CME

Cardiorenal syndrome: Understanding the connections between cardiac and renal disease

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ABSTRACT

Renal and cardiac diseases are nearly ubiquitous in hospitalized patients and common causes of morbidity in outpatients. Although the connection between the heart and kidneys is relatively well known in the medical community, a more formal classification for the clinical interplay of the two systems has been developed only recently. Cardiorenal syndrome was described by Italian nephrologist Claudio Ronco in 2008. This classification allows for justification of management strategies in these complex patients and will guide further research studies.

Keywords: cardiorenal syndrome, cardiac disease, renal disease, acute kidney injury, chronic kidney disease, erythropoietin

Learning objectives

- Recognize the five types of cardiorenal syndrome.
- Describe the pathophysiologic connections between the cardiac and renal systems that lead to a diagnosis of cardiorenal syndrome.
- Identify optimal treatment and prevention strategies for patients with concurrent cardiac and renal disease.

Renal and cardiac diseases are nearly ubiquitous in hospitalized patients and are common causes of morbidity in outpatients. Although the connection between the heart and kidneys is relatively well known in the medical community, a more formal classification for the clinical interplay of the two systems has been developed only recently. Cardiorenal syndrome was described by Italian nephrologist Claudio Ronco in 2008.[1] This classification allows for justification of management strategies for these complex patients and will guide further research studies.

The classification of comorbid cardiac and renal diseases into cardiorenal syndrome was developed to better understand the pathophysiologic connections between the two organ systems and to promote the codiagnosis and treatment of cardiac and renal dysfunction. Cardiorenal syndrome is divided into five subtypes to distinguish the primary organ of dysfunction as well as the acute or chronic nature of the disease (**Table 1**).

An estimated 82.6 million Americans suffer from at least one form of cardiovascular disease.[2] One-third of patients admitted with heart failure also have acute kidney injury (AKI). Even a modest increase in serum creatinine is correlated with increased morbidity.[3] Chronic kidney disease (CKD) is found in more than 40% of patients with cardiovascular disease.[4] Cardiac and renal diseases are highly prevalent, and dysfunction in one organ system often complicates the other (**Figure 1**).

PATHOPHYSIOLOGY

The pathophysiology of cardiorenal syndrome is complex because of the bidirectional communication that exists between the cardiac and renal systems. Heart failure, whether resulting from systolic or diastolic dysfunction or both, is associated with renal dysfunction. Renal hypoperfusion resulting from systolic dysfunction leads to activation of the renin-angiotensin-aldosterone system (RAAS). In turn, activating the RAAS increases BP through increased blood volume and vasoconstriction. The RAAS activates the sympathetic nervous system, contributing to venous congestion and further vasoconstriction as well as causing hypertrophy, apoptosis, and fibrosis of cardiomyocytes and renal tubular cells.[5] Increased central venous pressure, associated with diastolic dysfunction, leads to renal vascular congestion. Renal perfusion pressure can be calculated by subtracting central venous pressure from mean arterial pressure. Therefore, as central venous pressure rises, renal perfusion pressure declines, further worsening kidney function.

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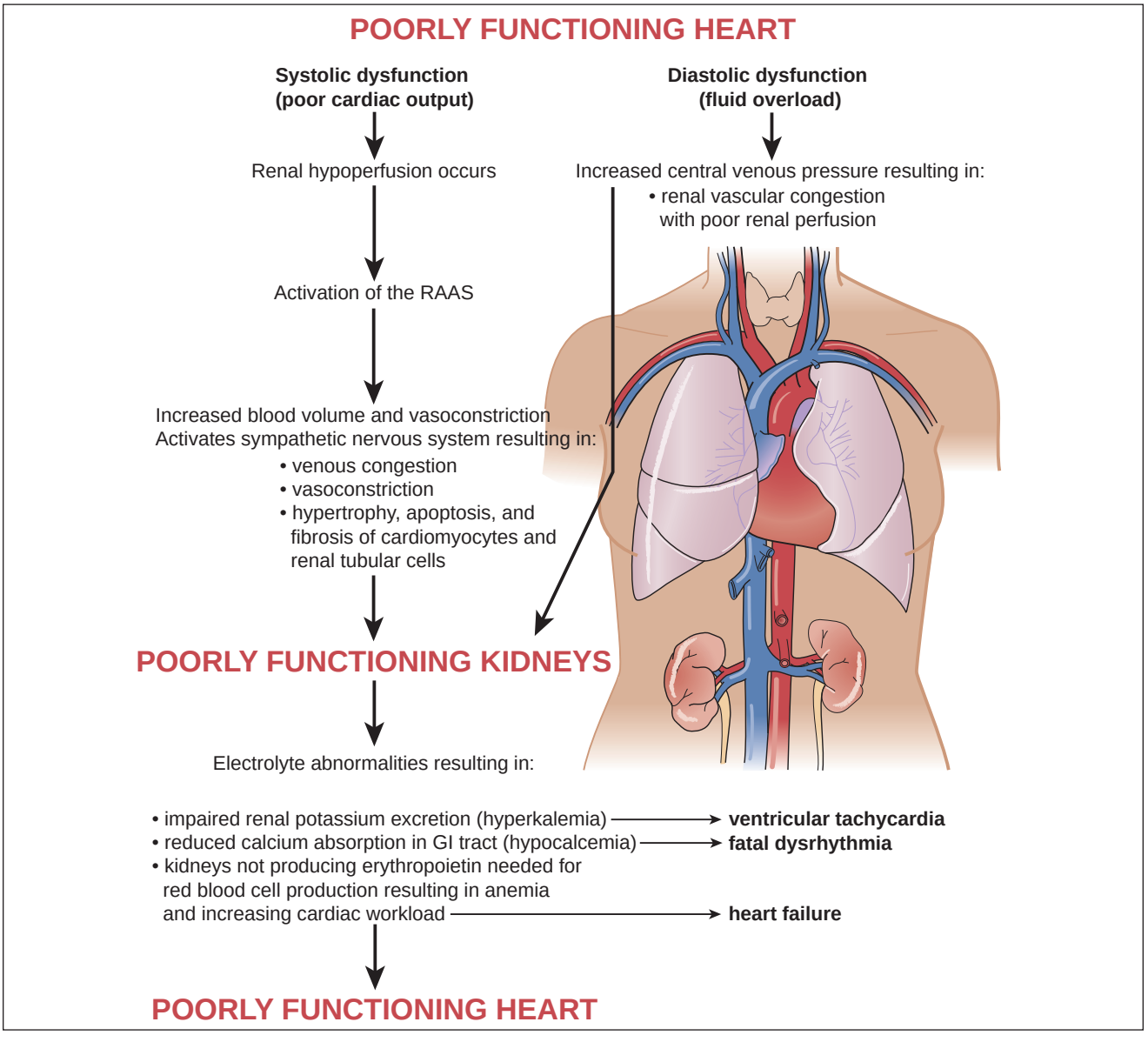
DOI: 10.1097/01.JAA.0000442697.65104.e2

Electrolyte abnormalities—particularly potassium and calcium abnormalities—become more prevalent as kidney function declines, increasing the risk of cardiac dysrhythmias. Hyperkalemia from impaired renal potassium excretion may manifest on ECG as peaked T waves, PR prolongation, and QRS widening. This can progress into torsades de pointes and quickly deteriorate into ventricular tachycardia. Hypocalcemia results from the decreased conversion of vitamin D to calcitriol, its biologically active form, by failing kidneys. Lower levels of calcitriol result in reduced calcium absorption.[6] Alterations in calcium levels can cause cardiac conduction abnormalities, including QT prolongation and even fatal dysrhythmias.

Inflammatory cytokines released during ischemic events cause cell damage and apoptosis, which are both linked to acute and chronic disease processes. Anemia is also implicated in cardiorenal syndrome pathophysiology. Erythropoietin, necessary for red blood cell production, originates in the kidneys and may be deficient in patients with renal disease. The resultant anemia increases cardiac workload and can lead to heart failure.

RISK FACTORS AND CLINICAL MANIFESTATIONS

Common modifiable risk factors for cardiac disease include hypertension, diabetes, dyslipidemia, cigarette smoking, and obesity. As expected, these are also risk factors for renal disease. Additional overlapping risk factors include advanced age and previous episodes of acute coronary syndrome.[1] Clinical manifestations of cardiac and kidney diseases are summarized in **Table 2**.



JENNIFER SMITH, MEDICAL ILLUSTRATOR

FIGURE 1

DIAGNOSTIC TESTING

Because kidney disease may be asymptomatic or manifest with vague symptoms, an astute assessment of patients at risk of developing kidney dysfunction includes laboratory tests such as serum creatinine and microscopic urinalysis in addition to clinical observation with urinary output measurements. Further assessment of patients with active kidney disease may include renal ultrasound to evaluate for perfusion problems, cystic disease, or other conditions.

Estimated glomerular filtration rate (eGFR) provides an approximation of the filtering capacity of the nephrons and is used to monitor the progression of CKD. Clinically, a commonly used formula to calculate eGFR is the modification of diet in renal disease (MDRD) formula, which uses serum creatinine, sex, race, and age. Obtaining a baseline eGFR allows for monitoring of kidney function as it fluctuates with the disease process. The eGFR in patients with CKD will be decreased but should remain stable if properly managed. The eGFR is also used to stage CKD. The staging system for CKD assigns patients into five categories based on eGFR: these stages range from slightly diminished function (stage 1) to end-stage renal disease (stage 5).

Although monitoring eGFR trends is useful for CKD, AKI is monitored through changes in serum creatinine. AKI is staged using the risk, injury, failure, loss, end-stage renal disease (RIFLE) criteria, which define the degree of kidney injury by serum creatinine increase, eGFR decrease, or urine output.[7]

Key points

- Cardiorenal syndrome is an acute or chronic dysfunction of the heart or kidneys that leads to acute or chronic dysfunction in the other organ system. The syndrome can be subdivided into five types.
- Common risk factors include advanced age, hypertension, diabetes, atherosclerotic disease, cigarette smoking, and obesity.
- The pathophysiology of cardiorenal syndrome is multifactorial and involves the bidirectional effects of poor cardiac output, renal hypoperfusion, renal vascular congestion, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, electrolyte abnormalities, erythropoietin, and elevation in inflammatory mediators.
- Patients may present with acute or chronic cardiac or renal dysfunction.
- Treatment begins with prevention of modifiable risk factors and anticipatory management strategies to protect both the cardiac and renal systems. Proper treatment is a balancing act involving concurrent management of cardiac and renal disease.

Microscopic urinalysis provides clues about the cause of kidney damage. Waxy casts are found in the urine of patients with long-standing CKD. Excessive proteinuria (more than 3.5 g/day) indicates glomerular disease; red cell casts are seen with acute or chronic glomerulonephritis. Microalbuminuria is another early indicator of kidney damage and is commonly used to monitor the risk of developing kidney disease.[8]

Two methods for assessing kidney function include serum creatinine and creatinine clearance. Serum creatinine is easy to obtain and is a component of a basic metabolic panel. Creatinine clearance is determined by analyzing a 24-hour urine collection. Both have shortcomings that may overestimate or underestimate kidney function and often fail to show changes before irreversible kidney damage has occurred. New biomarkers of kidney disease are on the horizon, including neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C. NGAL is produced by epithe-

TABLE 1. The five types of cardiorenal syndrome[1]

Type	Definition	Example of inciting condition
1	Acute cardiac decompensation is complicated by AKI	• Acute decompensated heart failure • Cardiac surgery or procedures • Cardiogenic shock • Hypertensive pulmonary edema • Myocardial infarction
2	Chronic cardiac dysfunction leads to CKD	• Diastolic heart failure • Systolic heart failure
3	AKI causes acute cardiac dysfunction	• Acute tubular necrosis • Glomerulonephritis • Outflow obstruction • Renal artery embolism
4	CKD causes chronic cardiac disease	• Diabetic nephropathy • Focal segmental glomerulosclerosis • Polycystic kidney disease
5	Cardiac and renal diseases develop in the presence of a systemic disorder	• Drug toxicity • Multiple myeloma • Sarcoidosis • Sepsis • Sickle cell disease • Systemic lupus erythematosus

TABLE 2. Components of cardiorenal syndrome[27-30]

Acute cardiac dysfunction (types 1, 3)

Acute heart failure
- Chest discomfort
- S_3 or S_4 heart sounds
- New or changed murmur
- Tachycardia
- Hypertension
- Elevated jugular venous pressure
- Cough
- Fatigue
- Tachypnea
- Rapidly worsening dyspnea
- Pulmonary edema (with crackles)

Acute MI
- Physical findings vary tremendously depending on the location and severity of the infarct
- Chest discomfort—pressure, dullness, aching, squeezing
- Pain radiating to left arm or neck
- New or changed murmur
- Palpitations
- Diaphoresis
- Dyspnea
- Pallor
- Agitation or restlessness
- Nausea
- Sense of impending doom

Dysrhythmia
- Irregular heart rate
- Palpitations
- Syncope
- Presyncope
- Dizziness
- Fatigue
- Patient may be asymptomatic

Chronic cardiac dysfunction (types 2, 4)

Chronic heart failure
- Shortness of breath--exertional progressing to dyspnea at rest
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Chronic nonproductive cough
- Fatigue
- Fluid retention, edema
- Cardiac enlargement, crackles, gallop rhythm, and pulmonary venous congestion in left ventricular dysfunction
- Elevated venous pressure, hepatomegaly, and dependent edema in right ventricular dysfunction

AKI (types 1, 3)

Prerenal AKI
- Tachycardia
- Orthostatic BP changes
- Dry mucous membranes
- Decreased skin turgor
- Thirst
- Orthostatic light-headedness
- Decreasing urine output

Intrinsic AKI
- Maculopapular rash
- Costovertebral angle tenderness
- Hematuria
- Hypertension
- Edema
- Flank pain
- Darkening of urine
- Edema
- Fever
- Malaise

Postrenal AKI
- Bladder distension
- Prostatic hypertrophy
- Costovertebral angle tenderness
- Hematuria
- Anuria or alternating oliguria and polyuria
- Flank or suprapubic pain

CKD (types 2, 4)
- Cardiomegaly
- Jugular venous distension
- Pericardial friction rub
- Hypertension
- Crackles
- Sallow appearance
- Easy bruising
- Edema
- Mental status changes
- Myoclonus and asterixis
- Fatigue
- Weakness
- Malaise
- Anorexia
- Nausea, vomiting
- Menstrual irregularities
- Restless legs
- Paresthesias
- Irritability
- Difficulty concentrating

Systemic infection (type 5)
- Hyperthermia
- Hypothermia
- Fever, chills
- Tachycardia
- Wide pulse pressure
- Tachypnea
- Rash
- Mental status changes
- Confusion
- Dizziness

lial cells and neutrophils in various tissues and is involved in ischemic renal injury. Cystatin C is a cysteine proteinase inhibitor that originates from nucleated cells and is produced at a constant rate that has not been found to vary as creatinine does with factors such as race, sex, age, and muscle mass. Fully functioning renal tubules prevent the excretion of cystatin C in the urine. Several trials have shown promise using both NGAL and cystatin C levels as early, sensitive, and specific markers of AKI.[9]

Electrolyte abnormalities can indicate declining kidney function. Elevated potassium and decreased calcium levels predispose patients to developing dysrhythmias. Because sudden cardiac death is a common cause of mortality in patients with cardiorenal syndrome, adequate assessment

of cardiac function in these patients is paramount. Electrocardiography provides a noninvasive measure of cardiac function that lets clinicians monitor for dysrhythmias, ischemic changes such as T-wave inversion and ST-segment depression, or ST-segment elevation caused by infarction. Obtaining cardiac troponin levels further assists providers in determining myocardial injury, inflammation, or infection. However, clinicians must remember that cardiac troponin levels may be elevated in patients with CKD who have no other signs or symptoms of a cardiac insult.[10] In addition to acute changes, ECG may provide nonspecific evidence of heart failure such as low-voltage QRS complexes, left ventricular hypertrophy, or axis deviation.

Echocardiography allows for a more quantitative assessment of cardiac function with estimation of ejection fraction. If a patient has clinical evidence of heart failure on physical examination, B-type natriuretic peptide (BNP) can be used to verify clinical suspicion. Elevated levels of BNP have a high sensitivity for heart failure. BNP has a low specificity, however, and is often elevated in patients with kidney disease.[11] Evidence of heart failure may be seen on a chest radiograph with cardiomegaly, Kerley B lines, and alveolar fluid.

TREATMENT

Screening at-risk patients for modifiable risk factors and managing patients before heart or kidney disease develop are keys to controlling cardiorenal syndrome. Preventive therapy for cardiac and renal disease includes weight control, diet modification, and smoking cessation accompanied by medical management of hypertension, dyslipidemia, and diabetes.[12] Dietary modifications for patients with cardiac or renal disease should include limiting alcohol, sodium, and fluid intake. Patients with renal disease also should have modest restrictions in dietary protein, potassium, phosphorus, and magnesium that do not lead to malnutrition.[13]

Classes of medications known to reduce morbidity and/or mortality in heart failure are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), beta-blockers, and aldosterone receptor antagonists. ACE inhibitors and ARBs are potent inhibitors of the RAAS, leading to afterload reduction and decreased cardiac workload. Although several clinical trials have demonstrated the renoprotective effects of ACE inhibitors and ARBs, providers are often wary of prescribing them because they are associated with worsening GFR and hyperkalemia, as outlined by the National Kidney Foundation's guidelines on the use of these drugs in patients with CKD.[14] Additionally, beta-blockers modulate the activity of the sympathetic nervous system and are known to increase survival in patients with heart failure. Regulation of aldosterone through the use of aldosterone receptor antagonists, such as spironolactone and eplerenone, reduces mortality in some patients with heart failure. In addition to improving survival, ACE inhibitors, ARBs, and aldosterone receptor antagonists can decrease proteinuria and potentially slow the progression of CKD.[15]

Some of the medications used to treat cardiovascular disease are associated with nephrotoxicity, especially when dosages are not properly adjusted for kidney function. Care must be taken to minimize renal insult without neglecting cardiac health. Many imaging procedures, including those in interventional cardiology, come with the risk of contrast-induced nephropathy, which is associated with an increase in inpatient mortality.[16] Simple measures such as monitoring the dose of radiocontrast medium may reduce the incidence of this complication.

Hemodialysis is associated with an increased risk of sudden cardiac death.[17] As an alternative, consider peritoneal dialysis, which is associated with a 48% lower risk of cardiac death over the first 2 years of treatment.[18]

Optimizing fluid balance is another challenge in treating patients with cardiac and renal dysfunction. Any variation from homeostasis puts stress on the heart and kidneys. No matter the type of cardiorenal syndrome, maintaining fluid balance is part of the treatment.[3,12,19-21] This usually involves treating fluid overload with diuretics, which should be titrated according to renal function and systolic BP.[1,22] Evaluate the patient's history of diuretic use to determine proper dosing, because chronic therapy with these agents contributes to resistance.[23] Diuretic resistance is defined as persistently elevated extracellular fluid volume despite near maximal doses of loop diuretics.[22]

When optimal fluid volume cannot be maintained by loop diuretic therapy alone, combinations of loop, thiazide, and potassium-sparing diuretic may overcome diuretic resistance.[24,25] If proper dosing and combination therapy fails to induce adequate diuresis, volume removal can be achieved through ultrafiltration, a mechanical process that removes plasma water across a semipermeable membrane without adjusting osmolality of the blood.[19] This process produces greater fluid and weight loss than IV diuretics and reduces the number of rehospitalizations for patients with heart failure.[26]

As previously discussed, a common barrier to treatment of cardiorenal syndrome is proper management of medications to effectively treat cardiac dysfunction without adversely affecting renal function. Diuretics and ACE inhibitors are known to cause alterations in renal perfusion that result in transient changes in renal function. Kidney disease complicates the use of many commonly used medications. For example, in patients with renal disease, metformin may cause lactic acidosis and statins can lead to rhabdomyolysis. As a result, patients with CKD are less likely than members of the general population to receive appropriate cardiovascular risk modification treatment.[1] Additionally, many large-scale controlled trials for heart disease medications exclude patients with

advanced renal disease. Therefore, data for appropriate dosing of mortality-reducing medications are lacking. This is not an excuse for the "therapeutic nihilism" that plagues cardiorenal syndrome.[3] With close monitoring of renal function, treatment of cardiovascular disease can reduce patient mortality despite the relative risk of advancing renal disease.

CONCLUSION

The combination of cardiovascular and renal disease is responsible for increased patient morbidity, mortality, and healthcare expenditures.[3] Cardiorenal syndrome classification streamlines understanding of interactions between the heart and kidneys and facilitates prevention, early diagnosis, and management of these acute and chronic disease states in at-risk populations. Future pharmacologic trials for cardiovascular diseases must include patients with all stages of renal disease, as these conditions often occur together. Management strategies for both renal and cardiac diseases need to be reassessed in order to optimize efficacy without compromising the function of either organ. **JAAPA**

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REFERENCES

1. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527-1539.
2. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation*. 2011;123(4):e18-e209.
3. Ismail Y, Kasmikha Z, Green HL, McCullough PA. Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment. *Semin Nephrol*. 2012;32(1):18-25.
4. US Renal Data System. *USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013. http://www.usrds.org/atlas.aspx. Accessed November 8, 2013.
5. Ronco C, Kaushik M, Valle R, et al. Diagnosis and management of fluid overload in heart failure and cardio-renal syndrome: the "5B" approach. *Semin Nephrol*. 2012;32(1):129-141.
6. Brunette MG, Chan M, Ferriere C, Roberts KD. Site of 1,25 (OH)2 vitamin D3 synthesis in the kidney. *Nature*. 1978;276 (5685):287-289.
7. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212.
8. Schaffer AC. Urinalysis and urine electrolytes. In: Lawry GV, McKean SC, Matloff J, Ross JJ, Dressler DD, Brotman DJ, Ginsberg JS, eds. *Principles and Practice of Hospital Medicine*. New York: McGraw-Hill; 2012.
9. Cruz DN, Fard A, Clementi A, et al. Role of biomarkers in the diagnosis and management of cardio-renal syndromes. *Semin Nephrol*. 2012;32(1):79-92.
10. Freda BJ, Tang WH, Van Lente F, et al. Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol*. 2002;40(12):2065-2071.
11. Kreder KJ, Williams RD. Urologic laboratory examination. In: Tanagho EA, McAninch JW, eds. *Smith's General Urology*. 17th ed. New York: McGraw-Hill; 2008.
12. House AA. Cardio-renal syndrome type 4: epidemiology, pathophysiology and treatment. *Semin Nephrol*. 2012;32(1):40-48.
13. Saxena A. Nutritional problems in adult patients with chronic kidney disease. *Clin Queries Nephrol*. 2012;1(3):222-235.
14. National Kidney Foundation. Clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. http://www.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm#table124. Accessed August 25, 2013.
15. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. *Kidney Int*. 2006;70(12):2116-2123.
16. Marenzi G, Assanelli E, Campodonico J, et al. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med*. 2009;150(3):170-177.
17. Shastri S, Sarnak MJ. Cardiovascular disease and CKD: core curriculum 2010. *Am J Kidney Dis*. 2010;56(2):399-417.
18. Lukowsky LR, Mehrotra R, Kheifets K, et al. Comparing mortality of peritoneal and hemodialysis patients in the first 2 years of dialysis therapy: a marginal structural model analysis. *Clin J Am Soc Nephrol*. 2013;8(4):619-628.
19. Jois P, Mebazaa A. Cardio-renal syndrome type 2: epidemiology, pathophysiology, and treatment. *Semin Nephrol*. 2012;32(1):26-30.
20. Chuasuwan A, Kellum JA. Cardio-renal syndrome type 3: epidemiology, pathophysiology, and treatment. *Semin Nephrol*. 2012;32(1):31-39.
21. Soni SS, Ronco C, Pophale R, et al. Cardio-renal syndrome type 5: epidemiology, pathophysiology, and treatment. *Semin Nephrol*. 2012;32(1):49-56.
22. Ellison DH. Disorders of extracellular volume: hypovolemia and hypervolemia. In: Lerma EV, Berns JS, Nissenson AR, eds. *Diagnosis and Treatment: Nephrology and Hypertension*. New York, NY: McGraw-Hill; 2009:11-21.
23. Kshatriya S, Kozman H, Siddiqui D, et al. The cardiorenal syndrome in heart failure: an evolving paradigm. *Am J Med Sci*. 2010;340(1):33-37.
24. Kociol R, Rogers J, Shaw A. Organ cross talk in the critically ill: the heart and kidney. *Blood Purif*. 2009;27(4):311-320.
25. House AA, Haapio M, Lassus J, et al. Therapeutic strategies for heart failure in cardiorenal syndromes. *Am J Kidney Dis*. 2010;56(4):759-773.
26. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49(6):675-683.
27. Bashore TM, Granger CB, Hranitzky P, Patel MR. Heart disease. In: Papadakis MA, McPhee SJ, eds. *Current Medical Diagnosis and Treatment*. 52nd ed. New York: McGraw-Hill; 2013.
28. Watnick S, Dirkx T. Kidney disease. In: Papadakis MA, McPhee SJ, eds. *Current Medical Diagnosis and Treatment*. 52nd ed. New York: McGraw-Hill; 2013.
29. Jui J. Septic shock. In: Tintinalli JE, Stapczynski JS, Cline DM, Ma OJ, Cydulka RK, Meckler GD, eds. *Tintinalli's Emergency Medicine*. 7th ed. New York: McGraw-Hill; 2011.
30. Sinert R, Peacock PR. Acute renal failure. In: Tintinalli JE, Stapczynski JS, Cline DM, Ma OJ, Cydulka RK, Meckler GD, eds. *Tintinalli's Emergency Medicine*. 7th ed. New York: McGraw-Hill; 2011.