Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 2015; 19(Supplement 1):93–107
doi: 10.1111/1744-9987.12293

Guideline

Japanese Society for Dialysis Therapy Clinical Guideline for "Hemodialysis Initiation for Maintenance Hemodialysis"

Yuzo Watanabe, Kunihiro Yamagata, Shinichi Nishi, Hideki Hirakata, Norio Hanafusa, Chie Saito, Motoshi Hattori, Noritomo Itami, Yasuhiro Komatsu, Yoshindo Kawaguchi, Kazuhiko Tsuruya, Yoshiharu Tsubakihara, Kazuyuki Suzuki, Ken Sakai, Hideki Kawanishi, Daijo Inaguma, Hiroyasu Yamamoto, Yoshiaki Takemoto, Noriko Mori, Kazuyoshi Okada, Hiroshi Hataya, Takashi Akiba, Kunitoshi Iseki, Tadashi Tomo, Ikuto Masakane, Tadao Akizawa, and Jun Minakuchi, for "Hemodialysis Initiation for Maintenance Hemodialysis" Guideline Working Group, Japanese Society for Dialysis Therapy

Japanese Society for Dialysis Therapy, Tokyo, Japan

THE PREPARATION OF GUIDELINES FOR HEMODIALYSIS INITIATION

In Japan, guidelines for initiation of chronic hemodialysis (Health Science Research Guidelines (1)), prepared by the Committee of Medical Research Project for Kidney Failure set up by the Japanese Ministry of Welfare in 1991, have been used as a criteria for initiation of dialysis for more than 20 years. Though this guideline is still utilized in the clinical field, the current characteristics of dialysis patients have largely changed compared to those days. Currently, the mean age of dialysis patients is more than 65 years, and patients with systemic vascular complications derived by diabetic nephropathy or nephrosclerosis account for more than 50% of dialysis patients (2). Furthermore, the concept of chronic kidney disease (CKD) has attracted attention worldwide, and there are advances in the standardization of various tests and assessment methods for kidney function. According to these circumstances, new guidelines for hemodialysis initiation have come forth from several other countries.

As clinical evidence pertaining to hemodialysis initiation for chronic renal failure has been compiled, there is an increasing demand to reassess these guidelines for dialysis initiation in Japan. On account of this increasing demand, the Japanese Society for Dialysis Therapy (JSDT) has prepared these guidelines with the cooperation of academic societies affiliated with JSDT.

SUBJECTS OF GUIDELINES FOR HEMODIALYSIS INITIATION

Patients subjected to this guideline are those who will be starting chronic hemodialysis as renal replacement therapy. Hemodialysis is a mainstream treatment in Japan, and approximately 95% of patients suffering from terminal renal failure are treated with hemodialysis. Criteria for patients showing acute kidney injury (AKI) including acute exacerbation of chronic renal failure might be applied to the guidelines for AKI (3).

In recent years, the number of patients with chronic kidney disease (CKD) has been growing worldwide. There has been a marked increase in patients whose CKD has progressed to terminal chronic renal failure and consequently require renal replacement therapy (4). For this reason, global

Address correspondence and reprint requests to Dr Yuzo Watanabe, Director, Kasugai Municipal Hospital, 1-1-1 Takagi, Kasugai City 486-8510, Japan. Email: yuzo@hospital.kasugai.aichi.jp
Published in J Jpn Soc Dial Ther 2013; 46: 1107–1155 (in Japanese)
Reprinted with permission from the *Journal of the Japanese Society for Dialysis Therapy*

preventive measures against CKD have been taken proactively by promoting awareness, early detection, and early state of treatment for CKD in order to prevent disease progression (5). The Japanese Society of Nephrology created an eGFR equation on the basis of serum creatinine, age, and gender in order to estimate glomerular filtration rate (GFR) (6). This equation can only be applied to patients over 18 years of age; hence, cases under 18 years of age have been excluded in a survey on hemodialysis initiation conducted by JSDT (7,8). Therefore, guidelines for pediatric patients are described in a separate chapter in detail. As for patients treated with peritoneal dialysis (PD), we recommend to follow the "JSDT Guideline for Peritoneal Dialysis" (9) in 2009. The patients who need restarting of hemodialysis by functional graft loss after kidney transplantation frequently suffer from patients' psychological issues, side effects associated with immunosuppressive drugs, and so on; therefore, these patients are also excluded from this guidelines (10). Discussion for preemptive kidney transplantation are now going on among Japan Society for Transplantation, Japanese Society for Clinical Renal Transplantation, and Japanese Society for Pediatric Nephrology; thus, these patients are also excluded from this guidelines. Guidelines for initiation of renal replacement therapy encompassing AKI, PD, and renal transplantation need to be clearly laid out in future because the treatment procedures described above are all for replacement therapy for renal disease irrespective of terminal stage or not.

GRADING EVIDENCE AND RECOMMENDATIONS

The grades of evidence levels and recommendations for clinical practice in these guidelines were determined according to those established by JSDT Assessment Committee on Evidence Levels (11), which were prepared on the basis of the position paper titled "Grading Evidence and Recommendations for Clinical Practice Guidelines in Nephrology" (12). This paper was published in 2006 by KDIGO and it is commonly used around the world for clinical guidelines for renal diseases. Grades for evidence levels are categorized as follows: (A) High, (B) Moderate, (C) Low, and (D) Very Low. It was unanimously decided that the data sampled by Japanese patients would be evaluated by raising the grade by one rank. Recommendations were evaluated on a scale of 1–2 as (1) Strongly Recommended and (2) Moderately Recommended.

CHAPTER 1. METHODS OF RENAL FUNCTION ASSESSMENT AT HEMODIALYSIS INITIATION

Statements

1. Renal function should not be assessed using only serum creatinine levels, but should also be assessed using a predictive equation on the basis of serum creatinine values (1A). The time of hemodialysis initiation should be determined by comprehensively assessing the levels of serum creatinine, changes in GFR with time, and the physical constitution, age, gender, and nutritional condition of the patient (1C).
2. The precise evaluation of renal function at the time of hemodialysis initiation is determined by a measuring method such as inulin clearance test, creatinine clearance (Ccr) calculated by 24-h collected urine specimen, or the sum of clearance values of creatinine and urea divided by 2: (Ccr + Curea)/2 (1C).

In this paper, eGFR, mGFR, and GFR are used to represent an estimated GFR (eGFR) using a predictive equation, a measured GFR (mGFR) using collected urine specimen or under the load of some special substance, and a GFR (GFR) indicating renal function in general sense.

Commentary

Assessment of renal function using serum creatinine levels alone

Serum creatinine levels can be affected by several factors such as increasing muscle mass after exercise, difference in gender, and nutritional conditions; therefore, estimation of renal function by serum creatinine levels alone is inadvisable (13). It has become evident that patients who can await hemodialysis initiation until serum creatinine values reach to a high level are likely to have a potency of secreting creatinine at a high level (14). Therefore, measured Ccr of those patients is contradictory high when compared to the values of eGFR determined by serum creatinine (15). Considering the above evidence, the decision to initiate hemodialysis should not be made solely based on serum creatinine levels. Moreover, the specific serum creatinine levels to decide initiation of hemodialysis cannot be determined at the present time.

Concerning GFR measurement method at the time of hemodialysis initiation

GFR is a basic parameter to assess renal function because it is provided by the volume of blood filtered through glomeruli per certain time.

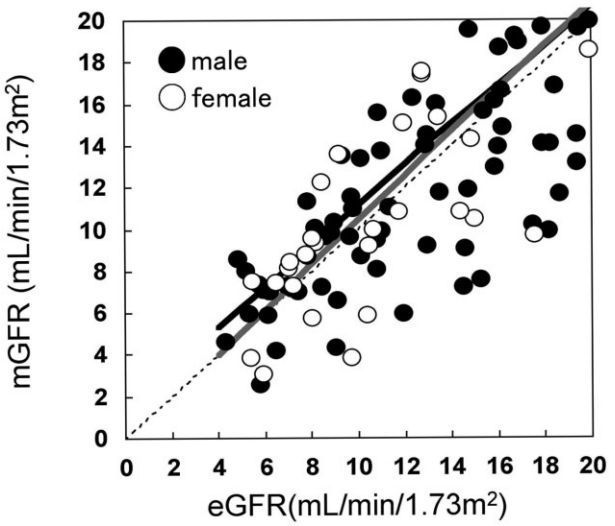

FIG. 1. The relationship between GFR (inulin clearance) and eGFR.

1. Inulin clearance: It is a gold standard for GFR measurement; however, the measurement procedure is troublesome, and it is not practical to conduct this test repeatedly when hemodialysis initiation is under consideration.
2. Ccr using 24-h urine collection: The conversion equation, GFR = 0.715 × Ccr (mL/min), is shown (6). But the index of this equation changes to 1.92 ± 0.08 at GFR < 40 mL/min/1.73 m^2 (6), and it is known that the gap between GFR and Ccr increases more as deterioration of renal function progresses further (14,16,17).
3. The average of Ccr and Curea: This is used to compensate for the limitations of Ccr measurement (18). This method, however, also overestimates GFR (19) because urea is secreted from the renal tubule when GFR < 8.0 mL/min/1.73 m^2.
4. GFR predictive equation devised by the Japanese Society of Nephrology [eGFR = 194 × creatinine value − 1.094 × age − 0.287 (×0.739 in the case of female patients)]: It is known as a simple and more precise method to calculate GFR in Japanese patients. This method can calculate eGFR in a patient with GFR < 15 mL/min/1.73 m^2, with approximately 30% accuracy of actually measured GFR using inulin clearance (20). However, as is clearly shown in Fig. 1, there are definite distinctions between eGFR and GFR values of individual cases. Furthermore, a GFR predictive equation based on serum cystatin C has been proposed (21). However, it is not appropriate as a renal function index at the time of hemodialysis initiation because it plateaus at 5–6 mg/L in patients with highly impaired renal function.
5. The Cockcroft-Gault Ccr predictive equation [Ccr = ({140 − age} × body weight {kg})/(72 × serum creatinine value {mg/dL})][3]: If serum creatinine test is performed using an enzyme method as practiced in Japan, the value of Ccr is overestimated compared to real GFR.

Moreover, another method that may be considered to assess the remaining renal function in PD is Kt/V urea nitrogen (UN) per week (22), but it is not commonly employed, where K: efficiency of a dialyzer in removing urea, t: period of dialysis, and V: body water volume. In addition to these methods, clearance of 99mTc-DTPA or dextran is utilized in some countries; however, they are not the prevailing methods in Japan.

Difference between mGFR and eGFR

When prognosis of chronic hemodialysis patients within 1 year after hemodialysis initiation was reviewed, mortality of patients who started hemodialysis with high levels of eGFR has been reported to be high (8,23–26), and the result is the same in Japan (7). However, it has been reported recently that, by using mGFR obtained from the average of Ccr and Curea as an index of GFR, starting hemodialysis with high values of mGFR does not necessarily reflect an unfavorable prognosis (27). A meta-analysis studying the prognosis of patients based on residual renal function at starting hemodialysis using 15 cohort studies revealed the following results: (i) life expectancy of patients who had been forced to initiate dialysis with high eGFR determined by equation method was not good; (ii) the prognosis of patients whose mGFR was high at hemodialysis initiation was not so bad (28). Thus, there is a discrepancy between eGFR and mGFR at the terminal stage of renal failure.

As stated above, precise assessment of renal function at the time of hemodialysis initiation should be made on the basis of GFR obtained from inulin clearance values and second selection might be the average of Ccr and Curea. But, it is not always possible to conduct these measurement methods in all cases at clinical practice. In such cases, confirmation of GFR < 15 mL/min/1.73 m^2 by eGFR values should be done, but the judgment from serum creatinine levels alone should not be done. Then, the timing of the initiation should be comprehensively assessed on the basis of chronological changes in levels of serum creatinine and eGFR over time, body weight, urine volume, uremic symptoms, and other factors.

CHAPTER 2. LENGTH OF MEDICAL CARE BY NEPHROLOGIST PRIOR TO HEMODIALYSIS INITIATION

Statements

3. When progressive renal dysfunction is observed and GFR is at levels of 15–30 mL/min/1.73 m^2, it is recommended to give the patient a detailed explanation pertaining to treatment of terminal renal failure, including conservative medical treatment and information regarding renal replacement therapy (RRT) (1D).
4. From a prognostic perspective, it is desirable to provide medical treatment for a period of more than 6 months before hemodialysis initiation in order to prevent an appearance of symptoms associated with renal failure (2C).

Commentary

In the event that terminal renal failure is anticipated in the near future, the following is recommended: 1) A satisfactory explanation regarding renal RRT should be provided to the patient and his/her family, and their consent should be obtained for the same; and 2) an opportunity should be provided to the patient to make his/her selection to receive optimum RRT. Prospective study evaluating the timing for starting explanation of RRT has not been studied at present. However, it is considered appropriate to start explanation when renal function deteriorates to the levels around 30 L/min/1.73 m^2 by eGFR (29). It is further recommended to provide thorough medical management and lifestyle guidance/dietary instructions or educational intervention to prevent further progression of renal failure; efforts must be made to delay hemodialysis initiation as much as possible. Furthermore, it is necessary to consider the timing and context of explanation of RRT evaluating with not only laboratory data but also the following conditions: the patient's original disease, social background such as age and personality of the patient, and the rate of deterioration of renal function.

It is recommended that the patient will be referred to a nephrologist when GFR reaches less than 50 mL/min/1.73 m^2 from the aspect of preventing CKD progression as well as educational intervention, and consequently he/she will be treated in collaboration with a nephrologist. However, for patients under 40 years of age, a referral to a specialist should be considered sooner, when a GFR < 60 mL/min/1.73 m^2 is reached; for those 70 years of age and over, a GFR < 40 mL/min/1.73 m^2 may be acceptable for specialist referral (30).

Educational intervention in a chronic renal failure patient and his/her family during the conservative period helps delay hemodialysis initiation and improve life prognosis of the patient after initiation (31,32). Outside Japan, evidence shows that early referral (ER) rather than late referral (LR) to a nephrologist can provide better blood pressure and anemia management, which suppresses the onset and progression of renal failure, and leads to a better life prognosis after hemodialysis initiation (1,33–47). However, the definition of ER varies from 1 month to 1 year prior to the initiation from literature. Moreover, ER can shorten the duration of hospital stay at the time of initiation and have beneficial effects on the quality of life (QOL) and mental health after hemodialysis initiation (48–50). Meanwhile, a study conducted with patients who were older than 67 years of age reported that the difference of medical care duration by nephrologist at pre-dialysis stage by 3 months less or more did not affect the life expectancy after hemodialysis initiation (51). Because comorbid complications frequently found in elderly patients might have a great effect on prognosis, further investigations are needed.

Studies in Japan have shown that patients who received a specialist's medical care for 6 months or more at pre-dialysis stage had a significantly higher survival rate after dialysis initiation compared to less than 6 months (52). A survey conducted by JSDT on patients who started dialysis also revealed that nephrologists' care for 6 months or more at pre-dialysis stage showed significantly higher survival rates at the time point of 1 year after dialysis initiation than the patients who had a referral to a specialist only 1 month before dialysis. The hazard risk of death was 0.568-fold in the cases with a care period of 6–12 months, and was 0.666-fold with a care period of 12–24 months (40), showing significantly improved survival rates (7).

Patients with impaired renal function should be examined by a nephrologist in collaboration with a primary care physician, in accordance with the CKD guidelines (29), because it is not realistic for specialists to provide all patients with such medical care. According to this concept and a study conducted by JSDT mentioned above, the statement in this guideline is presented as follows: "Patients with impaired renal function are desirable to be treated and followed up with collaboration of nephrologist for over 6 months prior to initiation of hemodialysis to prevent the manifestation of renal failure symptoms."

CHAPTER 3. PREPARATION FOR DIALYSIS INITIATION

Statement

5. It is recommended that arteriovenous fistula (AVF) and arteriovenous graft (AVG) be created at least 1 month prior to the initiation from the viewpoint of life prognosis after hemodialysis initiation (2C).

Commentary

To create vascular access (VA) smoothly, appropriate selection of VA type individually according to patient's condition, preservation of unilateral side forearm vein planning to make VA, and assessment for proper cardiac function tolerable after AVF and/or AVG formation are necessary. In the "Guidelines Pertaining to Creating and Repairing Vascular Access for Chronic Hemodialysis" (53) published by JSDT in 2011, it is recommended that the timing for creation of VA depends on residual renal function as eGFR ≤ 15 mL/min/1.73 m^2 considering the appearance of symptoms related with renal failure. Furthermore, it is stated in these guidelines that AVF and AVG should be created at least 2–4 weeks and 3–4 weeks, respectively, prior to the first dialysis puncture. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend making VA 6 months or at least a few months prior to the initiation of dialysis (54). It has been reported that, compared to LR, ER allows for the efficient creation of VA by enabling proper planning of dialysis initiation, improving the prognosis after hemodialysis initiation (55,56), and accordingly reducing healthcare expenses (57). However, one study reported that the introduction to hemodialysis by intravenous double lumen catheter showed a slight prolongation of life expectancy after hemodialysis initiation compared to the creation of VA at the timing of CKD stage 4, and it suggested that making VA too early is not recommendable (58).

A statistical survey conducted by JSDT showed that permanent VA had been created 0.7 ± 3.8 months prior to dialysis initiation in cases where death occurred within 1 year after the initiation, whereas it had been created 2.0 ± 6.6 months prior to the initiation in cases that survived (7). An earlier creation of VA significantly improved the death risk in cases where VA had been created 1–3 months prior to initiation of dialysis as compared with those that had been created 1 month prior to the initiation including on the initiation day. The death risk, within a year, for patients whose VA was created 1 month prior to initiation was 0.539; it was 0.365 in cases where VA had been created 3–6 months prior to the initiation (59). Consequently, it is recommended that VA be created at least 1 month prior to dialysis initiation from the viewpoint of the patient's survival on long-term hemodialysis treatment.

The specific time to create VA should be determined individually depending upon factors such as patient's age, original renal diseases, rate of deterioration of renal function, presence or absence of cardiovascular complications, and the patency of autologous vein. It has been reported that, even in an ER group, there were no significant differences in hospitalization rate, frequency of blood transfusion, and prognosis after hemodialysis initiation compared with those of an LR group, in the clinical setting that VA had not been created prior to hemodialysis initiation (60). On the contrary, the patients who participated in educational programs at the pre-dialysis stage and received a briefing about RRT were likely to have VA in high rate at start of hemodialysis, and the life expectancy within 90 days of hemodialysis initiation was good (61). Based on these findings, establishment of educational system wherein patients can thoroughly understand and accept dialysis initiation is necessary, and making a strong relationship with doctors who can create VA is important to create VA at an appropriate time.

CHAPTER 4. TIMING OF HEMODIALYSIS INITIATION

Statements

6. The judgment on the time to initiate hemodialysis is allowed when a residual renal function shows progressive deterioration and reaction to GFR < 15 mL/min/1.73 m^2 in spite of sufficient optimal conservative treatment (1D). However, the decision of starting hemodialysis should be determined based on a comprehensive assessment of renal failure symptoms, daily life activities, and nutritional status, which are not relievable without hemodialysis treatment (1D).
7. Life prognosis after initiation of hemodialysis can be favorable as long as patients can endure under conservative treatment until the GFR < 8 mL/min/1.73 m^2, even when the symptoms of renal failure are observed. However, from the viewpoint of life prognosis, it is recommended that hemodialysis should be initiated prior to a GFR of 2 mL/min/1.73 m^2, even if there are no symptoms of renal failure (2C).

Commentary

Timing of hemodialysis initiation

The renal function of patients at the time of dialysis initiation in Japan was reported as a mean eGFR of 5.00 mL/min/1.73 m^2 between 1989 and 1990 (62), and it increased to 6.52 mL/min/1.73 m^2 in 2007; however, the proportion of patients who accounted for an eGFR > 10 mL/min/1.73 m^2 was only 10.6% (7,63–67). In contrast, a relatively earlier starting hemodialysis using eGFR as the renal function index is a recent trend found in the United States (68), Europe (69), and Canada (70). The guidelines for hemodialysis initiation were settled in these countries individually; most of those recommend starting hemodialysis at 10–20 mL/min/1.73 m^2 using the eGFR value as a standard (71–74).

Symptoms of renal failure and daily life activities

Symptoms of renal failure included are listed. When these symptoms become difficult to control with conventional therapy, initiation of hemodialysis must be considered, keeping in mind comprehensive considerations including renal function. According to the registry data of JSDT in 1989, the most frequent symptoms of renal failure at the time of initiation were digestive symptoms (30.8%) and heart failure and/or pulmonary edema (21.1%) (75). The relationship between patients' survival and the symptom that was the main cause of hemodialysis initiation was studied among those who were registered in 2004 as incident patients. It indicated that disturbance of consciousness, refractory edema (pleural effusion, ascites, and pericardial fluid), cardiac failure, pulmonary edema, and peripheral neuropathy showed a high hazard ratio of mortality, suggesting that these symptoms are key factors for deciding dialysis initiation. Visual impairment is another critical symptom to decide hemodialysis initiation. Prevalence of blindness has shown a trend toward improvement with recent advances in ophthalmologic treatment; however, the progression of rapid visual impairment as a part of uremic retinopathy is also a key condition to decide for hemodialysis initiation. Decreases in daily life activities should also be considered as determining conditions for dialysis initiation.

Nutritional status

Malnutrition and/or nutritional impairment is an indicator for considering initiation of hemodialysis. It is recommended that nutritional assessment is done utilizing subjective global assessment (SGA) and lean body mass, serum albumin level, and protein catabolic rate (PCR) comprehensively (47,71–74,76). But, to decide specific indices or values for deciding a criterion for hemodialysis initiation, further investigations are necessary (77).

Timing of hemodialysis initiation in terms of renal function

Past reports recommending early hemodialysis initiation and its issues. It has been pointed out that early initiation of dialysis may prolong survival, prevent complications due to uremia, and, thus, improve QOL (18,78–83). With this background, in the K/DOQI guidelines (1997 edition), eGFR below 10 mL/min/1.73 m^2 was suggested to be a dialysis initiation criterion (84), which was raised to 15 mL/min/1.73 m^2 in the 2006 edition (71). Despite that the benefit of early hemodialysis initiation still remains under controversy (85), the number of patients starting hemodialysis with eGFR ≥ 10 mL/min/1.73 m^2 is increasing every year in the United States (24,68). However, complications related with long-term hemodialysis might be likely to occur even with early initiation. Furthermore, a change into a constrained lifestyle as well as an increase in medical care expenses are inevitable from early initiation of dialysis. Patients who need hemodialysis with high eGFR levels are prone to have more severe complications, and this is the reason why they are inevitable from early hemodialysis initiation (25,70,86–88). Poor life prognosis of those who started hemodialysis with high eGFR levels was reported even in nondiabetic nephropathy patients without any complications except hypertension (26).

Observational studies suggesting linkage between early initiation of hemodialysis and poor prognosis. As a result of the above-mentioned reports, many recent observational studies have reported that early dialysis initiation at a high GFR stage may result in poor life prognosis (23,89–93). More recently, two meta-analyses supporting these data have been published. A meta-analysis of 15 observational studies conducted by Susantitaphong et al. indicated that with every increase in eGFR of 1 mL/min/1.73 m^2 at the time of initiation, hazard ratio (HR) was 1.037 [95% confidence interval (CI) 1.030–1.045, $P < 0.001$], and high mortality was significantly correlated with an increase in eGFR (94). Another meta-analysis of 10 observational studies including the IDEAL study (discussed later) showed that the odds ratio of early initiation versus all deaths was 1.33 (1.18–1.49) (95). Regarding the amount of urine volume, a sub-analysis of the CHOICE study done in

the United States revealed a correlation between residual urine volume 1 year after dialysis initiation and a good prognosis (96).

Intervention trial with early/late initiation of dialysis as an intervention point. Multicenter randomized controlled trials (RCTs) named as IDEAL study were conducted in Australia and New Zealand to examine dialysis initiation timing on the basis of eGFR (97). A total of 628 patients at CKD stage 5 participated in this study and were divided into two groups: an early initiation group, in which the hemodialysis was started with an eGFR at 10–14 mL/min/1.73 m^2; and a late initiation group, in which the dialysis was started with an eGFR at 5–7 mL/min/1.73 m^2. This study was performed with a median of 3.6 years of follow-up. There are issues to be considered when it comes to its actual application: limitations that hemodialysis was started in 80% of the patients in the late initiation group before reaching eGFR of 7 mL/min/1.73 m^2. However, there was no significant difference between the two groups pertaining to any end point including patients' mortality (97). Sub-analysis also revealed that medical costs were higher in the early initiation group, and prognosis adjusted with QOL was not significantly different (98). Thus, the IDEAL study data show that hemodialysis can be delayed until eGFR reaches 7 mL/min/1.73 m^2 if symptoms are not observed.

Importance of aggressive conservative treatment at pre-dialysis CKD stage. It is suggested that dialysis initiation can be postponed well by providing optimal pre-dialysis conservative treatment. One study reported from Italy demonstrated that 23 out of 30 nondiabetic CKD stage 5 patients whose eGFR had reached 11 mL/min/1.73 m^2 maintain their life without hemodialysis for approximately 1 year with eGFR around 6 mL/min/1.73 m^2, though seven patients needed hemodialysis initiation (99). In another study, two groups were compared: one group in which 56 elderly nondiabetic CKD patients with eGFR of 5–7 mL/min/1.73 m^2 were immediately initiated on hemodialysis, and the other group in which again 56 patients were provided with a low-protein diet of 0.3 g protein/kg/day and observed without hemodialysis. The low-protein diet group was able to postpone dialysis by a median of 10.7 months (eGFR was 4.3 mL/min/1.73 m^2 at the time of dialysis initiation). There was no significant difference in life prognoses between the two groups; further, the group in which dialysis was immediately initiated had a higher hospitalization rate (HR 1.50, 95% CI: 1.11–2.01) (100). Although these two studies dealt with only nondiabetic patients, they demonstrated that hemodialysis initiation can be safely postponed by providing an appropriate conservative treatment at pre-dialysis stage.

Review on timing of dialysis initiation and prognosis studied in Japan. An annual report from JSDT indicated that the lower the eGFR value at the time of hemodialysis initiation, the better the life prognosis after the initiation (101), though effects of complications cannot be ruled out. Therefore, in a survey of patients for whom hemodialysis had been started in 2007, various concurrent diseases at the time of initiation were adjusted using the Charlson comorbidity index (CCI) (102) as a complication score, and life prognoses by eGFR were investigated. The data demonstrated that the mortality risk of patients' hemodialysis initiation with eGFR < 2 mL/min/1.73 m^2 was significantly higher than that of patients with eGFR of 4–6 mL/min/1.73 m^2 (7), while one-year prognosis after hemodialysis initiation adjusted with several confounders was almost the same when patients with eGFR levels of 2–8 mL/min/1.73 m^2 were divided into 4 classes by increments of 2 mL/min/1.73 m^2 (7). Therefore, from the viewpoint of post-dialysis initiation life prognosis, hemodialysis initiation should be postponed until GFR becomes less than 8 mL/min/

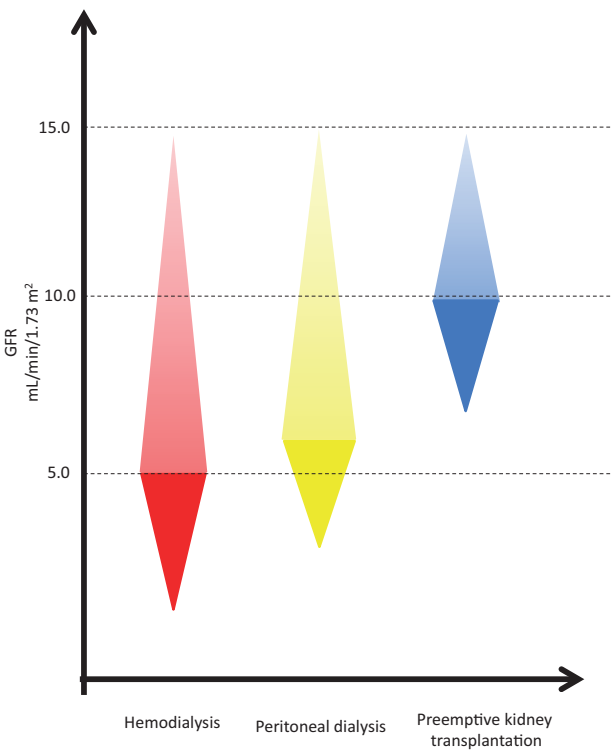

FIG. 2. Image of RRT initiation timing and residual renal function.

1.73 m^2 as long as the patient's condition permits, even if symptoms of renal failure are observed. Meanwhile, it is certain, at least in terms of residual renal function, that hemodialysis initiation with GFR < 2 mL/min/1.73 m^2 leads to a poor life prognosis. At the same time, similar poor life prognosis was found even when there was no manifestation of symptoms. According to annual reports from JSDT in 1989 and 1990, the mean eGFR of patients of incident patients without any symptoms was 4.74 mL/min/1.73 m^2, and a univariate analysis among these patients revealed that the mortality risk of patients who started hemodialysis with eGFR ≥ 6 mL/min/1.73 m^2 was higher compared to that with eGFR range of 4–6 mL/min/1.73 m^2. After adjustment with age, gender, and primary disease, patients who started hemodialysis with eGFR > 10 mL/min/1.73 m^2 again showed significantly high HR 2.05 (95% CI 1.17–3.58) than those who started with eGFR 4–6 mL/min/1.73 m^2 (8). Although there is no specific GFR level for patients without symptoms that can be recommended to initiate dialysis with certainty, it is recommended to initiate hemodialysis when GFR reaches 2 mL/min/1.73 m^2 even if there is no manifestation of symptoms using a measured GFR.

Comparison with other renal replacement treatments. Peritoneal dialysis requires initiation while there is still some residual renal function even without any manifestation of symptoms, and the recommended GFR level for starting peritoneal dialysis is approximately 6 mL/min/1.73 m^2. As for preemptive kidney transplantation, it necessitates surgical procedure under general anesthesia; therefore, it should

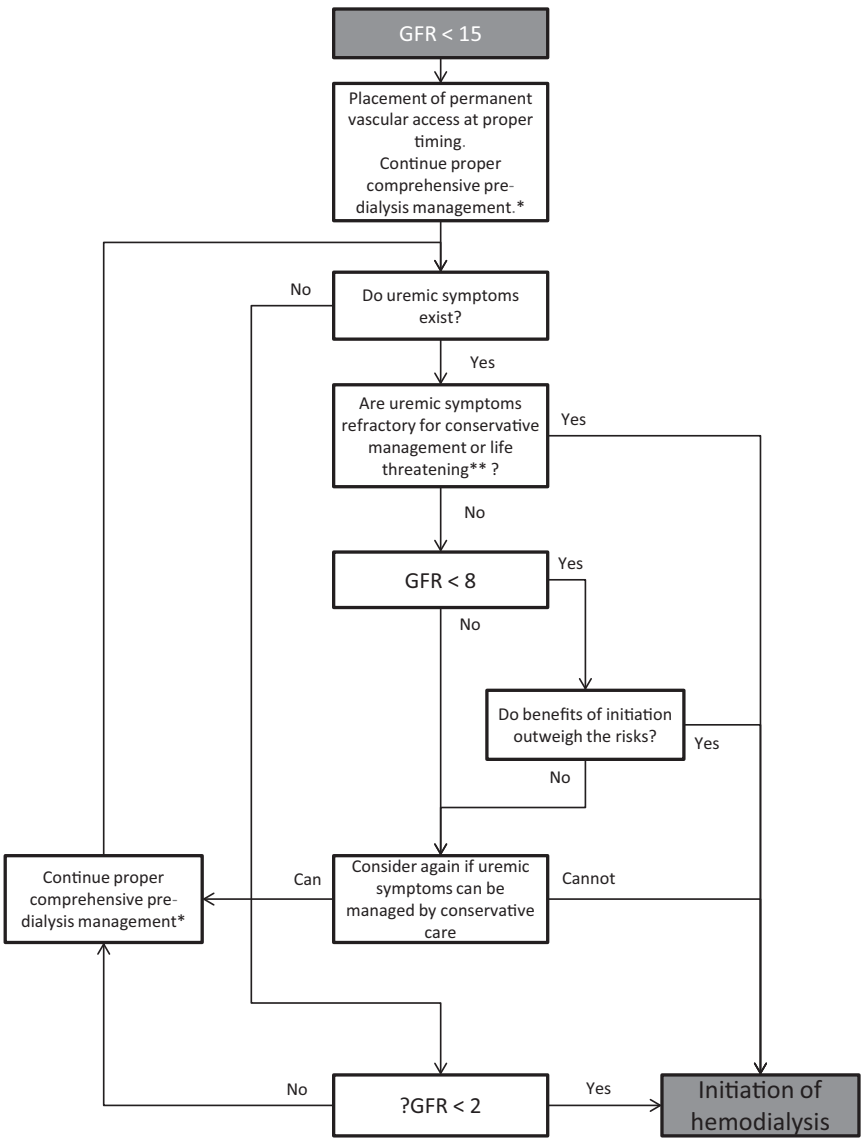

FIG. 3. Process hierarchy diagram for initiation of hemodialysis.
*Comprehensive management by teams comprised from multiple professionals.
**Presence of severe hyperkalemia, congestive heart failure, metabolic acidosis, uremic encephalopathy, or uremic pericarditis. GFR, glomerular filtration rate.

be done at a more early stage of CKD 5 compared to peritoneal dialysis. Since hemodialysis is not so much dependent on residual urine volume compared with peritoneal dialysis, hemodialysis initiation is considered at a later stage of CKD 5 when renal failure symptoms become difficult to control. Thus, the optimum timing of dialysis initiation may differ depending upon the selection of treatment option (Fig. 2). The practical timing of dialysis initiation is determined not on the basis of eGFR or serum creatinine values, but on assessment of renal function such as a measured GFR over time or a careful observation of manifestation of renal failure symptoms. As shown in Figure 3, once renal function is determined to have an eGFR < 15 mL/min/1.73 m^2, RRT initiation should be considered if a progressive decrease in renal function (an increase in serum creatinine over time) is observed while providing conservative management.

CHAPTER 5. PRECAUTIONS AFTER DIALYSIS INITIATION

Statement

8. Patients with acute kidney injury due to malignant hypertension, rapid progressive glomerulonephritis, lupus nephritis, and nephrotic syndrome may be able to withdraw from dialysis treatment after recovery of renal function, even after hemodialysis is once initiated. In such conditions, careful observation is required (Recommendation Grade, D).

Commentary

Withdrawal after the initiation of hemodialysis has been reported in non-negligible number of cases in the registry date of JSDT (101) and USRDS (103). Among them, hemodialysis was stopped for some patients because of poor systemic condition; meanwhile, withdrawal from hemodialysis sua sponte (on his/her own initiative) is frequently seen in the United States. In particular, the patients who showed acute exacerbation on chronic renal failure can withdraw from hemodialysis after the elimination of exacerbation causes. The correct percentages of withdrawal after recovery from malignant hypertension, rapidly progressive glomerulonephritis, lupus nephritis, and nephrotic syndrome have not been unfortunately evaluated so far. Therefore, even after the initiation of hemodialysis, it is necessary to observe the patients at all times to determine whether or not dialysis treatment can be withdrawn, because withdrawal strongly affects the patient life and medical cost. There are no evidences concerning the point of return from hemodialysis to determine what time is appropriate for withdraw. The necessity of maintaining hemodialysis should be determined from the perspective of body fluid control and solute removal (uremic toxin and electrolyte correction). Based on the management of body fluid, if water removal through dialysis becomes unnecessary in some continuous period, withdrawal from hemodialysis may be possible. On the other hand, the idea of spontaneous recovery has been stated for solute removal in acute kidney injury (AKI). It is recommended that withdrawal from hemodialysis could be tried in the patients who showed the natural decline of serum and increase in Ccr of 20 mL/min/1.73 m^2 or greater under stable RRT from the studies of AKI. Of course, this idea cannot be available for chronic hemodialysis; however, it may be helpful for the discussion of withdrawal.

CHAPTER 6. CHRONIC HEMODIALYSIS INITIATION IN PEDIATRIC PATIENTS

Preparation for dialysis initiation

Statements

9. In the event that the GFR value decreases to around 60 mL/min/1.73 m^2, it is recommended that a physician consult a pediatric nephrologist familiar with chronic CKD treatment in the pre-dialysis phase (2D).
10. In the event that the GFR value decreases to around 30 mL/min/1.73 m^2, it is recommended that a physician consult a pediatric nephrologist familiar with RRT treatment (2D).
11. In the event that hemodialysis initiation is needed, it is recommended that consent regarding VA be obtained and thorough consideration be given with regard to the choice of VA and appropriate time to create it (2D).

Commentary

Key points in childhood CKD treatment are as follows: 1) inhibition of renal failure progression; 2) mitigation of growth impairment, which is a pathognomonic complication in pediatric patients; 3) prevention of complication of cardiovascular diseases (CVDs) closely associated with life prognosis; and 4) therapeutic planning of lifetime renal failure treatment. Growth impairment starts to manifest when GFR falls below 60 mL/min/1.73 m^2, and many factors, such as mineral and bone disorder (MBD), primary underlying disease, age of renal failure onset, poor energy intake, abnormal protein and amino acid

metabolism, metabolic acidosis, electrolyte abnormality, anemia, and endocrine system disorder (particularly growth hormone-growth factor system), are involved in this pathological condition (104). Therefore, proper diagnosis for growth impairment (short stature) is required to be made by a pediatric nephrologist and meticulous treatment given for each above-mentioned factor causing growth impairment. Furthermore, serum calcitriol level starts to fall in early CKD stage 2, whereas levels of fibroblast growth factor 23 and, subsequently, parathyroid hormone (PTH) start to rise (105). If GFR falls below 30 mL/min/1.73 m^2, serum phosphorus levels begin to rise (105), and metabolic acidosis also becomes pronounced (106). The concept of taking vascular calcification and life prognosis into consideration in CKD-MBD and treatment can be applied to children as well as adults. In fact, proper control of calcium, phosphorus, and PTH levels in children is important in terms of prevention of CVD complication as well as preventive therapy for CKD-MBD (107–109). For that reason, an appropriate CKD-MBD treatment is required to be given by a pediatric nephrologist at an early stage of CKD (110). Indeed, in a case where a pediatric nephrologist familiar with renal failure treatment provided a child at CKD stages 2–4 with follow-up care until RRT was initiated, it was observed that the conservation of renal function, serum phosphorus levels, serum calcium phosphate product levels, serum PTH levels, serum hemoglobin levels, and urgent dialysis initiation frequency were significantly well controlled (111). At present, however, only 41% of patients at a stage when GFR ≥ 20 mL/min/1.73 m^2 are referred to a nephrologist, and 31% of the referred patients are forced to initiate RRT within 1 month after the referral (112). Consulting with a pediatric nephrologist tends to be delayed in clinical practice.

Because there are several issues specific to children that need attention before RRT initiation, when the GFR falls to approximately 30 mL/min/1.73 m^2, and the progression to terminal renal failure in the future is deemed to be inevitable, a nephrologist familiar with peritoneal dialysis, hemodialysis, and kidney transplant is finally sought (113). RRT may be chosen after a patient and his/her family are given a thorough explanation without bias regarding advantages and disadvantages of the three types of RRT (peritoneal dialysis, hemodialysis, and renal transplant), and they have completely understood the explanation. If there is no absolute contraindication to each therapeutic approach, the choice of treatment is made based on the choice of the pediatric patient and his/her family and whether or not an assistant is present. RRT initiation may not be a choice of treatment depending upon the patient's condition, such as severe concurrent diseases or complications other than renal disease. Therefore, each case should be handled according to the recommendation (proposal) published by JSDT pertaining to chronic hemodialysis therapy initiation and postponement of the therapy for terminal patients (114). If hemodialysis is chosen, a discussion about the creation of VA is imperative (115). If hemodialysis is expected to continue for an extended period of time (more than a year as a rough guide), it is recommended that AVF be created (115,116). However, if no experienced VA surgeon is available, hemodialysis is not recommended for a pediatric patient, because blood vessels are so thin that it is difficult to create AVF. If AVF is forcefully created, it may damage the blood vessels, which may make the AVF creation difficult later in life when it is required. Hence, this situation must be avoided. In addition, it is recommended that the blood vessel diameter be at least 2.5 mm to create AVF (117) and the patient weigh at least 20 kg (116). Because it requires several months (up to 6 months) for AVF to develop in many cases, the therapeutic plan needs to be prepared well in advance (115). Furthermore, in the event that it is decided to create an AVF, it is necessary to consider preserving the blood vessels on the side of the planned AVF. In contrast, in children, with a body weight less than 20 kg or with complications, such as limb contractures and skeletal maldevelopment, in whom creating an AVF is difficult, a cuffed catheter can be used (115,118). In the event that hemodialysis using the catheter is performed, the patency of the right internal jugular vein should be confirmed beforehand. A comprehensive planning including the possible switching to peritoneal dialysis or renal transplant schedule in advance is also required (115). Considering the future creation of AVF or renal transplant, it is recommended to avoid a catheter insertion into the subclavian vein or vena cava as much as possible (115). With regard to the procedures and considerations in cuffed catheter implantation, it is suggested to refer to the "Guidelines for Creation and Repair of Vascular Access for Chronic Hemodialysis," the Japanese Society for Dialysis Therapy 2011 edition (119). Incidentally, infectious diseases associated with the use of a catheter, catheter kinking, thrombosis, and venous injury (obstruction) are potential complications, whereas the biggest advantage is there is no risk of centesis and minimal pain.

Timing of dialysis initiation

Statements

12. In the event that symptoms of refractory renal failure (growth impairment in children) are observed during conservative medical management, dialysis initiation should be considered (2D).
13. Even if the condition is asymptomatic, in general if GFR falls below 10 mL/min/1.73 m^2, dialysis initiation should be considered (2D).

Commentary

There are no definite criteria for dialysis initiation based on evidence. NKF K/DOQI guidelines recommend that dialysis be initiated if difficult-to-control symptoms of renal failure manifest during conservative medical management even if GFR > 15 mL/min/1.73 m^2. In fact, according to the data of cases reported from the Netherlands and Belgium, where RRT was initiated between September 2007 and December 2010, 22% of the cases were initiated on dialysis when GFR ≥ 15 mL/min/1.73 m^2 (120). Furthermore, pediatric case reviews comparing rates of hospitalization due to hypertension or pulmonary edema after dialysis initiation using GFR values (one group with GFR > 15 mL/min/1.73 m^2 and the other group with GFR ≤ 15 mL/min/1.73 m^2) revealed that the group with the higher GFR at the time of initiation had a lower hospitalization risk after RRT initiation (121) than the group with the lower GFR. At present, there are no definite criteria for dialysis initiation, and, thus, it is deemed appropriate that dialysis initiation be determined by comprehensively assessing symptoms of refractory renal failure during conservative medical management (metabolic acidosis, hyperkalemia, hypocalcemia, hyperphosphatemia, hypertension, inundation symptoms, renal osteodystrophy, nausea/vomiting, loss of appetite, undernutrition, growth impairment, etc.) or the degree of disability in daily life (difficulty in commuting to nursery school/kindergarten or school). On the other hand, there are also guidelines that recommend dialysis initiation be considered before GFR reaches 6 mL/min/1.73 m^2 (122,123) or when GFR reaches 8–10 mL/min/1.73 m^2 even if the condition is asymptomatic (124). According to a retrospective study on the timing of RRT initiation in renal hypoplasia and dysplasia cases (which are the most common cases among causative disorders of pediatric terminal renal failure), although serum potassium levels, phosphorus levels, and bicarbonate ion levels were relatively well maintained and the condition was asymptomatic even when the GFR progressed to fall below 10 mL/min/1.73 m^2, acute upper respiratory inflammation and gastroenteritis necessitated a considerable number of patients to undergo urgent dialysis (125). Therefore, it appears safe to consider initiation of dialysis in pediatric patients even if the condition is asymptomatic. Dialysis may be started when GFR falls below 10 mL/min/1.73 m^2. However, in properly managed cases without definite manifestation of renal failure symptoms, the medical evidence is not sufficient to establish the criteria for dialysis initiation solely from the perspective of renal function, and, thus, this issue of dialysis initiation criteria remains to be further investigated.

CHAPTER 7. RECOMMENDED STUDIES TO COMPILE FUTURE EVIDENCE

These guidelines were intended to be objective guidelines for hemodialysis initiation and were created on the basis of both domestic and international evidence. However, it is true that there are a number of guidelines that should be verified to confirm whether they can be applied to cases in Japan because many references were taken from literature published in Europe and the United States. To make these guidelines more comprehensive and evidence based, it is anticipated that investigations listed below be conducted in the years to come. In addition, the guidelines encompassing all renal replacement therapies are expected to be developed hereafter.

- Development of simplified and accurate GFR measurement methods at the terminal stage of renal failure
- Development of objective and easy methods to measure total body water and condition of hemostasis
- Observational studies or intervention trials on the timing of educational intervention
- Intervention trials in which the timing of therapy initiation is defined by a nephrologist
- Studies to determine the most essential symptom (among all symptoms) useful to assess the need for dialysis initiation
- Development of nutritional assessment and hematological indices useful for dialysis initiation
- Intervention trials following IDEAL study regarding early and late dialysis initiation or reviews on IDEAL study conducted as per protocol
- Cohort study on CKD G5 to be conducted in Japan
- Effect of renal function at the time of dialysis initiation on the post-initiation life prognosis and

effects of renal function at the time of referral to a nephrology institution on life prognosis are to be investigated
- Clinical studies pertaining to criteria for dialysis initiation in the very elderly or elderly people
- More detailed investigations on patients withdrawn from dialysis or further investigations on the timing of dialysis withdrawal

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) (reviewed Jan 26 2015 by correspondent author). Conflict of interest declarations: Yuzo Watanabe has received honoraria from Chugai Pharmaceutical Co., Ltd, and Kyowa Hakko Kirin Co., Ltd. Kunihiro Yamagata has received research funds and honoraria from Chugai Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Dainihon Sumitomo Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, and Shionogi Pharmaceutical Co., Ltd. Shinichi Nishi has received honoraria from Kyowa Hakko Kirin Co., Ltd, Novartis Pharma K.K., Astellas Pharma Inc., and Tanabe Mitsubishi Pharmaceutical Co., Ltd. Noritomo Itami has received honoraria from Chugai Pharmaceutical Co., Ltd. Ken Sakai has received honoraria from JMS Co., Ltd. Kazuhiko Tsuruya has received research funds and honoraria from Chugai Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Torii Pharmaceutical Co., Ltd, Fuso Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, and Baxter Co., Ltd. Hideki Hirakata has received honoraria from Chugai Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd, and Japan Tobacco Inc. Yoshiharu Tsubakihara has received research funds and honoraria from Kyowa Hakko Kirin Co., Ltd, Chugai Pharmaceutical Co., Ltd, Tanabe Mitsubishi Pharmaceutical Co., Ltd, and Asahi-Kasei Pharmaceutical Co., Ltd, and belonged to endowed courses at Osaka University. Hideki Kawanishi has received research funds and honoraria from Chugai Pharmaceutical Co., Ltd, Bayer Yakuhin Ltd, Kyowa Hakko Kirin Co., Ltd, Astellas Pharma Inc., Nikkiso Co., Ltd, and Japan Tobacco Inc. Hiroyasu Yamamoto has received honoraria from Chugai Pharmaceutical Co., Ltd, and Kyowa Hakko Kirin Co., Ltd. Takashi Akiba has received research funds and honoraria from Kyowa Hakko Kirin Co., Ltd, Japan Tobacco Inc., Toray Industries Inc., Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd, Otsuka Pharmaceutical Co., Ltd, and Toray Medical Co., Ltd. Kunitoshi Iseki has received research funds and honoraria from Teijin Pharma K.K and Chugai Pharmaceutical Co., Ltd. Kazuyoshi Okada has received research funds and honoraria from Kyowa Hakko Kirin Co., Ltd, Shionogi Pharmaceutical Co., Ltd, and Daiichi Sankyo Pharmaceutical Co., Ltd. Kazuyuki Suzuki has received honoraria from Kyowa Hakko Kirin Co., Ltd, and Gambro Co., Ltd. Masashi Tomo has received research funds and honoraria from Chugai Pharmaceutical Co., Ltd, and Kyowa Hakko Kirin Co., Ltd. Ikuto Masakane has received honoraria from Toray Medical Co., Ltd, and Kyowa Hakko Kirin Co., Ltd. Tadao Akizawa has received research funds, transportation fee to attend social meetings, and honoraria from Kyowa Hakko Kirin Co., Ltd, Chugai Pharmaceutical Co., Ltd, Bayer Yakuhin Ltd, Astellas Pharma Inc., Tanabe Mitsubishi Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Baxter Co., Ltd, Japan Boehringer Ingelheim Japan Co., Ltd, and Reata Pharmaceutical Co., Ltd.

Jun Minakuchi has received honoraria from Nikkiso Co., Ltd, and Bayer Yakuhin Ltd. (No other members declare the existence of any conflicts of interest.)

LIST OF ABBREVIATIONS

AKI: acute kidney injury
AVF: arteriovenous fistula
AVG: arteriovenous graft
BMI: body mass index
CAPD: continuous ambulatory peritoneal dialysis
CARI: Caring for Australasians with Renal Impairment
Ccr: creatinine clearance
CGN: chronic glomerulonephritis
CKD: chronic kidney disease
DMN: diabetic nephropathy
eCcr: estimated creatinine clearance
eGFR: estimated glomerular filtration rate
ER: early referral
GFR: glomerular filtration rate
HR: hazard ratio
IDEAL study: The Initiating Dialysis Early and Late study
K/DOQI: Kidney Disease Outcomes Quality Initiative
LR: late referral
NECOSAD: Nederlandse Coöperatieve Studie naar de Adequaatheid van Dialyse
PCR: protein catabolic rate
PNA: protein equivalent of total nitrogen appearance
QOL: quality of life
REIN: Réseau Epidémiologie et Information en Néphrologie
RRT: renal replacement therapy
SGA: subjective global assessment

REFERENCES

1. Kawaguchi Y, Mimura H. Studies on preparation of guidelines for chronic hemodialysis initiation, Research report on medical research project for kidney failure in health science in 1991 in Japan; 1992;125–32.
2. Nakai S, Suzuki K, Masakane I et al. Overview of regular dialysis treatment in Japan (as of 31 December 2008). *Ther Apher Dial* 2010;14:505–40.

3. Brochard L, Abroug F, Brenner M et al. An official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of acute renal failure in the ICU Patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med* 2010;181:1128–55.
4. Yamagata K, Iseki K, Nitta K et al. Chronic kidney disease perspectives in Japan and the importance of urinalysis screening. *Clin Exp Nephrol* 2008;12:1–8.
5. Levey AS, Eckardt KU, Tsukamoto Y et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes(K-DIGO). *Kidney Int* 2005;67:2089–100.
6. Matsuo S, Imai E, Horio M et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92.
7. Yamagata K, Nakai S, Masakane I et al. Ideal timing and predialysis nephrology care duration for dialysis initiation; from analysis of Japanese dialysis initiation survey. *Ther Apher Dial* 2012;16:54–62.
8. Yamagata K, Nakai S, Iseki K et al. Late dialysis start did not affect long-term outcome in Japanese dialysis patients: long-term prognosis from Japanese Society for Dialysis Therapy Registry. *Ther Apher Dial* 2012;16:111–20.
9. The Japanese Society for Dialysis Therapy. 2009 JSDT Guideline for Peritoneal Dialysis. *J JSDT* 2009;42:285–315.
10. Steinman TI, Becker BN, Frost AE et al. Guidelines for the referral and management of patients eligible for solid organ transplantation. *Transplantation* 2001;71:1189–204.
11. Fukagawa M, Tsukamot Y, Tsubakibara Y et al. Grading evidence levels and recommendations for guidelines. *J JSDT* 2010;43:347–9.
12. Uhlig K, Macleod A, Craig J et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;70:2058–65.
13. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function:new insights into old concepts. *Clin Chem* 1992;38:1933–53.
14. Beddhu S, Samore MH, Roberts MS et al. Creatinine production, nutrition, and glomerular filtration rate estimation. *J Am Soc Nephrol* 2003;14:1000–5.
15. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
16. Shemesh O, Golbetz H, Kriss JP et al. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 1985;28:830–8.
17. Jagenburg R, Attman PO, Aurell M et al. Determination of glomerular filtration rate in advanced renal insufficiency. *Scand J Urol Nephrol* 1978;12:133–7.
18. Dombros N, Dratwa M, Feriani M et al. European best practice guidelines for peritoneal dialysis. 2 The initiation of dialysis. *Nephrol Dial Transplant* 2005;20(Suppl 9):ix3–ix7.
19. Bauer JH, Brooks CS, Burch RN. Renal function studies in man with advanced renal insufficiency. *Am J Kidney Dis* 1982;2:30–5.
20. Horio M, Imai E, Yasuda Y et al. Relationship between serum creatinine, creatinine clearance, estimated GFR, and measured GFR in patients with GFR ≦ 20 mL/min/1.72 m^2. *J JSDT* 2011;44:55–8.
21. Horio M, Imai E, Yasuda Y et al. GFR estimation using standardized serum cystatin C in Japan. *Am J Kidney Dis* 2013;61:197–203.
22. Rodrigo E, de Francisco AL, Escallada R et al. Measurement of renal function in pre-ESRD patients. *Kidney International* 2002;61:S11–S17; doi:10.1046/j.1523-1755.61.s80.4.x.
23. Traynor JP, Simpson K, Geddes CC et al. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. *J Am Soc Nephrol* 2002;13:2125–32.
24. Rosansky SJ, Clark WF, Eggers P et al. Initiation of dialysis at higher GFRs:is the apparent rising tide of early dialysis harmful or helpful? *Kidney Int* 2009;76:257–61.
25. Lassalle M, Labeeuw M, Frimat L et al. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. *Kidney Int* 2010;77:700–7.
26. Rosansky SJ, Eggers P, Jackson K et al. Early start of hemodialysis may be harmful. *Arch Intern Med* 2011;171:396–403.
27. Grootendorst DC, Michels WM, Richardson JD et al. The MDRD formula does not reflect GFR in ESRD patients. *Nephrol Dial Transplant* 2011;26:1932–7.
28. Susantitaphong P, Altamimi S, Ashkar M et al. GFR at initiation of dialysis and mortality in CKD:a meta-analysis. *Am J Kidney Dis* 2012;59:829–40.
29. Clinical practice guidelines for hemodialysis adequacy, update 2006. Hemodialysis Adequacy 2006 Work Group. *Am J Kidney Dis* 2006;48(Suppl 1):S2–90.
30. Japanese Society of Nephrology.CKD Practice Guidelines 2012.2012.
31. Devins GM, Mendelssohn DC, Barre PE et al. Predialysis psychoeducational intervention and coping styles influence time to dialysis in chronic kidney disease. *Am J Kidney Dis* 2003;42:693–703.
32. Devins GM, Mendelssohn DC, Barre PE et al. Predialysis psychoeducational intervention extends survival in CKD:a 20-year follow-up. *Am J Kidney Dis* 2005;46:1088–98.
33. Sesso R, Belasco AG, Ajzen H. Late diagnosis of chronic renal failure. *Braz J Med Biol Res* 1996;29:1473–8.
34. Chandna SM, Schulz J, Lawrence C et al. Is there a rationale for rationing chronic dialysis? A hospital based cohort study of factors affecting survival and morbidity. *BMJ* 1999;318:217–23.
35. Jungers P, Massy ZA, Nguyen-Khoa T et al. Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. *Nephrol Dial Transplant* 2001;16:2357–64.
36. Stoves JBC, Newstead CG. Specialists follow up of patients before end stage renal failure and its relationship to survival on dialysis. *Postgrad Med J* 2001;77:586–8.
37. Cass A, Cunningham J, Arnold PC et al. Delayed referral to a nephrologist:outcomes among patients who survive at least one year on dialysis. *Med J Aust* 2002;177:135–8.
38. Roderick P, Jones C, Drey N et al. Late referral for end-stage renal disease:a region-wide survey in the south west of England. *Nephrol Dial Transplant* 2002;17:1252–9.
39. Lin CL, Wu MS, Hsu PY et al. Improvement of clinical outcome by early nephrology referral in type ?diabetics on hemodialysis. *Ren Fail* 2003;25:455–64.
40. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis* 2003;41:310–8.
41. Kazmi WH, Obrador GT, Khan SS et al. Late nephrology referral and mortality among patients with end-stage renal disease:a propensity score analysis. *Nephrol Dial Transplant* 2004;19:1808–14.
42. Winkelmayer WC, Owen WF Jr, Levin R et al. A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 2003;14:486–92.
43. Khan SS, Xue JL, Kazmi WH et al. Does predialysis nephrology care influence patient survival after initiation of dialysis? *Kidney Int* 2005;67:1038–46.
44. Schwenger V, Morath C, Hofmann A et al. Late referral—a major cause of poor outcome in the very elderly dialysis patient. *Nephrol Dial Transplant* 2006;21:962–7.
45. Hasegawa T, Bragg-Gresham JL, Yamazaki S et al. Greater first-year survival on hemodialysis in facilities in which patients are provided earlier and more frequent pre-nephrology visits. *Clin J Am Soc Nephrol* 2009;4:595–602.
46. Chen SC, Hwang SJ, Tsai JC et al. Early nephrology referral is associated with prolonged survival in hemodialysis patients even after exclusion of lead-time bias. *Am J Med Sci* 2010;339:123–6.
47. de Jager DJ, Voormolen N, Krediet RT et al. Association between time of referral and survival in the first year of

dialysis in diabetics and the elderly. *Nephrol Dial Transplant* 2011;26:652–8.
48. Goransson LG, Bergrem H. Consequences of late referral of patients with end-stage renal disease. *J Intern Med* 2001;250: 154–9.
49. Caskey FJ, Wordsworth S, Ben T et al. Early referral and planned initiation of dialysis:what impact on quality of life? *Nephrol Dial Transplant* 2003;18:1330–8.
50. Yokoyama Y, Yamazaki S, Hasegawa T et al. Impact of early referral to nephrologist on mental health among hemodialysis patients:a Dialysis Outcomes and Practice Patterns Study-(DOPPS). *Nephron Clin Pract* 2009;113:c191.
51. Winkelmayer WC, Liu J, Chertow GM, Tamura MK. Predialysis nephrology care of older patients approaching end-stage renal disease. *Arch Intern Med* 2011;171:1371–8.
52. Nakamura S, Nakata H, Yoshihara F et al. Effect of early nephrology referral on the initiation of hemodialysis and survival in patients with chronic kidney disease and cardiovascular diseases. *Circ J* 2007;71:511–6.
53. The Japanese Society for Dialysis Therapy. Guidelines pertaining to creating and repairing vascular access for chronic hemodialysis. *J Jpn Soc Dial Ther 2011 Ed* 2011;44:855–937.
54. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006;48(Suppl 1):S248–73.
55. Chesser AM, Baker LR. Temporary vascular access for first dialysis is common, undesirable and usually avoidable. *Clin Nephrol* 1999;51:228–32.
56. Lorenzo V, Martn M, Rufino M et al. Predialysis nephrologic care and a functioning arteriovenous fistula at entry are associated with better survival in incident hemodialysis patients:an observational cohort study. *Am J Kidney Dis* 2004;43: 999–1007.
57. Wu LC, Lin MY, Hsieh CC et al. Planned creation of vascular access saves medical expenses for incident dialysis patients. *Kaohsiung J Med Sci* 2009;25:521–9.
58. Hiremath S, Knoll G, Weinstein MC. Should the arteriovenous fistula be created before starting dialysis?: a decision analytic approach. *PLoS One* 2011;6:e28453.
59. The Japanese Society for Dialysis Therapy.Current status of dialysis therapy in Japan 2006, as of December 31. 2007.
60. Mendelssohn DC, Curtis B, Yeates K et al. Suboptimal initiation of dialysis with and without early referral to a nephrologist. *Nephrol Dial Transplant* 2011;26:2959–65.
61. Lacson E Jr, Wang W, DeVries C et al. Effect of a nationwide predialysis educational program on modality choice, vascular access, and patient outcomes. *Am J Kidney Dis* 2011;58:235–42.
62. Kawaguchi Y, Nihei H, Hirasawa Y et al. *A Study Regarding Preparation of Guidelines for Hemodialysis Initiation. 1992 Health Science Research: Renal Failure Healthcare Research Project Report (Group Leader: Mimura N)*. Sakura: Sakura National Hospital, 1992; 125–32.
63. The Japanese Society for Dialysis Therapy. Illustrated present status of chronic dialysis therapy in Japan as of December 31, 2007. Tokyo, 2008.
64. The Japanese Society for Dialysis Therapy. Illustrated present status of chronic dialysis therapy in Japan as of December 31, 2008. Tokyo, 2009.
65. Kawaguchi Y, Wada T. *A Review on Criteria for Chronic Dialysis Initiation and Validity Based on Follow-up Survey. 1995 Health Science Research: Renal Failure Healthcare Research Project Report (Group Leader: Mimura N)*. Sakura: Sakura National Hospital, 1995; 84–7.
66. Kawaguchi Y, Wada T. *A Study on Establishing Guidelines for Dialysis Initiation and Follow-up Survey. 1993 Health Science Research: Renal Failure Healthcare Research Project Report (Group Leader: Mimura N)*. Sakura: Sakura National Hospital, 1993; 156–64.
67. Nakai S, Watanabe Y, Masakane I et al. Present status of chronic dialysis therapy in Japan (as of December 31, 2011). *J JSDT* 2013;46:1–76.
68. Collins AJ, Foley R, Herzog C et al. Excerpts from the United States Renal Data System 2007 annual data report. *Am J Kidney Dis* 2008;51:S1–320.
69. Stel VS, Tomson C, Ansell D et al. Level of renal function in patients starting dialysis:an ERA-EDTA Registry study. *Nephrol Dial Transplant* 2010;25:3315–25.
70. Clark WF, Na Y, Rosansky SJ et al. Association between estimated glomerular filtration rate at initiation of dialysis and mortality. *CMAJ* 2011;183:47–53.
71. Hemodialysis Adequacy Work G. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis* 2006;48(Suppl 1):S2–90.
72. Levin A, Hemmelgarn B, Culleton B et al. Guidelines for the management ofchronic kidney disease. *CMAJ* 2008;179: 1154–62.
73. European Best Practice Guidelines for Haemodialysis I. 3When to start dialysis. *Nephrol Dial Transplant* 2002; 17(Suppl 7):10–1.
74. Kelly J, Stanley M, Harris D. The CARI guidelines. Acceptance into dialysis guidelines. *Nephrology(Carlton)* 2005; 10(Suppl 4):S46–60.
75. The Japanese Society for Dialysis Therapy. Illustrated present status of chronic dialysis therapy in Japan as of December 31, 2006. Tokyo, 2007.
76. de Mutsert R, Grootendorst DC, Boeschoten EW et al. Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. *Am J Clin Nutr* 2009;89:787–93.
77. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. *J Am Soc Nephrol* 2010;21:223–30.
78. Bonomini V, Feletti C, Scolari MP et al. Benefits of early initiation of dialysis. *Kidney Int* 1985;17(Suppl):S57–9.
79. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function:new insights into old concepts. *Clin Chem* 1992;38:1933–53.
80. Churchill DN. An evidence-based approach to earlier initiation of dialysis. *Am J Kidney Dis* 1997;30:899–906.
81. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. *Am J Nephrol* 1995;15: 283–9.
82. Hakim RM, Lazarus JM. Initiation of dialysis. *J Am Soc Nephrol* 1995;6:1319–28.
83. Kim SG, Kim NH. The effect of residual renal function at the initiation of dialysis on patient survival. *Korean J Intern Med* 2009;24:55–62.
84. NKF-DOQI clinical practice guidelines for hemodialysis adequacy. National Kidney Foundation. *Am J Kidney Dis* 1997;30:S15–66.
85. Korevaar JC, Jansen MA, Dekker FW et al. When to initiate dialysis:effect of proposed US guidelines on survival. *Lancet* 2001;358:1046–50.
86. Kausz AT, Obrador GT, Arora P et al. Late initiation of dialysis among women and ethnic minorities in the United States. *J Am Soc Nephrol* 2000;11:2351–7.
87. Obrador GT, Arora P, Kausz AT et al. Level of renal function at the initiation of dialysis in the U. S. end-stage renal disease population. *Kidney Int* 1999;56:2227–35.
88. Wilson B, Harwood L, Locking-Cusolito H et al. Optimal timing of initiation of chronic hemodialysis? *Hemodial Int* 2007;11:263–9.
89. Fink JC, Burdick RA, Kurth SJ et al. Significance of serum creatinine values in new end-stage renal disease patients. *Am J Kidney Dis* 1999;34:694–701.
90. Beddhu S, Samore MH, Roberts MS et al. Impact of timing of initiation of dialysis on mortality. *J Am Soc Nephrol* 2003;14:2305–12.
91. Kazmi WH, Gilbertson DT, Obrador GT et al. Effect of comorbidity on the increased mortality associated with early initiation of dialysis. *Am J Kidney Dis* 2005;46:887–96.

92. Stel VS, Dekker FW, Ansell D et al. Residual renal function at the start of dialysis and clinical outcomes. *Nephrol Dial Transplant* 2009;24:3175–82.
93. Hwang SJ, Yang WC, Lin MY et al. Impact of the clinical conditions at dialysis initiation on mortality in incident haemodialysis patients:a national cohort study in Taiwan. *Nephrol Dial Transplant* 2010;25:2616–24.
94. Susantitaphong P, Altamimi S, Ashkar M et al. GFR at initiation of dialysis and mortality in CKD:a meta-analysis. *Am J Kidney Dis* 2012;59:829–40.
95. Pan Y, Xu XD, Guo LL et al. Association of early versus late initiation of dialysis with mortality:systematic review and meta-analysis. *Nephron Clin Pract* 2012;120:c121–31.
96. Shafi T, Jaar BG, Plantinga LC et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients:the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease(CHOICE) Study. *Am J Kidney Dis* 2010;56:348–58.
97. Cooper BA, Branley P, Bulfone L et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;363:609–19.
98. Harris A, Cooper BA, Li JJ et al. Cost-effectiveness of initiating dialysis early:a randomized controlled trial. *Am J Kidney Dis* 2011;57:707–15.
99. Di Micco L, Torraca S, Pota A et al. Setting dialysis start at 6.0 mL/min/1.73 m2 eGFR- a study on safety, quality of life and economic impact. *Nephrol Dial Transplant* 2009;24:3434–40.
100. Brunori G, Viola BF, Parrinello G et al. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly:a prospective randomized multicenter controlled study. *Am J Kidney Dis* 2007;49:569–80.
101. Nakai S, Masakane I, Shigematsu T et al. An overview of regular dialysis treatment in Japan(as of 31 December 2007). *Ther Apher Dial* 2009;13:457–504.
102. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies:development and validation. *J Chronic Dis* 1987;40:373–83.
103. USRDS. Section I;patient survival. 2009 USRDS Annual data report. 2010;671–716.
104. Haffner D, Nisel R. Growth and puberty in chronic kidney disease. In: Geary DF, Schaefer F, eds. *Comprehensive Pediatric Nephrology*. Philadelphia: Mosby, 2008; 709–32.
105. Wesselin-Perry K, Salusky IB. Chronic kidney disease mineral and bone disorder. In: Avner Avner ED, Harmon WE, Niaudet P, Yoshikawa N, eds. *Pediatric Nephrology*. Heidelberg: Springer, 2009; 1755–83.
106. Kraut JA, Madias NE. Consequence and therapy of the metabolic acidosis of chronic kidney disease. *Pediatr Nephrol* 2011;26:19–28.
107. Goodman WG, Goldin J, Kuizon BD et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478–83.
108. Schroff RC, Donald AE, Hiorns MP et al. Mineral metabolism and vascular damage in children on dialysis. *J Am Soc Nephrol* 2007;18:2996–3003.
109. Lilien MR, Groothoff JW. Cardiovascular disease in children with CKD or ESRD. *Nat Rev Nephrol* 2009;5:229–35.
110. Japanese Society for Dialysis Therapy. Clinical practice guidelines for mineral and bone disorder associated with chronic renal disease. *J JSDT* 2012;45:301–56.
111. Menon S, Valentini RP, Kapur G et al. Effectiveness of a multidisciplinary clinic in managing children with chronic kidney disease. *Clin J Am Soc Nephrol* 2009;4:1170–5.
112. van Stralen KJ, Tizard EJ, Jager KJ et al. Determinants of eGFR at start of renal replacement therapy in paediatric patients. *Nephrol Dial Transplant* 2010;25:3325–32.
113. VanDeVoorde RG, Warady BA. Management of Chronic Kidney Disease. In: AvnerAvner ED, Harmon WE, Niaudet P, Yoshikawa N, eds. *Pediatric Nephrology*. Heidelberg: Springer, 2009; 1661–92.
114. Okada K, Oohira S, Itami N et al. Recommendation (proposal) pertaining to chronic hemodialysis therapy initiation and postponing the therapy for terminal patients. *J JSDT* 2012;45:1090–5.
115. Chand DH, Valentini RP, Kamil ES. Hemodialysis vascular access options in pediatrics:considerations for patients and practitioners. *Pediatr Nephrol* 2009;24:1121–8.
116. Zaritsky JJ, Salusky IB, Gales B et al. Vascular access complications in long-term pediatric hemodialysis patients. *Pediatr Nephrol* 2008;23:2061–5.
117. Gradman WS, Lermer G, Mentster M, Rodrigues H, Kamil ES. Experience with autogenous arteriovenous access for hemodialysis in children and adolescence. *Ann Vasc Surg* 2005;19:609–12.
118. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for 2006 update:hemodialysis adequacy, peritoneal dialysis adequacy, and vascular access. *Am J Kidney Dis* 2006;48:S176–S322.
119. The Japanese Society for Dialysis Therapy. The Japanese Society for Dialysis Therapy, 2011 edition. Guidelines for creation and repair vascular access for chronic hemodialysis. *J JSDT* 2011;44:857–937.
120. Tromp WF, Schoenmaker N, van der Lee JH et al. Important differences in management policies for children with end-stage renal disease in the Netherlands and Belgium-report from RICH-Q study. *Nephrol Dial Transplant* 2012;27:1984–92.
121. Atkinson MA, Oberai PC, Neu AM et al. Predictors and consequences of higher estimated glomerular filtration rate at dialysis initiation. *Pediatr Nephrol* 2010;25:1153–61.
122. European Best Practice Guidelines for hemodialysis Part 1. *Nephrol Dial Transplant* 2002;17(Suppl 7):S1–S111.
123. Rees L, Feather S, Schroff R. Haemodialysis clinical practice guidelines for children and adolescents. *Br Assoc Paediatric Nephrology* 2008. http://www.renal.org/docs/default-source/special-interest-groups/bapn/clinical-standards/bapn-hd-standards-and-guidelines.pdf?sfvrsn=2 (reviewed Jan 26, 2015)
124. European best practice guidelines for peritoneal dialysis. *Nephrol Dial Transplant* 2005;20(Suppl 9):ix3–ix7.
125. Honda K, Akioka Y, Sugawara N et al. Considerations on the choice of renal replacement therapy and its timing of initiation for renal hypoplasia and dysplasia. *Jpn J Pediatr Nephrol* 2012;25:1–4.