Answers and Explanations

Question 1
Answer A: Repeat serum ferritin and transferrin saturation
Despite initial enthusiasm, hepcidin is not emerging as a useful marker of iron sufficiency. In one study, hepcidin concentrations were found to be variable from dialysis-to-dialysis. Among 28 hemodialysis patients it was found that although hepcidin was related with CRP, the variability over a 6 week period was between 12 and 85%. This variability in clinically stable patients reduces the usefulness of this biomarker. In another study hepcidin was found not to be predictive of iron needs. Both Hepcidin 20 and Hepcidin 25 were measured by SELDI-TOF in one study and both failed to predict accurately the improvement in Hgb after IV iron. In contrast percent hypochromic red cells had an area under the curve of .84 and CHR had an area under curve of .70. Serum ferritin concentration and transferrin saturation tends to vary from one assay to the next and from week to week. Even bone marrow biopsy does not rule out iron restricted erythropoiesis.

- Ford BA, Eby CS, Scott MG, Coyne DW: Intra-individual variability in serum hepcidin precludes its use as a marker of iron status in hemodialysis patients. Kidney Int 78:769-773, 2010

Question 2
Answer C: Home BP recording for 4 days after mid-week dialysis or interdialytic ambulatory BP recording if available
The patient has intra-dialytic hypertension. Ambulatory BP recording in these patients is often high. Reducing dry-weight often improves intradialytic hypertension and interdialytic ambulatory BP recording. But before reducing dry-weight, the first step in managing hypertension is establishing a correct
diagnosis. Pre-dialysis BP correlates poorly with either home or ambulatory BP. Treatment of post-dialysis blood pressure may increase intradialytic hypotension. Home BP monitoring correlates best with ambulatory BP and target organ damage. In a prospective study, compared to predialysis BP, home BP and ambulatory BP was found to be of greater value at predicting all-cause mortality among hemodialysis patients.


**Question 3**

**Answer A: Use high molecular cut-off fibers and increase dialysis time from 3.5 hours to 4.5 hours**

Increasing dialysis time is the most effective and practical way to improve clearance of low molecular weight proteins while ensuring adequate dialysis delivery in this patient. The European Best Practices Guidelines recommend 4 hour dialysis thrice weekly as the bare minimum prescription. High molecular cut-off filters can improve low molecular weight protein clearance. Increasing dialysate flow has little effect on either urea or low molecular weight protein clearance. Two conventional dialyzers may increase urea clearance but will have little effect on low molecular protein clearance. Cool dialysate has little effect on dialysis adequacy although it can mitigate hemodynamic instability.


**Question 4**

**Answer C: Serum cystatin C**

The usual way to assess residual renal function is to calculate an average of urea and creatinine clearances. However, if this test is unavailable or cannot be obtained, serum cystatin C level is a better reflection of residual renal function. Both blood urea nitrogen and serum creatinine are influenced by factors other than residual renal function. Urinary cystatin C is of little value in estimating residual renal function.


**Question 5**

**Answer A: Tetany**

Tetany and spasm of the muscles of hand and forearm during BP cuff inflation are known to be associated with hypocalcemia. Secondary hyperparathyroidism can be provoked with a fall in ionized calcium. Hyponatremia, hypokalemia and increase in FGF-23 level are unlikely with sodium citrate.


**Question 6**

**Answer B: Epoprostenol**

Epoprostenol can effectively anticoagulate during dialysis. Enoxaparin is low molecular weight heparin and can provoke heparin-induced thrombocytopenia. Likewise heparinization is not recommended. Tinzaparin and clopidogrel are likely less effective than epoprostenol.


Question 7

Answer C: His dialysate sodium should be reduced to 135mEq/L, his dietary sodium should be restricted to 1.5g/d, and his dry weight should be reduced.

Cramping, fatigue and intradialytic hypotension are poor proxies of volume state. The patient is hypertensive and on 4 drugs. Unless dry-weight is reduced he is unlikely to have improvement in BP. Hgb is >10 g/dL on a high dose of epoetin. He is already hypertensive and increasing Hgb further with further epoetin administration may aggravate hypertension.

A cross-sectional study on 1084 clinically stable patients on HD showed that the mean pre-HD plasma sodium was 136.7 ± 2.9 mEq/L, resulting in the majority of subjects (n = 904, 83%) being dialyzed against a positive sodium gradient, while the mean sodium gradient was 4.6 ± 4.4 mEq/L. After HD, the plasma sodium increased 91% of the patients, reaching a mean post-HD plasma sodium of 141.3 ± 2.5 mEq/L. The sodium gradient was independently associated with IDWG (70 g/mEq/L, P < 0.0001) and post-HD thirst (r = 0.11, P = 0.02). The BEST approach to treat him is to avoid Na overloading him and reduce dry-weight.


Question 8
Answer A: Increased macrophage infiltration, production of vascular endothelial growth factor-C, increased lymphangiogenesis

Besides external sodium balance, the redistribution of sodium between the skin and circulation may provide extrarenal regulation of body fluid volume and BP control. These data have emerged mostly from animal experiments. For example, feeding a high-salt diet in rats leads to hypertonic sodium accumulation in the skin. Accumulation of salt without water in the skin turn provokes macrophage recruitment and increased hyperplasia of the lymphcapillary network. The mechanisms underlying these effects on lymphatics involve production of lymphangiogenic growth factor in the skin. Activation of tonicity-responsive enhancer binding protein in macrophages causes vascular endothelial growth factor (VEGF)-C secretion by macrophages. Interrupting VEGF-C signaling augments interstitial hypertonic volume retention and elevates BP in response to high salt diet despite increased expression of endothelial nitric oxide synthase. Thus, macrophages may serve as important regulators of volume and pressure through the production of lymphangiogenic factors


Question 9
Answer A: Change dialysate potassium to 4 mEq/L and increase dialysis time to 5 hours.

A case report of a patient with Leriche syndrome illustrates the problem of slow transfer in potassium from the lower body to the upper body. In this patient who presented with severe hyperkalemia, two hours into emergency dialysis EKG signs of hypokalemia were noted. However, on terminating dialysis there was prompt hyperkalemia. It was noted that slowing dialysis to allow potassium to equilibrate from the lower body to the upper body may reduce this disequilibrium of potassium between body compartments. Although concentration of potassium was reported in this patient who had severe hyperkalemia at the onset of dialysis it is quite likely that patients with vascular disease have similar disequilibrium for other analytes such as phosphorus or urea. Terminating dialysis is not a good option as this may promptly cause hyperkalemia. Infusion of dopamine or epinephrine may cause more ventricular ectopy and may even trigger fatal cardiac arrhythmias.


**Question 10**

**Answer A: Reduce dry weight and increase treatment time to 4 hours**

Dialysis duration should be at least 4 hours. Patient has a flat slope on RPV so she is likely to be volume overloaded. Therefore Answer A is correct. Answer C is incorrect because at present no one class of drugs can be recommended for all patients. A meta-analysis of agents that block the renin-angiotensin system found that although these drugs reduce left ventricular mass index they do not improve cardiovascular event rate among hemodialysis patients. Another review concludes that agents that block the renin-angiotensin system cannot be recommended for all patients. Dialysate sodium is already lower than plasma Na and weight gains between dialysis suggest that dietary Na intake is appropriately low. There is no role of loop diuretics even when given in high dose, as high as 250 mg intravenously of furosemide, among anuric hemodialysis patients. Measurements using tissue Doppler echo images found that central cardiac hemodynamics were unaltered when anuric hemodialysis patients were given even high doses of loop diuretics.


Agarwal R: Hypervolemia is associated with increased mortality among hemodialysis patients. *Hypertension* 56:512-517, 2010


Hayashi SY, Seeberger A, Lind B, Gunnes S, Alvestrand A, do Nascimento MM, Lindholm B, Brodin LA: Acute effects of low and high intravenous doses of furosemide on myocardial

**Question 11**

**Answer C: 10.0 g/dl**

The current label allows ESA use only if Hgb is <10 g/dL and that too to avoid transfusions. No goal Hgb is recommended. If Hgb is >12 g/dL, these drugs should not be used.

- Prescribing information for darbepoetin and epoetin.

**Question 12**

**Answer C: Hypertension**

Both the Frequent Hemodialysis network trials showed an improvement in BP and reduction in the antihypertensive medications when patients were dialyzed more frequently. Depression, dose of epoetin, serum albumin, or cognitive function did not improve.


Levin NW, Raimann JG, Rocco MV: Should the knowledge gained from the Frequent Hemodialysis Network (FHN) trials change dialysis practice? *Curr Opin Nephrol Hypertens* 20:577-582, 2011

**Question 13**

**Answer A:** Increasing the time on dialysis to 4 hours and changing dialysate sodium prescription to 138 mEq/L

Reducing the ultrafiltration rate by increasing the dialysis time is most likely to mitigate intradialytic hypertension. Withholding antihypertensive drugs or administering midodrine may or may not mitigate dialysis hypotension; they are of uncertain value. Increasing bicarbonate did not mitigate the hypotensive episodes in a randomized trial. Reducing dialysate Na may reduce interdialytic weigh gain. Increasing dialysis time may reduce the hemodynamic stress of rapid ultrafiltration.


**Question 14**

**Answer A:** Cognitive behavioral therapy to improve sleep hygiene

The benefit of cognitive behavioral therapy in the treatment of insomnia in dialysis-dependent patients has been demonstrated in a randomized controlled trial of 72 sleep-disturbed hemodialysis patients. The intervention included psychiatrist-oriented, video-assisted sessions during thrice-weekly hemodialysis treatment and group discussions after the completion of hemodialysis sessions. This led to significant improvements in sleep quality, efficiency, and duration, patient-reported symptoms of fatigue, depression, and anxiety and decrease in serum C-reactive protein, interleukin-18, oxidized low density lipoprotein cholesterol. In contrast, there is no high-level evidence for the benefit with drugs (zolpidem or trazadone), or hemodialysis treatment time on sleep disorders in dialysis-dependent patients.

**Question 15**

**Answer B: Refer patient for CKD education.**

Results from the IDEAL clinical trial indicate that there is no difference in patient survival, cardiovascular events, infectious complications, or dialysis-related complications in patients initiating dialysis at lower compared to higher level of renal function. Hence, there is little evidence to support initiation of dialysis simply based upon renal clearances. Furthermore, there is a high prevalence of sub-optimal initiation of dialysis (viz., with a central venous catheters) with its attendant risk for adverse events. This patient is minimally symptomatic (easy fatigability), has mild hypervolemia (trace lower extremity edema), and does not have any indications for emergent dialysis. Hence, dialysis can be delayed in this patient while keeping him under close observation. This time can be best used by educating the patient about chronic kidney disease, treatment options, and complications to allow the patient to make an informed choice about dialysis therapy and timely placement of access.


**Question 16**

**Answer A: Fewer atherosclerotic cardiovascular events**

There have been three large clinical trials in populations that included dialysis-dependent patients to determine the potential benefits of lipid lowering with statins. SHARP is the largest such trial completed to date and enrolled 9270 patients with chronic kidney disease that were randomly assigned to treatment with simvastatin-ezetimibe, or placebo. The study demonstrated a 17% lower risk for atherosclerotic cardiovascular events in the treated population. However, there was no effect on either all-cause or cause-specific mortality. The results of the study are applicable to the dialysis population as the study cohort included 3023 patients treated with hemodialysis or peritoneal dialysis at the time of inception of the study. Moreover, over 2000 patients reached end-stage renal disease and started
dialysis therapy during the course of the study. Statistical analyses of interaction showed that there was no association between the presence of end-stage renal disease at the time of enrollment in the study and the potential benefit vis-à-vis the reduction in atherosclerotic cardiovascular events. Put differently, the benefit of the intervention was the same for dialysis-dependent patients as for patients with earlier stage chronic kidney disease.

Post-hoc analyses of the AURORA clinical trial have also demonstrated a 32% lower risk for fatal/non-fatal cardiovascular events in hemodialysis patients with diabetes treated with rosuvastatin. However, there was no significant difference in the other outcomes.

The ability of statins to lower atherosclerotic cardiovascular events without affecting all-cause or cardiovascular mortality suggests that the contribution of atherosclerosis to overall death risk in dialysis-dependent patients is not as large as in the general population.


Question 17

Answer B: Decrease digoxin dose to 0.125 mg every other day.

In an observational study of patients undergoing hemodialysis treatment in facilities owned by Fresenius Medical Care, individuals treated with digoxin had a 28% higher risk for death. While there was no association between the dose of digoxin and death risk, mortality rates were higher in the sub-group of individuals with serum digoxin > 1.5 ng/ml and low pre-dialysis serum potassium. There are no specific guidelines for the safe range for serum digoxin levels in dialysis-dependent patients. However, the American College of Cardiology/American Heart Association recommends that digoxin be dosed to
achieve serum levels of 0.5-1.0 ng/ml. In this given individual, the serum digoxin levels are higher than this range and it would be prudent to lower to dose to achieve a lower serum digoxin levels.

There is also evidence linking the composition of the dialysate bath with risk for sudden death in dialysis-dependent patients (dialysate potassium < 2 mEq/L and calcium < 2.5 mEq/L). In this individual, the dialysate potassium and calcium concentrations are 2.0 and 2.5 mEq/L respectively, and hence, there is limited rationale to make change these concentrations.


Question 18
Answer B: Hypoglycemia
The symptoms of palpitations, and sweating followed by an alteration in sensorium in patient with diabetes mellitus are highly suggestive of hypoglycemia. This patient is treated with icodextrin which is absorbed via the lymphatics in the blood stream where it is metabolized to maltose, maltriose, and other oligosaccharides. While most commercially available glucometers measure glucose, some measure reducing substances which includes maltose (glucometers using glucose dehydrogenase pyrroloquinoline). Use of such glucometers will result in over-estimation of blood glucose; the magnitude of this over-estimation can range from 50 to 150 mg/dl. Hence, in the absence of information of the nature of the glucometer used to measure blood glucose, this icodextrin-treated patient should be assumed to have and be treated as having hypoglycemia.


Question 19
Answer E: Validated method for monitoring is not available
The cumulative incidence of encapsulating peritoneal sclerosis is 0.4-2.7% of all patients treated with peritoneal dialysis, with the only predictable risk being the length of time of treatment with peritoneal dialysis. Nevertheless, the risk for an individual at any given point in time is low. Yet, there are no validated methods to identify an individual at high risk for developing encapsulating peritoneal sclerosis.
Small, single-center studies have suggested that either a reduction in osmotic conductance (assessed from a peritoneal equilibration test), biomarkers (dialysate effluent IL-6 and CA-125 levels), and morphometery (mesothelial cell area in the dialysate effluent) can be used to identify individuals who develop encapsulating peritoneal sclerosis. However, none of these methods have been independently validated and cannot be recommended for routine use in clinical practice. Evidence to date also does not seem to support the use of repeated computed tomography in otherwise asymptomatic patients to identify individuals who subsequently develop encapsulating peritoneal sclerosis.


**Question 20**

**Answer B: N-acetyl cysteine**

There are two clinical trials – one in patients undergoing hemodialysis, and the other in patients undergoing peritoneal dialysis – that have demonstrated that the co-administration of N-acetyl cysteine with aminoglycosides is associated with a reduction in the ototoxicity of the drug as measured by audiometry. The second of the two clinical trials was recently published and was undertaken in 60 patients treated with peritoneal dialysis who were randomly assigned to receive 600 mg twice daily of N-acetyl cysteine or placebo. Only 1 of 30 patients who received 600 mg twice daily of N-acetyl cysteine developed hearing loss detectable on pure tone audiometry when compared to 21/30 control patients. This provides support for the use of N-acetyl cysteine in dialysis-dependent patients treated with aminoglycosides.


**Question 21**

**Answer A: Surgical consult for an emergent removal of the peritoneal dialysis catheter tonight**

It is widely agreed that fungal peritonitis is an absolute indication for PD catheter removal. However, thus far, the data on the precise timing for catheter removal have been scant. In an analysis of 94 episodes of fungal peritonitis, patients in whom the PD catheter was not removed within 24-hours of diagnosis of the infection had a 13.7-fold higher death risk. These data indicate that a diagnosis of fungal peritonitis should be considered a surgical emergency and the PD catheter should be removed within 24-hours.


**Question 22**

**Answer B: Discontinue diphenhydramine**

This patient has evidence of decrease in cognitive function, which is identifiable in 66-73% of unselected HD and PD patients with no history of stroke with the use of psychometric tests. The prevalence of cognitive impairment increases with advancing age, and lower educational attainment. It is important to identify and correct potentially reversible causes of decline in cognition. There is evidence that dialysis-dependent patients treated with H1-receptor antagonists or opioids are more likely to have impaired executive function. In contrast, studies thus far have been unable to demonstrate any association between cognitive impairment and modifiable dialysis related factors (like dietary intakes, anemia, or hemodynamic measures). Thus, in this individual, a trial of discontinuation of diphenhydramine appears warranted.

Question 23
Answer C: Should not be attempted because chances of an adequately functioning catheter are low
In patients with refractory peritonitis, removal of the peritoneal dialysis catheter is often indicated. Successful resumption of long-term treatment with peritoneal dialysis, however, is often difficult. In a single-center study from Hong Kong, peritoneal dialysis catheter could be successfully re-inserted in only 51 of the 100 patients in who the peritoneal dialysis catheter was removed. Of these 51 patients, 11 had to be transferred to hemodialysis after a mean of 8 months. Thus, long-term peritoneal dialysis was possible in only 40% of the patients.

It would be useful to identify a sub-group of individuals in who the probability of long-term PD is so low that reinsertion of the peritoneal dialysis catheter should not be attempted. In a study from the same center in Hong Kong, a persistent intra-abdominal collection was present in 14% of all cases in which PD catheters were removed (n=30). The aspirate of this collection was sterile in 83% of cases, re-accumulated in 57%, 30% of the patients died and only 10% were able to re-start PD. This study suggests that patients with persistent intra-abdominal collections 5-7 days after removal of PD catheter for refractory peritonitis should transfer to long-term HD without subsequent attempts at re-initiating PD.

Question 24
Answer A: Higher net ultrafiltration volume

The potential benefits of the use of icodextrin in patients treated with peritoneal dialysis have been examined in several randomized controlled trials. The results from nine clinical trials with 1190 patients have been summarized in a meta-analysis. The data indicate that icodextrin generates higher ultrafiltration volume during the long dwell when compared with 1.5%, 2.5%, or 4.25% dextrose. The higher ultrafiltration volume is achieved with lower carbohydrate absorption (greater ultrafiltration efficiency), and leads to higher small solute clearances. Furthermore, there is no difference in the rate of decline of residual renal function in patients treated with icodextrin or dextrose based solutions for the long dwell. There is no consistent evidence for benefit on any other clinical measure (viz., blood pressure, glycemic control).


Question 25
Answer A: Improvements in perioperative mortality that are larger than seen in individuals without ESRD

Between 1988 and 2003, the annual rate of coronary artery bypass grafting in ESRD patients has doubled. During that same period, there has been a substantial decrease in in-hospital mortality (31% to 5%), and median length of stay (25 d to 13d), but an increase in non-routine discharges (skilled nursing or intermediate care facilities, short-term hospital, home healthcare). Declines in peri-operative mortality have been substantially greater for ESRD patients than those without – while the peri-operative mortality of ESRD patients decreased from 31% to 5.4% that of patients without ESRD decreased from 4.7% to 1.8%. Thus, the magnitude of improvement has been greater in patients with ESRD than those without.