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The Anglerfish and Uremic Toxins

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It is surprising that after 60 years of dialysis for renal failure, the uremic toxin or toxins have not been definitively identified nor the mechanism responsible for their excretion determined. One might say “it all begins with dialysis”. While the clinical features of uremia were many and reasonably well described before dialysis, with the introduction of hemodialysis and peritoneal dialysis, along with the subsequent introduction of erythropoietin for control of anemia, exchange resins for the control of hyperkalemia and hyperphosphatemia and vitamin D for control of secondary hyperparathyroidism and bone disease, the clinical picture of renal failure today is hard to define, and uremia has come to be defined by the measurement of blood urea nitrogen and creatinine [1]. Serum creatinine concentration is employed to estimate glomerular filtration rate, while urea is often assumed to be a surrogate marker for a uremic toxin. Urea and creatinine are both very effectively filtered through dialysis membranes during hemodialysis. Urea kinetics (either Kt/V or URR) are used to judge the adequacy of dialysis. The success of hemodialysis in prolonging the lives of patients with chronic renal failure and the subsequent federal funding of hemodialysis focused attention on the role of filtration in the treatment of uremia and led to an explosion of technology seeking to develop membranes that might be more efficient for the filtration of small molecules and to improving techniques for

peritoneal dialysis, with the rationale that the greater porosity of the peritoneal membrane might allow for the filtration of larger “middle-molecules”. To date, the evidence that differences in the porosity of artificial membranes, techniques of hemodialysis, or dialysis time significantly improve outcome, is not convincing [3]. This is the nub of the conundrum—that while improved dialysis membrane technology and dialysis techniques have had little effect on patient survival in chronic renal failure, residual renal function, represented by renal creatinine clearance of as little as 0.5 ml/min and small increments in renal Kt/urea, is associated with substantially better patient survival [4].

Perhaps the time has come to reconsider the questions of the nature of uremic toxin(s) and how uremic toxin(s) are excreted by the kidney. Enter, the anglerfish (*Lophius americanus*)! As described in his lecture on the evolution of the kidney, Homer Smith pointed out that this marine teleost (bony) species which evolved some 100-130 million years ago is distantly related to prochordates living in sea water 500 million years ago. These early marine ancestors were in osmotic equilibrium with the sea and evolved a kidney which consisted solely of tubules that served to secrete nitrogenous wastes into a coelome that connected with the exterior. When life moved into fresh water, glomerular filtration evolved as the mechanism by which fish maintained osmotic integrity, and the tubules acquired transporters which reclaimed the filtered glucose and the other

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How Efficacious Is Exercise Training in ESRD Patients? A Review of the Evidence From RCCTs

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Introduction

Dozens of studies highlighting the benefits of exercise training in patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis therapy have been published in the past 20 to 30 years (reviewed in [1-3]). Similar to what is seen in other patients with chronic disease, exercise training in ESRD patients has been shown to improve traditional cardiovascular disease (CVD) risk factors (e.g., plasma lipid profiles, blood pressure), and various metrics related to physical function (e.g., aerobic capacity/ VO_2 max). While the data are impressive in many regards, there are also significant shortcomings, as many were pilot studies with a relatively small number of subjects, the exercise interventions were often short (e.g., 2-3 months), and very few contained randomized control groups. More recently, several longer-term randomized controlled clinical trials (RCCTs) examining the efficacy of endurance and/or

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The Anglerfish and Uremic Toxins

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“valuable substances”, but these fish still relied on tubular secretion to dispose of toxic wastes. When, further along in evolution, fish returned to sea water, glomerular filtration no longer served a purpose and glomeruli became smaller, less numerous, and in some instances, e.g., the anglerfish, disappeared entirely [5]. Some marine fish are truly aglomerular, others simply have only minimal glomerular filtration. Beyenbach concluded, “The secretion of organic anions in proximal tubules from vertebrates as ancient as the hagfish and as modern as the post modern human illustrates the persistence of some renal transport systems in the course of vertebrate evolution” [6]. It is likely that the “organic anions” include uremic toxins generated by the metabolism of nitrogen-based nutrients (proteins), and that these fish eliminate uremic toxins by tubular secretion rather than filtration. Beyenbach demonstrated that fluid is drawn, osmotically, into these non-filtering tubules and is excreted as urine [6].

In 2002, Grantham described the secretion of solute and fluid into the lumina of isolated rabbit renal tubules and observed that this transport was stimulated when uremic plasma or compounds with an arylamine structure such as p-amino hippurate were added to the bathing medium [7]. Grantham speculated that “under conditions of markedly reduced or complete cessation of glomerular filtration, mammalian proximal tubules could secrete hippurate and similar substances” and “...elimination of some of the potentially toxic products normally excreted by the kidneys...would serve a useful survival function” [7]. Writing about renal tubular transport, Smith was remarkably prescient in stating “there are a number of independent transport systems involved in the tubular reabsorption of glucose, phosphate, sulfate, amino acids, etc. In tubular excretion, on the contrary, apparently all substances share a common element in one of two transport systems because, in all instances in which an adequate examination has been made, the loading of the tubules with one substance depresses the tubular excretion of all other substances in one of two groups. This is presumably a result of competition within the transport system rather than an inhibitory or toxic action, since it is freely reversible.” [8] It is now evident that “transport systems” that Smith inferred are membrane transport proteins. OAT1, the PAH transporter, is localized on the basolateral border of the S2 segment of proximal renal tubular cells and interacts with a wide range of small endogenous substances. OAT3, another member of the family of OAT transporters expressed on the basolateral membrane of proximal and distal tubular cells of the rat, similarly exhibits a wide range of substrate specificities [9]. These two members of the OAT family of transporters appear to account for the renal secretion of a great number of small protein-bound organic anions [10]. These protein-bound substances, possible uremic toxins, circulate with little physiologic effect until they arrive at the peritubular capillaries. The OAT transporters on the basolateral border of proximal renal tubular cells shift the equilibrium between free and bound solute so

that free solute is available for excretion by the proximal tubular cells of the kidney in much the same way as other specific cell surface receptors target the delivery of protein-bound hormones and other small molecules to their appropriate sites of action.

There is accumulating evidence to suggest that indoxyl sulfate, a protein-bound arylamine, may be a uremic toxin. Indoxyl sulfate is produced by the action of colonic bacteria (*E. coli*) on dietary tryptophan to produce indole which is absorbed and hydroxylated and sulfated in the liver to yield indoxyl sulfate [10]. Indoxyl sulfate is known to be transported by OAT1 and OAT3 transporters on the basolateral membrane of renal tubular cells [11, 12], and eliminated by the OATP transporter SLCO4C1 on the apical membrane [13]. Indoxyl sulfate concentration is increased in serum in experimental animals with reduced nephron mass, and in patients with chronic renal disease [1]. In the rat 5/6 nephrectomy model, administration of indoxyl sulfate was found to induce faster progression of chronic renal failure [12].

How is the toxicity of indoxyl sulfate mediated? While it is possible that increased concentrations of indoxyl sulfate compete for excretion with other potentially toxic molecules, there is abundant evidence that indoxyl sulfate might exert its toxicity by induction of a host of genes that mediate inflammation and fibrosis. Indoxyl sulfate has been reported to induce free radical production and to activate the transcription factor, NF- κ B in human proximal renal tubular cells [14]. 3-indoxyl sulfate has been reported to be a high potency endogenous ligand for the human aryl hydrocarbon receptor, a powerful ligand-activated transcription factor [15]. Gene arrays from the kidneys of rats with 5/6 nephrectomy revealed 139 genes whose expression was increased and 45 genes whose expression was decreased as compared with normal controls. Studies in 5/6 nephrectomized rats, fed AST-120, a micro-crystallized form of carbon shown to bind indole in the intestine and reduce the load of indoxyl sulfate, were reported to show that many genes that were differentially expressed in uremic rats (including TGF- β 1, TIMP-1, and OAT1) were normalized [16, 17].

Since two organic anion transporters, OAT1 and OAT3, account for most of the transport of small organic anions across the basolateral membrane of proximal tubular cells, substrate inhibition or competitive inhibition might be important in determining the secretion of putative uremic toxins such as indoxyl sulfate. If residual renal function represents the activity of organic ion transporters that play an important role in the maintenance of patients with end-stage renal disease, drugs which might compete for the OAT1 or OAT3 transporters might be added to those we consider potentially harmful in patients with end-stage renal disease.

With the insights gained from the anglerfish and the knowledge of membrane transporters, we can look beyond the dialysis membrane at the possible role that measures to reduce the load of toxins generated by the

human biome, to bind uremic toxins in the gut, or even measures that might upregulate transporters for uremic toxins in residual nephrons or other epithelia, might serve in the treatment of uremia.

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How Efficacious Is Exercise Training in ESRD Patients? A Review of the Evidence From RCCTs

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resistance exercise training in ESRD patients have been published [4-9]. While some results from these trials support the notion that exercise training improves physical function and reduces CVD risk, much of the data are impressive, or in some cases even negative. As a result, some researchers and clinicians have begun to publicly question the efficacy acquired transporters of exercise training in this population. The primary purpose of this review is to: 1) briefly summarize the findings from recent major RCCTs and other selected studies that have evaluated the efficacy of exercise training on markers of CVD risk and physical function in ESRD patients; 2) discuss potential reasons for some of the equivocal findings from these studies, and 3) discuss the potential for future research to clarify these discrepancies. While not intended to be an exhaustive review of the literature, we have focused on results from several recent studies we believe to be the most significant to date in terms of sample size, intervention length, outcomes measured, and other methodological considerations.

Effects of Exercise Training on Measures Related to Muscle Mass and Physical Function in ESRD

ESRD patients suffer from a variety of co-morbid conditions that contribute to declines in physical functioning. Protein malnutrition, muscle catabolism, and wasting are especially common, and these lead to reduced muscle strength, aerobic capacity, and low levels of physical activity. Both resistance and endurance exercise training have the potential to improve, or at the very least, prevent declines in physical function in ESRD patients. Indeed, one consistent finding in the exercise-related literature in ESRD patients is that endurance exercise training significantly improves maximal aerobic capacity across a wide range of exercise prescriptions (reviewed in [3]). In a recent review by Johansen, the mean improvement in VO_2 peak following endurance exercise training interventions in 18 studies in ESRD patients was around 17% [10]. However, an interesting observation that has been made is that these improvements seem to plateau at levels well below sedentary matched controls. One hypothesis for this is that limitations in aerobic capacity are both peripheral (skeletal muscle) and central (cardiovascular) in nature [11], and that aerobic training alone may not adequately improve peripheral uptake of oxygen. Consistent with this hypothesis, it appears as though exercise interventions that combine both resistance and aerobic training have demonstrated greater improvements in aerobic capacity in this population (reviewed in [12]). Nevertheless, the observation that many types of exercise

improve maximal oxygen uptake in dialysis patients is an important finding because declines in aerobic capacity and physical function contribute to high levels of physical inactivity in ESRD patients, which in turn contributes to losses in lean mass and ultimately muscle wasting.

Losses in muscle mass are a significant concern because of the strong association between lean body mass and mortality in the dialysis population [13]. Furthermore, reduction in muscle mass may lead to reductions in the ability to perform activities of daily living which may further exacerbate other common comorbidities such as CVD. However, many factors likely contribute to muscle wasting, making it a complex problem to control [14]. Despite numerous well designed and well executed studies attempting to minimize losses in muscle mass in ESRD patients, interventions investigating nutrition, exercise, and combinations of the two have exhibited generally inconsistent or somewhat underwhelming results.

One of the first RCCTs that examined the effects of exercise training on muscle mass in ESRD patients was the Nandrolone and Exercise Trial (NEXT) conducted by Johansen et al. [5]. This was a 12-week intervention that examined the individual and combined effects of thrice weekly nandrolone decanoate treatment and resistance exercise training on body composition, strength, and function. The resistance training consisted of five lower body resistance exercises using ankle weights three days per week during dialysis. The intensity of the program was fairly vigorous, starting with two sets of each exercise at 60% of each patient's three repetition max (3RM) strength, progressing to three sets per session, with additional weight added as tolerated. An important finding from this study was that both the nandrolone treatment and resistance training resulted in significant increases in the cross sectional area (CSA) of the main muscle group being exercised—the quadriceps (measured by MRI)—and the combined treatments had an additive effect. In addition, the groups that received resistance training also had increases in leg muscle strength. By contrast, resistance training surprisingly did not improve several functional measures such as gait speed, stair climbing, or ability to rise from a chair. Furthermore, there was a paradoxical increase in whole body fat mass (assessed by dual-energy X-ray absorptiometry, DXA) in the resistance training group, while lean mass did not change. In summary, this progressive resistance training program had some important benefits (increased quadriceps CSA and strength), but did not increase whole body lean mass or improve performance on several functional tests.

In another recent RCCT called the Progressive Exercise for Anabolism in Kidney Disease (PEAK) Study, Cheema “et al.” investigated a large cohort of patients after 12 weeks of progressive resistance exercise training, compared to a control group receiving usual care [4]. This was another fairly rigorous training program in which 10 different exercises (two sets of eight repetitions for each exercise) were performed with the patients seated in their dialysis chairs three days per week using free weights for upper body exercises and ankle weights for leg exercises. The target rating of perceived exertion (RPE) for each exercise was 15 to 17 of 20 (“hard to very hard”). In contrast to the NEXT study, thigh cross sectional area (measured by CT scan) did not increase significantly in the resistance trained group (+1.3%, $P = NS$) compared to the control group (-0.7%, $P = NS$). This may be due to the fact that the CSA measurements in the PEAK study captured muscles that were not targeted (hamstring) as well as muscle groups that were targeted (quadriceps) by the exercise intervention. Despite no improvement in muscle CSA, there was a significant improvement muscle strength, as well as in muscle attenuation, an indicator of muscle quality/lipid infiltration, in the exercising group.

In a continuation of the PEAK study [12], the resistance training intervention was extended out to 24 weeks, while the control group that received usual care for the first 12 weeks crossed over to an identical 12-week resistance training program. Though the changes between the groups were not statistically significant, in the 24 week training group there was a continued trend for an increase in thigh CSA during weeks 12 to 24 (+1.8% vs baseline, $P=NS$). Surprisingly, thigh CSA continued to decline in the control/cross-over group during weeks 12 to 24 (-1.4% vs baseline, $P=NS$) despite undergoing resistance training during this period. At 24 weeks there was also no difference in muscle attenuation (lipid infiltration/muscle quality) between the two groups. However, muscle strength and exercise capacity did improve in the 24-week training group throughout the trial. The author's primary conclusion from this study was that resistance training did not improve muscle CSA or quality (lipid content) at 24 weeks. Despite this, the trends for an increase in thigh CSA at 24 weeks and the significant improvements in strength at 12 and 24 weeks are somewhat encouraging.

Kopple et al. also recently conducted a RCCT to examine potential mechanisms by which exercise training improves exercise capacity in ESRD patients [8]. In this study, patients were randomized into one of the following four groups: 1) endurance training

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alone, 2) resistance training alone, 3) endurance + resistance training, or 4) no training, with all exercise conducted immediately prior to dialysis (three days per week). The endurance training consisted of cycling at a moderate intensity for up to 40 minutes per session. The resistance training consisted of up to two sets of three leg exercises (leg extension, curl, and press) on exercise machines at a resistance up to 80% of their 5RM strength. The combined endurance and resistance exercise group performed approximately 1/2 of each exercise protocol. The primary outcomes tested included changes in body composition as well as changes in the expression of genes involved in muscle metabolism.

An important finding from this study was that exercise training resulted in several beneficial changes in mRNA levels that should promote muscle anabolism. Most of these beneficial transcriptional changes were related to increases in the anabolic protein IGF-I and reductions in the protein synthesis inhibitor myostatin. Despite improvements in these markers of muscle turnover, there were no changes in body composition (whole body or regional lean and fat mass) as assessed by DXA or bioelectrical impedance. In summary, similar to the NEXT[5] and PEAK[4, 12] studies, there were both positive and negative findings, making it difficult to evaluate the efficacy of exercise in ESRD patients based on these data.

One potential concern with exercising patients with ESRD is that many are in a perpetual catabolic state, and hemodialysis further stimulates protein loss and catabolism[15].

While acute exercise is obviously an energy expending process, chronic exercise training is generally considered an anabolic intervention. Indeed, several studies involving acute exercise interventions indicate that exercise transiently improves muscle protein turnover in ESRD patients. Furthermore, acute nutritional supplementation and exercise appear to have additive effects on whole body and muscle protein metabolism over the course of a single dialysis session (reviewed in[16]). Recently, Dong et al. conducted a 6-month randomized trial to examine the chronic effects of nutritional supplementation and concomitant resistance training on body composition and strength in ESRD patients [17]. In this study, patients were randomized to one of two groups: 1) oral, intradialytic nutritional supplementation, or 2) nutritional supplementation + resistance exercise training. Patients in the resistance training group performed three sets of 12 repetitions on a leg press machine at an intensity of 70% of their 1RM strength immediately before their dialysis session three days per week.

Unfortunately, there were no significant differences between groups in terms of change in body weight, total lean mass, leg lean mass, or leg strength at six months. When data from the nutrition only and nutrition + resistance exercise group were combined, there was a significant increase in 1RM leg strength compared to baseline; however, lean mass was still not significantly increased over baseline levels. Because the study did not include a control group that did not receive a nutritional supplement, it was not possible to discern if the nutritional supplement alone or the nutrition + resistance training preserved strength or body mass compared to a group receiving usual care. In summary, the evidence from this study does not support the hypothesis that resistance exercise training significantly improves muscle mass or strength more than nutritional supplementation alone.

Perhaps the greatest evidence for resistance exercise maintaining lean mass in ESRD patients comes from a recent study conducted by Chen et al. [9]. Patients were randomly assigned to a control group or to a group that used progressive, low-intensity, intradialytic resistance training using multiple exercises with ankle weights for 24 weeks. Despite the low exercise intensity, patients in the resistance training group had a 4.2% and 5.0% increase in whole body and leg lean mass, respectively. This was compared to a 3.2% reduction in both whole body and leg lean mass in the control group ($P < 0.05$ for the change between groups). In addition, several measures of leg strength and physical function also improved significantly in the resistance training, but not the control group. It is noteworthy that the improvements in strength and body composition in this study were so robust, given the inconsistent findings from the exercise training studies reviewed above that have used higher intensity exercise protocols. This finding warrants additional studies comparing the effects of different exercise training intensities on muscle strength and function.

In summary, while some of the results from the above studies indicate positive effects of exercise training on body composition and physical function, many of these results are somewhat disappointing in terms of the quantity and consistency of improvements. There are a variety of potential reasons for these seemingly equivocal results. For one, the exercise prescriptions that have been used in some of these studies may have been below the threshold at which significant anabolic adaptations may occur. A majority of exercise studies in ESRD patients have used intradialytic training, which is often preferred for a variety of reasons, including reducing patient burden and improving exercise compliance[18]. Indeed, each of the RCCTs reviewed above utilized exercise training pro-

ocols that occurred either during, or immediately preceding, the patient's dialysis session. Unfortunately, intradialytic exercise limits the intensity and types of exercise protocols to those that can be performed while confined to a chair (e.g., cycling and resistance training with ankle weights). The resistance training literature suggests that full body strength training protocols using combinations of free weights and/or resistance training machines above 60% of 1RM strength are a preferred approach for improving strength and muscle mass[19]. While this type of training regime should be encouraged for all capable patients, it is unrealistic to expect that it will be adopted by hemodialysis patients on a widespread basis, so creative approaches for promoting resistance training are needed.

Perhaps recognizing the limits of intradialytic resistance training with ankle weights, the studies by Dong et al. [17] and Kopple et al. [8] used a somewhat novel protocol by having the patients exercise immediately prior to their dialysis sessions on resistance training machines presumably in the waiting rooms or facilities adjacent to their dialysis clinics. Though an interesting concept, it is also unlikely that this approach could be widely adopted due to financial and space considerations at most dialysis clinics. Indeed, one concern with the exercise protocol in the study by Dong et al. was that only one type of exercise (leg press) was performed. More favorable results may have been seen in this study had additional exercises (e.g., leg extensions, hamstring curls, etc.) been conducted. Of course, this would have required additional weight training equipment in the facility, and may have therefore been impractical.

Another concern with each of these recent RCCTs [4, 5, 8, 9, 12, 17] is that the length of the interventions may not have been sufficient to capture all of the potential benefits. A general hypothesis in these studies was that exercise training would improve physical function, muscle strength, or mass. However, considering the multiple co-morbid conditions and severe decline in physical function that many ESRD patients suffer from, a more appropriate goal may be to simply maintain their health and functioning relative to a control group getting usual care. The length of the exercise intervention in each of these studies was between three and six months, which may not have been sufficient to fully capture expected declines in the control group. In fact, trends for improvements in strength, function, and body composition were noted in several of these studies, and it is possible that statistically significant differences may have been seen had the interventions been extended for 9 to 12 months or longer. While this would be ideal, high dropout rates and low compliance with interventions are common in this population due primarily to

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high morbidity and mortality rates. As a result, conducting longer-term interventions in this population will be extremely challenging.

In the next issue, we will review the effects of exercise training on cardiovascular disease risk in end-stage renal disease patients, draw conclusions from the presented aspects and discuss future directions for the study and application of exercise training in end-stage renal disease patients [TO BE CONTINUED]

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14TH INTERNATIONAL CONFERENCE ON DIALYSIS - ADVANCES IN CKD 2012 -

Day 1			
Wednesday, January 25, 2012			
		Speaker	Faculty Information
7:15am-7:55am	Breakfast		
7:55am-8:00am	Welcome	Peter Kotanko, MD	Renal Research Institute, New York, NY
8:00am-8:25am	How to personalize the dialysis prescription	Madhukar Misra, MD	University of Missouri, Columbia, MO
8:25am-8:50am	Novel PD solutions—what are the clinical implications?	Achim Joerres, MD	Charité University Hospital, Berlin, GERMANY
8:50am-9:05am	Implementing programs for AKI in developing countries	Mary Carter, PhD, MPH, MBA	Renal Research Institute, New York, NY
9:05am-9:30am	Long-term care of the kidney transplant recipient	Heidi M. Schaefer, MD	Vanderbilt University Medical Center, Nashville, TN
9:30am-9:50am	Discussion		
9:50am-10:10am	Break		
	What makes routine dialysis a geriatric specialty?		
10:10am-10:35am	Renal replacement therapy in geriatric ESRD patients—a clinical approach	Jeroen P. Kooman, MD, PhD	University of Maastricht, Maastricht, THE NETHERLANDS
10:35am-11:00am	Can physical and occupational rehabilitation make a difference to outcomes?	S. Vanita Jassal, MD	University Health Network, Toronto, ON, CANADA
11:00am-11:25am	What are the considerations for life decisions in ESRD?	Christopher R. Blagg, MD, FRCP	Northwest Kidney Centers, Seattle, WA
11:25am-12:10pm	Keynote: Endotoxemia in the progress of CKD—bystander or culprit?	Chris W. McIntyre, MD	University of Nottingham, Derby, UK
12:10pm-12:30pm	Discussion		
12:30pm-1:30pm	Lunch		
1:30pm-1:55pm	What are the impacts so far of the bundle on patient care?	Franklin W. Maddux, MD, FACP	Fresenius Medical Care, Waltham, MA
1:55pm-2:55pm	Debate: Quantification of phosphorus and calcium balance is necessary to control bone mineral metabolism in HD patients	Frank Gotch, MD (yes) David A. Bushinsky, MD (no)	University of California, San Francisco, CA University of Rochester, Rochester, NY
2:55pm-3:20pm	A critical evaluation of blood volume measurement during hemodialysis	C.F.M. Franssen, MD, PhD	University Medical Center Groningen, Groningen, THE NETHERLANDS
3:20pm-3:45pm	Discussion		
3:45pm-4:00pm	Break		
	Pediatric		
4:00pm-4:25pm	AKI in children—what are the long-term consequences?	Stuart L. Goldstein, MD	Cincinnati Children's Hospital, Cincinnati, OH
4:25pm-4:50pm	Hypertension in pediatric patients—Implications for the future of cardiovascular health	Joseph T. Flynn, MD, MS	Seattle Children's Hospital, Seattle, WA
4:50pm-5:00pm	Discussion		
5:30pm-6:30pm	Welcome Reception		
Day 2			
Thursday, January 26, 2012			
	Dialysis technology	Speaker	Faculty Information
7:15am-8:00am	Breakfast		
8:00am-8:25am	Update on smart HD membranes—anything new under the sun?	William H. Fissell, MD	Cleveland Clinic, Cleveland, OH
8:25am-8:50am	Plasmapheresis in immunologic renal disease: why, when, and how	Charles D. Pusey, Dsc FRCP	Imperial College London, London, UK
8:50am-9:15am	The challenges of providing RRT in decompensated liver cirrhosis	Thomas A. Gonwa, MD, FASN	Mayo Clinic in Florida, Jacksonville, FL
9:15am-9:40am	Unrecognized dialyzer clotting: a problem without consequence?	Jeffrey J. Sands, MD, MMM	Fresenius Medical Care, Celebration, FL
9:40am-10:00am	Discussion		
10:00am-10:20am	Break		
10:20am-10:45am	Genetics of vascular calcification. Basic science and clinical implications	Manfred Boehm MD	Translational Medicine Branch, National Institute of Health Bethesda, MD
10:45am-11:10am	Use of mineralocorticoid receptor blockers in pre-dialysis CKD; results and concerns	Philip J. Klemmer, MD	University of North Carolina At Chapel Hill, Chapel Hill, NC
11:10am-12:10am	Debate: PD as a first treatment is a preferred option for the US	Joanne M. Bargman, MD, FRCPC (yes) John B. Stokes, MD, MMM (no)	University Health Network, Toronto, ON, CANADA University of Iowa, Iowa City, IA
12:10am-12:20pm	Discussion		
12:20pm-1:20pm	Lunch		
1:20pm-2:05pm	Keynote: Suicidal red blood cell death—pathophysiology and clinical aspects	Florian Lang, MD	Eberhard-Karls-University of Tuebingen, Tuebingen, GERMANY
2:05pm-2:30pm	Volume control—is it more difficult in PD than in HD?	John Burkart, MD	Wake Forest University Medical Center, Winston Salem, NC
2:30pm-2:40pm	Discussion		
2:40pm-3:00pm	Break		
	Comorbidities		
3:00pm-3:25pm	The difficult vascular access case problem	Alexander S. Yevzlin, MD	University of Wisconsin School of Medicine, Madison, WI
3:25pm-3:50pm	Sudden death in dialysis patients: are there significant modifiable factors?	Patrick H. Pun, MD, MHS	Duke University Medical Center, Durham, NC
3:50pm-4:15pm	Diagnosis of cardiovascular disease in CKD	Peter A. McCullough, MD, MPH	St. John Providence Health System, Providence, RI
4:15pm-4:30pm	Discussion		
Day 3			
Friday, January 27, 2012			
		Speakers	
7:15am-8:00am	Breakfast		
8:00am-8:25am	Events before death in HD—a global perspective	Peter Kotanko, MD	Renal Research Institute, New York, NY
8:25am-8:50am	Blood pressure (BP) history trumps BP level in HD patient outcomes	Len Usvat, MCP	Renal Research Institute, New York, NY
8:50am-9:50am	Debate: Initiation of dialysis after the IDEAL Study: Clinical judgment is most important	Daniel E. Weiner, MD MS (yes) Martin Kuhlmann, MD (no)	Tufts Medical Center, Boston, MA Vivantes Klinikum im Friedrichshain, Berlin, GERMANY
9:50am-10:05am	Discussion		
10:05am-10:30am	Break		
10:30am-11:00am	Oral presentations of the three best abstracts		
	Outcomes in the Frequent Hemodialysis Network (FHN) trials		
11:00am-11:10am	Cardiovascular changes including blood pressure	Christopher T. Chan, MD, FRCPC	Toronto General Hospital, Toronto, ON, CANADA
11:10am-11:20am	Bone mineral metabolism	John Daugirdas, MD, FACP	University of Illinois at Chicago, Chicago, IL
11:20am-11:30am	Nutrition	George A. Kaysen, MD, PhD	University of California, Davis, CA
11:30am-11:55am	Dialysis after the FHN trials: volume control, dose or what else?	Michael V. Rocco, MD, MSCE	Wake Forest University School of Medicine, Winston-Salem, NC
11:55am-12:15pm	Discussion		



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