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CANADIAN SOCIETY OF NEPHROLOGY GUIDELINES/RECOMMENDATIONS

CLINICAL PRACTICE GUIDELINES AND RECOMMENDATIONS ON PERITONEAL DIALYSIS ADEQUACY 2011

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The brief of this Canadian Society of Nephrology (CSN) work group pertains to "adequacy of peritoneal dialysis [PD]." The aim was to update the previous set of guidelines published in 1999 (1). This update is required because of the publication, since 1999, of a significant number of important new studies advancing knowledge about adequacy in PD.

The general sentiment of the work group, even more so than was the case when the previous guidelines were drawn up, is that the term "adequacy" must be much more broadly defined. It should not be considered to apply to clearances alone, even though the term has been loosely used that way in the past. For present purposes, the group considered that adequate dialysis requires attention to volume status and nutrition as well as to clearances. Because volume status is critically related to blood pressure and other cardiovascular (CV) risk factors, it was felt to be important to address those topics also. Indeed, given the high cardiac mortality rates of dialysis patients, no area in their care is more worthy of focus than CV risk reduction. Clearances, volume, and nutrition are all profoundly influenced by residual renal function (RRF), and so a section on preservation of RRF has been given a prominent position. Glycemic control and the broader issue of the consequences of exposure to hypertonic glucose are also addressed.

Obviously, other areas of clinical care are also critical to provision of "adequate dialysis" (for example, maintenance of a good access, prevention of infection, calcium and phosphate management), but it was not felt appropriate to include those topics, given that they have been well addressed in other guideline documents.

As is customary in contemporary guideline documents, we have distinguished "clinical practice guidelines," which are based on strong published evidence, from "clinical practice recommendations," which are based on weaker evidence combined with the opinions of the work group. Not surprisingly and quite appropriately, the group generated many more recommendations than guidelines.

In most cases, evidence only from studies in PD patients was considered. However, in circumstances in which such studies were lacking, consideration was given to high-quality studies addressing relevant issues in other populations. Such studies included patients on

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hemodialysis (HD), patients with earlier stages of chronic kidney disease (CKD), and patients with CV disease. The risks of extrapolating such data to the PD population are recognized, but the therapeutic issues, especially in the area of CV disease, are so important and immediate that, pending the performance of analogous studies in PD patients, there is no reasonable alternative to this approach. Such extrapolations are, however, designated as recommendations, rather than as guidelines.

As the Reference section indicates, the work group has drawn liberally on the clinical practice guidelines of other expert bodies, both nephrologic and cardiologic, but at all times, it has attempted to apply them in the context of the Canadian PD population.

The work group included 8 nephrologists from around the country who are very involved in the clinical care of PD patients. Another nephrologist (RS), although not involved regularly with such patients, was included because she has expertise in epidemiology and evaluation of the medical literature and so took the role of ensuring objectivity. Finally, the Chair of the CSN Guidelines Committee (MT) is an *ex officio* member of the work group.

The guidelines that follow are intended to reflect the available evidence and the human and financial resources in Canada at the time of publication. While most proven therapies are currently funded in Canada, there may be only limited evidence, or evidence measured only by nonclinical endpoints, for the effectiveness with regard to clinical outcome of many therapies. Such therapies are either not funded or funded only for select groups of patients. Health care professionals are often uncomfortable taking resource constraints and medication costs into account when making therapeutic decisions. However, in health care systems with constrained budgets, directing excessive resources toward expensive, marginally effective therapies limits the resources available to be used for other effective therapies. Because physicians are often in a good position to compare the benefits and risks of specific therapies, they should take an active role in deciding which therapies should be made available, by reimbursement, to Canadian patients. Thus, resource implications have been considered for each guideline presented in this document, although only after a thorough consideration of the safety and effectiveness of the therapy or test in question.

METHODS AND PROCESS FOR GUIDELINE DEVELOPMENT

Content expertise was a prerequisite, but geographic factors were also considered when choosing the work group members. In addition to content expertise, it was necessary that the work group chair have no personal financial or research relationships with companies manufacturing products relevant to the care of PD patients. The work group was asked to apply both its content expertise and an English-language-focused literature search aimed at identifying randomized trials to identify new evidence.

A search strategy was designed to identify all relevant randomized controlled trials (RCTs) of PD in MEDLINE (1950 to 10 March 2010) and multiple Cochrane databases (Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Health Technology Assessments to 10 March 2010). All citations were reviewed in duplicate by 2 work group members, and potentially relevant articles were retrieved for review and (if relevant) incorporation into the guidelines at the discretion of the work group. Although this approach might be criticized for lack of methodologic rigor, such an approach is pragmatic and has been used and advocated by others (2).

The guidance that follows is intended to rely on evidence and, where possible, to avoid opinion-based statements. Other renal work groups have made a distinction between clinical practice guidelines and clinical practice recommendations, with guidelines being provided when the work group felt that the evidence was sufficiently strong to make definitive statements about the appropriateness of clinical practice (3). Alternatively, clinical practice recommendations were provided for statements based upon a lesser grade of evidence. The main reason for making this distinction is to highlight areas in which adherence to a guideline would be particularly likely to improve outcomes. Although this goal is reasonable, distinguishing between guidelines and recommendations is clearly inherently subjective.

The evidence in support of each guideline is graded using the scheme developed by the Canadian Hypertension Education Program (4) and used by the CSN Guidelines Committee (5) in the past (Figures 1 – 3).

When there is a lack of agreement between studies or when a lack of good-quality evidence made it difficult to create clinical practice guidelines, the work group provides an overview of existing evidence, which the members hope will guide management by practitioners. Where possible, specific research recommendations to close relevant research gaps are also provided.

The entire work group reviewed and modified the first draft of this document. The document underwent peer review by selected individuals (members and nonmembers of the CSN). After peer review, the document was revised by the work group in response to comments received and then distributed to all members of the CSN and to relevant stakeholders, including the Kidney Foundation of Canada and provincial ministries of health.

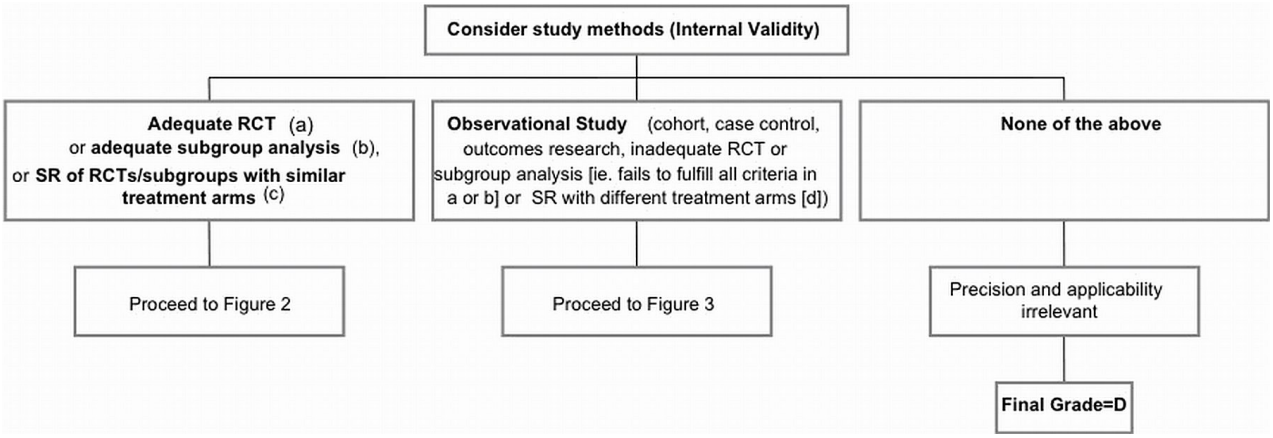

Figure 1 — Algorithm for assigning evidence grades to therapy recommendations. (a) Randomized clinical trial (RTC) with blinded assessment of outcomes (if applicable), intention-to-treat analysis, adequate follow-up (that is, at least 90%, or losses to follow-up are too few to materially affect the results), and sufficient sample size to detect a clinically important difference with power greater than 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 examine subgroup to detect a clinically important difference with power greater than 80%. (c) Systematic review (SR, also called a meta-analysis) in which the comparison arms are derived from head-to-head comparisons within the same RCT. (d) Systematic review in which the comparison arms are derived from different placebo-controlled RCTs, and then extrapolations are made across RCTs.

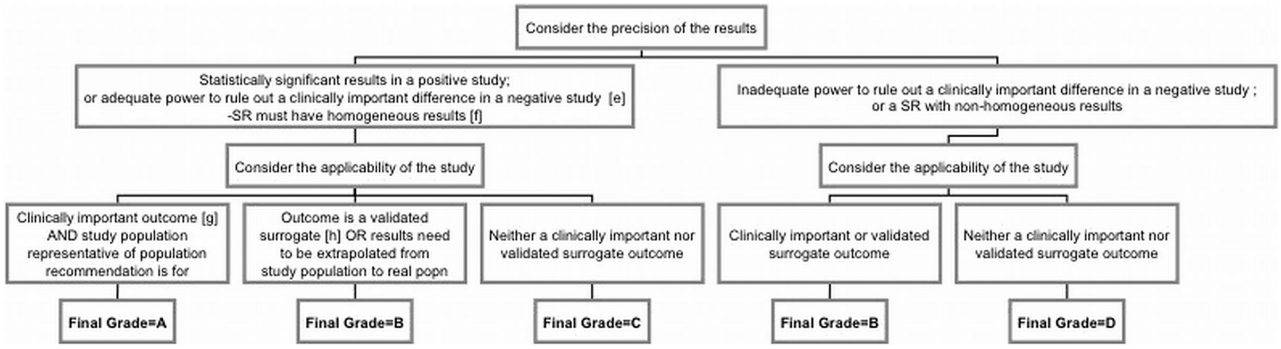

Figure 2 — Algorithm for assigning evidence grades to therapy recommendations (continued from Figure 1) for adequate randomized controlled trials (RCTs), systematic reviews, or subgroup analyses. (e) Adequate power in a negative study implies that 95% confidence limits exclude a clinically important difference. (f) Effect estimates in each study included in the systematic review (SR) are qualitatively similar (that is, in the same direction). (g) "Hard" endpoints such as death, stroke, myocardial infarction, hospitalization, and need for dialysis, or measures of quality of life. (h) Endpoints that have consistently been shown to be associated with the clinical endpoint 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 endpoint.

SECTION 1: MAINTENANCE OF RRF

1.1 MEASUREMENT OF RRF

Recommendations:

1.1.1 Residual renal urine volume and residual renal Kt/V (rKt/V) should be measured every 3 – 6 months in patients with a peritoneal Kt/V (pKt/V) of less than 1.7 weekly, especially if RRF is rapidly declining. In all other PD patients, rKt/V and urinary volume should be measured together with pKt/V when clinically indicated (see Recommendation 2.1.5) (grade D, opinion).

1.1.2 It may help clinical understanding use a mean of 24-hour urine urea and creatinine clearance to express RRF as a glomerular filtration rate (GFR) in milliliters per minute (grade D, opinion).

1.2 USE OF ANTIHYPERTENSIVE AGENTS AND DIURETICS TO PRESERVE RRF

Recommendations:

1.2.1 Per recommendations by the Canadian Hypertension Education Program (CHEP), BP should be controlled to less than 130/80 mmHg *provided that this is not associated with signs and symptoms*

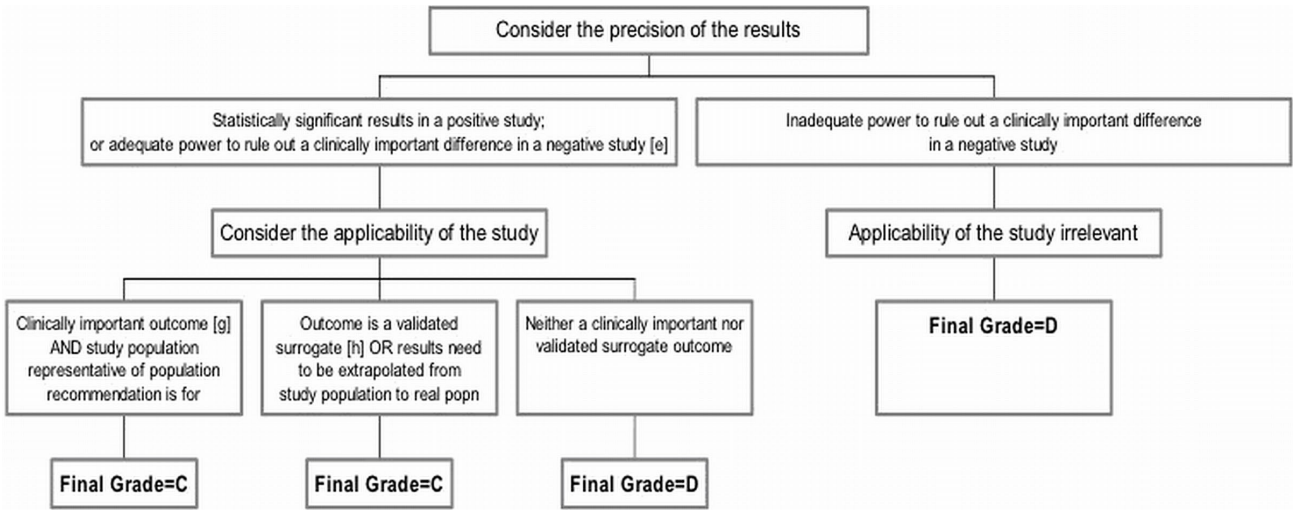

Figure 3 — Algorithm for assigning evidence grades to therapy recommendations (continued from Figure 1) for observational studies. (e) Adequate power in a negative study implies that 95% confidence limits exclude a clinically important difference. (f) Effect estimates in each study included in the systematic review are qualitatively similar (that is, in the same direction). (g) "Hard" endpoints such as death, stroke, myocardial infarction, hospitalization, and need for dialysis, or measures of quality of life. (h) Endpoints that have consistently been shown to be associated with the clinical endpoint 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 endpoint.

of postural hypotension or volume depletion (grade D, opinion).

1.2.2 Angiotensin converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be strongly considered, unless contraindicated, in all PD patients with significant (>100 mL daily) urine output (grade B).

1.2.3 Strong consideration should be given to the use of high-dose oral furosemide (up to 250 mg daily) and oral metolazone (up to 5 mg daily) in all PD patients with significant (>100 mL daily) urine output, *provided that this is not associated with signs and symptoms of postural hypotension or volume depletion* (grade B).

Background: Observational studies have shown a strong and consistent association between higher levels of RRF and improved patient survival on PD (6–10). The mechanistic link between RRF and patient survival has not been established with certainty, but higher levels of RRF are associated with improved volume control, better BP control, greater clearance of protein bound molecules, less systemic inflammation, and superior nutrition status (11–15). Urinary volume and residual renal clearances of urea and creatinine both appear to have prognostic importance (6). The residual renal GFR is reasonably well approximated by the mean of the renal urea and creatinine clearance (16).

Maintenance of residual renal clearance has been associated with better BP control, and two randomized clinical trials have suggested that ACEIs or ARBs preserve residual renal clearance independent of their BP effects (17–20). A dose of 250 mg daily of oral furosemide leads to better preservation of urine volume and sodium excretion, but has no effect on residual renal clearance (21). In the same study, patients also received metolazone 5 mg daily if daily urine output was less than 500 mL. No randomized prospective trial has examined whether better BP control results in better preservation of RRF in PD, and so recommendations concerning BP targets are extrapolated from the literature on earlier stages of CKD and from general Canadian guidelines on hypertension.

Substances known to be nephrotoxic in the non-dialysis population are generally avoided in PD patients with preserved RRF. Short courses of aminoglycoside therapy for peritonitis may not cause a long-term loss of RRF (22,23). Use of intravenous contrast dye should be minimized, although observational data suggest that there may be no long-term effects on residual renal clearances, at least when low-osmolality contrast is used and when coexistent nephrotoxic agents and volume depletion are avoided (24). Volume depletion can lead to decreases in urine output and residual renal clearance (17).

Observational data suggest that a run-in period of HD before the start of PD may have detrimental effects on RRF (25). Patients starting PD with a failing renal transplant may lose renal function as immunosuppressive

medication is tapered, but whether the benefits of prolonging the duration of immunosuppression outweigh the risks is unknown (26). The effect of PD modality on RRF is controversial. Some studies showed that automated PD (APD) is associated with more rapid loss of RRF; others did not (17,27–30). Randomized controlled trials of biocompatible PD solutions (with normal pH, low levels of glucose degradation products, and bicarbonate/lactate buffer) have not consistently showed better maintenance of residual renal clearance over at least 1 year of follow-up (31–33).

1.3 RESEARCH

Recommendations:

1.3.1 A prospective clinical trial to examine usual compared with tight BP targets and their effect on rate of loss of residual renal clearance among PD patients is needed. Such a trial could also further elucidate the interaction between suppression of proteinuria and preservation of residual renal clearance in this population.

1.3.2 A prospective clinical trial to examine rapid compared with slow tapering of immunosuppression for patients with failing renal grafts who are initiating PD is needed.

SECTION 2: SMALL-SOLUTE CLEARANCE

2.1 PRESCRIPTIONS AND TARGETS

Guideline:

2.1.1 For continuous ambulatory PD (CAPD), the usual starting prescription need not exceed 4×2-L exchanges daily (grade A) (7).

Recommendations:

2.1.2 If patients are experiencing uremic symptoms or are clinically not doing well, and if there is no identifiable cause other than insufficient dialysis, the prescription (that is, the pKt/V) should be increased, especially if the total Kt/V (that is, the pKt/V and rKt/V combined) is less than 1.7 (grade C).

2.1.3 For CAPD, lower volumes or fewer exchanges than 4×2 L daily can be used for smaller individuals or for those with significant RRF, especially if the total Kt/V is greater than 1.7 (opinion).

2.1.4 For APD, the recommended starting prescription (18,34–36) should be designed to achieve a target total Kt/V of 1.7 or more, and should take into account membrane transport characteristics, with the number of nighttime exchanges typically ranging from 3 to 5 (opinion).

2.1.5 A measurement of total Kt/V should be carried out 4 – 6 weeks after initiation of PD (37,38). The measurement of total Kt/V should be repeated if there is an unexplained or unexpected change in the patient's clinical status or a problem with ultrafiltration (UF) (opinion).

2.1.6 Strategies that are effective when attempting to raise clearance in CAPD are increases in dwell volume and addition of extra exchanges (37); however, the small risk of mechanical complications should be considered when dwell volumes are increased, and the substantial risk of noncompliance should be considered when a fifth manual exchange is added (grades A and C) (37,39,40).

2.1.7 The most effective strategy when attempting to raise clearance in APD is to ensure that the patient has a day dwell. The next most effective strategies are the introduction of an additional day dwell (that is, 1 daytime exchange) and larger nighttime dwell volumes (37,41). Other options to consider are increasing the cycler time and the frequency of cycles (grade C) (37,39,42).

2.1.8 In a patient who is underweight or overweight, the calculation of Kt/V should use the patient's ideal body weight to estimate *V* (grade C).

Background: Two large RCTs have looked at clearance in CAPD. The best and largest showed no outcome benefit for patients receiving a mean weekly pKt/V of 2.12, achieved using CAPD with more than 4 exchanges daily or volumes larger than 2 L as required to target a weekly peritoneal creatinine clearance of 60 L, as compared with a control group of patients receiving a mean weekly pKt/V of 1.6, achieved using conventional 4×2 L daily CAPD (grade A) (7). The second trial showed no benefits for a total weekly Kt/V of 1.7 – 2.0 as compared with >2.0 (grade A). The latter trial did show a reduction in erythropoietin dose for a total weekly Kt/V of 1.7 – 2.0 compared with a Kt/V of 1.5 – 1.0 (grade C) (43). High-quality evidence therefore shows that starting CAPD with prescriptions in excess of 4×2 L daily is not indicated.

Prospective cohort and retrospective analyses show no survival benefit for higher pKt/V levels within the usual therapeutic range (9,10,44). No available high-grade clinical evidence supports higher clearance targets for fast compared with slow compared with average peritoneal transporters (45,46) or for APD compared with CAPD. The results of the ADEMEX study (7) have therefore been extrapolated to APD patients. No additional benefit has been proven for measurement of peritoneal creatinine clearance in addition to Kt/V. A significant proportion of patients now start PD "early," and for quality of life

reasons, use "incremental" or low-dose PD prescriptions while they still have substantial RRF (47,48). Increases in peritoneal clearance have economic and lifestyle costs, and may be associated with greater mechanical discomfort (7,39,43).

It is recommended that total Kt/V be measured using 24-hour dialysate and urine collections soon after the patient has been stabilized on PD—that is, after 4 – 6 weeks. This is typically the time when the initial peritoneal equilibration test (PET) will also be done. If the weekly pKt/V is less than 1.7, and if achievement of the target total Kt/V depends on residual renal clearance, it is important that rKt/V be re-measured every 3 – 6 months because it will tend to decline with time. If the rKt/V is no longer sufficient to maintain the total Kt/V at target, the peritoneal prescription needs to be increased, with the total Kt/V being re-measured until the target is achieved. If the weekly pKt/V is greater than 1.7, it is not likely to change substantially while the peritoneal prescription remains the same. It is therefore not essential to re-measure pKt/V routinely unless there is an unexplained or unexpected change in the patient's clinical or laboratory status.

A randomized trial of 82 patients performed in the early 1990s showed no difference in BP or in patient or technique survival between APD and CAPD (30). However, compared with CAPD, APD was associated with fewer peritonitis episodes and hospitalizations. These findings require confirmation in a more contemporary PD population. A second randomized trial comparing APD with CAPD in 34 patients demonstrated that APD was associated with significantly more time for work, family, and social activities, although no differences in health-related quality of life scores as measured by the Medical Outcomes Study Short Form 36 were observed (27). Recent registry data from 4128 patients showed no significant differences in patient survival or death-censored technique failure between CAPD and APD (49). Despite findings in some, but not other, observational studies, there is no conclusive evidence that APD is associated with more rapid loss of RRF (50–52). Therefore, the clinical evidence is insufficient to favor CAPD over APD or vice versa; the decision should, where possible, be driven primarily by patient preference.

When it is not possible to achieve adequate dialysis for mechanical, lifestyle, or other reasons, consideration should be given to transferring the patient to HD; however, such a decision needs to take into account the medical and social circumstances of the patient, the patient's own wishes, and where relevant, the wishes of the patient's caregivers. Furthermore, the risk of a venous catheter for HD must be weighed against the benefits of higher total solute clearance.

In patients who have large fat stores, the true Kt/V will be underestimated if total weight is used for the calculation of urea distribution volume *V.* A more accurate estimate for *V* can be derived using the ideal body weight for the particular patient (based on sex, height, and body frame). Similarly, in malnourished patients, Kt/V will be systematically overestimated given their lower *V.* And therefore again, *V* should be estimated using ideal or desirable body weight.

SECTION 3: VOLUME MANAGEMENT

3.1 MAINTENANCE OF EUVOLEMIA AND DIAGNOSIS OF HYPERVOLEMIA

Recommendations:

3.1.1 All PD patients should have regular clinical assessments of volume control (opinion).

3.1.2 A 2.5% or 4.25% dextrose PET should be carried out no sooner than 4 weeks after initiation of PD. This test should be subsequently repeated if there are unexplained or unexpected changes in volume status or UF (opinion).

Background: Fluid overload is common in contemporary PD populations (53,54) and has been associated with adverse clinical outcomes such as hypertension, left ventricular hypertrophy, congestive heart failure, and hospitalization (55–57). Evidence from observational studies suggests that control of volume in hypertensive PD patients improves BP (58); however, no RCTs show that improved volume control lowers morbidity or mortality rates. Nonetheless, given that CV disease is the most common cause of morbidity and mortality in this population, maintenance of normovolemia is considered to be a central component of adequate PD. As such, all patients should undergo volume status assessment at regular intervals. The frequency of assessment is determined by the clinical stability of the patient, but assessment should occur at least every 1 – 3 months.

A number of investigators have reported on the relationship between volume or sodium removal (or both) and outcome in PD. In prospective observational studies, higher daily sodium and volume removal were associated with a lower risk of death (59,60). The intuitive link is that higher sodium and volume removal indicate better control of volume status, resulting in reduced mortality; however, this association may merely reflect the fact that greater sodium or fluid intake (which should approximate removal in steady state) is a marker of a healthier patient (61). The work group suggests that that a low net daily

peritoneal UF volume (<750 mL in anuric patients or <250 mL in patients with RRF) be an indication for careful evaluation of volume status (looking for evidence of fluid overload) and of dietary fluid and food intake (looking for evidence of insufficient intake or malnutrition).

Volume depletion may also occur in PD patients. Depletion is associated with hypotension, cramps, malaise, and declining urine output (62). Therefore, notwithstanding the foregoing recommendations, efforts should be made to avoid inappropriate symptomatic volume depletion.

In many, although not all, studies addressing the issue, peritoneal transport status in CAPD patients has been shown to be predictive of important outcomes (63,64), but this predictive association may not be the case for patients treated with APD and icodextrin (45,46). Nonetheless, evaluation of peritoneal transport status can assist in determining an appropriate PD prescription—for example, use of shorter dwells or use of APD with icodextrin day dwells (or both) in rapid transporters.

The most practical method of assessing peritoneal transport status is with a 2.5% dextrose PET (65) or a modified (4.25% destrose) PET (66). The PET should be performed a minimum of 4 weeks after initiation of PD because earlier testing may not accurately reflect the transport status of patients established on PD (67). Routine monitoring of transport status is not necessary; however, repeating the PET may assist in management when unexplained changes in volume status occur.

Fluid overload in PD patients is often multifactorial. The diagnostic approach should be systematic, with history-taking and clinical examination focusing on

- salt and water intake,
- blood glucose control in diabetic patients,
- cardiac status,
- changes in RRF,
- adherence to the PD prescription,
- appropriateness of the PD prescription,
- mechanical complications such as leaks and catheter dysfunction, and
- change in peritoneal membrane function.

Peritoneal membrane failure should be diagnosed only after consideration of other causes of fluid overload. In particular, it is essential that mechanical causes of UF failure, such as a peritoneal leak or catheter dysfunction, be ruled out. If UF failure is suspected, assessment with a modified (4.25% destrose) PET is warranted (66). A peritoneal UF volume of less than 400 mL over 4 hours with a 4.25% dextrose PET is a good indicator of UF failure.

3.2 TREATMENT OF HYPERVOLEMIA

Recommendations:

3.2.1 Sodium intake should be restricted to 65 mmol (1500 mg) or less daily in patients with hypervolemia (grade C).

3.2.2 In patients with RRF, high-dose diuretics (furosemide 250 mg with or without metolazone 5 mg daily) increase sodium excretion and urine volume (grade B).

3.2.3 Hypertonic 4.25% dextrose solution may be required to achieve euvolemia; however, sustained use of such solution is not desirable (grade C).

3.2.4 Icodextrin solution is preferred over glucose-based dialysate for long-duration (>8-hour) dwells (grade C).

Background: In the absence of mechanical complications and peritoneal membrane UF failure, a combination of strategies should be considered in managing the hypervolemic patient, including salt and water restriction, high-dose diuretics in patients with RRF, use of more hypertonic glucose-based dialysis solution, avoidance of long-duration glucose-based dialysate dwells, avoidance of high-frequency cycling in APD, and icodextrin dialysis solution for dwells longer than 8 hours.

The CHEP recommends an "adequate" intake of sodium of 65 mmol (1500 mg) or less daily for prevention or treatment of hypertension in normal adults (68). This recommendation does not directly address the problem of hypervolemia in PD patients; however, the work group felt this guide was reasonable given the greater sodium sensitivity of individuals with kidney disease compared with members of the general population.

The use of high-dose diuretics in individuals with RRF is supported by a RCT conducted in incident CAPD patients who received either furosemide 250 mg daily (plus metolazone 5 mg daily if urine output remained below 500 mL in 24 hours) or no diuretics and who were followed for 12 months. Compared with the control group, patients treated with diuretics experienced an increase in urine output and urinary sodium excretion with no difference in the rate of loss of RRF (21). In the opinion of the work group, thiazide diuretics alone are generally ineffective in promoting diuresis in PD patients.

There is evidence of an association between cumulative exposure to hypertonic glucose dialysate and loss of peritoneal membrane UF capacity (69). Compared with use of 4.25% dextrose, use of icodextrin increases UF volumes in long-duration (>8-hour) dwells (70,71), and compared with 2.5% or 1.5% dextrose, icodextrin leads to a sustained reduction in extracellular fluid volume in PD patients with apparent fluid overload (72,73).

Furthermore, glucose-sparing PD prescriptions improve glucose control in diabetic PD patients (74) and are associated with less weight gain and a less adverse lipid profile (72,75,76). Icodextrin is recommended for dwells longer than 8 hours, such as the day dwell in APD and the overnight dwell in CAPD. Although there is preliminary evidence that combination PD solutions based on mixtures of icodextrin and glucose can enhance UF when used in long-duration and short-cycled dwells, and that twice-daily icodextrin may be safe and may enhance UF in patients with evidence of UF failure, these strategies require further research (77–79).

Congestive heart failure is a common comorbidity in PD patients. Evaluation with echocardiography and referral to a cardiologist should be considered in these individuals. Ischemic heart disease may be the cause of congestive heart failure, and investigations for coronary artery disease should be considered in patients who may be candidates for percutaneous or surgical revascularization. The nephrologist plays an important role in the achievement and maintenance of normovolemia, by the strategies outlined earlier, in such patients. It is also reasonable to apply other treatments—such as the use of ACEIs, ARBs, and beta-blockers—shown to be effective in RCTs conducted in the general population, although the magnitude of the benefit in PD patients is uncertain. The safety of spironolactone in the dialysis setting is not well established. Severe hyperkalemia, although uncommon, has been reported in HD patients receiving that medication (80). Use of low doses (25 mg daily, for example) has been reported to be safe in trials with small numbers of CAPD patients (81). The work group suggests cautious use of this medication if it is indicated, with close monitoring of serum potassium levels (82).

3.3 ASSESSMENT AND MANAGEMENT OF BP

Recommendations:

3.3.1 Patients with hypertension should be assessed for hypervolemia and, if appropriate, treated as outlined in the recommendations in "3.2 Treatment of Hypervolemia" (grade C).

3.3.2 Target BP to 130/80 mmHg or lower; optimal BP is uncertain (grade D).

3.3.3 The preferred antihypertensive agents are ACEIs or ARBs; however, comorbid conditions should be taken into account when prescribing antihypertensives (grade B).

Background: Blood pressure should be measured at every clinic visit. The technique for BP measurement is described in the CHEP recommendations (68). Sitting and standing BPs should both be measured. The role of ambulatory or home BP monitoring has not been well studied in the PD population, but it is generally encouraged and may be of particular use in individuals with difficult-to-manage hypertension—particularly if changes in BP cannot be related to changes in volume status.

In the general population, the relationship between hypertension and risk of adverse outcomes is well documented. Hypertension is common in patients on PD, with more than 80% of prevalent patients in some studies being affected (83,84); however, the evidence associating hypertension with adverse outcomes is limited in this population. A continuous relationship between systolic BP and increased risk of mortality in PD has been reported (85). However, at least one study showed that a systolic BP of 110 mmHg or less was associated with increased mortality, and a protective effect was observed with a systolic BP above 120 mmHg (86). Another study showed a variable relationship between BP and mortality with time, higher BP being associated with lower mortality early and with higher mortality in the long term (87). The association between low BP and adverse outcomes observed in some studies may relate to the effects of confounding by comorbid occult cardiac disease. This reverse epidemiology has also been observed in the HD population.

The evidence from randomized trials supports treatment of hypertension in the general population. Given the lack of hypertension treatment trials in PD patients, the optimal BP target remains uncertain. However, the work group felt that it was appropriate to extrapolate from the existing evidence in other individuals at high CV risk. A target BP of 130/80 mmHg or lower is therefore recommended, as advised by the CHEP for people with diabetes and CKD (88). However, because observational studies demonstrate an association for systolic BP of 110 mmHg or lower with adverse outcomes, clinicians should use caution in lowering BP below that level. Furthermore, in some people, symptomatic orthostatic hypotension and loss of RRF may occur at BPs higher than the recommended target. In such patients, the target of 130/80 mmHg or less is inappropriate, and BP should be maintained at the minimum tolerable value that does not produce such consequences.

Hypertension is associated with volume overload in PD patients (89). The initial approach to hypertension should therefore involve assessment of volume status and treatment of hypervolemia as clinically indicated. In one small study, PD patients who were hypertensive but not necessarily hypervolemic showed improved BP control with dietary sodium restriction (to about 1600 mg daily) with or without the addition of hypertonic (4.25% dextrose) exchanges; however, that intervention was

accompanied by a reduction in residual urine volume (58). Thus, the impact on RRF should be considered with such interventions, and volume depletion should be avoided.

Short-duration dwells such as those used in high-frequency APD may be associated with less effective sodium as compared with fluid removal because of sodium sieving during UF and because of inadequate time for diffusive sodium removal (29,90). Nonetheless, there is little evidence that this lower sodium removal leads to worse clinical outcomes, and it appears that BP and volume control are possible in APD with use of icodextrin for the long daytime dwell (30,91–94). Finally, although the utility of hypertonic glucose solutions for volume removal in both CAPD and APD is not disputed, the work group emphasizes minimization of dialysate glucose exposure by giving priority to other strategies for achieving normovolemia.

If antihypertensive agents are required, preference should be given to the use of an ACEI or ARB. In a large observational study (50) and in subsequent smaller, randomized open-label trials conducted in CAPD patients (19,20), ACEIs and ARBs reduced the rate of loss of RRF. No prospective trials have demonstrated a reduction in mortality in PD patients treated with an ACEI or ARB. In a retrospective cohort study, patients treated with one of those agents had a lower relative risk of death in a multivariate analysis; however, conclusive evidence is lacking (95,96). Comorbidities should also be taken into account when prescribing antihypertensives. For example, beta-blockers may be the preferred first-line antihypertensive in patients with symptomatic coronary artery disease.

SECTION 4: MANAGEMENT OF CV DISEASE IN PD PATIENTS

4.1 DYSLIPIDEMIA

Recommendations:

4.1.1 Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors), with or without the cholesterol absorption inhibitor ezetimibe, should be considered in all adult PD patients to lower the level of serum low-density lipoprotein cholesterol (LDL-C) (grade B).

4.1.2 Fasting lipid levels—total cholesterol (TC), triglycerides (TGs), LDL-C, and high-density lipoprotein cholesterol (HDL-C)—should be measured annually in PD patients (opinion).

4.1.3 Where possible, dialysate glucose exposure should be minimized by giving priority to other strategies to maintain normovolemia (opinion).

4.1.4 Avoid combination therapy with statins and fibrates (opinion).

Background: The Canadian Cardiovascular Society recommends a primary target of less than 2.0 mmol/L for LDL-C in patients at high risk of a CV event (≥20% over 10 years), including those on long-term dialysis (97). However, the evidence for the effectiveness of lipid-lowering agents in patients on dialysis is not robust. Observational studies have demonstrated that, in HD and PD patients, the relationship between TC and mortality is described by a "reverse J-shaped" curve (98–100) and that it is confounded by serum albumin and other measures of inflammation or malnutrition. Other observational studies indicated that therapy with statins affords a survival benefit in end-stage renal disease (ESRD) patients, including in those on PD (101–103), but that fibrates do not (102).

A recently conducted meta-analysis (104) demonstrated that, in patients with CKD, statins significantly reduced CV mortality and events; meta-regression analysis demonstrated that the degree of renal impairment had no effect on the magnitude of that risk reduction. However, at the time of writing, two RCTs in HD patients had evaluated the effects of lipid-lowering therapy on important clinical endpoints. The 4D trial (105) randomized 1255 diabetic HD patients with an LDL-C between 2.1 mmol/L and 4.9 mmol/L to atorvastatin (20 mg) or placebo. Treatment with atorvastatin resulted in a 42% lowering of LDL-C; however, no difference was observed in the composite endpoint of cardiac death, nonfatal myocardial infarction, and stroke. The international multicenter randomized AURORA study (106) evaluated the impact of rosuvastatin (10 mg) or placebo on a composite CV outcome in 2776 maintenance HD patients. Despite a 43% reduction in LDL-C and a 27% reduction in C-reactive protein with statin therapy, no difference was observed in any of the primary or secondary outcomes or in pre-specified subgroups, including a group with known pre-existing CV disease. A trend toward an increased risk of hemorrhagic stroke was observed with rosuvastatin in diabetics, similar to that seen in the 4D trial. The results of the SHARP study (107) of more than 9000 patients with advanced CKD or ESRD (including 500 on PD) were presented at the 2010 American Society of Nephrology annual meeting. Patients were randomized to either a combination of simvastatin (20 mg) and ezetimibe (10 mg) or to placebo and were followed for a median of 4.9 years. Treatment with simvastatin and ezetimibe reduced LDL-C by more than 30% at 2.5 years and was associated with a significant absolute risk reduction of 2.1% (number needed to treat: 48) in major atherosclerotic

events, defined as the combination of myocardial infarction, coronary death, ischemic stroke, or any revascularization procedure ($p = 0.0022$). A smaller, nonsignificant difference in the primary outcome was observed in the subgroup of 3023 dialysis patients (1.5% absolute risk reduction). Notably, the primary outcome was changed during the trial—to "major atherosclerotic events" from "all major vascular events"—based on findings from other trials that suggested that non-atherosclerotic vascular events (that is, hemorrhagic stroke and other causes of cardiac death) were not responsive to therapy lowering LDL-C.

Patients on PD tend to have a more atherogenic lipid profile than do HD patients; the former have higher TC, TGs, and lipoprotein(a) levels (108), which may worsen over time. The lipid profile of PD patients is presumably related to cumulative dialysate glucose exposure (109). That hypothesis is supported by observations in small studies of a beneficial impact on lipid profile with the substitution of icodextrin or amino acid–based solutions for glucose-based ones (75,110,111). The SHARP study included 500 patients on PD; however, results have not as yet been presented for that subgroup, which would undoubtedly be underpowered to detect a statistically significant difference in the primary outcome. It would seem unlikely that there will ever be a sufficiently large RCT in PD patients to assess the impact of LDL-C lowering therapy on important clinical outcomes. Nevertheless, statins and ezetimibe have been shown to be effective in reducing cholesterol, including LDL-C and TGs, in PD patients, and these agents are safe (112,113). Based on the high baseline CV risk of patients on PD, their more atherogenic lipid profile, and the body of evidence available, the work group recommends that LDL-C lowering therapy with statins, with or without ezetimibe, should be considered in all PD patients regardless of baseline LDL-C.

Triglycerides are clearly associated with risk for CV disease; however, whether TG levels are an independent risk factor for CV disease is unclear; the observed risk is substantially attenuated when adjusted for other known risk factors, including HDL-C (114–117). Nevertheless, treatment with a statin appears to have the greatest benefit in patients with an elevated LDL-C, low HDL-C, and elevated TGs (that is, a high TC:HDL ratio) (118). In the general population, treatment with a fibrate in at-risk subjects with low HDL, high TGs, or both, did not reduce CV events except in the subgroup of subjects with TGs above 2.26 mmol/L (119). Because of the inconclusive nature of this literature in the general population, practice guidelines do not currently recommend the achievement of specific TG targets to prevent future CV events (97). Based on the aforementioned *post hoc* analysis (118), however, a TC:HDL ratio below 4.0 has been suggested as a secondary target in those at high risk of a future CV event when LDL-C is less than 2.0 mmol/L. That goal can usually be achieved by increasing the statin dose. Treatment with simvastatin and ezetimibe in the SHARP study was associated with an 11.7% reduction in TG levels.

Evidence supporting the use of lipid-lowering agents other than statins and ezetimibe has been weak. In the general population, fibrates may reduce CV events, but not CV mortality or total mortality (120–123), with an increased risk of non-CV mortality (122). A subgroup analysis of a large RCT evaluating the role of fibrates in reducing CV events in patients with CKD (Cockcroft–Gault creatinine clearance < 75 mL/min) demonstrated a significant reduction in coronary death or nonfatal myocardial infarction (124). Observational data on the use of fibrates in dialysis patients indicate these agents can be used at reduced dosages, but that such use is not associated with improved outcomes (102). When used in conjunction with statins, fibrates are associated with a reversible increase in creatinine (especially fenofibrate) (120) and with a markedly increased risk of rhabdomyolysis (especially gemfibrozil) (125,126). This risk appears to be increased in the presence of CKD (125). Nicotinic acid has not been studied in PD patients, and current evidence does not demonstrate a reduction in CV events despite this agent's ability to lower TGs and LDL-C and to increase HDL-C in the general population (122,123). Sevelamer appears to reduce LDL-C and TGs while increasing HDL-C in dialysis patients (127); however, a meta-analysis of existing RCTs does not demonstrate any CV benefit for sevelamer in the treatment of hyperphosphatemia (128). Other bile-acid sequestrants, including cholestyramine, have been shown to increase TG levels (129–131), which are often already high in PD patients. Based on the lack of consistent data in the general population regarding the use of agents other than statins or ezetimibe for lipid-lowering therapy, the work group makes no recommendations regarding their use in PD patients for the management of dyslipidemia. If fibrates are to be used at all, given the concerns discussed here, they should not be used in combination with a statin.

4.2 CORONARY ARTERY DISEASE/CHRONIC HEART FAILURE

Comprehensive guidelines exist for the management of patients with stable and unstable coronary artery disease and chronic heart failure (132–138). Patients with ESRD, including those on PD, have been systematically excluded from the numerous trials used to develop those guidelines. There is evidence from an observational

study that, compared with noninvasive management, intervention with coronary artery bypass grafting or percutaneous coronary intervention is associated with a better outcome in the ESRD population (139). A modestly sized RCT demonstrated that carvedilol improved 2-year survival in HD patients with heart failure (New York Heart Association functional classes II – III and left ventricular ejection fraction < 0.35) (140). A study randomizing HD patients without overt heart disease to the ARB candesartan or to placebo demonstrated a reduction in mortality and CV events with candesartan (141); a study with the ACEI fosinopril did not (142).

Historically, in patients with CKD and ESRD, there has been a culture of "renalism"—that is, avoidance of the use of agents shown to be of benefit in acute myocardial infarction, including acetylsalicylic acid, beta-blockers, and ACEIs (143,144). A similar phenomenon has also been observed in the use of coronary angiography in these patients (145,146). The work group therefore reiterates here that CKD, including ESRD, is not a reason to avoid the use of such agents. The risk of hyperkalemia must be considered, although that risk is considered low for ACEIs or ARBs in PD and for spironolactone in oligoanuric HD patients (147,148).

Low molecular weight heparins (LMWHs) are renally excreted and are therefore felt to be relatively contraindicated in ESRD. A meta-analysis of studies comparing unfractionated heparin with LMWHs did not identify an increased risk of bleeding with LMWHs; however, the number of patients include in the analysis was low (149). Further studies are needed to determine whether LMWHs can be used safely in patients with ESRD who require systemic heparin therapy.

4.3 RESEARCH

Recommendations:

4.3.1 There is a need for an updated systematic review and meta-analysis of the impact of lipid-lowering therapy in ESRD patients, including those on PD.

4.3.2 There is a need for RCTs evaluating the role of various anticoagulant and revascularization strategies in dialysis patients with acute coronary syndrome, including those on PD.

SECTION 5: NUTRITION IN PD

5.1 NUTRITION

Recommendation:

5.1.1 Nutritional status should be monitored at routine clinical visits by the physician and by other members of the health care team, including a registered dietician (opinion).

Background: Malnutrition is common in the ESRD population. In PD patients, indices of nutrition have been shown to be predictive of important clinical endpoints, including patient survival. These indices of nutrition include body weight, protein equivalent of nitrogen appearance (PNA), subjective global assessment, lean body mass, serum albumin and prealbumin, and blood urea. It is recommended that nutrition status be assessed every 3 months—more frequently if there are concerns. It is recognized that malnutrition in PD patients is multifactorial and may result from poor oral nutrient intake, poor knowledge about nutrition, systemic inflammation, inadequate control of uremia, metabolic acidosis, impaired anabolism, socio-economic problems, impaired gastric emptying, and other gastrointestinal and medical comorbidities.

The approach to malnutrition should therefore involve regular assessment by a multidisciplinary team, including the physician, dietician, nurse, and social worker. In particular, counseling by a dietician should be provided at the time of PD start and every 6 months subsequently, with more frequent assessments by the multidisciplinary team if there are concerns. Assessment should include history taking; physical examination; routine blood tests, including levels of urea, phosphate, and albumin; and measurements of dietary intake, including PNA in association with measurement of urea clearances.

5.2 NUTRITIONAL SUPPLEMENTS

Recommendations:

5.2.1 Enteral nutritional supplements should be considered for patients with mild-to-severe malnutrition (grade B). However, certain supplements may be poorly tolerated by individual patients, and thus close monitoring is required (grade A).

5.2.2 The use of intraperitoneal amino acid supplements is not recommended in the treatment of malnutrition because of the poor quality of evidence in their favor (grade C) and because of concerns about side effects.

5.2.3 If intraperitoneal amino acids are used, more than 1 daily exchange is not recommended (grade A), and close monitoring for precipitation of acidosis and uremia is required (grade B).

Background: Enteral nutritional supplements are frequently prescribed in PD patients who have low protein intake. The efficacy of these agents has not been studied rigorously. Three RCTs looked at 3 various protein supplements in PD patients (150–153). All were small, with limited statistical power, and all examined surrogate clinical outcomes only. Of the 3 supplements examined,

2 were poorly tolerated and had limited efficacy. The 3rd, a dried-egg supplement, was well tolerated and improved some surrogate outcomes, including dietary protein and caloric intake and serum albumin; however, the population studied was particularly malnourished, and the product is not commercially available in North America. Other nonrandomized studies have also shown supplements to have limited efficacy (150).

To summarize, use of enteral supplements is not supported by high-grade clinical evidence, but the studies are not of sufficient size and quality to be conclusive. Malnutrition is associated with poor prognosis and, provided that nutritional supplements are tolerated, there is no evidence of harm from using them in an attempt to remedy the malnutrition. Supplements appear to raise protein intake, and pending better evidence, their use should be considered in patients with poor protein intake and associated mild-to-moderate malnutrition.

Intraperitoneal amino acids are commercially available and have been studied in a number of RCTs (154,155). Those trials were small and examined only surrogate outcomes. Only one RCT had a follow-up longer than 3 months. Demonstrated benefits have been modest and include better maintenance of protein intake and of some anthropometric measurements. In the largest and longest study, most patients treated with 1 exchange of amino acid solution daily required oral sodium bicarbonate to treat metabolic acidosis, a complication that is itself known to promote malnutrition (155). Worsening of uremia is also a recognized side effect of the use of amino acid solution, especially if more than 1 daily exchange is used. Concomitant calorie ingestion is required to facilitate nitrogen anabolism. There is some evidence that protein anabolism of these agents can be enhanced if intraperitoneal glucose is given in association with them as part of a cycler PD prescription, but those findings cannot yet be extrapolated to standard clinical care (156). For all those reasons, intraperitoneal amino acids cannot at present be recommended for the treatment of malnutrition in PD patients. However, if amino-acid solutions are used for any reason, the amount should be limited to 1 daily 2-L bag, and close monitoring is required to detect and treat any acidosis or worsening uremia.

5.3 CORRECTION OF IMPAIRED ANABOLISM, ACIDOSIS, AND GASTROPARESIS

Recommendations:

5.3.1 For malnourished patients, anabolic steroids—specifically nandrolone decanoate 100 mg intramuscular injection weekly—should be considered for up to 6 months' use (grade B). Oral megestrol acetate may also be considered, but supporting evidence is weak. The use of recombinant growth hormone, ghrelin, or insulin-like growth factor 1 is not recommended (grade D).

5.3.2 Serum venous bicarbonate should be maintained in the high-normal range (27 – 28 mmol/L) by using dialysis solutions containing 40 mmol buffer per liter and by prescribing oral sodium bicarbonate as required (grade A).

5.3.3 Prokinetic agents should be considered in PD patients with symptoms that suggest delayed gastric emptying (grade B).

Background: There is a substantial body of evidence indicating that uremia is associated with poor appetite and impaired anabolism, as well as with muscle wasting, malnutrition, and decreased physical function. Treatment strategies based on nutritional supplements alone have been disappointing, and so administration of anabolic agents and of appetite stimulants has been studied. Small randomized trials in malnourished HD and PD patients have shown anabolic and other nutrition benefits for recombinant growth hormone and for recombinant insulin-like growth factor 1 (157–159); however, because of concerns about side effects and cost, neither agent has been studied in large randomized trials, and neither can be recommended for routine use in malnutrition.

Anabolic steroids—specifically 100–200 mg nandrolone decanoate given as an intramuscular injection once weekly—has been studied in two RCTs in dialysis patients (160,161). The first study, which was small, included only 9 PD patients and involved 6 months of treatment and follow-up. The results showed that the agent was safe in the doses used and led to significant improvements in lean body mass and in clinically important functional outcomes. A subsequent randomized trial, larger but shorter in duration, included HD patients treated for only 3 months. Safety was again shown, and the improvements in lean body mass were confirmed, but not those in functional performance. The same study showed beneficial effects from exercise. The shorter duration of the second study may explain some of the difference in results.

Megestrol acetate has been studied in dialysis patients, but no good RCTs have been conducted. There is some suggestion that this agent increases appetite and improves nutrition status, but the quality of the evidence is weak (162). Lower doses need to be used in renal failure patients because of side effects. In a small short-term crossover randomized trial in 9 malnourished PD patients, subcutaneous ghrelin was shown to improve food intake, but the evidence is too preliminary and too short-term to underpin a recommendation for clinical use (163).

Two RCTs have addressed the effects of correction of metabolic acidosis in PD patients (164,165). Those studies had 200 and 60 patients respectively, and both had 1 year of follow-up. In each case, oral sodium bicarbonate and calcium carbonate were used to raise serum bicarbonate, and in one study, the control group received PD solution with lower levels of lactate (35 mmol/L compared with the usual 40 mmol/L). In both studies, serum bicarbonate rose to the high end of the normal range (27 – 28 mmol/L), and in both, increases in protein intake and decreases in hospitalization were observed. One study reported improvement in anthropometric indices; the other showed a rise in subjective global assessment status. In the high-bicarbonate group, there was no evidence of complications related to sodium overload or hypertension, although that possibility has to be considered. The maintenance of high-normal serum bicarbonate (27 – 28 mmol/L) in PD patients is therefore recommended.

Gastric emptying is known to be impaired in renal failure patients, particularly those having diabetic ESRD. This problem may be accentuated in patients on PD. In small numbers of dialysis patients with delayed gastric emptying, including some on PD, prospective studies of 3 prokinetic agents—domperidone, metoclopramide, and erythromycin—have showed an association with acceleration of gastric emptying and with a rise in serum albumin (166,167). Some of these agents have been given by the intraperitoneal route, but oral use is more convenient.

5.5 RESEARCH

Recommendations:

5.5.1 Further studies to determine the optimum serum bicarbonate level in PD patients are needed.

5.5.2 Further investigations into the initial promising observations on the use of anabolic steroids in malnourished PD patients would be helpful.

In both the foregoing areas, positive results in randomized trials do not appear to have convinced practicing physicians to alter practice.

SECTION 6: MANAGEMENT OF HYPERGLYCEMIA

6.1 GLYCEMIC CONTROL

Guideline:

6.1.1 Patients using icodextrin exchanges must employ a glucometer that uses the glucose oxidase or hexokinase method (grade A).

Recommendations:

6.1.2 Control of hyperglycemia in the PD population should adhere to the recommendations of the Canadian Diabetes Association where possible (hemoglobin A_{1C} < 7.0%, fasting plasma glucose 4 – 7 mmol/L) (grade B). However, clinicians must take into account the risk of hypoglycemia in individual patients, with particular regard to age, comorbidity, stability, and other circumstances.

6.1.3 The use of metformin should be avoided in dialysis patients (grade C).

6.1.4 Some sulfonylureas and repaglinide can be used to control hyperglycemia in PD patients, provided that the risk of hypoglycemia is appreciated. Thiazolidinediones can also be used, but given possible CV risks, they are not the preferred agents in this population.

6.1.5 Short-acting agents such as gliclazide and repaglinide are preferred in the PD population.

Background: Nondiabetic patients starting PD may develop diabetes as a result of the absorbed glucose load from PD solutions, and diabetic patients starting PD may note deterioration in their glucose control—situations that clinicians should anticipate.

Few data exist to guide the management of diabetes in this population. A randomized trial evaluating the benefits of a comprehensive diabetes care program in the dialysis population included a small number of PD patients. It found that the intervention group achieved superior glucose control and experienced reduced hospitalization and amputation rates over a 1-year period (168). Extrapolation from data in the general population (169) seems reasonable, but in the HD population at least, a correlation has not been demonstrated between hemoglobin A_{1C} and survival (170). *However, clinicians caring for these patients need to take into account the risk of hypoglycemia in individual patients, with particular regard to age, comorbidity, stability, and other circumstances*.

Few data overall, and no outcome data, describe the use of oral agents in the control of diabetes in PD or HD patients. Metformin has certainly been reported to induce severe lactic acidosis in this situation (171), although the incidence of that complication is unknown. There are reports of glyburide pharmacokinetics being uninfluenced by HD (172), but some of that agent's active metabolites are retained in renal failure and may lead to prolonged hypoglycemia. There are reports of the safe use of thiazolidinediones and glucosidase inhibitors in small groups of HD (173) and PD patients, and there is also some evidence that the thiazolidinediones may reduce insulin requirements (174). However, some of these agents have unfavorable pharmacokinetic or side-effect profiles, and manufacturers often do not recommend

their use in renal failure. If they are prescribed, the recipients must be closely monitored (175). In particular, given recently published concerns about the possible CV risks of thiazolidinediones, the work group suggests that these agents not be considered the preferred agents in this population. Many clinicians have experience with gliclazide and repaglinide in this population, and those agents are effective in some patients, but no comprehensive safety or efficacy data have been reported. Insulin is probably the most effective agent, but may be difficult to introduce for elderly patients already having difficulty coping with the demands of PD.

Most Canadian centers use subcutaneous rather than intraperitoneal insulin. Although no large trial has been performed, there is observational evidence that intraperitoneal insulin use is associated with a significantly increased rate of peritonitis (176,177). Because peritonitis is a leading cause of technique failure in PD (178), this disadvantage of intraperitoneal insulin is believed by many nephrologists to outweigh its possible benefits. Other described disadvantages of the intraperitoneal route of insulin administration compared with the subcutaneous route include the development of hepatic subcapsular steatosis (179), the need for larger doses of insulin, and the development of a more atherogenic lipid profile (177). Reported benefits of intraperitoneal insulin include improved glucose control in some (but not all) studies (44) and a more physiologic plasma insulin profile (180).

For self-monitoring of glucose in patients using any icodextrin exchanges, a glucometer using the glucose oxidase or hexokinase methods is a must (181,182). Other methods can yield falsely high glucose readings because of maltose and other absorbed icodextrin metabolites registering as glucose. The higher readings can encourage the use of additional insulin or oral agents, producing hypoglycemia that may not be detected.

6.2 GLUCOSE-SPARING STRATEGIES

Recommendation:

6.2.1 To reduce peritoneal glucose exposure, every effort should be made to minimize the use of solutions containing high glucose concentrations, including use of diuretics, dietary sodium restriction, and icodextrin solutions as clinically appropriate to achieve required UF and volume control.

Background: There is good evidence from observational studies that chronic exposure of the peritoneum to glucose is quantitatively linked to the development of rapid solute transport status over time (183), which may eventually lead to UF and technique failure (184). That response may occur more rapidly in anuric APD patients and may be moderated by the use of icodextrin (69). Furthermore, replacement of some glucose exchanges with icodextrin may also improve glucose control and metabolic profile (110), because glucose absorption from the peritoneum may play an important role in the unfavorable metabolic profile of even nondiabetic PD patients (186). These concerns have given rise to the concept of glucose-sparing PD regimens, in which other strategies are used to minimize glucose exposure (187).

DISCLOSURES

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TABLE 1
Conflict of Interest Statements for Members of the Canadian Society of Nephrology Peritoneal Dialysis (PD) Guideline Work Group[a]

Member	Type of potential conflict of interest	Role	Period	Sponsor
Bargman	Honoraria	Speaker or writer		Amgen
	Honoraria	Speaker or writer		Baxter
Blake	Honoraria	Speaker	1–2 times annually during the past 5 years	Baxter
Brimble	None			
Davison	None			
Hirsch	None			
McCormick	Honoraria	Speaker	1–2 times annually during the past 5 years	Baxter
Suri	Grant funding			Fresenius
	Grant funding			Mitsubishi
Taylor	None			
Tonelli	None			
Zalunardo	None			

[a] The list is restricted to companies that make products relevant to the care of PD patients; last 3 years only.

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