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********** *ANSWERS TO* **********

THE NEPHROLOGY QUIZ & QUESTIONNAIRE: 2003

Dear Friends & Members of the ASN:

But for a few "myoclonic jerks" in our computer, this year's Nephrology Quiz and Questionnaire in San Diego came off quite well. The eight cases provided some interesting, albeit controversial, insights into a wide array of clinical disorders.

The number of responses to our pre-meeting e-mailing of the cases and questions to training program directors and practicing nephrologists in the US was greater than ever. We also sent the material to colleagues in Australia and Japan. These responses were presented at San Diego and compared with those of the live audience. The use of Audience Response Pads, and the anonymity they provide, allowed several hundred attendees at the session to vote on the answers to all the questions. Some of the responses were surprising but there weren't many notable differences between the US , Australian and Japanese nephrologists. Perhaps we'll have additional countries participate next year and award Gold, Silver and Bronze medals for this Nephrologic Olympiad!

I'm resending the cases, questions and providing you with the ANSWERS supplied by the panel. Please send your questions/comments to me at rnarins@pol.net and either I'll answer them directly or send them on to the authors for their responses.

Thanks for taking part in this exercise and I look forward to seeing you in Saint Louis next October or at the Board Review Course in San Francisco August 28 September 3, 2004.

Happy New Year!

Robert G. Narins, M.D.
Director, Postgraduate Education, ASN

FLUID-ELECTROLYTE DISORDERS: STANLEY GOLDFARB

CASE ONE : A 49-yr-old Caucasian woman with a known diagnosis of HIV-AIDS was brought to the emergency room (ER) by her husband because of generalized weakness. The patient's mild dementia had been attributed to AIDS. Earlier in the evening she complained of not feeling well and suddenly became very weak. In the ER she was alert and oriented but could not recall the earlier events of the evening.

Past Medical History : She had herpes zoster infection, hepatitis and denied seizures or syncope. She drank 68 beers daily, smoked tobacco for many years, and while she occasionally smoked crack cocaine she had not used it for >24 h. Her medications included didanosine (DDI), trimethoprim sulfamethoxizole (Septra®), amytriptoline(Elavil®), albuterol(Ventolin®) inhaler, and diphenhydramine.

Physical Examination: well-nourished, well-developed female. Vital signs were: temperature 36.9°C (98.4°F); blood pressure 159/95 mm Hg; heart rate 100 beats/min; respirations 20 breaths/min. Examinations of the head and neck were unremarkable; cardiac evaluation revealed a regular tachycardia; there were rales at both bases; the abdomen was unremarkable; rectal examination was heme negative; the neurological examination was non-focal but there was generalized muscle weakness.

Laboratory Studies: Electrolytes: Serum: Na 129 mEq/L, K 1.8 mEq/L, Cl 58 mEq/L, CO 2 55 mEq/L Urinary; K 21 mEq/L, Cl 42 mEq/L, Na 64 mEq/L

BUN 35 mg/dL, Creatinine 2.8 mg/dL, Glucose 112 mg/dL

Calcium 12.5 mg/dL, PO 4 4.0 mg/dL, Mg 1.5 mg/dL
Hematocrit 47%
Arterial Blood Gases (room air): pH 7.56, PO2 73 mm Hg, PCO2 65 mm Hg, HCO3 57 mEq/L.
Head computed tomography (CT) scan was normal. No lumbar puncture was done.

Which ONE of the following diagnoses BEST accounts for this patient's acid-base and electrolyte disturbances?

A. Primary hyperparathyroidism
B. Surreptitious vomiting

C. Primary hyperaldosteronism
D. Antacid abuse
E. Diuretic abuse

ANSWER TO CASE ONE: Answer **A** , primary hyperparathyroidism, is very unlikely because the severe alkalemia seen in this case is quite atypical for the disorder.

Surreptitious vomiting, answer **B** , is ruled out because the loss of gastric HCl and the accompanying volume contraction should decrease the urinary Cl level. The hyperchloruria in this case weighs heavily against option B.

Primary Hyperaldosteronism, choice **C** , is unlikely because of the lack of hypertension and the failure of this diagnosis to explain the hypercalcemia.

Thiazide diuretics, option **E** , are known to produce hypercalcemia but it is typically less severe than is seen in this patient. The hypercalcemia seen with thiazides is usually associated with underlying primary hyperparathyroidism.

Patients such as paraplegics may have accelerated bone resorption. Because bone is potentially a large source of alkali in the form of carbonate crystals, bone resorption could produce a concomitant increase in bicarbonate levels. This disorder would not cause alkalemia and alkalosis to the degree found in this case.

Option **D** , alkali abuse or the milk-alkali syndrome, secondary to the use of calcium containing antacids, is the best diagnosis for this patient.

These data (shown below) summarize a survey of patients with hypercalcemia complicating antacid abuse (Beall et al.) While the patient described in Case One is more severely alkalotic than Beal's, the other parameters are typical:

Typical Features of Antacid Abuse Hypercalcemia

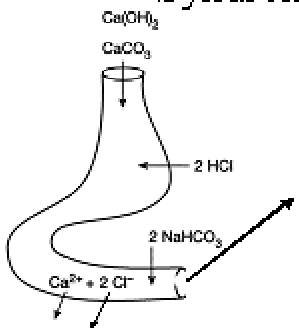
Calcium	11-19.3 mg/dl
PO4	1.4 – 6.3 mg/dl
HCO3	28 - 37 mEq/L
BUN	20 – 140 mg/dl
Creatinine	0.5-3.2 mg/dl

Beall DP Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. Medicine. 74(2):89-96, 1995 Mar

Beall DP Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. Medicine. 74(2):89-96, 1995 Mar

The following cartoon explains one possible mechanism:

Pathogenesis of Milk Alkali Syndrome



Hypothesis 1- CaCO3 neutralizes protons leaving CaCl2 behind to be absorbed in small bowel. NaHCO3 secreted by pancreas is not buffered by HCl from stomach and is also reabsorbed in small bowel.

From: Lin SH, Lin YF, Cheema-Dhadli S, Davids MR, Halperin ML Nephrol Dial Transplant. 2002 May;17(5):708-14

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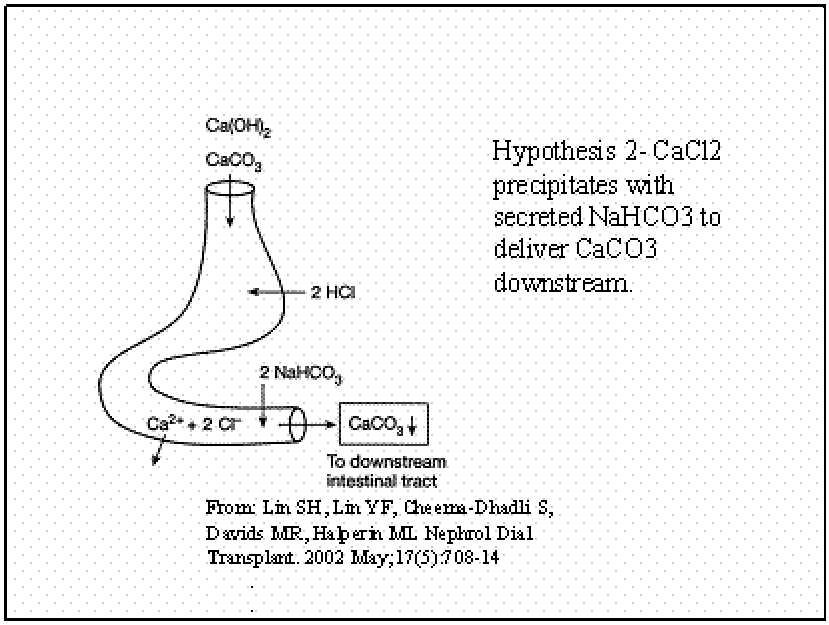
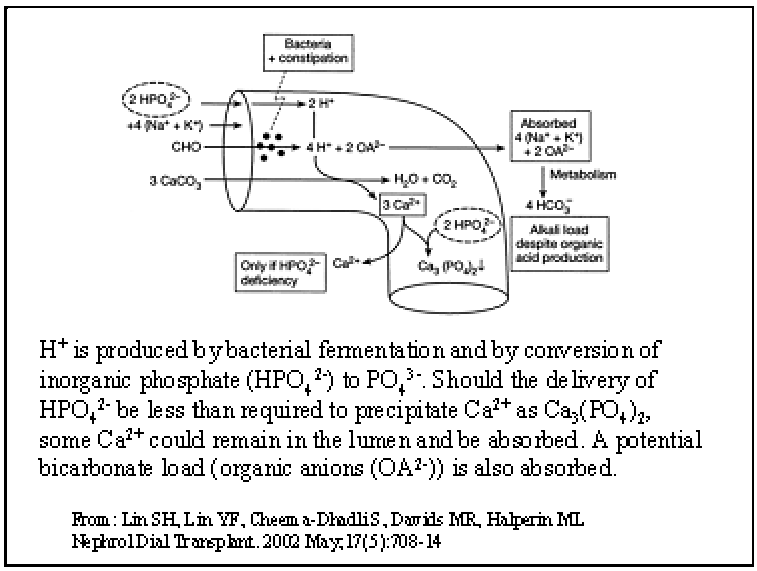
The next hypothesis of Lin et al, suggests that a more complex mechanism, described by the following two diagrams, could better explain the pathogenesis. CaCO3 is reformed when CaCl2 enters the portion of the small intestine exposed to alkaline pancreatic secretions:



From: Lin SH, Lin YF, Cheema-Dhadli S, Davids MR, Halperin ML Nephrol Dial Transplant. 2002 May;17(5):708-14

The key to this formulation is that bacteria in the large intestine generate organic acids that are then buffered by the CaCO3 delivered distally. This liberates organic anions which are subsequently absorbed and converted via the Krebs Cycle to bicarbonate as protons are consumed in those reactions (see below):



From: Lin SH, Lin YF, Cheema-Dhadli S, Davids MR, Halperin ML Nephrol Dial Transplant. 2002 May;17(5):708-14

CASE TWO : A 35-yr-old woman was admitted to the hospital with a 2-week history of pneumonia that was unsuccessfully treated at home with oral ciprofloxacin. Fever, green sputum, a relentless cough and diffuse chest pain (related to the cough) required frequent and increasing use of diphenhydramine (200 mg/day), codeine (150 mg/day) and acetaminophen (4 g/day). Her past medical history was negative except for mild intermittent alcohol abuse. Increasing lethargy and dyspnea prompted her family to bring her to the emergency room.

Past Medical History: negative except for the excess alcohol intake. She denied drug abuse, intake of other medications and previous surgery.

On admission the patient was confused, disoriented and had a productive cough.

Physical Examination: BP 125/85 mmHg, Pulse: 80/min, Respirations. 20/min, Temp 100.6 F (38.1 C); She was lethargic but otherwise well oriented; well nourished and without edema, cyanosis or clubbing. Right lower lobe consolidation was noted, abdominal and neurological examinations were normal. The remainder of the examination was not contributory.

Chest x-ray revealed a cavitating right lower lobe abscess in an area of consolidation.

Laboratory Studies: The patient's sputum culture grew-out staphylococcus Aureus.

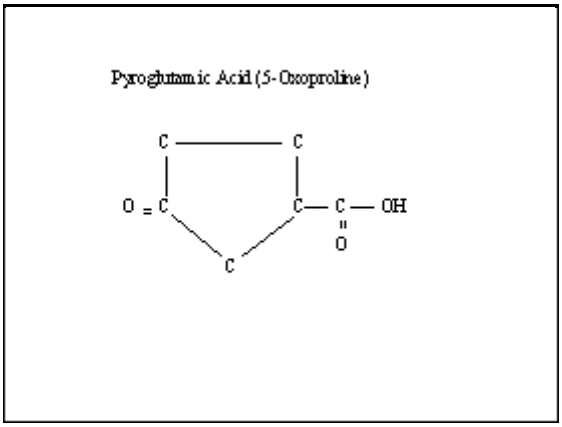
Hematocrit 34 %, Hemoglobin 11 g/dL, WBC 21,000 cells/cu l, Platelets normal
Na 135 mEq/L, K 4.5 mEq/L, Cl 97 mEq/L, HCO 3 7 mEq/L;
Calcium 10.2 mg/dL, Pi 5.0 mg/dL, Uric acid 9.5 mg/dL;
Serum osmolality 293 mOsm/L
Serum creatinine 1.4 mg/dL, BUN 30 mg/dL, Glucose 126 mg/dL
Arterial Blood Gases (room air): pH 7.17, pCO 2 18 mmHg, HCO 3 6.4 mEq/L, pO 2 , 100 mm Hg
Serum lactate 3.1 mEq/L, Ketones negative at 1:1 dilution of serum
Urine: pH 5.5, Ketones trace positive, no protein or blood; Sediment: a rare uric acid and a rare calcium oxalate crystal were seen.

Which ONE of the following disorders is the MOST LIKELY cause of this patient's metabolic disturbances?

A. Heterozygous ornithine transcarbamylase deficiency
B. Sepsis
C. Ethylene glycol poisoning
D. L-5-oxoprolinuria
E. D-Lactic acidosis

ANSWER TO CASE TWO:

This case is an example of drug induced L-5-oxoprolinuria, also known as pyroglutamic acidosis (option **A**). Pyroglutamic acid or 5-oxoproline is a metabolic product of the gamma-glutamyl cycle involved in the synthesis of glutathione (see below):

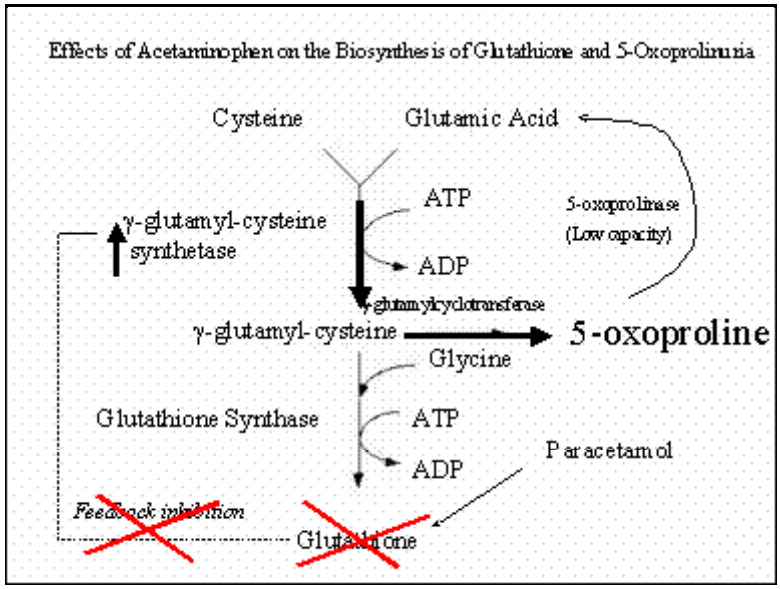


In addition to the hereditary form of oxoprolinuria, which is associated with metabolic acidosis and hemolytic anemia in the newborn, a number of cases of an apparently acquired form have been described with the above noted characteristics. The following is a list of these causes:

1. StevensJohnson syndrome and severe burns
2. Prematurity
3. Glycine deficiency Patients on artificial diets
4. Acetaminophen (paracetamol)
5. Vigabatrin (anti-epileptic)

In circumstances in which glutathione is depleted, the activity of ?-glutamyl-cysteine synthetase is increased leading to increased formation of ?-glutamyl-cysteine which, in turn, leads to increased synthesis of oxoproline as the glutathione synthase enzyme has limited capacity (as does

the 5- oxoprolinase enzyme). These changes all result in increased production of the strong metabolic acid, 5-oxoproline (see below).



The other answers are incorrect for the following reasons.

Option A: Heterozygous ornithine transcarbamylase deficiency. Hyperammonemia is always present in this disorder. This patient's normal blood ammonia level therefore excludes this diagnosis.

Option B: Sepsis. Although this could have been a possible diagnosis, the minimal elevation of blood lactate leaves the explanation for the acidosis unanswered and argues strongly against this choice.

Option C: Ethylene glycol poisoning. The absence of renal failure and the minimal crystalluria, argue persuasively against this selection.

Option E: D-Lactic acidosis. In this disorder, bacteria accumulating in the GI tract (usually with an anatomically altered intestinal tract) are responsible for formation of D-lactic acidosis. The absence of any history of GI disease, bowel surgery or the exposure to high glucose loads, virtually excludes this choice.

Reference: Pitt and Hauser (Transient 5-oxoprolinuria and high anion gap metabolic acidosis: clinical and biochemical findings in eleven subjects. Clin Chem. 1998 Jul;44(7):1497-503).

TRANSPLANTATION CASES: DONALD HRICIK

CASE THREE : A 40 yr-old Caucasian man with progressive renal failure due to idiopathic focal and segmental glomerulosclerosis (FSGS) seeks your opinion about kidney transplantation. He presented with the nephrotic syndrome six years earlier, and his serum creatinine concentration has slowly risen from 1.7 mg/dL to its current value of 3.5 mg/dL, despite an early trial of high-dose corticosteroids and plasmapheresis. His creatinine clearance is currently 23 mL/min. The patient's 45 yr-old brother has 0 of 6 HLA antigen matches but is anxious to donate a kidney and is medically suitable.

Which ONE of the following choices provides the BEST advice to the recipient and donor?

A. Transplantation is contraindicated because of the high risk of recurrent FSGS.
B. Transplantation is reasonable but in this case must utilize a cadaveric donor.
C. Living-donor transplantation is reasonable and should be performed before the recipient requires dialysis.
D. Living-donor transplantation is reasonable but should be postponed until after the recipient has begun dialysis.

ANSWER TO CASE THREE:

Option A: Incorrect. Although there has been a traditional concern that recurrence of FSGS may be more common after living-donor transplantation, the benefits of living-donor transplantation on graft survival appear to outweigh any concerns about recurrence. This was demonstrated most cogently in the USRDS analysis by Cibrik et al.(Cibrik D, et al: Am J Transplant 2003; 3:64).

Option B: Correct. The benefits of preemptive transplantation are now clear-cut. The duration on dialysis has been described as the most important modifiable risk factor negatively affecting renal allograft survival. IT has been shown that he shorter the exposure to dialysis, the better the eventual transplant outcome. (Cosio F, et al: Kidney Int 1998; 53: 767. Meier-Kriesche HU, et al: Kidney Int 2000; 58: 1311. Mange KC, et al: N Engl J Med 2001; 344: 726. Meier-Kriesche HU, et al: Transplantation 2002; 74: 1377)

Option C: Incorrect. Please see the answer to option B.

Option D: If preemptive transplantation with a live donor can be performed, there is no need to list for cadaveric transplantation. Again, please see the answer to option B.

***If you have trouble reading this email, please click here.**

To Our Understanding Friends and Colleagues:

Yes, we had a typo in the answers to the Nephrology Quiz and Questionnaire.

Case Three: In the answers we sent, Options B & C were inadvertently reversed.

The correct answer is CHOICE C (as originally presented with the case). The answer, OPTION B, actually refers to choice C and should be relabeled OPTION C.

As you know, we in the US do a lot of pre-emptive things, including transplantation!

The error was mine; Dr. Hricik is absolved! Be human and forgive me, it's divine!

Robert G. Narins, MD

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Option C: Incorrect. Please see the answer to option B.

Option D: If preemptive transplantation with a live donor can be performed, there is no need to list for cadaveric transplantation. Again, please see the answer to option B.

CASE FOUR : A 63 yr-old African American man with ESRD secondary to hypertension and type II diabetes mellitus is scheduled to soon receive a kidney transplant from his son. He seeks your opinion about his post-transplant medications. Atorvastatin, 20 mg/d, was started 2 years earlier when his fasting total cholesterol was 230 mg/dL and LDL cholesterol 135 mg/dL. Angioplasty and stent placement for single-vessel coronary artery disease were performed 3 years ago. The patient's transplant center has informed him that he will receive maintenance immunosuppression with cyclosporine, mycophenolate mofetil, and corticosteroids.

Which ONE of the following choices provides this patient with the BEST ADVICE regarding the use of an HMG-CoA-reductase inhibitor after kidney transplantation?

A. This class of agents is contraindicated because of the prohibitive risk of rhabdomyolysis when used with cyclosporine
B. Atorvastatin should be continued after transplantation but the transplant center will suggest an upper dose limit
C. Use of a statin is encouraged because it will minimize the patient's risk of acute rejection
D. The atorvastatin will likely be stopped by the transplant center because the

patient's hyperlipidemia will probably improve if the kidney transplant is successful.

ANSWER TO CASE FOUR:

Option A: Incorrect. Most reported cases of rhabdomyolysis in transplant recipients have occurred 1) with lovastatin, 2) in heart transplant recipients receiving high doses of cyclosporine, and 3) in patients receiving other lipid-lowering drugs (usually fibric acid derivatives) which are also known to increase the risk of rhabdomyolysis. Recent experience indicates that, in relatively low doses, these agents are safe and effective.

Option B : Correct. The increased risk of rhabdomyolysis in patients receiving a statin and cyclosporine relates to cyclosporine-induced cholestasis and decreased biliary secretion of the statin. Thus, in the presence of cyclosporine, blood levels of any given statin are 2 - to 9-fold higher in the presence of cyclosporine than is seen in controls. For this reason, most transplant physicians are reluctant to increase the dose of statins to the upper limits accepted in the general population.

Option C: Incorrect. Randomized, placebo-controlled trials in heart and kidney transplant recipients at UCLA suggested that treatment with pravastatin not only lowered cholesterol levels, but also was associated with reduced rates of acute rejection. In these studies, treatment with pravastatin was associated with reduced activity of natural killer cells, suggesting that the drug was intrinsically immunosuppressive. However, the recent ALERT trial, involving 2100 patients randomized to fluvastatin or placebo, showed no effect of this statin on the incidence of acute rejection or graft survival. (Multiple abstracts 2003 ASN meeting).

Option D: Very Incorrect. The incidence of hyperlipidemia after kidney transplantation ranges between 60 and 90% depending on its definition. Hyperlipidemia rarely, if ever, improves after kidney transplantation. (Hricik , DE . Hyperlipidemia in renal transplant recipients. *Graft* 3:11-19, 2000).

ESRD & DIALYSIS CASES: SARAH PRICHARD

CASE FIVE : A 77-yr-old Caucasian man with unspecified cystic disease began hemodialysis via a well-functioning native AV fistula. He had no other

co-morbidities, was normotensive and his echocardiogram revealed normal ventricular function.

The patient received three 4-hour dialyses/wk and felt well. His URR exceeded 70%, his BP averaged 130/80 mmHg before and 120/80 mmHg after dialysis.

Eighteen months after starting dialysis he complained of retrosternal chest pain and an EKG revealed non-specific ST-T wave changes. He was admitted to a coronary care unit for his recurrent pain. Angiography was performed and a stent was placed in his LAD. Again, his LV function, assessed by angiography and echocardiography, was excellent. Calcifications were seen on his mitral valve leaflets and the maximum pressure gradient across the aortic valve was calculated to be 35 mmHg. He had a systolic ejection murmur. He was discharged on long-acting nitrates, aspirin and simvastatin.

The patient remained well for another 18 months when he had another episode of chest pain. His EKG demonstrated an anterior infarct, his tropinins were increased and an echocardiogram showed a LV ejection fraction of 35%. The remainder of his cardiac findings were unchanged. Ramipril, 5mg/d, was added to his drug regimen.

A year later he developed hypotensive episodes and chest pain during dialysis. His new pre-dialysis BP was 105/65 mmHg. His inter-dialytic weight gain averaged 2 kg. He had dyspnea on exertion and at rest. A fixed deficit was seen on his repeat DIP-MIBI nuclear scan, which was unchanged from a year earlier. He did not have peripheral edema and his neck veins were minimally elevated. His systolic ejection murmur persisted but was actually reduced in duration and intensity. His nitrates and ramipril were discontinued but his symptoms and clinical findings remained unchanged.

Which ONE of the following choices would now be BEST for this patient?

A. Change his dialysis regimen to short daily treatments, 6/week
B. Consider replacing hemo with peritoneal dialysis.
C. Perform Na profiling and ultrafiltration during dialysis to maximize fluid removal.
D. Ask a cardiac surgeon to evaluate the patient for possible valvular surgery.
E. To exclude an atypical presentation of a critical coronary lesion, you must repeat his cardiac angiogram

ANSWER TO CASE FIVE: This patient has arteriosclerotic heart disease (ASHD) and aortic stenosis, with the latter being more poorly documented in the last 18 months. His symptoms are those of poor cardiac output without overt fluid overload or florid heart failure, i.e., shortness of breath (SOB), very poor exercise tolerance, intolerance of ultrafiltration and/or minimal weight gain.

No possible change in his dialysis regimen will improve his cardiac output at this stage of his disease. This makes choices A, B and C incorrect and leaves options D (valve problem) and E (critical coronary lesion) as the only viable alternatives. Although the clinical history and the negative DIP-MIBI argue against answer E they cannot absolutely rule it out. Thus, answer E remains a possibility, albeit an unlikely one.In favor of answer D (a valve problem), is the following: the clinical history is typical of aortic stenosis (AS). The shortened murmur is characteristic of AS that has progressed to a critical stage. Furthermore, in heavily calcified aortic valves, it becomes difficult to measure valve area due to technical difficulties created by the calcification. When the ejection fraction decreases, the maximum gradient across the valve can decrease even as the stenosis increases. In our case, neither the valve area nor the gradient is recorded in the most recent echo, possibly because of the technical issue and what might have been an unexciting gradient. However AS must be considered likely, even in the absence of this recent data, based on the early echo which did show a modest gradient at that time. AS is well documented to be more rapidly progressive in patients with CRF, especially those on dialysis. The increase in progression has been reported to be 2 to 3 times greater than that in the general population. It has also been associated with higher calcium and phosphate levels. Thus, answer D is the more correct one.

References:

Wongpraparut N et al; Determinants of progression of aortic stenosis in patients aged 40 over years. Am J of Cardiology Volume 89, number 3, 2002.

Urena P et al; Evolutive aortic stenosis in hemodialysis patients analysis of risk factors Nephrologie 1999;20:pp217-225.

Perkovic V; Accelerated progression of calcified aortic stenosis in dialysis patients Nephron Clinical Practice 2003;94:pp240-45.

CASE SIX : When a 47-yr-old Caucasian male with FSGS began CAPD his urinary output was 1.3 L/d and his creatinine clearance was 6 mL/min. He weighed 78kg and had no other significant co-morbidities. Prior to initiating CAPD his BP was controlled (usually 140/85 mmHg) with enalapril 20mg/d, and metoprolol 50mg bid. Six weeks after initiating CAPD with 2.5 L of 1.5% glucose dialysate X4/d, a Peritoneal Equilibration Test (PET) revealed a D/P Cr ratio at 4 hours of 0.58. Simultaneously, his Kt/V exceeded the target value of 2.1/wk and his BP decreased to 120/75 mmHg while receiving the same medications. Nine months after starting CAPD his weekly Kt/V decreased to 1.7 and his combined urine output and peritoneal UF was 1.2 L/d. Lost residual renal function accounted for the decrease in Kt/V. He had 2+ pretibial edema and his BP increased to 155/90 mmHg. His CAPD prescription was changed to the following: X5/d: 2.5 L each, with 3 of the exchanges using 2.5% glucose solution and 2 exchanges using 1.5% glucose solution. Subsequently his BP decreased to 120/75 mmHg and his adequacy target was achieved. His total fluid output (urine and dialysis UF) was now 1.7 L/d. Automated PD (APD) was initiated to minimize his daytime exchanges. The new APD prescription was: five 2L exchanges of 2.5% glucose solution given over 10 hours on the cycler overnight and one 2.5 L exchange of 4.25% glucose during the day. His total fluid output remained at 1.7 L/d. His BP, however increased significantly to 160/95 mmHg on the same anti-hypertensive regimen. Which ONE of the following choices would provide the BEST dialysis prescription for treating his hypertension? A. Change the overnight bags used on the cycler to two 5 L bags, one of 2.5% glucose and the other of 4.25% glucose and keep unchanged the number and volume of the exchanges. B. Change the daytime dwell to 2L of 7.5% icodextrin. C. Add another 2 L exchange of 2.5% glucose at 1800 hrs and drain it at 2200 hrs. D. Change the nighttime prescription to 3 exchanges of 2.5L of 2.5% glucose and add an evening exchange as outlined in option C (above).

E. Add a 2.5L exchange of 7.5% icodextrin in the evening.

ANSWER TO CASE SIX: This patient developed hypertension when dialysis therapy was changed from CAPD to APD and this occurred despite adequate Kt/V and fluid removal. The implication is that the patient has had less sodium removal with the new treatment. Is this possible with a change from CAPD to APD?

Current understanding of peritoneal physiology leads us to explain why this can occur. Fluid transfer into the peritoneal space occurs first under the

influence of aquaporin 1 channels that exist in the peritoneal endothelial cells. These channels, stimulated by the crystalloid osmotic forces of the glucose-rich peritoneal fluid, transfer sodium-free water into the peritoneum. This can be demonstrated by measuring the intraperitoneal sodium concentration which decreases early in a PD exchange. As the exchange progresses, sodium diffuses into the peritoneum through the mid-size peritoneal pores. During a long exchange diffusive forces will return the peritoneal fluid sodium concentration close to that of plasma. This diffusion rate is a function of the effective surface area of the peritoneum. In patients who are slow transporters, as in Case Five, the aquaporin channels will be in tact and will drive water into the peritoneum . However, the diffusion of sodium will be poor since these low transporters have a low effective peritoneal surface area.

It follows that if a slow transporter is given frequent short exchanges; he/she can effectively remove water but will have less sodium removal because the latter depends on diffusion. This is known as sodium sieving, i.e., the removal of free- water in excess of sodium, and such patients can develop hypernatremia during periods of hypertonic, frequent exchanges.

The correct answer to this question requires that the patient be given exchanges that allow adequate time and conditions for sodium diffusion as well as the water removal.

Answer A gives more hypertonic overnight exchanges and will worsen the situation because the greater hypertonicity of the 4.25% solution will further drive the aquaporin function without allowing time for diffusion.

Answer B uses icodextrin during the day. This 7.5% solution is isotonic and does not depend on aquaporin function for fluid removal but acts as a colloid equivalent. It does not create sodium sieving. Increased sodium removal has been demonstrated with icodextrin, but this is a function of the increase in the total drainage volume. This patient does not need extra drainage volume and the current prescription gives a long daytime exchange of a glucose solution which will allow diffusion of sodium to occur.

Answer C increases the total volume of solution used and therefore increases cost. The patient is adequately dialyzed and does not need the extra volume of dialysis. This answer does not address the sodium sieving problem overnight.

Answer E also uses icodextrin which adds cost like answer C.

Answer D is the best answer because the total daily fluid volume stays the same which keeps the cost stable. This option lengthens the nighttime exchanges which will allow for more sodium diffusion and it gives a 4-hour evening exchange which is long enough to allow both sodium and water removal with little net sodium sieving.

Reference:

Rodriguez-Carmona and Fontan MP; Sodium removal in patients undergoing CAPD and automated peritoneal dialysis. Peritoneal Dialysis International Vol. 22, No 6 pp. 705-713, 2002.

GLOMERULONEPHRITIS: GERALD APPEL

CASE SEVEN : A 58-yr-old Caucasian female with a six-year history of rheumatoid arthritis was previously treated with gold salts, penicillamine and various NSAID's. For the past 6 months she has taken rofecoxib (25 mg/day), hydrochlorothiazide for mild hypertension and antacids for ulcer disease.

Over the past 3 weeks she developed pedal and leg edema, a 5.5 Kg wt gain and her serum creatinine rose from 0.7 to 2.8 mg/dL. Evaluation shows a BP 130/82 mm Hg and 2+ pretibial and pedal edema.

Laboratory Data: WBC 5,600/mm3, Hematocrit 32%, platelets Normal. Urinalysis: 4+ protein, 15-20 RBC's/hpf and oval fat bodies were seen; Urine protein 4.5 g/day.

Her ANA was positive at 1:160 but the following serologic tests were negative or normal: complement levels, HBV, HCV and HIV.

Which ONE of the following histopathological findings is MOST LIKLEY to be found on her renal biopsy?

A. Secondary AA amyloidosis
B. Fibrillary glomerulonephritis
C. Collapsing focal glomerulosclerosis
D. Proliferative immune complex glomerulonephritis
E. Acute interstitial nephritis plus minimal change disease

ANSWERS TO CASE SEVEN: This 58 year old female with hypertension and rheumatoid arthritis has previously received gold, penicillamine and NSAID therapy and for the past six months has only been taking rofecoxib daily. Over the course of past three weeks she developed edema, a rising creatinine (to 2.8 mg/dl), 4.5 g proteinuria/day, and has a positive ANA of 1:160.

The most likely diagnosis is E, acute interstitial nephritis and minimal change nephrotic syndrome. Although by having rheumatoid arthritis this patient is predisposed to developing secondary AA amyloid (answer A) , it would not lead to edema and proteinuria and progressive renal failure over a three week period .Fibrillar GN , answer B, is a rare disease and can only be diagnosed by electron microscopy. Answer C, collapsing FSGS, occurs predominantly in African Americans and is associated with massive proteinuria. Although the course does progress rapidly, it would not lead to an elevation of the creatinine from 0.7 to 2.8 mg/dl in three weeks. Although this patient has a positive ANA, so do many patients with rheumatoid arthritis. Her complement is normal and there are no red blood cell casts in her urinary sediment making answer D, immune complex GN, unlikely.

Acute interstitial nephritis associated with minimal change nephrotic syndrome has been reported with use of NSAID's. Recent reports document its occurrence with COX II inhibitors as well. Typically the syndrome appears in someone receiving the medications, often for many months, who suddenly develops the nephrotic syndrome and a rising creatinine often with microhematuria.

Most patients recover from both the ARF and the nephrotic syndrome by just discontinuing the medications. Infrequently, patients approaching dialysis will require a short course of corticosteroid therapy to resolve their lesions.

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CASE EIGHT: A 24-yr-old single Caucasian female has had SLE for 5 years. Prior therapy entailed pulse IV cyclophosphamide given in two 6 month cycles

with follow up doses every 3rd month and for the last 8 months she has taken only oral prednisone (10 mg/d).

She is referred to you for increasing proteinuria and an increase in her anti-DNA antibody titer.

Laboratory Data: BUN 22 mg/dL, creatinine 1.1 mg/dL, Urinalysis has 10-15 RBC's/hpf and a rare RBC cast, Proteinuria 4.2 g/d; antiDNA titer is highly positive and serum complement is depressed.

Renal biopsy: diffuse global proliferative lesions in 14 of 22 glomeruli, 2 of which show crescents and one shows necrotizing features. Immunofluorescence and electron microscopy show moderate subendothelial and mesangial immune deposits. There is only mild interstitial fibrosis (< 10%).

EIGHT A. Which ONE of the following regimens offers the BEST therapy for this patient?

A. M onthly pulse doses of 0.5 - 1.0 g/m2 IV cyclophosphamide; initially for 6 months then continued every 3rd month.
B. Increased daily oral corticosteroid for 6 months.
C. IV solumedrol plus IV pulse doses of 0.5 1.0 g/m2 cyclophosphamide monthly for 6 months, followed by doses every 3rd month
D. Cyclosporine for 4-6 months
E. 500 mg IV pulse doses of cyclophosphamide every 2 weeks for 6 doses followed by azathioprine orally

ANSWERS TO CASE EIGHT A: This 24 year old Caucasian female has had two prior courses of intravenous (IV) cyclophosphamide for lupus nephritis and now presents with a clinical flare and biopsy documented diffuse proliferative disease with crescents and necrotizing features. Traditionally, the best therapeutic regimens in this setting were provided by answers A or C; IV monthly cyclophosphamide 0.5-1g/m2 with or without solumedrol pulses for 6 months followed by cyclophosphamide doses given every third month for a variable period. The addition of solumedrol to the regimen results in no greater toxicity but yields a greater remission rate. Both regimens are superior to answer B, i.e., steroids alone, and cyclosporine, answer D, has not been effective as monotherapy for severe proliferative disease. However, a recent new regimen, answer E, 500 mg IV pulses of cyclophosphamide every two weeks for 6 doses followed by oral azathioprine, has been just as effective in

the EuroLupus trial as the more prolonged regimen of higher dose IV cyclophosphamide. Given that this patient has already had two course of cyclophosphamide the newer low dose, short term regimen would minimize cyclophosphamide complications. It should be stressed that the EuroLupus trial was carried out almost entirely in Caucasians and the efficacy of this regimen has yet to be established in African Americans.

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EIGHT B: If the above patient were 32-yrs-old which ONE of the following would offer a potentially important therapeutic advantage?

A. IV gamma globulin monthly for 6 months
B. Oral mycophenolate mofetil for 6 months
C. IV cyclosporine followed by azathioprine for 6 months
D. Tacrolimus for 6 months
E. AntiCD 40 ligand monoclonal antibody therapy

ANSWER TO CASE EIGHT B: If the patient were 32 years old and desirous of having children, avoiding cyclophosphamide entirely would be advantageous for preventing infertility. Answer B, oral mycophenolate mofetil (MMF) has been used in several studies to treat severe lupus nephritis. The University of Miami trial demonstrated that it was more effective than continued IV cyclophosphamide for maintenance therapy of lupus nephritis. In the Chan study reported in the New England Journal of Medicine, and in the recent FDA trial, which included many African Americans, MMF was less toxic and as effective at inducing remissions as IV cyclophosphamide. Although neither of these studies has long term follow up data yet, given the patient described in case 8 having already had two courses of cyclophosphamide, a trial of MMF is very reasonable. The other therapies, IV gamma globulin, IV cyclosporine, tacrolimus, and antiCD40 ligand, have either not been studied in sufficient numbers of patients or not been shown to have a satisfactory efficacy or acceptable toxicity.

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