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Guideline

Japanese Society for Dialysis Therapy Clinical Guideline for "Maintenance Hemodialysis: Hemodialysis Prescriptions"

Yuzo Watanabe, Hideki Kawanishi, Kazuyuki Suzuki, Shigeru Nakai, Kenji Tsuchida, Kaoru Tabei, Takashi Akiba, Ikuto Masakane, Yoshiaki Takemoto, Tadashi Tomo, Noritomo Itami, Yasuhiro Komatsu, Motoshi Hattori, Michio Mineshima, Akihiro Yamashita, Akira Saito, Hidemune Naito, Hideki Hirakata, and Jun Minakuchi, for "Maintenance Hemodialysis: Hemodialysis Prescriptions" Guideline Working Group, Japanese Society for Dialysis Therapy

Japanese Society for Dialysis Therapy, Tokyo, Japan

INTRODUCTION

The Japanese Society for Dialysis Therapy (JSDT) has published Clinical Guidelines for Maintenance Hemodialysis: Hemodialysis Prescription. These evidence-based guidelines focus on the characteristics of the dialysis performed in Japan. The number of elderly patients undergoing long-term hemodialysis (HD) is higher in Japan than in other countries. The purpose of the guidelines is to provide recommendation for long-term, stable HD. The main body of the guidelines shows the current recommended minimal standards for HD performed in Japan (i.e. HD at a blood flow rate of at least 200 mL/min using an ultrapure dialysis fluid with a flow rate of at least 500 mL/min and a high-performance membrane (HPM) dialyzer, three times per week for at least 4 h). Although most of the guidelines are evidence based, the recommendations for stably maintaining the condition of patients undergoing long-term HD are presented as opinions. Nevertheless, according to a report by the JSDT Renal Data Registry (JRDR), a considerable number of dialysis facilities have not followed the recommended minimal standards. We hope that at least the minimal standards recommended in the guidelines will be adopted by all dialysis facilities.

The guidelines consist of three parts. The main part of the guidelines is in Chapters 1–4 and presents the basics of HD prescriptions, such as the removal of solutes (substances of low-to-middle molecular weight), control of body fluid, and evaluation of treatment effect. The patients targeted in these prescriptions are HD outpatients in a stable condition; inpatients and patients with severe complications are excluded.

In Chapter 5, blood purification methods that lack sufficient supportive evidence but may be effective to improve the prognosis of HD patients are explained. Therefore, the evidence level and advisability of these methods are not shown in Chapter 5.

Chapter 6 presents the guidelines for pediatric HD. The number of pediatric HD patients is small and sufficient evidence to formulate guidelines is not available in Japan. Therefore, the evidence level and advisability of HD in pediatric patients are not shown in Chapter 6.

Although survival rates related to dialysis therapy in Japan are the highest worldwide (1), there are still many ongoing discussions on whether or not Japan should have a specific dialysis prescription guideline to achieve standardization. This high HD efficacy rate is based on the comparison between Japan and other countries; there are still differences in survival rate among facilities in Japan. In addition, the current quality level of HD may vary in the future, depending on the changes in economic and social conditions.

Address correspondence and reprint requests to Dr Hideki Kawanishi, MD, Tsuchiya General Hospital, 3-30 Nakajima-cho, Naka-ku, Hiroshima 730-8655 Japan. Email: h-kawanishi@tsuchiya-hp.jp
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TABLE 1. *Grading of recommendations and evidence*[†]

Grade for strength of recommendation	Strength	Wording
Level 1	Strong	"We recommend . . . should"
Level 2	Weak	"We suggest . . . might"
No grade[‡]	–	"It is reasonable"
Grade for quality of evidence		Quality of evidence
A		High
B		Moderate
C		Low
D		Very low

[†]Each statement is shown as a combination of the grade and level of evidence, such as 1A or 2C. [‡]The expectation is that it is reasonable to follow this statement as it is a consensus statement based on expert opinion.

Therefore, we believe that this is the appropriate time to establish guidelines, because dialysis treatment has matured technologically, and a certain level of quality of HD has been attained.

Evidence levels and strengths of recommendations are defined and presented in combination, based on an evidence grading system adapted from the Kidney Disease Improving Global Outcomes position paper (2) and JSDT modification (3,4). As shown in Table 1, the strength of the recommendation is graded as either 1 ("strong": i.e. "we recommend" you do it, for positive recommendations, and "we recommend" you do not do it, for negative recommendations) or 2 ("weak": "we suggest" you do it, or "we suggest" you do not do it). For the final category, "No grade" ("it is reasonable"), there is insufficient evidence available to give a grade; however, these ungraded statements are based on a consensus of expert opinion, and the expectation is that consideration should be given to follow the statement.

CHAPTER 1 DIALYSIS DOSE (SMALL SOLUTES) AND DIALYSIS TIME

Statements

1. Dialysis dose is expressed by the single-pool Kt/V for urea (spKt/V). (1B)
2. Measurement of the dialysis dose is done at least once a month.
3. Recommended delivered dialysis dose by spKt/V is the following:
   1) The minimal adequate dose is 1.2. (1B)
   2) The target dose is 1.4 or higher. (2B)
4. The recommended minimal dialysis time is 4 h or longer. (1B)

*These recommendations are for patients with maintenance HD three times per week for less than 6 h.

Commentary

1. Dialysis Dose (Small Solutes)

Index and frequency of measurement

Among small solutes, urea (molecular weight, 60), a final product of protein metabolism impaired by uremia, is a clinically useful marker (5,6). Urea is water-soluble and diffuses across the cell membrane almost freely. A simple mathematical kinetic model, termed the single-pool model (also known as the one-compartment model), can be applied to urea, because urea is assumed to be uniformly distributed in the body fluid (7). In addition, the National Cooperative Dialysis Study (NCDS) conducted in the USA demonstrated that time averaged concentration of blood urea nitrogen (TAC_{BUN}) and protein catabolic rate (PCR, a nutrition index) are important factors related to the prognosis of dialysis patients, including complications and death (8). In the post hoc analysis of NCDS, Gotch and Sargent (9) demonstrated the usefulness of Kt/V for urea calculated from a single-pool model (spKt/V) where "K" is a clearance for urea (mL/min), "t" is the dialysis time (min), and "V" is the volume of urea distribution (≈ total body fluid volume) (mL). Since then, spKt/V has been widely accepted and used as a dialysis dose. Many studies have been carried out using spKt/V as an index. In particular, several equations of spKt/V have been developed by Daugirdas (10), one of which, the so-called "second generation of Daugirdas' equation" (Daugirdas' equation), is used worldwide. In Japan, an equation developed by Shinzato et al., which correlates well with Daugirdas' equation (11), has been used for many years. Considering the above as background, the guidelines adopted spKt/V, frequently used at dialysis facilities, as an index. It is recommended to measure dialysis dose regularly at least once a month, along with regular blood tests.

Dialysis dose and prognosis

After NCDS, many observational studies on the relationship between dialysis dose and prognosis were conducted in Europe and in the USA. Results showed that crude death rate decreases with increasing dialysis dose and with increasing time (12,13), the mortality decreases with increasing dialysis dose (14–17), and the decrease in mortality slows down when the urea reduction rate (URR) is approximately 65% (spKt/V ≈ 1.2) (14) or spKt/V is approximately 1.3 (16). On the basis of these findings, the guidelines of the National Kidney Foundation in the USA, the "Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines," recommended spKt/V of 1.2

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as the minimal adequate dose (18). In the subsequent second large-scale prospective intervention study on dialysis dose, the Hemodialysis (HEMO) study (19), improvement of prognosis was not observed when the dialysis dose was increased to spKt/V of more than 1.2 as recommended by the KDOQI guidelines. However, note that the dialysis prescription in the HEMO study was short high-efficiency HD and the dialysis prescriptions were quite different from those in Japan.

According to the JRDR report, mortality rate tends to decrease with increasing dialysis dose, similar to the results of studies in foreign countries. The decrease in mortality rate is statistically significant for spKt/V of up to 1.8 using $1.0 \leq spKt/V < 1.2$ as a standard reference (20,21). A recent report has also shown that the decrease in mortality was statistically significant for spKt/V exceeding 1.8 using $1.4 \leq spKt/V < 1.6$ as a reference (22). In addition, the possibility of decreasing mortality rate by increasing dialysis dose through prolonged dialysis time, not by short high-efficiency HD, was suggested.

Issues related to Kt/V

Previous observational studies showed a relative increase in mortality rate (reverse J-shaped curve phenomenon) at $spKt/V \geq 1.68$ (23) or $URR \geq 71\%$ ($spKt/V \approx 1.4$) (24). However, the results in Japan indicate that mortality gradually decreases for spKt/V of up to approximately 1.8, and the reverse J-shaped curve phenomenon was not observed (20–22). The factors underlying the reverse J-shaped curve phenomenon may be the high proportion of patients with a small body size and thin malnourished patients in the high dialysis dose group. In other words, the phenomenon is due to the fact that Kt/V_{urea} is affected by the body size of patients, although the adverse effect of a high dialysis dose may not be excluded (23,24). When the relationship between dialysis dose and prognosis is examined, the mortality decreases up to Kt_{urea} (that is not indexed by V) values of 50.7 L (25) and 47.7 L (22) for the patients in the USA and Japan, respectively, and the reverse J-shaped curve phenomenon was not observed with increasing dialysis dose. From these findings, it may be difficult to determine overdialysis only from Kt/V_{urea}.

Sex, body size, and dialysis dose

According to previous reports, lower mortality at higher spKt/V was observed to be more pronounced in females than in males (26–28). The reasons behind this are considered to be a higher urea production per unit body fluid volume in females, or the higher sensitivity to uremic toxin in females, rather than the smaller body size of females (29). Therefore, when dialysis dose is expressed by Kt/V_{urea}, the target dialysis dose may not be the same between sexes (30,31).

The factors related to body size (body mass index [BMI], body weight [BW], body fluid volume, body surface area [BSA]) are independent prognosis factors and the relationship between dialysis dose and prognosis is reported to depend on body size (32–34). The reason behind this is the difference in the body composition depending on body size. Specifically, because the organs producing uremic toxin are relatively larger in patients with a small body size than in patients with a large body size, a higher dialysis dose may be required for patients with a small body size when the dialysis dose is expressed by Kt/V_{urea} (35,36). Therefore, normalizing methods of dialysis dose using uremic toxin generation (metabolism) level or indices related to metabolism (BSA and $BW^{0.67}$) have been proposed (37–40). A report showed that dialysis dose corrected by using BSA correlated with mortality and that the reverse J-shaped curve phenomenon was not observed (41).

Recommended dialysis dose

According to the KDOQI guidelines (18), the minimal adequate dose is spKt/V of 1.2 and the target dose is spKt/V of 1.4; a higher dose is recommended for females and patients with small body size ($V \leq 25$ L). The European Best Practice Guidelines (EBPG) (42) recommend the prescribed dose (prescribed Kt/V) to be a urea-equilibrated Kt/V (eKt/V) of 1.2 ($\approx$ spKt/V of 1.4), considering the possibility that the delivered dose is lower than the prescribed dose. Moreover, eKt/V of 1.4 is recommended for females and patients with high comorbidities. In Japan, a minimal adequate dose higher than that stated in the guidelines in Europe and the USA, that is, an $spKt/V \geq 1.4$, is desirable on the basis that

1) the higher the Kt/V, the lower the mortality in observational studies in Japan and,
2) the body size of Japanese patients is significantly smaller than that of patients in Europe and the USA.

Note that spKt/V of 1.2 is recommended as the minimal adequate dose for patients for whom a high dialysis dose is not applicable or patients with a large body size.

2. Dialysis Time

Dialysis time and prognosis

To increase Kt/V_{urea}, it is necessary to increase dialysis efficiency (K), dialysis time (t), or both.

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According to the JRDR report, the mortality rate of patients with a dialysis time of less than 4 h increases with decreasing dialysis time, and the mortality rate of patients with a dialysis time of more than 4 h decreases with increasing dialysis time among patients on conventional dialysis [three times per week for 3 to 5 h] (20–22). The Dialysis Outcomes and Practice Patterns Study (DOPPS) (43,44) also showed that mortality rate decreases with increasing dialysis time up to 4.5 h. When the results of studies in Japan are compared with those in Europe and in the USA, the decrease in mortality with increasing dialysis time is more pronounced in Japan (43,44). In addition, the poor prognosis of patients receiving dialysis for less than 4 h has been shown in many reports (45–47). A Japanese report showed that a decrease in mortality rate may not be expected even when Kt/V_{urea} is increased for the patients receiving dialysis for less than 4 h (22).

Recommended dialysis time

Dialysis time is one of the important independent factors that determine dialysis dose. According to Japanese reports, mortality rate decreases with increasing dialysis duration adjusted with Kt/V_{urea} (20,21). In DOPPS, dialysis time was examined by stratifying the patients with different values of Kt/V_{urea}, revealing that mortality rate decreases with increasing dialysis time, regardless of Kt/V_{urea} (43). These findings strongly suggest that dialysis time is a prognostic factor that is independent of Kt/V_{urea}. In addition, dialysis with longer time has an advantage in controlling body fluid volume, providing slower ultrafiltration rate (UFR). For example, the incidence of dialysis hypotension decreases owing to a decreased UFR, and the treatment of hypertension is facilitated, because dry weight (DW) can be easily maintained (43,44,48–50). From the above, the recommended dialysis time is 4 h or longer for patients receiving HD three times per week in the guidelines.

Blood flow rate and dialysis fluid flow rate

To increase removal of small solutes, such as urea, increasing not only dialysis time but also blood flow rate (Q_B) and dialysis fluid flow rate (Q_D) is effective (51,52). However, there have been few studies on the relationship between Q_B and prognosis to the best of our knowledge. According to the JRDR analysis (22,53), a decrease in mortality rate with increasing Q_B for up to 250–300 mL/min was suggested when $200 \le Q_B < 220$ mL/min was used as the reference. Although dialysis facilities in Japan are concerned about the increased load on the cardiovascular system with increasing Q_B, an increase in blood flow of the vascular access or acute changes in cardiac function or blood pressure was not observed for $400 \le Q_B < 500$ mL/min (54–59). In fact, an increase in mortality rate was not observed for high-efficiency dialysis performed even under $Q_B \ge 400$ mL/min (56,60). In addition, among patients in the high dialysis dose group with high Q_B in the HEMO study, the incidence of death related to cardiac events did not increase (19,61). On the other hand, to the best of our knowledge, there has been no report on the relationship between Q_D and prognosis, particularly by intentionally changed Q_D. Considering that the effective $Q_B : Q_D$ is approximately 1:2 (52,62,63), prescription of the appropriate Q_B and Q_D is desired in order to effectively utilize the remaining and limited treatment time of patients and new highly functional dialyzers (51,52,63–67).

CHAPTER 2 DIALYSIS DOSE AND EFFECT: β2-MICROGLOBULIN (β2M)

Statements

1. Predialysis serum β2M level at the maximum intervals is a factor related to prognosis. (1B)
2. The dialysis conditions are recommended to achieve the maximum predialysis serum β2M concentration < 30 mg/L. (2C)
3. The dialysis conditions are preferred to achieve the maximum predialysis serum β2M concentration of 25 mg/L. (Opinion)
4. Decreasing the concentrations of substances with greater than β2M can improve the prognosis of patients. (Opinion)

Commentary

1. β2M as Uremic Substance

β2M is the main constituent protein in dialysis amyloidosis, a complication of long-term dialysis treatment, and it needs to be removed proactively during HD therapy (5,68–69). With increasing number of years on dialysis, there is an increase in the number of patients who report symptoms of bone pain, joint pain, mobility disorder, and neuralgia. The clinical condition that is common to these patients is the accumulation of amyloid in tissues such as bones, synovium, and ligaments. These symptoms are called dialysis-related amyloidosis (DRA) (70,71). In Japan, dialysis membranes that can efficiently remove β2M have been recommended, as β2M was identified as the main constituent protein

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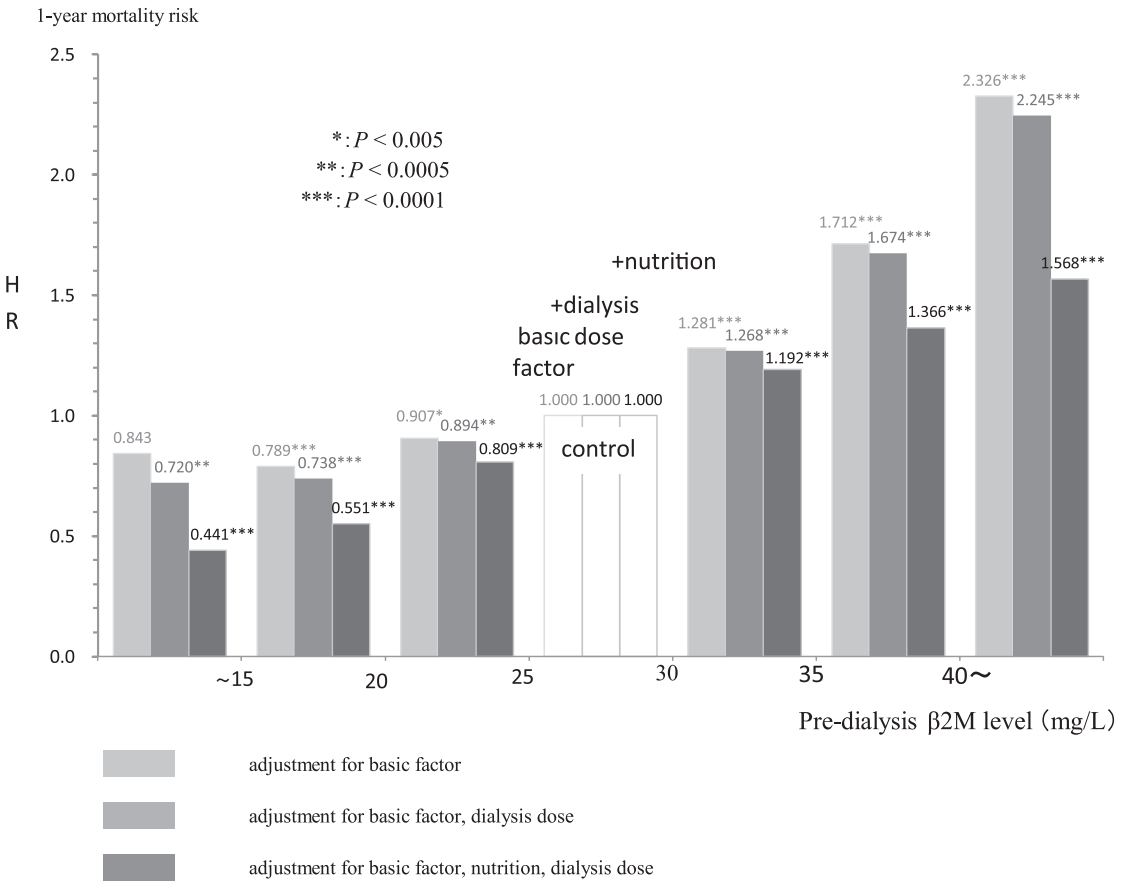

Pre-dialysis serum β2-microglobulin level and outcome

β2M	adjustment for basic factor			adjustment for basic factor, dialysis dose			adjustment for basic factor, nutrition, dialysis dose		
(mg/L)	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
＜15	0.843	(0.711～1.000)	0.0503	0.720	(0.606～0.854)	0.0002	0.441	(0.371～0.525)	＜0.0001
15≦＜20	0.789	(0.714～0.872)	＜0.0001	0.738	(0.668～0.815)	＜0.0001	0.551	(0.498～0.609)	＜0.0001
20≦＜25	0.907	(0.853～0.965)	0.0019	0.894	(0.841～0.951)	0.0004	0.809	(0.761～0.861)	＜0.0001
25≦＜30	1.000	(control)	control	1.000	(control)	control	1.000	(control)	control
30≦＜35	1.281	(1.211～1.355)	＜0.0001	1.268	(1.199～1.341)	＜0.0001	1.192	(1.127～1.261)	＜0.0001
35≦＜40	1.712	(1.594～1.839)	＜0.0001	1.674	(1.558～1.798)	＜0.0001	1.366	(1.271～1.467)	＜0.0001
40≦＜	2.326	(2.148～2.519)	＜0.0001	2.245	(2.073～2.431)	＜0.0001	1.568	(1.447～1.700)	＜0.0001
no data	1.409	(1.339～1.482)	＜0.0001	1.283	(1.217～1.351)	＜0.0001	1.053	(0.996～1.112)	0.0672

FIG. 1. Predialysis serum β2M level and mortality. β2M, β2-microglobulin; CI, confidence interval; HR, hazard ratio.

in dialysis amyloidosis by Gejyo et al. (72). It is also reported, however, that there is no correlation between serum β2M concentration and the incidence of dialysis amyloidosis (73).

Recently, researchers have reported that β2M is not only a uremic toxin that should be removed but also a predictor related to the prognosis of dialysis patients (74–76). The mortality rate decreased when the predialysis serum β2M concentration was from 27.5 to 34 mg/L, as reported by the HEMO study and Okuno et al. (76), suggesting that the decrease in concentrations of uremic substances, including β2M, is important in dialysis therapy. In the JRDR report (as of December 31, 2009), predialysis serum β2M levels were divided into groups at intervals of 5 mg/L. The 1-year mortality rate of the patients who belong to groups with a level lower than 25 mg/L and that of the patients in groups with a level 30 mg/L or higher was compared with the mortality rate of a group with 25 ≤ predialysis serum β2M level < 30 mg/L as a reference (Fig. 1) (77). When the data were adjusted using basic factors such as sex, age, number of years on dialysis, and primary disease, mortality rate increased with increasing predialysis serum β2M level. This trend remains the same even when the data are further adjusted for Kt/V. This finding suggests that the observed relationship between predialysis serum β2M level and prognosis is almost

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independent of the dialysis dose for small solutes. When the data were further adjusted for nutrition-related indices, such as PCR, albumin level, total cholesterol level, BMI, and percent creatinine production rate, the mortality rate of the group with a predialysis serum β2M level less than 25 mg/L decreased further, and the high mortality of the group with a predialysis serum β2M level of 30 mg/L or higher also decreased. Therefore, this finding suggests that the prognosis of patients with good nutritional status is improved by further decreasing the serum β2M level.

According to the JRDR report (as of December 31, 2010), approximately 71% of patients had a predialysis serum β2M concentration of less than 30 mg/L (78). A predialysis serum β2M concentration of less than 25 mg/L is considered to be achievable by optimizing the dialysis conditions.

2. Determination of Dialysis Conditions

In current dialysis therapy with super high-flux dialyzers, β2M can be removed by diffusion without the aid of convection (ultrafiltration), because the molecular weight of β2M is not very high and is just about 11 800 (79). Therefore, one of the efficient methods for decreasing β2M concentration in HD is increasing blood flow rate (Q_B) (80), which would also increase the so-called internal filtration. In addition, increasing the area of dialysis membranes increases the rates of diffusion and internal filtration, thus providing higher clearance for β2M (80). Furthermore, serum β2M concentration can be more efficiently decreased when a dialysis membrane with a higher permeability for β2M is used (80). The reduction rate for β2M per dialysis session is reported to be 60% or more under $Q_B \geq 200$ mL/min using an HPM dialyzer with β2M clearance ≥ 50 mL/min (80). In addition, use of a β2M adsorption column is another option to obtain a high β2M removal rate (81). Increasing the dialysis time to more than 4 h is also known to be effective (82).

It is important to monitor serum β2M concentration regularly. The monitoring interval is recommended to be every 3 months. Purification of dialysis fluid is most important for dialysis performed under the above-mentioned conditions and the use of ultrapure dialysis fluid is indispensable. Serum albumin concentration should also be measured regularly, because some HPM dialysis membranes cause a large amount of albumin loss (refer to Chapter 5-1). In Japan, hemodiafiltration (HDF) and protein-permeable HD have been actively carried out, and it has been frequently reported that the prognosis of patients is improved by decreasing the concentrations of substances greater than β2M (79,83–86). Then it is important to prescribe dialysis conditions to achieve effective clearance of such substances.

CHAPTER 3 OPTIMIZATION OF DW

Statements

1. Body fluid control in dialysis patients is important. BW gain after maximum interdialytic period is within 6%. (2B)
2. A fluid removal rate of 15 mL/kg/h or lower is recommended. (2B)
3. To control the BW gain, dialysis patients are requested to receive guidance on limitations of salt and water intake. (1B)
4. Quality of life (QOL) and prognosis of dialysis patients depend on the optimization of DW. (2B)

Definition of DW

The term DW was first proposed by Thomson et al. in 1967 (87) and is the BW of patients after the maximum removal of extracellular fluid by dialysis. DW is further defined as follows:

1. The BW of a patient without symptoms of overhydration, such as edema.
2. The BW of a patient when the amount of body fluid is reduced to the minimum by fluid removal during dialysis.
3. The BW of a patient who expects to develop hypotension or shock with any further fluid removal.

The DW of a patient is the BW when the patient may have gone into shock as a result of any further removal of fluid. The DW based on this definition is the "true DW." Several ultrafiltration methods are currently used, including extracorporeal ultrafiltration method (ECUM), HDF, and long-time dialysis. Fluid removal to a state of "true DW" is possible if the patients undergo dialysis for a long duration; however, patients may go into shock. The concept of DW that is the BW of patients following the removal of extracellular fluid by dialysis is widely accepted even today.

In this chapter, as the index of DW, we use the "BW at which an appropriate volume of body fluid is maintained, a marked decrease in blood pressure does not occur during dialysis, and the load to the cardiovascular system is small for long-term dialysis life" defined in the JSDT guidelines for management of cardiovascular diseases in patients on chronic HD (88).

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An appropriate control of body fluid eventually leads to normal blood pressure of patients, which is important in terms of improving the QOL and prognosis of dialysis patients.

Commentary

1. Body fluid control in dialysis patients is important. BW gain after maximum interdialytic period is within 6%.

The amount of body fluid in dialysis patients is dependent on the amounts of salt and water intake, urine volume, and amount of fluid removed by dialysis. Improper control of body fluid volume induces hypertension and adversely affects the cardiovascular system (89–92). Although there is also a discussion on whether the maximum allowable BW gain of 6% is appropriate or not, according to the JRDR report, the prognosis of patients with BW gain ≤ 2% or ≥ 6% in interdialytic period is poor (93,94).

According to the United States Renal Data System (USRDS), a BW gain ≥ 4.8% leads to a poor prognosis (95). There are several other reports: BW gain ≥ 5.7% leads to a poor prognosis (96); BW gain = 3.5% is appropriate (97); and mortality rate is the lowest in patients with a BW gain in the range of 2.5–5.7% of DW (98–100). However, these are all observational studies and no randomized controlled trials (RCTs) have been done that provide evidence. Then the guidelines recommend that BW gain after a 2-day interdialytic period is within 6% on the basis of the reports by JRDR.

2. A fluid removal rate of 15 mL/kg/h or lower is recommended.

The rate of fluid removal is not necessarily based on sufficient medical data. However, a fluid removal rate of 15 mL/kg/h is equivalent to a fluid removal of 6% of total BW in a 4-h dialysis. Excessive fluid removal may adversely affect prognosis, as reported by the JRDR, that is, the prognosis of patients with a BW gain > 6% is poor (94) and a dialysis duration < 4 h leads to a poor prognosis (94). Therefore, a fluid removal rate of 15 mL/kg/h is reasonable.

Results in DOPPS showed that a fluid removal rate of 10 mL/kg/h or higher increases mortality rate (43); this report, however, does not aim to evaluate an optimal fluid removal rate. According to a 5-year prospective multicenter study, the mortality rate increases at fluid removal rate ≥ 12 mL/kg/h (100).

The guidelines recommend a BW gain of less than 6% in a maximum interdialytic period as stated in Statement 1. If a BW gain of 6% is removed in a 4-h treatment, a fluid removal rate of 15 mL/kg/h is derived. Similar results are obtained by the analysis of the relationship between the fluid removal rate and prognosis by the JRDR (94).

In actual dialysis, food intake during dialysis, the saline load by priming, and the amount of saline used for blood return are added, and the fluid removal associated with these factors is not reflected by BW. Therefore, if a fluid removal rate of 15 mL/kg/h is followed, BW is decreased by approximately 5% by dialysis for 4 h. Patients with a BW gain greater than 5% should receive guidance on limiting salt intake first. If the BW cannot be controlled by limiting salt intake, a dialysis longer than 4 h is taken into consideration.

Recent papers have reported that a dialysis time of 5 h produces a better prognosis than that of 4 h (49,100). According to the JRDR report, better prognosis is obtained for 4.5 or 5 h dialysis than for 4 h dialysis (94). Therefore, it is recommended to prolong the dialysis time rather than to carry on 4 h dialysis with an unreasonably high fluid removal rate.

3. To control BW gain, dialysis patients are requested to receive guidance on limitations of salt and water intake.

BW gain during the interdialytic period indicates the accumulation of body fluid and salt in the body. A serum Na concentration of 140 mEq/L is equivalent to a saline solution of 8.2 g/L. Namely, accumulation of 8.2 g of salt in the body means accumulation of 1 L of water (amount of body fluid = BW). As stated in Statement 1, to suppress a BW gain within 6% after the maximum interdialytic period, control of salt intake is indispensable. By limiting salt intake, blood pressure decreases (101,102), body fluid volume becomes normal (103), and thirst is alleviated, which reduces the amount of water intake (103–105).

The KDOQI guidelines recommend a daily salt intake of 5 g or less (106). A daily salt intake of 5 g is equivalent to a BW gain of 1.5 kg during the interdialytic period. Indeed, 1 g of salt is excreted with the sweat and stool. However, Na salts other than NaCl are included in the diet and no correction is needed for these salt intake levels. Medical staff should limit the amount of salt intake of patients with a high BW gain and should not limit the amount of water intake without limiting the amount of salt intake of such patients. Limiting the amount of salt intake is of primary importance for patients with a high BW gain.

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For patients with hyponatremia, limiting the amount of water intake is recommended. For most patients, predialysis serum Na concentration is in the range of 136–145 mEq/L. The amount of water intake should be limited for patients with predialysis serum Na level ≤ 135 mEq/L. The sources of fluid leading to excess water intake include rice gruel, tea, and water for oral medicine.

4. QOL and prognosis of dialysis patients depend on optimization of DW.

Scribner stated that administration of drugs for antihypertension is not necessary for dialysis patients if their DW is properly maintained (107). Proper control of body fluid could achieve normal blood pressure in most dialysis patients (108,109). As stated above, improper control of body fluid volume induces hypertension and adversely affects the cardiovascular system. Therefore, the prognosis of dialysis patients can be improved by optimizing DW (48,104,106,110–113). The decrease in blood pressure during dialysis causes muscle cramps and general malaise after dialysis, as well as poor outcomes (93,114). Setting excessively high DW would induce a burden on the heart, which may lead to a need for emergency dialysis.

APPENDIX I

Optimal salt intake

In the formulation of the guidelines, we considered a salt intake of less than 6 g/day, which is recommended for patients with hypertension by the Standards for Dietary Prescription for Patients with Chronic Kidney Disease 2007 (115), the Japanese Society of Hypertension (116), and the Japan Diabetes Society. However, this value is not included in the statements, because a salt intake of 6 g/day is equivalent to a BW gain of 2.2 kg after a 2-day interdialytic period, that is, 7.3% BW gain for patients with a BW of 30 kg.

APPENDIX II

Determination of DW

In general, the following are used as indices for determining DW.

① No marked decrease in blood pressure during dialysis.
② No hypertension (blood pressure is approximately 140/90 mm Hg at the start of the first dialysis in a week).
③ No edema.
④ No lung congestion on chest X-ray images.
⑤ A cardiothoracic ratio of 50% or less (53% or less for female patients).

However, each of the above indices has problems and we should always pay attention to the following exceptions.

① (No marked decrease in blood pressure during dialysis.) Blood pressure decrease is caused by dysfunction of the autonomic nervous system, decreased cardiac function, arrhythmia, and acetate intolerance, in addition to the decrease in circulating blood volume during fluid removal. These factors should be eliminated.
② (No hypertension [blood pressure is approximately 140/90 mm Hg at the start of the first dialysis in a week.]) A DW decrease of approximately 0.3 kg per week is desirable to decrease DW for the purpose of controlling blood pressure. One should pay attention to the fact that a decrease in blood pressure occurs several weeks after the decrease in DW (time lag phenomenon) (117).
③ (No edema.) Factors that worsen symptoms of edema, such as hypoalbuminemia and venous thrombosis, should be eliminated.
④ (No lung congestion on chest X-ray images.) Lung congestion can continue for patients with decreased cardiac function and left heart failure.
⑤ (A cardiothoracic ratio of 50% or less [53% or less for female patients.]) For patients with myocardial hypertrophy, valvular disease, decreased cardiac function, transverse position of the heart, increased shunt blood flow, and marked anemia, the cardiothoracic ratio does not necessarily reflect the circulating blood volume. The cardiothoracic ratio should always be evaluated on a regular basis.

When the "BW of patients with an appropriate amount of body fluid, without the risk of marked decrease in blood pressure during dialysis, and with the long-term dialysis treatment with a limited load to the cardiovascular system" (88) defined in the guidelines for management of cardiovascular diseases in patients on chronic HD by the JSDT is used as the index of DW, the following questions may arise.

① What is the optimal body fluid volume?
② What is the extent of blood pressure decrease during dialysis?
③ What is the BW at which the load on the cardiovascular system is small for long-term dialysis?

Please refer to the JSDT guidelines for the determination of DW (88).

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CHAPTER 4 EVALUATION OF DIALYSIS QUALITY IN ORDER TO ACHIEVE THE OPTIMAL DIALYSIS DOSE AND SUFFICIENT CLINICAL EFFECTS

Statements

1. The therapeutic efficacy of dialysis is evaluated regularly using both short-term and medium- to long-term indices. (1B)
   1) Intra-dialytic hemodynamics and the efficiency of removing small solutes are used as the short-term indices.
   2) Predialysis serum β2M concentration, nutritional status, and QOL are used as the medium- to long-term indices.
2. Dialysis prescription is changed based on the evaluation of dialysis treatment to satisfy the above indices. (Opinion)

Commentary

The aim of regular maintenance dialysis treatment is to provide longer survival with higher QOL of patients. To this end, dialysis facilities should regularly evaluate whether the dialysis dose is high enough to improve the uremic symptoms of patients. The therapeutic efficacy of dialysis should be evaluated both by short-term indices, including the safety and stability of each dialysis session and the efficiency of removing uremic toxins, and medium- to long-term indices, including maintenance levels of uremic toxins, improvement of uremic symptoms, and nutritional status.

1. Evaluation of Treatment Effect Using Short-Term Indices

The short-term indices include the intra-dialytic hemodynamic changes and the efficiency of removing small solutes. To assure a sufficient dialysis dose, safe and stable dialysis treatment should be consistently provided to patients. In this respect, intra-dialytic hypotension is the main issue. A marked blood pressure decrease during dialysis and postdialysis orthostatic hypotension are the factors that worsen the prognosis of patients (114,118). Causes of dialysis hypotension include inappropriate DW, decrease in the circulating plasma volume caused by rapid fluid removal, deteriorated cardiac function, and dysfunction of the autonomic nervous system. Causes of intra-dialytic hypotension should be immediately clarified and be treated (88).

The efficiency of removing small uremic toxins during each dialysis session, particularly the normalized urea clearance (Kt/V), has been proved to be one of the prognostic factors of dialysis patients by various cross-sectional and cohort studies. In these studies, the target Kt/V to decrease mortality rate has been addressed (9,20). In the recent analysis of JRDR, Kt/V is identified as an independent prognostic factor (22). The guidelines recommend a regular monthly monitoring of Kt/V (refer to Chapter 1).

2. Evaluation of Treatment Effect Using Medium- to Long-Term Indices

The treatment effect should also be evaluated using medium- to long-term indices, such as the maintenance level of uremic toxins (predialysis serum β2M concentration), nutritional status, and QOL indices (e.g. depression, sleep disorder), which are confirmed to be closely related to the dialysis dose and prognosis of the patients.

Early in the history of dialysis therapy, the target substances of dialysis were small solutes, such as urea and phosphate. However, in the last two decades, the target has been changed to β2M, and other low molecular weight proteins (LWMPs) greater than β2M, and protein-bound uremic toxins. Among these uremic toxins, only β2M can be commercially measured worldwide and has been proved to be closely related to uremic symptoms and DRA. It was also found in previous major cohort analyses that the predialysis serum β2M level is a prognostic factor (74,76). From the above, the guidelines recommend regular monitoring of predialysis serum β2M level as explained in Chapter 2.

Nutritional status is one of the most important prognostic factors (119) and is a good medium- to long-term dialysis index. In particular, muscle mass estimated from percent creatinine generation rate (120) is an independent prognostic factor (121). Dialysis prescription and nutritional care that can maintain muscle mass are essential factors for the success of treatment. The nutritional status should be evaluated comprehensively by the subjective assessment of nutritional status, physical measurements, body composition analysis, and blood biochemical parameters. Malnutrition in dialysis patients is a complex of various factors, such as the accumulation of uremic toxins, weak inflammatory responses caused by poor biocompatibility of dialysis treatment, poor appetite, and nutrient loss during dialysis (122). To develop a treatment intervention after nutritional assessment, causes of malnutrition should be clarified. First, the presence of inflammation should be excluded. Therefore, it is desirable that serum C-reactive protein is also measured in the nutritional screening. Repeated nutritional assessment at least once every 6 months is recommended to evaluate the effect of the intervention.

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TABLE 2. *Change in dialysis prescription*

Increase (decrease) dialysis efficiency
• Increase (decrease) blood flow rate
• Increase (decrease) dialysate flow rate
• Increase (decrease) membrane area of dialyzer
• Change the membrane type of dialyzer
Increase (decrease) the duration and frequency of dialysis
Use of special dialysis membrane
• High performance membrane
Addition of filtration-based treatment
• Online hemodiafiltration

Among uremia-induced neuropsychiatric symptoms that deteriorate the QOL of dialysis patients, depression (123), insomnia (124), and pruritus (125) are reported to be prognostic factors. It is reported that most uncomfortable uremic symptoms would disappear when nocturnal long home HD is carried out (126). It suggests that underdialysis is one of the most important keys that cause the multiple complaints in dialysis patients. It is recommended to develop an appropriate dialysis prescription to improve such symptoms, instead of simply treating symptoms by medications.

3. Changing Dialysis Prescription

When the current dialysis prescription provided to a patient is considered to hinder improvement of the uremic symptoms or to adversely affect the daily life of the patient, the dialysis prescription should be changed as summarized in Table 2. Unfortunately, we are not able to propose a common dialysis prescription that would be effective for every patient and every symptom. One prescription may cause different responses in each patient. Therefore, the intervention plan should be evaluated whether it could improve the symptom. If the intended effect is not obtained, another prescription may be taken into consideration. A comprehensive approach is necessary, because the blood pressure changes during dialysis and uremic symptoms are closely related to patients' compliance in medication, diet, and other lifestyle elements.

CHAPTER 5-1 DIALYSIS MEMBRANE SELECTION

Statement

HPM dialyzers should be used.

Commentary

The KDOQI guidelines state that the use of poorly biocompatible cellulose membranes should be discouraged. The EBPG recommends the use of highly biocompatible high-flux membranes with large pores to improve morbidity and mortality. The EBPG also recommends avoiding dialysis membranes that strongly activate complement, white blood cells, and inflammatory responses. However, a meta-analysis conducted by MacLeod et al. failed to clearly demonstrate the superiority of synthetic polymer membranes (127). Unlike in other countries, HPM dialyzers have been adopted in Japan, and the context surrounding the criteria for the selection of dialysis membranes in the Japanese guidelines differs from that in guidelines from other countries. Therefore, during the formulation of these guidelines, HPM dialyzers must be described in the context of the selection of dialysis membranes.

The concepts underlying the development of HPM dialyzers are explained next. During the 1970s, the identity of middle molecular weight uremic toxins that formed part of the middle molecule hypothesis proposed by Babb et al. (128) and approaches to their efficient removal were discussed. This led to an attempt to remove these middle molecular weight toxins by hemofiltration (HF), but HF did not have beneficial effects on patients. By the end of the 1970s, themes being discussed focused on the accumulation of toxins as a consequence of uremia, substances that could be removed by HF, and the low clearance rates of such accumulated toxins. Focusing on the fact that LMWPs that have lower molecular weights than albumin are removed by glomerular filtration, researchers determined that dialysis using a dialyzer that can remove small proteins can achieve certain clinical benefits, including improvements in anemia and joint pain. HPM dialyzers are discussed in the following sections.

1. Requirements for HPM Dialyzers

When considering the requirements for HPM dialyzers, familiarity with the background to their designation is very important. Membranes with high UFR, including high-flux membranes and high-permeability membranes, were considered to be HPMs and they were referred to as such in the context of dialyzers in the 1970s. Dialyzers equipped with new membranes that provided greater clinical benefits followed, and they included those capable of adsorbing proteins and leaking albumin, despite having low UFRs, and these were also classified as HPM dialyzers. In 1985, Gejyo et al. (72) identified β2M as the amyloid precursor protein in DRA. In those days, only a few types of dialysis membrane were available that could efficiently remove LMWP. Therefore, dialyzers performing adsorption-based

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removal and those with highly biocompatible membranes that reduced inflammatory protein production were also regarded as HPM dialyzers.

Now, many dialyzers can efficiently remove LMWP, and the definition of HPM dialyzers is changing gradually. In 2005, the JSDT classified dialyzers according to their functions, and defined HPM dialyzers as those with a β2M clearance of at least 10 mL/min (129). In 2013, the JSDT added albumin permeability and specific functions that included adsorption capability to the classification criteria (130).

2. Clinical Effects

The improvement of DRA is the most important clinical effect required of HPM dialyzers, and this provided the background to their development. The JSDT undertook a statistical survey that showed that HPM dialyzers are effective in the treatment of DRA (131). In addition, Koda et al. reported that the use of HPM dialyzers lowered the risk of carpal tunnel syndrome, which, along with mortality, is a manifestation of DRA (132). Because HPM dialyzers remove substances that cannot be removed by conventional dialyzers and are superior with regard to biocompatibility, they are expected to have a variety of clinical benefits for dialysis patients, including improvements in prognoses, appetite, malnutrition, syndromes associated with DRA, for example, joint pain and suppressing DRA development, renal anemia, pruritus, skin pigmentation, skin keratosis, restless leg syndrome, irritation, insomnia, acute renal failure, and native kidney function (133). An RCT that compared high- vs. low-flux membranes reported that the use of high-flux membranes improves the prognoses of dialysis patients with diabetic nephropathy and those with albumin levels of <4.0 g/dL (83).

3. Uremic Toxins Should Be Removed

Uremic toxins of a relatively high molecular weight that cannot be removed by conventional dialyzers are the targets of HPM dialyzers. Currently targeted uremic toxins include those that conform to the classical definition and those substances associated with vascular lesions and chronic inflammation (134) and, among these, substances with molecular weights of 10 000–30 000 Da should be removed by HPM dialyzers. However, placing limits around the targets is currently difficult, and new target substances will be identified as a result of further pathological clarification in the future.

As noted previously, HPM dialyzers have the potential to improve patients' prognoses and their dialysis-related complications, and are considered suitable for use in dialysis therapy.

CHAPTER 5-2 CONVECTION-BASED BLOOD PURIFICATION METHODS

Statements

1. HDF should enhance the removal of small proteins, reduce the production of inflammatory cytokines, and improve patients' prognoses.
2. HDF should be considered a therapy for nonspecific symptoms, including itching, joint pain, malaise, and poor appetite. Patients with dialysis hypotension should be considered for treatment with HD using a high-flux dialyzer and ultrapure dialysate.

Note: Predilution online HDF using a large volume of dialysate and a hemodiafilter that allows the permeation of small proteins up to the size of albumin is commonly practiced in Japan.

Commentary

In 2008, JSDT formulated a Standard on Microbiological Management of Fluids for Hemodialysis and Related Therapies (135). Online HDF has been available in Japan since April 2010, and it resulted from the approval of corresponding artificial dialysis systems. Since April 2012, online HDF has been covered by national health insurance in Japan. Online HDF is suitable for patients with a variety of pathologies who regularly undergo maintenance dialysis.

1. Comparative Effects of Online HDF and HD

   1) Reduction in β2M levels and the effects of treatment on DRA

Online HDF is reportedly superior to HD at reducing β2M levels, a small precursor protein that is associated with DRA (136–138). Indeed, HDF is highly effective at removing LWMPs, particularly β2M.

Nakai et al. examined the DRA suppression effects of different blood purification therapies in 1196 patients. They reported that online HDF and push–pull HDF significantly reduce the relative risk of DRA compared with HD using a conventional (low-flux) membrane (relative risk = 1), demonstrating that HDF is effective for treating DRA (131). Furthermore, Locatelli et al. reported that HDF significantly delays the need for carpal tunnel surgery (139).

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2) Improvements in anemia

It has been reported that compared with HD, postdilution online HDF significantly decreases the resistance index for erythropoiesis-stimulating agents (ESAs) and the erythropoietin dose-to-hematocrit ratio (140). However, a 21-month RCT conducted in Italy showed that neither anemia nor ESA resistance improved among patients undergoing predilution online HDF (141). Thus, findings regarding the effects of online HDF on anemia and ESA resistance are inconsistent.

3) Improvements in inflammation

The RISchio CArdiovascolare nei pazienti afferenti all'Area Vasta In Dialisi (RISCAVID) study, a prospective observational trial of patients undergoing online HDF or HD with a 30-month follow-up period, showed that online HDF significantly reduces the levels of inflammatory cytokine and interleukin-6 (IL-6) (142). In a crossover study of 31 patients, Carracedo et al. found that online HDF significantly reduces the production of the cluster of differentiation (CD)$14^{+}CD16^{+}$ monocyte-derived cells, which frequently generate inflammatory cytokines. Compared with high-flux HD, online HDF suppresses the production of IL-6 and tumor necrosis factor-α, which are generated by stimulating monocytic cells (143). Ramirez et al. reported that online HDF significantly suppresses the increased production of endothelial microparticles and endothelial progenitor cells compared with high-flux HD, which shows its potential to alleviate vascular endothelial damage (144).

4) Effects on dialysis hypotension

Locatelli et al. investigated the effects of online HDF on the prevention of dialysis hypotension in a study carried out in Italy. They reported that predilution online HDF prevents dialysis hypotension in a way that is similar to predilution online HF. This effect was attributed to the increased sodium load as observed in high-sodium HD (145).

5) Improvements in prognoses

Analysis of the results from DOPPS European patients determined that mortality among patients undergoing postdilution online HDF was 35% lower than that among patients undergoing HD using low-flux membranes (146).

The RISCAVID study showed that postdilution online HDF reduced cardiovascular mortality compared with bicarbonate HD (where 95% of patients used synthetic polymer membranes or low-flux membranes) and that online and offline HDF reduced total mortality to a greater extent than bicarbonate HD (142). Vilar et al. carried out a comparative analysis of the long-term outcomes associated with postdilution online HDF and HD using high-flux membranes. They reported that online HDF significantly improved patient prognoses compared with HD using high-flux membranes, although there were no significant differences between the two dialysis methods in relation to their effects on anemia, bone metabolism, nutritional status, and blood pressure (147). A study that compared online HF with HD using low-flux membranes found that patients undergoing online HF had improved prognoses (148).

Recently, the results from three RCTs investigating the effects of online HDF on survival rates have been reported. The three RCTs reported are the CONvective TRAnsport STudy (CONTRAST) (149) that compared postdilution online HDF and low-flux HD, a study undertaken in Turkey (150) that compared postdilution online HDF and high-flux HD, and the Estudio de Supervivencia de Hemodiafiltracion On-Line or On-Line Hemodiafiltration Survival (ESHOL) (151), which also compared postdilution online HDF and high-flux HD. The CONTRAST study found that all-cause mortality decreased by 38% among patients undergoing online HDF at a convection volume of >21.95 L, but there were no significant differences in relation to all-cause mortality and cardiovascular mortality between patients undergoing postdilution online HDF and low-flux HD (149). The Turkish study also found reductions in all-cause mortality and cardiovascular mortality by 46% and 71%, respectively, among patients undergoing online HDF with a convection volume of >17.4 L, but there were no significant differences between the study groups (150). The ESHOL study found that all-cause mortality, cardiovascular mortality, and infectious disease mortality decreased by 30%, 35%, and 55%, respectively, among patients undergoing online HDF and that the incidence of dialysis hypotension decreased by 28%. In accordance with the CONTRAST study and the Turkish study, the ESHOL study determined that all-cause mortality among patients undergoing online HDF with high convection volumes of >23 L and >25 L decreased by 40% and 45%, respectively (151). These results indicate that patients treated with online HDF have better prognoses than those treated with low-flux HD, and that prolonged online HDF is considered superior to high-flux HD. However, a substantial body of evidence demonstrating the advantages of online HDF in relation to patients' prognoses is yet to be gathered.

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2. Status of Online HDF in Japan

Predilution HDF is a feature of the online HDF method used in Japan (152). Hemodiafilters that use HPMs with a β2M clearance rate of at least 50 mL/min are very frequently used in Japan. Indeed, it has been reported that their rates of use are at least 90% and 95% in HD and HDF, respectively (153).

Although clearances in predilution online HDF have been examined in countries other than Japan, the number of patients investigated is limited, and the relatively large convection volume (≥60 L) per dialysis session that is used in Japan is rarely used among overseas patients (154–157). Compared with postdilution online HDF, predilution online HDF, using albumin-permeable hemodiafilters, provides a good balance between albumin leakage and the removal of small proteins (158). In addition, many studies demonstrate that predilution online HDF also alleviates patients' complaints associated with dialysis, including itching, bone and joint pain, and poor appetite; hence, predilution online HDF should be considered a modality that may relieve these complaints (159).

Note that all convection-based blood purification methods, including online HDF, must satisfy the dialysis prescription and the conditions recommended in the guidelines.

CHAPTER 5-3 DIALYSIS SCHEDULE

Statements

1. Long intermittent HD refers to HD performed with a duration of at least 6 h per session, and frequent HD refers to HD administered at least five times per week.
2. The dialysis time or frequency should be increased in the following patient situations:
   1) Patients with symptoms that cannot be controlled by conventional HD:
      (1) Patients with symptoms of cardiac failure or hemodynamic instability during dialysis;
      (2) Patients who remain hypertensive despite fluid removal, the administration of antihypertensive agents, and the restriction of salt intakes;
      (3) Patients who remain hyperphosphatemic despite dietary controls and phosphate control
   2) Patients who are stable under conventional HD and are expected to benefit more from dialysis with increased dialysis times and/or frequencies.

Commentary

Currently, HD is performed as an intermittent regimen, and many patients undergo HD for a total of 12 h per week only, which means that the complete replacement of their kidney function by dialysis is impossible. While this conventional HD (Table 3) is the minimum treatment necessary to maintain life, it is inadequate in preventing dialysis-related complications and in improving outcomes. Increasing the amount of time spent on dialysis each week would address this issue, and would establish programs of long intermittent and frequent HD. In addition, increasing the amount of time spent on dialysis each week enables patients, including those who are already stable under their current HD program, to achieve internal balances that more closely resemble those of healthy people, which should improve their clinical outcomes.

1. Definitions

The definitions of frequent HD and long intermittent HD are specified in the International Quotidian Dialysis Registry (160) and in the Frequent Hemodialysis Network (FHN) Trials (161), but the definitions differ slightly among studies. In this guideline, long intermittent HD is defined as HD three times per week for at least 6 h, which is based on the International Quotidian Dialysis Registry definition, and it considers the context in which dialysis takes place in Japan. Although data on dialysis for ≥5 h per session are included in the International Quotidian Dialysis Registry, dialysis that lasts for <6 h is categorized as conventional dialysis, because the duration of dialysis that is specified for healthcare reimbursement in Japan is at least 5 h.

Frequent HD is defined as HD that occurs at least five times per week, and it is classified into short frequent HD that lasts for 1.5–3 h and long frequent HD that lasts for 6–10 h that generally occurs at night, and is also known as daily nocturnal HD. Frequent HD with a duration of 3–6 h is not clearly

TABLE 3. *Definitions and terms*

- Conventional intermittent HD: 3 sessions per week, 3–6 h per session
- Long intermittent HD: 3 sessions per week, ≥6 h per session
- Frequent HD (daily HD, quotidian HD): ≥5 sessions per week
  - Short frequent HD (short daily HD): ≥5 sessions per week, 1.5–3 h per session
  - Conventional-hour frequent HD: ≥5 sessions per week, 3–6 h per session
  - Long frequent HD (long daily HD, frequent nocturnal HD, daily nocturnal HD): ≥5 sessions per week, ≥6 h per session

HD, hemodialysis.

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categorized and is defined in the guidelines as conventional-hour frequent HD. The terms "frequent HD" and "daily HD" are used interchangeably by different researchers, with the latter term being used mainly in Western countries. However, the guidelines adopt the term frequent HD.

Note that alternate-day HD (seven times per fortnight) and four times weekly HD are not discussed in the guidelines, because evidence supporting their benefits is limited, but benefits from these approaches can be expected in the future.

2. Adequacy

1) Patients with symptoms that cannot be controlled by conventional HD

This section discusses those patients with symptoms of cardiac failure or hemodynamic instability and those who remain hypertensive despite fluid removal, administration of antihypertensive agents, and restriction of salt intake.

Using long intermittent HD can reduce the UFR and increase the total amount of fluid removed, leading to improved control of body water levels (48,162) and the effective stabilization of hemodynamics (163). Prolonged dialysis can reduce the incidence of dialysis hypotension, particularly in elderly patients with complications (49). An RCT showed that while blood pressure was controlled to a greater extent among patients undergoing HD at home for 6–8 h per session than among patients undergoing in-center HD for 3.5–4.5 h per session, there were no significant differences in relation to changes in BW and the amount of extracellular fluid (164). In addition, an RCT with a fixed DW showed that patients who were undergoing long intermittent HD had well-controlled blood pressures (165). In general, longer dialysis treatments facilitate the achievement of target DWs, and lead to well-controlled blood pressure and the administration of lower doses of antihypertensive agents (48,162).

Frequent HD can suppress increases in BW during interdialysis periods and is effective in stabilizing hemodynamics. Studies show that increasing the frequency of dialysis treatment is beneficial for patients with poorly controlled BW and patients with complications (166,167). Furthermore, a lower incidence of dialysis hypotension has been reported (168). A Japanese clinical study also showed that in-center frequent HD undertaken six times per week for 2 h, which had been switched from conventional intermittent HD, significantly reduced the blood pressure despite increasing DW (169).

Left ventricular hypertrophy tends to be found among dialysis patients and is a factor influencing their poor prognoses. Frequent HD reportedly decreases the incidence of left ventricular hypertrophy (170). An FHN RCT recently carried out in North America compared in-center HD six times per week for 1.5–2.75 h, total dialysis time of 12.7 ± 2.2 h per week, with HD three times per week for 2.5–4.0 h, total dialysis time of 10.4 ± 1.6 h per week, and it found that frequent HD significantly decreases the left ventricular mass index (LVMI) (171), which may relate to BW and blood pressure being well controlled by frequent HD. A meta-analysis reported that frequent HD and long intermittent HD lead to significant decreases in the LVMI and improvements in the left ventricular ejection fraction (EF) (172). Further reports show that long frequent HD prevents dialysis hypotension, controls blood pressure during dialysis, improves the EF, and prevents left ventricular failure (173,174). Another report showed that daily nocturnal HD reduces peripheral vascular resistance and increases the vasoactive reaction (175). In summary, both long intermittent and frequent HD facilitate the control of BW, resulting in improvements in blood pressure and cardiac function.

2) Patients who have persistent hyperphosphatemia

The benefit of prolonged HD is the clearance of relatively low molecular weight solutes, including urea, because this process depends on diffusion. However, prolonged dialysis is also effective at reducing levels of phosphate, which has a low molecular weight, is more abundant within the tissues than in the blood, and its transport rate is complicated and affected by various factors, including the acid-base equilibrium (176,177). For patients with poor phosphate control, longer and/or more frequent HD is the most effective means of reducing phosphate levels (178). However, the kinetics of phosphate in the body are complicated, and the extent to which it is reduced and its levels in the serum will vary according to the dialysis conditions. For example, a longer dialysis time results in a greater reduction in the phosphate level, (82,177–178) but it rarely increases the removal rate (82). In addition, a much longer dialysis duration may increase the risk of phosphate being transported into the blood from the bones (179).

Frequent HD reduces serum phosphate levels and the need to use phosphate binders (180,181). However, increases in phosphate intake as a result of increased food intake should be considered (182). Therefore, increase in food intake should be accompanied by increase in dialysis time, even when frequent HD is undertaken, to reduce phosphate levels

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(181). An FHN trial showed that serum phosphate levels significantly decreased among patients undergoing HD six times weekly, where the mean dialysis duration was 154 min per session (171,183).

Daily nocturnal HD reduces serum phosphate levels and markedly reduces the use of phosphate binders, despite increases in phosphate intake from food (180,183–184). In addition, supplementing the dialysate with phosphate is required to prevent hypophosphatemia (185). In conclusion, reductions in phosphate levels are enhanced as total weekly dialysis times increase. It has been reported that when the total dialysis time is at least 38 h per week, the serum phosphate level can be maintained <5.0 mg/dL without using phosphate binders (178).

3) Patients who are stable under conventional HD and are expected to benefit more from dialysis of increased times and frequencies

Short HD times increase mortality, regardless of the delivered dialysis dose (20,43). The JRDR, which includes 71 000 patients, showed that after adjusting for Kt/V_{urea}, mortality decreased with increasing dialysis times among patients undergoing HD for no more than 5.5 h per session (20). In addition, mortality from cardiovascular complications decreased among patients undergoing longer HD that lasted for 8 h and was undertaken three times per week, mainly because blood pressure was well controlled (48,162). A retrospective observational study that involved 415 patients who were undergoing short frequent HD at European and American facilities showed that the 5- and 10-year survival rates were 68% and 42%, respectively. When these data were compared with those in USRDS after matching the patients' characteristics, the 50% survival rate was 2.5–10.9 years longer for patients undergoing short frequent HD than for those undergoing conventional HD. Furthermore, survival was 9–15 years longer among patients undergoing short frequent HD at home compared with those undergoing conventional HD. These data are similar to those from patients receiving cadaveric renal transplantations in North America (186). An analysis of the Canadian Daily Nocturnal HD Registry that included 247 patients undergoing daily nocturnal HD determined that the 1- and 5-year survival rates were 95.2% and 80.1%, respectively (187).

The results from the FHN trials carried out in North America have been published (161,171,183, 188) and are described next. The effects of short frequent treatments with HD were compared with those of conventional HD among patients treated at dialysis centers. The findings obtained were clear, because the survey comprised a large patient population and was conducted with patients treated at centers (170). The LVMI and physical health composite scores were the primary outcome measures, and they were significantly better among patients undergoing short frequent HD treatments. In addition, serum phosphate levels and systolic blood pressures, which were the secondary outcome measures, were significantly lower.

In another FHN trial, the effects of daily nocturnal HD undertaken at home were compared with the effects of treating patients at home with conventional HD. In this trial, patients receiving conventional intermittent HD at dialysis centers were initially targeted for trial participation, but patients receiving conventional HD at home were selected after the patients had been screened. Therefore, patients who were treated at home and received nocturnal HD were compared with those treated at home by conventional HD. The comparison showed that the conventional HD group included patients who had undergone HD for a relatively long time, and conversely, that the daily nocturnal HD group included patients who had undergone HD less frequently. As a result, no significant differences were found in relation to the primary outcomes, and only the secondary outcomes, which included serum phosphate levels and systolic blood pressures, showed significant differences. These findings may have also been caused by the small patient population (188).

These findings indicate that frequent HD improves cardiac function and QOL to a greater extent than conventional HD undertaken three times weekly. However, no significant differences were found in relation to different dialysis times and frequencies among patients whose HD was undertaken at home, and the results only demonstrate the effectiveness of home HD. The Australia and New Zealand Dialysis and Transplant Registry also shows the advantage of home HD over in-center HD, but no significant differences are apparent in relation to mortality between those patients treated at home with conventional HD and those treated at home with frequent or long intermittent HD (189).

3. Disadvantages

1) Longer HD is associated with the excessive removal of solutes during each dialysis session

When HD is performed for longer durations using commercial dialysates, minerals including potassium, phosphorus, and calcium are removed in excess, and complications such as hypokalemia, hypophosphatemia, hypocalcemia, and the resulting reductions

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in bone mass, cause concern. In these patients, blood flow and dialysate flow should be adjusted, and a dialysate of an appropriate composition should be selected. Calcium and phosphorus levels in the dialysate, in particular, should be appropriately adjusted during daily nocturnal HD (183,184). Furthermore, losses of trace elements and proteins should also be considered when selecting a dialyzer. Thus, the composition of commercial dialysates is generally designed for use in conventional HD undertaken three times weekly, and if they are used for different HD regimes, their safety must be stringently assured.

2) Frequent HD is associated with the deterioration of vascular access and increases in pain levels that relate to frequent punctures

The FHN trials showed that the incidence of failure of vascular access was higher among patients undergoing frequent HD (171,188,190). However, this could mean that abnormalities are being detected earlier, because regular vascular access is accompanied by frequent observations. In addition, self-puncturing techniques, such as the buttonhole puncture method and instruments that facilitate these, have become available. These techniques facilitate home HD and are expected to alleviate the pain associated with punctures.

3) The greater use of dialysis-related materials increases the amount of medical waste generated

Frequent HD is currently performed using the same types of dialyzers, blood circuits, and dialysate supply systems as those used for conventional HD. The increased use of these dialysis-related materials cannot be avoided when patients undergo frequent HD. Systems specifically designed for frequent HD should be developed in the future.

CHAPTER 6 PEDIATRIC GUIDELINES ON MAINTENANCE HD PRESCRIPTIONS

Status and features of pediatric patients undergoing dialysis to be considered in the formulation of dialysis prescription guidelines

The number of pediatric patients regularly undergoing HD is much smaller than the number of adult patients regularly undergoing HD, because the number of pediatric patients with end-stage renal failure is small, children tend to undergo kidney transplantation relatively early and before progression to end-stage renal failure, and often, peritoneal dialysis is selected for infants and school children. Therefore, large-scale studies, such as the HEMO Study and RCTs that are conducted among adult patients cannot be implemented for pediatric patients. Hence, it is very difficult to formulate evidence-based guidelines for maintenance HD prescriptions for pediatric patients.

Furthermore, children's protein and water intakes are higher per unit BW than those of adults, and their BUN levels, blood phosphorus levels, and fluid removal cannot be appropriately controlled by a conventional HD regimen administered three times per week for 4 h. For children undergoing dialysis, the goals of treatment should allow the children to develop physical, psychomotor, and social skills in ways that are comparable with the development of the same skills in healthy children. To achieve these goals, severe dietary restrictions, multiple hospital visits over long periods, and painful therapies, including needle punctures, should be avoided as much as possible. Therefore, pediatric maintenance HD treatment has intrinsic issues. These issues include monitoring the patient's physical growth and nutritional status, difficulties associated with the selection of vascular access through either an arteriovenous fistula or a long-term indwelling catheter, and the challenges associated with the optimization of DW, which involves determining whether the increase in BW has resulted from a patient's growth or overhydration.

This chapter was prepared with reference to previously developed guidelines and recent original research papers. The information from these sources was adapted to provide guidance on diagnosis and treatment in ways that are suitable for Japan. This chapter recommends administering HD to pediatric patients, which has caused fewer complications thus far. Furthermore, given that HD is the most established method for minimizing future adverse impacts, it offers good prognoses. This chapter focuses on pediatric patients who weigh 20 kg or more and who can undergo dialysis using a standard HD machine that is available throughout Japan. However, most of the statements in this chapter are the authors' opinions, because only limited evidence is available on HD for pediatric patients. Therefore, readers are advised that they should completely understand the other chapters that focus on adult patients before they read this chapter.

1. HD Doses for Pediatric Patients and Their Effects

Statement

Pediatric patients should receive a minimum of the same delivered dialysis dose that is recommended for adult patients.

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Commentary

1) Small Solute and Dialysis Times

The protein intake per unit of BW for children is necessarily higher than that for adults; hence, solute removal is required. Moreover, the risk of complications should be minimized to ensure the children enjoy long lives. Therefore, on the basis of empirical data, it is recommended that HD should be administered at least three times per week for 4 h.

An analysis of the JRDR for adults shows that mortality tends to decrease as the delivered dialysis dose increases, and the analysis concluded that the target dialysis dose should be spKt/V of 1.4 per dialysis, which is based on the smaller body size of Japanese adult patients compared with their European and American counterparts (refer to Chapter 1). Whether this target value is appropriate for children remains unclear. However, we consider that the minimum adequate dose for children is spKt/V of 1.4 per dialysis, and we recommend that the delivered dialysis dose for each patient be determined considering the patient's body growth, nutritional status, and social activities. Hence, and as mentioned previously, it is recommended that pediatric patients are administered with HD, because this is the most established method, is associated with the fewest complications, and offers the best prognoses for children. However, given that uremia affects physical and psychomotor development in children, it is important to regularly check and evaluate the number of days a child spends in the hospital, the amount of growth attained, and their attendance in kindergarten or school. Appropriate dialysis prescriptions and adequate nutritional intakes are essential for the growth of pediatric HD patients.

For pediatric patients who are stable, the dialysis dose should be evaluated together with the PCR. It has been reported that patients who underwent nocturnal dialysis at hospitals three times per week for 8 h with their spKt/V increasing from 1.74 to 2.15 were energetic because restrictions on their dietary and water intakes had been removed, and that their left ventricular hypertrophy improved. In addition, the number of days that the pediatric patients and their caregivers were absent from school and work, respectively, reduced by 81% (191). If patients are thought to have been administered an insufficient dialysis dose or to have excessive fluid, dialysis should be performed three times or more per week and increasing the amount of time spent on dialysis should be considered. Benefits from frequent dialysis using a simple at-home HD system with children have also been reported (192).

A recent study has proposed normalization of the dialysis dose, which would be based on the amounts by which the level of Glomerular Filtration Rate decreases in relation to the BSA that is associated with metabolism, as opposed to the body fluid volume (Kt/V), because the production of uremic toxins is closely related to metabolism (37). Because children's metabolic rates tend to be higher than those of adults, pediatric patients are considered to require a higher dialysis dose than adult patients when the dialysis dose is based on Kt/V. It has been suggested that pediatric patients, particularly those aged <10 years, require dialysis for 6–8 h per session or at least four times per week to achieve a desired dialysis dose that is normalized to the BSA (193).

In the future, higher dialysis doses for pediatric patients will be attempted by administering more frequent or prolonged HD (194). When this occurs, the effects of the time restrictions imposed by dialysis treatments on the social and mental development of children and their relationships with family members must be thoroughly considered.

2) β2M

Kt/V is based on the level of urea, a substance with a low molecular weight, and it is a necessary, but not entirely adequate, parameter. Therefore, for adult patients, it is proposed that the dialysis dose is evaluated based on the level of β2M, a small protein in the blood (refer to Chapter 2).

For pediatric patients, the clearance of urea as well as middle molecular weight toxins and small proteins should be examined to determine the HD dose. However, only limited evidence exists to support the correlation between serum β2M levels and the prognoses of or complications among pediatric HD patients. Among healthy children, infants aged 5–6 days and 1 year show serum β2M levels that are 2- and 1.5-fold higher, respectively, than those of adults. Children aged approximately 8 years show serum β2M levels that are close to those of adults (195). However, much remains to be clarified regarding changes in β2M production, its distribution capacity, and its clearance in children during their growth periods. Therefore, it is difficult to determine specific target values that will provide the appropriate HD doses for pediatric patients.

2. Appropriate Control of Body Fluids

Statement

The appropriate control of body fluids is important to improve QOL, achieve better prognoses in relation to cardiovascular diseases, and to improve long-term outcomes.

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Commentary

A report showed that 80% of pediatric patients with end-stage renal failure already had left ventricular hypertrophy when they began dialysis (196). The appropriate control of body fluids is important to improve QOL, to achieve better prognoses associated with cardiovascular diseases, and to improve the long-term prognoses of dialysis patients. However, appropriately evaluating and controlling BW in pediatric patients are difficult, because compared with adult patients, they have larger amounts of body fluid and require higher energy inputs per unit BW; hence, they show higher rates of BW increases during the interdialysis periods. Thus, greater care should be taken when treating pediatric HD patients compared with adult patients.

1) Evaluation of Body Fluid Volume

Methods for evaluating DW include pre- and postdialysis blood pressure measurements, measurements of the cardiothoracic ratio, echo-based measurements of the inferior vena cava diameter, bioimpedance-based measurements of body composition, and measurements of various hormone levels, including postdialysis atrial natriuretic peptide levels. The age and body size of pediatric patients must be considered in the DW evaluation, because blood pressures, cardiothoracic ratios, and the water content of children's bodies differ according to their age. For example, the body water content is approximately 75% of the BW at birth, 60% of the BW in 1-year-old infants, and 60% and 50% of the BW of male and female adolescents, respectively, which is almost equivalent to the water content of adults' bodies (197). Pediatric hypertension is defined as blood pressure in the 95th percentile or greater after correction for age, height, and BW. When diagnosing pediatric hypertension, the criteria stated in the Hypertension Treatment Guidelines 2009 provided by the Japanese Society of Hypertension should be referenced (198). Although blood pressure measurements taken during the latter half of dialysis sessions and after dialysis can be used to evaluate DW, blood pressure measurements alone may be insufficient to accurately evaluate DW, because some pediatric patients will not complain about the unpleasant symptoms they are experiencing, and their blood pressures may decrease because of the excessive amount of fluid being removed each hour, despite obtaining the appropriate DW.

2) Control of Body Fluid Volume

The BW gain by pediatric patients during the interdialysis period is inevitably larger than that of adult patients, because pediatric patients require higher energy levels and water intake per unit of BW. To safely maintain the appropriate body fluid volume and BW, various actions should be taken, including adjusting the fluid removal rate and the sodium level in the dialysate, evaluating changes in the blood volume during dialysis using a hematocrit measurement system, for example, Crit-Line, and increasing the time and frequency of dialysis (199–201). Because fluid removal may be difficult to perform on pediatric dialysis patients during 4-h sessions undertaken three times per week during their growth periods, the dialysis schedule should contain some flexibility, it should not require strict adherence to the regimen described previously, and it should enable the body fluid volume to be adjusted, as necessary. Note that school activities play major roles in the healthy physical and mental development of children; hence, caregivers at dialysis facilities should consider nocturnal dialysis schedules and should consult with the patients, their family members, and school staff to enable patients to participate fully in school and social activities without encountering problems.

3. Appropriate Dialysis Dose and the Evaluation of Treatment Effect

Statements

1. The dialysis dose should be appropriately evaluated to account for the extent of growth and the nutritional status of children.
2. The dialysis dose should be evaluated together with the PCR.
3. Factors that affect the social activities of children should be regularly evaluated, including their hospitalization frequency, growth extent, nutritional status, and attendance at kindergarten or school.
4. DW should be evaluated at least once a month.

Commentary

Children are expected to grow, but malnutrition caused by uremia may impair their growth. Therefore, growth, including changes in BW, should be closely monitored and considered in the treatment of children. It has been reported that mortality is high among pediatric patients who are short in stature and have low BMIs (202). Evaluating both the adequacy of children's dialysis dose and their nutrient intake is important not only for their normal growth but also to assure favorable prognoses. Under stable conditions, the normalized PCR (nPCR), which indicates

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the PCR per postdialysis BW, is considered almost equal to protein intake (202). A study has shown that the nPCR does not always correlate with an increase in the dialysis dose (203). The evaluation of the nPCR with the dialysis dose is recommended, because the nPCR reflects the malnutrition status more sensitively than the serum albumin level (204). The BWs and BMIs were higher among pediatric HD patients with nPCRs ≥1 g/kg/day than among those with lower nPCRs (205,206).

Uremia also affects physical and psychomotor development. Growth impairment that is observed before the start of dialysis is considered difficult to improve by HD alone (207). The dialysis dose, as well as the extent of growth, hospitalization frequency, and attendance at kindergarten or school, should be checked regularly, and if decreases in the extent of growth or in the frequency of participation in social activities are found, the reasons for them should be identified. The degree of growth of pediatric HD patients is examined regularly by measuring their height and BW, plotting the data onto the growth curve of healthy Japanese children, and evaluating temporal changes in the standard deviation scores with respect to standard height and annual growth rates. For pediatric patients aged 10 years or older, attention should be paid to the development of secondary sex characteristics, in addition to their height and BW.

CHAPTER 7 SAMPLING METHODS OF BLOOD AND DIALYSATE

1. Evaluation of Dialysis Dose

Indices of dialysis dose, solute removal, and the sampling methods of blood and dialysate are mentioned below.

A. Indices

(1) Kt/V_{urea}

Kt/V_{urea} is an index of the degree to which urea is removed in one dialysis session (i.e. dialysis dose). Although various definitive equations of Kt/V_{urea} have been proposed as described below, no absolute equation has been selected. It is important to use one of these appropriate equations consistently for each patient.

1) Gotch and Sargent's equation (Kt/V_{urea}) (9)

This model assumes the one-compartment model with no effect of fluid removal and urea production.

$$Kt/V = \ln(BUN_{pre}/BUN_{post}) \quad (1)$$

where BUN_{pre} and BUN_{post} are the predialysis and postdialysis BUN concentrations, respectively.

2) Shinzato et al.'s equation (208)

This model assumes the one-compartment model with no effect of fluid removal. Theoretical representation of this model may be found at the following URL: http://optimal-dialysis.jp/download.html

3) Daugirdas' equation

Single-pool Kt/V_{urea} (spKt/V) (209)

Daugirdas proposed several definitive equations of Kt/V_{urea}. The following model assumes the one-compartment model with consideration of the effect of fluid removal and urea production.

$$spKt/V = -\ln(R - 0.008t) + (4 - 3.5R) \times \frac{\Delta V}{BW_{post}} \quad (2)$$

where R is the ratio of the postdialysis BUN to the predialysis BUN concentration (= BUN_{post}/BUN_{pre}), t is the dialysis duration (h), ΔV is the fluid removal per HD session (L), and BW_{post} is the postdialysis BW of the patient (kg).

Equilibrated Kt/V_{urea} (eKt/V) (10,11)

This equation is based on the so-called regional blood flow model.

$$eKt/V = spKt/V - 0.6\frac{spKt/V}{t} + 0.03 \quad (3)$$

(2) Reduction rate (RR)

Definition: RR is an index of the solute clearance and is calculated using the predialysis and postdialysis blood solute concentrations (C_{pre} and C_{post}, respectively) as follows.

$$RR = 1 - \frac{C_{post}}{C_{pre}} \quad (4)$$

Usually, the obtained value is multiplied by 100 to be expressed in percentage.

For solutes of large molecular weight, the RR should be corrected by considering the effect of blood condensation caused by fluid removal (210).

$$\begin{aligned} RR &= 1 - \frac{V_{Ppost}C_{post}}{V_{Ppre}C_{pre}} = 1 - \frac{V_{Bpost}(1 - H_{post})C_{post}}{V_{Bpre}(1 - H_{pre})C_{pre}} \\ &= 1 - \frac{H_{pre}(1 - H_{post})C_{post}}{H_{post}(1 - H_{pre})C_{pre}} \end{aligned} \quad (5)$$

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where H_{pre} and H_{post} are the predialysis and postdialysis hematocrit values.

(3) Solute removal (M)

Estimated from the amount of solute in the dialysate discharged from the dialyzer, which is entirely or partially stored. M is considered to be an absolute index of cleared solute but does not include the amount of solute trapped by the membrane. M basically depends on the predialysis solute level (C_{pre}). The higher the C_{pre}, the higher the M when the dialysis prescription (therapeutic conditions) is fixed.

(4) Clear space (CS) and CS rate (CSR)

Definition: CS indicates the normalized amount of removed solute and is given as follows.

$$CS = M/C_{pre} \tag{6}$$

The effect of C_{pre} is eliminated. CS is given in the unit of volume (space), depends on the distribution space of the solute of interest in patients (V), and corresponds to the distribution space for solute removed in one dialysis session. CSR, expressed as CS/V, is used to compare the CS values among patients.

B. Sampling Methods

(1) Predialysis and postdialysis blood sampling

To determine predialysis concentration, the patient's blood should be sampled at the time of puncture of dialysis access before being connected to the blood circuit, in order to avoid the effects of dilution.

To determine postdialysis concentration, the patient's blood should be sampled by the slow flow method (211) to minimize the effects of access recirculation and urea rebound. Specifically, the dialysate flow is stopped immediately after the dialysis session (practical end of dialysis) and the blood flow rate is reduced to 50–100 mL/min. After 1 to 2 min, the patient's blood is sampled from the port close to the patient on the A-side line.

(2) Sampling of spent dialysate

Refer to the following measurement procedure to obtain an accurate value.

1) Storing entire dialysate
2) Storing entire dialysate every 1 h
3) Storing a part of dialysate (syringe extraction method, fluid removal line storage method)

2. Performance Evaluation of Hemodialyzers and Hemodiafilters

Indices for performance evaluation of hemodialyzers and hemodiafilters (dialyzers/diafilters), and the sampling procedure for determining these indices are in accordance with the Methods of Evaluating Performance of Blood Purification Devices 2012 (212) as explained below.

A. Indices of Performance

(1) Clearance (CL)

CL is an index of the solute removal for dialyzers/diafilters and is defined as follows.

$$CL = \frac{Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo}}{C_{Bi}} \tag{7}$$

where Q is the flow rate, C is the concentration of solute, and the subscripts B, i, and o indicate the blood, inlet, and outlet, respectively.

For solutes of small molecular weight, such as urea and creatinine, the flow rate of whole blood is substituted into Q_{Bi} in Equation 7. For solutes of medium molecular weight, such as β2M, the flow rate of plasma is substituted into Q_{Bi}. The plasma concentrations obtained from clinical observations are substituted into C_{Bi} and C_{Bo}. For solutes of large molecular weight, such as α1-microglobulin and albumin, CL-based evaluation is difficult because of their large decrease with time.

(2) UFR

UFR is an index of water permeability of dialyzers/diafilters and is defined as follows.

$$UFR = \frac{V_F}{T_F \cdot TMP} \tag{8}$$

where T_F is the filtration time (h), V_F is the amount of filtrate stored for T_F (mL), and TMP is the transmembrane pressure (mm Hg). TMP is generally calculated using Equation 9.

$$TMP = (P_B - P_D)_{av} - \pi_P = \frac{P_{Bi} + P_{Bo}}{2} - \frac{P_{Di} + P_{Do}}{2} - \pi_P \tag{9}$$

where P is the pressure (mm Hg) and π_P is the colloidal osmotic pressure.

B. Measurement Technique

(1) CL

- Dialysis conditions, including flow rate, should be in accordance with the

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Methods of Evaluating Performance of Blood Purification Devices 2012 (212) provided by the JSDT.
- CL should be evaluated 60 min after the start of the dialysis session. If CL is expected to vary by more than 20% over 240 min, measurement of CL 240 min after the start of dialysis treatment is recommended.
- Dialysate outlet (C_{Do}), blood outlet (C_{Bo}), and inlet (C_{Bi}) should be sampled in this order with great care so as not to affect the flow of dialysate or blood.
- Flow rates of blood (Q_B) and dialysate (Q_D) should be measured beforehand. Use of the actual blood flow rate is recommended to evaluate Q_B during dialysis.

(2) UFR
- Dialysis conditions, including flow rate, should be in accordance with the Methods of Evaluating Performance of Blood Purification Devices 2012 (212) provided by the JSDT.
- UFR should be measured in the mode of ECUM after the treatment.

Conflict of interest: The JSDT has been making the best effort to avoid any actual and potential conflicts of interest for there to be a neutral and fair process of guideline development. In 2010, the JSDT developed a new system for working group members to declare any potential conflicts of interest. All members of JSDT guideline development groups are now required to provide signed declaration forms to state any actual or potential conflicts of interest. These forms are updated yearly, or sooner if an individual member's status changes. Further information is available at: http://www.jsdt.or.jp/jsdt/1236.html (Japanese).

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APPENDIX I

Members of the guideline working group

Yuzo Watanabe, chairman of the working group of "Maintenance Hemodialysis," Kasugai City Hospital, Aichi

Hideki Kawanishi, chairman of the working group of "Maintenance Hemodialysis: Hemodialysis Prescriptions" Tsuchiya General Hospital, Hiroshima

Kazuyuki Suzuki, Kawasemi Clinic, Miyagi

Shigeru Nakai, Fujita Health University, Aichi

Kenji Tsuchida, Kawashima Hospital, Tokushima

Kaoru Tabei, Saitama Medical Center Jichi Medical University, Saitama

Takashi Akiba, Tokyo Women's Medical University, Tokyo

Ikuto Masakane, chairman of the subcommittee of guideline development, Yabuki Hospital, Yamagata

Yoshiaki Takemoto, Osaka City University Hospital, Osaka

Tadashi Tomo, chairman of the academic committee, Oita University Hospital, Oita

Noritomo Itami, Nikko Memorial Hospital, Hokkaido

Yasuhiro Komatsu, St Luke's International Hospital, Tokyo

Motoshi Hattori, Tokyo Women's Medical University, Tokyo

Michio Mineshima, Tokyo Women's Medical University, Tokyo

Akihiro Yamashita, Hosei University, Tokyo

Akira Saito, Shonan East General Hospital, Kanagawa

Hidemune Naito, Naito Medical Research Center, Hyogo

Hideki Hirakata, past chairman of the academic committee, Fukuoka Red Cross Hospital, Fukuoka

Jun Minakuchi, past president of the JSDT, Kawashima Hospital, Tokushima

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