Clinical Pearls in Nephrology

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At the 2001 American College of Physicians (ACP) Annual Conference, a new teaching format to aid physician learning, *"Clinical Pearls,"* was introduced. Understanding 3 qualities of physician learners allowed the design of Clinical Pearls to be created. First, we physicians enjoy learning from cases. Second, we like concise practical points that we can use in our practice. Finally, we take pleasure in problem solving.

In the Clinical Pearls format, speakers present a number of short cases in their specialty to a general internal medicine audience. Each case is followed by a multiple-choice question answered live by attendees using an audience response system. The answer distribution is shown to attendees. The correct answer is then displayed and the speaker discusses teaching points, clarifying why one answer is most appropriate. Each case presentation ends with a "Clinical Pearl," defined as a practical teaching point, generally not well known to most internists and supported by the literature.

Clinical Pearls is currently one of the most popular sessions at the ACP meeting. As a service to its readers, *Mayo Clinic Proceedings* has invited a selected number of these Clinical Pearl presentations to be published in our Concise Reviews for Clinicians section. The following "Clinical Pearls in Nephrology" is one of them.

CASE 1

A 50-year-old man with a history of bladder cancer presents with abnormal findings on urine cytology. Computed tomographic urography is planned for further evaluation, and you are asked for advice on minimizing the risk of contrast-induced nephropathy.

Medications

Enteric-coated aspirin, 81 mg/d
Lisinopril, 10 mg/d

Laboratory Results

Sodium, 145 mEq/L (to convert to mmol/L, multiply by 1)
Potassium, 3.8 mmol/L
Creatinine, 1.7 mg/dL (to convert to μmol/L, multiply by 88.4).
Estimated glomerular filtration rate (GFR), 46 mL/min per 1.73 m^2 (reference range, >90 mL/min per 1.73 m^2)

Question

Which *one* of the following prophylactic measures would be the *best* option for minimizing the risk of contrast-induced nephropathy in this patient?

a. Oral ascorbic acid and oral hydration
b. Oral *N*-acetylcysteine, 1200 mg twice daily for 48 hours, and intravenous saline
c. Oral hydration
d. Intravenous administration of 5% dextrose and 150 mEq of sodium bicarbonate at 1 mL/kg per hour
e. Intravenous administration of 200 mg of aminophylline and 0.45% sodium chloride at 1 mL/kg per hour

Discussion

Contrast-induced nephropathy, a well-recognized complication of procedures and imaging studies requiring the use of iodinated contrast medium, is linked to increased morbidity. Although a variety of definitions exist, it is generally defined as an increase in serum creatinine level greater than or equal to 0.5 mg/dL or an increase in creatinine level greater than or equal to 25%. Deterioration in renal function is usually identified within 48 to 72 hours after exposure to contrast medium and may occasionally be irreversible. Patients of advanced age and those with diabetes, heart failure, liver failure, existing renal disease, or multiple myeloma are at increased risk. Agents with potential to impair renal response, such as angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, diuretic agents, and nonsteroidal anti-inflammatory drugs, should be withdrawn around the time of the procedure if possible. High contrast medium osmolality and large volumes of contrast medium have been implicated and are generally avoided. Multiple prophylactic measures involving the use of antioxidants and hydration protocols continue to be studied. Periprocedural intravenous hydration has proven to be superior to oral hydration. Although volume expansion with a sodium bicarbonate–based infusion was advantageous in prior trials, recent studies have shown it to have no benefit over sodium chloride and, according to some reports, to potentially add harm in subpopulations.[1] Orally administered acetylcysteine acting as a scavenger of oxygen-derived free radicals has been found to add benefit,

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although this incremental benefit is modest when 24-hour hydration protocols are in place (and in several trials no benefit has been evident).[2] Despite somewhat ambiguous or conflicting data, it is reasonable to use oral *N*-acetylcysteine in view of its low cost and minimal adverse effect profile. Aminophylline and ascorbic acid have also been studied without conclusive evidence of benefit.

Clinical Pearl

Periprocedural intravenous volume expansion has been demonstrated to reduce the incidence of contrast-induced nephropathy. The addition of *N*-acetylcysteine to prophylactic protocols may confer a modest additional benefit.

CASE 2

A 60-year-old woman is brought to the clinic in a wheelchair by her husband. She reports progressive skin tightening and a palpable "woody feeling" in the lower extremities, leading to decreased ambulation. She has a medical history of osteomyelitis and diabetic chronic kidney disease while receiving hemodialysis and was hospitalized 6 months previously for a minor stroke from which she has completely recovered. Her blood pressure is 120/70 mm Hg, her pulse is 72 beats/min and regular, and her extremities appear woody and sclerotic, with nonpitting swelling in both lower extremities.

Medications

Darbepoetin, 60 μg subcutaneously monthly
Pioglitazone, 15 mg/d orally
Furosemide, 60 mg/d orally
Aspirin, 81 mg/d orally

Laboratory Results

Sodium, 140 mEq/L
Potassium, 4.0 mmol/L
Hemoglobin, 10.5 g/dL
Creatinine, 2.0 mg/dL

Question

Which <u>one</u> of the following is <u>most likely</u> associated with the changes in her extremities?

a. Anti-Scl 70 antibodies
b. Darbepoetin alfa
c. Pioglitazone
d. Gadolinium contrast agent
e. Antinuclear antibody

Discussion

Nephrogenic systemic fibrosis, previously called *nephrogenic fibrosing dermopathy*, is a rare debilitating, fibrosing disorder predominantly involving the skin in patients with renal failure, especially those receiving long-term hemodialysis. Fibrosis extension to muscle, heart, and lung characterizes the systemic involvement. A link to gadolinium contrast agents used to enhance magnetic resonance imaging led to a manufacturer's warning to minimize exposure in patients with an estimated glomerular filtration rate of less than 30 mL/min per 1.73 m^2 in 2006. Gadolinium, a nonionic hyperosmolar contrast agent, is excreted renally and is thought to be the reason for the increased disease prevalence in patients with impaired renal function. This patient has stage 5 chronic kidney disease and likely underwent magnetic resonance imaging studies with gadolinium during her stroke and/or osteomyelitis evaluations. Various therapeutic approaches for nephrogenic systemic fibrosis have been attempted with minimal success, including cyclophosphamide, hydroxychloroquine, sodium thiosulfate, ultraviolet A1 phototherapy, extracorporeal photopheresis, and renal transplant.[3] Results of therapeutic agents have been difficult to reproduce, leaving minimal to no treatment options to date. Renal transplant or reinstitution of renal clearance is thought to be the best treatment option, and therefore a nephrology referral would be reasonable.[4] Erythrocyte-stimulating agents (eg, darbepoetin and erythropoietin) were suspected to be implicated in the disease before gadolinium but are no longer thought to be the dominant pathogenic factor. Although pioglitazone may cause peripheral edema, it would not produce the distinctive hardening of the skin seen in this disorder. Antinuclear antibodies and Scl-70 antibodies may be detected in various forms of systemic sclerosis but are generally not detected in nephrogenic systemic fibrosis.

Clinical Pearl

Patients with acute renal failure or those with chronic kidney disease who have a glomerular filtration rate of less than 30 mL/min and receive gadolinium are at increased risk of nephrogenic systemic fibrosis.

CASE 3

A 35-year-old woman diagnosed as having chronic fatigue syndrome 1 year previously presents with spells of light-headedness and palpitations during the day. Symptoms are most notable with changing from a seated or supine position to standing. She has no other symptoms but recalls that she had an upper respiratory tract infection a few weeks previously, which she treated with over-the-counter agents. She has an office-based blood pressure of 124/85 mm Hg (lying), 120/80 mm Hg (sitting), and 114/78 mm Hg (standing) and an office-based heart rate

of 90 beats/min (lying), 102 beats/min (sitting), and 120 beats/min (standing). Her urine sodium excretion rate is 140 mmol/24 h.

Additional studies confirm your diagnosis and have excluded the neuropathic variant; however, the patient continues to have symptoms despite initial recommendations.

Question

Which *one* of the following would be the *most appropriate* next step in the management of this patient?

a. Order an assessment of plasma renin activity (supine and standing positions, 15 minutes each)
b. Advise that the patient wear knee-high compression stockings
c. Initiate midodrine therapy
d. Counsel the patient to maintain a supine position for most of the day with minimal exertion
e. Place the patient on a high-sodium diet and order 24-hour urine collection for sodium measurement

Discussion

This patient has postural tachycardia syndrome (POTS), defined as the development of orthostatic symptoms associated with a heart rate increase greater than or equal to 30 beats/min, usually to greater than or equal to 120 beats/min without orthostatic hypotension and within 10 minutes of upright tilt. It is thought to be the earliest and most consistent measurable finding of orthostatic hypotension. Although its exact prevalence is unknown, it is thought to be 5 to 10 times as common as orthostatic hypotension. In one study, as many as 40% of patients with chronic fatigue syndrome had evidence of orthostatic intolerance, about half of which had POTS.[5] Many had a preceding viral illness. The evaluation consists of measurements with an upright tilt test, assessment of adrenergic response with standing via measurement of plasma catecholamine levels, 24-hour urine sodium excretion, and electrocardiography.[6] Other studies may include autonomic reflex screening, thermoregulatory sweat testing, echocardiography, and use of the Holter monitor. Systematic approaches are recommended on the basis of the type of POTS, classified according to the underlying mechanism: neuropathic, hyperadrenergic, or deconditioning. All patients are advised on adequate volume expansion with a high-salt diet and increased fluid intake. Repeating a 24-hour urine sodium study would be reasonable to determine whether the patient is adherent to simple dietary measures before prescribing medication. A target urine volume of 1.5 to 2.5 L/d and sodium excretion of 170 mmol/24 h are generally recommended. Patients are also educated on physical maneuvers to increase venous return, prescribed graduated compression stockings (to the thigh or waist level), and informed of water bolus therapy. Agents such as fludrocortisone, midodrine (neuropathic POTS), propranolol, or clonidine (hyperadrenergic POTS) may be beneficial depending on the type of POTS. Exercise training programs are recommended in the deconditioned POTS group, whereas recommendations for more bed rest would simply lead to further exacerbation of the syndrome. Testing of plasma catecholamine levels is generally indicated; however, plasma renin activity has no role in the diagnosis of POTS.

Clinical Pearl

POTS is a common disorder of orthostatic intolerance with a high prevalence in patients with chronic fatigue syndrome. Initial management is directed at a high-sodium diet and adequate volume intake.

CASE 4

A 55-year-old woman presents with sinus congestion and a sore throat of 3 days' duration. She has been taking an oral decongestant with some symptomatic relief. She continues to smoke. Her body mass index is 30 (calculated as the weight in kilograms divided by the height in meters squared), and her blood pressure is elevated at 170/90 mm Hg. She is counseled by your nursing staff, and her oral decongestant is discontinued. She returns to the office 5 weeks later for a blood pressure check, at which time her body mass index is 29, her blood pressure is 165/80 mm Hg, and her pulse is 84 beats/min and regular. Findings on examination are otherwise unremarkable. The patient's serum electrolyte levels are normal, with a creatinine level of 0.8 mg/dL.

Question

Which *one* of the following is the *best* recommendation for treating the patient's blood pressure at this time?

a. Prescribe 10 mg/d of amlodipine
b. Counsel the patient to reduce sodium intake and exercise daily for 30 minutes
c. Prescribe 12.5 mg/d of hydrochlorothiazide and 10 mg/d of lisinopril
d. Counsel cessation of tobacco use and a 4.5-kg (10-lb) weight loss
e. Prescribe 25 mg/d of chlorthalidone

Discussion

This patient has essential hypertension. General recommendations include lifestyle modification as the first line of therapy. She received counseling on lifestyle measures, and her body mass index improved to 29 at her follow-up visit. Weight loss of 10 kg and dietary sodium restriction (2.4 g/d) may lead to blood pressure reductions of 2 to 20 mm Hg depending on the amount of weight loss and adherence to diets. It is unlikely

that the patient will reach a target blood pressure of less than 140/80 mm Hg with either of these lifestyle measures alone, and amlodipine monotherapy may not lead to target achievement. A recent epidemiological study revealed that 74% of patients surveyed were aware of hypertension, but only 65% were being treated and only 41% of those treated had optimal blood pressure control.[7] This patient has stage 2 hypertension, which should have been reevaluated in 1 month. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure panel recommended initiation of antihypertensive therapy in the form of a 2-drug regimen for optimal control in patients with stage 2 hypertension.[8]

Clinical Pearl

Limited time should be allowed for lifestyle measures in patients with stage 2 hypertension, and most patients will require a 2-drug regimen for initial therapy.

CASE 5

A 55-year-old man with hypertension and nephrolithiasis is admitted to a rehabilitation unit for persistent lower extremity weakness from a thoracic spinal cord injury related to a fall. His blood pressure is 160/80 mm Hg, and his heart rate is 94 beats/min. Findings on electrocardiography are unremarkable.

Laboratory Results

- Potassium
  - Hospital day 1, 4.2 mmol/L
  - Hospital day 33, 5.8 mmol/L
- Creatinine, 0.9 mg/dL
- Sodium, 140 mEq/L
- Arterial blood gas on room air
  - Po_2, 65 mm Hg
  - Pco_2, 40 mm Hg
  - Bicarbonate, 24 mEq/L (to convert to mmol/L, multiply by 1)
  - pH, 7.40

Current Medications

- Amlodipine, 5 mg/d
- Ibuprofen, 200 mg as needed (last dose 3 days previously)
- Heparin, 5000 U subcutaneously twice daily

Question

Which *one* of the following would be the *best* approach to managing this patient's potassium level?

a. Prescribe fludrocortisone
b. Change to low-molecular-weight heparin
c. Discontinue ibuprofen
d. Discontinue heparin if possible; use loop diuretic and sodium polystyrene sulfonate therapy as needed
e. Low-dose sodium bicarbonate infusion (10-20 mEq/h)

Discussion

This patient developed heparin-induced hyperkalemia. Whether administered in small doses subcutaneously or intravenously, heparin has been found to decrease plasma aldosterone concentrations, leading to increases in measured serum potassium levels. The mechanism is thought to be attributable to direct inhibition of the adrenal gland's zona glomerulosa, with selective reduction in aldosterone production.[9] Substantial potassium elevations are appreciated in patients concomitantly treated with other drugs or clinical states that limit potassium excretion, such as angiotensin-converting enzyme inhibitors, potassium-sparing diuretics, advanced diabetes (hyporenin hypoaldosteronism), and renal insufficiency. Other offending agents commonly encountered in practice include nonsteroidal anti-inflammatory drugs, β-blockers, cyclosporine, tacrolimus, and trimethoprim-sulfamethoxazole. Hyperkalemia has also been associated with low-molecular-weight heparin use, making this change in therapy less optimal.[10] Fludrocortisone is beneficial in patients with volume-contracted states; however, blood pressure control is likely to worsen in this patient. Some patients benefit from volume expansion and normalization of serum pH. A loop diuretic and oral sodium polystyrene sulfonate therapy as needed may ameliorate potassium levels and improve blood pressure control. However, it should be noted that cases of intestinal necrosis[11] have been associated with this therapy, especially in the postoperative state or in other conditions of decreased intestinal motility.

Although ibuprofen is a known cause of hyperkalemia, the low dose and remote history of use in this patient make it a less plausible etiology. Sodium bicarbonate may be more appropriate in acidemic states; however, this patient's pH is normal. Additionally, sodium bicarbonate could worsen his hypertension.

Clinical Pearl

Consider heparin as a source for unexplained hyperkalemia in hospitalized patients.

CASE 6

A 60-year-old woman presents with maculopapular rash, fever, and fatigue and reports decreased urine output. Laboratory tests reveal a serum creatinine level of 3.5 mg/dL (baseline, 1.0 mg/dL). She has peripheral eosinophilia, and urine eosinophils are detected. Her history is notable for

recent antibiotic exposure beginning 2 weeks previously for refractory sinusitis.

Question

Which *one* of the following is the *next* best step in the management of this patient?

a. Discontinue antibiotic treatment and recheck creatinine level in 3 days
b. Check fractional excretion of sodium
c. Perform a skin biopsy of the rash
d. Initiate prednisone therapy
e. Initiate anti–immunoglobulin E therapy (omalizumab)

Discussion

Like the previous case, this patient has acute interstitial nephritis (AIN) with the classic rash, fever, and eosinophilia features. Interstitial nephritis may be attributed to processes including sarcoidosis, lupus nephritis, tubulointerstitial nephritis, and uveitis syndrome, as well as other autoimmune disorders. Medication-related AIN remains the most common of all interstitial nephritides, having an estimated prevalence of approximately 70%. Classically, methicillin and other β-lactam antibiotics were the offending agents. In this case, an antibiotic was again the source, and findings on biopsy were consistent with AIN; however, many patients with acute renal failure never undergo biopsy. Treatment of AIN with corticosteroids had been somewhat controversial[12] until the recent publication of a multicenter retrospective review of treatment outcomes in 61 patients with biopsy-proven AIN.[13] The responsible drugs were antibiotics in 56% of patients, nonsteroidal anti-inflammatory drugs in 37%, and other drugs in 7%. The level of serum creatinine was not only higher in the untreated group, but half were still receiving long-term dialysis when followed up 6 to 60 months later. It was also suggested that delays in treatment (average of 34 days after the withdrawal of the offending agent) limited the improvement in renal function, returning it to baseline levels. Early withdrawal of the offending agent is essential. In this case, initiation of prednisone, which could be provided at a dose of 40 to 60 mg/d for a few weeks followed by a slow taper during the next 2 to 3 months, may lead to better renal outcomes. Infectious prophylaxis should also be instituted at the time of higher corticosteroid use.

Because the diagnosis is fairly secure on clinical grounds in this case, the other testing options would be unnecessary. Anti–immunoglobulin E therapy has not been tested in this disease.

Clinical Pearl

To enhance the recovery of renal function in patients with drug-induced AIN, prompt initiation of corticosteroid treatment and withdrawal of the offending agent are suggested.

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Correct answers: Case 1: *b*, Case 2: *d*, Case 3: *e*, Case 4: *c*, Case 5: *d*, Case 6: *d*