

Concomitant Lung and Kidney Disorders in Critically Ill Patients: Core Curriculum 2022

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The lungs and kidneys are cooperative and interdependent organs that secure the homeostasis of the body. Volume and acid–base disorders sit at the nexus between these two systems. However, lung–kidney interactions affect the management of many other conditions, especially among critically ill patients. Therefore, management of one system cannot proceed without a thorough understanding of the physiology of the other. This installment of AJKD's Core Curriculum in Nephrology discusses the complex decision-making required in treating concomitant respiratory and kidney disorders. We cover systemic diseases of the pulmonary and glomerular capillaries, acute decompensated heart failure, management of acid-base disorders in acute respiratory distress syndrome and chronic obstructive pulmonary disease, and venous thromboembolism. Through a case-based approach, we weigh the factors affecting the risks and benefits of therapies to enable the reader to individualize treatment decisions in these challenging scenarios.

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Diffuse Alveolar Hemorrhage

Diagnosis of Diffuse Alveolar Hemorrhage

Case 1: A 65-year-old woman with a history of hypertension and diabetes is admitted to the intensive care unit (ICU) for acute hypoxemic respiratory failure requiring mechanical ventilation. Vital signs show a temperature of 37.9°C, heart rate of 75 beats/min, and blood pressure of 106/68 mm Hg. Her respiratory rate (RR) is 22 with a set rate of 18 on the ventilator. Her arterial blood gas examination shows pH 7.36, arterial partial pressure of CO₂ (Paco₂) of 32 mm Hg, partial pressure of O₂ (Pao₂) of 75 mm Hg on a fraction of inspired O₂ of 0.5, and positive end-expiratory pressure (PEEP) of 10 cm H₂O. On examination, there is no saddle-nose deformity or nasal crusting. She has coarse crackles on chest auscultation bilaterally without wheezing. Suctioning through the endotracheal tube reveals pink sputum. She has no heart murmur, right ventricle (RV) heave/parasternal lift, edema, or rash. Laboratory test results are notable for a white blood cell count of 16 × 10³/μL, hemoglobin level of 8.9 (baseline, 12) g/dL, and platelet count of 230 × 10³/μL. Serum creatinine level (Scr) is 2.9 (baseline, 1.2) mg/dL, and urinalysis shows 45 red blood cells (RBCs) per high-power field and proteinuria (3+). Noncontrast computed tomography of the chest reveals patchy ground-glass infiltrates bilaterally, without effusions or cardiomegaly. Blood cultures are obtained, and antibiotic therapy is administered.

Question 1: What should be the next step in management?

- a) Transbronchial biopsy
- b) Noncontrast computed tomography of the abdomen

- c) Bronchoscopy with bronchoalveolar lavage
- d) Kidney biopsy

For the answer to the question, see the following text.

Bilateral ground-glass infiltrates (Fig 1A) and blood-tinged sputum may be present in many common conditions such as multifocal pneumonia, pulmonary edema, and acute respiratory distress syndrome (ARDS). A high index of suspicion is required to diagnose diffuse alveolar hemorrhage (DAH). In this patient, the low hemoglobin level and active urine sediment with hematuria and albuminuria should prompt consideration of this diagnosis. Confirmation of DAH requires bronchoscopy with sequential bronchoalveolar lavage. With the bronchoscope wedged in a subsegmental bronchus, 50 mL of sterile saline solution is instilled and suctioned back into 3 separate containers. The hallmark of DAH is progressively bloodier-appearing fluid with higher RBC counts with each instillation, indicating that the hemorrhage originates in the alveoli rather than the bronchi. Bronchoalveolar lavage fluid should also be sent for Gram stain and culture to assess for infection. Thus, the best answer to question 1 is (c). Choice (a), transbronchial biopsy, may help diagnose the cause of DAH, but this procedure may be nondiagnostic or contraindicated in conditions that cause DAH such as coagulopathies. Noncontrast computed tomography of the abdomen, choice (b), would be the diagnostic test of choice to assess for kidney stones, but the presence

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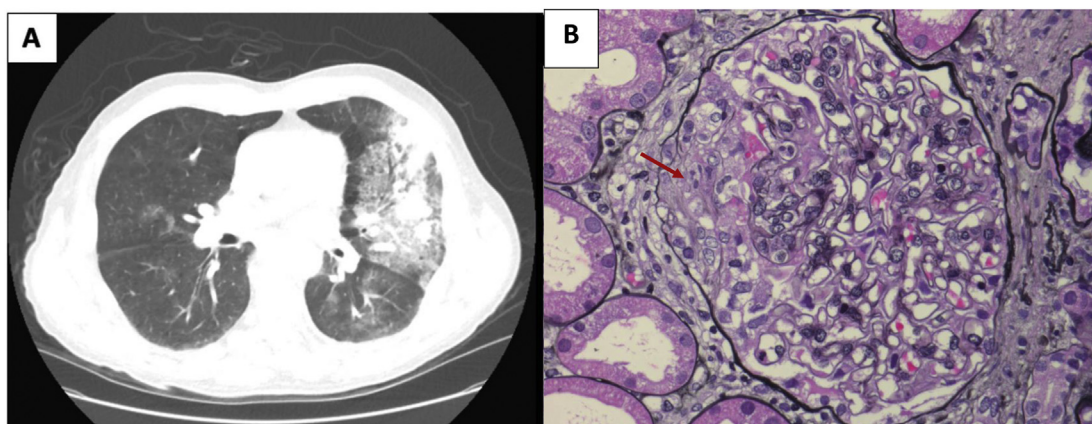


Figure 1. Diffuse alveolar hemorrhage with glomerulonephritis: (A) noncontrast chest computed tomography shows patchy ground-glass infiltrate and (B) glomerulus with crescent formation (arrow). Image B courtesy of Roberto Nicosia, MD.

of concomitant albuminuria suggests a glomerular source of hematuria. Choice (d), a kidney biopsy, may ultimately be necessary, but this invasive procedure should not be performed before other noninvasive testing.

Causes of DAH and Glomerulonephritis

The causes of DAH are myriad and include bleeding disorders, infections, pulmonary vascular disease, drugs, malignancy, connective tissue diseases, and small-vessel vasculitis. The clinical history and examination can help narrow the differential diagnosis. In this patient, the presence of significant hematuria, albuminuria, and acute kidney injury (AKI) suggests glomerulonephritis. Examination of the urine for dysmorphic RBCs and RBC casts should be part of the evaluation, but the absence of these findings does not exclude the diagnosis of glomerulonephritis. The most common cause of concomitant DAH and glomerulonephritis is antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), followed by anti-glomerular basement membrane (GBM) disease. Other causes of DAH and glomerulonephritis are outlined in [Box 1](#). Workup includes enzyme-linked immunosorbent assay

(ELISA) testing for anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO) antibodies, anti-GBM serology, antinuclear antibodies (ANAs), anti-double-stranded DNA (dsDNA) antibodies, and rheumatoid factor as a rapid test for cryoglobulinemia.

Interpretation of Laboratory Results

Question 2: Both PR3-ANCA and MPO-ANCA are often positive in which condition?

- Eosinophilic granulomatosis with polyangiitis
- Infective endocarditis
- Drug-induced vasculitis
- Anti-GBM disease

For the answer to the question, see the following text.

For the diagnosis of ANCA vasculitis, ELISAs for PR3 and MPO antibodies are the preferred tests because of the lack of standardization of ANCA immunofluorescence. The sensitivity of PR3- and MPO-ANCA ranges from 70% to 90% and correlates with disease activity. Therefore, the absence of a positive ANCA result does not completely exclude the diagnosis of GPA or MPA. The specificity of the ELISA test is approximately 95% for GPA and MPA.

The positive and negative predictive values of ANCA vary by the population studied. ANCA positivity has been associated with a variety of diseases, including endocarditis, inflammatory bowel disease, sarcoidosis, and almost all connective tissue disorders. Houben et al examined the records of 237 patients with a positive ANCA test in The Netherlands and found that only half had ANCA-associated vasculitis. However, in a selected population of patients with DAH, the positive predictive value of ANCA immunofluorescence for pulmonary capillaritis on lung biopsy approaches 100%. Further, in one small study of patients with concomitant DAH and glomerulonephritis with positive immunofluorescence results for ANCA, 19 of 19 kidney

Box 1. Causes of Diffuse Alveolar Hemorrhage With Glomerulonephritis

- ANCA vasculitis
- Anti-glomerular basement membrane antibody disease
- IgA vasculitis
- Drug-induced vasculitis (cocaine, hydralazine)
- Thrombocytopenia
- Systemic lupus erythematosus
- Infective endocarditis with septic emboli
- Cryoglobulinemia

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; Ig, immunoglobulin.

biopsies showed evidence of necrotizing and crescentic glomerulonephritis. There are few data on the negative predictive value of ANCA, but it was found to be approximately 80% in one study. The presence of both PR3- and MPO-ANCA strongly suggests a drug-induced vasculitis. Culprit drugs include levamisole, a contaminant of cocaine; and hydralazine, with which high-titer ANA positivity may also be seen. Therefore, (c) is the best answer to question 2.

Antibodies to GBM can be found in the serum of 90% of patients with anti-GBM disease. However, the sensitivity and specificity depend on the quality of the ELISA. The use of native or recombinant human antigen substrates has a specificity of 90%-100%. Anti-GBM disease may coexist with ANCA vasculitis.

Diffuse alveolar hemorrhage is a rare complication of systemic lupus erythematosus that occurs in 2%-5% of people. Both pulmonary capillaritis and bland hemorrhage have been found on lung biopsy in this condition. However, a platelet count $<50 \times 10^3/\mu\text{L}$ is uncommon, suggesting the mechanism of hemorrhage is due to vasculitis rather than ineffective clotting. ANA is almost universally positive in this condition, and hypocomplementemia and anti-dsDNA antibodies are often present. The specificity of ANA in the setting of DAH has not been well studied.

Role of Tissue Biopsy

Histopathologic patterns on lung biopsy seen in DAH include pulmonary capillaritis, bland hemorrhage, or diffuse alveolar damage. Pulmonary capillaritis is the most common finding and may be accompanied by palisading granulomas in GPA, linear immunoglobulin (Ig) G staining in anti-GBM disease, or granular IgA in IgA vasculitis. However, a finding of pulmonary capillaritis alone is nonspecific and does not aid in the differentiation among causes of DAH and glomerulonephritis, which may be treated differently. A kidney biopsy is more likely to yield a definitive diagnosis. Notably, bronchoscopy is still an important part of the workup to confirm the presence of DAH and to rule out infection before beginning immunosuppressive therapy.

In clinical practice, kidney biopsies are performed in 30%-50% of patients with glomerulonephritis and positive ANCA serology. In this population, they may serve to identify concomitant kidney disease and predict response to treatment. Better outcomes are seen posttreatment in patients with a greater proportion of glomeruli with cellular crescents rather than sclerosis (Fig 1B). In the setting of negative serologic findings, a kidney biopsy is indicated to confirm the diagnosis given the risks of immunosuppressive treatment. For example, infective endocarditis with septic emboli may present with DAH, glomerulonephritis and positive ANCA. Immunosuppressive therapy could severely exacerbate this condition. In addition, plasmapheresis is indicated in the treatment of anti-GBM disease with DAH, but it may not be of benefit in ANCA vasculitis with DAH.

In critically ill patients undergoing mechanical ventilation, kidney biopsy is often deferred because of concerns about risks, despite a paucity of data. Percutaneous ultrasound-guided kidney biopsy is associated with a higher risk of bleeding complications in critically ill patients than in patients not hospitalized in an ICU: 22% vs 7%. The decision about whether to pursue a kidney biopsy requires consideration of patient characteristics and institutional safety data.

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Heart Failure

Management of Worsening Kidney Function

Case 2: A 53-year-old man with chronic kidney disease (CKD) stage 3 and heart failure with reduced ejection fraction of 35% has been hospitalized for a heart failure exacerbation and transferred to the ICU because of a serum potassium level of 6 mEq/L and an increasing oxygen requirement. He notes that his breathing has become more labored and that he last voided approximately 8 hours earlier. He is sitting upright in bed and appears uncomfortable and dyspneic. Vital signs are notable for a heart rate of 90 beats/min, blood pressure of 126/79 mm Hg, RR of 29, and O₂ saturation on pulse oximetry of 91% on 10 L of O₂ by nasal cannula. On examination, the patient has a jugular venous pressure of 12 cm H₂O, use of accessory respiratory muscles, bilateral crackles, and peripheral lower-extremity edema (1+). Peripheral capillary refill is 2 seconds. Electrocardiography does not show signs of ischemia or changes consistent with hyperkalemia. During the previous 3 days, Scr has steadily increased from 1.7 to 2.6 mg/dL. N-terminal pro-B-type natriuretic peptide (BNP) level is 3,500 pg/mL, and troponin is undetectable. Lactate level is 1.8 mmol/L.

Urinalysis is not performed because the patient has not produced urine. As a result of his AKI, diuretic therapy was stopped 2 days earlier. Calcium, insulin, and glucose have been administered for hyperkalemia.

Question 3: What is your first step in management?

- a) Start dobutamine infusion
- b) Place a pulmonary artery catheter to guide management
- c) Urgent dialysis
- d) High-dose diuretic agents

For the answer to the question, see the following text.

This patient has a diagnosis of acute decompensated heart failure (ADHF). His worsening kidney function is most likely due to renal venous congestion as evidenced by his elevated jugular venous pressure and peripheral edema. Among patients with ADHF, central venous pressure correlates better with worsening kidney function than cardiac index. The most imminent threats to this patient are hyperkalemia and respiratory distress. He has already been treated with calcium chloride to reduce his risk of arrhythmia from hyperkalemia and with insulin/glucose to transiently shift potassium intracellularly. The next steps are to remove potassium from his body and relieve his respiratory distress. High-dose diuretic agents may succeed in treating both, and thus the best answer to question 3 is (d). A veno-vasodilator such as nitroglycerin may also be used in this acute period to decrease left ventricular filling pressures and avoid intubation.

Even though hyperkalemia is an indication for dialysis in the setting of decreased urine output, the patient has not received an adequate trial of diuretic therapy. In the CARRESS-HF trial of patients with ADHF and worsening kidney function, ultrafiltration at 200 mL/h showed no benefit over diuretic agents in

achieving a goal urine output of 3–5 L/d. The initiation of dialysis would also result in a delay in treatment due to the time required to place a catheter. Furosemide also acts as a venodilator to reduce excessive preload and enhances active alveolar fluid reabsorption, which can lead to an improvement in symptoms before diuresis ensues. Therefore, choice (c) is incorrect. Patients with ADHF have a higher plasma diuretic concentration threshold for natriuresis and a lower maximum effect or “ceiling.” The goal is to maximize time above the threshold concentration (Fig 2). Loop diuretic therapy should be initiated intravenously at 2.5 times the total oral dose. For example, a patient receiving oral furosemide 40 mg twice a day should be initiated on intravenous furosemide treatment at 100 mg twice a day. This strategy was superior in relieving dyspnea and improving weight loss compared with the initiation of intravenous diuretic agents at a dose equivalent to the oral dose in the Diuretic Optimization Strategies Evaluation trial.

Choice (a) is incorrect because the patient does not have delayed capillary refill, SBP <90 mm Hg, or an elevated lactate level to suggest that current cardiac output is insufficient to maintain adequate organ perfusion. Standard therapies have not yet failed; therefore, choice (b) is incorrect. His AKI alone is not a reason for pulmonary artery catheterization because its use in ADHF had no effect on outcomes including change in serum creatinine in the ESCAPE trial.

Diuretic Resistance

Case 2 (continued): High-dose furosemide is given, and a urine output of 80–100 mL/h is achieved. On repeat check, his potassium level has decreased to 5.3 mEq/L. Intravenous furosemide is titrated to 100 mg every 8 hours, but urine output continues to be only 100 mL/h. Blood pressures are in

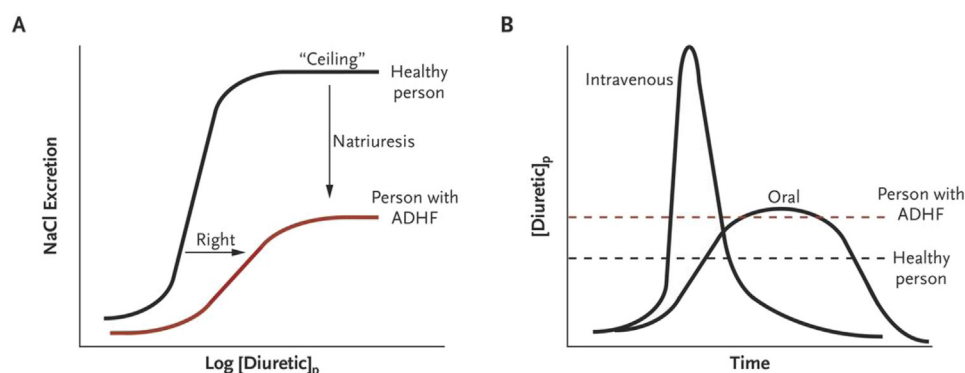


Figure 2. Loop diuretic pharmacodynamics. (A) The dose–response curve (plotted with diuretic concentration on the x axis) shifts to the right and has a lower ceiling in people with acute decompensated heart failure (ADHF). (B) Intravenous doses may achieve more time in range above the plasma threshold concentration (dashed lines). Graphic ©2017 Massachusetts Medical Society. Adapted from Ellison and Felker (*N Engl J Med*. <https://doi.org/10.1056/NEJMra1703100>) with permission of the copyright holder.

the range of 120/60 mm Hg, and he remains volume overloaded.

Question 4: Which of the following additions to his current treatment would be expected to augment urine output?

- a) Nesiritide
- b) Nitroglycerin
- c) Metolazone
- d) Dopamine

For the answer to the question, see the following text.

This patient's inadequate response to an optimized dose of loop diuretic agent can be characterized as diuretic resistance. Diuretic resistance may occur if renal venous congestion persists but is most often due to compensatory distal tubular sodium reabsorption (Fig 3). Strategies that target these distal segments improve urine output but have not been shown to reduce symptoms or mortality in large studies. In the 3T trial, patients with diuretic resistance were randomized to

adjunctive treatment with tolvaptan (a vasopressin antagonist), intravenous chlorothiazide, or metolazone. Weight loss and urine volume improved in all groups, but there was less natriuresis with tolvaptan (thus, the best answer to question 4 is [c]). Because of its cost, lack of superiority to metolazone in altering sodium excretion, and potential liver toxicity, tolvaptan is not routinely used. As noted earlier, nitroglycerin can be used in acute pulmonary edema to decrease left ventricular filling pressures and avoid the need for mechanical ventilation. However, in patients in stable condition, vasodilator therapy does not result in significant reductions in weight or N-terminal proBNP level. Dopamine and nesiritide have also been studied, and neither agent improved urine output at 72 hours when added to standard diuretic therapy in the ROSE randomized controlled trial.

There are currently insufficient data regarding the effects of aldosterone antagonists and carbonic anhydrase (CA) inhibitors in the setting of diuretic resistance in ADHF. The ATHENA study did not show a benefit with high-dose spironolactone, but patients in this study were not diuretic-resistant. Older studies show that acetazolamide was

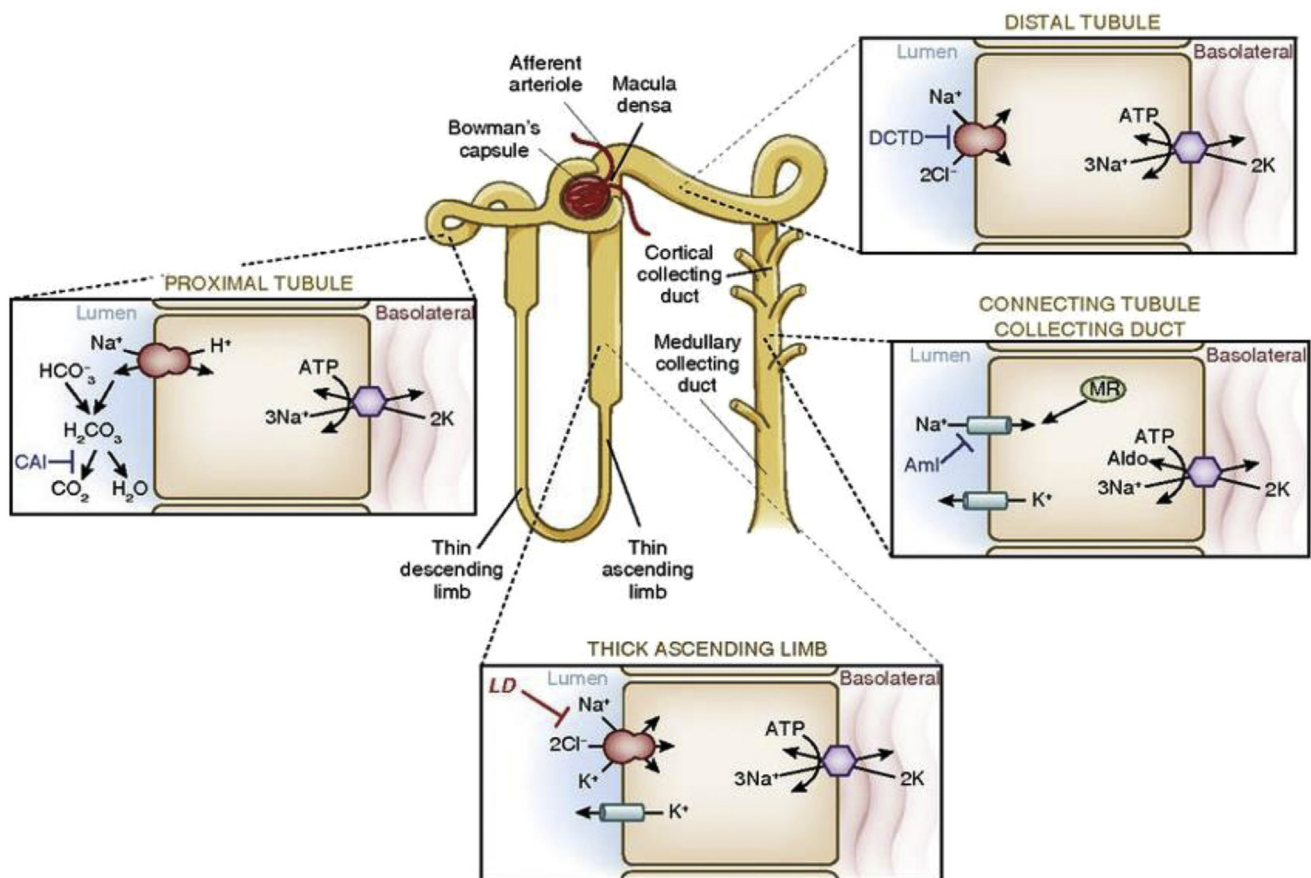


Figure 3. Sites of sodium reabsorption and diuretic action. Aml, amiloride; CAI, carbonic anhydrase inhibitor; DCTD, distal convoluted tubule diuretic (thiazide); LD, loop diuretic. Graphic ©2019 American Society of Nephrology. Reproduced from Ellison (*Clin J Am Soc Nephrol*. <https://doi.org/10.2215/cjn.09630818>) with permission of the copyright holder.

Table 1. Adjunctive Medications and Outcomes in Patients Receiving Loop Diuretic Agents for Acute Decompensated Heart Failure

Medications	Dose	Mechanism of Action	Outcomes	Representative Studies
Metolazone, chlorothiazide	5 mg orally 2×/d, 500 mg IV 2×/d	Thiazide diuretic	Increased urine output and weight loss in diuretic resistant population	3T
Tolvaptan	30 mg orally 1×/d	V2 receptor antagonist	(1) Increased urine output and weight loss in diuretic resistant population; (2) no improvement in dyspnea	(1) TACTICS-HF; (2) 3T
Dopamine	2 µg/kg/min	Renal vasodilator	No increase in urine output in patients with decreased kidney function	ROSE
Nitroglycerin infusion	0.01 µg/kg/min	Systemic venodilator	(1) Decrease in pulmonary capillary wedge pressure; (2) reduced need for mechanical ventilation in severe pulmonary edema when added to furosemide	(1) VMAC; (2) Cotter et al ^b
Transdermal and sublingual nitrates	Dose titration to target SBP 90-100 mm Hg	Systemic venodilator	No increase in weight loss	GALACTIC
Spironolactone	100 mg orally 1×/d	Mineralocorticoid receptor antagonist	No improvement in dyspnea, urine output, or NT-proBNP	ATHENA-HF

Abbreviations: 3T, Comparison of Oral or Intravenous Thiazides vs Tolvaptan in Diuretic Resistant Decompensated Heart Failure; ATHENA-HF, Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure; GALACTIC, Effect of a Strategy of Comprehensive Vasodilation vs Usual Care on Mortality and Heart Failure Rehospitalization Among Patients With Acute Heart Failure; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROSE, Renal Optimization Strategies Evaluation; SBP, systolic blood pressure; TACTICS-HF, Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure; VMAC, Vasodilation in the Management of Acute Congestive Heart Failure.

^bCotter et al, 1998 (*Lancet*. [https://doi.org/10.1016/S0140-6736\(97\)08417-1](https://doi.org/10.1016/S0140-6736(97)08417-1)).

effective in diuretic-resistant patients with a metabolic alkalosis. The ADVOR randomized controlled trial will assess the efficacy of adjunctive acetazolamide in augmenting urine output and reducing the development of a metabolic alkalosis early in the course of ADHF. Notably, the aforementioned studies (also listed in Table 1) included only patients with heart failure with reduced ejection fraction. Patients with heart failure with preserved ejection fraction may not tolerate aggressive diuresis as well.

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Acid-Base Disorders

Permissive Hypercapnia in ARDS

Case 3: A 48-year-old man with alcohol use disorder presented with fever, abdominal pain, and dyspnea several days after an episode of heavy drinking. Workup revealed bilateral lower-lobe infiltrates on a chest radiograph and increased lipase and amylase levels. His oxygenation by pulse oximetry was <80%, and he was intubated for ARDS because of pancreatitis and likely aspiration pneumonia. Arterial blood gas on a tidal volume of 6 mL/kg, RR of 30, fraction of inspired O₂ of 0.8, and PEEP of 14 cm H₂O showed a severe respiratory acidosis with inadequate renal compensation: pH 7.14, PaCO₂ of 73 mm Hg, PaO₂ pressure of 75 mm Hg, and bicarbonate level of 23.9 mM. Attempts to increase ventilation were limited by the need for lung-protective ventilation. He was in hemodynamically stable condition, alert when sedation was held, and synchronous with the

ventilator. The team considered administering sodium bicarbonate to improve his acidemia.

Question 6: What is an absolute indication for attempting correction of a respiratory acidosis?

- a) Worsening hypoxemia
- b) Increased intracranial pressure
- c) Hyperkalemia
- d) pH <7.25

For the answer to the question, see the following text.

Though low pH is associated with increased mortality, interventions that simply fix a number and dismiss the underlying pathophysiology are unlikely to improve outcomes. Acute respiratory acidosis in the absence of any serious underlying nonpulmonary disease is the least dangerous of the four primary acid-base disorders. Patients with P_{aCO_2} values as high as 500 mm Hg and pH <6.6 have survived without sequelae. Such tolerance is possible when oxygenation and perfusion are adequate to permit active intracellular pH defense via adenosine triphosphatase proton pump-mediated proton extrusion and sodium ion/proton exchange in a number of critical organs, particularly the brain and heart.

In ARDS, in which hypercapnia arises from a combination of physiologic dead space and lung-protective ventilation (tidal volume <6 mL/kg of ideal body weight and plateau airway pressure <30 cm H₂O), P_{aCO_2} in the range of 80–100 mm Hg is generally well tolerated. Although the lower tidal volumes themselves may be responsible for the better outcomes with lung-protective ventilation, considerable animal data in various lung injuries have shown that imposed respiratory acidosis decreases inflammation and improves lung compliance. Hypercapnia may also improve oxygenation by potentiating hypoxic pulmonary vasoconstriction and thereby improving ventilation/perfusion matching. Severe respiratory acidosis generally does not cause an appreciable change in serum potassium. Its effects on other organ systems include renal vasoconstriction and cerebral vasodilation. In cases of increased intracranial pressure, respiratory acidosis should be corrected to reduce cerebral blood flow and intracranial pressure. Therefore, the best answer to question 6 is (b).

Effects of Sodium Bicarbonate Administration

Question 7: What are potential effects of giving sodium bicarbonate to the patient described in case 3?

- a) Positive fluid balance
- b) Decrease in tissue oxygenation by shifting the hemoglobin-dissociation curve to the left
- c) Increase in P_{aCO_2} if given as rapid pushes
- d) All of the above

For the answer to the question, see the following text.

Treatment with sodium bicarbonate may cause hypokalemia, volume overload, reduction in ionized calcium, and impairment in oxygen offloading to the tissues by shifting

the hemoglobin oxygen dissociation curve to the left. Because of the lack of benefit and potential for harm, the authors do not administer sodium bicarbonate for a pure respiratory acidosis. However, in patients with a mixed respiratory and metabolic acidosis, it may be reasonable. For example, in patients with myocardial disease, a pH <7.2 may decrease inotropy and worsen cardiac output. Even though small randomized controlled trials have not shown an improvement in cardiac output with administration of sodium bicarbonate compared with saline solution, this therapy could be considered for individual patients with cardiomyopathies. We would also administer sodium bicarbonate preferentially in the setting of hyperkalemia because this intervention decreased the rates of kidney replacement therapy (KRT) in the BICAR-ICU trial. Additionally, bicarbonate should be repleted if continuing losses from diarrhea were contributing to the metabolic acidosis. Absolute indications for administering sodium bicarbonate are cases of ethylene glycol, methanol, or salicylate toxicity, in which increasing the pH keeps toxic metabolites in the uncharged form to reduce tissue penetration and enhance urinary excretion by ionic trapping.

One concern with sodium bicarbonate administration is that the CO_2 - HCO_3 reaction will increase P_{CO_2} . However, in the ranges of clinically relevant acidemia, an acid dissociation constant of 6.1 of the CO_2 - HCO_3 reaction will lead to a 10% dehydration of the added HCO_3 to CO_2 . Therefore, if a 50-mEq ampule of sodium bicarbonate is pushed rapidly, P_{CO_2} may transiently increase by 5 mm Hg. When sodium bicarbonate is administered slowly (eg, 150 mEq added to 1 L 5% dextrose), this effect is minimal. In patients who are not undergoing mechanical ventilation, the extra volume may precipitate intubation, and caution should be exercised. For question 7, (d) is the best answer, and there is no compelling reason to use sodium bicarbonate for treatment of this patient's hypercapnic respiratory failure.

Kidney-Lung Cross-Talk in ARDS

In mechanically ventilated patients, ventilation can be augmented by increasing the tidal volume or respiratory rate. However, these maneuvers may result in ventilator-induced lung injury, which includes overdistension of the lung and shear stress from the opening and closing of lung units, called atelectrauma. These processes damage the lung epithelium and worsen capillary permeability, contributing to ARDS. In the landmark ARDSNet study, a lung-protective strategy of low tidal volumes of 6 mL/kg of ideal body weight and plateau pressures <30 cm H₂O reduced mortality and days with kidney failure. Additionally, a small randomized controlled trial by Rainer et al found that lung-protective ventilation significantly decreased the risk of AKI compared with conventional ventilation. Data suggest that this beneficial effect is due to the attenuation of ventilator-induced lung injury and its consequent inflammatory response. Conversely, in

animal models of kidney ischemia-reperfusion injury, pulmonary expression of epithelial sodium channel (ENaC), adenosine triphosphatase sodium/potassium pump, and aquaporins are down-regulated, which may decrease active alveolar fluid reabsorption and worsen pulmonary edema. Clearly, kidney and lung function are closely interrelated, and the goal of the clinician should be to treat the patient rather than protect one organ system.

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Liberation From Mechanical Ventilation

Case 4: A 72-year-old woman with severe chronic obstructive pulmonary disease (forced expiratory volume in the first second of expiration = 20% predicted) and heart failure with reduced ejection fraction (ejection fraction = 40%) experienced increasing sputum, dyspnea, and cough combined with increasing peripheral edema several days after visiting a grandchild with a cold. On presentation, she had tachypnea with severe wheezing. With a face mask with high-flow 28% oxygen, her arterial O₂ saturation by pulse oximetry was 85%. Arterial blood gas examination showed an acute-on-chronic respiratory acidosis: pH 7.29, PaCO₂ of 73 mm Hg, PaO₂ of 55 mm Hg, and bicarbonate level of 34 mM. Despite treatment with methylprednisolone, frequently administered nebulized albuterol/ipratropium, and furosemide, she became somnolent and was intubated. On hospital day 4, her arterial blood gas findings were pH 7.47, PaCO₂ of 54 mm Hg, PaO₂ of 89 mm Hg, and bicarbonate level of 38.2 mM on a tidal volume of 500 mL, RR of 16, fraction of inspired O₂ of 0.3, and PEEP of 5 cm H₂O. A spontaneous breathing trial was attempted, but she had low minute ventilation. Because of concern that her alkalemic pH was hindering her liberation from the ventilator, the team considered the use of acetazolamide to facilitate extubation.

Question 8: Which of the following is an expected effect of acetazolamide?

- a) Decrease in airway resistance

- b) Increase in serum bicarbonate level
- c) Decreased time on the ventilator
- d) Increase in tidal volume

For the answer to the question, see the following text.

Acetazolamide has a long history of use as a respiratory stimulant. In the kidney, CA inhibition results in reduced proximal bicarbonate reabsorption and proton secretion in the distal nephron. This causes a decrease in serum bicarbonate level of 4-6 mM, with greater decreases in elderly patients and those with CKD; thus, choice (b) is incorrect. This effect may stimulate ventilation by reducing pH and subsequently increasing tidal volume; thus, choice (d) is correct.

The belief that metabolic alkalosis decreases respiratory drive, resulting in a failed spontaneous breathing trial, forms the basis for the use of acetazolamide to enhance liberation from mechanical ventilation. However, retrospective studies show that the duration of mechanical ventilation in patients with chronic obstructive pulmonary disease is not related to acid-base status. Leading causes of prolonged mechanical ventilation include reduced respiratory muscle strength, hyperinflation, and airway resistance. Acetazolamide does not affect airway resistance, so choice (a) is incorrect. The preponderance of data, including retrospective studies and, more recently, the large DIABLO randomized controlled trial, suggest that acetazolamide does not enhance weaning from mechanical ventilation or alter other clinically relevant outcomes. Therefore, choice (c) is incorrect.

In specific populations, the use of CA inhibitors may cause harm. People with limited ventilatory capacity due to very severe chronic obstructive pulmonary disease, neuromuscular disease, or restrictive lung disease may not be able to augment ventilation. In these cases, inhibition of CA can lead to a metabolic acidosis without compensatory hyperventilation to moderate it. Further, if acetazolamide serum concentration is high and erythrocyte CA is inhibited, this may result in an increase in PaCO₂. CA found on the capillary endothelium and in RBCs rapidly catalyzes the conversion of CO₂ to bicarbonate, which maintains the capillary Pco₂ lower than the tissue Pco₂ and permits CO₂ to efficiently transfer into the blood (Fig 4). If RBC CA is inhibited, greater tissue-to-blood and blood-to-alveolar gas Pco₂ gradients are required to keep CO₂ elimination at a steady state. Figure 5 illustrates the changes in venous (tissue) and PaCO₂ that arise with increasing acetazolamide-mediated inhibition of RBC CA in conditions when patients can breathe more (Fig 5A) and when they are unable (Fig 5B). Low cardiac output states may also increase the difference between the arterial and venous (tissue) Pco₂. In the case provided above, acetazolamide is unlikely to enhance liberation from mechanical ventilation and may worsen the

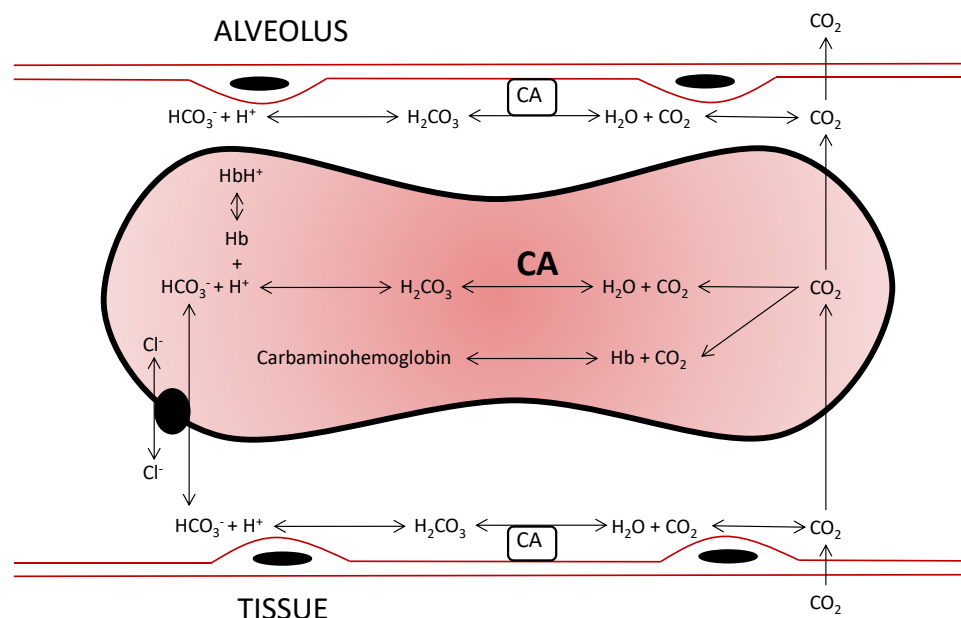


Figure 4. Red blood cell (RBC) in transit through a capillary. CO₂ diffuses out of tissues, across the capillary endothelium into the blood plasma, and into the RBCs. Carbonic anhydrase (CA) on the capillary endothelium and in the RBCs catalyzes the conversion of CO₂ to bicarbonate, thereby keeping the capillary partial CO₂ pressure lower than that in the tissue, allowing efficient transfer of CO₂ into the blood. At the alveolus, CA on the capillary endothelium catalyzes the conversion of bicarbonate to CO₂, thereby facilitating rapid diffusion of CO₂ into the alveolar airspace. Hb, hemoglobin. Graphic ©2017 American Thoracic Society. Adapted from Adamson and Swenson (*Ann Am Thorac Soc* [an official journal of the American Thoracic Society]. <https://doi.org/10.1513/annalsats.201701-016fr>) with permission of the copyright holder.

respiratory acidosis in addition to producing the intended metabolic acidosis.

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3.5 mg/dL, estimated glomerular filtration rate (eGFR) of 24 mL/min/1.73 m², and hemoglobin level of 11 g/dL. His troponin level is increased to 1.5 ng/mL, and BNP level is increased to 900 pg/mL. For the past 3 months, he has been treated with darbepoetin 60 µg every month for symptomatic anemia due to CKD.

Question 9: What is the next step in management?

- a) Administer a 500-mL intravenous fluid challenge
- b) Start vasopressor therapy
- c) Perform transthoracic echocardiography
- d) Administer furosemide

For the answer to the question, see the following text.

Venous Thromboembolism

Hemodynamic Management in Acute Pulmonary Embolism

Case 5: A 64-year-old man with stage 4 CKD presents to the ICU with hypoxemic respiratory failure. On presentation, his blood pressure is 95/68 mm Hg, pulse is 112 beats/min, RR is 30, and oxygen saturation is 86% while breathing ambient air. On examination, jugular venous pressure is increased at 8 cm H₂O and heart rhythm is regular. He has unilateral right lower-extremity swelling without tenderness or erythema, and all extremities are warm. Given this history, a computed tomographic angiogram of the chest is obtained, and he is found to have partial filling defects in the distal left main and right main pulmonary arteries. Unfractionated heparin infusion is initiated. Laboratory findings are notable for a serum creatinine of

Acute pulmonary embolism causes an increase in pulmonary vascular resistance through several mechanisms: (1) acute obstruction and reduction of a portion of the total pulmonary vascular bed, (2) increased vagal and sympathetic nervous system activation, (3) hypoxic pulmonary vasoconstriction in regions of low ventilation/perfusion ratios, and (4) release of vasoconstricting mediators by platelets and thrombin-rich clots, such as histamine, thromboxane A₂, and serotonin. The RV must generate higher pressures to overcome this increase in afterload, but RV dysfunction occurs when the pulmonary vascular resistance exceeds this capability.

Accurate and precise volume assessment is crucial because of the narrow therapeutic window of fluids in this condition.

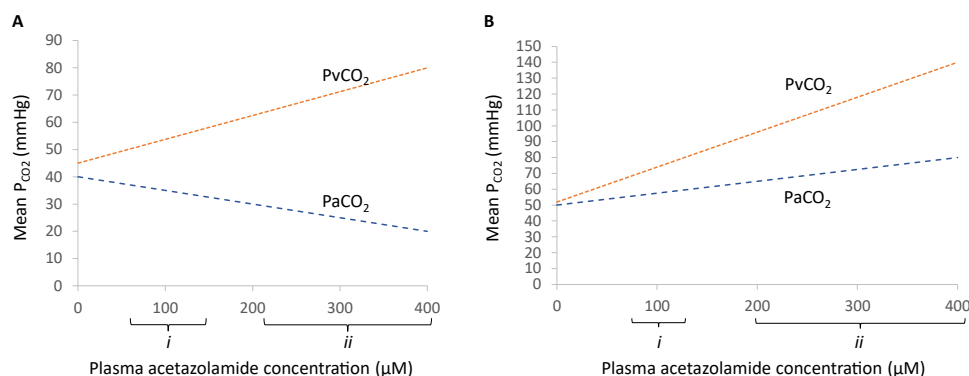


Figure 5. Arterial and venous partial CO₂ pressure concentrations at increasing plasma acetazolamide concentrations. (A) The approximate plasma acetazolamide concentration–carbon dioxide tension relationship in people with normal lung function and respiratory muscle strength. (B) The carbon dioxide tension–plasma acetazolamide concentration relationship in people with severe obstructive lung disease and inability to increase minute ventilation. (i) Expected plasma acetazolamide concentration range in healthy younger people with normal kidney function at doses of 2–5 mg/kg and (ii) expected plasma acetazolamide concentration range for 2–5-mg/kg dosing in elderly patients and those with decreased kidney function. Graphic ©2017 American Thoracic Society. Adapted from Adamson and Swenson (*Ann Am Thorac Soc* [an official journal of the American Thoracic Society]. <https://doi.org/10.1513/annalsats.201701-016fr>) with permission of the copyright holder.

In patients with volume depletion, small fluid challenges may improve cardiac index. However, caution must be taken to avoid RV overload, which can drive a vicious cycle of decreases in cardiac output. In this setting, the volume-induced increase in RV wall stress impairs RV systolic function and promotes tricuspid annular dilation, worsening tricuspid insufficiency. The regurgitant valve decreases forward RV stroke volume. Further, as a result of ventricular interdependence, high end-diastolic RV volume displaces the interventricular septum toward the left ventricle (LV), creating a D-shaped LV and impeding LV diastolic filling. The end result is decreased LV stroke volume, shock, and hypoperfusion of the myocardium. The increased LV end-diastolic pressures may also be reflected back to the left atrial and pulmonary artery pressures, increasing RV afterload (Fig 6).

In the patient in case 5, perfusion is currently maintained as judged by his warm extremities and mean arterial pressure, making choices (a) and (b) incorrect. His increased jugular venous pressure, troponin, and BNP suggest that he may have RV dysfunction, but these are not specific or precise tests. Although troponin and BNP are useful for risk stratification in the general population, people with CKD may have minor increases in these biomarkers at baseline. Therefore, a better assessment of the patient's RV function is necessary to appropriately respond to changes in hemodynamic parameters, and the best answer to question 9 is (c).

Risk of Venous Thromboembolism in CKD

Many studies have shown an increased risk for venous thromboembolism (VTE) in the setting of CKD; however, the magnitude of this effect varies. Kumar et al found that the incidences of pulmonary embolism were 66 per 100,000 among persons with normal kidney function, 204 per

100,000 in CKD without KRT, and 527 per 100,000 in kidney failure with KRT (Table 2). Wattanakit et al found that the risk of VTE in patients with CKD with an eGFR of 15–59 mL/min/1.73 m² is approximately 2-fold compared with those with an eGFR >90 mL/min/1.73 m². Notably, in the first study, patients were older and had more comorbidities. The increased risk attributable to CKD is similar to other risk factors such as bed rest, prolonged immobilization, and obesity. Mortality rates are significantly higher for persons with CKD (6.7%) versus those with normal kidney function (3.2%) in whom VTE develops. Additionally, the median hospital stay is longer and rates of discharge to home are lower.

Pathophysiology of VTE in CKD

In CKD, including kidney failure with KRT, abnormalities exist in both clotting and bleeding function. CKD is a pro-coagulant state associated with abnormalities in the coagulation cascade due to increased tissue factor, von Willebrand factor, factor XIIIa, factor VIIa, and fibrinogen and reduced tissue plasminogen activator. However, the phenotypes in kidney failure with KRT are heterogeneous, with some patients exhibiting increased bleeding risk and others typifying a prothrombotic state. Laboratory assays do not help distinguish among these phenotypes. In TREAT, VTE was statistically more common in patients randomized to receive darbepoetin (2%) than placebo (1.1%).

Management of VTE in CKD

Question 10: Which of the following medications should be dose-adjusted or avoided in this patient?

- a) Apixaban
- b) Warfarin
- c) Unfractionated heparin
- d) Enoxaparin

For the answer to the question, see the following text.

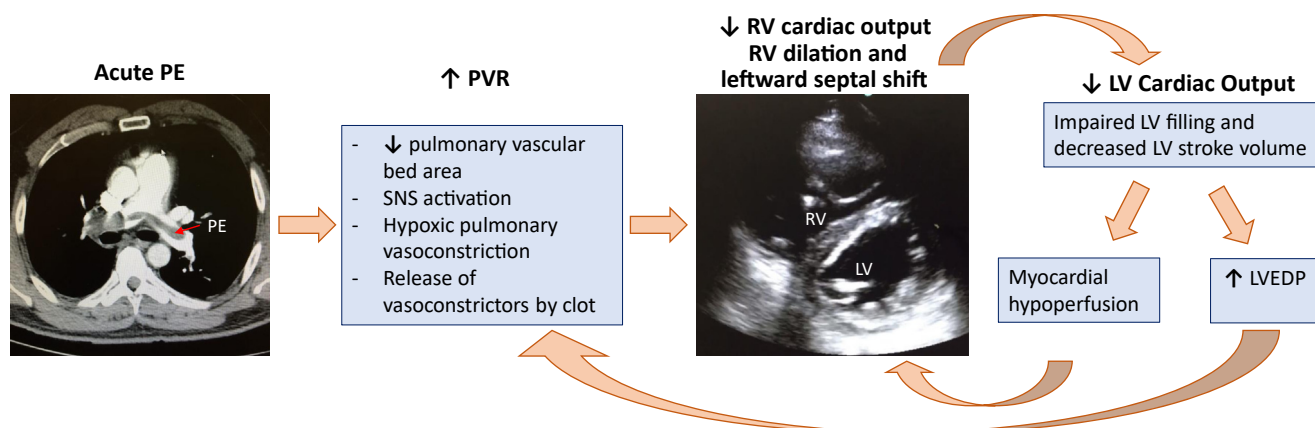


Figure 6. Mechanisms of hemodynamic compromise in acute pulmonary embolism. IVS, interventricular septum; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; SNS, sympathetic nervous system.

The current recommendations from the American College of Chest Physicians are to treat deep vein thrombosis/pulmonary embolism without an associated cancer with direct oral anticoagulant agents (grade 2B recommendation) over direct vitamin K antagonists and with direct vitamin K antagonists over low molecular weight heparin (grade 2C). However, in the setting of decreased eGFR, vitamin K antagonists are recommended. Direct oral anticoagulant agents were not considered as a first-line therapy in this population because patients with an eGFR <30 mL/min were excluded from landmark trials in which they were studied. However, pharmacokinetic data and retrospective studies suggest that direct oral anticoagulant agents are a reasonable therapeutic option when eGFR is >15 mL/min. Recommendations for dose reduction in the setting of eGFR <30 mL/min come from the drug manufacturer and from small studies (Table 3).

For case 5, assuming the patient's eGFR remains at 24 mL/min/1.73 m², he can be treated with warfarin or a direct oral anticoagulant agent. Apixaban is commonly used for patients with CKD because it is predominantly

metabolized in the liver. Dose reduction is required only if Scr is >1.5 mg/dL and weight is <60 kg or age is >80 years. Enoxaparin is renally cleared, and standard dosing results in increased factor Xa levels and an increased risk of bleeding in patients with an eGFR <30 mL/min. Adjusting the dose based on factor Xa levels may mitigate this risk, but we prefer to avoid the use of enoxaparin in this patient population. Warfarin and unfractionated heparin are safe for use in decreased eGFR and do not require dose adjustment. Therefore, the best answer to question 10 is (d).

Risks and Safety of Continuing Erythropoiesis-Stimulating Agent Therapy After VTE

When the patient in case 5 has undergone anticoagulation, can he safely resume treatment with an erythropoiesis-stimulating agent (ESA)? Despite many trials showing that ESAs themselves predispose to the development of VTE when targeting hemoglobin levels of 12-13 g/dL, no study has answered the question whether they can be safely restarted when a patient has begun therapeutic anticoagulation.

In the 4 major trials investigating the use of ESAs in dialysis recipients and in those with earlier stages of CKD, there was increased cardiovascular risk, including death, with high hemoglobin targets of 13-15 g/dL. It is thought that higher doses required for "ESA resistance" may be associated with cachexia and increased levels of inflammatory markers and may therefore contribute to the development of thrombosis. The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) anemia guideline recommends consideration of withholding ESAs in patients with a history of stroke (grade 1B recommendation) or malignancy (grade 1B); they do not make a recommendation in the setting of VTE.

Based on the available evidence, the decision to resume an ESA should be individualized based on patient factors

Table 2. Age-Standardized Frequency of PE by Kidney Disease Category

Age Group	PE per 100,000 Persons		
	Normal Kidney Function	CKD	KFRT
20-44 y	24	137	682
45-54 y	51	236	367
55-64 y	80	312	312
65-74 y	154	220	456
≥75 y	249	304	462
All	66	204	527

Abbreviations: CKD, chronic kidney disease; KFRT, kidney failure with replacement therapy; PE, pulmonary embolism.

Based on information in Kumar et al, 2021 (*Clin J Am Soc Nephrol.* <https://doi.org/10.2215/CJN.00250112>).

Table 3. Oral Anticoagulant Agents and Their Properties

Oral Anticoagulant	Mechanism of Action	Metabolism	Dialyzable	Dose Adjustment
Warfarin	Vitamin K antagonist	Cytochrome P450 type 2C9	No	No
Dabigatran	Direct thrombin inhibitor	Renal excretion 80%	Yes	Yes
Rivaroxaban	Factor Xa inhibitor	Renal excretion 66%, 36% as unchanged drug	No	Yes
Apixaban	Factor Xa inhibitor	Cytochrome P450 type 3A4, renal excretion 27%	Partial	No
Edoxaban	Factor Xa inhibitor	Cytochrome P450 type 3A4, 50% renal excretion (unchanged)	No	Yes

Based on information in Jain et al, 2019 (*Clin J Am Soc Nephrol*. <https://doi.org/10.2215/CJN.02170218>).

including (1) the level of hemoglobin at which symptoms develop, (2) the dose of ESA required, and (3) kidney transplant candidacy. Shared decision-making with the patient is of the utmost importance.

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