Practice Recommendations for the Use of L-Carnitine in Dialysis-Related Carnitine Disorder

National Kidney Foundation

Carnitine Consensus Conference

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References are not cited within this report. However, they are included in the supplement to this issue of the American Journal of Kidney Diseases, *which contains reports regarding each topic that was considered by the panel.*

These recommendations are not intended to be guidelines or standards of care. Instead, they have been developed to provide the best available information and expert opinion in decision-making for the clinician. The recommendations should not be considered as prescribing an exclusive course of management.

INTRODUCTION

KIDNEY DISEASE is often accompanied by altered hormonal and biochemical homeostasis secondary to progressive loss of kidney function. Examples of these abnormalities include anemia from impaired erythropoietin production, osteodystrophy from reduced vitamin D metabolism, neuropathy from altered folic acid metabolism, and reduced linear growth from growth hormone abnormalities in children. Most of these conditions represent functional deficiencies rather than absolute deficiencies, in that their correction requires the use of pharmacologic doses of the associated hormones or nutrients.

Another functional deficiency that occurs with kidney disease and is magnified by dialysis is a disturbance in the homeostatic control of carnitine. Originally described as carnitine deficiency, the disorder that develops in dialyzed patients differs from the classic genetic or primary (systemic) carnitine deficiencies in that it represents a functional deficiency that can be corrected with pharmacologic doses of L-carnitine.

This condition, sometimes referred to as dialysis-related carnitine deficiency, actually may be better defined as a dialysis-related carnitine disorder (DCD), which manifests itself as a syndrome of clinical problems and symptoms, most notable of which are anemia that is hyporesponsive to erythropoietin therapy, intradialytic hypotension, cardiomyopathy, and skeletal muscle dysfunction manifested as generalized fatigability (see algorithm in Fig 1). Biochemically, the syndrome is associated with a significant reduction of tissue carnitine content, low plasma free carnitine concentration, and an increase in the ratio of plasma acylcarnitine to free carnitine.

On September 8-10, 2002, The National Kidney Foundation convened an interdisciplinary consensus panel that met in Chicago, Illinois, to review the scientific and clinical evidence and to provide expert opinion regarding the use of L-carnitine in dialysis patients. The panel reviewed the published evidence and reported clinical experience. Using a deliberative, consensus building process, the panel developed the following best practice recommendations regarding the clinical manifestations, diagnosis, evaluation, and treatment of DCD. In addition, desired treatment outcomes were defined.

The initial draft of the document developed by the participants was then subjected to review by a cross-section of representatives from dialysis and related fields. The following report represents the results of the consensus meeting as modified subsequent to the expert review. It is intended to provide guidance regarding the clinical manifestations, diagnosis, and treatment of DCD.

On November 8, 2002, the Centers for Medicare & Medicaid Services (CMS) issued a Pro-

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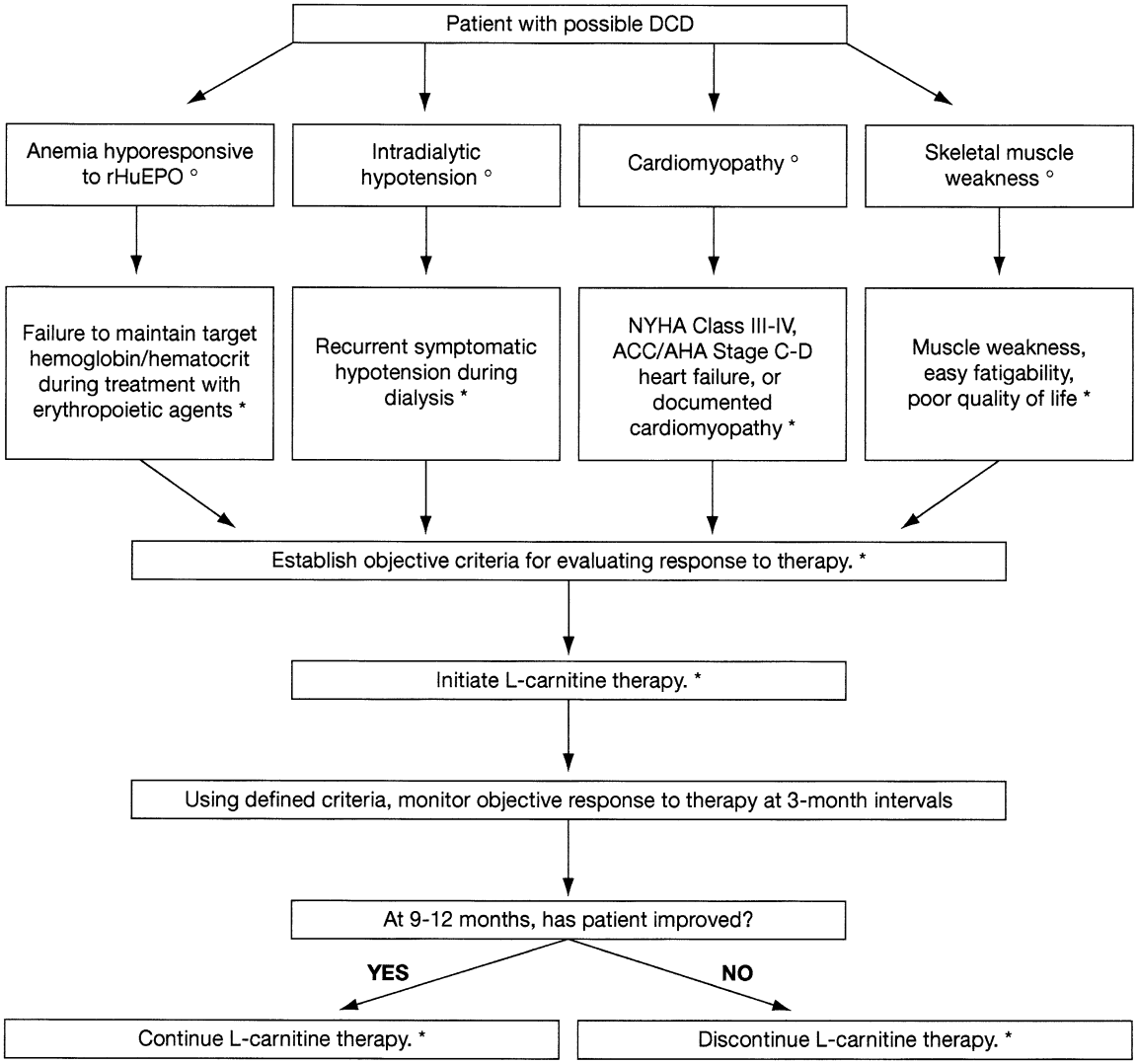

Fig 1. Recommended approach to the evaluation and treatment of a patient with a possible dialysis-related carnitine disorder. °Patient should be evaluated for other possible causes and managed with standard therapies prior to diagnosis of DCD. *See text for details.

gram Memorandum (PM) that provides a framework for national L-carnitine reimbursement decisions for use of L-carnitine in dialysis patients. Based on a careful analysis of the literature, this CMS Program Memorandum acknowledges the value of L-carnitine therapy in selected dialysis patients and attempts to address the complexity of the available scientific and clinical evidence regarding this therapy. However, the document is rather broad in its conclusions, allowing considerable latitude in its interpretation.

The intent of the NKF consensus conference was to define more clearly the clinical conditions associated with DCD and to link them to measurable improvements that allow for the prospective evaluation of L-carnitine replacement therapy. The recommendations from the conference were not designed to be a response to the CMS PM and neither were they necessarily intended to mirror those contained in the PM. Rather, the participants were asked to develop best practice recommendations that reflected their careful evaluation of the literature and their extensive clinical experience with L-carnitine. The consensus meeting participants acknowledged the importance of providing clear justification in support

of these practice recommendations to help ensure appropriate use of this therapy.

The panel considered four clinical conditions as indications for treatment with L-carnitine—anemia, intradialytic hypotension, cardiomyopathy, and muscle weakness (see algorithm in Fig 1). The clinical manifestations of these four conditions may overlap substantially. Thus, intradialytic hypotension overlaps with cardiomyopathy, and anemia overlaps with cardiomyopathy, easy fatigability, and muscle weakness. Nevertheless, because the manifestations of each of these conditions are clinically distinguishable, because any one of them may be the dominant presentation in an individual case, and because outcome measures of each condition are different from that of the others, the panel decided to consider them individually. Since there is little published or clinical experience with the use of L-carnitine in peritoneal dialysis patients, the recommendations contained in this report relate primarily to the use of L-carnitine in hemodialysis patients.

The recommendations presented in this report are organized by interventions for each of these four conditions. The level of evidence for each of these recommendations is variable. Evidence is strongest for the treatment of anemia, weakest for muscle weakness, and moderate for intradialytic hypotension and cardiomyopathy.

There are some differences between the recommendations of the panel and the clinical practice guidelines of NKF Kidney Disease Outcomes Quality Initiative (K/DOQI). The clinical practice guidelines follow established methods for development of an evidence report on which each guideline is based. The panel recognized that current literature and clinical experience leave unanswered questions that do not allow the development of clinical practice guidelines for the use of L-carnitine in dialysis patients. As such, the recommendations made by the panel are not based on the same type of process as used in the development of clinical practice guidelines and neither can they be as focused or detailed as guidelines. Rather, the panel anticipates that the recommendations made will provide direction to clinicians treating dialysis patients and will offer specific criteria to evaluate and document the outcomes of the intervention.

A systematic, prospective collection of data on the clinical use of L-carnitine and the resultant measurable patient outcomes, as recommended in this document, would substantially expand the understanding of the value of this therapy. To achieve that goal, the panel recommended that a national registry be created to collect prospective data on measurable patient outcomes in those who are treated with L-carnitine as a component of the implementation of these best practice recommendations.

GENERAL PRINCIPLES

- L-carnitine is an essential cofactor in normal fatty acid metabolism.
- L-carnitine is a critical metabolic cofactor for normal energy production in cardiac and skeletal muscle.
- Dialysis-related carnitine disorder (DCD) is a functional deficiency similar to other metabolic functional deficiencies that occur with kidney disease (vitamin D, iron, erythropoietin, folic acid, and growth hormone in children).
- DCD is not the same as primary (systemic) carnitine deficiency. In addition to clinical differences, biochemically DCD appears to be associated with the presence of an abnormally high ratio of plasma acylcarnitine to free carnitine concentrations.
- Given the complicated mechanisms involved in the clinical disorders that have been associated with DCD, it is essential that prior to the initiation of L-carnitine therapy, patients be evaluated and treated with other established therapies for underlying medical conditions that may cause symptoms similar to those of DCD.
- The available literature indicates a lack of homogeneity in individual patient response to L-carnitine therapy. There is currently insufficient evidence to accurately preselect those who will have a measurable benefit from L-carnitine administration. Therefore, the recommendations below assume that patients should be given an adequate trial of therapy while evaluating outcome measures specific to the clinical indication for which treatment was initiated.
- The evaluation and treatment of a patient with a possible dialysis-related carnitine

disorder should be systematic and objective (see algorithm in Fig 1).

RECOMMENDATIONS

Diagnosis of DCD

(1) The detection and diagnosis of DCD, and the decision to treat maintenance dialysis patients with L-carnitine, should be based on clinical signs and symptoms.

Rationale:

- The majority of studies reviewed show a benefit from the use of L-carnitine for the clinical conditions that appear in this document (see *Clinical Manifestations of DCD* below), but variations in study designs, study population size, as well as heterogeneity of response within treatment groups prevent the generalizability and universal applicability of the reported results. However, when considered in the aggregate, the available reports contain a constellation of specific clinical findings that characterize DCD (see algorithm in Fig 1).

(2) Documentation of a low plasma free carnitine concentration or elevated acylcarnitine/carnitine ratio is not essential for the clinical diagnosis of DCD. While normal concentrations of plasma free carnitine are helpful in excluding DCD, low concentrations are not predictive of clinical response to L-carnitine therapy. Monitoring plasma free carnitine or acylcarnitine/carnitine ratios during L-carnitine therapy is not necessary.

Rationale:

- Altered carnitine homeostasis is a common sequela of kidney failure that is accentuated during dialysis and may lead to adverse outcomes. The healthy kidney plays an essential role in conserving carnitine stores. However, in patients receiving maintenance dialysis, the loss of carnitine via dialysis, together with possible reductions in dietary intake and endogenous synthesis, lead to a depletion of the carnitine pool. In addition, patients with kidney failure exhibit an increase in the acylcarnitine to carnitine ratio in plasma and other body compartments. The presence of coexisting abnormalities of fatty acid metabolism in dialysis patients contributes to the accumulation of acylcarnitines. The abnormalities in carnitine homeostasis may have profound biochemical effects in skeletal muscle, cardiac muscle, and red blood cells. However, the exact relationship of the biochemical changes with the severity of the clinical symptoms that have been associated with DCD, or their value in determining response to therapy, have not been established.
- The available information on L-carnitine loss during dialysis is based on the current practice of thrice weekly hemodialysis. More frequent dialysis is likely to intensify L-carnitine losses in maintenance hemodialysis and deserves further study. Patients initiated on more frequent dialysis should be monitored closely for DCD.
- While dialysis patients often exhibit a low plasma free carnitine concentration and an increased plasma acylcarnitine/carnitine ratio, little evidence exists to support the use of these measurements to predict or monitor clinical response to L-carnitine therapy. Plasma carnitine represents a very small fraction of the total body carnitine pool and will fluctuate in response to hemodialysis. Short-term changes in plasma free carnitine concentrations may not correlate with changes in other carnitine compartments. Although some observational studies have shown an association between low plasma free carnitine concentrations and high acylcarnitine/carnitine ratios, most randomized prospective trials have not evaluated the relationship between these measurements and response to L-carnitine therapy. Routine measurement of plasma free carnitine concentrations is not justified due to the cost of testing and the lack of relationship of plasma carnitine concentrations to patient symptoms. Nevertheless, while the data regarding measurement of plasma carnitine concentrations are inconclusive for the diagnosis of DCD or predicting response to L-carnitine therapy, a normal plasma free carnitine concentration and a normal acylcarnitine/carnitine ratio in a dialysis patient may be helpful in excluding DCD as a cause of observed clinical symptoms.

- Prospective, randomized studies are necessary to evaluate the routine use of plasma carnitine concentrations or acylcarnitine/carnitine ratios in dialysis patients.

(3) Measurement of plasma free carnitine, as currently required by reimbursement policies, and related components (acylcarnitine, total carnitine) should employ analytical techniques and methods that have been standardized and defined by the reporting laboratory.

Rationale:

- Plasma acylcarnitines may undergo hydrolysis over time during sample storage at varying temperatures, leading to an overestimation of plasma free L-carnitine concentrations. Because these acylcarnitines accumulate in dialysis patients, the potential impact of ex vivo hydrolysis should be recognized and excluded as a contributor to the reported L-carnitine concentrations. As such, the reporting laboratory should develop a standard blood sample collection and handling protocol and should validate the stability of samples.
- Protocols for obtaining blood samples for measurement of L-carnitine or acylcarnitines should specify that samples be obtained prior to the initiation of the dialysis procedure.

TREATMENT OF DCD

(4) Treatment of DCD should consist of only L-carnitine.

Rationale:

- Although not currently available as commercial pharmaceutical products, racemic mixtures containing the D- and L-isomers are toxic. Toxicity is caused by the D-isomer. Over-the-counter preparations containing D-carnitine should be avoided by dialysis patients.

(5) The recommended dose of intravenous L-carnitine is 20 mg/kg total body weight. Due to its high degree of removal with each dialysis, the dose must be administered following the end of the dialysis procedure.

Limited experience with oral L-carnitine dosing precludes making a recommendation for oral therapy for conditions related to DCD.

Rationale:

- While earlier studies used lower doses of L-carnitine, most recent trials in dialysis patients have used intravenous L-carnitine at a dose of 20 mg/kg total body weight, administered after each dialysis. Data from these studies support the efficacy and safety of intravenous therapy. Dose response studies have been inconclusive, but efficacy and safety data suggest that doses higher than 20 mg/kg intravenously may not confer additional benefit.
- There are no comparative efficacy studies of the intravenous and oral routes of administration. However, there are differences in pharmacokinetics between the two routes of administration. Studies involving healthy subjects have shown that only approximately 15% of an oral dose of L-carnitine is absorbed. The remainder of the dose undergoes bacterial-mediated degradation to trimethylamine (TMA) and trimethylamine-N-oxide (TMAO), which are normally cleared by the kidneys but may accumulate in dialysis patients. The potential toxic effects of these metabolites have not been elucidated; however, studies in dialysis patients suggest that TMA and its breakdown product dimethylamine may cause cognitive impairment and malodorous breath.
- While oral carnitine has been used in randomized trials of DCD therapy, the importance of the pharmacokinetic differences between intravenous and oral therapy has not been evaluated in clinical trials of DCD. The results of studies with one route of administration cannot be used to support the use of the other route of administration.

(6) Treatment with L-carnitine should be guided by the following recommendations:

(a) After initiation of therapy with L-carnitine, clinical response to treatment should be evaluated at 3-month intervals.

(b) When the desired outcomes for the specific clinical manifestation (see below) have been attained, titration to the lowest effective dose should be considered.

(c) L-carnitine therapy should be discontinued if no clinical improvement has occurred within 9 to 12 months.

Rationale:

- Pharmacokinetic studies indicate that repeated dosing of L-carnitine following each dialysis results in a new steady-state plasma carnitine concentration in about 6 to 8 weeks, remaining constant for at least 6 months. A longer time, possibly up to 12 months, may be required to replenish tissue carnitine stores. These pharmacokinetic data are supported by observations that favorable patient response to L-carnitine therapy may require several months to be fully realized. If patient improvement is not documented within 9 to 12 months, there is little justification for continued treatment with L-carnitine.
- If a favorable response occurs, L-carnitine therapy should be continued. Few studies have examined recurrence or worsening of symptoms following discontinuation of treatment.

CLINICAL MANIFESTATIONS OF DCD

Anemia

(7) Administration of L-carnitine is recommended for dialysis patients who:

(a) Are unable to maintain a target hemoglobin/hematocrit (11-12 g/dL/33-36%) with use of erythropoietin-based products, and

(b) Require recombinant human erythropoietin (rHuEPO) doses >300 units/kg/week intravenously or >200 units/kg/week subcutaneously (or an equivalent dose of other erythropoietin-based products), in spite of adequate iron stores (transferrin saturation >20%, ferritin >100 ng/mL), and without any other identifiable cause of anemia or hyporesponse to erythropoietin. (See K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease. Update 2000. Guideline 20. See *http://www.kdoqi.org*.)

Response to L-carnitine should be evaluated at 3-month intervals. Patient evaluation should include:

- **Attainment and maintenance of target hemoglobin/hematocrit, AND**
- **Reduction of dose of erythropoietin-based product.**

L-carnitine therapy should be discontinued if no clinical improvement has occurred within 9 to 12 months.

Rationale:

- In dialysis patients, there is an inverse correlation between plasma carnitine concentrations and dose requirements for rHuEPO. The beneficial effect of L-carnitine appears to be related to stabilization of the red blood cell (RBC) membrane, thereby improving RBC survival time. Randomized clinical studies with L-carnitine therapy have shown significant increases in hematocrit with or without rHuEPO therapy and reductions in rHuEPO dose requirements with L-carnitine therapy. Among the clinical manifestations of DCD, the level of evidence is strongest for the use of L-carnitine in the control of anemia.
- Randomized clinical studies have been limited to the use of L-carnitine during the maintenance phase of anemia treatment. No recommendation can be made regarding the use of L-carnitine during the initiation phase of anemia treatment with erythropoietin-based products.
- The current K/DOQI guidelines for treatment of anemia define an inadequate response to rHuEPO therapy as failure to achieve target hemoglobin/hematocrit in the presence of adequate iron stores at a dose of 450 units/kg/wk intravenously (IV) or 300 units/kg/wk subcutaneously (SC). However, the available evidence indicates a favorable response to L-carnitine at lower doses of erythropoietin and justifies initiation of L-carnitine therapy when dose requirements for rHuEPO exceed 300 units/kg/wk IV or 200 units/kg/wk SC, or an equivalent dose of other erythropoietin-based products during the maintenance phase of anemia management.

Intradialytic Hypotension

(8) Administration of L-carnitine is recommended for hemodialysis patients who, without clinically identifiable causes, repeatedly experience symptomatic intradialytic hypotension that requires a therapeutic intervention.

Response to L-carnitine should be evaluated at 3-month intervals. Patient evaluation of the response to L-carnitine should include:

- **Reduced frequency of hypotensive episodes, OR**
- **Reduced clinical symptoms.**

L-carnitine therapy should be discontinued if no clinical improvement has occurred within 9 to 12 months.

Rationale:

- Intradialytic hypotension (IDH) is defined as a sudden drop in systolic blood pressure to less than 90 mmHg, a more than 30 mmHg drop in mean arterial blood pressure, or a more than 30 mmHg drop in systolic blood pressure from baseline that is accompanied by symptoms.
- IDH is associated with significant morbidity. If persistent, hypotension can decrease the effectiveness of dialysis and lead to serious complications.
- One recent study showed a correlation between hypotension and low plasma carnitine concentrations. Several studies support the effectiveness of long-term L-carnitine therapy in reducing the frequency and severity of hypotensive episodes during dialysis. However, prior to L-carnitine treatment, patients should be evaluated for other possible causes and treatment of IDH. (See K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy. Update 2000. Guideline 16. See *http://www.kdoqi.org*.)
- IDH is multi-factorial, but cardiovascular dysfunction is a common cause.

Cardiomyopathy

(9) Administration of L-carnitine is recommended for dialysis patients who have:

- **New York Heart Association (NYHA) functional class III-IV or American College of Cardiology/American Heart Association (ACC/AHA) Stage C-D heart failure symptoms, OR**
- **Symptomatic cardiomyopathy with documented impaired ejection fraction, AND**
- **Not responded adequately to standard medical therapy.**

Response to L-carnitine should be evaluated at 3-month intervals. Patient evaluation should be based on either of the following:

- **Improvement in NYHA class or ACC/AHA stage, OR**
- **Objective measurements of improved cardiac function**

L-carnitine therapy should be discontinued if no clinical improvement has occurred within 9 to 12 months.

Rationale:

- NYHA Class III and IV heart failure are defined as the following:
  - *Class III:* Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
  - *Class IV:* Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.
  - (See *http://216.185.112.5/presenter.jhtml?identifier=4569*.)
- ACC/AHA Stage C and D heart failure are defined as the following:
  - *Stage C:* Patients who have current or prior symptoms of heart failure associated with underlying structural heart disease.
  - *Stage D:* Patients with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions.
  - (See *http://www.acc.org/clinical/guidelines/failure/hf_index.htm*)
- While there are no large, well-controlled clinical trials, studies specific to dialysis patients have generally shown that L-carnitine can have beneficial effects on a number of cardiac parameters. As cardiac disease is the most common cause of intradialytic hypotension and death in end-stage renal disease (ESRD) patients, these findings may be particularly important for this population. Moreover, since the relationship between conventional cardiac risk fac-

tors and cardiac disease is less clear in this population, the role of therapies such as L-carnitine that address therapy of cardiomyopathy specific to the dialysis population deserves consideration and further evaluation.

- Recommending an echocardiogram or other objective assessment of cardiomyopathy as a basis for initiating L-carnitine therapy was strongly considered. For most patients with the degree of cardiomyopathy at which L-carnitine therapy may be recommended, the results of an echocardiogram or other cardiac study likely will be available. However, when such a study cannot be obtained, clinical evaluation of symptoms at the stated functional classification (NYHA Class III-IV, ACC/AHA Stage C-D) was considered sufficient to determine the need for L-carnitine therapy.

Muscle Weakness and Functional Well Being

The administration of L-carnitine is recommended for selected patients with symptoms such as muscle weakness and fatigability that affect their quality of life. L-carnitine should be reserved for those patients in whom other causes have been excluded and who have been unresponsive to standard therapies.

Response to L-carnitine should be evaluated at 3-month intervals with an appropriate objective instrument. The same evaluation instrument should be used before and during therapy.

L-carnitine therapy should be discontinued if no clinical improvement has occurred within 9 to 12 months.

Rationale:

- The available evidence is weakest for the response of muscle weakness and functional well being to L-carnitine therapy. However, the central role of L-carnitine in muscle function and the limited number of reports showing improvement in muscle strength and functional well being following L-carnitine justify consideration of treatment of selected patients.
- Certain measurement tools have been used successfully to assess the function and quality of life of dialysis patients, and may be used to measure and document response to L-carnitine therapy. These include, but are not limited to any one of the following:
  - Physical therapy or exercise physiology evaluation
  - Sit-to-stand-to-sit test
  - 6-minute walk test
  - SF-36 Health Status Questionnaire
  - Sickness Impact Profile
  - Kidney Disease Quality of Life instrument
  - Functional requirements to perform sedentary, light, and medium work, as defined by the Social Security Administration (SSR 83-10)
  - Nursing pain intensity rating scale (0-10)
  - Assessment of ability to perform activities of daily living
  - Other changes in function or behavior documented by the treatment team may be considered.

An appropriate measurement tool should be selected to document baseline function and quality of life. The same evaluation instrument should be used consistently before and during therapy to document response to treatment. Use of more than one measurement tool before and during therapy may be beneficial.

APPENDIX

The following individuals were members of the consensus panel: Patricia Blakely, MD, Inland Nephrology, Redlands, CA; Garabed Eknoyan, MD, Baylor College of Medicine, Houston, TX; Allan Evans, PhD, School for Pharmaceutical Molecular and Biomedical Sciences, University of Australia, Adelaide, Australia; Mandeep Grewal, MD, Nephrology Associates, Chattanooga, TN; Charles Hoppel, MD, Case Western Reserve University College of Medicine, Louis Stokes VA Hospital, Cleveland, OH; Joel Kopple, MD, Harbor UCLA Medical Center, Torrance, CA; Craig Langman, MD, Feinberg School of Medicine, Children's Memorial Medical Center, Northwestern University, Chicago, IL; Sandra Lauriat, MD, FMC Mockingbird, Dallas, TX; Derrick L. Latos, MD, FACP, Nephrology Associates, Inc, West Virginia University School of Medicine, Wheeling, WV; Jill

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