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EXECUTIVE SUMMARY

INTRODUCTION
Chronic dialysis is a common and expensive therapy for end stage renal disease. The number of patients prescribed this therapy is increasing with time. Using a variety of measures, a number of articles studying patients in both the US and other countries have reported the prevalence of malnutrition in this population to range from 25% to 73%. Malnutrition increases morbidity, mortality, and cost, and produces growth retardation in children. It is therefore important to determine methods to adequately assess the nutritional status of dialysis patients, to prevent malnutrition from occurring in these patients, and to adequately treat malnutrition once it is discovered. This evidence report addresses nutritional prognostic, diagnostic, and treatment issues in dialysis patients.

METHODS
We performed a systematic review to assemble and critically appraise relevant studies answering the clinical questions of interest. The technical experts for this Evidence Report are the members of the National Kidney Foundation (NKF) Dialysis Outcomes Quality Initiative (DOQI) Workgroups. With their input we formulated the following key clinical questions:

Question 1. Which measure of nutritional status best predicts patient morbidity/ mortality (and growth rate in children) in chronic dialysis patients?

Question 2. Which measure is the best diagnostic test for protein/ calorie nutritional status in chronic dialysis patients?
Question 3. What is the effect of acid/base status on nutritional measures in chronic dialysis patients?

Question 4. Which levels of intake of protein and calories in chronic dialysis produce the lowest morbidity/mortality?

Question 5. Which levels of intake of protein and calories in predialysis patients produce the lowest morbidity at the initiation of dialysis?

Question 6. How does resting energy expenditure in dialysis patients compare with resting energy expenditure in patients not on dialysis?

Question 7. Which nutritional interventions produce the lowest morbidity/mortality (and best growth in children) or the most optimum changes in nutritional status in dialysis patients?

Question 8. Is interdialytic weight gain a good measure for dietary compliance or a good prognostic indicator in dialysis patients?

Question 9. Which measure of L-carnitine nutritional status best predicts patient morbidity/mortality in chronic adult dialysis patients?

Question 10. What are the best measures of L-carnitine nutritional status in chronic adult dialysis patients?

Question 11. Does L-carnitine supplementation in chronic adult dialysis patients improve morbidity/mortality?
Question 12. What are the toxic/ adverse effects of L-carnitine in adult chronic dialysis patients?

Question 13. Does growth hormone therapy improve morbidity/ mortality in pediatric chronic dialysis patients?

Question 14. Does vitamin or mineral supplementation improve morbidity/ mortality in pediatric dialysis patients? (Calcium, magnesium, and vitamin D were not examined.)

A structured database search of two computerized bibliographic databases (MEDLINE, EMBASE) was performed in collaboration with a librarian experienced in searching computerized bibliographic databases and performing “evidence-based” systematic reviews. We also hand-search the Journal of Renal Nutrition since it was not indexed in these bibliographic databases. Additionally, referrals from the technical experts were reviewed. For Questions 9-12 an extensive carnitine bibliography was provided by Sigma Tau, Rome, Italy.

Articles addressing the clinical questions were included in the selection steps detailed below. Animal studies, letters, editorials, reviews, case reports, and abstracts of meeting proceedings were excluded.

After loading articles from MEDLINE, EMBASE, technical expert referrals, and the Sigma Tau bibliography into an electronic database, one reviewer performed an initial title review and selection. Two independent reviewers then selected articles based on article abstracts. Selection disagreements were resolved by consensus. English language articles selected at the abstract stage were then reviewed and selected by two independent reviewers. Information was abstracted from the articles by one abstracter and verified by a second. Articles that were rejected at this stage were coded using the following codes:
R1: Editorial, letter, review, case report, article published as abstracts
R2: Article doesn’t answer clinical question of interest
R3: Article doesn’t have study design of interest
R4: Pediatric Article (rejected from the adult questions only)
R5: Not human
R6: Adult article (rejected from the pediatric questions only)

English titles, and English abstracts when available, of selected foreign language articles were sent to all technical experts for review. A foreign language article was abstracted by someone fluent with that particular language if any technical expert indicated an article would potentially contribute to the evidence in a particular area.

Because of the volume of accepted articles, further selections were made based on article study design. For prognostic articles, only those with prospective cohort or historical prospective cohort designs were included for further analysis. For diagnostic articles, only those where the authors compared a test with what they considered to be a gold standard for nutritional status were included for further analysis. For treatment articles, only those with a prospective design with concurrent controls were included for further analysis. (These restrictions did not apply to the carnitine sections or to the pediatric sections.) After article abstraction, evidence tables were produced from a subset of abstracted data elements and presented to the technical experts (also called workgroups) during meetings in Los Angeles in August 1998 and January 1999. The technical experts accepted or rejected articles based on the study methods, and adequacy in addressing the clinical questions.
RESULTS
The initial literature search identified 19,272 MEDLINE and 4,943 EMBASE titles. In addition, the technical experts referred 134 articles for review, and the Sigma Tau bibliography contained 138 references not found by other means. This review yielded 24,487 titles. Of these, 22,362 titles were rejected, leaving 2,125 titles. Abstracts of these articles were reviewed and 1,021 were rejected, thus leaving 1,104 articles. One hundred and seventy of these were foreign language articles whose titles and abstracts were sent to the technical experts. Of these, 102 were not selected for further evaluation, 2 were selected but could not be translated, and 66 were further evaluated. Of the 934 English language articles, 29 were unobtainable, leaving 971 English and foreign language articles to be abstracted. Of these, 640 were rejected (R1-R6) and the remaining 331 were sent to the technical experts along with evidence tables for these articles created from the abstraction forms. The technical experts rejected 81 articles either because the article did not adequately address a clinical question of interest or because the article was of poor study design, thus leaving 250 accepted articles.

Question 1: Which measure of nutritional status best predicts patient morbidity/mortality in chronic dialysis patients?

We identified 46 studies which assessed the value of nutritional measures as predictors of morbidity/mortality in patients on chronic dialysis. Many articles studied albumin and anthropometrics as prognostic factors, with other factors being less well studied. There is consistent evidence that serum albumin is related to mortality in dialysis patients. Other prognostic factors have been studied less frequently and/or have had less consistent results.
Question 2: Which measure is the best diagnostic test for protein/ calorie nutritional status in chronic dialysis patients?

Our literature search identified 29 studies pertaining to diagnostic tests for protein/ calorie nutritional status. A consistent gold standard for the diagnosis of nutritional status in dialysis patients was absent. Given this limitation, some support was found for the validity of serum albumin, pre-albumin, creatinine, protein catabolic rate (PCR), protein equivalent of total nitrogen appearance (PNA), the subjective global nutritional assessment (SGA), anthropometric measurements, the dual x-ray photon absorptiometry (DEXA), and transferrin.

Question 3: What is the effect of acid/ base status on nutritional measures in chronic dialysis patients?

Nine studies dealing with acid/ base status and nutrition in general supported the hypothesis that correcting acidosis improved nutritional status.

Question 4: Which levels of intake of protein and calories in chronic dialysis patients produce the lowest morbidity/ mortality (also optimal changes in nutritional parameters and best nitrogen balance)

The 16 articles identified contained primarily nitrogen balance articles and in general indicate that a dietary protein intake of 1.2g per kilogram per day is necessary to avoid nitrogen imbalance.

Question 5: Which levels of intake of protein and calories in predialysis patients produce the lowest morbidity at the initiation of dialysis?

Two meta-analyses assessing the effect of a low protein diet on predialysis patients both reached the conclusion that such diets have a significant mortality benefit.
Question 6: How does resting energy expenditure in dialysis patients compare with resting energy expenditure in patients not on dialysis?

The gold standard for the five articles selected was indirect calorimetry and the majority of evidence indicates there is little difference in resting energy expenditure between dialysis patients and patients not on dialysis.

Question 7: Which nutritional interventions produce the lowest morbidity/mortality or the most optimum changes in nutritional status in dialysis patients?

These 18 articles contained studies of both enteral and parenteral supplementation as well as counseling. Results were inconsistent and no conclusion could be drawn.

Question 8: Is interdialytic weight gain a good measure for dietary compliance or a good prognostic indicator in dialysis patients?

The 12 identified articles did not support a clinically important correlation between interdialytic weight gain and dietary compliance or patient outcomes.

Questions 9-12: Carnitine Supplementation

We identified 33 studies where serum triglycerides were the outcome, five studies where cardiac function and arrhythmia were the outcome, six studies where symptoms of malaise asthenia, muscle cramps, weakness and fatigue were the outcome, five studies where exercise capacity and muscle strength were the outcome, and 10 studies where anemia was the outcome. This evidence on potential beneficial effects of carnitine is moderately extensive but of uneven quality. Sufficient evidence to prove a benefit for carnitine was not found for any outcome. The outcome with the best evidence of benefit was anemia. Several clinical trials reported statistically significant improvements in hematocrit or decreases in erythropoietin requirements. However, in none of these studies was the effect on anemia the primary outcome, so these results must be viewed with caution as results of secondary
outcomes usually are known to overestimate efficacy. There is no evidence that administration of carnitine in standard doses is associated with side effects.

Pediatrics Questions 1-14:
The evidence specific to pediatric patients was very sparse, with the exception of growth hormone. One placebo-controlled double blind cross over trial of growth hormone in prepubertal children with chronic renal failure provided strong evidence that growth hormone treatment could greatly improve height velocity in such children. Other studies reported that the improvement in linear growth in patients treated with dialysis is not as great as that observed in patients with stable chronic renal failure and that the gain in height across subsequent years is diminished.

Conclusion
A large number of studies have been published in the medical literature on nutrition in dialysis patients. Through the series of selection steps detailed above, approximately 1 in 20 of the 24,487 articles obtained from various sources was selected for data abstraction. Of these, approximately 3% were unavailable, and two thirds were further rejected once the article was read and evaluated. Of the remaining one third (331 articles), the technical experts rejected approximately 1 in 4, leaving 250 accepted articles. Of these 250 accepted articles, pediatric nephrology patients were the subjects in approximately one fourth, with adult patients being the subjects in the remaining three fourths. There is sufficient evidence of validity for some diagnostic, prognostic, and treatment procedures. This report will provide the evidence for the development of clinical practice guidelines by the Nation Kidney Foundation Dialysis Outcomes Quality Initiative.
INTRODUCTION

Of the nearly 200,000 patients in the US with end stage renal disease (ESRD) in 1990, 70% were receiving either hemodialysis or peritoneal dialysis as renal replacement therapy (1). The estimated cost of care for all patients with ESRD in 1990 was US$7.26 billion. It is estimated that nearly 300,000 patients in the US will have ESRD in the year 2000, with an attendant rise in the costs of care. The number and cost of patients with ESRD worldwide are even greater.

The prevalence of malnutrition in dialysis patients has been studied in various countries using various methods. Anthropometric measures and albumin were significantly below normal in 37% to 70% of hemodialysis patients in Thailand (2). Eighty-two percent of continuous ambulatory peritoneal dialysis (CAPD) patients in Mexico were found to be malnourished (3). Using subjective global assessment, serum chemistries, and anthropometric measures, 51% of elderly Italian dialysis patients were found to be malnourished (4). In Pakistan, 34% to 70% of hemodialysis patients were found to be malnourished when assessed by albumin levels and various anthropometric measures (5). Malnutrition in Spanish hemodialysis patients was found to range from 40% to 73% (6; 7), and was found to be 54% in Denmark (8). A number of studies in the US have found the prevalence of malnutrition to range from 25% to 70% using a variety of assessment tools including anthropometric measures, blood tests, and composite and global assessments (9-12). One US study, however, found many patients to have anthropometric measurements not dissimilar to those in the general population (13).
A number of causes have been proposed for malnutrition in dialysis patients. These include the catabolic state of dialysis, the loss of nutrients during the dialysis procedure, the predialysis protein-restricted diet frequently prescribed, abnormal metabolism of nutrients, and dialysis-induced anorexia (14). Malnutrition increases morbidity, mortality, and cost, and produces growth retardation in children. Thus, it in incumbent on the nephrology community to determine methods to adequately assess the nutritional status of dialysis patients, to prevent malnutrition from occurring in these patients, and to adequately treat malnutrition once it is discovered. To these ends, the National Kidney Foundation has commissioned a systematic review of nutrition in chronic renal failure, the details of which are contained in this report.
METHODS

We performed a systematic review that “involves the application of scientific strategies, in ways that limit bias, to the assembly, critical appraisal, and synthesis of all relevant studies that address a specific clinical question.” (15; 16) A glossary of terms related to systematic reviews is listed in Appendix A.

CLINICAL QUESTIONS

With the guidance of the technical experts of the National Kidney Foundation (NKF) Dialysis Outcomes Quality Initiative (DOQI) Workgroup (Appendix B) we formulated the following clinical questions:

Question 1. Which measure of nutritional status best predicts patient morbidity/ mortality (and growth rate in children) in chronic dialysis patients? The technical experts chose to review only the following measures:

- Pre-albumin
- Albumin
- Anthropometric measures (height, weight, skinfold thickness, body mass index (BMI), percent of normal body weight, percent of ideal body weight, post-dialysis body weight)
- Bio-electric impedance
- Urea nitrogen appearance
- Pre-dialysis creatinine
- More than 1 of the above measures
- Subjective Global Assessment
- Dietary history
- Cholesterol
- Transferrin
- PCR/PNA
- Prognostic nutrition index
- Acute phase protein (C-reactive protein)
- Alpha-1 glycoprotein
- DEXA
- IGF in pediatric patients
Question 2. Which measure is the best diagnostic test for protein/ calorie nutritional status in chronic dialysis patients? The technical experts chose to review only the following measures:

- Pre-albumin
- Albumin
- Anthropometric measures (height, weight, skinfold thickness, body mass index (BMI), percent of normal body weight, percent of ideal body weight, post-dialysis body weight)
- Bio-electric impedance
- Urea nitrogen appearance
- Pre-dialysis creatinine
- More than 1 of the above measures
- Subjective Global Assessment
- Dietary history
- Cholesterol
- Transferrin
- PCR/PNA
- Prognostic nutrition index
- Acute phase protein (C-reactive protein)
- Alpha-1 glycoprotein
- DEXA
- IGF in pediatric patients

Question 3. What is the effect of acid/ base status on nutritional measures in chronic dialysis patients?

Question 4. Which levels of intake of protein and calories in chronic dialysis produce the lowest morbidity/mortality? The technical experts chose to also review the following:

- The most optimum changes in nutritional status using measures from question #1 above?
- Best nitrogen balance
- Best growth in children

Question 5. Which levels of intake of protein and calories in predialysis patients produce the lowest morbidity at the initiation of dialysis? (Though this question was addressed by both adult and pediatric groups, the pediatric group chose to use these articles to inform Question 4, while the adult group chose to write a separate guideline for this section.)
Question 6. How does resting energy expenditure in dialysis patients compare with resting energy expenditure in patients not on dialysis?

Question 7. Which nutritional interventions produce the lowest morbidity/mortality (and best growth in children) or the most optimum changes in nutritional status in dialysis patients? The technical experts chose to review the following measures from Question 1 above.

- Intradialytic supplementation
- Intra-PD supplementation
- Tube feeding
- Oral supplements
- Nutrition counseling
- Acid/base correction
- Intravenous supplementation

Question 8. Is interdialytic weight gain a good measure for dietary compliance or a good prognostic indicator in dialysis patients?

Question 9. Which measure of carnitine nutritional status best predicts patient morbidity/mortality in chronic adult dialysis patients? The technical experts chose to review only the following measures:

- Plasma carnitine levels
- Plasma acylcarnitine levels
- Muscle carnitine levels

Question 10. What are the best measures of carnitine nutritional status in chronic adult dialysis patients? (Question 11 was addressed first, with Question 10 being addressed if carnitine supplementation at any carnitine/acylcarnitine level was felt to change outcomes.) The technical experts chose to review only the following measures:

- Plasma carnitine levels
- Plasma acylcarnitine levels
- Muscle carnitine levels

Question 11. Does carnitine supplementation in chronic adult dialysis patients improve morbidity/ mortality? The technical experts chose to also review the following:

- Hypertriglyceridemia
- Anemia
- Intradialytic dysrhythmias
- Exercise tolerance
- Left ventricular dysfunction
- Quality of life

Question 12. What are the toxic/ adverse effects of L-carnitine in adult chronic dialysis patients?

Question 13. Does growth hormone therapy improve morbidity/ mortality in pediatric chronic dialysis patients?

Question 14. Does vitamin or mineral supplementation improve morbidity/ mortality in pediatric chronic dialysis patients? (calcium, magnesium, and vitamin D were not examined.)

Literature Review

A structured database search of 2 computerized bibliographic databases (MEDLINE, EMBASE) was performed with the following specifications:

- Language: English and non-English articles
- Dates: 1966 through 1997
- Subjects: Human.
- Article types: letters, editorials, reviews, case reports, and abstracts of meeting proceedings were excluded.

The search was performed in collaboration with a librarian experienced in searching computerized bibliographic databases and performing “evidence-based” systematic reviews. The MEDLINE search strategies are detailed in Appendix C. The EMBASE strategies were similar.
We also hand-search the Journal of Renal Nutrition since it was not indexed in the bibliographic databases listed above. Additionally, referrals from technical experts were reviewed. For Questions 9-12, an extensive carnitine bibliography was provided by Sigma Tau, Rome, Italy.

Inclusion and Exclusion Criteria
Articles meeting the specifications listed above, and addressing at least 1 of the clinical questions detailed above were included. All others were excluded.

Article Selection and Abstraction
After loading articles from MEDLINE, EMBASE, technical expert referrals and the Sigma Tau bibliography into an electronic database, one reviewer performed an initial title review of these articles, applying the above inclusion and exclusion criteria. Abstracts were requested for all articles accepted at the title screening phase. Two independent reviewers then screened the abstracts and applied the above inclusion and exclusion criteria. Selection disagreements were resolved by consensus. English language articles accepted at the abstract screening phase were obtained and divided into the appropriate sections (see above) based on the clinical question the article addressed. These articles were then reviewed by two independent reviewers. Information was abstracted from the articles (see below) by one abstracter and verified by a second. Disagreements were resolved by consensus. Articles rejected at the abstraction stage were coded using the following:

- R1: Editorial, letter, review, case report, article published as abstracts
- R2: Article doesn’t answer clinical question of interest
- R3: Article doesn’t have study design of interest
- R4: Pediatric Article (rejected from the adult questions only)
- R5: Not human
- R6: Adult article (rejected from the pediatric questions only)
Article publication language was not limited to English in order to increase precision and reduce systematic errors (17), and because of the potential publication bias for positive studies in the English literature (18). After discussing the process of foreign language article selection with the technical experts, we decided to send the English titles, and English abstracts when available, to all technical experts for review. A foreign language article was abstracted by someone fluent with that particular language if any technical expert indicated that an article would possibly contribute to the evidence in a particular area.

Because of the volume of accepted articles, selections were further made based on article study design. For prognostic articles, only those with prospective cohort or historical prospective cohort designs were included for further analysis. For diagnostic articles, only those where the authors compared a test with what they considered to be a gold standard for nutritional status were included for further analysis. For treatment articles, only those with a prospective design with concurrent controls were included for further analysis. (These restrictions did not apply to the carnitine sections or to the pediatric sections.)

After article abstraction (see below), evidence tables were produced from a subset of abstracted data elements and presented to the technical experts during meetings in Los Angeles in August, 1998 (adult technical experts), January, 1999 (pediatric technical experts), and during a series of subsequent conference calls. The technical experts accepted or rejected articles based on the study methods and adequacy in addressing the clinical questions. The article selection process is detailed in Appendix D. The final selected articles are listed in Appendix E.

Critical Appraisal Method for Prognostic Articles

For each prognostic article (Questions 1, 3, 4, 5, and 8), we abstracted data to answer the following questions (19):

16
• What was the type of study?
• What were the three most frequently occurring co-morbid conditions?
• Was there a representative and well-defined sample of patients at a similar point in the course of disease?
• What was the follow-up time period?
• Were the outcome criteria objective and application of them unbiased?
• Was adjustment made for important known prognostic factors?
• What were the results?

In addition, we abstracted a number of data elements that addressed study population and dialysis characteristics that might have affected the study results:

• Number of patients at start of study
• Years on dialysis
• Age of patients
• Type of dialysis
• Dialysate
• Membrane and whether it was reused
• Dialysis schedule
• For HD, type of vascular access
• Economic status
• Race
• Residual renal function

A copy of the article abstraction form is in Appendix F.

Critical Appraisal Method for Diagnostic Articles

For each diagnostic article (Questions 2 and 6), we abstracted data to answer the following questions (20; 21):

• What was the type of study?
• What were the three most frequently occurring co-morbid conditions?
- Was there an independent blind comparison with a reference (gold) standard?
- Did results of the test being studied influence the decision to perform the reference standard?
- Was the spectrum of patients in the study similar to the spectrum seen in dialysis centers?
- Was the test methodology described well enough to be reproducible?
- What were the results?

In addition, we abstracted a number of data elements that addressed study population and dialysis characteristics that might have affected the study results. These were the same as for the prognosis sections listed above.

A copy of the article abstraction form is in Appendix F

Critical Appraisal Method for Treatment Articles

For each treatment article (Questions 7, 13, and 14), we abstracted data to answer the following questions (22; 23):

- What was the type of study?
- What were the three most frequently occurring co-morbid conditions?
- What were the Jadad quality scores?:
  - Randomization score ?
  - Double blind score ?
  - All patients accounted for score ?
- Were all patients analyzed in the treatment group to which assigned?
- Were the treatment groups similar at baseline?
- Were the treatment groups treated equally except for the studied intervention?
- What were the results?
In addition, we abstracted a number of data elements that addressed study population and dialysis characteristics that might have affected the study results. These are the same as for the prognosis sections listed above.

The Jadad quality scores have been empirically shown to distinguish the effect size between reports of clinical trials. It assesses clinical trials in three domains: randomization, blinding, and withdrawals and dropouts. Scores range from 0-5 with higher scores indicating better quality. (24-28).

The algorithm for the Jadad quality scores is shown in Appendix G. A copy of the article abstraction form is in Appendix F.

Evidence Synthesis

Due to sparseness of data and clinical heterogeneity among studies, we did not perform meta-analysis. Therefore, our synthesis of the evidence is qualitative.
RESULTS

DISTRIBUTION OF EVIDENCE

The initial literature search identified 19,272 MEDLINE and 4,943 EMBASE titles. In addition, the technical experts referred 134 articles for review, and the Sigma Tau bibliography contained 138 references not found by other means. This review yielded 24,487 titles. Of these, 22,362 titles were rejected as not meeting the inclusion criteria, leaving 2,125 titles. Of these, 1,021 were rejected at abstract screening as not meeting the inclusion criteria, thus leaving 1,104 articles. One hundred and seventy of these were foreign language articles whose titles and abstracts were sent to the technical experts. Of these, 102 were not selected for further evaluation, 2 were selected but could not be translated, and 66 were further evaluated. Of the 934 English language articles, 29 were unobtainable, leaving 971 English and foreign language articles to be abstracted. Of these, 640 were rejected (R1-R6) and the remaining 331 were sent to the technical experts along with evidence tables for these articles created from the abstraction forms. The technical experts rejected 81 articles thus leaving 250 accepted articles entering into this evidence report (figure 1). These articles are divided by questions and listed in Appendix E. Evidence tables for each question are detailed in Appendix H.
FIGURE 1. ARTICLE SELECTION PROCESS

Medline 19,272
Embase 4,943
Sigma Tau 138
Technical Expert referrals 134

Titles reviewed 24,487

Selected titles, abstracts reviewed 2,125

Rejected at title stage 22,362

Selected abstracts, articles ordered 1,104

Rejected at abstract stage 1,021

Articles reviewed and abstracted 971

Rejected (R1-R6) 640

Selected articles reviewed by technical experts 331

Articles Accepted 250

Rejected by technical experts 102
Unable to translate 2
Abstracted 66
Foreign language sent to technical experts 170

Articles unavailable 29

Rejected by technical experts 81
Question 1: Which measure of nutritional status best predicts patient morbidity/mortality in chronic dialysis patients?

Our literature search identified 46 studies which assessed the value of nutritional measures as predictors of morbidity/mortality in patients on chronic dialysis. The great majority of these studies were prospective in nature and several had follow-up of five years or more of duration. They were evenly distributed between studies of patients on hemodialysis and peritoneal dialysis (18 studies of hemodialysis, 15 studies peritoneal dialysis, 12 studies of both).

The best studied nutritional measure by far was serum albumin, which was reported in 35 studies. Most of these studies reported a statistically significant association between lower serum albumin and higher mortality, and this was true for patients on hemodialysis and peritoneal dialysis. Other nutritional prognostic factors were studied less frequently and had less consistent results.

Details of studies are provided in Evidence Table 1.

Question 2: Which measure is the best diagnostic test for protein/calorie nutritional status in chronic dialysis patients?

For this study question, we identified 29 studies of which 12 were prospective cohorts, 15 were cross-sectional assessments of diagnostic tests and nutritional status, and two had study designs that were unclear. Both hemodialysis and peritoneal dialysis patients were studied. A great variety of possible diagnostic tests were assessed and the reference standard for nutritional status also varied between studies. The results were not consistent across studies. However, some support was found for the validity of serum albumin, pre-albumin, creatinine, protein catabolic rate (PCR), protein equivalent of total nitrogen appearance (PNA), the subjective global nutritional assessment (SGA), anthropometric measurements, the dual x-ray photon absorptiometry (DEXA), and transferrin.
Full details of the individual studies are presented in Evidence Table 2.

Question 3: What is the effect of acid/base status on nutritional measures in chronic dialysis patients?

Our literature search identified nine studies providing evidence relevant to this study question. Five of these studies were randomized clinical trials, two were prospective cohort studies, one was a clinical trial and one was a cross sectional analysis.

In a prospective, randomized, double-blind, controlled trial, Otte and colleagues (1990) assessed the effects of a bicarbonate-based hemodialysis fluid compared with an acetate-based one in 16 patients on chronic hemodialysis. The study was cross-over in design so that each patient served as their own control. The period of time on each dialysate was 12 weeks. Blood chemistries were measured at the start and every 4 weeks throughout the study and the anthropometrics were measured at the start, at 12 weeks and at the end of the study. Dietary assessments by a dietician were performed periodically and adverse events were registered by the nursing staff during each dialysis. Other than a slight metabolic acidosis that was more pronounced in patients on acetate dialysis, no differences were found between groups in any of the outcomes measured.

In a controlled trial (Graham, 1997), six patients on chronic hemodialysis were randomly assigned in a cross-over trial to standard dialysis or dialysis with 40 mmol of bicarbonate. Oral sodium bicarbonate was given in addition as needed to correct acidosis. Treatment resulted in an increase in the subject’s mean bicarbonate concentration from 18.5 mmol per liter to 24.8 mmol per liter and a subsequent increase in pH from 7.36 to 7.40. While no significant differences in anthroprometrics and body mass index were noted, radioactive leucine infusion tests demonstrated that leucine appearance from body protein decreased significantly with
correction of acidosis. The authors interpreted their results as indicating that correction of acidosis in hemodialysis is beneficial in terms of protein turn-over.

In Stein and colleagues (1997), 200 consecutive patients who were newly placed on continuous ambulatory peritoneal dialysis were randomized in a single blinded fashion to receive a high or a low alkali-dialysis for one year. Other measures were taken to correct acidosis in the high alkali group. By one year of follow-up, persons randomized to the high-alkali group had a greater increase in body weight and mid-arm circumference than those in the low-alkali group; however, there was no difference in tricep skin fold thickness, serum albumin or dietary protein intake. The high-alkali group had fewer hospital admissions and spent less days in the hospital per year than the low-alkali group.

A randomized clinical trial involved 46 patients who were stable on hemodialysis (Williams, 1997). The study was single blind double crossover trial with six months during each period. The study reported a significant improvement in triceps skin-fold thickness for patients in the high bicarbonate dialysate compared to those in the low bicarbonate dialysate. There were no statistically significant differences in other measures of nutrition including serum albumin concentration, mid-arm muscle circumference, and the normalized protein catabolic rate.

In the randomized clinical trial by Brady and colleauge (1998), 36 patients who had been stable for at least three months on hemodialysis were divided into two groups, one of whom was dialyzed against a standard bicarbonate bath and the second group was dialyzed against a high-alkali bicarbonate bath. The subjects randomized to the high-alkali bicarbonate bath in addition received oral sodium bicarbonate as necessary. After 16 weeks of treatment, there were no statistically significant differences between groups in the nutritional parameters measured, which were serum albumin and the total lymphocyte count.
In a clinical trial (Harris, 1995) tested the effects of standard dialysate, a high bicarbonate dialysate, and “modeled” bicarbonate dialysate for 4 weeks each in 9 stable adult patients on hemodialysis. Modeled bicarbonate dialysate is a procedure where lower bicarbonate concentrations are used early in dialysis to reduce intracellular shifting of phosphate and higher bicarbonate is used during the last hour of dialysis to correct the acidosis, and has been postulated to more safely improve phosphate removal. The trial was a double blind cross-over trial of the three treatments with a washout period between treatments. Oral bicarbonate therapy was given to both the high bicarbonate dialysate and the modeled bicarbonate dialysate groups in order to maintain plasma bicarbonate concentrations at 24-26 mmol per liter. The authors reported no difference among groups in any of the outcome measures including measures of phosphate clearance, plasma concentration of the urea, total calcium, blood pressure and symptoms.

The two cohort studies (Dumler, 1996 and Kang, 1997), involve 79 and 106 peritoneal dialysis patients, respectively, and had follow-up periods of 21 months and two years. No effect of mild acidosis was found on measures of nutritional status in either study.

In a cross-sectional analysis by Movilli and colleagues (1998), 81 patients on chronic hemodialysis had a variety of blood chemistry and nutritional measures assessed along with bicarbonate. The authors report a modest correlation between serum albumin level and serum bicarbonate levels and an inverse correlation between the normalized protein catabolic rate and increasing serum bicarbonate.

In summary, most (but not all) studies support an association between correction of acidosis and better nutritional status.

Further details can be found in Evidence Table 3.
Question 4: Which levels of intake of protein and calories in chronic dialysis patients produce the lowest morbidity/mortality (also optimal changes in nutritional parameters and best nitrogen balance)?

Our literature search identified 16 articles describing 15 studies that were all prospective cohorts. Both peritoneal dialysis and hemodialysis patients were studied. Most of the studies were small with only six studies having more than 20 patients. The length of follow-up was anywhere from a few days to several years. In general the studies showed that increasing dietary protein intake was associated with improvement in nutritional status measures, such as serum albumin, pre-albumin, cholesterol, and measures of nitrogen balance.

Two studies (Kopple, 1969A & B; Archiaedo, 1990) also reported patient outcomes. In the study of Kopple and colleagues (1969), no difference was found between patients with a lower dietary protein intake and those with a higher dietary protein intake in terms of infection and cardiovascular accidents. Both serum albumin and body weight increased in the patients prescribed a high dietary protein intake. Uremic symptoms were more common in the patients with a higher dietary protein index. In Archiaedo and colleagues (1990), 136 patients were followed prospectively for one year. Patients were divided at baseline into five groups based on historical data, one of which was “inadequate protein intake.” Patients on an inadequate diet of less than 0.8 grams of protein per kilogram per day had a greater number of hospital days per year than patients receiving an adequate diet.

In general the studies show that a dietary protein intake of 1.2 grams per kilogram per day is necessary to avoid nitrogen imbalance.

The details of all studies are presented in Evidence Table 4.
Question 5: Which levels of intake of protein and calories in predialysis patients produce the lowest morbidity at the initiation of dialysis?

Our literature search identified two meta-analyses dealing with low protein diet and patient outcomes, and additional studies including randomized clinical trials, prospective cohorts, and nitrogen balance studies.

The first meta-analysis (Fouque, 1992), assessed six randomized clinical trials covering 890 patients with mild-to-severe renal failure who were followed for at least one year. The difference in protein intake between groups in a trial needed to be at least 0.2 grams of protein per kilogram per day in order to be included. The results of this data synthesis were that patients randomized to the low protein diet had an odds ratio of renal death of 0.54 relative to control with a 95% confidence interval of 0.37 to 0.79.

The second meta-analysis (Pedrini, 1996), assessed the effect of low protein diets on patients with chronic renal disease stratified by whether the renal disease was diabetic or non-diabetic in etiology. In both strata, five randomized clinical trials were identified, comprising 1413 patients with non-diabetic renal disease and 108 patients with diabetic nephropathy. For patients with non-diabetic renal disease, the relative risk of renal failure or death was reported in the pooled analysis as 0.67 with a 95% confidence interval of 0.5 to 0.89. For patients with diabetic nephropathy, a low protein diet significantly slowed the increase in the urinary albumin level or the decline in the glomerular filtration rate with a relative risk of 0.56 and a 95% confidence interval of 0.40 to 0.77.

Therefore, the results of both meta-analyses are consistent with the hypothesis that a low protein diet has a significant benefit in decreasing death for patients with both diabetic and non-diabetic renal disease. The results of the individual prospective cohorts and other studies were in general agreement with the meta-analysis.
The details of all studies presented in Evidence Table 5.

Question 6: How does resting energy expenditure in dialysis patients compare with resting energy expenditure in patients not on dialysis?

Our literature search identified five studies that assessed the energy expenditure of patients using indirect calorimetry. Studies ranged in size from eight to 25 patients. Four studies addressed patients on hemodialysis and one addressed patients on continuous ambulatory peritoneal dialysis.

Three studies (Olevitch, 1994; Schmeweiss, 1990; Montian, 1986), reported no difference in energy expenditure either between patients on hemodialysis and control patients or between patients with chronic renal failure during periods of hemodialysis and the inter-dialytic period.

One study (Ikizler, 1996), did report a difference in energy expenditure both between chronic hemodialysis patients and normal patients and in patients with chronic renal failure on hemodialysis compared to the period of time between dialysis.

The one study of patients on peritoneal dialysis (Harty, 1995), reported no significant difference in resting energy parameters between patients on peritoneal dialysis and non-uremic control patients.

In summary, the majority of evidence indicates there is little difference in resting energy expenditure between dialysis patients and patients not on dialysis.

Full details of all articles are presented in Evidence Table 6.

Question 7: Which nutritional interventions produce the lowest morbidity/mortality or the most optimum changes in nutritional status in dialysis patients?

Our literature search identified 18 studies relevant to this question. Nine of these were randomized clinical trials and nine were controlled clinical trials or cohort studies. Of the nine
randomized clinical trials, only four had a Jadad score greater than or equal to three, a threshold which has previously been used to characterize good quality studies. The clinical trials studied small numbers of patients, generally between ten and thirty. A variety of oral supplements or changes in the dialysate were assessed. Most of the studies reported mixed results with some nutritional parameters improving and others showing no difference between groups. A clear conclusion from these studies cannot be drawn.

The details of identified studies are reported in Evidence Table 7.

Question 8: Is interdialytic weight gain a good measure for dietary compliance or a good prognostic indicator in dialysis patients?

Our literature search identified 12 studies relevant to this study question. These were prospective or retrospective cohort studies, most of which had methodologic flaws. The results of the studies were mixed. Most studies reported no correlation or only a weak correlation between interdialytic weight gain and dietary compliance on patient outcome.

The details of all studies are reported in Evidence Table 8.

Questions 9-12: Carnitine Supplementation

Question 9: Which measure of carnitine nutritional status best predicts patient morbidity/ mortality in chronic adult dialysis patients?

Question 10: What are the best measures of carnitine nutritional status in chronic adult dialysis patients?

Question 11: Does carnitine supplementation in chronic adult dialysis patients improve morbidity/ mortality?

Question 12: What are the toxic/ adverse effects of L-carnitine in adult chronic dialysis patients?
Carnitine is known to be an essential co-factor in fatty acid and energy metabolism. It has also been shown that patients on maintenance dialysis usually have low serum free L-Carnitine concentrations and that skeletal muscle carnitine is sometimes decreased. Therefore there have been several studies investigating the effect that replacement of L-Carnitine has on a variety of patient outcomes, including serum triglycerides, cardiac functions and arrhythmia, malaise asthenia, muscle cramps, weakness and fatigue, exercise capacity, and anemia. Studies will be summarized within each of these outcomes.

**Elevated Serum Triglycerides**

Our literature search identified 33 studies relevant to the question of the effect of L-Carnitine administration on elevated serum triglycerides. Ten of these were randomized clinical trials of which eight had a Jadad score greater than or equal to three, a threshold that has been proposed as defining “good” quality.

Of these, five studied intravenous administration or oral administration and one gave L-Carnitine in the dialysite. Seven of these studies did not report any statistically significant affect of L-Carnitine administration on triglycerides while one did report statistical significance. Of the two other randomized clinical trials with Jadad scores less than three, one gave L-Carnitine orally and one gave it intravenously. Both studies reported a positive effect on triglycerides of L-Carnitine administration.

The remaining non-randomized studies reported mixed results. Details of all studies are reported in Evidence Table 9.

In summary, data from randomized clinical trials generally do not support a beneficial effect of L-Carnitine administration on elevated serum triglycerides in patients on maintenance dialysis although this conclusion was not reached by all studies.
Cardiac Function and Arrhythmia

Our literature search identified five studies relevant to the question of the effect of L-Carnitine administration on cardiac function and arrhythmia. Three of these were randomized clinical trials of which 2 had a Jadad score greater than or equal to 3. Almost all of the studies measured the cardiac outcomes differently, including dialysis-associated arrhythmia, heart volume, ejection fraction, blood pressure and pulse rate, and measures of cardiac size.

Of the 2 best quality randomized clinical trials, neither reported a significant change in cardiac outcomes. Details of all studies are summarized in Evidence Table 10.

In summary, there is no evidence that L-Carnitine supplementation improves cardiac outcomes in patients on maintenance dialysis.

Malaise Asthenia, Muscle Cramps, Weakness and Fatigue

Our literature search identified six studies that provided evidence assessing the effect of L-Carnitine administration on any of the symptoms malaise asthenia, muscle cramps, weakness and fatigue occurring, either interdiallytically or in the post dialysis period. Four of these were randomized studies of which all scored greater than or equal to three on Jadad scale. Two studies reported significant effects of carnitine supplementation and two studies did not. Details of all studies are reported in Evidence Table 11.

In summary, there is mixed evidence regarding the effect of L-Carnitine supplementation on improvement in symptoms of malaise asthenia, muscle cramps, weakness and fatigue in the interdialytic and post dialectic symptoms.
Exercise Capacity

Our literature search identified five studies providing relevant to the question of L-Carnitine supplementation on exercise capacity or muscle strength. Of these, three were randomized clinical trials; all had a Jadad score greater than or equal to three.

One study (Ahmad, 1990) reported an improvement in some measures of exercise capacity but not others. Another study (Albertazzi, 1980) reported a significant improvement in subjective muscle strength. The last study (Fagher, 1985) reported no significant difference between treatment and placebo arms and maximum strength or dynamic endurance.

Details of all studies are summarized in Evidence Table 12.

In summary, there is mixed evidence on the effect of L-Carnitine supplementation on improvement in exercise capacity on patients on maintenance dialysis.

Anemia

It has been proposed that Carnitine deficiency may reduce erythrocyte half-life by adversely influencing the integrity of the erythrocyte membrane. Our literature search identified ten studies providing information relevant to the question of whether L-Carnitine supplementation improves anemia or decreases erythropoietin requirements in patients on maintenance dialysis.

Of these, five studies were randomized and four of these had a Jadad score greater than or equal to three. Of these four studies, three reported an improvement in hemoglobin or hematocrit and one did not.

The details of all studies are summarized in Evidence Table 13.
In summary, there is evidence from several small randomized trials that L-Carnitine supplementation may improve anemia in patients on maintenance dialysis. In several of these studies, the effect of L-Carnitine supplementation on anemia was not a primary outcome of interest, but rather a secondary analysis and therefore these findings require confirmation in a randomized clinical trial where treatment of anemia is the primary outcome of interest.

As our literature search did not identify convincing evidence of a benefit of carnitine supplementation, the technical experts decided there was no need to search for evidence regarding measurement and prognosis (Questions 9 and 10).

Regarding possible side effects of carnitine, most studies made no mention of side effects. Four studies specifically stated no side effects occurred, one study stated there was “some euphoria” with carnitine administration, and one study reported one patient had nausea. In sum, there is no evidence that carnitine in standard doses is associated with serious side effects.

Pediatrics Question 1: Which measure of nutritional status best predicts patient morbidity/ mortality (and growth rate in children) in chronic dialysis patients?

Our literature search identified one study possibly relevant to this question. In this study (Chan, 1978) 19 pediatric patients between the ages of five and seventeen were followed prospectively for up to 59 months. All patients were on chronic hemodialysis. The patients were noted to be consuming far fewer calories and protein per day than recommended and growth was in general one to four standard deviations below the mean for age.

In addition to this article there were three articles that dealt with insulin-like growth factor 1 (IGF-1). Two of these were prospective cohorts and one was a cross-sectional study. The cross-sectional study (Besbas, 1998), reported an association between lower IGF-1 levels and patients with malnutrition as defined by tricep skin fold thickness. However, neither of the
prospective cohort studies (Jasper, 1991; Hodson, 1992) identified a significant correlation between IGF-1 levels and growth rates or nutritional parameters. In summary, there is evidence that IGF-1 is not correlated with growth retardation in children with chronic renal failure.

Details of the articles are listed in Evidence Table 14.

Pediatrics Question 2: Which measure is the best diagnostic test for protein/calorie nutritional status in chronic dialysis patients?

Our literature search identified three studies relevant to this question. One study was a retrospective cohort study, and the other two were cross sectional studies. Patients on hemodialysis and on peritoneal dialysis were included. One study correlated skin fold thickness and bioelectrical impedance and reported a high correlation between these two (Stefanidis, 1996). A second study assessed the correlations between dual energy x-ray absorptiometry, lean body mass, and urinary excretion of creatinine and reported high correlations between all three (Cochat, 1996). A third study assessed the relation between insulin-like growth factor 1 (IGF-1) and protein energy malnutrition as defined by anthropometric measures in seventeen children with chronic renal failure on maintenance hemodialysis. Transferrin and serum albumin were not correlated with anthropometric measures while IGF-1 was significantly correlated (Besbas, 1998).

Full details of studies are presented in Evidence Table 15.

Pediatrics Question 3: What is the effect of acid/base status on nutritional measures in chronic dialysis patients?

We identified no studies pertaining to pediatrics and relevant to this question.

Pediatrics Question 4 and Question 5: Which levels of intake of protein and calories in chronic dialysis produce the lowest morbidity/mortality? Which
levels of intake of protein and calories in predialysis patients produce the lowest morbidity at the initiation of dialysis?

Our literature search identified 24 studies relevant to these two questions. Sixteen of these were prospective cohort studies. Two were retrospective cohort studies and three were cross sectional studies. In addition there were three randomized trials of a low protein diet. Most studies assessed either dietary energy intake or dietary protein intake on growth or nutritional measures such as serum albumin, transferrin and cholesterol. Children on both hemodialysis and peritoneal dialysis were studied. Follow-up times ranged from one year to as much as ten years. Results were mixed and there was not a consistent correlation across studies between protein and energy intake and the outcomes measured.

All three RCTs (Wingen, 1992; Kist, 1993; Uauy, 1994) of low protein diet concluded that the low protein diet was of minimal or no value.

Full details of included studies are in Evidence Table 16.

Pediatrics Question 6: How does resting energy expenditure in dialysis patients compare with resting energy expenditure in patients not on dialysis?

We identified no studies pertaining to pediatrics and relevant to this question.

Pediatrics Question 7: Which nutritional interventions produce the lowest morbidity/ mortality (and best growth rate in children) or the most optimum changes in nutritional status in dialysis patients?

We identified 11 studies relevant to this question. Of these, one was a small randomized controlled trial that included seven patients on continuous ambulatory peritoneal dialysis and which assessed the effect of added amino acids in the dialysate on measures of plasma, glucose and amino-acids. The study reported that the amino-acid dialysate was less effective than traditional glucose-containing dialysates by the standard measures of filtration. However, the amino-acid dialysate had some significant metabolic advantages in the short-term. The
observational studies assessed a variety of protein and calorie supplements including amino-acid dialysates, nasal gastric tube feedings and oral supplements on a variety of outcomes including height, weight, serum albumin, hospital admissions, catheter infections and peritonitis. Results were mixed and findings were not consistent across studies.

Full details of these studies can be found in Evidence Table 17.

Pediatrics Question 8: Is interdialytic weight gain a good measure for dietary compliance or a good prognostic indicator in dialysis patients?

We identified no studies pertaining to pediatrics and relevant to this question.

Pediatrics Question 13: Does growth hormone therapy improve morbidity/mortality in pediatric chronic dialysis patients?

Our literature search identified 14 studies relevant to this study question. One of these studies (Hokken-Koelega, 1991) was a placebo-controlled double blind cross over trial of growth hormone treatment in pre-pubertal children with chronic renal failure. In this study, 16 children with chronic renal failure and severe growth retardation were given biosynthetic growth hormone at a dose of four international units per meter squared per day. Height velocity increased in every patient during the time in every patient during the time on growth hormone. Compared to placebo, the height velocity increase while on growth hormone was 0.9 centimeters greater per six months. This study proved that growth hormone treatment could greatly improve height velocity in children with chronic renal failure and growth retardation. The other studies identified in our literature search were observational and assessed either the effects of growth hormone on different types of patients or the effect of different levels of growth hormone. The general conclusion from these studies is that the improvement in linear growth in patients treated with dialysis is not as great as that observed in patients with stable chronic renal failure and that the gain in height across subsequent years is diminished.
Pediatric Question 14: Does vitamin or mineral supplementation improve morbidity/ mortality in pediatric dialysis patients? (Calcium, magnesium, and vitamin D were not examined.)

Our literature search identified three studies relevant to this question. Two studies (Kriley, 1991; Warady, 1994) were cross-sectional examinations of dietary intake and determinations of vitamin stores or concentrations. Both of these studies reported that the levels of many vitamins were normal or greater than normal in both children and infants receiving peritoneal dialysis and also on a vitamin supplementation regimen. The third study (Zlotkin, 1987) assessed the affect of zinc absorption from glucose and amino acid dialysis solutions in children on peritoneal dialysis. This study reported that there is a significant net absorption of zinc from glucose containing dialysis solutions and concluded that peritoneal dialysis does not contribute to zinc depletion.

The details of all studies can be found in Evidence Table 19.
SUMMARY

A large number of studies have been published in the medical literature on nutrition in dialysis patients. Through the series of selection steps detailed above, approximately 1 in 20 of the 24,487 titles obtained from various sources was selected for data abstraction. Of these, approximately 3% were unavailable, and two thirds were further rejected once the article was read and evaluated in greater detail. Of the remaining 331 articles, the technical experts rejected approximately 1 in 4, leaving 250 accepted articles.

Of these 250 accepted articles, pediatric nephrology patients were the subjects in approximately one fourth, with adult patients being the subjects in the remaining three fourths. Of the questions pertaining to adults, Question 9 (which measure of carnitine nutritional status best predicts patient morbidity/mortality in chronic adult dialysis patients?) and Question 10 (what are the best measures of carnitine nutritional status in chronic adult dialysis patients?) were not addressed because there was insufficient evidence to conclude (for Question 11) that carnitine supplementation in chronic adult dialysis patients improves morbidity or mortality. Of the questions pertaining to pediatric patients, Question 3 (what is the effect of acid/base status on nutritional measures?), Question 6 (how does resting energy expenditure in dialysis patients compare with resting energy expenditure in patients not on dialysis?), and Question 8 (is interdialytic weight gain a good measure for dietary compliance or a good prognostic indicator in dialysis patients?) contained no accepted articles.
Question 1: Which measure of nutritional status best predicts patient morbidity/ mortality in chronic dialysis patients?

We identified 46 studies which assessed the value of nutritional measures as predictors of morbidity/ mortality in patients on chronic dialysis. Many articles studied albumin and anthropometrics as prognostic factors, with other factors being less well studied. There is consistent evidence that serum albumin is related to mortality in dialysis patients. Other prognostic factors have been studied less frequently and/ or have had less consistent results.

Question 2: Which measure is the best diagnostic test for protein/ calorie nutritional status in chronic dialysis patients?

Our literature search identified 29 studies pertaining to diagnostic tests for protein/ calorie nutritional status. A consistent gold standard for the diagnosis of nutritional status in dialysis patients was absent. Given this limitation, some support was found for the validity of serum albumin, pre-albumin, creatinine, protein catabolic rate (PCR), protein equivalent of total nitrogen appearance (PNA), the subjective global nutritional assessment (SGA), anthropometric measurements, the dual x-ray photon absorptiometry (DEXA), and transferrin.

Question 3: What is the effect of acid/ base status on nutritional measures in chronic dialysis patients?

Nine studies dealing with acid/ base status and nutrition in general supported the hypothesis that correcting acidosis improved nutritional status.

Question 4: Which levels of intake of protein and calories in chronic dialysis patients produce the lowest morbidity/ mortality (also optimal changes in nutritional parameters and best nitrogen balance)?

The 16 articles identified contained primarily nitrogen balance articles and in general indicate that a dietary protein intake of 1.2g per kilogram per day is necessary to avoid nitrogen imbalance.
Question 5: Which levels of intake of protein and calories in predialysis patients produce the lowest morbidity at the initiation of dialysis?

Two meta-analyses assessing the effect of a low protein diet on predialysis patients both reached the conclusion that such diets have a significant mortality benefit.

Question 6: How does resting energy expenditure in dialysis patients compare with resting energy expenditure in patients not on dialysis?

The gold standard for the five articles selected was indirect calorimetry and the majority of evidence indicates there is little difference in resting energy expenditure between dialysis patients and patients not on dialysis.

Question 7: Which nutritional interventions produce the lowest morbidity/mortality or the most optimum changes in nutritional status in dialysis patients?

These 18 articles contained studies of both enteral and parenteral supplementation as well as counseling. Results were inconsistent and no conclusion could be drawn.

Question 8: Is interdialytic weight gain a good measure for dietary compliance or a good prognostic indicator in dialysis patients?

The 12 identified articles did not support a clinically important correlation between interdialytic weight gain and dietary compliance or patient outcomes.

Questions 9-12: Carnitine Supplementation

We identified 33 studies where serum triglycerides were the outcome, five studies where cardiac function and arrhythmia were the outcome, six studies where symptoms of malaise asthenia, muscle cramps, weakness and fatigue were the outcome, five studies where exercise capacity and muscle strength were the outcome, and 10 studies where anemia was the outcome. This evidence on potential beneficial effects of carnitine is moderately extensive but of uneven quality. Sufficient evidence to prove a benefit for carnitine was not found for any outcome. The outcome with the best evidence of benefit was anemia. Several clinical trials reported statistically significant improvements in hematocrit or decreases in
erythropoietin requirements. However, in none of these studies was the effect on anemia the primary outcome, so these results must be viewed with caution as results of secondary outcomes usually are known to overestimate efficacy.

There is no evidence that administration of carnitine in standard doses is associated with any serious side effects.

Pediatrics Questions 1-14:
The evidence specific to pediatric patients was very sparcce, with the exception of growth hormone. One placebo-controlled double blind cross over trial of growth hormone in prepubertal children with chronic renal failure provided strong evidence that growth hormone treatment could greatly improve height velocity in such children. Other studies reported that the improvement in linear growth in patients treated with dialysis is not as great as that observed in patients with stable chronic renal failure and that the gain in height across subsequent years is diminished.
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(Uncontrolled) before and after study
A prospective study where a cohort is determined to be the control group before an intervention, and the same cohort is determined to be the treatment group after the intervention. Outcomes are measured during both the control period and the treatment period and then compared. There is not a separate group acting as concurrent controls.

Blinding (synonym: masking)
Keeping secret group assignment (e.g. to treatment or control) from the study participants or investigators. Blinding is used to protect against the possibility that knowledge of assignment may affect patient response to treatment, provider behaviours (performance bias) or outcome assessment (detection bias). Blinding is not always practical (e.g. when comparing surgery to drug treatment). The importance of blinding depends on how objective the outcome measure is; blinding is more important for less objective outcome measures such as pain or quality of life. See also single blind, double blind and triple blind.

Case series
An uncontrolled observational study involving an intervention and outcome for more than one person.

Case study (synonyms: anecdote, case history, single case report)
An uncontrolled observational study involving an intervention and outcome for a single person.
Case-control study (synonyms: case referent study, retrospective study)
A study that starts with identification of people with the disease or outcome of interest (cases) and a suitable control group without the disease or outcome. The relationship of an attribute (intervention, exposure or risk factor) to the outcome of interest is examined by comparing the frequency or level of the attribute in the cases and controls. For example, to determine whether thalidomide caused birth defects a group of children with birth defects (cases) could be compared to a group of children without birth defects (controls). The groups would then be compared with respect to the proportion exposed to thalidomide through their mothers taking the tablets. Case-control studies are sometimes described as being retrospective as they are always performed looking back in time.

Clinical trial (synonyms: therapeutic trial, intervention study)
A trial that tests out a drug or other intervention to assess its effectiveness and safety. This general term encompasses randomised controlled trials and controlled clinical trials.

Cohort study (synonyms: follow-up, incidence, longitudinal, prospective study)
An observational study in which a defined group of people (the cohort) is followed over time and outcomes are compared in subsets of the cohort who were exposed or not exposed, or exposed at different levels, to an intervention or other factor of interest. Cohorts can be assembled in the present and followed into the future (a "concurrent cohort study"), or identified from past records and followed forward from that time up to the present (a "historical cohort study"). Because random allocation is not used, matching or statistical adjustment must be used to ensure that the comparison groups are as similar as possible.
Control

1. In clinical trials comparing two or more interventions, a control is a person in the comparison group that receives a placebo, no intervention, usual care or another form of care.
2. In case-control studies a control is a person in the comparison group without the disease or outcome of interest.
3. In statistics control means to adjust for or take into account extraneous influences or observations.
4. Control can also mean programs aimed at reducing or eliminating the disease when applied to communicable (infectious) diseases.

Controlled clinical trial

Refers to a study that compares one or more intervention groups to one or more comparison (control) groups. Whilst not all controlled studies are randomised, all randomised trials are controlled.

Cross-sectional study (synonym: prevalence study)

A study that examines the relationship between diseases (or other health related characteristics) and other variables of interest as they exist in a defined population at one particular time. The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.

Cross-over trial

A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment are switched to another. For example, for a
comparison of treatments A and B, half the participants are randomly allocated to receive them in
the order A, B and half to receive them in the order B, A. A problem with this design is that the
effects of the first treatment may carry over into the period when the second is given.

**Double blind (synonym: double masked)**

Neither the participants in a trial nor the investigators (outcome assessors) are aware of which
intervention the participants are given. The purpose of blinding the participants (recipients and
providers of care) is to prevent performance bias. The purpose of blinding the investigators
(outcome assessors, who might also be the care providers) is to protect against detection bias.
See also blinding, single blind, triple blind, concealment of allocation.

**EMBASE (Excerpta Medica database)**

A European-based electronic database of pharmacological and biomedical literature covering 3,500
journals from 110 countries. Years of coverage - 1974 to present.

**Gold standard**

The method, procedure or measurement that is widely accepted as being the best available against
which new interventions should be compared. It is particularly important in studies of the
accuracy of diagnostic tests. For example, handsearching is sometimes used as the gold standard
for identifying trials against which electronic searches of databases such as MEDLINE are
compared.
**Historical control**

Person or group for whom data were collected earlier than for the group being studied. Because of changes over time in risks, prognosis, healthcare, etc. there is a large risk of bias (in studies that use historical controls) due to systematic differences between the comparison groups.

**Intention-to-treat**

An intention-to-treat analysis is one in which all the participants in a trial are analyzed according to the intervention to which they were allocated, whether they received it or not. Intention-to-treat analyzes are favoured in assessments of effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.

**MEDLINE (MEDlars onLINE)**

An electronic database produced by the United States National Library of Medicine. It indexes millions of articles in selected (about 3,700) journals. It is available through most medical libraries, and can be accessed on CD-ROM, the Internet and by other means. Years of coverage - 1966 to present.

**Methodological quality (synonyms: validity, internal validity)**

The extent to which the design and conduct of a trial are likely to have prevented systematic errors (bias). Variation in quality can explain variation in the results of trials included in a systematic review. More rigorously designed (better 'quality') trials are more likely to yield results that are closer to the 'truth'. See also external validity, validity.
Observational study (synonym: non-experimental study)
A study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received the intervention of interest) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies (randomised controlled trials).

Odds ratio (OR)
The ratio of the odds of an event in the experimental (intervention) group to the odds of an event in the control group. Odds are the ratio of the number of people in a group with an event to the number without an event. Thus, if a group of 100 people had an event rate of 0.20, 20 people had the event and 80 did not, and the odds would be 20/80 or 0.25. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome. When the event rate is small, odds ratios are very similar to relative risks.

Per protocol analysis
Analysis performed where only patients remaining in the study at study conclusion are analyzed.

Placebo
An inactive substance or procedure administered to a patient, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit to the patient through a belief that s/he is receiving treatment. Placebos are used in clinical trials to
blind people to their treatment allocation. Placebos should be indistinguishable from the active intervention to ensure adequate blinding.

**Prospective study**

In evaluations of the effects of healthcare interventions, a study in which people are divided into groups that are exposed or not exposed to the intervention(s) of interest before the outcomes have occurred. Randomised controlled trials are always prospective studies and case control studies never are. Concurrent cohort studies are prospective studies, whereas historical cohort studies are not (see cohort study), although in epidemiology a prospective study is sometimes used as a synonym for cohort study. See retrospective study.

**P-value**

The probability (ranging from zero to one) that the observed results in a study, or results more extreme, could have occurred by chance. In a meta-analysis the P-value for the overall effect assesses the overall statistical significance of the difference between the treatment and control groups, whilst the P-value for the heterogeneity statistic assesses the statistical significance of differences between the effects observed in each study.

**Quality score**

A value assigned to represent the validity of a study either for a specific criterion, such as allocation concealment, or overall. Quality scores can be use letters (A, B, C) or numbers. An advantage of using letters is that the order of best to worst may be more obvious than for numbers.
Quasi-random allocation

A method of allocating participants to different forms of care that is not truly random; for example, allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study (e.g. alternation).

Random allocation

A method that uses the play of chance to assign participants to comparison groups in a trial, e.g. by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual or unit being entered into a trial has the same chance of receiving each of the possible interventions. It also implies that the probability that an individual will receive a particular intervention is independent of the probability that any other individual will receive the same intervention. See also concealment of allocation, quasi-random allocation, randomization.

Randomization

Method used to generate a random allocation sequence, such as using tables of random numbers or computer-generated random sequences. The method of randomization should be distinguished from concealment of allocation because of the risk of selection bias despite the use of randomization, if there is not adequate allocation concealment. For instance, a list of random numbers may be used to randomize participants, but if the list is open to the individuals responsible for recruiting and allocating participants, those individuals can influence the allocation process, either knowingly or unknowingly.
Randomized control trial (RCT) (synonym: randomized clinical trial)

An experiment in which investigators randomly allocate eligible people into (e.g. treatment and control) groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups. NOTE: when using randomized controlled trial as a search term (publication type) in MEDLINE, the US spelling (randomized) must be used.

Relative Risk (RR) (synonym: risk ratio)

The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk of one indicates no difference between comparison groups. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes a RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

Retrospective study

A study in which the outcomes have occurred to the participants before the study commenced. Case control studies are always retrospective, cohort studies sometimes are, randomized controlled trials never are. See prospective study.

Statistical significance

An estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance, usually expressed as a P-value. For example, a P-value of 0.049 for a risk difference of 10% means that there is less than a one in 20 (0.05) chance of an association that is as large or larger having occurred by chance and it could be said that the results are
"statistically significant" at \( P = 0.05 \). The cut-off for statistical significance is usually taken at 0.05, but sometimes at 0.01 or 0.10. These cut-offs are arbitrary and have no specific importance. Although it is often done, it is inappropriate to interpret the results of a study differently according to whether the P-value is, say, 0.055 or 0.045 (which are quite similar values, not diametrically opposed ones).

**Washout period**

The stage in a cross-over trial when treatment is withdrawn before the second treatment is given. Washout periods are usually necessary because of the possibility that the intervention administered first can affect the outcome variable for some time after treatment ceases. A run-in period before a trial starts is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.
ADULT TECHNICAL EXPERTS

Joel D. Kopple, M.D.
Professor of Medicine and Public Health
University of California, Los Angeles
Schools of Medicine and Public Health
Chief, Division of Nephrology and Hypertension
Harbor-UCLA Medical Center
Torrance, California

Suhail Ahmad, M.B.,B.S.
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University of Washington, Medical Director, Scribner Kidney Center, Seattle

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(CONTINUED)

PEdiATRIC TECHNiCAL EXPERTS

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Professor of Pediatrics
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UCLA School of Medicine

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Chair, Division of Pediatric Nephrology
Vice Chair, Department of Pediatrics
Medical College of Virginia
Richmond

Richard Fine, M.D.
Professor and Chairman
Department of Pediatrics
SUNY at Stonybrook School of Medicine

Craig B. Langman, M.D.
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Professor of Pediatrics
University of Missouri - Kansas City School of Medicine
Chief, Section of Pediatric Nephrology
Director, Dialysis and Transplantation
The Childrens Mercy Hospital
Appendix C: Search Strategies

Strategies for Questions 1-8

#1965-April, 1998

1) hemodialysis/
2) hemodiafiltration/
3) hemodialysis, home/
4) hemofiltration/
5) hemodiafiltration/
6) peritoneal dialysis/
7) peritoneal dialysis, continuous ambulatory/
8) 1 or 2 or 3 or 4 or 5 or 6 or 7
9) kidney, artificial/
10) dialysis/
11) 9 or 10
12) kidney failure, chronic/
13) 8 or 11
14) renal replacement therapy/
15) 8 or 11 or 12 or 14
16) 8 or 12 or 14
17) nutrition assessment/
18) nutrition surveys/
19) diet surveys/
20) 17 or 18 or 19
21) nutrition/
22) diet/
23) energy intake/
24) nutritional requirements/
25) nutritional status/
26) 21 or 22 or 23 or 24 or 25
27) nutrition disorders/
28) protein deficiency/
29) protein-energy malnutrition/
30) 27 or 28 or 29
31) caloric intake/
32) exp dietary proteins/
33) nutritionS.tw.
34) proteinS.tw.
35) caloriS.tw.
36) dh.fs.
37) exp diet therapy/
38) 1 or 2 or 3 or 4 or 5 or 6 or 7
39) skinfold thickness/
40) anthropometry/
41) body mass index/
42) body height/
43) body surface area/
44) body weight/
45) creatinine/
46) cholesterol/
47) exp proteins/
48) kidney function tests/
49) blood urea nitrogen/
50) diet records/
51) subjective global assessment.tw.
52) acute phase protein.tw.
53) prognos$.tw.
54) prognosis/
55) npna.tw.
56) npcr.tw.
57) pcr.tw.
58) pna.tw.
59) protein catabolic rate.tw.
60) (protein adj4 nitrogen appearance).tw.
61) body water/
62) electric impedance/
63) or/39-62
64) predialysis.tw.
65) energy expenditure.tw.
66) resting energy.tw.
67) exp energy metabolism/
68) nitrogen/
69) nitrogen.tw.
70) reference values/
71) reference standards/
72) dh.fs.
73) intradialytic.tw.
74) diet therapy/
75) diet, protein-restricted/
38) 20 or 26 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

76) nutritional support/
Strategies for Questions 1-8 (continued)

77) enteral nutrition/
78) parenteral nutrition/
79) parenteral nutrition, home/
80) parenteral nutrition, home total/
81) parenteral nutrition, total/
82) parenteral nutrition, home total/
83) (nutrition$ adj4 counsel$).ti,ab,sh.
84) (oral adj4 supplement$).tw.
85) tube feeding/
86) food, formulated/
87) or/64-86
88) health education/
89) patient education/
90) patient education.tw.
91) counsel$.tw.
92) or/88-91
93) 38 or 63 or 87
94) 16 and 93
95) 8 and 92
96) 94 or 95
97) 96 not letter.pt.
98) 97 not editorial.pt.
99) 98 not news.pt.
100) 99 not case report/
101) 100 not animal/
102) limit 100 to human
103) 101 or 102
Search strategy for Questions 9-12

1)  hemodialysis/
2)  hemodiafiltration/
3)  hemodialysis, home/
4)  hemofiltration/
5)  hemodiafiltration/
6)  peritoneal dialysis/
7)  peritoneal dialysis, continuous ambulatory/
8)  1 or 2 or 3 or 4 or 5 or 6 or 7
9)  kidney, artificial/
10) dialysis/
11) 9 or 10
12) kidney failure, chronic/
13) 8 or 11
14) 8 or 11 or 12
15) carnitine/
16) acetylcarnitine/
17) palmitoylcarnitine/
18) 15 or 16 or 17
19) 541-15-1.rn.
21) 14992-62-2.rn.
22) l-carnitine.tw.
23) carnitine.tw.
24) bicarnesine.tw.
25) vitamin bt.tw.
26) vitamin b t.tw.
27) or/18-26
28) 8 and 27
29) 14 and 27
30) 29 not letter.pt.
31) 30 not news.pt.
Search strategy for Question 13, 14 and IGF (Pediatric Question 1)

1) renal replacement therapy/
2) hemodialysis/
3) hemodiafiltration/
4) hemodialysis, home/
5) hemofiltration/
6) hemodiafiltration/
7) peritoneal dialysis/
8) peritoneal dialysis, continuous ambulatory/
9) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10) limit 9 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
11) 10 not letter.pt.
12) 11 not review.pt.
13) 12 not editorial.pt.
14) 13 not case report/
15) insulin-like growth factor i/
16) somatomedins/
17) 14 and 15
18) 14 and 16
19) 14 and igf.tw.
20) 14 and insulin like growth.tw.
21) or/17-20
22) exp minerals/
23) 14 and 22
24) vitamins/
25) ascorbic acid/
26) bioflavonoids/
27) vitamin a/
28) vitamin b complex/
29) vitamin e/
30) vitamin k/
31) vitamin u/
32) 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33) 14 and 32
34) 23 or 33
APPENDIX D: BIBLIOGRAPHY OF ACCEPTED ARTICLES*

References for Questions 1-12 - Adults

Question 1 - adults

Reference ID: 12089

Reference ID: 3778

Reference ID: 2672

Reference ID: 1975

Reference ID: 789

Reference ID: 4907

Reference ID: 6826

Reference ID: 4841

* Reference ID numbers correspond with those listed in the evidence tables.
APPENDIX D: BIBLIOGRAPHY OF ACCEPTED ARTICLES (CONTINUED)


Question 2 - adults


Question 3 - adults


Question 4 - adults
   Reference ID: 7291

   Reference ID: 5993

   Reference ID: 4072

   Reference ID: 13048

   Reference ID: 12547

   Reference ID: 2389

   Reference ID: 1610

   Reference ID: 9955

   Reference ID: 13558

    Reference ID: 13518
Reference ID: 1281

Reference ID: 18223

Reference ID: 18335

Reference ID: 18071

Reference ID: 4949

Reference ID: 8089

Reference ID: 16003

Reference ID: 10663

Question 5 - adults

Reference ID: 1880


Question 6 - adults


Question 7 - adults


Reference ID: 7159

Reference ID: 3712

Reference ID: 3345

Reference ID: 15171

Reference ID: 14429

Reference ID: 14431

Reference ID: 1560

Reference ID: 1368

Reference ID: 15176
   Reference ID: 6964

   Reference ID: 10

   Reference ID: 6546

   Reference ID: 7976

   Reference ID: 14418

   Reference ID: 1

Question 8 - adults

   Reference ID: 15003

   Reference ID: 2455
   Reference ID: 3643

   Reference ID: 10639

   Reference ID: 14799

   Reference ID: 4885

   Reference ID: 2254

   Reference ID: 7471

   Reference ID: 1996

    Reference ID: 2406

    Reference ID: 18837

    Reference ID: 12140

Question 9 – adults
None selected

**Question 10 – adults**

None selected

**Questions 11, 12 – adults**

   Reference ID: 51

   Reference ID: 154

   Reference ID: 130

   Reference ID: 118

   Reference ID: 55

   Reference ID: 435

   Reference ID: 671
   Reference ID: 139

   Reference ID: 439

    Reference ID: 108

    Reference ID: 467

    Reference ID: 106

    Reference ID: 110

    Reference ID: 478

    Reference ID: 484

    Reference ID: 50
Reference ID: 59

Reference ID: 41

Reference ID: 152

Reference ID: 511

Reference ID: 88

Reference ID: 18

Reference ID: 78

Reference ID: 69

Reference ID: 70

81
Reference ID: 555

Reference ID: 109

Reference ID: 68

Reference ID: 47

Reference ID: 603

Reference ID: 56

Reference ID: 296

Reference ID: 3

Reference ID: 612
Reference ID: 614

Reference ID: 119

Reference ID: 71

Reference ID: 42

Reference ID: 102

Reference ID: 61

Reference ID: 243

Reference ID: 116

Reference ID: 94
Reference ID: 62
References for Pediatric Sections

Question 1 - pediatrics

A-Peds

   Reference ID: 14484

IGF-Peds

   Reference ID: 7719 (also in B section)

   Reference ID: 23

   Reference ID: 30

Question 2 - pediatrics

   Reference ID: 7719 (also in IGF section)

   Reference ID: 1666

   Reference ID: 1944

* Reference ID numbers correspond with those listed in the evidence tables.
Question 3 – pediatrics

None selected

Question 4 - pediatrics

   Reference ID: 28

   Reference ID: 132

   Reference ID: 1311

   Reference ID: 4965

   Reference ID: 4966

   Reference ID: 4997

   Reference ID: 5041

   Reference ID: 5143
Reference ID: 8807

Reference ID: 10271

Reference ID: 11953

Reference ID: 16260

Question 5 - pediatrics

Reference ID: 2282

Reference ID: 3871

Reference ID: 5007

Reference ID: 5041
Reference ID: 5510

Reference ID: 7784

Reference ID: 11503

Reference ID: 16464

Reference ID: 16465

Reference ID: 16466

Reference ID: 16467

Reference ID: 16468

Question 6 – pediatrics
None Selected

Question 7 - pediatrics
APPENDIX D: BIBLIOGRAPHY OF ACCEPTED ARTICLES (CONTINUED)

Reference ID: 17651

Reference ID: 7039

Reference ID: 6682

Reference ID: 5068

Reference ID: 17648

Reference ID: 6044

Reference ID: 17650

Reference ID: 9639

Reference ID: 4

Reference ID: 17649
Reference ID: 3385

Question 8 – pediatrics

None Selected

Question 13 – pediatrics

Reference ID: 18823

Reference ID: 7590

Reference ID: 977

Reference ID: 5933

Reference ID: 10

Reference ID: 4470
7. Schaefer F, Wuhl E, Haffner D, Mehls O. Stimulation of growth by recombinant human
growth hormone in children undergoing peritoneal or hemodialysis treatment. German
Study Group for Growth Hormone Treatment in Chronic Renal Failure. Advances in
Reference ID: 3451

during peritoneal dialysis or following renal transplantation. Pediatric Nephrology.
Reference ID: 2634

effects of recombinant human growth hormone in children with end-stage renal disease.
Reference ID: 7841

10. Tonshoff B, Dietz M, Haffner D, Tonshoff C, Stover B, Mehls O. Effects of two years of
growth hormone treatment in short children with renal disease. The German Study Group
for Growth Hormone Treatment in Chronic Renal Failure. Acta Paediatrica Scandinavica -
Reference ID: 6449

composition of children with chronic renal failure during growth hormone treatment.
Pediatric Nephrology. 1994;8:201-4.
Reference ID: 3946

children before and after renal transplantation. German Study Group for Growth Hormone
Reference ID: 4182

13. Wuhl E, Haffner D, Nissel R, Schaefer F, Mehls O. Short dialyzed children respond less to
growth hormone than patients prior to dialysis. German Study Group for Growth
Reference ID: 1671

intake have a negative effect on the growth of children with chronic renal disease before and
Reference ID: 18821

Question 14 – pediatrics
Reference ID: 47

Reference ID: 27

Reference ID: 176
Date: _______________

Reference ID Number: ________

First author’s last name: ________________________

Reviewer: MH SK SW ES TT GD

Publication year: 19____

Type of study: Case control / Prospective cohort / Retrospective cohort / Unsure

-If not a prospective cohort and not a carnitine or pediatric article, Stop-

Study population and dialysis characteristics:

Number of patients at start of study: ___________________

Years on dialysis: ______________

Age of patients: ______________

Type of dialysis: HD __________, CAPD ______________

Dialysate: _____________________

Membrane: ____________________, Reused? Y/N

Dialysis schedule: _______ exchanges/day for CAPD, _________ sessions/wk @ _________ hrs/session for HD

For HD, vascular access: ____Temporary, ____Permanent

Economic status: ____________________________________________

Race: _______________________________________________________

Residual renal function: ______________________________________
Top 3 co-morbid conditions: ______________________________________


Representative and well-defined sample of patients at a similar point in the course of disease?  Y / N

Follow-up time period: ____________________________________________

Outcome criteria objective and application of them unbiased?  Y / N

Adjustment for important known prognostic factors (see above)?  Y / N

Reported results (point estimate and confidence interval or p-value):

<table>
<thead>
<tr>
<th>Outcome:</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
</tr>
</thead>
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<tr>
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<tr>
<td>Prog factor 1:</td>
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<tr>
<td>CI or p-value</td>
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<tr>
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<tr>
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<tr>
<td>Prog factor 4:</td>
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<tr>
<td>CI or p-value</td>
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</table>

Comments:

_________________________________________________________________

_________________________________________________________________
APPENDIX E: ABSTRACTION FORMS (CONTINUED)

NKF Diagnostic Article Abstract Form

Date:__________________
Reference ID Number: _________
First author’s last name: ________________________
Reviewer: MH SK SW ES TT GD MP
Publication year: 19_____
Type of study:  Prospective / Retrospective / Unsure
Study population and dialysis characteristics:
Number of patients at start of study: ______________
Years on dialysis: ______________
Age of patients: ______________
Type of dialysis:    HD __________,    CAPD ______________
Dialysate: ___________________
Membrane: ____________________,    Reused?   Y/N
Dialysis schedule: _________ exchanges/day for CAPD,    _____________
sessions/wk  @  _________ hrs/session for HD
Dose of dialysis (Kt/V): ____________________________________
For HD, vascular access: _____Temporary,   _____Permanent
Economic status: _____________________________________________
Race: _______________________________________________________
Residual renal function: _______________________________________
Top 3 co-morbid conditions: ________________________________

Independent blind comparison with a reference (gold) standard? Y / N

(If Yes, list reference standard: ________________________________)

--If No and not carnitine or pediatric article, Stop--

Did results of test influence decision to perform the reference standard? Y / N

Spectrum of patients in study similar to spectrum seen in dialysis centers? Y / N

Test methodology described well enough to be reproducible? Y / N

Results (test characteristics):

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>LR+</th>
<th>LR-</th>
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</thead>
<tbody>
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</table>

Comments:
________________________________________________________________________
________________________________________________________________________
NKF Treatment Article Abstract Form

Date: _______________________

Reference ID Number: _________

First author’s last name: ________________________

Reviewer: MH SK SW ES

Publication year: 19____

Type of study: Case control / RCT / Non-randomized clinical trial / Cross-over / Unsure

-If not a clinical trial and not a carnitine or pediatric article, Stop-

Study population and dialysis characteristics:

Number of patients at start of study: ___________________

Years on dialysis: ______________

Age of patients: __________________

Type of dialysis: HD _________, CAPD _____________

Dialysate: ___________________

Membrane: ____________________, Reused? Y/N

Dialysis schedule: _______ exchanges/day for CAPD, ___________ sessions/wk @ _________ hrs/session for HD

For HD, vascular access: ____Temporary, _____Permanent

Economic status: ________________________________

Race: _________________________________________

Residual renal function: ___________________________
Top 3 co-morbid conditions: ____________________________

Jadad and Schulz score (see scoring guidelines):

- Randomization score (0,1 or 2) _______
- Double blind score (0,1 or 2) _______
- All patients accounted for score (0 or 1) _______

Analyzed in treatment group to which assigned?  Y / N

Treatment groups similar at baseline?  Y / N

Treatment groups treated equally except for studied intervention?  Y / N

Treatments and sample size (Intention to treat and Per Protocol):

<table>
<thead>
<tr>
<th>Treatment/Control</th>
<th>ITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx1=______________</td>
<td>___</td>
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<tr>
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<td>Rx3=______________</td>
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<tr>
<td>Rx4=______________</td>
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Reported results (point estimate and confidence interval):

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<tr>
<th>Outcome/result:</th>
<th>Rx1</th>
<th>Rx2</th>
<th>Rx3</th>
<th>Rx4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1-ITT________</td>
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<td>___</td>
<td>___</td>
<td>___</td>
</tr>
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<td>No. 1-PP________</td>
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<tr>
<td>No. 3-PP________</td>
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</tbody>
</table>
APPENDIX E: ABSTRACTION FORMS (CONTINUED)

No. 4-ITT________________________ _____ _____ _____ _____
No. 4-PP________________________ _____ _____ _____ _____
No. 5-ITT________________________ _____ _____ _____ _____
No. 5-PP________________________ _____ _____ _____ _____
No. 6-ITT________________________ _____ _____ _____ _____
No. 6-PP________________________ _____ _____ _____ _____

Adverse effects:

No 1: ___________________ _____ _____ _____ _____
No 2: ___________________ _____ _____ _____ _____
No 3: ___________________ _____ _____ _____ _____
No 4: ___________________ _____ _____ _____ _____

Comments:

_______________________________________________________________
_______________________________________________________________
APPENDIX F: TREATMENT ARTICLE QUALITY SCORE ALGORITHM

1. Was the study described as randomized?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop-outs?

Give a score of 1 point for each ‘Yes’ or 0 points for each ‘No’

Give 1 additional point each

If randomization/blinding appropriate

Deduct 1 point each

If randomization/blinding inappropriate

Scoring Range: 0-5
Poor Quality < 3

Jadad et al. Controlled Clinical Trials 1996;17:1-12
GUIDELINES FOR ASSESSMENT: JADAD QUALITY SCALE

1. Randomization

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

2. Double blinding

A study must be regarded as double blind if the word “double blind” is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessment nor the study participant could identify the intervention being assessed, or if in the absence of such a statement for use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and Dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawals in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statements or withdrawals, this item must be given no points.
### APPENDIX G: EVIDENCE TABLES

<table>
<thead>
<tr>
<th>abbreviation</th>
<th>meaning</th>
</tr>
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<tr>
<td>#</td>
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<tr>
<td>↑</td>
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<tr>
<td>↓</td>
<td>decreased</td>
</tr>
<tr>
<td>Δ</td>
<td>change</td>
</tr>
<tr>
<td>μmol/l</td>
<td>micro moles per liter</td>
</tr>
<tr>
<td>AA</td>
<td>Amino Acid (also see EAA, NEAA)</td>
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<tr>
<td>AC</td>
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<tr>
<td>ADV</td>
<td>Antipyrine Distribution Volume</td>
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<td>AMC</td>
<td>Arm Muscle Circumference</td>
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<td>asymp.</td>
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<tr>
<td>BA</td>
<td>&quot;Before and After&quot; study (no concurrent controls)</td>
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<td>BIA-PA</td>
<td>Bioimpedance Analysis-Phase Angle</td>
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<td>bicarbonate</td>
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<td>BMI</td>
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<tr>
<td>BSA</td>
<td>Body Surface Area</td>
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<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
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<tr>
<td>Bwt</td>
<td>Body Weight</td>
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<tr>
<td>CAPD</td>
<td>Continuous Ambulatory Peritoneal Dialysis</td>
</tr>
<tr>
<td>cf</td>
<td>compared with</td>
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<tr>
<td>Cr</td>
<td>Creatinine</td>
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<td>CRF</td>
<td>Chronic Renal Failure</td>
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<tr>
<td>CPD</td>
<td>Chronic Peritoneal Dialysis</td>
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<tr>
<td>d</td>
<td>days</td>
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<tr>
<td>DEI</td>
<td>Dietary Energy Intake</td>
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<tr>
<td>DEXA</td>
<td>dual energy X-ray absorptiometry</td>
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<tr>
<td>DF</td>
<td>Discriminant Function</td>
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<tr>
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### Appendix G: Evidence Tables (continued)

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<td>Intradialytic Weight Gain</td>
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<td>IU</td>
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<td>in vivo neutron activation analysis</td>
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<td>Potassium</td>
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<td>Mid-arm circumference</td>
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<td>MAMC</td>
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<td>NSD</td>
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NB: data in italics not reported in study but inferred by abstractor