Introduction

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J Am Soc Nephrol 17: S1–S27, 2006. doi: 10.1681/ASN.2005121372

In 1999, the Canadian Society of Nephrology (CSN) published clinical practice guidelines (CPG) for the treatment of patients with chronic kidney disease (1,2). In 2003, responding to new evidence and emerging controversies, the CSN Executive Committee recognized the need to update these guidelines and establish new guidelines in areas of perceived clinical need. Updating the hemodialysis guidelines was given high priority. Guidelines for other areas of nephrology, such as peritoneal dialysis, anemia management, and nondialysis chronic kidney disease management, would be developed or revised in a staggered manner over 3 to 5 yr. The overriding objective of the guideline process was to establish national guidelines to improve the quality of health care delivered to patients with chronic kidney disease in Canada.

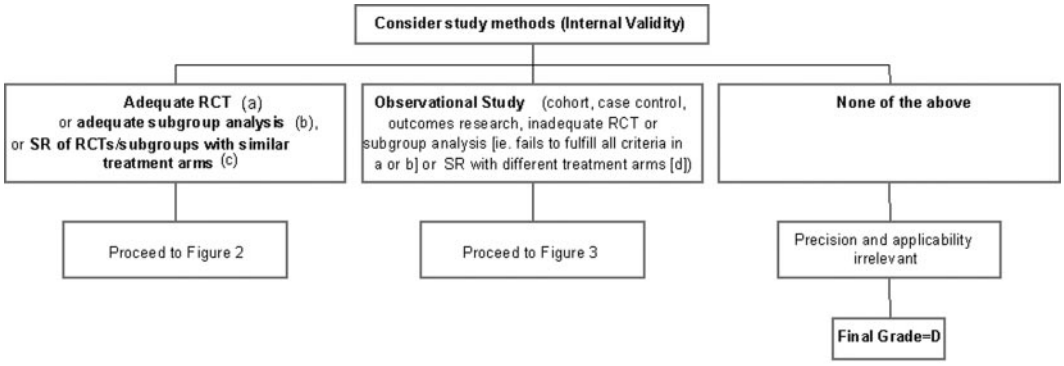
The guidelines that follow are intended to rely on evidence and avoid opinion-based statements where possible. The guidelines are also intended to reflect human and financial resources available throughout Canada at the time of their writing.

Methods

Guideline Workgroups are directly responsible for the content of each section. A Workgroup Chair is chosen based upon content expertise and participation in the previous CSN CPG. The Workgroup is then populated by nephrologists with recognized content expertise and, when necessary, allied health professionals and/or patient representatives.

Workgroups are asked to utilize the extensive content and methodologic review of the relevant literature obtained by the prior CSN guidelines (1) and prior publications of the relevant Kidney Disease Outcomes Quality Initiative (KDOQI) Workgroups (3–7). This literature is supplemented by using two methods to locate additional evidence. First, the Workgroup members use their content expertise to identify new evidence. Second, a focused literature search of English-language nephrology and general medical journals is performed by the content experts. The Workgroups assume that new evidence of sufficient magnitude to warrant the revision of existing national guidelines would be discovered using these two methods. Although this approach might be criticized for lack of methodologic rigor, such an approach is pragmatic and has been utilized and advocated by others (8,9).

The grading of the evidence supporting each recommendation is based upon the scheme developed by the Canadian Hypertension Education Program (Figures 1, 2, and 3) (10). Recommendations are developed only if they are "strongly recommended" by each Workgroup, *i.e.*, the Workgroup is confident that adherence will do more good than harm. Other status statements within each document are not made. Because



Definitions:

a Randomized clinical trial with blinded assessment of outcomes (if applicable), intention-to-treat analysis, adequate follow-up (ie. at least 90%, or losses to follow-up are too few to materially affect the results), and sufficient sample size to detect a clinically important difference with power > 80%.

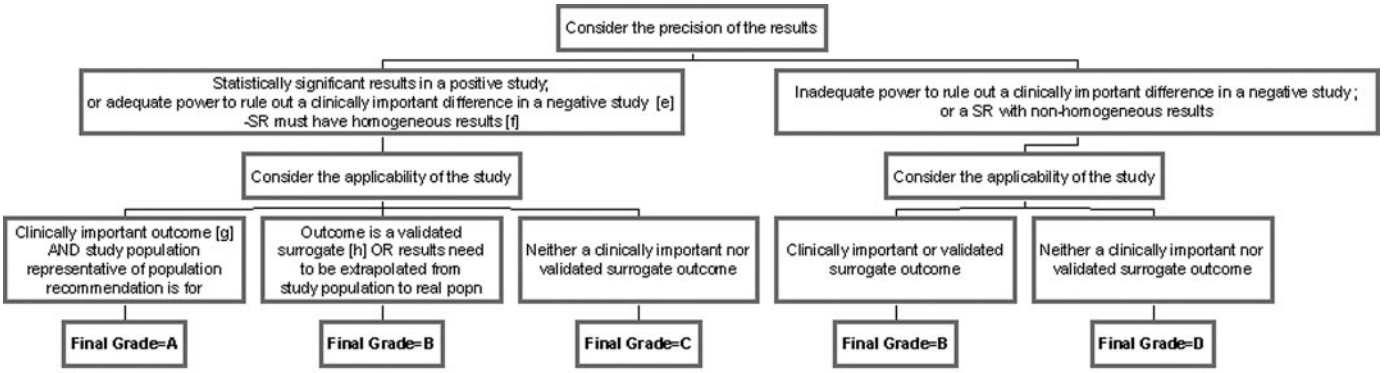
b Subgroup analysis was a-priori, done within an adequate RCT, one of only a few tested, and there was sufficient sample size within the examined subgroup to detect a clinically important difference with power > 80%.

c Sytematic review (SR, also known as meta-analysis) in which the comparison arms are derived from head-to-head comparisons within the same RCT.

d SR in which the comparison arms are derived from different placebo-controlled RCTs, then extrapolations are made across RCTs.

Figure 1. Algorithm for assigning evidence grades to recommendations.

ISSN: 1046-6673/1703-0001



Definitions:

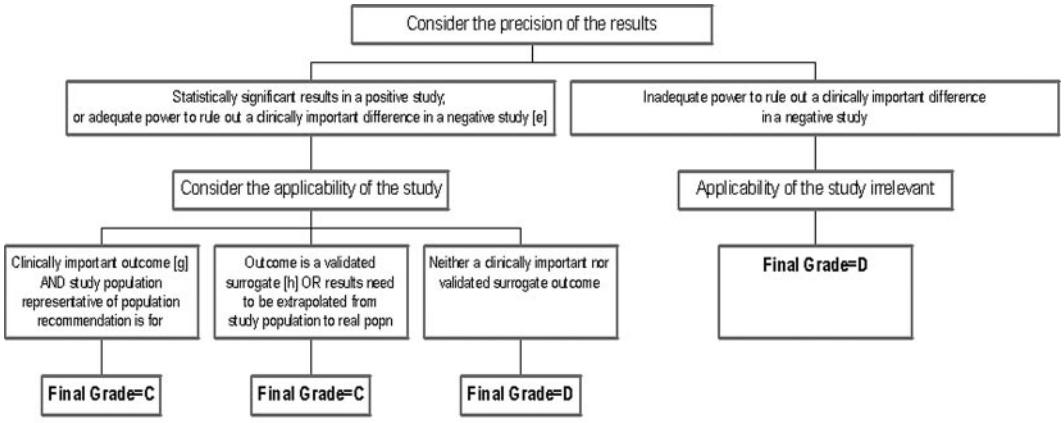
e Adequate power in a negative study implies that 95% CI exclude a clinically important difference.

f Effect estimates in each study included in the systematic review are qualitatively similar (ie. in the same direction).

g "Hard" endpoints such as death, stroke, myocardial infarction, hospitalization, and need for dialysis.

h Endpoints which have been consistently shown to be associated with the clinical end point in multiple studies (observational or RCT), and RCTs have consistently demonstrated that improvement in the surrogate translates into a consistent and predictable improvement in the clinical end point.

Figure 2. Algorithm for assigning evidence grades to recommendations (continued from Figure 1, for adequate randomized trials, systematic reviews, or subgroup analyses).



Definitions:

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h Endpoints which have been consistently shown to be associated with the clinical end point in multiple studies (observational or RCT), and RCTs have consistently demonstrated that improvement in the surrogate translates into a consistent and predictable improvement in the clinical end point.

Figure 3. Algorithm for assigning evidence grades to recommendations (continued from Figure 1, for observational studies).

of limited trial data within several clinically important areas, the Workgroups may be forced to make limited, opinion-based recommendations. These will be explicitly stated. The distinction between grading of evidence and the perceived importance of each recommendation must not be confused. In this regard, a recommendation receiving a Grade D is just as relevant and important to the Workgroup as a recommendation receiving a Grade A. Finally, in some instances it may not be appropriate to make a recommendation because of lack of agreement between studies or lack of good-quality evidence. In these situations, specific research recommendations will be stated.

The hemodialysis Workgroup met initially in May 2004 at the

CSN Annual Meeting and again in January 2005. The Chair of the CSN CPG Committee (B. Culleton) and the Chair of the Workgroup (K. Jindal) reviewed and modified the first draft of the hemodialysis guidelines. The document was then formally reviewed by four Canadian nephrologists chosen for their specific research or clinical experience. The document was modified in response to this internal review and a second draft was distributed to all members of the CSN. Comments from this external review were considered in detail and the final revised draft of the hemodialysis guidelines was completed in September 2005.

Sponsorship

Financial support for the CPG process has been provided by an educational grant from Amgen Canada to the CSN.

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CHAPTER 1: Hemodialysis Adequacy in Adults

Kailash Jindal (Workgroup Chair), Christopher T. Chan, Clement Deziel, David Hirsch, Steven D. Soroka, Marcello Tonelli, and Bruce F. Culleton (CPG Chair)

I. Hemodialysis Adequacy

Recommendations

1. **All hemodialysis patients should have regular global assessments of dialysis adequacy. (Grade D, opinion) Assessment of hemodialysis adequacy should include urea clearance, volume control, blood pressure, mineral metabolism, and clinical symptoms. (Grade C)**
2. **The minimum acceptable target for urea clearance during hemodialysis is a single-pool Kt/V of 1.2 or percent reduction of urea (PRU) of 65% three times per week. (Grade C)**
3. **Hemodialysis centers should consider offering a range of options, including more frequent or sustained treatment times, for those patients with dialysis inadequacy. (Grade D, opinion)**

Background

Urea clearance as assessed by Kt/V or PRU is a surrogate for dialysis dose. Although practice guidelines have traditionally emphasized the role of urea clearance, this parameter is only one component of dialysis adequacy.

The National Cooperative Dialysis Study (NCDS) established that higher dialysis dose resulted in reduced morbidity (1), although the intensity of dialysis in both treatment groups was considerably lower than in current practice. More recently, observational studies have suggested that urea clearance below a single-pool Kt/V of 1.2 or PRU of 65% three times per week is associated with increased mortality (2–6). Although observational data from patients treated with thrice-weekly and quotidian hemodialysis suggest that even higher levels of urea clearance are associated with better clinical outcomes (7–12), a well-designed, randomized study found no benefit of a single-pool Kt/V target of 1.65 compared with 1.25 (13). Although this study cannot exclude a mortality benefit <25%, there is no evidence to support increasing the target Kt/V above currently recommended levels. Since no grade A evidence (apart from the NCDS) indicates that increasing hemodialysis dose will reduce morbidity or mortality, it is possible that reducing the target Kt/V to levels <1.2 might not compromise clinical outcomes. However, in the absence of an adequately powered randomized study to confirm this hypothesis, the Committee continues to recommend a target single-pool Kt/V of >1.2.

Higher levels of urea clearance might be a marker for longer dialysis times, better control of blood pressure (BP) and extracellular fluid volume, or higher clearance of larger molecular weight substances. However, the use of high-flux dialyzers, which remove higher molecular weight toxins more efficiently, does not appear to reduce mortality, making the latter possibility less likely (13). Although the hypothesis that improved volume control will reduce mortality is attractive, it remains untested in hemodialysis patients. Nonetheless, optimal control of extracellular fluid volume and BP are rational goals given the large body of evidence linking these characteristics to better health outcomes. Longer dialysis duration or more frequent dialysis treatments may aid in achieving these clinical objectives.

To ensure that patients are receiving the prescribed urea clearance, the clinician must regularly monitor and measure the dose delivered. Urea clearance should be measured at least every 8 wk. Examples of acceptable techniques for estimating delivered dose are formal single-pool urea kinetics, PRU or urea reduction ratio (URR), and Kt/V natural logarithm formulae.

Of the three suggested techniques, single-pool urea kinetics predicts the dose delivered most accurately. However, the goal of monitoring urea clearance is to ensure that patients receive at least a minimum dose of therapy. Although PRU does not take into account urea removal by ultrafiltration, measurements using this technique will underestimate the dialysis dose, which would not compromise patient care. Similarly, the contribution of residual renal function can be ignored. Because all three parameters correlate with mortality, there is no strong reason to recommend one in particular. Clinicians should consider reproducibility, ease of use, and familiarity when selecting a measure of urea clearance for use in their hemodialysis programs. To facilitate comparisons between units, the index of urea clearance used should be consistent within a hemodialysis program. Methods for measuring urea clearance appear in Appendix A.

Clinicians should recognize that staff and patients may conduct themselves differently on the day when the dose of therapy is being measured. Therefore, clinicians are encouraged to use some additional techniques, which may be less precise but permit the measurement of the dose of hemodialysis delivered on a daily basis (*e.g.*, volume of blood processed, average pump speed, and duration of treatment), and to correlate them with the more formal dosage measurement.

In addition to considering urea clearance and volume status, the clinician must consider many other measures and indicators in assessing a patient's health and prescribing treatment, including control of extracellular volume and BP, uremic symptoms, quality of life, control of hyperphosphatemia, adequate nutritional status, and treatment of anemia. (See the guidelines on Mineral Metabolism and Management of Blood Pressure in Hemodialysis Patients for details).

Hemodialysis centers should have a continuous quality improvement/patient review system in place that recognizes pa-

tients who are receiving suboptimal dialysis adequacy, identifies the cause, and corrects it. This process may be facilitated by the use of multidisciplinary sit-down rounds in addition to regular contact between patients and nephrologists (14).

Although there are no randomized studies demonstrating that nocturnal, daily, or sustained hemodialysis treatments improve clinical outcome compared with standard care (12), multiple observational studies indicate that such treatments may improve surrogate outcomes in select patients at a reasonable cost (7–9,15–20). Recognizing that this evidence base is inconclusive, hemodialysis centers should consider offering a range of options for hemodialysis including more frequent or sustained treatment times, especially for patients in whom standard dialysis appears inadequate. (See the guideline on Frequent and Sustained Hemodialysis). On the other hand, less frequent dialysis may be acceptable for brief periods in patients with greater levels of residual kidney function, or those in whom the primary indication for dialysis is control of extracellular fluid volume rather than solute clearance (*i.e.*, those with renal insufficiency due to severe heart failure).

II. Managing Suboptimal Dialysis Adequacy

Recommendations

1. **Confirm dialysis inadequacy by assessing procedural issues and vascular access function. (Grade D)**
2. **Once dialysis inadequacy is confirmed, increase one or more of the following treatment parameters: dialysis time, needle diameter, dialyzer KoA, or dialysis frequency. (Grade D)**

Background

When the patient fails to receive the minimum target dose of dialysis or when there is a significant drop in the dose of dialysis being delivered, the clinician should consider procedural issues (prescription, anticoagulation, appropriate measurement of dialysis dose, optimization of needle placement) and inadequate access function (Table 1).

The following techniques may be used to increase urea clearance and possibly dialysis adequacy:

- blood flow rate (21,22)
- dialyzer KoA (21)
- dialysis time (23)
- dialysis frequency (23)
- dialysate flow (24–26)
- needle size (27)
- ensuring adequate anticoagulation (28)

Consideration could also be given to use of a newer dialytic modality such as more frequent or sustained hemodialysis.

Table 1. Initial approach to low or inadequate delivered hemodialysis

Check Procedural Issues

1. Was the dialysis prescription followed?
   - blood flow rate
   - duration of treatment
   - intradialytic hypotension or other factors necessitating interruption of treatment
   - dialysate flow
   - specific dialyzer
   - volume of blood processed
2. Was anticoagulation adequate?
3. Was the dialyzer total cell volume (TCV) adequate? (for reprocessed dialyzers)
4. Was blood sampling appropriate? Consider repeating the clearance measurement.
5. Was needle placement appropriate and optimal?

Assess Access Function

1. Examine vascular accesses for evidence of dysfunction.
2. In arteriovenous accesses, consider measuring access blood flow, preferably using an ultrasound dilution technique. If indicated, perform angiography to rule out stenosis.
3. If access blood flow measurements are not available, consider estimating access recirculation using blood-based urea measurements.
4. Review needle placement and access configuration. Using loop grafts, ensure accurate knowledge of direction of flow. With needles inserted, compressing the graft between the needles results in pulsation only in the arterial needle.

III. Quality of Care

Recommendations

1. **A single person or a multi-professional team should be responsible for the quality of the medical care and have the authority to establish universal standards of care for the unit. (Grade D, opinion)**
2. **Validated clinical protocols or algorithms should be considered to reduce inappropriate variability in quality of dialysis care. (Grade D)**

Background

To ensure the quality of medical care for all patients, all those involved in providing care must be accountable. In a multiprofessional setting, the combination of a number of different professionals with different priorities dealing with complex situations may lead to variations in standards of practice and care. To ensure that the guidelines are applied uniformly to all patients in the unit, the individual or management team accountable for the quality of medical care must be clearly identified. The multidisciplinary team/dialysis program should evaluate its practice *via* Continuous Quality Improvement.

Maximizing patient adherence is critical to the long-term success of therapy. An environment that encourages optimal care may include the patient's primary care physician and appropriate specialists (*e.g.*, gynecologists, endocrinologists) in the patient's care. There is evidence that an individualized, patient-centered approach improves clinical performance compared with standard care (29).

Nonadherence may be the result of a number of factors (*e.g.*, socioeconomic, educational, emotional) that are beyond the patient's control and may require specific attention from physicians or allied health personnel. The clinician should provide appropriate information about renal failure and its treatment, and encourage patients to have continuing contact with their primary care physicians. The information provided to patients should account for educational level and language differences.

The increasing number of hemodialysis patients may potentially compromise the ability of clinicians to provide optimal care. Although management of hemodialysis patients is complex and multifactorial, many of the individual components of care (management of metabolic bone disease or anemia, control of extracellular fluid volume) are amenable to protocolization. Although no studies indicate that such protocols improve clinical outcomes, they appear to improve process of care in patients with and without end-stage renal disease (ESRD) (30,31). Protocolization of these facets of care would be expected to free more of clinicians' time to devote to other aspects that require more individualized attention.

Recommendations for Research

1. An adequately powered, randomized study to determine the impact of aggressive control of BP and extracellular fluid volume (*versus* standard care) on mortality, morbidity and hospitalization should be a high priority.
2. Since available evidence focuses on process-based outcomes, additional randomized trials evaluating the impact of bedside decision support systems, clinical protocols, or multidisciplinary care teams on clinical outcomes such as morbidity or hospitalization would be useful for formulating policy.

Appendix A

Drawing Samples for Measuring Urea Clearance

1. Predialysis and postdialysis samples must be drawn at the same dialysis session.
2. Draw predialysis blood from the arterial needle before administering any saline or heparin.
3. When central lines are used and if heparin and/or saline is used, withdraw at least 10 cc of blood before drawing the blood sample. The blood withdrawn may then be returned to the patient.
4. The postdialysis [urea] blood sample must not be diluted by either recirculation or saline.
5. For formal urea kinetic modeling, the sample must be drawn before any rebound; therefore, the slow flow/stop pump technique must be used. For other techniques (PRU and log prediction of Kt/V), the blood sample may be taken postdialysis when the possibility of access and cardiopulmonary recirculation is eliminated. To eliminate the possibility of cardiopulmonary recirculation, draw the sample at least 2 to 3 min postdialysis. To facilitate longitudinal comparisons, the sampling technique for the unit should be clearly stated, documented, and consistent from treatment to treatment and between patients.

Background

Because the goal is to ensure at least a minimum standard, a postdialysis sample is preferable and easier to obtain than a stop flow sample. Although the postdialysis sample may be more variable (due to rebound), it will tend to underestimate rather than overestimate delivered dialysis.

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CHAPTER 2: Management of Blood Pressure in Hemodialysis Patients

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I. Blood Pressure Measurement—Timing and Targets

Recommendations

1. **Use predialysis blood pressure to guide therapy. (Grade C)**
2. **Target predialysis blood pressure to be <140/90 (Grade C); optimal blood pressure is unknown.**
3. **Ambulatory recording devices or home self-measurement should be applied to patients where difficulty occurs in reaching target blood pressure levels. (Grade D, opinion)**

Background

Blood pressure (BP) varies significantly in hemodialysis patients depending upon the time taken: predialysis, postdialysis, or interdialytic. It is currently unknown which time period correlates best with long-term patient outcome, given the lack of treatment trials (1–3). It is difficult to relate usual clinical BP measurements in hemodialysis patients to published research studies because usual systolic and diastolic pressures both pre- and postdialysis are significantly higher by about 14/5 mmHg than if measured according to standardized American Heart Association criteria (4).

There is convincing evidence in the general population that hypertension is associated with increased cardiovascular mortality and morbidity, and that its control can reduce these adverse consequences (5). Observational studies in the hemodialysis population have demonstrated that hypertension is also associated with adverse consequences in these patients, especially with longer-term follow-up (6–9). Although there are no controlled trials demonstrating that control of BP by dialytic or pharmacologic means in hemodialysis patients reduces these mortality and morbidity rates, it would seem reasonable to generalize from the extensive evidence available for the general population with hypertension (2,3).

Long-term observational studies suggest that even mean arterial BP of >98 mmHg is associated with an increased risk of death compared with lower pressures (8). Other observational studies, performed in populations with older patients having a higher prevalence of cardiovascular comorbidity than the study cited above, suggest that low pre- and/or postdialysis BP may be associated with a higher risk of death than BP in excess of 140 to 150 mmHg systolic (10,11). The discrepancy between the above observations may well be an artifact of the confounding of reduced BP by severe cardiac disease (12).

Given the absence of enough data to define an optimal BP in the dialysis population, the committee selected a target predialysis BP of <140/90 mmHg. The lower target of <130/80 mmHg recommended by the Canadian Hypertension Education Program (13) for patients with diabetes or chronic kidney disease was not selected, because there are two randomized clinical trials documenting no benefit for a lower target in nondialysis patients (14,15) and associative studies (above) suggesting possible risks for the lower target in dialysis patients.

II. Management of Hypertension

Recommendations

1. **Limit patients to a dietary sodium intake of 80 to 100 mEq/d. (Grade C)**
2. **Reduce patient weight gradually by ultrafiltration, targeting for the "dry" weight, as antihypertensive medications are withdrawn. (Grade C)**
3. **"Paradoxical" rises in BP during individual dialysis/ultrafiltration sessions should be corrected by further gradual volume removal. (Grade D)**

Background

In nondialysis hypertensive patients, dietary sodium restriction may lower BP by 4.2/2.0 mmHg to 5.2/3.7 mmHg (16). It is also possible to control hypertension in many hemodialysis patients by restriction of dietary sodium to <100 mEq/d and aggressive and recurrent efforts to reduce body weight by ultrafiltration during dialysis to the "dry" weight. "Dry" weight may be defined as the lowest attainable weight at which patients are normotensive without antihypertensive medications and do not have symptoms of postural hypotension or intra/postdialytic hypotension. During this process of probing for "dry" weight, antihypertensive medications are gradually withdrawn (8,17). In turn, improved survival is associated with better BP control (8,18). Paradoxical elevation of BP during ultrafiltration is associated with volume overload and can be corrected by further aggressive reduction in target body weight (19).

The lag phenomenon has been described in hemodialysis patients whereby BP reduction lags behind reduction in volume status for weeks to months (20). Thus, efforts to control BP by reduction of dry weight must be gradual but persistent.

There is preliminary, nonrandomized evidence that extended forms of hemodialysis such as nocturnal dialysis and short daily dialysis are effective in improving BP control (21). In contrast, there is no convincing evidence at this time that intradialytic volume monitoring is effective in reducing symptoms or improving BP control. In fact, a recent randomized trial

suggests that intradialytic volume monitoring may be harmful (22).

4. **Avoid positive sodium balance induced by hypertonic dialysate and/or sodium profiling during volume status adjustment. (Grade C)**
5. **Reduce dialysate temperature when intradialytic hypotension limits ultrafiltration. (Grade C)**
6. **If antihypertensive agents are required, select agents with pharmacokinetics suitable for dialysis patients and appropriate for existing comorbid conditions. (Grade D)**

Background

Hypertonic dialysate and sodium profiling may induce net positive sodium balance in some patients, worsening hypertension and interdialytic thirst (23–25).

Lowering dialysate temperature is often effective in moderating intradialytic hypotension during attempts to achieve dry weight, particularly for hypothermic patients. A minimum dialysate temperature of 35°C has been used if feedback-controlled isothermic dialysis is not available (26,27).

There are no published controlled trials of specific antihypertensive agents in dialysis patients, and retrospective studies have provided conflicting evidence for the possible survival benefits of various classes of antihypertensive drugs (28–30). Long-acting (renally-excreted) agents such as atenolol, perindopril, or lisinopril can control hypertension occurring in dialysis patients. Administered thrice weekly after dialysis, these agents can assist in BP control without inducing significant hypotension (31,32).

Recommendations for Research

1. Treatment trials are required in which specific BP targets in hemodialysis patients are compared with regard to mortality and morbidity outcomes.
2. Randomized trials are needed to determine the optimal use of specific classes of antihypertensive agents in hemodialysis patients.

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CHAPTER 3: Mineral Metabolism

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Management of Serum Phosphate, Serum Calcium, and Parathyroid Hormone

Recommendations

1. **Serum phosphate levels should be monitored and maintained within the normal range. (Grade C)**
2. **To optimize control of serum phosphate, use restriction of dietary phosphate (Grade D), adjust the dialysis prescription (Grade D), and use oral phosphate binders. (Grade C)**

Background

Elevated serum phosphate is common in individuals with stage 5 chronic kidney disease. Multiple studies have shown that elevated serum phosphate is associated with increased morbidity and mortality due to cardiovascular disease in the hemodialysis population (1–5). Increased serum phosphate is also involved in the pathogenesis of secondary hyperparathyroidism (6,7).

The current Kidney Disease Outcomes Quality Initiative (K/DOQI) target level for serum phosphate levels (0.80 to 1.78 mmol/L) was partially based upon studies showing an association between cardiovascular disease morbidity and mortality and elevated serum phosphorus. In at least two of these studies, the association only reached significance at higher levels of serum phosphate (>2 mmol/L) (1,3). Decreasing phosphate levels toward the normal or target range might be associated with decreased mortality. However, to date, no randomized trials support this hypothesis.

To achieve an optimal phosphate level, the following strategies can be used:

a. Restriction of dietary phosphate. A phosphorus intake of 800 to 1000 mg per day is recommended to help achieve serum phosphorus levels of 0.80 to 1.78 mmol/L. On an intake of 1000 mg per day, about 60 to 70% is absorbed. Dietary counseling has been shown to improve phosphate control in hemodialysis patients (8,9). Further research is warranted to ascertain whether phosphorus levels differ on a diet high in plant protein *versus* animal protein.
b. Removal of phosphate by hemodialysis. Phosphate is mainly intracellular; therefore, clearance of phosphate during hemodialysis follows a pattern of most efficient clearance within the first 1 to 2 h with a plateau, and then rebounds within the first 4 h after the end of the treatment (10). The amount of phosphate removed is dependent also on the predialysis level. On average, about 900 to 1000 mg of phosphate can be removed per dialysis treatment. High-flux (*versus* low-flux) efficiency membranes may have higher phosphate clearances but phosphate removal is not significantly altered. Dialysis phosphate clearance may be improved by the use of frequent and longer dialysis, especially nocturnal hemodialysis (10,11).
c. Use of phosphate binders. Given that most hemodialysis patients are in positive phosphate balance, there is a need to use phosphate binders to decrease phosphate absorption in the gut.

Because of the concern with aluminum toxicity, calcium-based binders continue to see extensive use. There has been increasing concern about the over-reliance of calcium-based phosphate binders due to the associated calcium load. Studies have found an association between daily calcium intake and coronary artery calcification (12–14) and calcification in other vascular beds (15). These data, plus extrapolation from studies of calcium balance and daily requirements, led the K/DOQI Mineral Metabolism Guideline Committee to recommend not exceeding the use of >1500 mg of elemental calcium in calcium-containing binders with a tolerable upper limit of 2500 mg for total calcium intake per day (16).

Despite the availability of several classes of phosphate binders, the majority of hemodialysis patients continue to have elevated phosphate levels (17,18). This illustrates the lack of efficacy of the available binders. When deciding on the choice and dose of binder(s) to use, it is important to realize that many of the clinical studies are of short duration (19–24), nonrandomized (20–22,25–31), open-label (19–22,25–28,30–38), or use no direct comparator (20–22,26–28,30,31,35). In addition, average medication doses or changes in laboratory parameters are not always reported, and adherence to binders ranges from 69 to 91%. As a result, available evidence does not allow the recommendation of one (or several) phosphate binders as superior to any other.

Recently, interest in the use of noncalcium-, nonaluminum-based binders has increased. Coronary artery calcification scores are lower in subjects treated with sevelamer compared with those treated with calcium binders (37). At the time of writing this guideline, only preliminary results were available from the Dialysis Clinical Outcomes Revisited (DCOR) trial. DCOR was a controlled clinical trial of approximately 2100 hemodialysis patients randomized to receive calcium-based phosphate binders or sevelamer. Three years after randomization, a 9% decrease in all-cause mortality (primary endpoint) was seen in those subjects assigned to sevelamer, although this did not reach statistical significance ($P = 0.30$) (39). Although subgroup analyses demonstrated that sevelamer use was associated with a reduction in mortality in subjects over 65 yr of age, interpretation of these data should await the final peer-

reviewed publication. It should also be kept in mind that, compared with calcium-containing phosphate binders, use of sevelamer is no better at controlling serum phosphate and is associated with greater health care costs (23,40).

3. Serum calcium levels should be monitored and maintained within the normal range. (Grade D)

Background

For the prevention of secondary hyperparathyroidism, individuals with kidney disease should have calcium levels maintained in the normal range defined by the testing laboratory. Although it is generally accepted that total serum calcium levels should be adjusted for serum albumin, Clase *et al.* found that total calcium had a higher correlation with the gold standard of ionized calcium measurement than many formulas (41).

Calcium-based phosphate binders contribute to the total daily calcium load in hemodialysis patients. Higher daily calcium intake is associated with poor outcomes including coronary calcification (13,14) and rapid progression of calcification in other vascular beds (42). Although several studies have reported an association between hypercalcemia and decreased survival (2,18,43), this finding is not consistent across all reports (1,44). Serum calcium is also inversely associated with intact parathyroid hormone (PTH) (44). In the setting of low PTH, suggesting low turnover bone disease, an increased calcium load cannot be incorporated into bone, and thus can precipitate into blood vessels, heart valves, and other soft tissues (45). Given that the above results and hypotheses are based upon associative data, may be confounded by vitamin D use, and have not been tested in controlled clinical trials, firm recommendations limiting the daily oral calcium intake cannot be made by this committee.

Dialysate calcium also impacts calcium balance. Fernandez *et al.* reported that the use of 1.25 mM dialysate calcium resulted in negative calcium balance, despite no change in serum ionized calcium values (46). However, compared with 1.75 mM dialysate calcium, 1.25 mM dialysate calcium led to higher parathyroid hormone levels and greater use of vitamin D.

4. Measure PTH levels on a regular basis (at a minimum every 4 mo) (Grade D, opinion) and direct therapy to avoid both high and low PTH levels. (Grade C)

5. Give priority to phosphate and calcium targets over the management of PTH. (Grade D, opinion)

6. Avoid intach PTH (iPTH) levels below 100 pg/ml (10.6 pmol/L) (Grade C); iPTH levels >500 pg/ml (53 pmol/L) should be treated if accompanied by symptoms or clinical signs of hyperparathyroidism. (Grade D, opinion)

7. Vitamin D sterols can be used in the treatment of secondary hyperparathyroidism, but should be discontinued when PTH levels decrease below target levels, or if calcium or phosphate levels increase above target levels. (Grade C)

8. Parathyroidectomy should be considered for those patients who have failed standard treatments and have persistently elevated PTH levels with systemic complications. (Grade D, opinion)

Background

Given that PTH is a major regulator of bone turnover and skeletal cellular activity, PTH is widely used as a surrogate marker instead of bone histomorphometric analysis (the gold standard). Recently, many questions have been raised about the method of PTH measurement, the normal or optimal range of the PTH level, and the correlation of PTH levels with bone histology. The principal method of measurement of PTH over the last couple decades has been a two-site immunometric technique called the "intact" PTH (iPTH) assay. This form of measurement has been widely used and is the basis of current classification schemes for bone turnover. It is now known that assays measuring iPTH also measure a large PTH fragment (PTH 7 to 84). This has led to assays specific for PTH 1 to 84 (biointact or whole PTH assays). Although these new assays appear promising, much of the data with renal bone disease and the correlation with PTH levels exist for iPTH measurements. On this basis, the current guidelines use target levels based upon the iPTH assay. Users of these guidelines are instructed to determine the assay used locally and use sound clinical judgment if the biointact or whole PTH assay is used.

Much of the research that correlates iPTH values to bone biopsy findings was done at least 10 yr ago, where iPTH levels <165 pg/ml (17.5 pmol/L) were associated with adynamic bone disease (low turnover disease) and iPTH levels >300 pg/ml (31.8 pmol/L) correlated with high turnover bone disease (47–49). However, it has also been shown that use of calcitriol modifies the relationship between iPTH and indices of bone formation and turnover (50).

Coen *et al.* used receiver-operator characteristic (ROC) curves to determine that a cutoff value of 210 pg/ml (22.3 pmol/L) for iPTH had a positive predictive value of 100 and a negative predictive value of 45 in predicting adynamic bone disease *versus* mixed osteodystrophy or high turnover disease (51). In the K/DOQI bone metabolism guidelines, summary ROC curves from 5 individual studies revealed that a threshold iPTH level of 150 to 200 pg/ml (15.9 to 21.2 pmol/L) had a sensitivity of 93% and specificity of 77% for diagnosis of high turnover bone disease, while a PTH value of 60 pg/ml (6.4 pmol/L) or less had a sensitivity of 70% and specificity of 87% for low bone turnover (16).

Controlling or preventing secondary hyperparathyroidism is important in patients with chronic kidney disease. Not only is there concern about renal bone disease, but also increasingly there is concern about other systemic toxicities. Several studies have shown that moderate to severe elevations of iPTH are associated with increased morbidity and mortality (1–3). In addition, decreased iPTH levels are also associated with increased morbidity and mortality (4,44,52). Therefore, iPTH values both above and below the current target range are undesirable.

Specific treatment strategies include maintaining normal calcium and phosphate levels. Calcium supplementation may also be needed to maintain serum calcium with the normal range. Vitamin D analogs $1\alpha(OH)D_3$ or $1,25(OH)_2D_3$ are used to treat patients with elevated PTH levels as they act by suppressing prepro-PTH-mRNA in the parathyroid cell. Vitamin D analogs

can be prescribed daily or intermittently, orally or intravenously. Clinical trials have been inconclusive in determining the best route of administration (53–55). Intravenous therapy after dialysis is an effective way to ensure compliance. All vitamin D analogues have the ability to increase serum levels of calcium and phosphate, and although this effect may be less with newer analogues, valid studies with relevant clinical outcomes are not available (5,56–63).

Parathyroidectomy is used for secondary hyperparathyroidism that is not controlled by standard medical therapy, and is associated with other clinical indications, such as elevated serum calcium or phosphate, tendon rupture, resistant anemia, or bone pain. A recent analysis of US Renal Data System data shows that although mortality is higher for the first 3 mo after parathyroidectomy, a survival advantage is apparent 20 mo postoperatively (64).

A calcimimetic agent, specifically cinacalcet, has recently been released for the treatment of secondary hyperparathyroidism in dialysis patients. Cinacalcet binds to the calcium-sensing receptor on the PTH gland cells and increases the sensitivity of the receptor to calcium. The largest study published confirmed that subjects treated with cinacalcet had a therapeutic response, with 43% achieving an iPTH level of <250 pg/ml (26.5 pmol/L) as compared with only 5% in the control group (65). The decrease in iPTH was seen at all levels of baseline iPTH. Additional benefits seen were significant decreases in serum phosphate, calcium and calcium × phosphorus product. Hypocalcemia can occur, but can be minimized by dose titration plus the addition of vitamin D analogues to maintain a normal serum calcium level. All the published studies with cinacalcet have been of relatively short duration, using the surrogate endpoints of iPTH, phosphate, and calcium. Longer-term use will be needed to determine the impact on use of phosphate binders, calcium supplements, and vitamin D analogues, and perhaps more importantly the impact of decreasing iPTH on morbidity and mortality.

Recommendations for Research

1. Although many studies have shown that elevated phosphate, calcium, and iPTH are associated with increased morbidity and mortality, prospective randomized studies are needed to determine whether achieving suggested targets for calcium and phosphate decreases mortality in hemodialysis patients.
2. Studies are needed to determine the appropriate target range of PTH (intact or whole assays) for normal bone metabolism in stage 5 chronic kidney disease patients on dialysis.
3. Evaluate the impact vitamin D sterols and calcimimetics on morbidity and mortality in hemodialysis patients.

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CHAPTER 4: Vascular Access

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I. Planning for Vascular Access

Recommendations

1. **Each center should establish a dedicated team for vascular access. (Grade D, opinion)**
2. **Preserve arm veins suitable for placement of vascular access. Preservation should begin in patients with progressive kidney disease and an estimated GFR of less than 30 ml/min. (Grade D, opinion)**
3. **The preferred type of vascular access is a radio-cephalic native vessel arteriovenous fistula. (Grade C)**

Background

Arteriovenous (AV) access–related complications result in considerable morbidity. With a dedicated access team, including a nephrologist, an access surgeon, an interventional radiologist, and a dialysis nurse, a center can develop and maintain skills that should lead to better patient care. Arm veins, particularly the cephalic veins of the nondominant arm, should not be used for venipuncture or intravenous catheters. In patients with advanced chronic kidney disease, the dorsum of the hand should be used for intravenous line. When venipuncture of the arm veins is necessary, sites should be rotated. Patients should wear a Medic Alert bracelet to inform hospital staff to avoid intravenous cannulation of essential veins.

The preferred type of access is a native AV fistula, followed by grafts and then central venous catheters (1–5). It has been shown that the relative risk of bacteremia is greater with central venous catheters than with AV fistulae (6). Compared with AV grafts, AV fistulae have been shown to be associated with better long-term survival, require less intervention to maintain patency, have lower infection rates, and lead to less health care expenditure (1–5,7). Data from the Canadian Organ Replacement Registry show equivalent patient survival on hemodialysis and peritoneal dialysis (8). This information should be considered before using central venous catheters for long-term hemodialysis as opposed to peritoneal dialysis, when both are technically feasible.

The preferred sites for placing the AV fistula are (in order of preference) the wrist (radiocephalic) and the elbow (brachiocephalic) (3,9,10). If it is not possible to establish either of these types of fistula, access may be established using either a transposed brachial-basilic vein fistula (3) or an AV graft of synthetic material (*e.g.*, polytetrafluoroethylene [PTFE]). The preferred site and type of graft is a forearm curved looped radiocephalic graft. This is followed by an upper arm straight graft (11). The least preferred sites and type of grafts are forearm straight radial cephalic and looped thigh grafts. However, the location for the graft placement is determined by each patient's unique anatomical restrictions, previous access history, and the surgeon's skill.

During the planning phase for a new vascular access, venography may be beneficial and may be considered in patients with the following:

- edema in the extremity in which an access site is planned,
- collateral vein development or accessory vein enlargement in any planned access site,
- differential extremity size, if that extremity is contemplated as an access site,
- current or previous subclavian catheter placement of any type in venous drainage of planned access,
- current or previous transvenous pacemaker in venous drainage of planned access,
- previous arm, neck, or chest trauma or surgery in venous drainage of planned access, or
- multiple previous accesses in an extremity planned as an access site.

For patients not yet on dialysis, the benefit of the information gained with venography must be weighed against the risk associated with exposure to radio-contrast media.

II. Access Timing, Placement, and Maturation

Recommendations

1. **Establish AV fistulae when the patient has an estimated GFR of 15 to 20 ml/min and progressive kidney disease. (Grade D, opinion)**

Background

It is important to create an AV fistula *at least* 3 to 4 mo before its anticipated use. More time may be necessary depending upon the site's referral and surgical wait times. Grafts can be used in patients who are not candidates for a primary AV fistula. Place dialysis PTFE AV grafts at least 3 to 6 wk before an anticipated need for hemodialysis. According to the available evidence, PTFE tubes are preferred over bovine grafts (12). There is no evidence available yet on the efficacy of newer synthetic materials. When using these materials, follow manufacturers' recommendations.

Cuffed and noncuffed hemodialysis catheters can be inserted immediately before their use because they do not require maturation time. Cuffed, tunneled, central venous catheters can be a valuable alternative to grafts, although there are concerns about infection, thrombosis, and dialysis adequacy. Adjust the catheter tip to the level of caval atrial junction or beyond. Subclavian access should be used only when jugular options

are not available. Catheter position should be confirmed using radiography, and the catheter tip should be readjusted as necessary to ensure proper position. The use of real-time, ultrasound-guided insertion may be an advantage in reducing insertion-related complications, particularly in patients who have had previous catheter insertions (13,14). Do not place jugular or subclavian hemodialysis catheters on the same side as a maturing AV access.

For patients with chronic kidney disease who need acute hemodialysis vascular access, use a noncuffed or a cuffed percutaneously inserted catheter. These catheters are suitable for immediate use and should not be inserted before needed (15). Femoral catheters should be at least 19 cm long to minimize recirculation. Noncuffed femoral catheters should be sutured in place and can be left in as long as there are no complications.

AV fistulae need time to mature before cannulation (at least one month, preferably 3 mo). Recent data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrates a large intercountry variability in the timing of AV fistula cannulation. The majority of fistulae in Europe are cannulated early—within 8 wk of creation. Early cannulation does not appear to be associated with subsequent fistula failure and may decrease exposure time to central venous catheters (16). As AV fistula maturation depends on artery and vein size and integrity as well as cardiac output, clinical judgment should be used in determining time to first use. The following procedures have been used in an attempt to enhance maturation of AV fistulae:

- fistula hand-arm exercise (*e.g.*, squeezing a rubber ball with or without a lightly applied tourniquet),
- selective obliteration of major venous side branches,
- rest, until swelling is resolved (for a new native AV fistula with induration and edema).

A new PTFE dialysis AV graft should not be cannulated until swelling has gone down enough to allow palpation of the course of the graft—ideally 3 to 6 wk after placement. Ideally, no attempt should be made to cannulate the graft for at least 14 d after placement. Use a venogram or other noncontrast study to evaluate central veins in patients with swelling that does not respond to arm elevation, or that persists >2 wk after dialysis AV access placement.

III. Monitoring and Maintenance of Vascular Access

Recommendations

1. **Measure access flow bimonthly in AV fistulae (Grade D) and venous pressure or access flow monthly in AV grafts. (Grade D)**
2. **Perform angiography if fistula flow decreases to <500 ml/min or drops >20% from baseline (Grade D); if AV graft flow decreases to <650 ml/min or drops >20% from baseline. (Grade D)**

Table 2. Methods to measure dynamic, static, and slow-flow venous pressures

*Dynamic Venous Dialysis Pressure Monitoring Protocol**

- Establish a baseline initiating measurements when the access is first used.
- Measure venous dialysis pressure from the hemodialysis machine at Qb 200 ml/min during the first 2 to 5 min of hemodialysis at every hemodialysis session.
- Use 15-gauge needles (or establish own protocol for different needle size).
- Assure that the venous needle is in the lumen of the vessel and not partially occluded by the vessel wall.
- Pressure must exceed the threshold three times in succession to be significant.
- Assess at same level relative to hemodialysis machine for all measurements.

Static Venous Pressure Measurement Protocol

- Turn the blood pump off and clamp tubing between the dialyzer and the venous drip chamber.
- Make static measurement (P) from venous transducer exactly 30 s after stopping blood flow.
- Determine in centimeters the height difference between the arm of the chair and blood in the venous drip chamber (H).
- Calculate estimated intra-access pressure: [eIAP = P + (0.35 × *H* + 3.4)]
- Measure mean arterial pressure (MAP).
- Calculate eIAP/MAP (absolute eIAP/MAP >0.5 or a progressive rise on repeated measurements indicates a stenosis/thrombosis beyond the venous needle site in AV grafts).

Slow Flow Venous Pressure Measurement Protocol

- Measure venous pressure from machine transducer at a blood flow of 50 ml/min during first 15 min of dialysis.
- Measure MAP.
- Calculate ratio of various pressures and MAP.
- Investigate any venous pressure/MAP ratio >0.6.

*To interpret the dynamic protocol, the clinician must obtain three measurements in succession above the threshold to eliminate the effect of variation caused by needle placement. Hemodialysis machines measure pressure with different monitors and tubing types and lengths. These variables, as well as needle size, influence venous dialysis pressure. The most important variable affecting the dynamic pressure at a blood flow of 200 ml/min is the needle gauge. It is essential to set thresholds for action based on machine manufacturer, tubing type, and needle gauge.

Background

Monitoring AV fistulae and grafts for hemodynamically significant stenosis, combined with corrective treatment, improves patency and decreases the incidence of thrombosis (17–24). A quality assurance program should collect and maintain data on each patient from the monitoring tests, clinical assessment, and dialysis adequacy measurements, and make this information available to all staff. The data should also be tabulated and

tracked within each dialysis center and benchmarked against regional or national standards.

Although recirculation studies have been shown to be useful for detecting AV fistulae stenosis, the recirculation only occurs when the total access flow is lower than the blood flow in the dialysate circuit. Therefore, the preferred method for monitoring AV fistulae is direct on-dialysis flow measures (18). When clinicians do not have access to on-dialysis flow measures, they can monitor AV fistulae using regular recirculation studies (25).

When using flow measures, clinicians should be aware that AV fistulae are capable of sustaining a lower blood flow than an AV graft without clotting, so a flow measurement <650 ml/min in an AV fistulae is less likely to indicate a reversible stenosis or subsequent clotting. However, relative changes in flow measurement are still a cause for concern. After a successful angioplasty, AV fistulae should be monitored monthly and investigated if a flow <500 ml/min or a drop of access flow >20% of baseline occurs (18–20).

When using access recirculation measures, clinicians should be aware that any access recirculation is abnormal and should be investigated. Recirculation >5% using non–urea-based methods and recirculation >15% measured using urea-based method is significant and should lead to angiography.

Methods for monitoring AV grafts include:

- intra-access flow including monitoring for changes in flow (26–33),
- static venous pressures (25),
- dynamic venous pressures (34),
- slow-flow venous pressure (35).

Blood access flows through AV grafts can be measured by indicator dilution or conductivity tracer techniques, using the Krivitski reversed line technique (28). In a prospective study of 170 chronic hemodialysis patients, May *et al.* demonstrated that access blood flow measurements were superior in the prediction of access thrombosis compared with static pressure monitoring or urea recirculation measurement (30). However, in a blinded, randomized, controlled trial of AV graft monitoring and angioplasty, monthly blood flow measurement did not improve graft thrombosis rate over and above the standard surveillance (dynamic venous pressure and physical examination) (36).

When using pressure measurements to monitor access, clinicians should be aware that static pressure measurements are more accurate than dynamic pressure measurements (25). Methods to measure dynamic, static, and slow-flow venous pressures are provided in the Table 2.

Other studies or information that may be useful in detecting AV graft stenosis include:

- measurement of access recirculation using urea concentrations;
- measurement of recirculation using dilution techniques (non–urea-based);
- unexplained decreases in the measured amount of hemodialysis delivered (urea reduction ratio, Kt/V);
- physical findings of persistent swelling of the arm with the graft, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in a graft;
- elevated negative arterial prepump pressures that prevent increasing to acceptable blood flow;
- venography/Doppler ultrasound.

Any finding of access dysfunction, whether based on the presence of access recirculation, low or deteriorating access blood flow rates, positive pressure tests, or any other test should be investigated using angiography to determine the appropriate intervention (*e.g.*, angioplasty, surgery).

In the process of investigating the dysfunction and taking corrective measures, it is vital that the clinician take interim measures to protect the patient. When the dialysis circuit blood flow exceeds the access flow, access recirculation will occur, which leads to inadequate dialysis. To optimize dialysis treatment, the dialyzer blood flow should be reduced to a level at or just below the patient's measured access blood flow rate. The clinician should make the appropriate corrections by time and dialyzer surface area to ensure that the patient receives the desired and prescribed Kt/V (urea).

IV. Infection Prevention in the Vascular Access

Recommendations

1. **Instruct all staff and patients on infection control measures. (Grade D, opinion)**
2. **Change catheter exit site dressings at each hemodialysis treatment (Grade D, opinion). Use dry gauze dressings and povidone iodine (Grade C), mupirocin (Grade C), or polysporin triple ointment (Grade A) at the catheter exit site.**

Background

Proper infection control procedures can significantly reduce the risk of infection. Catheter care and accessing the patient's circulation should be sterile procedures. During catheter connect and disconnect procedures, nurses and patients should wear a surgical mask or face shield. Nurses should also wear gloves during all connect and disconnect procedures, although the evidence for sterile *versus* nonsterile gloves is inconclusive. Use a clean technique for needle cannulation for all cannulation procedures. Ensure that only trained dialysis staff or caregivers change hemodialysis catheter dressings and manipulate catheters that access the patient's bloodstream and minimize contamination.

A randomized control trial of dry gauze dressing with povidone iodine ointment at the catheter exit site, along with sterile dressing technique, resulted in a significant reduction in *Staphylococcal aureus* exit site infections, bacteremia, and catheter tip colonization (37). The beneficial effect was most evident in *S. aureus* carriers. Similar results have recently been reported using mupirocin and polysporin triple ointment (38). In the recent study by Lok *et al.*, polysporin triple ointment was associated with a survival benefit (39).

Routine monitoring for staphylococcal nasal carrier status and its management remains controversial. Although some

studies have shown reduction in *S. aureus* bacteremia in hemodialysis patients with nasal mupirocin ointment, development of antimicrobial resistance remains an important concern.

V. Managing Vascular Access Complications

Recommendations

1. **Use percutaneous angioplasty to treat all hemodynamically significant stenoses in patients with AV fistulae and AV grafts (Grade D); if percutaneous angioplasty is not possible, use surgical revision.**
2. **In the case of AV fistulae aneurysm formation, surgically intervene if the skin overlying the fistula is compromised, the aneurysm is expanding, or available puncture sites are limited. (Grade D)**
3. **In the case of AV grafts, surgically intervene in the presence of graft degeneration and pseudoaneurysm formation. (Grade D)**
4. **Correct thrombosis of an AV graft with pharmacomechanical or mechanical thrombolysis or surgical thrombectomy. (Grade D)**

Background

Angioplasty is the preferred treatment for both fistulae and graft stenosis (21,22,34,40,41). In native vessel AV fistulae, the most common site of stenosis/thrombosis is near AV anastomosis, distal to the insertion of an arterial needle (40,42). Stenosis, as well as the clinical parameters used to detect it, should return to within acceptable limits after the intervention.

Centers should monitor stenosis treatment outcomes on the basis of patency. It is this committee's opinion that reasonable patency goals (for the center as a whole) for angioplasty and surgical revision in the absence of thrombosis are:

- Angioplasty: 50% unassisted patency at 6 mo; for all patients, no more than 30% residual stenosis postprocedure and resolution of physical indicator(s) of stenosis.
- Surgical revision: 50% unassisted patency at 1 yr.

If angioplasty is required >2 times within 3 mo and the patient is a good surgical candidate, referral for surgical revision may be consdiered. Stents are useful in selected instances (*e.g.*, central venous stenosis, limited residual access sites, surgically inaccessible lesions, contraindication to surgery) when angioplasty fails.

The choice of technique to correct thrombosis should be based on the center's expertise. Treatment should be performed as rapidly as possible (within 24 h) after detection of thrombosis to minimize the need for temporary access. The access should be evaluated by fistulogram for residual stenosis postprocedure. Residual stenosis should be corrected by angioplasty or surgical correction. Outflow venous stenoses are present in >85% of instances of thrombosis of AV grafts. The need for percutaneous transluminal angioplasty or surgical revision is expected in most instances.

Monitoring tests used to screen for venous obstruction should return to normal after the intervention. Centers should monitor outcome results on the basis of patency. It is this committee's opinion that minimum reasonable goals (for the center as a whole) for percutaneous thrombolysis and surgical revision thrombectomy should be:

- Percutaneous thrombolysis with angioplasty: 40% unassisted patency and functionality at 3 mo.
- Surgical thrombectomy and revision: 50% unassisted patency and functionality at 6 mo and 40% unassisted patency and functionality at 1 yr.
- Immediate patency (patency to next hemodialysis session): 85% for both techniques.

Prophylaxis of access thrombosis has not been extensively studied. A recent, randomized, double-blind, placebo-controlled trial of coumadin *versus* placebo failed to demonstrate a difference in thrombotic events in newly placed AV grafts. Major bleeding was also more common in patients assigned to coumadin therapy (43). There is also some question whether the widespread use of acetylsalicylic acid may be counterproductive (44). Although a small, randomized trial has provided some enthusiasm for the use of fish oil in the prevention of AV graft thrombosis (45), additional trials are required before widespread use of this therapy could be recommended.

5. **Treat hand ischemia from arterial steal with a distal revascularization internal ligation procedure. If this fails or is not feasible, consider ligation of the AV fistula or graft. (Grade D)**
6. **Treat symptomatic central vein stenosis with percutaneous transluminal angioplasty. Place a stent only after failed angioplasty. (Grade D)**
7. **Treat dysfunctional tunneled hemodialysis catheters with instillation/infusion of tPA using a protocol. (Grade D, opinion)**

Background

Significant hand ischemia occurs in 2 to 8% of patients with AV access. Risk factors include female sex, age >60 yr, diabetes, and use of brachial artery as a donor vessel. A 10-yr retrospective review of this complication in Athens, Greece, revealed 28 of 569 patients with proximal AV access developed this complication (46). The Distal Revascularization Interval Ligation procedure, which includes an arterial ligation placed just distal to the AV graft or anastomosis and short bypass from a point 4 to 5 cm proximal to the inflow of the access to a point just distal to the ligation, was performed in 23 of these patients. Immediate relief of symptoms occurred in all and 1-yr patency was 69% (46).

Central vein stenosis can result in significant arm swelling when an AV access is created on the ipsilateral side. When a patient has central vein stenosis and significant arm swelling, percutaneous angioplasty should be performed. Angioplasty can be repeated in case of recurrence. A stent should be placed after more than one recurrence or a failed angioplasty (47).

A protocolized approach is recommended for management of a dysfunctional hemodialysis catheter. Catheter dysfunction is defined as failure, based on catheter-related thrombotic or mechanical factors, to attain and maintain an extracorporeal blood flow sufficient to perform the prescribed hemodialysis

without significantly lengthening or altering the hemodialysis treatment. A common cause for this dysfunction is the development of a fibrin sheath around the catheter, which can develop shortly after insertion. The fibrin sheath acts as a nidus for thrombus and biofilm formation. With the unavailability of urokinase, tissue plasminogen activator (tPA) has been used to restore catheter patency reduced by thrombosis. Instillation of 2 mg tPA in each lumen for a median of 24 h resulted in patency in >80% of cases (48). Given the available information, treatment of a dysfunctional permanent catheter using a protocol for tPA instillation is recommended (Table 3). If adequate flow is not achieved, consideration can be given to the use of low-dose systemic tPA. Although there is no specific trial, this recommendation is based on systemic urokinase use (49). The reader should keep in mind that valid evidence to support the manner of tPA instillation (dwell *versus* advancing *versus* infusion protocols) and the duration of the therapy is lacking. If adequate flow is still not achieved, perform radiographic studies followed by intervention. In patients with contraindications to systemic administration of tPA, fibrin sheath stripping (50) and catheter exchange over a guidewire are alternative options.

8. **Treat extensive infection of a dialysis AV graft with parenteral antibiotics and total graft resection. (Grade D)**
9. **Treat infections of primary AV fistulae as subacute bacterial endocarditis with 6 wk of antibiotic therapy. (Grade D)**

Table 3. Algorithm for malfunctioning central venous catheter

Criteria

- Inability to maintain sustained pump speed >200 ml/min for one hemodialysis run.
- Difficulty aspiring from either lumen of the catheter.
  - Check for kinks beneath catheter clamps.
  - Change patient position.
  - Flush vigorously.
  - Reverse lumens.

tPA Procedure

- tPA instillation for 30 min predialysis (or instill tPA at the end of dialysis in preparation for the next dialysis session).
- Aspirate lumen(s) and attempt dialysis; if flow is established, proceed with dialysis.
- If flow is not established:
  - Infuse 4 mg tPA over 1 h.
  - Reverse lines connecting venous blood line to arterial port.
  - Run infusion *via* pump into venous drip chamber.
  - If both limbs of the catheter have sluggish flows, the lines may be reversed after 30 minutes.
- If flow is still not established, refer to Radiology for management of fibrin sheath, if present.

10. **Treat central venous catheter-related bacteremia with systemic antibiotics and catheter exchange over a wire. (Grade D)**
11. **Treat catheter tunnel infections without bacteremia with parenteral antibiotics and appropriate local measures. Catheter removal is indicated if the infection fails to respond to 2 wk of therapy. (Grade D)**

Background

Use of central venous catheters is associated with a significantly higher risk of bacteremia compared with AV fistulae. With AV grafts, the infection risk is moderate (1,6,51). It may be possible to eradicate a local graft infection with a combination of incision and local resection of the infected portion of the graft and systemic antibiotics (52). However, extensive infection of a graft requires total resection of the graft along with parenteral antibiotics. Tunneled cuffed catheter infection is a serious problem. Appropriate treatment depends on the nature of the infection (53–55).

In patients with cuffed or noncuffed central venous catheters and suspected bacteremias, AV fistulae, or AV graft infections, start treatment with 1 to 2 g cefazolin depending on patient weight, and 1.5 mg/kg gentamycin postdialysis after blood cultures are drawn. In patients with known cephalosporin allergy, or in centers with a predominance of coagulase negative staphylococcal catheter related infections, use 15 mg/kg vancomycin instead of cefazolin. Once blood culture results are available in stable asymptomatic patients without exit site or catheter tunnel tract involvement, the catheter should be changed over a wire and antibiotic treatment continued for 2 to 4 wk as clinically indicated. In all cases, definitive therapy should be based on the organism(s) isolated. For patients with central venous catheters, the catheter should be removed, rather than exchanged, in all instances if the patient is clinically unstable or if the patient remains symptomatic for >36 h (53–55).

In patients with difficult access, clinicians can attempt antibiotic treatment without changing the catheter. However, the success of such catheter salvage is low (54,55). A new, permanent access should not be placed until blood cultures, performed after cessation of antibiotic treatment, have been negative for at least 48 h.

Catheter exit site infections are characterized by redness, crusting, and exudate at the exit site in the absence of systemic symptoms and negative blood cultures. Treatment includes proper local exit site care and oral or parenteral antibiotics based on culture and sensitivity. The catheter typically does not need to be removed. If there is tunnel drainage, treat with parenteral antibiotics (antistaphylococcal or antistreptococcal therapy pending culture report) in addition to following appropriate local measures. Definitive therapy should be based on culture results. Do not remove the catheter unless the infection fails to respond to therapy or the patient is clinically unstable. If the infection fails to respond after 2 wk of therapy, remove the catheter and replace it using a different tunnel and exit site.

For all access-related infections, empiric therapy should be regularly evaluated in conjunction with specialists in infectious

diseases or microbiology so that therapy reflects the changing microbiology and sensitivities that are unique to the local environment.

VI. Quality of Care Standards

Background

Primary AV fistulae should be constructed in all suitable new patients who elect to receive hemodialysis as their initial form of renal replacement therapy. After failure of every dialysis AV access, all patients should be re-evaluated for possible construction of a primary AV fistula. Ultimately, >60% of prevalent patients should have a native AV fistula (1). Each center should establish a database to track the types of accesses created and the complication rates. Centers should work to achieve the following target rates:

- The rate of graft thrombosis should not exceed 0.5 thrombotic episodes per patient year at risk (34).
- After adjusting for initial failures (*e.g.*, failures within the first 2 mo of fistula use), the rate of thrombosis of native AV fistulae should be <0.25 episodes per patient year at risk. Dialysis centers should examine their thrombosis rates and the underlying causes as part of an ongoing Quality Assurance/Continuous Quality Improvement program.
- The rate of infection should not exceed 0.01 episodes per patient year at risk for primary AV fistula and 0.1 episodes per patient year at risk for AV grafts (6).
- For tunneled cuffed catheters, the recommended target rate of systemic infection is <0.5 episodes per patient year at risk (6).
- The primary access failure rates of dialysis AV grafts in the following locations and configurations should not be >15% in forearm straight grafts, 10% in forearm loop grafts, and 5% in upper arm grafts (3,11,56).
- The cumulative patency rate of all dialysis AV grafts should be at least 70% at 1 yr, 60% at 2 yr, and 50% at 3 yr (40,41).

Recommendations for Research

1. To improve the clinicians' ability to monitor and intervene successfully, future research should include a randomized prospective trial on intervention based on access flow measurements in both AV fistulae and PTFE grafts.
2. Randomized trials should be performed to assess the suitability of clinical and vascular studies before AV access creation to improve AV access maturation.
3. Appropriate trials for prevention of venous thrombosis in AV grafts should be performed.
4. Appropriate studies to determine characteristics that would influence/predict the successful creation and maturation of fistulas are required.

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CHAPTER 5: Frequent and Sustained Hemodialysis

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Introduction

There is an emerging body of evidence which suggests that frequent hemodialysis may provide significant clinical advantages for patients with end-stage renal disease (ESRD) over conventional hemodialysis (CvHD). The aim of this chapter is to provide a rational, evidence-based approach for the clinical use of frequent hemodialysis.

For the purpose of this chapter, short daily hemodialysis (SDHD) is defined as hemodialysis prescribed at 5 to 6 sessions per week, 2 to 3 h of treatment per session. Nocturnal hemodialysis (NHD) is defined as hemodialysis prescribed at 5 to 6 sessions per week during sleep, 6 to 8 h treatment per session. The location of renal replacement therapy has not been specified. SDHD is most commonly administered in-center, whereas NHD is usually provided at a home setting but not exclusively.

As there is also ongoing interest in sustained treatment hemodialysis and such practice is showing resiliency, we will provide a rational, evidence-based approach for the clinical use of sustained hemodialysis. Thrice-weekly sustained hemodialysis (TWSHD) is defined as hemodialysis prescribed at 3 sessions per week, >4 h treatment per session.

I. Assessment of Adequacy and Dose of Frequent and Sustained Hemodialysis

Recommendations

1. **Consider control of clinical parameters, including blood pressure (BP), extracellular fluid volume control, anemia, mineral metabolism, and nutritional status when evaluating for dialysis adequacy. (Grade D, opinion)**

Background

SDHD, NHD, and TWSHD deliver enhanced small solute clearance in comparison to conventional therapies. Although multiple dosing constructs based on urea kinetics have been proposed, none have been validated (1–3). Furthermore, the optimal dose of frequent or of sustained hemodialysis has not been defined. Although it is clear that *all forms* of intensive hemodialysis will exceed the current recommended guideline of hemodialysis adequacy, there is no available evidence for a specific target. In addition to urea kinetics, clinicians must consider clinical indicators (*i.e.*, BP, extracellular fluid volume control, anemia management, control of mineral metabolism, nutritional status, and overall cardiovascular health) when using frequent or sustained hemodialysis. Clinicians should consider adjusting duration and frequency of dialysis to provide the best possible clinical outcome while balancing patient burden, quality of life, and costs.

II. Clinical Indications for the Use of Frequent and Sustained Hemodialysis

Recommendations

1. **In patients with poorly controlled BP, consider the use of frequent hemodialysis (Grade D) or sustained hemodialysis. (Grade C)**
2. **In patients with significant left ventricular hypertrophy or impaired left ventricular systolic function, consider the use of frequent hemodialysis as adjunctive therapy. (Grade D)**
3. **In patients who exhibit hemodynamic instability with conventional hemodialysis, the use of frequent hemodialysis should be considered. (Grade D, opinion)**

Background

Hypertension is an adverse prognosticator in patients with ESRD (4). SDHD (5) and NHD (6) have been shown to improve BP control in observational studies. TWSHD has been shown to improve BP control in one randomized study (7) and in numerous observational studies (8–15). Current evidence suggests that SDHD lowers BP by decreasing extracellular fluid volume (3). In contrast, NHD decreases BP in patients with ESRD primarily *via* lowering total peripheral resistance (16). In addition, NHD has been documented to augment flow-mediated dilation (16), which suggests that intensive hemodialysis may have a protective vascular effect. In line with this observation, reduced vascular resistance and phenomena other than volume contraction underlying lower BP have been documented in TWSHD (7,17,18). Further research is required to elucidate the impact of frequent or of sustained dialysis on BP control and clinical outcomes using long-term, prospective, controlled studies.

Left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction are potent cardiovascular risk factors in patients with ESRD (19). To date, numerous medical approaches have been attempted to improve cardiac geometry and systolic function in ESRD patients with limited success (20). NHD and SDHD have been shown in nonrandomized clinical studies to be associated with regression of LVH (5,6,21). NHD was documented in a small clinical series to restore impaired left ventricular systolic function (22). The use of frequent hemodialysis may allow improved control of left ventricular geometry and systolic function. Further research is required to examine the magnitude and impact of both SDHD and NHD on these potent cardiovascular surrogate endpoints. There is no study of LVH regression with TWSHD. Furthermore, there is a high prevalence of LVH in many observational studies of TWSHD (12,13,23).

Hemodynamic instability during conventional hemodialysis

is not uncommonly encountered. Usual manifestations include severe leg cramping and intradialytic hypotension (24). Conversion to frequent hemodialysis has been shown to improve patients' overall sense of well-being (25). Of note, intra- and interdialytic hemodynamic instability were greatly improved upon conversion to frequent hemodialysis (26). In the London Daily/Nocturnal Hemodialysis Study, it was reported that intradialytic symptoms decreased with the use of SDHD or NHD. It is interesting to note that the time required to recover from dialysis therapy was substantially lower with frequent hemodialysis in comparison to conventional hemodialysis. It has been suggested that frequent hemodialysis decreased the potential for intra- and interdialytic hemodynamic instability because of the lack of rapid removal of fluid in excess of interstitial refilling (27). More research is needed to optimally titrate the hemodynamic profile of ESRD patients with the use of frequent hemodialysis. With respect to TWSHD, one randomized crossover study comparing 4-h *versus* 5-h sessions in TWSHD found less intradialytic and postdialytic hypotension with the longer session, but an increase in other peridialytic symptoms (28).

4. **In patients with refractory hyperphosphatemia and/or secondary hyperparathyroidism, consider the use of NHD as adjunctive therapy. (Grade D, opinion)**
5. **In patients with refractory peripheral vascular disease and ectopic calcification, consider the use of NHD as salvage therapy. (Grade D, opinion)**
6. **In patients who exhibit chronic malnutrition, consider the use of frequent hemodialysis as salvage therapy. (Grade D, opinion)**

Hyperphosphatemia and secondary hyperparathyroidism in conjunction with hypercalcemia have emerged as important contributors to vascular calcification and cardiovascular death in the ESRD population (29–31). Normalization of phosphate balance and superior control of secondary hyperparathyroidism has been shown by NHD in an observational study (32). SDHD has not resulted in a comparable decrease in phosphate level as seen in NHD. The longitudinal impact of enhanced control of phosphate and lowering of parathyroid hormone axis by NHD on vascular biology and renal osteodystrophy remains to be clarified.

Peripheral vascular disease remains a leading cause of cardiovascular morbidity and mortality in the ESRD population. Thus far, medical therapy has not resulted in significant success in the improvement of uremia-associated peripheral vascular disease (33). Improvement in peripheral vascular flow as measured by arterial Doppler was documented in one patient after conversion from CvHD to NHD (34). It is plausible that any improvement in peripheral vascular disease may occur through resolution of ectopic calcification, which has been reported with the use of NHD (35). It is proposed that normalization of phosphate balance in conjunction with augmentation of uremia control facilitates the resorption of ectopic calcification. There is no published data documenting the impact of SDHD on peripheral vascular disease in ESRD.

Impaired nutritional parameters, including lean body mass, serum albumin, and protein intake, continue to be potent predictors of clinical outcome in ESRD patients (36,37). Observational studies suggest that frequent hemodialysis improves nutritional status of ESRD patients despite a theoretical concern of overdialysis of water-soluble nutrients (38). SDHD has been shown to improve albumin, lipid status, and protein anabolism (39–42). Similarly, NHD improves nitrogen balance, lipid status, and dietary intake in ESRD patients (41,43,44). Current evidence on the impact of frequent hemodialysis on malnutrition is limited by its observational nature and short duration of follow-up. The paucity of long-term or controlled evidence reflects the importance of further research in this domain.

Recommendations for Research

1. There is growing enthusiasm for the routine clinical use of frequent hemodialysis. It is important to note that there has not yet been any randomized controlled data to support the use of SDHD or NHD (45). Thus far, frequent hemodialysis shows early promise in improving clinical outcomes in ESRD patients. Correction of sleep apnea (46), improvement in cardiac autonomic balance (16), and amelioration of homocysteine level (47) continue to suggest that augmentation of uremic clearance is associated with improved surrogate endpoints, especially with NHD. By providing enhanced clearance, frequent hemodialysis represents a unique opportunity for the renal community to gain further insights into the basic science of uremia and its impact on other body systems. The true clinical effect of frequent hemodialysis can only be elucidated by a longitudinal, controlled, clinical study. Finally, the widespread implementation of frequent hemodialysis may only be achieved if barriers in cost, social perception, and hemodialysis training are studied in a systematic manner.
2. Interest in TWSHD stems from sometimes exceptional survival data and BP management in mostly uncontrolled populations. As incremental hemodialysis is gaining popularity and because some patients may accept overnight sustained hemodialysis but not on a daily basis, it is important that such endeavors be explored in a rigorous, prospective manners. NHD provides not only frequent but also sustained hemodialysis compared with CvHD. Dialysis duration is readily recognized as a critical factor for water removal independent of Kt/V urea. The time dependence of uremic toxins other than water, like phosphate, and of surrogate markers of survival, like LVH, needs to be studied.

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