439
48. Bonomini V, Mioli V, Albertazzi A, Scolari P. Daily-dialysis programme: indications and results. *Nephrol Dial Transplant* 1998; 13: 2774–2777
49. Buoncristiani U, Fagugli R, Ciao G *et al*. Left ventricular hypertrophy in daily dialysis. *Miner Electrolyte Metab* 1999; 25: 90–94
50. Twardowski ZJ. Daily dialysis: is this a reasonable option for the new millennium? *Nephrol Dial Transplant* 2001; 16: 1321–1324
51. Raj DS, Ouwendyk M, Francoeur R, Pierratos A. Plasma amino acid profile on nocturnal hemodialysis. *Blood Purif* 2000; 18: 97–102
52. Spanner E, Suri R, Heidenheim AP, Lindsay RM. The impact of quotidian hemodialysis on nutrition. *Am J Kidney Dis* 2003; 42 [Suppl 1]: S30–S35
53. Galland R, Traeger J, Arkouche W, Cleaud C, Delawari E, Fouque D. Short daily hemodialysis rapidly improves nutritional status in hemodialysis patients. *Kidney Int* 2001; 60: 1555–1560
54. Galland R, Traeger J, Arkouche W, Delawari E, Fouque D. Short daily hemodialysis and nutritional status. *Am J Kidney Dis* 2001; 37 [1 Suppl 2]: S95–S98
55. Galland R, Traeger J. Short daily hemodialysis and nutritional status in patients with chronic renal failure. *Semin Dial* 2004; 17: 104–108
56. Schulman G. Nutrition in daily hemodialysis. *Am J Kidney Dis* 2003; 41 [3 Suppl 1]: S112–S115
57. Vos PF, Zilch O, Kooistra MP. Clinical outcome of daily dialysis. *Am J Kidney Dis* 2001; 37 [1 Suppl 2]: S99–S102
58. Schulman G. Daily hemodialysis: the time has come? *Con Am J Kidney Dis* 2005; 45: 798–803
59. Lindsay RM, Al-Hejaili F, Nesrallah G. Calcium and phosphate balance with quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [Suppl 1]: S24–S29
60. Depner TA. Benefits of more frequent dialysis: lower TAC at the same Kt/V. *Nephrol Dial Transplant* 1998; 13 [Suppl 6]: 20–24
61. Johnson EM, Attman O., Samuelsson O., Haraldsson B. Improved clearance of iohexol with longer haemodialysis despite similar Kt/V for urea. *Nephrol Dial Transplant* 1999; 14: 2407–2412
62. Kjellstrand CM. Rationale for daily hemodialysis. *ASAIO J* 2001; 47: 438–442
63. Fagugli RM, De SR, Buoncristiani U, Lameire N, Vanholder R. Behavior of non-protein-bound and protein-bound uremic solutes during daily hemodialysis. *Am J Kidney Dis* 2002; 40: 339–347
64. Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A. Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. *Kidney Int* 1998; 53: 1399–1404
65. Achinger SG, Ayus JC. The role of daily dialysis in the control of hyperphosphatemia. *Kidney Int Suppl* 2005; 95: S28–S32
66. Sigrist MK, Devlin L, Taal MW, Fluck RJ, McIntyre CW. Length of interdialytic interval influences serum calcium and phosphorus concentrations. *Nephrol Dial Transplant* 2005; 20: 1643–1646

67. Fagugli RM, Vanholder R, De SR *et al*. Advanced glycation end products: specific fluorescence changes of pentosidine-like compounds during short daily hemodialysis. *Int J Artif Organs* 2001; 24: 256–262
68. Fragedaki E, Nebel M, Schupp N *et al*. Genomic damage and circulating AGE levels in patients undergoing daily versus standard haemodialysis. *Nephrol Dial Transplant* 2005; 20: 1936–1943
69. Floridi A, Antolini F, Galli F, Fagugli RM, Floridi E, Buoncristiani U. Daily haemodialysis improves indices of protein glycation. *Nephrol Dial Transplant* 2002; 17: 871–878
70. Rao M, Muirhead N, Klarenbach S, Moist L, Lindsay RM. Management of anemia with quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [Suppl 1]: S18–S23
71. Klarenbach S, Heidenheim AP, Leitch R, Lindsay RM. Reduced requirement for erythropoietin with quotidian hemodialysis therapy. *ASAIO J* 2002; 48: 57–61
72. Buoncristiani U. Fifteen years of clinical experience with daily haemodialysis. *Nephrol Dial Transplant* 1998; 13 [Suppl 6]: 148–151
73. Lindsay RM, Kortas C. Hemeral (daily) hemodialysis. *Adv Ren Replace Ther* 2001; 8: 236–249
74. McFarlane PA, Bayoumi AM, Pierratos A *et al*. The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis. *Kidney Int* 2003; 64: 1004–1011
75. Blagg CR, Lindsay RM. The London Daily/Nocturnal Hemodialysis study. *Am J Kidney Dis* 2003; 42 [Suppl 1]: S1–S2
76. Halpern SD, Berns JS, Israni AK. Willingness of patients to switch from conventional to daily hemodialysis: looking before we leap. *Am J Med* 2004; 116: 606–612
77. Lindsay RM, Leitch R, Heidenheim AP, Kortas C. The London Daily/Nocturnal Hemodialysis Study design, morbidity and mortality results. *Am J Kidney Dis* 2003; 42 [Suppl 1]: S5–S12
78. McFarlane PA, Pierratos A, Redelmeier D.A. Cost savings of home nocturnal versus conventional in-center hemodialysis. *Kidney Int* 2002; 62: 2216–2222
79. Mohr PE, Neumann PJ, Franco SJ, Marainen J, Lockridge R, Ting G. The case for daily dialysis: its impact on costs and quality of life. *Am J Kidney Dis* 2001; 37: 777–789
80. Kroeker A, Clark WF, Heidenheim AP *et al*. An operating cost comparison between conventional and home quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [Suppl 1]: 49–55
81. Kjellstrand C, Ting G. Daily hemodialysis: dialysis for the next century. *Adv Ren Replace Ther* 1998; 5: 267–274
82. Lindsay RM, Heidenheim AP, Leitch R *et al*. Short daily versus long nocturnal hemodialysis. Daily/Nocturnal Dialysis Study Group. *ASAIO J* 2001; 47: 449–455
83. Twardowski ZJ. Blood access complications and longevity with frequent (daily) hemodialysis and with routine hemodialysis. *Semin Dial* 1999; 12: 451–454
84. Quintaliani G, Buoncristiani U, Fagugli R *et al*. Survival of vascular access during daily and three times a week hemodialysis. *Clin Nephrol* 2000; 53: 372–377
85. Alloatti S, Molino A, Manes M *et al*. Long nocturnal dialysis. *Blood Purif* 2002; 20: 525–530
86. Pierratos A, Ouwendyk M, Francoeur R *et al*. Nocturnal hemodialysis: three-year experience. *J Am Soc Nephrol* 1998; 9: 859–868
87. Friedman AN, Bostom AG, Levey AS, Rosenberg IH, Selhub J, Pierratos A. Plasma total homocysteine levels among patients undergoing nocturnal versus standard hemodialysis. *J Am Soc Nephrol* 2002; 13: 265–268
88. Al-Hejaili F, Kortas C, Leitch R *et al*. Nocturnal but not short hours quotidian hemodialysis requires an elevated dialysate calcium concentration. *J Am Soc Nephrol* 2003; 14: 2322–2328
89. Pierratos A. Nocturnal home haemodialysis: an update on a 5-year experience. *Nephrol Dial Transplant* 1999; 14: 2835–2840
90. Chan C, Floras JS, Miller JA, Pierratos A. Improvement in ejection fraction by nocturnal haemodialysis in end-stage renal failure patients with coexisting heart failure. *Nephrol Dial Transplant* 2002; 17: 1518–1521
91. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney Int* 2002; 61: 2235–2239
92. Chan CT, Harvey PJ, Picton P, Pierratos A, Miller JA, Floras JS. Short-term blood pressure, noradrenergic, and vascular effects of nocturnal home hemodialysis. *Hypertension* 2003; 42: 925–931
93. Chan CT, Jain V, Picton P, Pierratos A, Floras JS. Nocturnal hemodialysis increases arterial baroreflex sensitivity and compliance and normalizes blood pressure of hypertensive patients with end-stage renal disease. *Kidney Int* 2005; 68: 338–344
94. Bugeja AL, Chan CT. Improvement in lipid profile by nocturnal hemodialysis in patients with end-stage renal disease. *ASAIO J* 2004; 50: 328–331
95. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *New Engl J Med* 2001; 344: 102–107
96. Chan CT, Hanly P, Gabor J, Picton P, Pierratos A, Floras JS. Impact of nocturnal hemodialysis on the variability of heart rate and duration of hypoxemia during sleep. *Kidney Int* 2004; 65: 661–665
97. Hanly PJ, Gabor JY, Chan C, Pierratos A. Daytime sleepiness in patients with CRF: impact of nocturnal hemodialysis. *Am J Kidney Dis* 2003; 41: 403–410
98. Walsh M, Culleton B, Tonelli M, Manns B. A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life. *Kidney Int* 2005; 67: 1500–1508
99. Maduell F, Navarro V, Torregrosa E *et al*. Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. *Kidney Int* 2003; 64: 305–313
100. Zimmerman DL, Swedko PJ, Posen GA, Burns KD. Daily hemofiltration with a simplified method of delivery. *ASAIO J* 2003; 49: 426–429

2. Flux and convection

Guideline 2.1

The use of synthetic high-flux membranes should be considered to delay long-term complications of haemodialysis therapy. Specific indications include;

(i) **To reduce dialysis-related amyloidosis (III)**
(ii) **To improve control of hyperphosphataemia (II)**
(iii) **To reduce the increased cardiovascular risk (II)**
(iv) **To improve control of anaemia (III)**

Guideline 2.2

In order to exploit the high permeability of high-flux membranes, on-line haemodiafiltration or haemofiltration should be considered.

The exchange volumes should be as high as possible, with consideration of safety. (Evidence level II).

Rationale

Solute removal in high-flux haemodialysis. Compared with low-flux haemodialysis (HD), with either cellulosic or synthetic membranes, high-flux HD has been shown to clear more middle molecular weight solutes. It also clears more of the smaller solutes, which are bound to plasma proteins, mainly albumin, and thus behave kinetically like middle molecules. β2-microglobulin (β2-m), a marker of the middle molecular weight uraemic toxins, belongs to the first group. Its enhanced removal in high-flux HD [1,2] results in long-term reductions in plasma levels, as demonstrated in several prospective randomized studies [3–6]. Similar findings have been reported for leptin [7], a middle molecular weight solute, involved in fat metabolism. On the other hand, intradialytic removal or long-term concentrations of smaller protein-bound solutes, retained in uraemia, such as homocysteine and AGEs, is not significantly influenced by high-flux HD [8,9]. Only the unbound fraction of such solutes is shown to be removed by high-flux membranes to a greater extent than low-flux membranes [8,9]. The total concentration in plasma is not reduced by standard high-flux dialysers, but can be reduced by using 'super-flux' dialysers which are permeable to albumin [10,11]. Among the favourable effects of high-flux HD, reduced circulating AGE-Apolipoprotein-B level has been described [12], as well as improved lipid profile, with significant reduction in triglyceride and increase in high-density lipoprotein (HDL) concentration and lipoprotein lipase (LPL) activity [13–15]. However, such favourable effects were absent or were not different from that shown with low-flux membranes in other randomized studies [8,16].

Solute removal in haemofiltration/haemodiafiltration. Middle molecular weight solute removal obtained with highly permeable and biocompatible membranes employed in convective and mixed diffusion/convection strategies is definitely higher than that attainable by 'internal filtration' in high-flux HD. Indeed, several randomized trials conducted in the last years have confirmed that haemofiltration (HF) and haemodiafiltration (HDF) achieve a significant enhancement and widening of the molecular spectrum of the removed uraemic compounds compared with both low-flux and high-flux HD. This has been demonstrated for small molecular solutes as urea, creatinine and phosphate [17–22], for middle molecular compounds as β2-m [17,19,20,22–25], cystatin C [24], leptin [20], retinol-binding protein [24] and for protein-bound solutes as p-cresol [23] and AGEs [26]. Moreover, enhanced removal by convection has been proven in controlled experimental settings for asymmetric dimethyl-arginine (ADMA) [27] complement fractions such as factor D [22,28], and fraction Ba [28], and with a contribution of absorption onto the membrane, for pro-inflammatory cytokines such as TNF-α and interleukins 1,6, and 8 [29].

Increasing evidence, provided by long-term prospective studies, demonstrates that increased removal obtained by high rates of fluid exchange with HDF and HF results in lower levels of small- and medium-large sized solutes. A prospective randomized study comparing high-flux HD with HDF at a relatively low infusion volume (8–12 l/session) found similar basal β2-m levels over a period of 24 months [5], but significant differences in basal β2-m levels emerged from a long-term prospective study in which a mean filtration volume of 21 l was applied [22]. Higher removal in HDF/HD *vs* high-flux HD was demonstrated in prospective trials for urea [30], phosphate [18,21,30], β2-m [25,30–35], factor D [22,31], homocysteine [31] and AGEs [26].

The maximum safe filtration rate is determined by the infusion mode, the blood flow rate, hydraulic permeability and surface area of the dialyser membrane and the patient's characteristics (haematocrit and total protein concentration, coagulability status). These factors, to a different extent, contribute to the establishment of the pressure regimen necessary for the planned filtration. Presently, a feedback control system preventing excessive trans-membrane pressure increase beyond a safe maximum value (i.e. 300 mmHg) by modulating infusion and filtration rate is the most advanced tool to avoid technical and clinical drawbacks of an excessive filtration [19]. In the absence of such equipment, the following general rules can be applied. Post dilution; the filtration rate should be limited to ~40% of plasma water flow rate, corresponding to ~25% of blood flow rate. Pre dilution; the infusion rate should not exceed the plasma water flow rate, to avoid loss of efficiency as a consequence of the excessive dilution of solute concentration. Ultrapure dialysate is mandatory for on-line production of the infusion fluid. The infusion fluid must be sampled periodically to ensure that it is free of endotoxin and meets the standards of microbial purity described in EBPG 1.

Clinical results of increasing flux. The above middle-molecular compounds have a pathogenic role or are markers of the most frequent long-term complications and causes of death in HD patients such as dialysis-related amyloidosis, cardio-vascular disease, secondary hyperparathyroidism, inflammation and malnutrition. Reduction of the accumulation and lower long-term levels of these compounds may prevent or delay the appearance of such complications. Significant reductions in the incidence of carpal tunnel syndrome and signs of dialysis-related amyloidosis have been reported in two large retrospective studies as a result of high-flux membranes [36] and of convective and mixed dialysis strategies [37] inducing lower chronic β2-m levels. These observations have been confirmed by two prospective studies conducted in small groups of patients but with long follow-up (2 and 6 years) [4,38], in which clinical signs of dialysis-related amyloidosis were shown to arrest or ameliorate as an effect of the use of high-flux membranes alone or coupled with β2-m adsorption columns. The increased ability of high-flux membranes to remove phosphate [17–21,39] may translate into lower serum phosphate level in the long term, as shown by some prospective studies [3,18,21]. Control of hyper-phosphataemia has been associated with improved patient survival in a large cohort of patients from two special studies of the USRDS [40]. A recent randomized study comparing high-flux and low-flux polysulfone membranes at similar efficiency (Kt/V) suggested that high-flux dialysis was more effective in terms of controlling renal anaemia and reducing the need of erythropoietin therapy [41]. These beneficial effects of high-flux dialysis have been attributed to the improved clearance of middle- and high-molecular weight toxins. Similar findings have been described in other prospective [42,43] and observational studies [44,45] performed in patients on convective and mixed therapies compared with low-flux haemodialysis. However, in patients who are, adequately dialysed, and not iron- and/or vitamin-depleted, this favourable effect was not confirmed in several trials comparing low-flux HD with high flux HD [46,47], acetate-free biofiltration (AFB) [48,49] or HDF [35].

Outcome in high-flux HD and HDF/HF. In the last decade, several observational studies from large databases have reported a reduced death risk in patients undergoing haemodialysis with high-flux membranes [36,50–55]. In some studies, such an effect has been associated with the increased removal of middle-molecular uraemic toxins promoted by these membranes [53,55] independently from the effects related to their high biocompatibility. The association between death risk in dialysis patients and levels of β2-m found in the above studies, was confirmed in the HEMO Study [56], the only randomized prospective study ever performed to assess the effect of high-flux membranes on mortality in haemodialysis patients. On the other hand, overall survival was not influenced significantly by high-flux membranes in an Italian study based on the Lombardy Registry of Dialysis and Transplant [37]. The HEMO Study provided more compelling evidence in this direction: among the 1846 patients enrolled in the study, high-flux membranes did not significantly affect the primary outcome of the all-cause mortality rate or the main secondary composite outcomes, including the rates of first cardiac hospitalization or all-cause mortality [2]. Possibly, the small mean difference in β2-m clearance between the low-flux and the high-flux group of the Study (3 ± 7 *vs* 34 ± 11 ml/min) prevented the achievement of a clearer difference in the overall outcome between groups.

The methodology of the HEMO study has been criticized and the validity of the final results questioned [57–59]. Subgroup analysis of the HEMO study were not in line with its general conclusions, showing that the high-flux intervention was associated with reduced risks of specific cardiac-related events, such as the decreased cardiac mortality and the composite outcome of first cardiac hospitalization or death from cardiac causes [60]. Although high-flux dialysis did not reduce all-cause mortality, it might improve cardiac outcomes. In addition, the effect of high-flux dialysis on all-cause mortality was shown to vary, depending on the duration of prior dialysis. In fact, in the subgroup that had been on dialysis for more than 3.7 years, randomization to high-flux dialysis was associated with significantly lower risk of all-cause mortality compared with low-flux dialysis [60,61]. These data are in favour of the view that patients with different durations of dialysis may be affected differently by high-flux membranes and suggest that their beneficial effect in reducing cardiovascular events may take time to result in a significant reduction of fatal events in chronic patients. In agreement with these findings, a significant effect on mortality has also been described in a subset of patients on HDF with high-flux polysulfone ($n = 20$) and on AFB with PAN ($n = 20$) [62], 32 patients randomized to pre-dilution HDF (33), and in a larger cohort of 650 selected patients after a two-year extension of a study with a thirty months follow up [63].

However, in spite of the above favourable premises, the positive effect of convective and mixed treatments on patient's survival is still unproven. This may be due to their relatively recent diffusion into routine practice and the scarce number of patients chronically treated with these strategies. Two studies, one registry study [37], and one small 2 years' prospective trial [35], not designed to study mortality of the techniques, did not show a significant difference between HDF and low-flux HD. However, more recently, some evidence has appeared to support the favourable impact of convective therapies: results from the European DOPPS Study [64] in 2165 patients followed from 1998 to 2001 showed that high-efficiency HDF patients, after adjustment for age, sex, fourteen comorbid conditions and time on dialysis, had a significant 35% lower mortality risk than those receiving low-flux HD (relative risk = 0.65, $P = 0.01$). These observational results suggest that HDF may improve patient survival independently of its higher dialysis dose. Great caution must be used while interpreting these findings, and definite confirmation with large prospective studies is required for their important clinical and economical implications.

Summary of evidence

High-flux membranes employed in convective and mixed diffusion/convection therapies achieve the maximal removal of small- and middle-molecular toxic solutes and, at least in the case of β2-m, establish lower long-term concentrations (Evidence II). Prolonged use of such membranes in high efficiency dialysis techniques helps prevent some long-term complications of the uraemic status, such as dialysis-related amyloidosis and hyperphosphataemia, and reduces cardiovascular risk and death (Evidence II).

References

1. Bonomini M, Fiederling B, Bucciarelli T, Manfrini V, Di Ilio C, Albertazzi A. A new polymethylmethacrylate membrane for hemodialysis. *Int J Artif Organs* 1996; 19: 232–239
2. Eknoyan G, Beck GJ, Cheung AK *et al*. Effect of dialysis dose and membrane flux in maintenance hemodialysis [comment]. *New Engl J Med* 2002; 347: 2010–2019
3. Ayli M, Ayli D, Azak A *et al*. The effect of high-flux hemodialysis on dialysis-associated amyloidosis. *Ren Fail* 2005; 27: 31–34
4. Kuchle C, Fricke H, Held E, Schiffl H. High-flux hemodialysis postpones clinical manifestation of dialysis-related amyloidosis. *Am J Nephrol* 1996; 16: 484–488
5. Locatelli F, Mastrangelo F, Redaelli B *et al*. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. *Kidney Int* 1996; 50: 1293–1302
6. Ward RA, Schaefer RM, Falkenhagen D *et al*. Biocompatibility of a new high-permeability modified cellulose membrane for haemodialysis. *Nephrol Dial Transplant* 1993; 8: 47–53
7. van Tellingen A, Grooteman MP, Schoorl M *et al*. Enhanced long-term reduction of plasma leptin concentrations by super-flux polysulfone dialysers. *Nephrol Dial Transplant* 2004; 19: 1198–1203
8. House AA, Wells GA, Donnelly JG, Nadler SP, Hebert PC. Randomized trial of high-flux vs low-flux haemodialysis: effects on homocysteine and lipids. *Nephrol Dial Transplant* 2000; 15: 1029–1034
9. Klemm A, Franke C, Busch M *et al*. Influence of hemodialysis membrane permeability on serum levels of advanced glycation end products (AGEs) and homocysteine metabolites. *Clin Nephrol* 2004; 61: 191–197
10. De Vriese AS, Langlois M, Bernard D *et al*. Effect of dialyser membrane pore size on plasma homocysteine levels in haemodialysis patients. *Nephrol Dial Transplant* 2003; 18: 2596–2600
11. van Tellingen A, Schalkwijk CG, Teerlink T *et al*. Influence of different haemodialysis modalities on AGE peptide levels: intradialytic versus long-term results. *Nephron Clin Pract* 2005; 100: c1–c7
12. Fishbane S, Bucala R, Pereira BJ, Founds H, Vlassara H. Reduction of plasma apolipoprotein-B by effective removal of circulating glycation derivatives in uremia. *Kidney Int* 1997; 52: 1645–1650
13. Blankestijn PJ, Vos PF, Rabelink TJ, van Rijn HJ, Jansen H, Koomans HA. High-flux dialysis membranes improve lipid profile in chronic hemodialysis patients. *J Am Soc Nephrol* 1995; 5: 1703–1708
14. Goldberg IJ, Kaufman AM, Lavarias VA, Vanni-Reyes T, Levin NW. High flux dialysis membranes improve plasma lipoprotein profiles in patients with end-stage renal disease. *Nephrol Dial Transplant* 1996; 11 [Suppl 2]: 104–107
15. Wanner C, Bahner U, Mattern R, Lang D, Passlick-Deetjen J. Effect of dialysis flux and membrane material on dyslipidaemia and inflammation in haemodialysis patients. *Nephrol Dial Transplant* 2004
16. Ottosson P, Attman PO, Knight C, Samuelsson O, Weiss L, Alaupovic P. Do high-flux dialysis membranes affect renal dyslipidemia? *ASAIO J* 2001; 47: 229–234
17. Lornoy W, Becaus I, Billiouw JM, Sierens L, Van Malderen P. Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. *Am J Nephrol* 1998; 18: 105–108
18. Minutolo R, Bellizzi V, Cioffi M *et al*. Postdialytic rebound of serum phosphorus: pathogenetic and clinical insights. *J Am Soc Nephrol* 2002; 13: 1046–1054
19. Pedrini LA, De CV. On-line mixed hemodiafiltration with a feedback for ultrafiltration control: effect on middle-molecule removal. *Kidney Int* 2003; 64: 1505–1513
20. Santoro A, Conz PA, De CV *et al*. Mid-Dilution: The perfect balance between convection and diffusion. *Contributions to Nephrology* 2005; 149: 107–114
21. Tuccillo S, Bellizzi V, Catapano F *et al*. Acute and chronic effects of standard hemodialysis and soft hemodiafiltration on interdialytic serum phosphate levels. [Italian]. *Giornale Italiano Di Nefrologia* 2002; 19: 439–445
22. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. *J Am Soc Nephrol* 2000; 11: 2344–2350
23. Bammens B, Evenepoel P, Verbeke K, Vanrenterghem Y. Removal of the protein-bound solute p-cresol by convective transport: a randomized crossover study. *Am J Kidney Dis* 2004; 44: 278–285
24. Krieter DH, Falkenhain S, Chalabi L, Collins G, Lemke HD, Canaud B. Clinical cross-over comparison of mid-dilution hemodiafiltration using a novel dialyzer concept and post-dilution hemodiafiltration. *Kidney Int* 2005; 67: 349–356
25. Schiffl H, D'Agostini B, Held E. Removal of beta 2-microglobulin by hemodialysis and hemofiltration: a four year follow up. *Biomat Artif Cells Im Biotechnol* 1992; 20: 1223–1232
26. Lin CL, Huang CC, Yu CC, Yang HY, Chuang FR, Yang CW. Reduction of advanced glycation end product levels by on-line hemodiafiltration in long-term hemodialysis patients. *Am J Kidney Dis* 2003; 42: 524–531
27. Schroder M, Riedel E, Beck W, Deppisch RM, Pommer W. Increased reduction of dimethylarginines and lowered interdialytic blood pressure by the use of biocompatible membranes. *Kidney Int* 2001; 59 [Suppl 78]: 19–24
28. Kaiser JP, Oppermann M, Gotze O *et al*. Significant reduction of factor D and immunosuppressive complement fragment Ba by hemofiltration. *Blood Purif* 1995; 13: 314–321
29. Bouman CS, van Olden RW, Stoutenbeek CP. Cytokine filtration and adsorption during pre- and postdilution hemofiltration in four different membranes. *Blood Purif* 1998; 16: 261–268
30. Ding F, Ahrenholz P, Winkler RE *et al*. Online hemodiafiltration versus acetate-free biofiltration: a prospective crossover study. *Artif Organs* 2002; 26: 169–180

31. Beerenhout CH, Luik AJ, Jeuken-Mertens SG *et al*. Pre-dilution on-line haemofiltration vs low-flux haemodialysis: a randomized prospective study. *Nephrol Dial Transplant* 2005
32. Lin CL, Yang CW, Chiang CC, Chang CT, Huang CC. Long-term on-line hemodiafiltration reduces predialysis beta-2-microglobulin levels in chronic hemodialysis patients. *Blood Purification* 2001; 19: 301–307
33. Santoro A, Mancini E, Bibiano L *et al*. Online convective therapies: results from a hemofiltration trial. *Contributions to Nephrology* 2005; 149: 51–57
34. Takenaka T, Itaya Y, Tsuchiya Y, Kobayashi K, Suzuki H. Fitness of biocompatible high-flux hemodiafiltration for dialysis-related amyloidosis. *Blood Purification* 2001; 19: 10–14
35. Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. *Nephrol Dial Transplant* 2000; 15 [Suppl 1]: 43–48
36. Koda Y, Nishi S, Miyazaki S *et al*. Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. *Kidney Int* 1997; 52: 1096–1101
37. Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi e Trapianto. *Kidney Int* 1999; 55: 286–293
38. Gejyo F, Kawaguchi Y, Hara S *et al*. Arresting dialysis-related amyloidosis: a prospective multicenter controlled trial of direct hemoperfusion with a beta2-microglobulin adsorption column. *Artif Organs* 2004; 28: 371–380
39. Zehnder C, Gutzwiller JP, Renggli K. Hemodiafiltration–a new treatment option for hyperphosphatemia in hemodialysis patients. *Clinical Nephrology* 1999; 52: 152–159
40. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31: 607–617
41. Ayli D, Ayli M, Azak A *et al*. The effect of high-flux hemodialysis on renal anemia. *J Nephrol* 2004; 17: 701–706
42. Eiselt J, Racek J, Opatrny K, Jr. The effect of hemodialysis and acetate-free biofiltration on anemia. *Int J Artif Organs* 2000; 23: 173–180
43. Lin CL, Huang CC, Chang CT *et al*. Clinical improvement by increased frequency of on-line hemodialfiltration. *Renal Failure* 2001; 23: 193–206
44. Bonforte G, Grillo P, Zerbi S, Surian M. Improvement of anemia in hemodialysis patients treated by hemodiafiltration with high-volume on-line-prepared substitution fluid. *Blood Purif* 2002; 20: 357–363
45. Lin CL, Huang CC, Yu CC *et al*. Improved iron utilization and reduced erythropoietin resistance by on-line hemodiafiltration. *Blood Purif* 2002; 20: 349–356
46. Locatelli F, Andrulli S, Pecchini F *et al*. Effect of high-flux dialysis on the anaemia of haemodialysis patients. *Nephrol Dial Transplant* 2000; 15: 1399–1409
47. Opatrny K, Jr., Reischig T, Vienken J *et al*. Does treatment modality have an impact on anemia in patients with chronic renal failure? Effect of low- and high-flux biocompatible dialysis. *Artif Organs* 2002; 26: 181–188
48. Basile C, Giordano R, Montanaro A *et al*. Effect of acetate-free biofiltration on the anaemia of haemodialysis patients: a prospective cross-over study. *Nephrol Dial Transplant* 2001; 16: 1914–1919
49. Schrander-vd Meer AM, ter Wee PM, Donker AJ, van Dorp WT. Dialysis efficacy during acetate-free biofiltration. *Nephrol Dial Transplant* 1998; 13: 370–374
50. Bloembergen WE, Hakim RM, Stannard DC *et al*. Relationship of dialysis membrane and cause-specific mortality. *Am J Kidney Dis* 1999; 33: 1–10
51. Chandran PK, Liggett R, Kirkpatrick B. Patient survival on PAN/AN69 membrane hemodialysis: a ten-year analysis. *J Am Soc Nephrol* 1993; 4: 1199–1204
52. Hornberger JC, Chernew M, Petersen J, Garber AM. A multivariate analysis of mortality and hospital admissions with high-flux dialysis. *J Am Soc Nephrol* 1992; 3: 1227–1237
53. Port FK, Wolfe RA, Hulbert-Shearon TE *et al*. Mortality risk by hemodialyzer reuse practice and dialyzer membrane characteristics: results from the USRDS dialysis morbidity and mortality study. *Am J Kidney Dis* 2001; 37: 276–286
54. Woods HF, Nandakumar M. Improved outcome for haemodialysis patients treated with high-flux membranes. *Nephrol Dial Transplant* 2000; 15 [Suppl 1]: 36–42
55. Leypoldt JK, Cheung AK, Carroll CE *et al*. Effect of dialysis membranes and middle molecule removal on chronic hemodialysis patient survival. *Am J Kidney Dis* 1999; 33: 349–355
56. Cheung AK, Rocco MV, Yan G *et al*. Serum β-2 Microglobulin Levels Predict Mortality in Dialysis Patients: Results of the HEMO Study 1. *J Am Soc Nephrol* 2005
57. Friedman EA. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *New Engl J Med* 2003; 348: 1491–1494
58. Locatelli F. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *New Engl J Med* 2003; 348: 1491–1494
59. Scribner BH, Blagg CR. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *New Engl J Med* 2003; 348: 1491–1494
60. Cheung AK, Levin NW, Greene T *et al*. Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. *J Am Soc Nephrol* 2003; 14: 3251–3263
61. Cheung AK, Sarnak MJ, Yan G *et al*. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. *Kidney Int* 2004; 65: 2380–2389
62. Chiappini MG, Ammann T, Selvaggi G, Bravi M, Traietti P. Effects of different dialysis membranes and techniques on the nutritional status, morbidity and mortality of hemodialysis patients. [Italian]. *Giornale Italiano Di Nefrologia* 2004; 21 [Suppl 30]: S190–S196
63. Chauveau P, Nguyen H, Combe C *et al*. Dialyzer membrane permeability and survival in hemodialysis patients. *Am J Kidney Dis* 2005; 45: 565–571
64. Canaud B, Bragg-Gresham JL, Marshall MR *et al*. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int* 2006; 69: 2087–2093

3. Dialysis dose methodology

Guideline 3.1

Delivered dialysis dose should be measured at least monthly. (Opinion)

Guideline 3.2

Dialysis dose should be measured using a validated method comparable with the reference method. The reference method is formal urea kinetic modelling using pre- and post-dialysis blood samples and taking ultrafiltration, urea generation and the post-dialysis rebound into account. (Opinion)

Guideline 3.3

Renal function may be taken into account in the dose measurement provided it is measured frequently enough to avoid overestimation as GFR falls, typically every 2 months. (Opinion)

Guideline 3.4

For three times weekly dialysis, dose should be quoted as eKt/V. For schedules other than three times weekly, dose should take frequency into account and be quoted as weekly standard Kt/V (stdKt/V), solute removal index (SRI) or equivalent renal clearance (EKR). (Opinion)

Rationale

Frequency of adequacy testing. Numerous studies have shown that low dialysis dose is associated with poor outcome [1–3] Inadequate dialysis may be difficult to detect clinically or by routine biochemical tests. Faults in the system for delivering dialysis (which includes the fistula, dialysis machine, prescription, schedule and dialyser) may be unpredictable and results in inadequate dialysis [4]. To prevent adverse effects on the patient due to inadequate dialysis, adequacy measurements are customarily taken monthly along with routine biochemical tests [5].

Adequacy measurements may be performed at every treatment without blood sampling using online clearance methods based on dialysate-side measurements [6,7].

Method of adequacy testing, need for a reference method. Various methods have been proposed and are in use for calculating dialysis dose. Dose calculated using many of these methods have been shown to relate to outcome. All methods are based on indirect measurement of mass of urea (or a urea surrogate) removed from the patient over a dialysis session. Differences between methods relate to the extent to which ultrafiltration, urea generation, residual renal function, urea distribution volume and the post-dialysis rebound are taken into account.

As long as a dialysis facility uses a validated method for calculating dose and applies it consistently and properly, it does not matter which method is used for routine surveillance of the patient. The need for a reference method arises when an external standard is applied (such as minimum recommended dose) and when results are to be exported to a registry or used in research. In this case, the relationship between any method in use for calculating dose and the reference method must be known.

The most common method for calculating dose cited in publications is the formal variable-volume, single-pool urea kinetic model of Gotch, returning the single-pool Kt/V (spKt/V) [8]. This has become the *de-facto* reference method for haemodialysis dose. The Gotch method requires input of pre- and post dialysis weight, height, sex, age, dialyser type, blood flow, dialysate flow, dialysis time, pre- and post-dialysis urea or BUN. The spKt/V returned by the reference method takes urea generation, ultrafiltration and urea distribution volume into account. The spKt/V can be calculated independently from both the dialysis prescription and blood urea measurements to validate the result.

When dialysis is applied intermittently as in haemodialysis, there is always a significant disequilibrium between body water compartments. This results in a significant post-dialysis urea rebound which takes 30–40 min to complete. Unless the post-dialysis sample is taken after the rebound is complete, the Gotch method will significantly overestimate dialysis dose. This overestimation is relatively greater in shorter dialysis, about 25% in a 2 h dialysis compared with 10% in a 5 h dialysis [9]. It has been shown that the Gotch method using an immediate post-dialysis blood sample can easily be corrected for these disequilibrium effects by applying an additional term with input of dialysis session duration (td) [10]. This equilibrated Kt/V (eKt/V) taking the post-dialysis rebound into account, has been validated in the HEMO study [11]. Since td is already required by the Gotch method and since the Gotch method already requires a computer to calculate, rebound correction, returning eKt/V adds no additional cost or logistical complexity.

Trouble shooting and validation. A major advantage of Kt/V is that it can be independently calculated from dialysis session time (*t*), an estimation of V using body weight and an estimation of K using blood flow, dialysate flow and dialyser urea clearance coefficient. Any discrepancy between the 'prescribed' Kt/V calculated in this way and the 'delivered' Kt/V calculated using pre- and post-dialysis blood samples can yield valuable diagnostic information. For example, incorrect sampling technique may cause the 'delivered' Kt/V to be much higher than 'prescribed' Kt/V.

Access recirculation may result in the 'delivered' Kt/V being less than 'prescribed' Kt/V.

Other methods for calculating adequacy. Other methods used for calculating dialysis dose may be easier to use, with fewer input variables, yet return a result which is a reasonable approximation of the Gotch method. The simplest of these is the urea reduction ratio (URR) which is the fall in blood urea concentration over the dialysis session divided by the pre-dialysis urea. URR can be expressed as Kt/V by the logarithmic transformation [12];

$$\mathrm{Kt/V} = \ln\left(\frac{1}{1 - \mathrm{URR}}\right)$$

This simple method for calculating Kt/V does not take ultrafiltration, urea generation or the post-dialysis rebound into account. For a 4 h dialysis with 2l of ultrafiltration, these effects approximately cancel out and the result is very close to eKt/V calculated by the reference method. For dialysis sessions shorter than 4 h or with <2l ultrafiltration, the URR method will significantly overestimate eKt/V. The URR method may be used as an approximation for practical purposes but should not substitute for monthly measurement of eKt/V by the reference method.

Online clearance methods are increasingly used to calculate dialysis dose without blood samples. The equipment is built-in to the dialysis machine and calculates dose from measurements of dialysate conductivity. Online clearance calculates a precise value for Kt. It estimates Kt/V using an estimation of V from inputs of patient weight, height, age and sex. These estimations of V are known to be an overestimate, causing Kt/V to be underestimated [13]. Kt/V calculated by online clearance is not necessarily automatically corrected for rebound, though this could easily be done by the equipment. Online clearance is not currently validated for haemodiafiltration or haemofiltration.

As long as the difference between Kt/V calculated by the online clearance and the reference method is taken into account, online clearance is an acceptable method for calculating haemodialysis on a treatment-by-treatment basis. Online clearance should not substitute for monthly measurements using the reference method.

Dialysis frequency other than three times per week. Three methods have been proposed to quantify dialysis dose in dialysis schedules other than three times per week, taking frequency of dialysis into account, the solute removal index (SRI) [14], standard Kt/V (stdKt/V) [15] and the equivalent renal clearance (EKR) [16].

SRI and stdKt/V are both equivalent to the 'weekly Kt/V' in peritoneal dialysis and are approximately equivalent to URR times the number of dialysis sessions per week. They are defined as the mass of urea removed (or generated) per week divided by the peak mass of urea in the patient in that week. For stdKt/V, the peak is defined as the mean pre-dialysis value, whereas in SRI, the peak is the highest of the pre-dialysis values.

In symmetrical dialysis schedules when the time between dialysis sessions are equal (e.g. daily or alternate day dialysis), SRI and stdKt/V are equal. Where dialyses schedules are asymmetrical, the two measures diverge. In a typical three times weekly dialysis schedule, SRI will be 0.87 times stdKt/V. In an extreme example, with 7 times per week dialysis, the stdKt/V will be the same whether all sessions are performed on the same day or performed daily. SRI will be reduced by 50%, if all dialyses are performed on the same day, influenced by the very high peak concentration after the longest interdialytic interval.

EKR expresses the dialysis dose as the continuous clearance required to achieve the same time averaged concentration. EKR is the urea generation rate divided by the time averaged concentration rate of urea. It uses the familiar units of ml/min.

All three dose measures can be calculated from the urea generation rate (G) and peak urea concentrations (TAC urea in the case of EKR) which can be computed using iterative solution of the Gotch equations with rebound correction. No additional inputs are required apart from frequency of dialysis.

SRI and stdKt/V can also be calculated from dialysate collections, using the same method as for peritoneal dialysis. In this method, a value for urea distribution volume (V) is required but there is no need for a post-dialysis sample or rebound correction.

Where dose is calculated using dialysate and plasma samples, the difference in protein concentrations in the samples will affect the measurement of urea concentration, causing dose to be overestimated unless it is taken into account [17]. V, calculated using anthropometric equations may be an overestimate, causing dialysis dose to be underestimated [13].

To assist in prescribing, stdKt/V can be converted to a 'per dialysis' eKt/V using the natural logarithm function (ln) as shown subsequently, where f is the frequency of dialysis.

$$\mathrm{eKt/V} = \ln\left(1 - \frac{\mathrm{stdKt/V}}{f}\right)$$

EKR differs from stdKt/V and SRI in that equivalent doses achieve the same time averaged urea concentrations (TAC) rather than peak concentrations (Table 1). This has the effect of giving more 'weight' to shorter, more intensive dialysis which reduces TAC more than peak concentrations. EKR is affected by asymmetry of dialysis schedule, but to a lesser extent than SRI. EKR can be corrected for body size as EKRc in ml/min/40l. EKRc is approximately five times stdKt/V in three times per week dialysis and four times stdKt/V in daily dialysis or if there is significant renal function where TAC is closer to peak concentration.

Table 1. Comparison of dose measures for differing dialysis schedules and renal function

Renal function	Dialysis prescription	Time (h)	Dialysis dose (per session)		Total clearance, renal + dialysis (per week)		
GFR (ml/min)	Frequency (per week)		eKt/V	spKt/V	stdKt/V	SRI	EKRc (ml/min)
8	No dialysis	–	0	0	2.0	2.0	8.0
5	2	4	1.2	1.4	2.4	2.3	13.4
3	2	6	1.8	2.2	2.3	2.2	14.4
2	3	3	0.9	1.1	2.3	2.0	12.1
0	3	4	1.2	1.4	2.2	2.0	12.9
0	3	8	2.4	2.9	3.1	2.5	21.2
0	Alternate day	4	1.2	1.4	2.6	2.6	15.2
0	6	2	0.6	0.7	2.8	2.3	13.8
0	7	2	0.6	0.7	3.3	3.3	16.2
0	7	8	2.4	2.9	8.1	8.1	55.1

In each case, V is 40 l, and dialyser clearance is 236 ml/min. For the dialytic schedules, fluid weight gain is 1 l/day.

Taking renal function into account. Patients may retain significant renal function for some years after starting haemodialysis [18,19]. It has been shown that the presence of residual renal function is associated with improved outcome in peritoneal dialysis and haemodialysis [20–22]. In peritoneal dialysis, current guidelines specify that, where there is significant renal function, it is measured every 2–4 months. In peritoneal dialysis, residual renal function may be quantified as the urea clearance and is expressed as 'weekly Kt/V' which is identical to the weekly SRI or stdKt/V. Current PD guidelines specify that 'weekly Kt/V' is calculated from mass of urea, in dialysate and urine. Since urea is absorbed by the renal tubules, urea clearance underestimates GFR by about 40%. Most software in current use actually calculates the renal component of 'weekly Kt/V' from the mean of urea and creatinine clearance, which has been shown to closely approximate GFR [23].

To be consistent with peritoneal dialysis practice and CKD guidelines, renal function may be quantified as GFR, calculated from the mass of urea and creatinine in an interdialytic urine collection and average concentrations of urea and creatinine in blood during the collection as described in the EBPG part 1 [24]. For reasons outlined in the EBPG part 1, we recommend using GFR rather than renal urea clearance when adding to the weekly dialysis dose measures EKR, stdKt/V or SRI. In this case, GFR may be added to the dialytic component of EKR to give a total (dialysis and renal) EKR. GFR in ml/min can be converted to a renal component of stdKt/V or SRI as follows;

$$\text{stdKt/V(renal)} = \frac{\text{GFR} \times 10\,080}{\text{V}}$$

Since a body surface area of $1.73\,\text{m}^2$ equates to a urea distribution volume of ~35.5 l, the renal component of stdKt/V or SRI is ~0.28 times GFR in ml/min/$1.73\,\text{m}^2$. Table 1 shows how different levels of GFR can be combined with varying HD schedules to achieve the same stdKt/V.

If the patient has a reduced dialysis prescription, relying on residual renal function to make up to the recommended minimum dose, there is a risk of inadequate dialysis if the renal function were to fail unexpectedly. For this reason, unless renal function has been shown to be exceptionally stable in an individual patient, renal function should be measured at least twice monthly or whenever a change is suspected. Where renal function is questionable, there are no recent results available or the results are suspect in any way, renal function should be assumed to be zero.

References

1. Bloembergen WE, Stannard DC, Port FK *et al*. Relationship of dose of hemodialysis and cause-specific mortality. *Kidney Int* 1996; 50: 557–565
2. Shinzato T, Nakai S, Akiba T *et al*. Survival in long-term haemodialysis patients: results from the annual survey of the Japanese Society for Dialysis Therapy. *Nephrol Dial Transplant* 1997; 12: 884–888
3. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985; 28: 526–534
4. Coyne DW, Delmez J, Spence G, Windus DW. Impaired delivery of hemodialysis prescriptions: an analysis of causes and an approach to evaluation. *J Am Soc Nephrol* 1997; 8: 1315–1318
5. Hecking E, Bragg-Gresham JL, Rayner HC *et al*. Haemodialysis prescription, adherence and nutritional indicators in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004; 19: 100–107
6. Polaschegg HD. On-line dialyser clearance using conductivity. *Pediatr Nephrol* 1995; 9 [Suppl]: S9–S11
7. Manzoni C, Di FS, Corti M, Locatelli F. Ionic dialysance as a method for the on-line monitoring of delivered dialysis without blood sampling. *Nephrol Dial Transplant* 1996; 11: 2023–2030
8. Sargent JA, Gotch FA. Mathematic modeling of dialysis therapy. *Kidney Int Suppl* 1980; 10: S2–S10
9. Tattersall JE, DeTakats D, Chamney P, Greenwood RN, Farrington K. The post-hemodialysis rebound: predicting and quantifying its effect on Kt/V. *Kidney Int* 1996; 50: 2094–2102

10. Daugirdas JT, Depner TA, Gotch FA *et al*. Comparison of methods to predict equilibrated Kt/V in the HEMO Pilot Study. *Kidney Int* 1997; 52: 1395–1405
11. Daugirdas JT, Greene T, Depner TA *et al*. Factors that affect postdialysis rebound in serum urea concentration, including the rate of dialysis: results from the HEMO Study. *J Am Soc Nephrol* 2004; 15: 194–203
12. *Lowrie* EG, Teehan BP. Principles of prescribing dialysis therapy: implementing recommendations from the National Cooperative Dialysis Study. *Kidney Int Suppl* 1983; 13: S113–S122
13. Wuepper A, Tattersall J, Kraemer M, Wilkie M, Edwards L. Determination of urea distribution volume for Kt/V assessed by conductivity monitoring. *Kidney Int* 2003; 64: 2262–2271
14. Keshaviah P. The solute removal index–a unified basis for comparing disparate therapies. *Perit Dial Int* 1995; 15: 101–104
15. Gotch FA. The current place of urea kinetic modelling with respect to different dialysis modalities. *Nephrol Dial Transplant* 1998; 13 [Suppl 6]: 10–14
16. Casino FG, Lopez T. The equivalent renal urea clearance: a new parameter to assess dialysis dose. *Nephrol Dial Transplant* 1996; 11: 1574–1581
17. Depner TA, Greene T, Gotch FA, Daugirdas JT, Keshaviah PR, Star RA. Imprecision of the hemodialysis dose when measured directly from urea removal. *Hemodialysis Study Group*. *Kidney International* 1999; 55: 635–647
18. Khan MS, Atav AS, Ishler MJ, Rehman A, Lozano JE, Sklar AH. Adjustment of hemodialysis dose for residual renal urea clearance: a two year study of impact on dialysis time. *ASAIO J* 2002; 48: 374–378
19. McCarthy JT, Jenson BM, Squillace DP, Williams AW. Improved preservation of residual renal function in chronic hemodialysis patients using polysulfone dialyzers. *Am J Kidney Dis* 1997; 29: 576–583
20. Szeto CC, Lai KN, Wong TY *et al*. Independent effects of residual renal function and dialysis adequacy on nutritional status and patient outcome in continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1999; 34: 1056–1064
21. Termorshuizen F, Dekker FW, van Manen JG *et al*. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 2004; 15: 1061–1070
22. Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. *Am J Kidney Dis* 2001; 38: 85–90
23. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470
24. Section I. Measurement of renal function, when to refer and when to start dialysis. *Nephrol Dial Transplant* 2002; 17 [Suppl 7]: 7–15

4. Minimum adeqate dialysis

Guideline 4.1

In anuric patients, treated by three times per week dialysis, the prescribed target eKt/V should be at least 1.2. Higher doses, up to 1.4 should be considered in females and those patients with high comorbidity. (Evidence level III)

Guideline 4.2

For patients with renal function or those with dialysis schedules other than three times per week, weekly dialysis dose should be at least equivalent to an SRI of 2. (Evidence level IV)

Rationale

Three times per week dialysis. The evidence guiding the minimum dose of dialysis has been challenged in the last few years.

A typical dialysis in Europe delivers an eKt/V of around 1.2 three times per week [1]. Numerous older studies have shown a relationship between outcome and dialysis dose, with eKt/V less than around 1 associated with worse outcome [2–4]. The recent HEMO study [5] failed to show any difference in outcome on an intention-to-treat basis between an eKt/V of 1.05 and 1.45. The same study showed that there was a very strong relationship between achieved dialysis dose and outcome within each arm [6]. This has been taken to demonstrate a strong dose-targeting bias effect in the study. It seems that the success or failure to achieve adequacy targets is more important than the target level. Since the HEMO study is the only large randomized controlled study designed to investigate dialysis dose, there is the possibility that the association between mortality and dose seen in most other studies could be the effect of this dose-targeting bias.

Subanalysis of the HEMO study demonstrated a significantly reduced mortality in females in the high-dose group (and corresponding non-significant increased mortality of males in the high-dose group). The DOPPS study also suggested that the optimal Kt/V might be higher for females than males. It showed a reducing mortality with eKt/V increasing to 1.2 in males and 1.3 in females.

The EBPG group interprets the available evidence to date for three times weekly dialysis as demonstrating that eKt/V <1 is almost certainly harmful. On the other hand, there is no benefit to increasing eKt/V above 1.2, at least in males. In routine clinical practice, dialysis dose is likely to be less well controlled than in clinical studies. Most errors of dialysis prescription or delivery tend to reduce delivered dialysis dose to value below expected. Therefore, it seems sensible to allow a 20% safety margin and recommend a minimum eKt/V of 1.2.

More frequent dialysis than three times per week. There is limited data from studies investigating outcome as a function of dialysis dose in schedules greater than three times weekly. Most daily or 6 times weekly dialysis schedules deliver a weekly SRI of much >2.0 (equivalent to eKt/V >1.2 three times weekly). A theoretical advantage of more frequent dialysis is that it is easier to increase SRI to levels >2.5 (3 is the maximum possible for three times weekly dialysis, unless very long times are employed).

Twice weekly dialysis. There is no published evidence supporting the safety of twice weekly dialysis. Some centres in Europe treat patients with residual renal function by twice weekly dialysis as part of an incremental or early start programme [7]. The maximum SRI practically achievable with twice weekly dialysis without renal function is <2. Therefore, the recommended minimum SRI of 2 would only be possible with demonstrated significant residual renal function.

Higher doses of dialysis. There is no evidence supporting the safety of dialysis dose exceeding 1.5 in three times weekly dialysis <15 h per week. The HEMO study failed to show any benefit from increasing dose above eKt/V of 1.05 [5].

Observational studies show a relatively high mortality associated with eKt/V >1.5 [8]. This is thought to be related to low body mass and high comorbidity in patients treated with high dose but a directly harmful effect of high dialysis dose cannot be excluded [9]. It is quite hard to achieve an eKt/V >1.5 with standard three times weekly schedules unless long session durations (>5 h) are employed.

The EBPG group interpret this evidence as indicating that there is no benefit to eKt/V>1.5 in standard three times weekly dialysis and there is the possibility that high dose may be harmful in this setting. On the other hand, more frequent or longer dialysis allows higher eKt/V to be delivered relatively easily. There are theoretical advantages to high eKt/V in combination with long or more frequent dialysis which deserve further study.

References

1. Hecking E, Bragg-Gresham JL, Rayner HC *et al*. Haemodialysis prescription, adherence and nutritional indicators in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004; 19: 100–107
2. Bloembergen WE, Stannard DC, Port FK *et al*. Relationship of dose of hemodialysis and cause-specific mortality. *Kidney Int* 1996; 50: 557–565
3. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985; 28: 526–534
4. Shinzato T, Nakai S, Akiba T *et al*. Survival in long-term haemodialysis patients: results from the annual survey of the Japanese Society for Dialysis Therapy. *Nephrol Dial Transplant* 1997; 12: 884–888

5. Eknoyan G, Beck GJ, Cheung AK *et al*. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *New Engl J Med* 2002; 347: 2010–2019
6. Greene T, Daugirdas J, Depner T *et al*. Association of achieved dialysis dose with mortality in the hemodialysis study: an example of 'dose-targeting bias'. *J Am Soc Nephrol* 2005; 16: 3371–3380
7. Khan MS, Atav AS, Ishler MJ, Rehman A, Lozano JE, Sklar AH. Adjustment of hemodialysis dose for residual renal urea clearance: a two year study of impact on dialysis time. *ASAIO J* 2002; 48: 374–378
8. Lowrie EG, Li Z, Ofsthun N, Lazarus JM. Measurement of dialyzer clearance, dialysis time, and body size: death risk relationships among patients. *Kidney Int* 2004; 66: 2077–2084
9. Salahudeen AK, Dykes P, May W. Risk factors for higher mortality at the highest levels of spKt/V in haemodialysis patients. *Nephrol Dial Transplant* 2003; 18: 1339–1344