CME MOC

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Hospital-acquired pneumonia

Weight-loss drugs are underused

A-fib and a stent: Give 3 drugs?

CT: When is contrast needed?

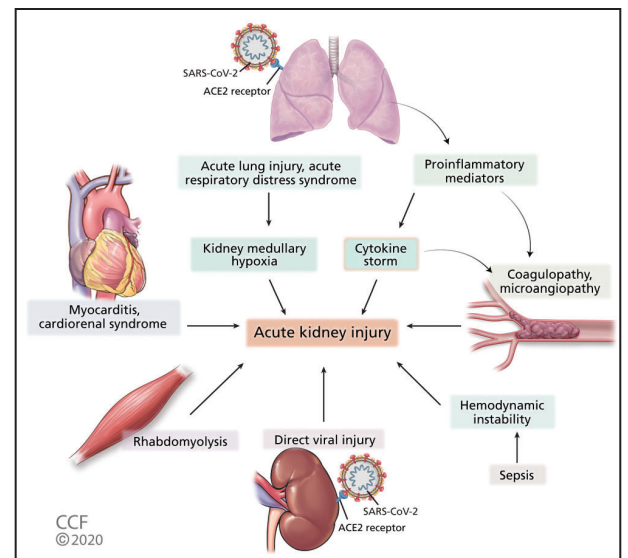Skin plaques, weakness

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Cholesterol embolization syndrome

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COVID-19 and the kidney

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WE CAN'T HUG YOU
BUT WE CAN SALUTE YOU

The public may have pandemic fatigue. But COVID isn't resting and neither can you. That's why we created **#UniteInGratitude**, a national campaign to thank and honor all healthcare workers with a flag of your own, made from the colors and fabrics you wear to the fight every day. We're selling this Gratitude Flag (and other gear) to unite the public in ongoing support for healthcare workers, with proceeds going to the CDC Foundation's Coronavirus Emergency Response Fund. Visit **UniteInGratitude.com** to learn more. And thank you for everything you do...*we salute you*.

#UniteInGratitude

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A sneaky vascular disease

We are well past the hypothesis stage in recognizing that inflammation plays a seminal role in the development and expression of atherosclerotic vascular disease (ASCVD). The hypothesis has matured into a model where clinical trials are being conducted that may ultimately home in on defining specific anti-inflammatory strategies that will augment our current lipid- and thrombosis-directed therapies in limiting the occurrence of cardiovascular events. A specific monoclonal antibody inhibitor of interleukin 1 beta (IL-1 beta) has been shown to modestly reduce cardiovascular events. Weekly methotrexate in doses used fairly successfully in patients with rheumatoid arthritis was ineffective, whereas colchicine may have benefit in preventing atherosclerotic events. The mechanism or mechanisms of action of these latter two medications are incompletely understood, although it is believed that at least part of colchicine's efficacy in treating gout is due to suppression of crystal-induced generation of IL-1 beta. The message seems to be that the model is correct, but specific proinflammatory targets still need to be identified.

These studies and the inflammatory concept of ASCVD have focused on the vascular atherosclerotic plaque, a complex physical structure involving and engaging in a dynamic way many cellular and soluble players, as well as being affected by rheologic factors. But even "simple" cholesterol-based structures—cholesterol crystals and some lipoproteins—have pro- and anti-inflammatory activity that can be clinically relevant. Perhaps when we understand better the response to cholesterol crystals, we will be even better able to manipulate the more complex plaque.

A syndrome that likely occurs (in a mild form) more commonly than we diagnose it is cholesterol embolization. Cholesterol crystals, which may be visualized histopathologically as vascular-occluding clefts, break loose from large-artery endovascular plaques and flow downstream until their flow is limited by luminal diameter. This embolization seems most often triggered by mechanical iatrogenic disruption by catheterization, but not always. Notably, the clinical course of cholesterol embolization syndrome is not the same as that of thromboembolism. The latter tends to present as an acute, rapidly developing event—stroke, myocardial or renal infarction, or foot or digital ischemia with often fairly rapid onset of tissue necrosis. This is likely due in part to the larger size of the occluded artery, as well as to the rapidly progressing thrombotic reaction that is triggered. With good timing, skill, and a little luck, this may respond well to thrombolysis, anticoagulation, thrombectomy, or a combination thereof.

But the cholesterol embolization syndrome behaves differently, which is why we may miss milder cases, and why, when more pronounced, it may superficially or convincingly mimic other vasculopathies, including some forms of vasculitis.
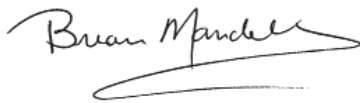
The cholesterol clefts and debris tend to lodge in smaller arteries and arterioles and not cause acute large infarctions with necrosis. The clinical course is often subacute over days to weeks with a staccato progression. It has been postulated that this is due to showers of the cholesterol emboli over time, but fitting with what we now more fully recognize about the phlogistic properties of cholesterol structures, it may also be due to an inflammatory response that evolves over several days or longer, triggered by

the cholesterol crystals—crystals that are more exposed than when they were buried within a vascular plaque. The more we learn about the specific response triggered by these crystals, the better able we may be to treat this syndrome and, perhaps, the plaque from whence they came. At present, the treatment for cholesterol embolization is limited to attacking the atherosclerotic process and its well-recognized comorbidities such as hypertension.

And the response to cholesterol embolization can be striking and surprising (reviewed by Ozkok[1]). The mechanical occlusions of arterioles and small deep cutaneous, fascial, and muscle arteries can cause livedo. But in addition, the crystals or the embolization process often trigger the acute-phase response with elevations in fibrinogen level, sedimentation rate, C-reactive protein level, and occasionally fever. These findings are consistent with the experimentally demonstrated ability of cholesterol crystals to activate mononuclear NLRP3 inflammasomes that elaborate IL-1 beta. The crystals also can activate complement, sometimes to a degree resulting in measurable depression of C3 or C4 levels. The crystals can elicit the elaboration of IL-5, which results in a mild to modest eosinophilia, and in the kidney may result in the diagnostically useful finding of eosinophiluria if a special stain (Hansel stain) is used with urine microscopy. Mild thrombocytopenia may also occur, which is diagnostically helpful in suggesting the embolization syndrome as opposed to a primary vasculitis syndrome such as polyarteritis nodosa. The latter can also cause livedo, an acute inflammatory response, slowly progressive renal dysfunction with a fairly bland urinalysis, and hypertension. Thrombocytopenia is not expected with a primary vasculitic syndrome (although eosinophilia may occur in some).

The general message from this discussion, and from the patient presented by Smith et al in this issue of the *Journal* (page 605) is that even in a patient with known significant ASCVD including peripheral vascular disease, paying attention to the nuances of the historical presentation and some basic laboratory studies can pay off. And further understanding of the cholesterol embolization syndrome may provide insights into the mechanisms and ultimately treatment of atherosclerotic disease.

Brian F. Mandell, MD, PhD
Editor in Chief

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CME | MOC

2020

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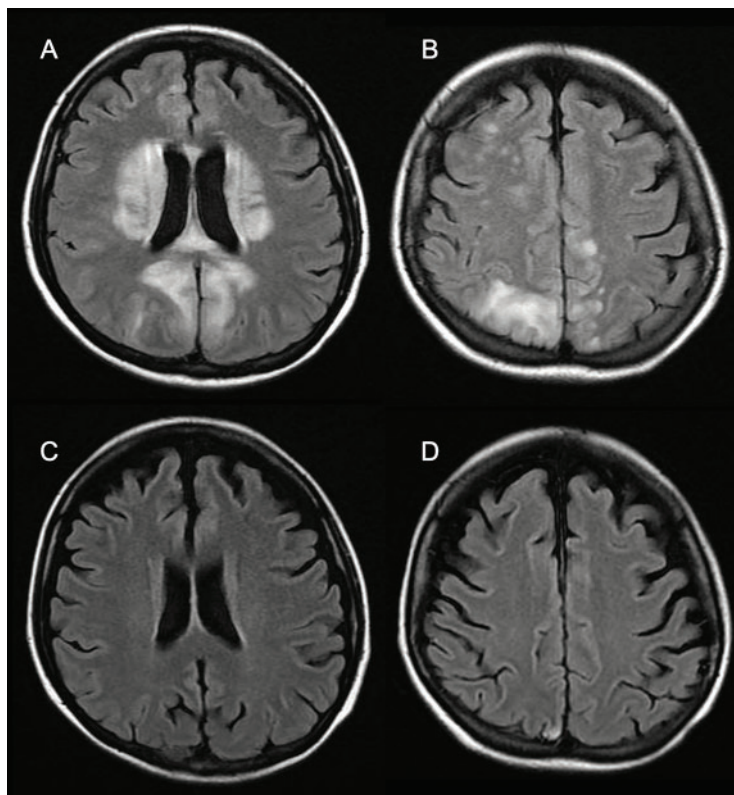
FIGURE 1. (A, B) Axial fluid-attenuated inversion recovery magnetic resonance imaging (MRI) of the brain showed bilateral cortical, subcortical, and, in the paraventricular region, hyperintense lesions of the parietal and occipital lobes with gyral swelling. (C, D) Follow-up MRI 4 months after presentation showed complete resolution of the lesions.

The R in PRES

To the Editor: We read with great interest the Clinical Picture report by Rai et al on posterior reversible encephalopathy syndrome (PRES).[1] We wish to highlight the lack of universal diagnostic criteria for this condition, especially regarding reversible clinical patterns.[2]

In the original report by Hinchey et al,[3] the presenting neurologic deficit resolved within 2 weeks in all 15 patients, but follow-up imaging was available in only 8. Most of them showed the disappearance of lesions on computed tomography (CT) or magnetic resonance imaging (MRI). Over the years, investigators have proposed other PRES phenotypes, including malignant, hemorrhagic, and atypical variants that might define prognosis

and predict recurrence.[2]

The following case of a young woman with PRES highlights the reversibility of different clinical, radiographic, and electroencephalographic parameters.

An 18-year woman presented with a history of subacute headache and seizures. Her past medical history was relevant for systemic lupus erythematosus, antiphospholipid syndrome, and hypertension. General examination was relevant for hypertension (blood pressure 160/90 mm Hg), and neurologic examination was unremarkable. Her laboratory work revealed normal kidney function (creatinine 0.91 mg/dL, reference range 0.6–1.2). Cerebrospinal fluid analysis revealed a normal opening pressure (12 mm H_2O, reference range 5–20), normal glucose level (67 mg/dL, reference range 40–70), and increased proteins (169 mg/dL, reference range 15–45). Leukocytes and erythrocytes were absent.

MRI of the brain showed high-signal lesions on the T2 fluid-attenuated inversion recovery (FLAIR) sequence within the cortex and subcortical paraventricular region of both parietal and occipital lobes, with gyral swelling but no associated restricted diffusion (**Figure 1A**, **Figure 1B**). No susceptibility artifact to indicate underlying hemorrhage or underlying mass lesions were identified.

We initiated levetiracetam, and epileptic activity halted. Headache improved after intense blood pressure control. Electroencephalography (EEG) showed generalized theta-delta range activity with asynchronous activity in the right hemisphere. The patient underwent repeat EEG 4 months after the event, which showed normal alpha rhythm with no underlying background abnormalities. MRI was also repeated at this time, showing the complete reversibility of the described lesions (**Figure 1C**, **Figure 1D**).

This case illustrates the reversibility of findings based on imaging and other criteria, including neurologic manifestations and EEG. We suggest these patients may have a better prognosis if all clinical and paraclinical features are reversed and well-documented at short-term follow-up, emphasizing the R in PRES.

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Trousseau sign and syndrome: Erroneous terms

To the Editor: Eponymous signs of latent tetany, tache cérébrale, and thrombosis with malignancy were ascribed to the French physician Armand Trousseau (1801–1867) in honor of his accomplishments.[1] His observed sign of thrombosis in association with malignancy should be grammatically distinguished by the possessive form, "Trousseau's sign," since he acquired the same disease that he described in association with a gastric tumor[2]; "[i]t is all up with me, the appearance of a patch of phlebitis last night leaves no loophole for doubt as to the nature of my illness" (p. 836).[3]

Trousseau, based on clinical lectures delivered at the Hôtel-Dieu, Paris, described the association of spontaneous coagulation and phlegmasia alba dolens (painful white inflammation) in patients with thrombosis and advanced tuberculosis and uterine and visceral cancer:

"I have long been struck with the frequency with which cancerous patients are affected with painful ædema in the superior or inferior extremities, whether one or other was the seat of cancer. This frequent concurrence of phlegmasia alba dolens with an appreciable cancerous tumor, led me to the inquiry whether a relationship of cause and effect did not exist between the two, and whether the phlegmasia was not the consequence of the cancerous cachexia. … I have thus been led to the conclusion, that when there is a cachectic state not attributable to the tuberculous diathesis nor to the puerperal state, there is most probably a cancerous tumor in some organ" (p. 287).[4]

Thus, Trousseau's sign of malignancy refers to the presence of spontaneous, migratory, painful edema and thrombosis involving the superficial and deep veins in patients with cancer.[4] "Trousseau syndrome" is an erroneous term since he never described a constellation of symptoms in this disease. A more appropriate designation is "cancer-associated thrombosis" and disease entities found in this condition, as noted by Dr. Maharaj and colleagues.[5]

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In Reply: We thank Dr. Yale and colleagues for their excellent discussion. As they note, Trousseau's sign was first described as migratory superficial thrombophlebitis in association with cancer. The case presented by us depicted this, with the observation of the astute French physician still in use 150 years later.

As described by others in more detail,[1] the concept of coexistent cancer and various features of hypercoagulability developed over the years, and the term *Trousseau's syndrome* evolved out of the medical literature. For instance, Sack et al[2] reported Trousseau's syndrome to include chronic disseminated intravascular coagulation, nonbacterial thrombotic endocarditis, and arterial thrombosis. In our case, the patient had not only Trousseau's sign but also acute cerebral infarcts. We think it is plausible that Trousseau's patients with migratory thrombophlebitis had some of these other signs, but the technology would not have existed then to confirm them.

Nevertheless, we certainly agree that converting "sign" to "syndrome" is a liberal use by formal semantics. The term *cancer-associated thrombosis* does seem best to characterize the syndrome in modern medical lexicon. We hope, however, that Trousseau's sign continues to be taught and recognized on the physical examination.

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Verrucous plaques on the face, dysphagia, and limb weakness

A 59-YEAR-OLD MAN with known chronic obstructive pulmonary disease and poorly controlled diabetes was referred to the hospital by his dermatologist. Two months earlier, he first noticed an itchy "bump" on the cutaneous portion of his upper lip, which then developed into multiple growths that had spread to the tip of his nose.

He reported several episodes of night sweats, dysphagia, and left-sided hand and leg weakness.

He had worked for 30 years in coal mines and sawmills. He was a smoker, with a 25-pack-year history. He lived in eastern Tennessee.

Physical examination confirmed numerous exophytic verrucous plaques on his upper cutaneous lip and nose (**Figure 1**). Results of serum chemistry, liver enzymes, and complete blood cell count were normal. Testing for human immunodeficiency virus infection was negative.

Biopsy of the facial lesions was performed, and he underwent magnetic resonance imaging of the brain and computed tomography of the chest.

Biopsy study showed pseudoepitheliomatous hyperplasia, and Grocott-Gomori methenamine silver staining (**Figure 2**) revealed broad-based budding yeasts measuring 8 to 20 µm in diameter and with thickened cell walls, features consistent with blastomycosis. Because of concern for disseminated disease, the patient was admitted for further workup.

■ **FURTHER EVALUATION AND DIAGNOSIS**

Magnetic resonance imaging of the brain revealed ring-enhancing lesions in the pons and inferior cerebellar peduncle. Computed tomography of the chest showed bilateral upper-

Figure 1. The patient presented with exophytic verrucous plaques on his upper cutaneous lip and nose.

lobe scarring and areas of bronchiectasis, as well as nodules in the upper lobes and ground-glass opacities. Urine antigen testing for *Blastomyces* was positive at 3.07 ng/mL (reference range for negative, 0 ng/mL).

Given these findings and the high likelihood of blastomycosis, sputum cultures and additional serologic testing were not ordered.

The patient was treated with intravenous amphotericin B for 6 weeks and oral voriconazole 200 mg twice daily for 1 year. His skin lesions and neurologic symptoms resolved. Repeat imaging at 4 months showed resolution of brain and chest lesions.
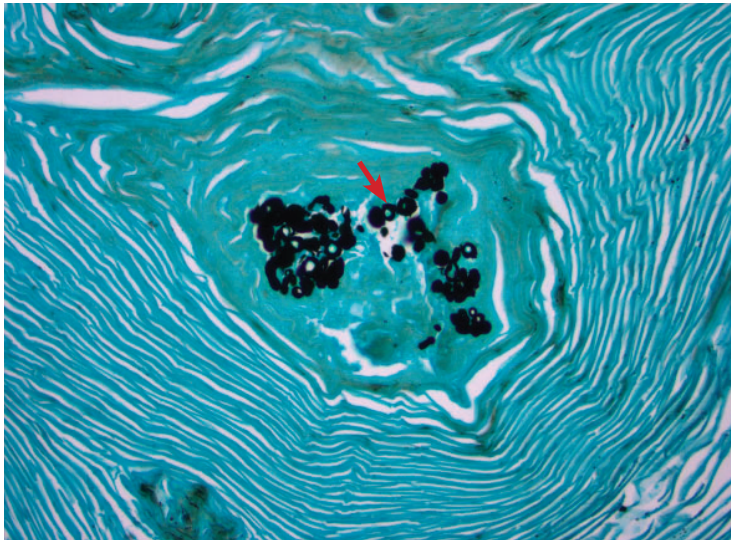
Figure 2. Grocott-Gomori methenamine silver staining revealed broad-based budding yeasts with thickened cell walls (arrow).

A high index of suspicion in endemic areas aids prompt diagnosis

■ BLASTOMYCOSIS: CLUES TO DIAGNOSIS

The differential diagnosis of cutaneous blastomycosis includes infection with dimorphic fungi (ie, growth forms that change from moldlike to yeastlike), basal cell carcinoma, squamous cell carcinoma, giant keratoacanthoma, lupus vulgaris, scrofuloderma, nocardiosis, atypical *Mycobacterium* infection, syphilis, bromoderma, iododerma, leishmaniasis, granuloma inguinale, lymphoma, and pyoderma gangrenosum.[1–3]

In the diagnosis of dimorphic fungal infections—including blastomycosis, histoplasmosis, and coccidioidomycosis—geographic location, epidemiologic factors, and exposure history are key considerations. Blastomycosis and histoplasmosis are endemic in the Ohio and Mississippi River valleys and southeastern areas of the United States (including eastern Tennessee), whereas coccidioidomycosis is endemic in the southwestern United States. All 3 can present as cutaneous lesions with systemic involvement. Culture and histopathology can help distinguish them.

Basal and squamous cell carcinomas and giant keratoacanthoma can also present as cutaneous plaques. These are easily diagnosed with histopathologic study, and systemic involvement would be uncommon.

Most cases of blastomycosis are considered sporadic. But outbreaks have been associated with recreational and occupational activities involving distribution of soil, including construction, underground exploration, tubing, and hunting.[4]

■ ROUTES OF TRANSMISSION

Blastomycosis is transmitted by inhalation of spores and can occur in both immunocompromised and immunocompetent individuals. Large series have shown that most cases of disseminated blastomycosis occur in nonimmunosuppressed individuals. Immunosuppressed patients develop more severe infection and are more likely to have symptomatic dissemination.[3]

B dermatitidis is typically inhaled and affects the lungs, causing pneumonia. However, hematogenous spread has been reported in 25% to 30% of cases.[5] The most common sites for hematogenous spread are the skin, bones, and joints. Rarely, primary skin infection may occur through direct inoculation.[6,7]

In our patient, the presumed source of infection was by inhalation.

Any patient presenting with cutaneous blastomycosis should be investigated for disseminated disease, particularly pulmonary involvement.

■ DIAGNOSTIC CHALLENGES OF BLASTOMYCOSIS

Diagnosis of blastomycosis can be challenging, and a high index of suspicion is key in endemic areas.

Culture is the gold standard for diagnosis, but Grocott-Gomori methenamine silver stain can show the presence of broad-based budding yeasts. Unfortunately, multiple biopsies are often necessary for diagnosis, as sensitivities of histology and culture have been reported to be as low as 9.7% and 61%, respectively. Cultures may take up to 4 weeks for results.[8]

Assays are also available for detection of *B dermatitidis* antigen in the serum or urine and can yield quicker results. The sensitivity of the urine antigen assay has been reported to be as high as 92.9%, whereas the serum assay is less sensitive.[9]

Cross-reactivity with *Histoplasma capsulatum* does occur, so a negative result should not preclude a diagnosis of blastomycosis.[10]

■ TREATMENT RECOMMENDATIONS

Treatment of blastomycosis depends on severity of illness, central nervous system (CNS) involvement, and the patient's immune status. For uncomplicated cases, itraconazole therapy is preferred and is curative in 95% of cases.

With CNS involvement or life-threatening infection, liposomal amphotericin-B is given. The recommended course is 1 to 2 weeks for severe infection or 6 weeks for CNS involvement. This can then be transitioned to 1 year of oral azole therapy.

Treatment guidelines recommend itraconazole as the preferred agent for all non-CNS disease. Fluconazole and voriconazole are alternatives in patients unable to tolerate itraconazole.[11] Fluconazole must be given at higher dosages and has higher reported failure rates; however, it has good cerebrospinal fluid penetration. Ultimately, further research must be done to determine the efficacy of various azole agents in step-down treatment of CNS blastomycosis.[12,13]

This patient's presentation highlights the clinical manifestations of disseminated blastomycosis and stresses the importance of maintaining a high index of suspicion in an endemic region.

■

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Miliary tuberculosis in a patient with end-stage liver disease
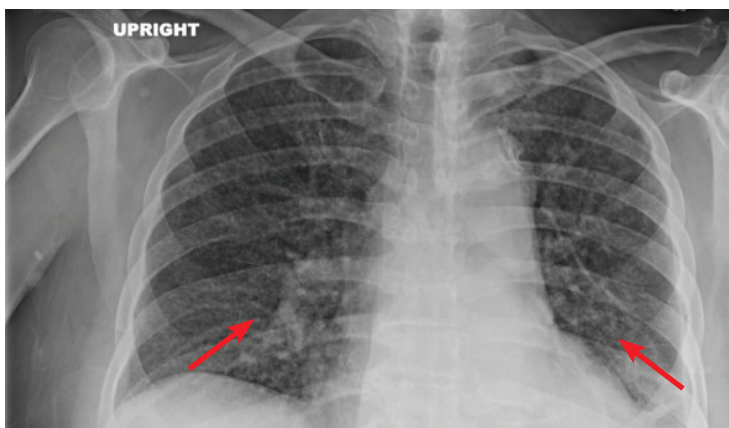
Figure 1. Chest radiography showed patchy left basilar consolidation with subtle, diffuse interstitial opacities (arrows) throughout both lungs.

A 52-year-old Mexican American man with end-stage liver disease due to alcohol abuse was admitted to the hospital because of altered mental status.

One month earlier, he had been hospitalized for culture-negative spontaneous bacterial peritonitis, at which time his liver disease was diagnosed on the basis of his history of heavy alcohol abuse, results of imaging and laboratory testing, and clinical findings. Liver biopsy was not performed at that time.

During that hospitalization, he had recurrent fevers that were attributed to bacterial pneumonia based on a chest radiograph that showed patchy left basilar consolidation with subtle, diffuse interstitial opacities throughout both lungs (**Figure 1**). This was treated with ceftriaxone.

He underwent additional testing that included viral hepatitis serologies, testing for human immunodeficiency virus (HIV), and

bacterial blood cultures; all were negative. Also negative were bacterial culture of the peritoneal fluid, acid-fast bacillus staining of the peritoneal fluid, and fungal staining of the peritoneal fluid; acid-fast bacillus culture and fungal culture of the peritoneal fluid were pending at discharge. No other workup for respiratory infection was done at that time.

■ INITIAL WORKUP

At the time of the current admission, the patient was confused and unable to communicate. He was a known smoker, but whether he used e-cigarettes was not known.

Results of initial laboratory testing were as follows:
- Platelet count 54×10^9/L (reference range 150–400), dropping rapidly to less than 10×10^9/L
- Hemoglobin 11.7 g/dL (13.5–16.5)
- Sodium 119 mmol/L (137–147)
- Creatinine 1.76 mg/dL (0.4–1.24).

Computed tomography (CT) of the chest without contrast revealed tiny nodular opacities in all lobes (**Figure 2**) and an irregular lytic lesion in the T9 vertebral body (**Figure 3**).

Three sputum acid-fast bacilli smears were negative.

The differential diagnosis was broad and included disseminated histoplasmosis, coccidioidomycosis, candidal infection, tuberculosis, cryptococcosis, cancer metastasis (particularly hepatocellular carcinoma or lung cancer, given his risk factors), sarcoidosis, silicosis, and hypersensitivity pneumonitis. Disseminated fungal or mycobacterial disease was believed to be more likely, based on the duration and progression of symptoms despite antibiotics (cef-
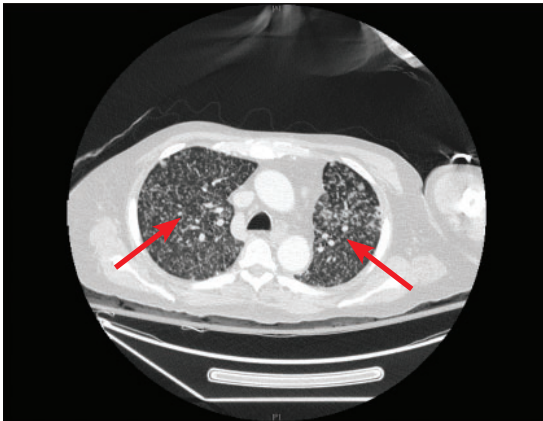
Figure 2. Computed tomography without contrast revealed tiny nodular opacities (arrows) in all lobes.
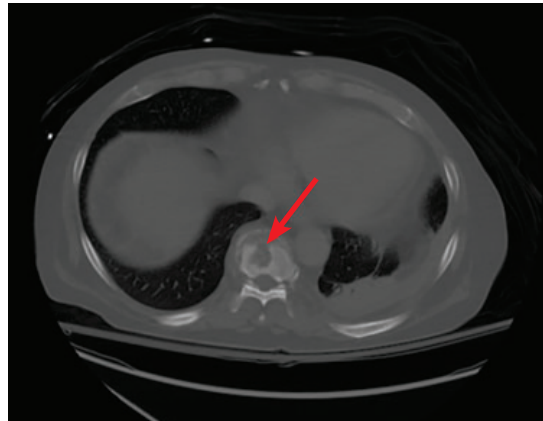
Figure 3. Computed tomography without contrast revealed an irregular lytic lesion in the T9 vertebral body (arrow).

triaxone for 7 days in the prior hospitalization, and levofloxacin started during this admission), the CT findings, and the recent negative peritoneal fluid culture. Hepatic encephalopathy was an initial consideration; however, his mentation did not improve with lactulose.

Sputum staining was negative for bacteria, fungi, and acid-fast bacilli.

Empiric treatment for tuberculosis was started with rifampin, ethambutol, levofloxacin, and 3-times-weekly amikacin. (Amikacin and levofloxacin were substituted for isoniazid and pyrazinamide due to his liver disease.) The empiric treatment was based on CT findings and a clinical scenario consistent with miliary tuberculosis in a patient with underlying liver disease who came from a country in which tuberculosis is common.

More tests for infections were negative: a respiratory viral panel, urine *Histoplasma* antibodies and antigen, *Legionella* antigen, HIV screening, bacterial and fungal sputum cultures, cryptococcal antigen, *Coccidioides* antibody and antigen, *Blastomyces* antigen, *Aspergillus* antigen, and (1-3)-beta-d-glucan.

He underwent bronchoalveolar lavage; the fluid had 360 cells/µL, with 56% monocytes, 23% lymphocytes, and 20% neutrophils. *Pneumocystis* polymerase chain reaction (PCR) testing, cytology, herpes simplex PCR, and bacterial culture of the fluid were negative.

Throughout the hospital stay, the patient's severe thrombocytopenia failed to improve despite multiple transfusions and intravenous

immunoglobulin. His platelet count eventually stabilized at 20 to 30×10^9/L.

■ HEMATOLOGIC EVALUATION

Hematologic conditions in the differential diagnosis in this patient included disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, immune-mediated destruction, splenic sequestration, and bone marrow infiltration from infection.

A hematologic workup revealed normal haptoglobin, mildly elevated lactate dehydrogenase at 232 U/L (reference range 135–225), total bilirubin 1.3 mg/dL (0.2–1.3), and direct bilirubin 0.3 mg/dL (< 0.2). Serum protein electrophoresis showed hypoalbuminemia and increased kappa and lambda free light chains with a normal ratio. Heparin-induced platelet antibody and platelet antibody testing were negative. Fibrinogen was reduced at 197 mg/dL, the international normalized ratio was elevated at 1.4, and the activated partial thromboplastin time was normal.

The initial immature platelet fraction was inappropriately normal at 6.0%, but was elevated at 32.8% on repeat testing 10 days later.

Peripheral smear showed normocytic anemia with anisocytosis, absolute lymphocytopenia, and marked thrombocytopenia with normal platelet morphology. No schistocytes or platelet clumping were seen.

He underwent bone marrow biopsy. The marrow was mildly hypercellular (50%) with

The severe thrombocytopenia failed to improve despite multiple transfusions and IV immunoglobulin

mild pancellular hyperplasia and multiple granulomas, a few of which were necrotizing. Acid-fast bacillus staining was negative. Megakaryocytes were increased, with normal morphology.

■ THROMBOCYTOPENIA WITH MULTIPLE CONTRIBUTING FACTORS

Based on the evaluation, the patient's thrombocytopenia was multifactorial, due to causes that included underlying cirrhosis, likely infiltration of *Mycobacterium tuberculosis*, and a possible immune-mediated component, which was considered because of the brisk fall in platelets after transfusion early in the hospital course and improvement in the rate of decline later in the course (after tuberculosis therapy, possibly due to decreased tuberculosis antigen load).

The diagnosis of miliary tuberculosis with pulmonary and peritoneal involvement was confirmed when a sputum culture grew M *tuberculosis*, as did a peritoneal fluid culture from the previous hospitalization.

Bone, bone marrow, and meningeal involvement was thought to be likely, although not proven. Presumed bone and bone marrow involvement was based on the lytic lesion on CT (**Figure 3**), thrombocytopenia, anemia, and results of bone marrow biopsy study. Meningeal involvement was suspected because of his confusion and headache, although lumbar puncture was not performed in view of his refractory thrombocytopenia requiring multiple transfusions, with intermittent active bleeding and platelet counts persistently below 10 × 10⁹/L.

If lumbar puncture had been done and the results had been positive, his total duration of treatment would have been extended to a total of 9 to 12 months, and we may have considered increasing the rifampin dose and prescribing adjunctive corticosteroids. The rifampin dose was eventually increased empirically because of possible meningeal involvement. Corticosteroids were considered for the same reason but were deferred, given the widespread burden of disease outside of the central nervous system and the potential for harm.

Unfortunately, the patient developed pro-gressive multiorgan dysfunction that led to a fatal arrhythmia.

■ FEATURES OF MILIARY TUBERCULOSIS

Miliary tuberculosis is a rare form of tuberculosis, accounting for up to 2% of cases. The mortality rate is up to 33%, in large part due to delay in diagnosis, which often happens in areas of low prevalence such as the United States.[1,2] A risk factor in this case was that the patient was born in Mexico, and though he had lived in the United States for more than 10 years, he occasionally traveled to Mexico.

The differential diagnosis for this patient's altered mental status and progressive pulmonary imaging abnormalities was broad. However, the history of culture-negative spontaneous bacterial peritonitis and progressive abnormalities on CT for more than 1 month despite treatment of bacterial pneumonia made disseminated fungal or mycobacterial disease more likely, and as noted, the workup rapidly pointed to tuberculosis during the second admission, and all tests for fungal infectious were negative.

Clinical findings

Clinical findings of miliary tuberculosis are nonspecific and may include fever, weight loss, anorexia, tachycardia, and night sweats for more than 6 weeks. There is no standardized approach to diagnosis,[2] but clinical clues that can be useful include symptoms consistent with tuberculosis, a classic miliary pattern or bilateral diffuse reticulonodular lung lesions on a background of miliary shadows on chest imaging, and microbiologic, histopathologic, or molecular evidence.[2]

Approaches to diagnosis

Radiographically, the classic miliary pattern is a widespread collection of uniform, discrete pulmonary opacities 2 mm or less in diameter. CT may show associated reticulation.[2] The miliary pattern may be seen on CT even when a chest radiograph is normal.[2]

Acid-fast bacillus smears, mycobacterial culture, or nucleic acid amplification testing of any involved tissue or fluid (eg, sputum, cerebrospinal fluid, ascites, bone marrow, lymph tissue) can be used to confirm the presence of M *tuberculosis*.[2–4] The diagnostic yield can vary

Clinical findings of miliary tuberculosis are nonspecific and may include fever, weight loss, anorexia, tachycardia, and night sweats for more than 6 weeks

drastically depending on the test and the tissue being tested.[4] Sharma and Mohan[4] combined data from several studies and calculated that culture and acid-fast bacillus smear had a sensitivity of 41% in sputum, 21% in cerebrospinal fluid, and 33% in urine.

Although combining data from different cohorts has limitations, the general principle that the diagnostic test performance varies by specimen type (and degree of bacillary prevalence) is accurate. For example, in cerebrospinal fluid, the sensitivity of acid-fast bacillus smear is 10% to 15% (though it is rapid and cheap), while culture is slow (4–6 weeks) and has 50% to 60% sensitivity, similar to the more rapid approved PCR assays (2–48 hours).[5]

Abnormalities on laboratory testing can include pancytopenia, hyponatremia (especially with meningeal involvement), hypercalcemia, and disseminated intravascular coagulation, though none of these are specific to miliary tuberculosis.[2,4,6]

Liver biopsy and lymph node biopsy, while invasive, tend to have higher yields.[4] Patients with cirrhosis are likely susceptible to tuberculosis infection due to immune dysfunction.[7] Extrapulmonary tuberculosis, including peritoneal and miliary types, is more common in patients with cirrhosis.[8–10] Both miliary tuberculosis and underlying cirrhosis have been shown to be independent predictors of death in patients with tuberculosis.[7,11]

Treatment

Tuberculosis treatment-related hepatotoxicity is more common in patients with underlying cirrhosis.[10] All of these factors were working against the patient in this case.

If the tuberculosis is drug-susceptible, treatment includes isoniazid, rifampin, ethambutol, and pyrazinamide for the first 2 months, followed by 4 months of isoniazid and rifampin (extended to a total of 9–12 months with bone or meningeal involvement).[2,3,6] If meningeal involvement is suspected, a higher dosage of rifampin (30 mg/kg/day) should be considered to improve central nervous system penetration, and adjunctive corticosteroids are recommended.[12]

In our patient, treatment was complicated by liver disease. There are currently no standardized treatments for tuberculosis in patients with severe liver disease. A regimen recommended by the Infectious Diseases Society of America and American Thoracic Society is rifampin and ethambutol for 12 months, with a fluoroquinolone for the first 2 months.[3] Any case of tuberculosis in a patient with underlying liver disease should prompt expert consultation.

In our patient, we used high-dose rifampin, ethambutol, levofloxacin, and, briefly, amikacin. Unfortunately, we were not able to cure him, and he died. ∎

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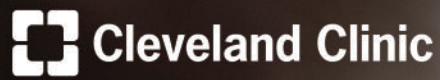
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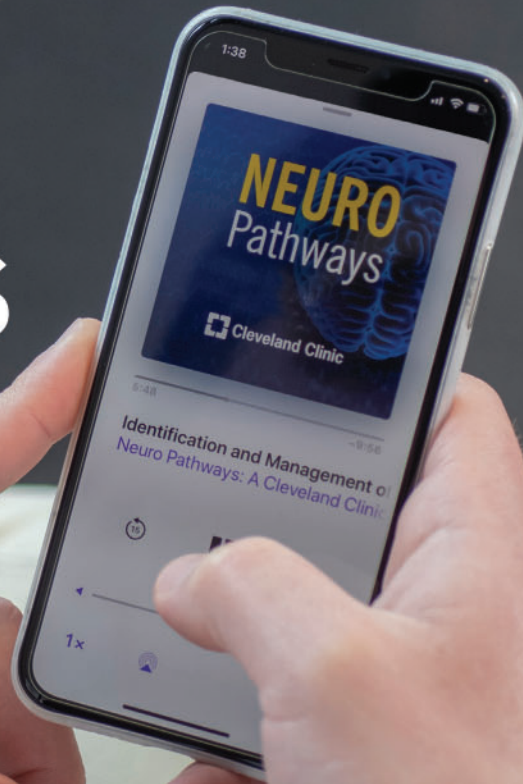
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Q: When is contrast needed for abdominal and pelvic CT?

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

A: Computed tomography (CT) is one of the most frequently utilized imaging modalities in medicine due to its ability to evaluate for a wide range of pathologies. The use of contrast agents, intravenous (IV) or oral, improves image quality by further delineating anatomical structures. However, contrast enhancement is not always necessary and does come with some risks. The appropriateness of contrast enhancement usually depends on the suspected diagnosis. In cases in which the diagnosis is uncertain, administration of contrast is reasonable, although the benefits should be weighed against any potential risks.

◼ INTRAVENOUS CONTRAST

All modern IV contrast agents are iodine-based. The iodine causes increased absorption and scattering of the incoming radiation, which serves to increase the attenuation or "brightness" of the tissue or organ.[1] Importantly, the IV contrast used in CT is distinct from the gadolinium-based IV contrast used in magnetic resonance imaging, meaning that there is no cross-reactivity between the two, which is important if the patient is allergic to one of them.

IV contrast is necessary for the evaluation of any kind of vascular disease, since it allows for easy identification of the blood vessel lumen.[1] In abdominal imaging, IV contrast is recommended in most cases.

◼ ORAL CONTRAST

The primary benefit of oral contrast is its ability to distend the bowels to help distinguish them from adjacent abdominal structures.

TABLE 1

Indications for intravenous contrast in abdominal and pelvic computed tomography

Intravenous contrast required

Gastrointestinal conditions
  Acute abdominal pain
  Abdominal trauma
  Abdominal mass
  Abdominal infection
  Gastrointestinal bleeding (if endoscopy is negative, use computed tomography angiography)
  Pancreatitis
  Liver cancer
  Cirrhosis
  Portal vein thrombosis
  Biliary obstruction
  Inflammatory bowel disease
  Small-bowel obstruction
  Appendicitis
  Diverticulitis
  Colitis

Urinary tract conditions
  Renal trauma
  Pyelonephritis
  Adrenal mass, cancer
  Renal mass, cancer
  Bladder mass, cancer

Vascular conditions (CT angiography required)
  Aortic dissection
  Abdominal aortic aneurysm
  Renovascular hypertension

Intravenous contrast not required
Hematoma
Bowel perforation/free air
Nephrolithiasis
Colon cancer screening (CT colonography)

Based on information in reference 3.

IV contrast poses a greater risk of nephropathy in patients with impaired renal function
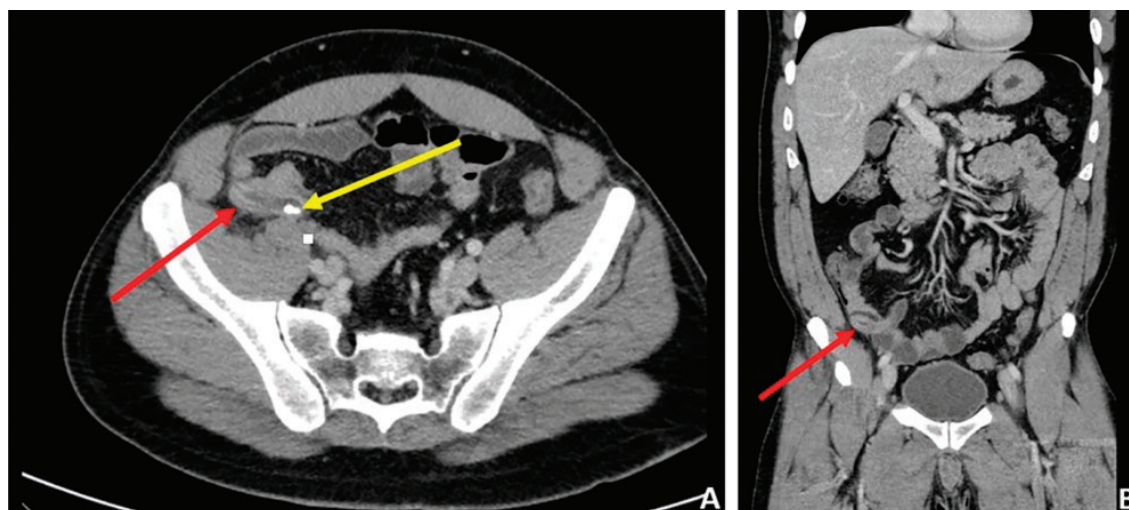
Figure 1. Computed tomography with intravenous contrast enhancement in a patient with right-lower-quadrant abdominal pain. Axial (A) and coronal (B) views reveal diffuse mural and periappendiceal edema, with thickening of the appendix (red arrows). Coarse calcification within the appendix (yellow arrow) likely represents an appendicolith.
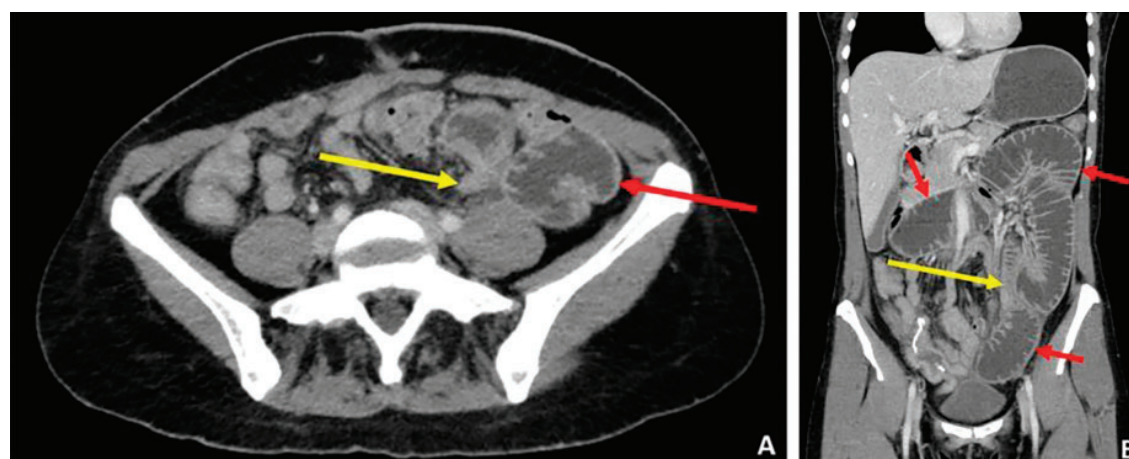
Figure 2. Computed tomography with a neutral oral contrast agent. Axial (A) and coronal (B) views reveal multiple loops of dilated bowel (red arrows) with a transition point—ie, site of sudden luminal narrowing (yellow arrows)—in the left lower quadrant, findings consistent with a small-bowel obstruction.

The decision to use contrast depends on the diagnosis suspected

Oral contrast comes in two forms: neutral or positive. Neutral oral contrast consists of water or a dilute, low-attenuation solution that mirrors water. Positive oral contrast is an iodinated (ie, gastrografin) or barium-based solution with high attenuation that further demarcates bowel by opacification.

The advent of multidetector CT, which offers improved resolution, has made it easier to differentiate abdominal structures without the need for the opacification with positive oral contrast. As a result, some have argued that neutral oral contrast may be preferable to positive oral contrast due to similar efficacy, cost-effectiveness, and easier patient tolerability.[2]

■ GENERAL INDICATIONS FOR CONTRAST USE IN ABDOMINOPELVIC CT

The decision to use contrast in abdominopelvic CT depends on the diagnosis suspected.

IV contrast is recommended in most cases (**Table 1**).[3] It is useful in the evaluation of

infection (appendicitis, colitis, diverticulitis, pyelonephritis) (**Figure 1**); inflammation (pancreatitis, inflammatory bowel disease), masses and malignancies; and vascular abnormalities (gastrointestinal bleeding, aortic dissection, abdominal aortic aneurysm). However, IV contrast is not necessary to diagnose bowel perforations, nephrolithiasis, or hematomas.

In vascular imaging, the study of choice is CT angiography, which is timed so that the image is taken when the IV contrast reaches the arterial system, making it easier to identify active bleeding.

The use of oral contrast is more controversial.[4–6] No clear consensus exists on the need for oral contrast, and expert opinion often drives current practices with regard to oral contrast use at academic medical centers.[6] In general, when the primary reason for CT is to evaluate the liver, gallbladder, pancreas, spleen, adrenal glands, or urinary tract, oral contrast is unnecessary.

Alternatively, when evaluating the gastrointestinal lumen or bowel wall, oral contrast may be beneficial (**Figure 2**). However, oral contrast is not needed in the diagnosis of appendicitis or diverticulitis, even though both are luminal disorders.[5]

Bowel "illumination" achieved with positive oral contrast is useful when searching for "breaks" in the bowel wall, such as what would be seen with fistulas and perforations, or for identifying fluid collections or abscesses between loops of opacified bowel.

Conversely, neutral oral contrast is preferred when evaluating for mural abnormalities or a suspected gastrointestinal bleed, as positive contrast will opacify and mask the luminal surface, making it challenging to identify the bleeding source.[4]

In patients presenting with nonspecific abdominal complaints, some would argue that the addition of the use of oral contrast optimizes the diagnostic yield of abdominal CT.[6] Woolen et al found that 89% of patients would prefer oral contrast if it had any diagnostic benefit.[7] Thus, in patients undergoing abdominal CT for vague or nonspecific complaints, the addition of oral contrast to the study appears reasonable.

TABLE 2

Premedication regimens for patients allergic to intravenous contrast

Elective (12- or 13-hour) regimen
Oral regimens

Prednisone 50 mg at 13 hours, 7 hours, and 1 hour before contrast administration, with or without diphenhydramine[a] 50 mg 1 hour before contrast administration

Methylprednisolone 32 mg at 12 and 2 hours before contrast administration, with or without diphenhydramine[a] 50 mg 1 hour before contrast

Intravenous regimen (for patients unable to take medications by mouth)

Hydrocortisone 200 mg at 13 hours, 7 hours, and 1 hour before contrast administration, with or without diphenhydramine[a] 50 mg 1 hour before contrast administration

Emergency regimen
Methylprednisolone 40 mg or hydrocortisone 200 mg immediately, then every 4 hours until contrast administration, with or without diphenhydramine[a] 50 mg 1 hour before contrast administration

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[a] The addition of diphenhydramine is optional. Evidence on its value is mixed.

Based on information in reference 8.

■ ADVERSE EFFECTS OF CONTRAST

IV contrast carries a risk of an allergic reaction (incidence 0.6%), which can manifest as urticaria, pruritus, bronchospasm with wheezing, or anaphylactic shock.[8] Several premedication regimens consisting of a steroid with or without an antihistamine are available for at-risk patients (**Table 2**).[8]

Risk of nephropathy

Another concern with IV contrast is its use in patients with underlying renal disease. These patients are at risk for developing contrast-induced nephropathy (CIN), which is an acute kidney injury (AKI) that develops within 48 hours of IV contrast administration. The diagnosis is fairly controversial, with some studies having found similar rates of AKI in patients undergoing CT with and without IV contrast.[9] IV contrast is considered unlikely to cause nephropathy in patients with normal renal function, but

can cause CIN in those with impaired renal function.[8]

Current guidelines for IV contrast administration are based on the estimated glomerular filtration rate (eGFR).[8,9] In general, patients with an eGFR of at least 30 mg/dL can receive IV contrast, whereas those with an eGFR less than 30 mg/dL (corresponding to stage 4 chronic kidney disease) are at high risk for renal failure. In these patients, a discussion should be held regarding the high probability of progression to end-stage renal disease, requiring dialysis.

Preventive measures to minimize the risk of contrast-induced nephropathy involve giving IV fluids at 100 mL/hour for 6 hours before and after contrast administration.[8,9] Historically, sodium bicarbonate and N-acetylcysteine have been used as adjunctive agents, although there is a lack of evidence supporting their use.[8,9]

Risks of oral contrast agents

Oral contrast is generally safe and well tolerated, although some patients can experience bothersome symptoms. Neutral contrast agents may contain osmotically active substances that can promote loose stools or diarrhea. Of the positive oral contrast agents, iodinated agents should be avoided in patients at risk for aspiration, as they can cause aspiration pneumonitis. Barium-based oral contrast agents should be avoided in patients with suspected perforations (can cause mediastinitis or peritonitis) or bowel obstruction, as retained barium can harden to form a "barolith," worsening the obstruction and requiring endoscopic or even surgical removal.[10] ∎

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should we give triple therapy to patients with atrial fibrillation after percutaneous intervention?

A: No. In patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI), the combination of an anticoagulant plus 2 antiplatelet drugs ("triple therapy") has been shown to lead to more bleeding events and a higher mortality rate than anticoagulation plus a single antiplatelet drug ("double therapy").[1]

Patients should start double therapy immediately after PCI and continue for 1 year, before transitioning to a direct-acting oral anticoagulant (DOAC) by itself.[1] If the patient is at high risk of a stroke but at low risk of bleeding, one can consider giving an anticoagulant plus 2 antiplatelet drugs (eg, clopidogrel plus aspirin) for a maximum of 1 month after PCI, and then stopping the aspirin for the remainder of the year.[1] Patients should then be maintained on a DOAC by itself after 1 year, with risks and benefits considered.

■ WHICH ANTICOAGULANT? WHICH ANTIPLATELET DRUGS?

Until recently, there were no randomized controlled trials that measured the differences in bleeding events and death with anticoagulation plus 2 antiplatelet drugs compared with anticoagulation plus 1 antiplatelet drug. Clinically, triple therapy has generally meant an oral vitamin K antagonist (eg, warfarin) as the anticoagulant plus, for the antiplatelet drugs, a $P2Y_{12}$ inhibitor (eg, clopidogrel) and aspirin.[2] Double therapy has meant an oral anticoagulant plus a $P2Y_{12}$ inhibitor only.[2]

Of the $P2Y_{12}$ inhibitors, clopidogrel was found to pose the lowest risk of bleeding (followed by ticagrelor in selected patients) and should be the platelet inhibitor of choice.[1] Of the oral anticoagulants, DOACs were found to be associated with fewer deaths and bleeding events than vitamin K antagonists and so should be the oral anticoagulants of choice.[3,4] Thus, warfarin and other vitamin K antagonists are no longer recommended in the treatment of atrial fibrillation after PCI.

■ BENEFITS OF ANTICOAGULATION

From 20% to 30% of ischemic strokes in the United States are related to atrial fibrillation.[5] Furthermore, nearly 3 million patients undergo PCI each year worldwide.[5] Therefore, anticoagulation is imperative to reduce the risk of embolization secondary to cardiac blood stasis in patients with atrial fibrillation who are undergoing coronary PCI.

■ EVIDENCE FOR DOUBLE THERAPY

The WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting?),[2] in 2013, was the first randomized trial to address the optimal antiplatelet therapy in patients on oral anticoagulation undergoing PCI.

This open-label trial, specifically designed to detect bleeding events, found that oral anticoagulation plus clopidogrel (double therapy) caused less bleeding than anticoagulation plus clopidogrel plus aspirin (triple therapy). Furthermore, there was no excess of ischemic events or tradeoff in efficacy (eg, increased incidence of stroke, stent thrombosis, or myocardial infarction) with double therapy compared with triple therapy.[2]

Triple therapy is aggressive and carries higher risks of bleeding and death

At 1 year, bleeding had occurred in 19.4% of the double-therapy group and 44.4% of the triple-therapy group (hazard ratio [HR] 0.36, 95% confidence interval [CI] 0.26–0.50, $P <$ .0001, number needed to treat 4). Also, 2.6% of the patients in the double-therapy group died, compared with 6.3% of the triple-therapy group (HR 0.39, 95% CI 0.16–0.93, $P =$ .027, number needed to treat 27).[2,6]

The **PIONEER AF-PCI trial** (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention),[3] in 2016, found that the DOAC rivaroxaban (in 2 different doses) in combination with a $P2Y_{12}$ inhibitor caused fewer bleeding complications than a vitamin K antagonist plus a $P2Y_{12}$ inhibitor plus aspirin. The rate of death from cardiovascular causes, myocardial infarction, or stroke was similar in the 3 treatment groups.

The **RE-DUAL PCI trial** (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention),[4] in 2017, found that the combination of the DOAC dabigatran plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) caused fewer bleeding complications than warfarin plus a $P2Y_{12}$ inhibitor plus aspirin, and was as effective.

The **AUGUSTUS**[7] **trial**, in 2019, was a 2-by-2 factorial trial that assigned patients who were planning to take a $P2Y_{12}$ inhibitor to receive apixaban or a vitamin K antagonist, and separately assigned them to receive aspirin or placebo. Apixaban, without aspirin, resulted in fewer bleeding events and hospitalizations without significant differences in the incidence of ischemic events.

The **ENTRUST-AF PCI trial**,[8] also in 2019, further demonstrated that a DOAC (edoxaban) plus a $P2Y_{12}$ inhibitor was noninferior to the combination of a vitamin K antagonist, $P2Y_{12}$ inhibitor, and aspirin.

■ PATIENTS AT HIGH RISK OF STROKE OR BLEEDING

For patients at high risk of stroke and low risk of bleeding, it is not unreasonable to extend triple therapy for up to 1 month after PCI.[1] However, after 1 month, double therapy should be used to reduce the risk of a bleeding event and death.[1] Anticoagulation plus a single antiplatelet drug should be used for only up to 1 year before switching to single oral non-vitamin K antagonist therapy only.[1]

For patients at low stroke risk and high bleeding risk, anticoagulation plus single-antiplatelet therapy should be started immediately after PCI, but continued for only up to 6 months, followed by a non-vitamin K antagonist only.[1] Furthermore, a proton-pump inhibitor can be considered, to further reduce the risk of bleeding in those at high risk during the period of anticoagulation and single-antiplatelet combination therapy.

■ TOOLS TO HELP DECISION-MAKING

The **CHA_2DS_2-VASc score** should be used to calculate the stroke risk in patients with atrial fibrillation. Points are given for **c**ongestive heart failure, **h**ypertension, **a**ge greater than 65 (or 2 points for age > 75), **d**iabetes, **s**troke (2 points), **v**ascular disease, and female **s**ex **c**ategory, for a maximum of 9 points. A score of 2 or higher indicates a high risk of stroke (≥ 2.2% per year).[9]

The **HAS-BLED score** can be used to estimate the risk of bleeding in a patient on anticoagulant therapy.[6,9] Points are given for **h**ypertension, **a**bnormal renal function, **ab**normal liver function, **s**troke, **b**leeding, **l**abile international normalized ratio, **e**lderly status, use of **d**rugs that predispose to bleeding, and use of **a**lcohol.[8] A score of 3 or more indicates a high risk of bleeding (≥ 5.8% per year).

■ WHEN TO DISCONTINUE THERAPY

Discontinuation of single-antiplatelet therapy after 1 year (or after 6 months in patients at high risk of bleeding but low risk of stroke) should follow the standard thromboembolism prevention protocol in patients with atrial fibrillation with an oral non-vitamin K antagonist only.[9]

The **AFIRE trial** (Atrial Fibrillation and Ischemic Events With Rivaroxaban),[10] in 2019, demonstrated no decrease in therapeutic effects with rivaroxaban by itself compared

Several trials found lower bleeding risk and comparable efficacy with 2 drugs rather than 3

TABLE 1

Anticoagulation after percutaneous coronary intervention in patients with atrial fibrillation

Time after PCI	Low risk of stroke, low risk of bleeding[a]	High risk of stroke, low risk of bleeding	Low risk of stroke, high risk of bleeding
0–1 month	DOAC plus $P2Y_{12}$ inhibitor	DOAC plus $P2Y_{12}$ inhibitor plus aspirin	DOAC plus $P2Y_{12}$ inhibitor
1–6 months	DOAC plus $P2Y_{12}$ inhibitor	DOAC plus $P2Y_{12}$ inhibitor	DOAC plus $P2Y_{12}$ inhibitor
6–12 months	DOAC plus $P2Y_{12}$ inhibitor	DOAC plus $P2Y_{12}$ inhibitor	DOAC only
After 12 months	DOAC only, discuss risks and benefits	DOAC only, discuss risks and benefits	DOAC only, discuss risks and benefits

[a]For example, with CHA_2DS_2-VASc score of 0 or 1 and HAS-BLED score of 0–2.

DOAC = direct-acting oral anticoagulant; PCI = percutaneous coronary intervention

with rivaroxaban combined with antiplatelet agents, and an increase in safety after 12 months.

For patients with CHA_2DS_2-VASc scores greater than 2, chronic anticoagulation should be advised.[9] For those with a score of 1 or 2, a conversation should be had regarding the risks and benefits.[9] Those with a score of 0 should not continue anticoagulation, and can consider taking only a single antiplatelet agent.[9]

◼ TAKE-HOME MESSAGES

- Triple therapy with anticoagulation plus 2 antiplatelet drugs is a very aggressive approach and carries a higher risk of bleeding events and death than double therapy with anticoagulation plus a single antiplatelet drug, with no tradeoff in efficiency.
- In patients with high ischemic risk and low bleeding risk, anticoagulation plus 2 antiplatelet drugs can be given for up to 1 month after PCI before discontinuing 1 of the antiplatelet drugs, ie, aspirin. **Table 1** summarizes the treatment protocol depending on a patient's ischemic and bleeding risk.
- The CHA_2DS_2-VASc and HAS-BLED scores should be used to determine a patient's thromboembolic risk and risk of a bleeding risk, respectively. ◼

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Overcoming obesity: Weight-loss drugs are underused

ALTHOUGH WEIGHT-LOSS DRUGS are safe and effective, they are underused by healthcare providers in the United States. In the struggle against obesity, we need all the tools at our disposal, including prescription drugs. In this article, we examine barriers and propose solutions.

◼ DIET AND EXERCISE FAIL FOR MOST

Obesity is a public health concern that has become a worldwide epidemic. An estimated two-thirds of US adults are either overweight (body mass index 25–29.9 kg/m^2) or obese (body mass index ≥ 30 kg/m^2).[1] Obesity is associated with a number of comorbidities such as hypertension, type 2 diabetes mellitus, cardiovascular diseases, obstructive sleep apnea, and infertility.[2] Obesity-related healthcare expenditures in the United States amount to over $150 billion annually.[1]

Lifestyle modifications continue to be the cornerstone of management, but most patients cannot achieve or maintain long-term meaningful weight loss by simply exercising or changing their diet. Pharmacotherapy is appropriate when lifestyle and behavioral interventions are ineffective and should be considered in all obese patients and in those with a body mass index 27 kg/m^2 or higher who have obesity-associated comorbidities.[3]

Until 2012, the lipase inhibitor orlistat was the only drug approved by the US Food and Drug Administration (FDA) for long-term treatment of obesity. Now there are 4 others: lorcaserin, phentermine and topiramate, naltrexone and bupropion, and liraglutide.[3] These drugs work by different mechanisms and result in a decrease of 5% to 10% in weight.[1]

In addition, antiobesity drugs are associated with reductions in high blood sugar, high blood pressure, low-density lipoprotein cholesterol, and severity of obstructive sleep apnea, and with improvement in cardiovascular and metabolic outcomes.[1] These favorable effects, likely mediated by weight loss, make antiobesity prescription drugs an attractive option, especially considering that alternative options such as surgery are associated with a variety of additional risks.

◼ WHY DON'T PHYSICIANS PRESCRIBE ANTIOBESITY DRUGS?

It is estimated that fewer than 2% of overweight and obese patients in the United States were ever prescribed antiobesity drugs.[4] This may be owing to a variety of barriers.

Physicians and patients are reluctant to talk about obesity

Many physicians are not familiar with antiobesity prescription drugs or may lack the time to address weight loss with their patients. Some may avoid speaking about obesity during clinic visits due to the stigma associated with the topic. These factors are compounded by lack of appropriate reimbursement to these clinicians.[5] This will result in missed opportunities for introducing antiobesity prescription drugs to the right patients.

Similarly, many patients avoid the topic of obesity because they feel ashamed, or they feel helpless to do anything about it or cannot afford to seek care for it. These factors are compounded by a lack of public health policies to prevent and counteract obesity in the United States.[5]

Successful management of obesity requires a multifaceted approach

Obesity bias, negative attitudes toward individuals who are overweight and obese, is prevalent in the healthcare setting and represents a major barrier to medical care for these patients. This was highlighted in a systematic review by Puhl and Heuer[6] that documented providers viewing their overweight and obese patients as "unmotivated," "noncompliant," "sloppy," and "lazy" and perceiving overweight as a behavioral problem caused by physical inactivity and food addiction. These negative attitudes were expressed not only by physicians and nurses but also by medical students, fitness professionals, and dietitians. Obesity bias has a substantial impact on healthcare utilization; obese patients who experience stigma are less likely to receive appropriate preventive care and counseling, and weight management.[6]

Drugs have adverse effects

Antiobesity prescription drugs are relatively safe but are not free of adverse effects that can affect tolerability. For instance, orlistat may cause bloating, diarrhea, and fecal incontinence, which tend to occur early in the treatment and subside as the patient learns to avoid fatty foods. Phentermine-topiramate is associated with dizziness, palpitations, and hand tremors owing to its sympathomimetic properties and may not be suitable for patients with arrhythmogenic heart diseases.[2]

Moreover, more than a dozen other drugs previously introduced for short- and long-term management of obesity were withdrawn by the FDA because of serious adverse effects.[2] Fenfluramine and phentermine ("fen-phen") was withdrawn in 1997 because of its association with valvular heart disease.[7] These events may have discouraged physicians from prescribing weight-loss drugs, and patients from taking them.

Another potential barrier to utilization of weight-loss drugs is adherence. Antiobesity drugs are often prescribed for a long duration, making adherence difficult for patients, especially if the desired weight-loss goal is not achieved. Furthermore, because of the modest effect of antiobesity drugs on weight, physicians may prescribe them at higher, off-label dosages or prescribe non-FDA-approved drugs. Additionally, patients may resort to less expensive over-the-counter drugs, or drugs that have a more potent weight-loss effect but may also be addictive, such as amphetamines.[8]

Insurance does not pay for them

Gomez and Stanford[9] found that only 11% of US health insurance plans offered coverage for antiobesity prescription drugs, in only 9 states. Medicaid had some form of coverage for antiobesity prescription drugs in only 8 states, and Medicare excluded all weight-loss drugs from part D coverage, even if prescribed for noncosmetic indications. This general lack of coverage may be partially due to a lack of studies of cost-effectiveness and of long-term cost-savings associated with weight loss achieved by drugs.[10]

Recently, there have been efforts aimed at expanding Medicare part D coverage of FDA-approved antiobesity drugs. An example is the introduction of the Treat and Reduce Obesity Act of 2019, which also supports Medicare coverage for behavioral counseling for obesity by allowing other qualified healthcare providers such as advanced practice providers to offer these services.[11]

■ PROPOSED SOLUTIONS

The underuse of pharmacotherapy for obesity should be met by initiatives to educate patients on the available drugs, their benefits, and potential adverse effects.

At the same time, physicians and other prescribers should enhance their understanding of these drugs and thus gain confidence in prescribing them. This can be achieved with an early curricular focus on managing obesity and by setting up dedicated fellowships in obesity medicine for additional training.

Efforts should also be geared toward developing new drugs that are even more effective and have fewer adverse effects. Several antiobesity drugs are under investigation.[1] As these new medications make their way from laboratory to pharmacy shelf, prescribers should be updated and encouraged to offer them to their patients.

Comprehensive health insurance coverage is also key. With the recognition of obesity as a disease, pharmacotherapies for it should be made affordable and accessible. Health policies are needed to lower the costs of weight-loss drugs and expand health insurance cov-

Obesity is a disease, not a stigma or series of bad choices

erage to include FDA-approved medications. Additionally, public awareness should be raised on the lack of efficacy data and potential adverse effects of non-FDA approved weight-loss drugs.

Successful management of obesity requires a multifaceted approach, starting with empathy stemming from the perception that obesity is a disease, not a stigma or series of bad choices. It is imperative that pharmacotherapy be used as an adjunct to lifestyle modifications and not as a substitute.

Physicians can assume an essential role, going beyond the treatment of obesity to address and manage underlying contributors, which include psychological stressors, socioeconomic barriers, dietary patterns, comorbidities, and drugs the patient is taking for those conditions.[12] This demands detailed history-taking, regular follow-up visits, and a holistic and multidisciplinary approach, including intensive behavioral therapy and engagement of psychologists, nutritionists, and medical specialists when indicated.[12] ■

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Peripheral artery disease and unusual skin findings

A 68-year-old man with peripheral artery disease and dry gangrene of the feet was admitted to the hospital from a subacute rehabilitation facility because of increasing edema and erythema in the right lower extremity, with scattered areas leaking serous fluid.

Five months previously, he had presented to a podiatrist with superficial ulceration of the fifth toe of his left foot and a purple hue to all toes of both feet, findings that were thought to represent ischemia. Evaluation for vasculitis indicated normal renal function and was negative for antinuclear antibody, rheumatoid factor, and cryoglobulins. His erythrocyte sedimentation rate was mildly elevated at 12 mm/hour (**Table 1**). Peripheral artery disease was diagnosed, manifesting as dry gangrene of his toes and feet. Risk factors for peripheral artery disease were treated optimally with antihypertensive drugs, a statin, and low-dose daily aspirin, although he continued to smoke.

Three months before the current admission, he underwent left femoral endarterectomy with angioplasty with the goal of treating his peripheral artery disease. However, the ischemic changes of his feet continued to progress, and he developed necrotic areas on the right foot (hallux and the fourth and fifth digits) and the left foot (hallux and the distal aspects of the second, third, and fifth digits). Three weeks before the current admission, he underwent angioplasty of the right superficial femoral artery.

At the rehabilitation facility, he received appropriate wound care for his gangrenous toes, but because of the severity he could no longer bear weight and required a mechanical lift for transfers. He had chronic lower

TABLE 1

The patient's laboratory evaluation 5 months earlier

Test	Value[a]	Reference range
Erythrocyte sedimentation rate	**12 mm/hour**	0–10
C-reactive protein	0.90 mg/L	< 5.00
Antineutrophil cytoplasmic antibodies immunoglobulin (Ig) G	< 1:20	< 1:20
Rheumatoid factor	10.2 IU/mL	0–14.0
Cardiolipin IgA	4.9 APL units	0.0–13.9
Cardiolipin IgG	4.5 GPL units	0.0–9.9
Cardiolipin IgM	< 2.5 MPL units	0.0–9.9
Nuclear antibody IgG	< 1:40	< 1:40
Cryocrit	< 1%	< 1%

[a]Abnormal results are shown in bold.

extremity pain with no report of sensory loss. Lower extremity strength was 3 on a scale of 5 and symmetric bilaterally.

The patient's history also included tobacco use, hypertension, chronic obstructive pulmonary disease, hypothyroidism, urinary retention, and constipation. He had previously received the diagnosis of iron deficiency anemia, but iron supplementation had been recently discontinued because his hemoglobin level had returned to normal. His medications on admission to the hospital included low-dose aspirin, atorvastatin, carvedilol, lisinopril, levothyroxine, acetaminophen, senna, polyethylene glycol, albuterol and mometasone-formoterol inhalers, as well as albuterol-ipratropium given by nebulization.

Figure 1. The patient's lower back and buttocks on initial presentation.

A 68-year-old man was admitted because of worsening skin problems in his legs

Physical examination

On admission, his blood pressure was 109/64 mm Hg, pulse 83 beats per minute, temperature 36.6°C (97.9°F), weight 84.4 kg, and oxygen saturation 97% on room air. He was alert and in no distress.

Cardiopulmonary and abdominal examinations were unremarkable. His right leg had brawny edema with ill-defined reddish discoloration from the knee downward, with scant yellowish fluid weeping through small open erosions of the skin. The left calf appeared normal without edema. He had no lymphadenopathy.

He had a purplish red reticular discoloration of the skin around the right knee and diffuse red, purple, and maroon discolorations over the lower back and buttocks (**Figure 1**), known to be present for about 2 weeks. The skin appeared intact with blanchable discoloration.

The chronic necrotic changes of the toes appeared unchanged and without subungual hemorrhage. Posterior tibial pulses were difficult to palpate.

Laboratory results

A complete blood count with differential and a basic metabolic panel were drawn (**Table 2**). His thyroid-stimulating hormone level, liver enzyme levels, and international normalized ratio were normal.

■ CHARACTERIZING THE SKIN PROBLEM

1 Which of the following is most consistent with the patient's skin findings?

☐ Pressure injury
☐ Ecchymosis
☐ Livedo reticularis
☐ Purpura fulminans

Livedo reticularis is the condition most consistent with our patient's skin findings. A descriptive term indicating reddish-blue spots in a netlike or lacy pattern, livedo reticularis is caused by decreased blood flow to the skin.

The cutaneous vascular microanatomy can be thought of as a deep arterial bed with superficially penetrating arterioles for blood supply and a dense superficial venous plexus. Under this model, any process that reduces cutaneous blood flow results in better visualization of the venous plexus.

Physiologic vasospasm (eg, from cold exposure) can lead to reversible cutaneous discoloration, known as physiologic (primary) livedo reticularis.

Irreversible (secondary) livedo reticularis can lead to necrotic skin lesions owing to a lack of blood flow in the superficial arterial vessels.[1,2] It has systemic associations and can be caused by the following:

- Hypercoagulable states such as antiphospholipid syndrome and thrombotic thrombocytopenic purpura
- Other autoimmune conditions, including various manifestations of vasculitis
- Conditions of embolization or deposition, such as cholesterol embolization syndrome and calcific uremic arteriopathy.

Pressure injury. The skin remains intact only in the first stage of pressure injury and deep-tissue pressure injury, in which the skin is ischemic but not infarcted. Pressure injury is most commonly diagnosed visually.

Unlike the findings in our patient, stage 1 pressure injuries are erythematous rather than purple-maroon and are typically described as nonblanchable. Although a blanch response may be elicited in early stage 1 pressure injuries, our patient's skin lesions were present in some form over the previous 2 weeks. Deep-tissue pressure injury is maroon or purplish in appearance but is also typically nonblanchable.[3]

In addition to these differences, the sites involved in this patient do not suggest pressure injury, making this diagnosis unlikely. Pressure injury typically involves skin over a bony prominence, such as the iliac crest, sacrum, or coccyx.[4] Furthermore, although this patient is chair-bound, he is alert, has intact sensation, and is unlikely to have sustained pressure over the areas of these lesions to create a pressure injury.

Ecchymosis is the result of extravasation of blood in the tissues, most commonly from blunt-force trauma. Less commonly, it is seen with severe pancreatitis or peritoneal hemorrhage,[5] with classic distributions being periumbilical (Cullen sign) and flank (Turner sign).[6]

Ecchymosis is unlikely in our patient, who has no history of trauma and no notable abdominal symptoms to suggest severe acute pancreatitis or retroperitoneal hemorrhage.

Purpura fulminans, despite its name describing deep purple lesions, is not related to ecchymosis. Purpura fulminans involves extensive infarction of the skin, with the petechiae and purpura quickly progressing to blood pooling and skin necrosis. Purpura fulminans can follow disseminated intravascular coagulopathy (intravascular thrombosis and hemorrhage) caused by bacterial infection, malignancy, or immunologic reactions. Patients are acutely ill with rapid deterioration; hence, purpura fulminans signals a dermatologic emergency.[7,8]

Although our patient's skin lesions were initially violaceous and purpuric, they progressed slowly and he was not acutely ill, so this diagnosis does not fit.

■ CASE CONTINUED: THE PROBLEM SPREADS

The patient's right leg erythema was thought to represent deep vein thrombosis, reperfusion injury from his prior angioplasty with reactive erythema and edema, or ischemic changes from progression of his peripheral arterial disease. Venous ultrasonography showed no evidence of deep vein thrombosis. Angiography of the right lower extremity was repeated, and balloon angioplasty of a newly found narrowing in the right femoral artery was performed.

TABLE 2

The patient's laboratory results on admission

Test	Value[a]	Reference range
Glucose	88 mg/dL	70–100
Sodium	**125 mmol/L**	135–148
Potassium	4.0 mmol/L	3.5–5.3
Chloride	93 mmol/L	92–108
Bicarbonate	**18 mmol/L**	22–30
Blood urea nitrogen	17 mg/dL	8–23
Creatinine	0.82 mg/dL	0.50–1.00
Calcium	**7.7 mg/dL**	8.2–9.6
Albumin	**2.8 g/dL**	3.8–5.1
Hemoglobin[b]	**9.9 g/dL**	13.1–17.5
Platelet count	328 × 10⁹/L	150–400
White blood cell count	**14.8 × 10⁹/L**	4.0–10.0
Hematocrit[b]	**28.4%**	40.0-51.0%
Red blood cell count	**3.31 × 10¹²/L**	4.6–6.0
Mean corpuscular volume	85.8 fL	80–100.0
Absolute neutrophil count	**11.4 × 10⁹/L**	1.7–6.5
Absolute lymphocyte count	**1.3 × 10⁹/L**	8.0–4.0
Absolute monocyte count	**1.2 × 10⁹/L**	0.2–1.0
Automated absolute neutrophil count	**9.9 × 10⁹/L**	1.7–6.5
Absolute eosinophil count	**1.0 × 10⁹/L**	< 0.6

[a]Abnormal results are shown in bold.
[b]Previous studies showed microcytic iron deficiency anemia with low ferritin, serum iron, and transferrin saturation.

The patient returned to the subacute rehabilitation facility, where he was evaluated 2 days later. The red, purple, and maroon appearance of the skin around the right knee persisted and now involved the left knee (**Figure 2**). The patient was referred to a dermatologist, and results of further laboratory tests (**Table 3**) and skin biopsy were obtained.

2 What is the most likely cause of this patient's livedo reticularis?

☐ Acquired thrombotic thrombocytopenic purpura
☐ Antiphospholipid syndrome
☐ Cholesterol embolization syndrome
☐ Thromboangiitis obliterans

Figure 2. The patient's lower extremities demonstrated evolving livedo reticularis.

Three months earlier, he underwent a left femoral endarterectomy with angioplasty

Cholesterol embolization can occur spontaneously[9] but is most often reported after cardiac catheterization and infrarenal aortic and infrainguinal vascular procedures.[10,11] Because our patient's skin findings developed 3 weeks after his lower extremity angiogram, cholesterol embolization syndrome should be strongly considered in the differential diagnosis.

Cholesterol embolization syndrome starts with rupture of atherosclerotic plaque in a proximal large-caliber artery such as the aorta or iliac artery, followed by embolization of plaque debris and settling of cholesterol crystals in distal small to medium arteries.[12] A foreign-body inflammatory response to the cholesterol emboli ensues.[12,13] End-organ damage results from both obstruction and inflammation.

Cholesterol embolization syndrome is a microembolic process rather than what occurs in the more common arterioarterial embolization syndrome. The latter involves embolization of a large organized thrombus overlying an atheromatous plaque, which travels distally to occlude large downstream arteries and leads to severe ischemia of target organs.[12]

Cutaneous manifestations of cholesterol embolization syndrome include livedo reticularis with characteristic reddish-purple spots distributed in a fishnet or lacy (reticulated) pattern, cyanosis due to microvascular isch-

emia, and ulceration that progresses to gangrene.[12,14] The skin of the lower extremities is most commonly affected; if both extremities are involved, findings are usually asymmetric.

The diagnosis can be made clinically, with findings usually presenting days to weeks after the procedure, and with blood tests indicating inflammation, eg, elevated C-reactive protein, erythrocyte sedimentation rate, and white blood cell count with eosinophilia.[12] However, because the syndrome can mimic several diseases, biopsy of an involved organ (eg, kidney, skin, muscle) is needed to confirm the diagnosis. Biopsy of a suspect skin ulcer is generally preferable to internal organ biopsy because of easy accessibility and less procedural morbidity.

Thrombotic thrombocytopenic purpura, along with other thrombotic microangiopathies, may have cutaneous manifestations, including livedo reticularis, petechiae, ecchymosis, and purpura.[15] Acquired thrombotic thrombocytopenic purpura is an autoimmune disorder that results in functional inhibition or increased clearance of the ADAMTS13 enzyme, which normally cleaves von Willebrand factor to avert inappropriate platelet aggregation. It manifests as a Coombs-negative hemolytic anemia with thrombocytopenia and results in organ dysfunction, most notably in the central nervous system. The autoantibody process is often triggered by infection, drugs, malignancy, or pregnancy, although many patients do not have an identifiable cause.[16]

This diagnosis is unlikely in our patient. He does not have thrombosis or thrombocytopenia, his anemia is chronic, his normal total bilirubin is not concerning for hemolysis, and he does not have neurologic symptoms.

Antiphospholipid syndrome is an autoimmune disease characterized by thrombosis and, often, thrombocytopenia and red blood cell hemolysis.[17] Unlike thrombotic thrombocytopenic purpura, antiphospholipid syndrome is not a microangiopathic hemolytic process, so schistocytes are not seen on peripheral smear. The pathophysiology involves inappropriate binding of antiphospholipid antibodies to endothelial surfaces, which leads to upregulation of adhesion molecules to promote inflammation and coagulation.[18] Antiphospholipid syndrome often occurs in patients with other un-

derlying autoimmune disorders (eg, systemic lupus erythematosus).

The thrombocytopenia is often mild (platelet count 50–150 × 10^9/L). Cutaneous manifestations commonly include livedo reticularis and livedoid vasculopathy (ie, painful and recurrent ulcerations).[17,18] The lack of thrombosis, thrombocytopenia, or hemolysis makes this diagnosis unlikely in our patient.

Thromboangiitis obliterans (Buerger disease) is an inflammatory vasculitis that affects primarily small to medium-sized arteries and veins and leads to the development of occlusive thrombi.[19] Although its cause remains unknown, it occurs primarily in younger men (usually before age 45) and is almost exclusively associated with tobacco use.[20]

Serologic markers of inflammation including erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, rheumatoid factor, and complement levels are usually unremarkable.[19,20]

Although our patient is male and uses tobacco, it would be unusual to present with an initial insult at his more advanced age. Also, his peripheral arterial disease is affecting his large arteries, which is not characteristic of Buerger disease.

■ CASE CONTINUED: CHOLESTEROL EMBOLIZATION SYNDROME

Our patient's complete blood cell count 3 weeks after his angiogram indicated a high white blood cell count with eosinophilia. His erythrocyte sedimentation rate and C-reactive protein level were also elevated after hospitalization, although his chronically gangrenous feet likely confounded the picture.

Punch biopsy of the skin revealed embolic cholesterol crystals, confirming a diagnosis of cholesterol embolization syndrome.

3 Which of the following is true about cholesterol embolization syndrome?

☐ Normal renal function after an event is highly unusual

☐ It is more likely to occur after left heart catheterization than peripheral vascular procedures

☐ It can be prevented by antiplatelet therapy before the procedure

TABLE 3		
Follow-up laboratory evaluation at the time of skin biopsy		
Test	**Value**[a]	**Reference range**
Erythrocyte sedimentation rate	**104 mm/hour**	0–10
C-reactive protein	**198.10 mg/L**	< 5.00 mg/L
Antineutrophil cytoplasmic antibodies immunoglobulin (Ig) G	< 1:20	< 1:20
Rheumatoid factor	10.7 IU/mL	0–14.0
Beta 2 glycoprotein IgG	1 U/mL	0–20
Beta 2 glycoprotein IgM	1 U/mL	0–20
Cardiolipin IgA	9.9 APL units	0.0–13.9
Cardiolipin IgG	6.7 GPL units	0–9.9
Cardiolipin IgM	< 2.5 MPL units	0–9.9
Nuclear antibody IgG	< 1:40	< 1:40

[a] Abnormal results are shown in bold.

☐ Subsequent angioplasty is not contraindicated

It is unknown if cholesterol embolization syndrome is a risk factor for recurrence after a subsequent similar procedure.[12,21] Hence, angioplasty procedures after diagnosis are not absolutely contraindicated, but careful risk-benefit analysis should be done since the initial occurrence suggests the presence of atherosclerotic plaque that may still be vulnerable to mechanical injury and repeat embolization. Whether benefits of further interventions likely outweigh the potential risk of recurrent cholesterol emboli should be considered on an individual basis.

About half of patients with cholesterol embolization syndrome have kidney involvement, presenting as a rise in serum creatinine with proteinuria. One mechanism of renal injury is thought to be vascular obstruction by cholesterol crystals, leading to tissue ischemia, cell necrosis, and inflammation.

The gastrointestinal tract is affected in 19% to 48% of patients, and the problem most commonly presents as bowel ischemia, which can result in gastrointestinal blood loss from mucosal ulcerations due to mucosal infarcts.

Cutaneous manifestations occur in 35% to

Cholesterol embolization can occur spontaneously, but most often after vascular procedures

Figure 3. The patient's right flank (left), lower back (middle), and right hip (right) demonstrated evolving ulceration and necrosis of lesions seen in Figure 1.

96% of patients, and those with renal manifestations are most commonly affected.[12,22] Although a decrease in renal function would support a diagnosis of cholesterol embolization syndrome, it is not uncommon for kidneys to be unaffected, as is the case for our patient.

Based on observational data, patients undergoing cardiac surgery or abdominal aortic repair are at more risk of developing cholesterol embolization syndrome than those having coronary angiography or minimally invasive procedures.[12] Its incidence after angiography or angioplasty is low (1%–2%), but it is likely underrecognized.[23,24]

Although cholesterol embolization syndrome can develop after angiography alone as a result of catheter introduction or manipulation, interventional procedures may increase the risk. A high index of suspicion for cholesterol embolization syndrome should be maintained regardless of the indication for angiography, arterial access site, or interventions performed.

No clinical evidence suggests that antiplatelet therapy helps prevent cholesterol embolization syndrome. Modifiable risk factor reduction (eg, blood pressure control, smoking cessation) may help prevent it.[23]

■ SUPPORTIVE MANAGEMENT

No specific treatments address cholesterol embolization syndrome, so management is primarily supportive by maintaining hemodynamic stability and optimizing nutrition. End-organ damage is associated with high morbidity and mortality risk and is particularly important to address.[12]

Severe skin lesions require appropriate wound care, appropriate bed support surfaces, and patient positioning to protect from fur-

Punch biopsy of the skin revealed embolic cholesterol crystals, confirming the diagnosis

ther injury and secondary infection.[25]

Steroids have been suggested to reduce inflammation caused by cholesterol crystals,[26,27] as have statins to help stabilize plaques.[28,29] However, neither therapy has been studied for cholesterol embolization syndrome in a randomized controlled trial.

Recurrent embolism rates have been reduced with surgical endarterectomy and bypass procedures, and data on the use of intraluminal stenting procedures is promising in some patients.[30] There is no role for anticoagulation or fibrinolytic therapy for managing the condition.

Some case series suggest that warfarin or fibrinolytics may lead to cholesterol embolization syndrome, although this association is unclear and not supported by clinical trial data. The best way to reduce recurrence may be to limit invasive intra-arterial studies and interventions.[12] Unfortunately, this is challenging, as many of these patients require such studies and procedures, given their medical complexity and severity of cardiovascular disease.

■ CASE CONTINUED: ULCER CARE

The patient had normal renal function, indicating his kidneys had been spared. He required no treatment other than care of the skin ulcers that developed from damage by cholesterol emboli.

Over the course of 4 weeks, his lesions, initially confluent, reticulated, and purplish, evolved into full-thickness necrotic ulcers (**Figure 3**). Four demarcated ulcers on his back and trunk (the largest being 3.5 cm × 8 cm) were 100% necrotic (eschar) tissue with open wound edges that drained a moderate amount of serosanguinous fluid.

Initially, a dry sodium-impregnated gauze

was used to debride the moist necrotic tissue through reverse osmosis. As the necrotic areas softened and were debrided, the wound base developed granulation buds with areas of thick, slough tissue (**Figure 4**). The wound was then managed with a honey-based product to address the high bacterial load in the ulcers, followed by a calcium alginate foam dressing to absorb the exudate while maintaining a moist wound. Surgical debridement was not required, and neither systemic nor topical antibacterial agents were used.

Five months after the patient's hospitalization, the ulcers had improved, and hydrocolloid dressings were used. At 8 months, all the ulcers were healed.

Unfortunately, his severe gangrene of the toes, which predated the cholesterol embolization syndrome, progressed to involve the midfoot and eventually required bilateral above-the-knee amputation. Once the patient was less catabolic from chronic gangrene, and after receiving excellent wound care and optimization of oral nutrition, the ulcers from his cholesterol emboli healed completely, and he regained his previous baseline health status.

■ TAKE-AWAY POINTS

- Skin lesions involving the disruption of arteries and subsequent ecchymosis, whatever the inciting mechanism, should prompt an evaluation for an underlying systemic cause.
- Cholesterol emboli should be suspected when characteristic skin lesions appear in

Figure 4. The patient's flank ulcer 2 months after treatment.

the days or weeks after angiography.
- Clinical history, physical examination, laboratory findings, and biopsy are essential for diagnosis.
- Renal and gastrointestinal complications are potentially the most serious end-organ manifestations of cholesterol embolization syndrome. However, skin lesions can progress to large necrotic ulcers, causing significant morbidity.
- No treatment is specific for cholesterol embolization syndrome, but complications must be managed.
- Smoking cessation and blood pressure control may reduce the risk.
- Substantial damage to skin can occur in cholesterol embolization syndrome, as in this case, with 8 months to complete resolution of what eventually became full-thickness necrotic ulcers. ■

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Promoting resiliency in adolescents during a pandemic: A guide for clinicians and parents

ABSTRACT

The COVID-19 pandemic has dramatically affected every aspect of daily life. Parents of adolescents, in particular, may be facing unique challenges in helping them navigate unexpected changes to their daily routine. This article discusses how adolescents may respond to stressful and traumatic situations and provides recommendations for clinicians who may be advising parents of adolescents or parenting their own children.

KEY POINTS

Young adults who are socially isolated during COVID-19 may experience intense feelings of loneliness, increasing their risk for depression and anxiety.

Primary care providers can help their adolescent patients by ensuring they continue to receive immunizations on time and have access to prescribed medications, as well as scheduling future well visits and contraceptive counseling when needed.

Family support is key to helping adolescents cope with the negative effects of stress caused by the pandemic.

When advising parents of teens, discuss ways in which they can support their child. This can include acknowledging their disappointment about missing important social events, encouraging time limits for social media, and helping them practice "adulting" skills such as planning and cooking meals.

THE COVID-19 PANDEMIC has introduced great global uncertainty, affecting every aspect of daily life and requiring sudden adaptation to ever-changing circumstances. Parents with children of all ages have seen enormous and unexpected changes in how their children are engaged in and out of the home. In particular, parents of adolescents may face unique challenges in helping their children navigate changes to their daily routine.

This article draws on experience from prior global catastrophes and suggests evidence-based counseling strategies for clinicians who are advising parents of adolescents and their families during the pandemic. These strategies can also be used by clinicians who are themselves parents of adolescents.

■ SOCIAL DISTANCING: A SOURCE OF STRESS FOR ADOLESCENTS

Adolescence is a developmental stage characterized by changes to parental and peer relationships, including a decrease in the amount of time spent with family and an increase in the amount of time spent with peers.[1] Many, but not all, experience a range of intense and volatile emotions.[2] A decrease in the quantity and quality of peer interactions for any reason can lead to intense feelings of loneliness,[3] which has been identified as a risk factor for mental health disorders such as depression and anxiety.[4] Loneliness has also been linked to impaired sleep quality,[5] eating disorders,[6] and increased risk of alcohol and drug abuse,[7] among other mental health concerns.

While these correlations have been observed across the life span,[8] adolescents are more likely to feel lonely due to the high value attached to peer friendships and romantic relationships during this developmental period.[3] Young adults who are socially isolated during COVID-19 may experience greater feelings of loneliness and may be at increased risk of depression.[3]

◼ EFFECTS OF STRESS ON CHILDREN AND ADOLESCENTS: THE ACE STUDY

Although no study has looked at the effects of a pandemic on adolescent health, the effects of various types of acute and chronic stress have been widely studied in children and adolescents. The Adverse Childhood Experience (ACE) study, conducted in the 1990s in San Diego, was one of the first to link stressful experiences in childhood with later mental and physical health outcomes.[9]

While the original ACE study focused on events of abuse or neglect, the adverse experiences included in later iterations of the study included a wide array of more insidious stressors such as parental stress, financial hardship in the household, and discrimination—many of which are present with the COVID-19 pandemic. These stressors resulted in depression and a higher prevalence of risky behaviors in pregnant women who experienced adverse childhood experiences and a higher risk of ischemic heart disease in adult survivors.[9–13]

Data from the ACE study also suggest that there is a dose-response relationship between the number of adverse childhood experiences and risk of negative health outcomes later in life. These include many leading causes of death in the United States such as cancer, stroke, diabetes, and suicide.[13,14] Certain individuals may be more predisposed to long-lasting adverse effects of stressful events, based on a complex interplay of genetic predisposition and environmental factors.[14]

Fortunately, if exposure to stressors resolves after a short time, and if the individual can learn effective coping mechanisms, research suggests that long-term effects can be mitigated.[15]

A decrease in peer interactions can lead to intense feelings of loneliness

◼ HOW CLINICIANS CAN HELP FAMILIES GET THROUGH THE PANDEMIC

Helping adolescent patients and their families attend to the basics remains important. The American Academy of Pediatrics notes that missed immunizations during a pandemic may lead to outbreaks of preventable illnesses.[16] Missed well visits or contraceptive counseling visits may result in increased teen pregnancies in the next year.

Additionally, children and adolescents with chronic disease may be more or less compliant with medication schedules when at home with parents, and access to medication may be interrupted because there are fewer routine trips to the pharmacy. Stress can cause chronic illness to flare, as well.

Astute clinicians can partner with their adolescent patients and the patients' parents on ways to support responsible self-care. For instance, ask the patient to consider using a smartphone app that automatically reminds users when it is time to take their medications. Patients can then teach their parents how to do the same.

Experience with other global tragedies reveals that disaster training courses can be useful for healthcare providers, including pediatricians, internists, and family physicians involved in the care of youth impacted by war or other tragedies.[17] These courses can help providers understand the context-specific health needs of children, the management of chronic conditions, and the care of children with special healthcare needs in conflict and postconflict settings, including the current one.

We recommend the following resources:

- **American Academy of Pediatrics.** www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/default.aspx
- **Administration for Children and Families.** www.acf.hhs.gov/trauma-toolkit/emergency-crisis-and-disaster
- **Centers for Disease Control and Prevention.** www.cdc.gov/childrenindisasters/children-disaster-help.html.

◼ FAMILY SUPPORT IS KEY

Research suggests that the negative effects of stress may be buffered by supportive rela-

tionships with adults, such as parents or other caregivers.[15] Refugee children in high-income countries showed improved mental health and well-being when they experienced high parental support and family cohesion, self-reported encouragement from friends, and positive experiences at school.[17,18] Youth in an indigent area of Rotterdam showed more resiliency when community ties were deepened through experiential learning, and were better equipped to address uncomfortable issues.[19] Abma et al[19] refer to these measures as "sowing seeds to harvest healthy adults."

With this in mind, parents can take several actions to support their teens during the COVID-19 pandemic.

Explain anxiety: The fight-or-flight response

Anxiety can be "normalized" and explained. It is the way the body alerts itself to danger, which is an appropriate initial response to COVID-19.

When explaining this series of complex metabolic events to a young person, keep it simple: anxiety activates your fight-or-flight response, which gives you a surge of adrenaline. This adrenaline allows you to detect the threat and outrun it, and is a useful mechanism. But if this response is constantly activated by potential threats, the body may not be able to tell the difference between a serious threat and a less serious threat, leading to severe anxiety about COVID-19.

Parents can help anxious adolescents channel their anxiety in more productive ways, such as doing craft projects (eg, learning to sew fabric masks for family members). The body is not made to live on constant adrenaline, so coping mechanisms such as yoga, meditation, taking a walk in nature, and listening to music when isolated at home can help. Writing, drawing, and anything creative can also activate other parts of the brain and calm the adrenaline surge. Parents can also encourage other distracting activities, such as going for a walk or jog outside (while continuing to stay away from others).

At the same time, it is also important to give teens privacy and space to be alone when needed,[20] such as in their bedroom or in another quiet space.

Addressing news and social media

A constant stream of news and social media can contribute to a sense of fear and helplessness for adolescents and their parents. As news articles continue to discuss the COVID-19 infection rate and the need to "flatten the curve," anxiety, depression, and emotional distress increase, a phenomenon referred to as the "second curve."[21]

We encourage parents to talk to adolescents about setting limits on the amount of time they spend reading about current events.[22] Parents may also choose to model this behavior by taking a break from social media at certain times of the day or week.[23]

Enforcing limits on time spent using technology may be more challenging than parents are used to, because the same devices used for reading the news, such as smartphones and laptops, are also being used now to attend virtual classes and stay connected with friends and family members. Parents may choose to modify previous limits set on technology use. However, it may be useful to continue to set some adjusted limits and expectations about times when technology should not be used, such as during dinner or after bedtime.

Parents should make time for adolescents to talk about news articles or social media posts they have seen, as current news articles can be upsetting for readers.[23]

Parents can discuss how some information on the Internet and social media may be incorrect or misleading. However, current information from reputable news sources can be equally upsetting, given the uncertainty of the current global situation. A particularly anxious or depressed child or adolescent may require curbing of media time and less discussion to avoid a constant state of anxiety or stress.

The parent or provider can also offer useful perspectives, helping to keep adolescents from overestimating the risks of COVID-19 or underestimating their own ability to keep themselves safe.[22]

Watch for downstream effects of stress

Some adolescents may experience an increase in somatic complaints such as chronic headaches and abdominal pain, with or without awareness of the role of stress in amplifying

Activities such as yoga, meditation, a nature walk, and listening to music can help one cope

this pain. Disrupted sleep cycles (excessive sleep or too little sleep) can also make the young person feel worse, be more irritable, or less resilient. Maladaptive coping strategies can emerge, including disordered eating, self-harm, and substance use. The adolescent's lack of abstract thought may impede the ability to see consequences in the moment.

Acknowledge uncertainty and disappointment

The inability to participate in team sports, attend in-person social events, and spend time with friends face-to-face may leave teenagers feeling bored, lonely, and sad. Loss of social milestones, including graduation and prom, can exacerbate these feelings in adolescents and parents.[20] While some of these events may be postponed and rescheduled for a later date, the adolescent may still feel a sense of grief or loss.[20]

Parents should anticipate and validate these feelings in their adolescent children. Many young people acknowledge the conflict between perceived selfish desires and the good of the larger community; allowing teens to share and reconcile their own needs with what they know is right can help them process this juxtaposition of feelings. Adolescents are perceptive and aware of the stress experienced by adults in the household and in society[22]; adult stress regarding canceled plans can therefore increase adolescents' stress level.

An "ask-tell-ask" approach can be particularly useful in engaging the young person, expressing empathy, and helping the adolescent get to the "right" solution a little more gracefully.

To use this model, parents can ask the adolescent how they think personal and family sacrifices, such as canceling a vacation or not visiting friends, can protect the community and contribute to decreasing the strain on local hospitals and healthcare workers.[22] After listening closely to their response, parents can fill in any information gaps in the adolescent's understanding while continuing to ask the adolescent what they think.

A partner in problem-solving, not a problem to be solved

If the parent requires help watching a younger sibling, the parent can ask, "I am going to need to get XYZ done, and I know you have homework to do. I am going to need some help to get this done. What works best for you? Or how should we best divide and conquer?"

Hold high expectations for adolescents, with flexibility. Ask what schedule works best for them to get work done, and also to get adequate sleep and time for online socialization, exercise, or other downtime. Brainstorm solutions that work for children and adolescents without disrupting the household.

Help adolescents assume responsibility for following guidelines

As time goes by and adolescents experience a growing sense of confinement at home, they may begin to question the guidelines for social distancing and may want to push the limits of what is allowed.

Parents can discuss with adolescents the most current US Centers for Disease Control and Prevention guidelines for social distancing and why they are important. Since the general public is now widely aware that older and immunocompromised individuals are at higher risk for complications from COVID-19, adolescents, particularly those who do not have immunodeficiencies, may not understand the importance of strictly adhering to the guidelines themselves since they are less likely to suffer negative effects of infection.

Abstract thought, or the ability to foresee consequences, is a cognitive development that happens in late adolescence, usually age 18 and older. Keeping examples more concrete can help ground the discussion in ways that connect the adolescent to the situation, as in the impact on a beloved elderly family member, or of a family member who has cancer or is otherwise immunocompromised.

Families can discuss how each member is responsible for staying home in order to protect themselves as well as the community. Adolescents may feel that meeting up with friends is not particularly risky for them personally, but doing so could put other people in the household at risk, including:

- Those who are immunocompromised, or otherwise at a higher risk for COVID-19
- A caregiver for a vulnerable individual
- An essential worker who comes into contact with other people outside the household.

Families can discuss how each member is responsible for staying at home to protect themselves and the community

Parents can model this behavior by strictly adhering to the guidelines themselves. If adolescents see their parents disregarding guidelines for social distancing, they may ask to do so themselves. "Do as I say, not as I do" has not worked well for children, adolescents, or adults.

Help adolescents develop life skills

While at home, parents can take opportunities to teach their adolescents life skills such as planning and cooking meals.[24] Adolescents can also help with chores such as laundry and dishes and practice "adulting." Experiential learning could include learning to manage a checking account and plan a weekly budget.

Laughter is some of the best medicine

Never underestimate the power of a good belly laugh to relieve tension. If laughter does not come naturally to a young person or a family, challenge the teen to find something on YouTube or Instagram that they find amusing and to share it with you. The same can be done by watching a fun movie together as a family. As Dr. Colleen Hacker[25] states, "Laughter is the antidote to stress." But remember always to laugh with, never at, the adolescent.

Instill a sense of gratitude

As part of the daily routine of family dinner, ask each family member to share something that they are grateful for. Gratitude highlights connection and is strongly linked to emotional well-being and life satisfaction.[26] The act of focusing on gratitude helps youth pay attention to what is positive in their life, instead of becoming overwhelmed by negatives.

Find joy and wonder in each day, and share that lens with one another

Finding small ways to be joyful can help the young and old survive rough times. Toddlers do this naturally; adolescents may need more guidance to start the process. Take a virtual tour of a museum or natural setting and then apply the same focus to walking through one's house or backyard.

Virtual input from grandparents and remote loved ones can also create personal connection to items or photos discovered on the "tour." This kind of connection benefits individuals across generations and can be a point for thoughtful reflection, shared laughter, and other emotions.

Keep in mind that each day does not have to be a whirlwind of activity from dawn to dusk. The forced slowdown of social isolation can be a time for families to pause, reflect, prioritize, and enjoy the simple things.

■ YOUNG PEOPLE THRIVE

Young people thrive with clear, caring, and open communication. Children take their cues from parents' anxiety levels and reactions to COVID-19. Although school-age children may lack the emotional maturity to tolerate uncertainty, adults and caregivers can ask about their fears, respond with openness and empathy, and problem-solve together. Adolescents—digital natives born and raised in an era of technology—may devise their own solutions to political, ethical, financial, and practical challenges posed by this pandemic. Approach them as a resource with whom to collaborate on innovative solutions in this new reality. ■

This can be a time for families to pause, reflect, prioritize, and enjoy the simple things

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COVID-19 and the kidney

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ABSTRACT

COVID-19 is primarily considered a respiratory illness, but the kidney may be one of the targets of SARS-CoV-2 infection, since the virus enters cells through the angiotensin-converting enzyme 2 receptor, which is found in abundance in the kidney. Information on kidney involvement in COVID-19 is limited but is evolving rapidly. This article discusses the pathogenesis of acute kidney injury (AKI) in COVID-19, its optimal management, and the impact of COVID-19 on patients with chronic kidney disease, patients with end-stage kidney disease on dialysis, and kidney transplant recipients.

KEY POINTS

AKI is common in COVID-19 and is associated with poor outcomes.

SARS-CoV-2 can damage the kidney through several mechanisms, including acute lung injury, sepsis, hemodynamic alterations, cytotoxic effects, cytokine release syndrome, rhabdomyolysis, coagulopathy, microangiopathy, and collapsing glomerulopathy.

Despite initial speculation, renin-angiotensin-aldosterone system inhibitors need not be discontinued in patients with COVID-19.

Treatment of AKI includes general management, pharmacologic management of COVID-19, hemodynamic and volume optimization, and extracorporeal therapies.

Pharmacotherapy for COVID-19 can be divided into antibacterial, antiviral, immunomodulatory, and anti-inflammatory drugs.

S EVERE ACUTE RESPIRATORY SYNDROME coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), gains entry into target cells through the angiotensin-converting enzyme 2 (ACE2) receptors. ACE2 receptors are present in the kidneys as well as the lungs, heart, and intestinal cells.[1–8]

The renin-angiotensin system plays an important role in human physiology. Angiotensin I is cleaved from angiotensinogen by renin and converted to angiotensin II by ACE. Angiotensin II causes systemic vasoconstriction and also enhances inflammation, endothelial cell dysfunction, oxidative stress, collagen synthesis in fibroblasts, and fibrosis in target organs.[7,9] ACE2 is a counterregulatory enzyme that breaks down angiotensin II to form angiotensin 1–7, which mediates vasodilation and attenuates angiotensin II-mediated inflammation.[7]

SARS-CoV, the virus that caused the SARS epidemic in 2003, downregulates expression of ACE2 after it enters the cell, and without the counterregulatory effects of ACE2, the deleterious effects of angiotensin II

TABLE 1

COVID-19: Incidence of acute kidney injury and need for kidney replacement therapy

Author	No. of patients	Incidence of acute kidney injury[a]	Use of kidney replacement therapy
Huang et al[5]	41	7%	7%
Chen et al[16]	99	3%	9%
Wang et al[6]	138	3.6%	1.4%
Yang et al[14]	52	29%	17%
Guan et al[4]	1,099	0.5%	0.8%
Zhou et al[15]	191	15%	5%
Cheng et al[13]	701	5.1%	Not reported
Arentz et al[22]	21	19.1%	Not reported
Richardson et al[18]	2,351	22.2%	3.2%
Pei et al[21]	333	6.6%	Not reported
Hirsch et al[17]	5,449	36.6%	5.2%
Cummings et al[20]	257	Not reported	31%
Fisher et al[19]	3,345	56.9%	4.9%

[a]As defined by the Kidney Disease Improving Global Outcomes criteria, ie, increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours or increase in serum creatinine to ≥ 1.5 times baseline within the previous 7 days.

are believed to lead to lung disease, including severe acute respiratory distress syndrome.[7,10]

The kidney has an abundance of ACE2 receptors and therefore may be one of the primary targets of SARS-CoV-2 infection.[7] ACE2 is expressed in the kidney much more than in the lungs, specifically on the brush border apical membrane of the proximal tubule and also at lower levels in the podocytes.[11] Virus particles were observed in the tubular epithelium and in podocytes in an autopsy series of COVID-19 patients.[12] TMPRSS2 is robustly expressed in the distal nephron but not the proximal tubule; it is unclear if other transmembrane serine proteases in the proximal tubule can mediate the priming step.[8]

■ INCIDENCE RATES VARY IN DIFFERENT REPORTS

The reported incidence of acute kidney injury (AKI) in COVID-19 ranged from 0.5% to 56.9% in various case series (**Table 1**).[4–6,13–22] The wide range is likely related to different definitions used and different populations studied.

A higher incidence has been reported in the United States than in China.[4–6,13–19] Also, studies from China reported the onset of AKI within a median of 7 to 14 days after admission, whereas a large study of patients hospitalized with COVID-19 in the United States[17] found that the onset tended to be early; 1,993 (36.6%) of 5,449 US patients developed AKI, and of these, 37.3% either arrived with it or developed it within 24 hours of admission. Of those with AKI, 31.1% reached stage 3 (the highest, defined as an increase of 3 times or more in serum creatinine within 7 days or start of kidney replacement therapy), and 14.3% needed kidney replacement therapy.

In another study,[20] 79 (31%) of 257 critically ill patients required kidney replacement therapy. A study contrasting AKI incidence between 3,345 patients with COVID-19 and 1,265 patients without COVID-19 hospitalized during the same time period showed that those with COVID-19 had a higher incidence of AKI (56.9% vs 37.2%), and more of them needed kidney replacement therapy (4.9% vs 1.6%).[19]

Black race has been shown to be independently associated with a higher risk of AKI in COVID-19.[17,19]

Higher mortality rate

AKI in COVID-19 is also associated with a higher risk of death.[13,21] A systematic review and meta-analysis[23] of 6 studies from China found that severe AKI in COVID-19 (defined as AKI stage 3 and AKI requiring kidney replacement therapy) was associated with a 3-fold higher risk of death.

A US study[17] reported a mortality rate of 35% in patients with AKI; of those who died, 91% had stage 3 AKI. The mortality rate was 55% in those needing kidney replacement therapy. Another study[19] showed an in-hospital mortality rate of 33.7% in those with COVID-19-associated AKI compared with 13.4% in those with AKI without COVID-19. Those with stage 3 AKI and COVID-19 had a 2.6-fold higher mortality rate than those with stage 3 AKI who did not have COVID-19.

There are limited data on the long-term prognosis of COVID-19 patients with AKI.
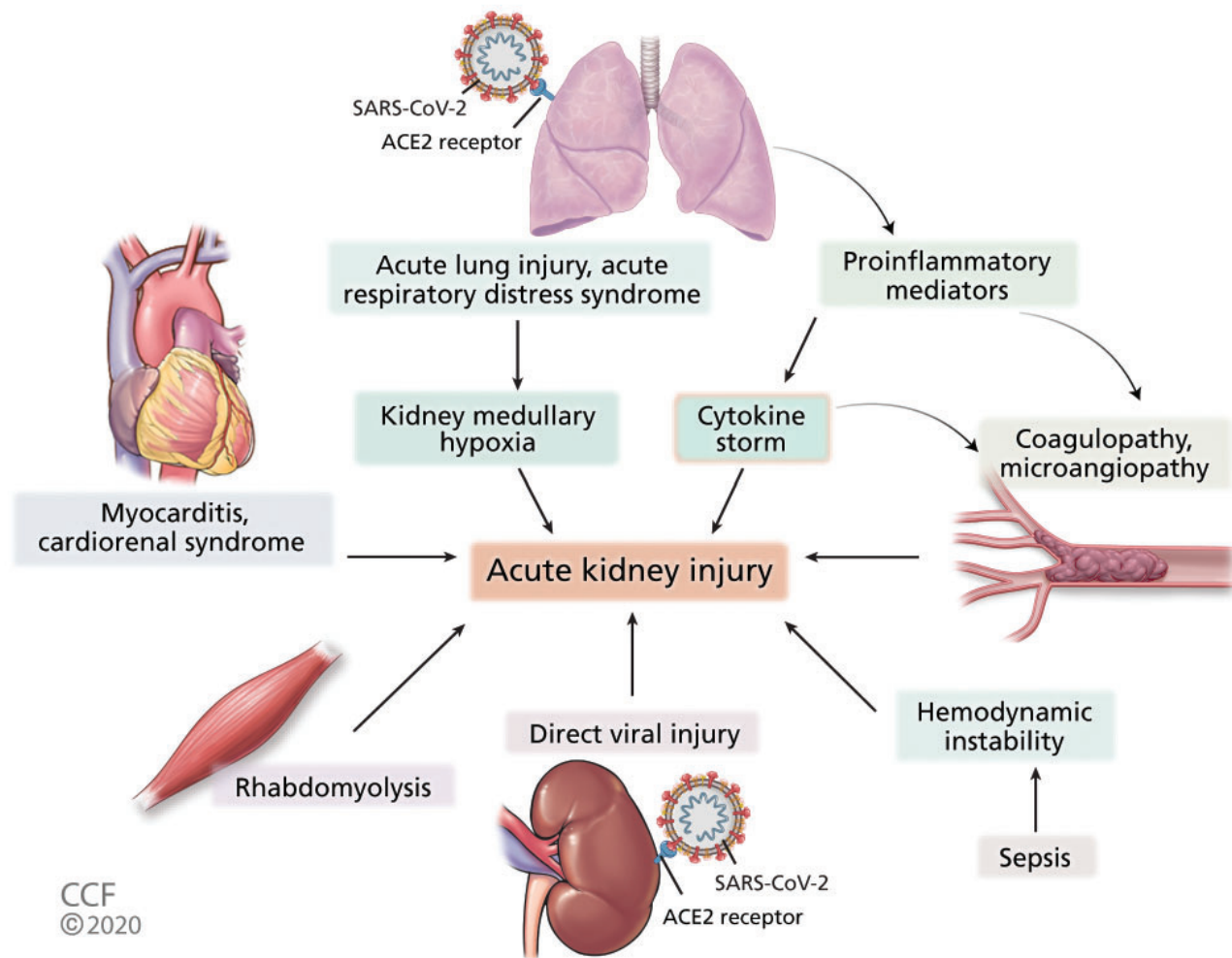
Figure 1. Pathophysiology of acute kidney injury in COVID-19 (ACE2 = angiotensin-converting enzyme 2; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2).

A single-center study from China reported that although the mortality rate was high in patients with AKI, nearly half of the patients recovered from AKI within 3 weeks of onset of infection.[21] A US study[17] reported a median creatinine level of 1.70 mg/dL (interquartile range 0.96, 3.50) at the time of discharge in patients with AKI, and 91% of hospitalized patients who needed kidney replacement therapy were still on it at the time of study censoring. Another study from the United States showed that fewer COVID-19 AKI patients recovered renal function than AKI patients without COVID-19 (42.3% vs 68.5%).[19]

Proteinuria and hematuria have been reported in patients with COVID-19, but their significance and impact on mortality are not yet known. An early report from China[13] found proteinuria in 43.9% and hematuria in 26.7% of patients. Subsequent studies from the United States reported 2+ or 3+ blood in 46% of patients, and 2+ or 3+ protein in 42% of patients on urine dipstick analysis. Another study showed proteinuria in 87% of patients.[17,20]

While the effects of ACE2 expression and viral entry on proteinuria are unknown, it is speculated that proteinuria could be related to viral replication, particularly in the podocytes.[11]

■ PATHOGENESIS OF ACUTE KIDNEY INJURY

Figure 1 shows the possible pathophysiologic mechanisms of AKI in patients with COVID-19.

Acute lung injury

Acute lung injury could lead to AKI through hemodynamic changes and reduced cardiac output with high intrathoracic pressure, inflammatory cytokines that lead to systemic inflammation, and reduction in kidney medullary perfusion due to hypoxemia.[24–26]

Sepsis

Sepsis, due to viral or bacterial infection, is associated with increased risk of AKI. Higher levels of inflammatory cytokines including interleukin 6 (IL-6), and maladaptive immune responses leading to microvascular dysfunction, increased vascular permeability, and tissue damage have been suggested as mechanisms of AKI in sepsis, along with hypoperfusion affecting the kidney microcirculation.[27]

A study from China early in the pandemic reported septic shock in 6.4% of COVID-19 patients.[4] Another study found that 59% of COVID-19 patients developed sepsis, 20% developed septic shock, and 15% developed secondary infection.[15] Bacterial co-infections have been reported in severely ill COVID-19 patients, which raises the possibility of sepsis playing a role in AKI in these patients.[16]

Hemodynamic alterations

Cardiorenal syndrome is another possible mechanism of AKI in patients with COVID-19. Viral myocarditis and cardiomyopathy with left ventricular dysfunction could lead to decreased perfusion to the kidneys, resulting in AKI.[26]

Cytotoxic effects
leading to tubular and podocyte injury

SARS-CoV-2 can potentially injure tubular cells and podocytes, leading to proteinuria, hematuria, and AKI. ACE2 is expressed in high amounts in the proximal tubular cells and podocytes, which may be the site of viral entry in the kidneys,[28] and studies have noted proteinuria and hematuria in COVID-19 patients.[13,17,20]

In an autopsy series by Su et al,[12] light microscopy showed proximal acute tubular injury with occasional frank tubular necrosis. Corona virus-like particles were also observed under electron microscopy in the proximal tubular epithelium and podocytes.[12,29]

In a preprint report of autopsy data on 6 patients from China,[30] viral nucleoprotein antigens were detected in the kidney tubules by immunohistochemical analysis, and virus-like particles were observed under electron microscopy. However, the rabbit monoclonal antibody against the SARS-CoV-2 nucleoprotein used in the autopsy series to detect virus particles has been described as having nonspecific positive staining of the kidney parenchyma in non-COVID-19 patients.[31]

Larsen et al[31] reported that in situ hybridization for SARS-CoV-2 did not detect viral RNA in the kidney.

Thus, there is conflicting evidence regarding the possible direct cytopathic effects of SARS-CoV-2 on tubular epithelial cells.

Cytokine release syndrome
or hyperinflammation

Viral and bacterial infections are known to cause excessive release of inflammatory cytokines that lead to organ damage.[32] Huang et al[33] reported that in the 2003 outbreak, SARS-CoV infection resulted in cytokine storm or hyperinflammation with increased levels of IL-6, IL-8, and interferon gamma, which led to increased vascular permeability and diffuse alveolar damage. As described above, patients with acute lung injury have an increased risk of AKI due to hemodynamic changes, hypoxia, and inflammatory cytokines.

Rhabdomyolysis

Case reports from the 2003 SARS epidemic described rhabdomyolysis of suspected viral etiology and AKI, but evidence of causation has been lacking.[34,35] Postmortem kidney histopathologic analysis of COVID-19 patients has shown pigmented casts in the kidney tubules and increased creatine kinase, possibly representing rhabdomyolysis of unclear etiology.[12]

Coagulopathy and microangiopathy

Coagulopathy has been noted in COVID-19 patients, with altered prothrombin time, activated partial thromboplastin time, D-dimer levels, fibrinogen levels, and fibrin degradation product levels and disseminated intravascular coagulation.[36,37] Release of inflammatory mediators and the uninhibited effects of angiotensin II can possibly trigger the coagulation cascade and predispose to hyperco-

SARS-CoV-2 gains entry into cells through ACE2 receptors

TABLE 2

Causes of acute kidney injury in COVID-19 patients

Cause	Supporting evidence
Prerenal (volume depletion)	Increased blood urea nitrogen: creatinine ratio (> 20), urine sodium < 20 mmol/L, fractional excretion of sodium < 1%
	Urine sediment may show hyaline casts
Acute tubular injury	Urine sodium > 20 mmol/L, fractional excretion of sodium > 1%
	Urine sediment with granular or muddy brown casts
Acute interstitial nephritis	Rash, eosinophilia, white blood cells on urine microscopy
	Urine sediment with white blood cell casts (urine eosinophils are not sensitive or specific)
Postrenal (obstruction)	Bladder scan with high postvoid residual volume, oliguria improving with Foley catheter placement
	Kidney ultrasonography showing hydronephrosis
Rhabdomyolysis	Increased serum creatine kinase and myoglobin in urine
	Positive urine dipstick for blood, no red blood cells on microscopy
Abdominal compartment syndrome	Increased intra-abdominal pressure (> 20 mm Hg)
Coagulopathy	Elevated prothrombin time, partial thromboplastin time, D-dimer, fibrinogen
Cardiorenal syndrome	Jugular venous distention, low ejection fraction on echocardiography, urine sodium < 20 mmol/L

agulability.[38] A high incidence of thrombotic complications has been reported even in those on prophylactic anticoagulation.[15,39–41] In a postmortem kidney histopathologic analysis, fibrin thrombi were present in the absence of red blood cell fragmentation and platelet thrombi, due to which a hypercoagulable state was suspected.[12]

Thus, endothelial cell dysfunction leading to activation of the coagulation cascade and thrombosis of the microcirculation may also play a role in AKI.[42]

Collapsing glomerulopathy

Collapsing glomerulopathy has been reported in kidney biopsies of patients with CO-VID-19.[31,43,44] In one report,[44] tubuloreticular inclusions were observed, which can be associated with viral infections. It is hypothesized that either the direct viral effect or presence of increased cytokines from the systemic inflammatory response, or both, can lead to a collapsing variant of focal segmental glomerulosclerosis, especially in patients with high-risk alleles of the APOL1 gene.[43]

■ MANAGEMENT OF ACUTE KIDNEY INJURY

Management of patients with a confirmed diagnosis of COVID-19 and AKI begins with an evaluation of the cause of AKI. A broad framework of prerenal, renal, and postrenal causes should be considered.

Taking the history, performing a physical examination, and ascertaining the timeline of AKI through chart review are important for diagnosis and management. Medications should be carefully reviewed, and any potentially nephrotoxic agents should be discontinued if possible. A Foley catheter should be considered to accurately measure urine output and to relieve possible obstruction.

Blood work, urinalysis, urine sediment examination for cells and casts, and imaging may help diagnose different causes of AKI.[45] **Table 2** summarizes laboratory and imaging studies that can help differentiate the causes.

The treatment of AKI can be divided into general management, pharmacologic management of COVID-19, optimizing hemodynamic and volume status, and extracorporeal therapies. Vaccines against COVID-19 are

The kidney may be a primary target for SARS-CoV-2 infection owing to its abundance of ACE2 receptors

currently under development, but none has been licensed for use so far.[46]

Renin-angiotensin system inhibitors and COVID-19

Initial concerns were raised regarding a possible association of renin-angiotensin system inhibitors (including ACE inhibitors and angiotensin II receptor blockers) with increased risk of COVID-19, due to possible increased expression of ACE2 based on animal models, and hence increased possibility of viral entry. However, there is no clinical evidence of harm with renin-angiotensin system inhibitors in COVID-19.[47–51]

In an observational analysis,[50] renin-angiotensin system inhibitors were not associated with increased risk of testing positive for COVID-19 or developing severe COVID-19. Likewise, in a population-based case-control study in Italy,[49] there was no evidence of increased risk of COVID-19 with the use of ACE inhibitors or angiotensin II receptor blockers.

Renin-angiotensin system inhibitors are also thought to have a possible protective effect through decreasing the level of angiotensin II, which is thought to exert an inflammatory effect.[7,52] Therefore, these drugs should not be discontinued in stable patients with COVID-19, and this has been emphasized by professional societies including the American College of Cardiology, American Heart Association, and European Society of Hypertension.[53,54] For inpatients with COVID-19, the decision to discontinue renin-angiotensin system inhibitors should be based on hemodynamic and clinical status, as well as kidney function trend.[52]

Pharmacologic management of COVID-19

Pharmacologic management of COVID-19 can be divided into antibacterial therapy, antiviral therapy, and immunomodulatory and anti-inflammatory therapy. Broad-spectrum antibiotics are usually started to treat secondary bacterial infection.[55]

Clinical trials are ongoing, and there are no drugs currently approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19. However, the FDA issued emergency use authorizations for remdesivir and convalescent plasma for hospitalized patients with COVID-19, and recently broadened the scope of remdesivir to include all hospitalized patients with COVID-19 regardless of severity.[56–58]

A full review of pharmacologic therapy for COVID-19 is beyond the scope of this review article, but **Table 3** lists selected drugs, their mechanisms of action, current evidence, and possible nephrotoxic effects.[7,56–72]

Optimizing hemodynamic and volume status

Hemodynamic alterations due to infection, and acute respiratory distress syndrome leading to impaired gas exchange, hypoxia, and right heart failure, can increase the risk of AKI. COVID-19 may lead to cardiogenic shock due to myocarditis and the resultant decrease in cardiac output, or distributive shock due to cytokine release syndrome, sepsis-induced systemic vasodilation, or both. Cytokine release may also lead to hypovolemic shock due to capillary leak and loss of intravascular volume.[73,74]

Therefore, optimizing hemodynamic and volume status is important. Early volume resuscitation should be initiated in hemodynamically unstable patients to reverse hypoperfusion to vital organs, particularly when patients first present with evidence of volume depletion due to fever and respiratory distress. A fine balance needs to be achieved, avoiding overly aggressive fluid resuscitation and fluid overload on the one hand, and overly conservative resuscitation and hypoperfusion on the other, with frequent hemodynamic assessment and echocardiograms. Therefore, an active approach with early resuscitation and early termination of fluid resuscitation should be implemented.[75]

Vasopressor therapy is needed to support blood pressure in patients with shock.

Diuretic therapy should be considered if volume overload is suspected in a hemodynamically stable patient, as in cardiorenal syndrome. Volume overload refractory to diuresis requires ultrafiltration, a form of kidney replacement therapy.

Extracorporeal organ support

Treatment of multiorgan dysfunction in critically ill patients with COVID-19 may necessitate extracorporeal organ support, including kidney replacement therapy, extracorporeal membrane oxygenation, and a left ventricular assist device.[26]

Black race is associated with a higher risk of AKI in COVID-19

TABLE 3

Selected therapies for COVID-19 [a]

Drug	Mechanism of action	Evidence, comments	Possible nephrotoxicity
Antiviral therapy			
Chloroquine, hydroxychloroquine	Prevent glycosylation of host receptors and inhibit viral entry into host cells	Initially thought to improve viral clearance and disease duration[60,61] but evidence is increasingly unsupportive	Podocytopathy of the kidney mimicking Fabry disease (rare)[57]
	Immunomodulatory effect through inhibiting cytokine production	The emergency use authorization of hydroxychloroquine for severe COVID-19 was revoked in June 2020, as potential risks outweighed the benefits[62]	
Lopinavir-ritonavir	Inhibits 3-chymotripsin-like protease	Antiretroviral combination drug approved for treatment of human immunodeficiency virus infection	Reversible acute kidney injury[57]
		No difference in viral clearance, mortality[63]	
		No benefit for patients with severe COVID-19 compared with standard care[63]	
Ribavirin and favipravir	Inhibit RNA polymerase and inhibit viral replication	Favipravir is currently being evaluated in clinical trials in the United States	
		No prospective data to support use of ribavirin	
Remdesivir	Inhibits RNA polymerase and inhibits viral replication	Possible improvement in oxygen support status in severe COVID-19 with remdesivir[58]	Potential mitochondrial toxicity with remdesivir[57]
		Use of remdesivir in COVID-19 patients was associated with shortened time to recovery, but overall 14-day mortality rate was not significantly different compared with placebo[66]	
		Emergency use authorization issued for use in severe COVID-19 and recently expanded use to include all hospitalized patients with COVID-19 regardless of severity.[56,57]	
Immunomodulatory and anti-inflammatory therapy			
Corticosteroids	Decrease Inflammation and decrease lung injury	Unpublished analysis from the United Kingdom showed a reduction in 28-day mortality rate in patients with severe COVID-19 on mechanical ventilation with the use of dexamethasone[65]	
Tocilizumab, sarilumab	Monoclonal antibodies against interleukin 6 receptor; decrease cytokine storm	Repeated doses of tocilizumab may be required to decrease interleukin 6 levels[7,59]	
		Tocilizumab is recommended by the Infectious Diseases Society of America only in the context of a clinical trial[72]	
Convalescent plasma, intravenous immunoglobulin	Viral antibodies from previously infected and recovered patients	Clinical improvement in 5 critically ill patients with COVID-19[68]	Proximal tubular injury with intravenous immunoglobulin[69]
		High-dose intravenous immunoglobulin reportedly effective in case series with severe COVID-19[69]	
		Convalescent plasma has been granted emergency use authorization for hospitalized patients with COVID-19.[58]	

[a] This information is current at the time of this publication but may change as new findings are published.
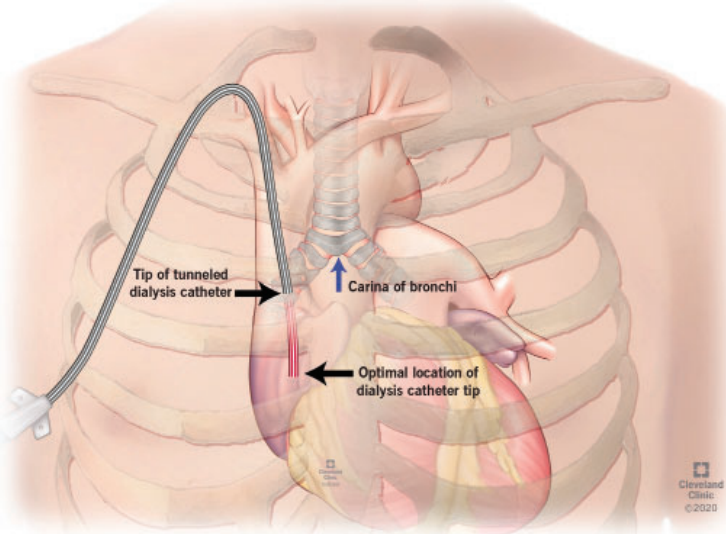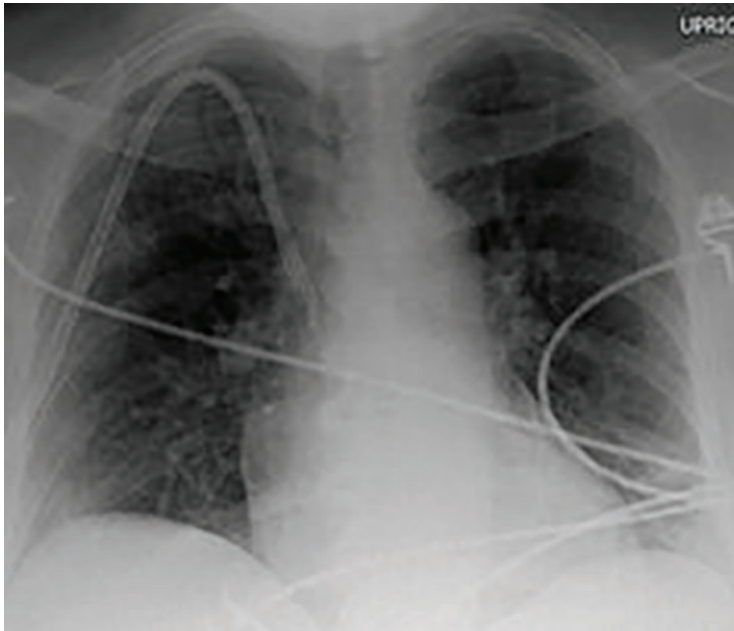
Figure 2. (Top) Radiography shows a short dialysis catheter with its tip in the superior vena cava in a patient with COVID-19 with frequent clotting. (Bottom) Illustration of the optimal location of the dialysis catheter in the mid-atrium.

Kidney replacement therapy

Up to 31% of critically ill patients with COVID-19 require kidney replacement therapy for severe AKI.[4–6,14–16,18,20] The indications for it in COVID-19 patients with AKI are the same as for other AKI patients. There is no evidence at this time to suggest a benefit for starting it early vs later.

Hemodynamically unstable patients on vasopressor therapy are started on continuous kidney replacement therapy and later transitioned to intermittent hemodialysis or peritoneal dialysis when their hemodynamic status improves. Convective forms of dialysis (hemofiltration) may in theory remove cytokines better but have not been proven to lead to better outcomes than diffusive forms. Continuous ultrafiltration can help reverse hypervolemia in cardiorenal syndrome and increased intra-abdominal pressure that may contribute to abdominal compartment syndrome.[26]

Challenges in kidney replacement therapy

A major challenge during continuous kidney replacement therapy in COVID-19 patients is frequent circuit clotting, thought to be due to upregulation of the coagulation system by inflammatory cytokines.[76] We have observed that circuit clotting seems to improve with heparin use, particularly when administered through the circuit (prefilter).

Also, malposition of the dialysis catheter tip should be ruled out. A short catheter length with the tip in the superior vena cava can lead to slow flows and catheter dysfunction.[77] **Figure 2** shows the chest radiograph of a patient with COVID-19 who had a short catheter that clotted frequently, and the optimal location of a tunneled dialysis catheter to optimize blood flow, which is essential in patients with increased clotting.

Hemodialysis in patients with acute respiratory distress syndrome who require prone positioning needs a coordinated and sequential timing protocol to provide adequate ventilatory support in the prone position and dialysis therapy in the supine position. A synchronized team approach should be implemented to coordinate and maintain the safety of vascular access during prone positioning. Prolonged intermittent renal replacement therapy may need to be considered rather than continuous therapy.

To limit exposure of dialysis nurses and technicians, we use extension tubing that allows dialysis machines to be placed outside the patient room. However, extension tubing increases circuit length and thus carries a risk of hypothermia, thrombosis, and blood loss. Therefore, appropriate warming systems should be implemented.[78] We have also installed video monitors that allow nurses to observe patients on dialysis without entering the room.

Dialysis, a finite resource

Hospital dialysis units may experience a shortage of dialysis supplies and dialysis technicians and nurses. A careful daily assessment of available dialysis resources is needed: a dialysis dashboard to track equipment, supplies, personnel, and patients should be implemented.

Permissive underdialysis, with shorter dialysis treatments and less-frequent treatments, may be needed to preserve supplies and to allow for treatment of more patients. Strategies to overcome shortages in prepared continuous kidney replacement therapy dialysis fluid includes preparing replacement fluid by inpatient pharmacies.[78] Our institution has been producing dialysis machine-generated ultrapure dialysate that was shown to be safe, effective, and economical in a cohort of 405 patients on continuous kidney replacement therapy.[79]

Other options include using peritoneal dialysis fluid as replacement fluid, or possibly emergently starting peritoneal dialysis using bedside tunneled peritoneal dialysis catheter placement. Nontunneled acute peritoneal dialysis catheter placement, a procedure rarely done in the United States, may be an option in dire situations, but is limited by operator experience and training, and thus only considered as a last resort when all other measures fail.[78,80]

Extracorporeal membrane oxygenation, direct hemoperfusion, and left ventricular assist devices

Lung and cardiac injury with COVID-19 can lead to hypoxia and decreased kidney perfusion, which can lead in turn to kidney medullary hypoxia and cardiorenal syndrome. Supporting the heart and lung in these conditions using left ventricular assist devices and extracorporeal membrane oxygenation can potentially help with renal perfusion. Direct hemoperfusion using a macroporous sorbent has been suggested as a treatment to adsorb and remove circulating cytokines and prevent cytokine release syndrome-induced end-organ damage.[26] All these modalities can be used in conjunction with continuous kidney replacement therapy to help manage the multiorgan failure commonly seen in critically ill patients with COVID-19.[26]

■ SPECIAL CONSIDERATIONS

COVID-19 and chronic kidney disease

Many patients with chronic kidney disease have multiple comorbidities such as diabetes and hypertension, which can predispose them to COVID-19. Chronic kidney disease is associated with a higher risk of severe infection.[13,81] A meta-analysis[81] showed that about 20% of patients with chronic kidney disease who contracted COVID-19 had severe disease, a 3-fold higher risk compared with those without chronic kidney disease. Those with COVID-19 and AKI had a higher prevalence of chronic kidney disease than those without AKI.[19]

Telemedicine can be used to monitor and manage patients with stable chronic kidney disease while minimizing their exposure.[82] The platforms must comply with Health Insurance Portability and Accountability Act standards.

COVID-19 and outpatient maintenance dialysis in end-stage kidney disease

Patients with end-stage kidney disease on maintenance dialysis usually have multiple comorbidities and are at increased risk of CO-VID-19. Unavoidable patient gathering and frequent travel to outpatient dialysis units can increase their risk of infection. Therefore, preventive strategies should be implemented to minimize transmission and protect patients on outpatient hemodialysis and peritoneal dialysis.[83]

The US Centers for Disease Control and Prevention, American Society of Nephrology, and International Society for Peritoneal Dialysis have issued interim infection control measures to help mitigate the risk of infection in dialysis patients.[84–86] Educating patients and healthcare workers on COVID-19 is imperative.[84–86]

Peritoneal dialysis patients should keep at least 2 weeks of dialysis supplies on hand. Nonessential visits to dialysis units should be avoided.[84] Screening for COVID-19 symptoms, temperature checks, and testing protocols for patients and staff at dialysis units should be implemented. Specific dialysis units can be dedicated to COVID-19 patients. Home hemodialysis, where feasible, is an effective alternative for outpatient hemodialy-

Patients with acute lung injury are at risk of AKI due to hemodynamic changes, hypoxia, and inflammatory cytokines

sis that implements social distancing while minimizing the need for frequent travel and transportation.[83]

COVID-19 and kidney transplant recipients

Kidney transplant recipients are at increased risk of infection, particularly from a depressed T-cell immune response due to immunosuppression.[87] The risk is highest during the first 3 months after transplant, particularly if patients receive induction therapy with lymphocyte-depleting agents.[88] Therefore, during the COVID-19 pandemic, elective kidney transplant should be performed with caution.[88]

Screening of donors is imperative because of a high tropism of the virus for the kidney, and programs are currently moving toward testing both donors and recipients before transplant.[89] In addition, symptomatic and high-risk donors under clinical suspicion for COVID-19 should postpone donation even if they test negative for SARS-CoV-2, given the potential for false-negative results.[89]

The evidence on COVID-19 infections in kidney transplant recipients is limited to case reports and case series.[87–93] Fever, cough, and myalgias are the most frequently reported symptoms,[90] although they are not always present.[91] Guillen et al[91] described a patient who presented with vomiting, dehydration, and conjunctivitis. In a cohort of 36 kidney transplant recipients, Akalin et al[93] reported diarrhea as the second most common symptom, after fever. Moreover, mild symptoms such as low-grade fever, mild cough, and normal white blood cell count have been suggested to occur in kidney transplant recipients due to the protective effect of immunosuppressive therapy against the cytokine storm.[92] Therefore, even mild or atypical symptoms should prompt COVID-19 testing in kidney transplant recipients.

The optimal management for kidney transplant recipients with COVID-19 is still being studied. The general consensus is to taper down immunosuppression while simultaneously protecting graft function and initiating antiviral, antibiotic, and anti-inflammatory therapy.[87–93] Immunosuppressive therapy should be tapered down to help mount an antiviral immune response and decrease the severity of symptoms.[87] Most authors suggest discontinuing antiproliferative drugs such as mycophenolate mofetil, but maintaining calcineurin inhibitor therapy at lower levels along with glucocorticoid therapy.[87–93] The role of pulse steroid therapy is controversial, but some authors suggest it has a beneficial anti-inflammatory effect while minimizing graft rejection.[87]

Antiviral therapy, such as the protease inhibitors ritonavir and lopinavir, was reported to be effective in some patients.[89] A possible role for remdesivir has been reported.[60] Due to strong drug interactions of protease inhibitors with calcineurin inhibitor therapy, calcineurin inhibitor dosage must be reduced substantially.[89,91] Tocilizumab blocks IL-6 receptors and can possibly reduce inflammation.[61,94]

Most of the patients in the reported cases recovered and their immunosuppressive therapy was gradually reintroduced.[87,88,90–92,95]

■ SCIENCE IS EVOLVING RAPIDLY

The science on COVID-19 is rapidly evolving, and new evidence is published on a daily basis. This review is based on our experience and is limited to evidence that is currently available.

AKI in patients with COVID-19 is associated with increased mortality. The etiology is multifactorial, and management is supportive, with possible need for extracorporeal therapies for critically ill patients.

Large-scale prospective clinical trials can help inform optimal management of AKI in COVID-19, and more retrospective data on clinical experience is needed to assess the impact and prognosis of COVID-19 on patients with chronic kidney disease or end-stage kidney disease, and in kidney transplant recipients. ■

A high incidence of thrombotic complications has been reported even in those on prophylactic anticoagulation

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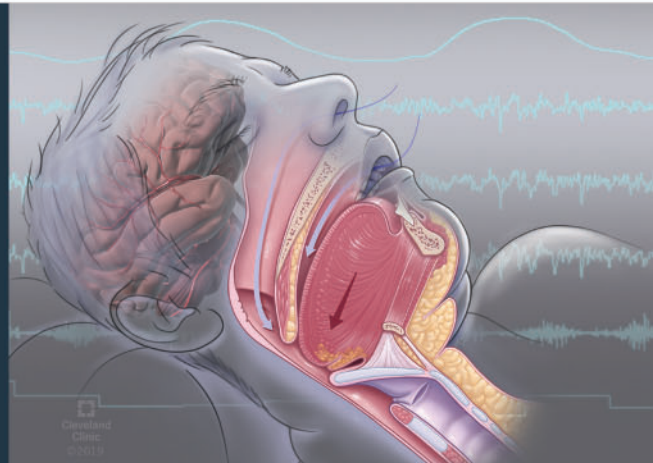78. Burgner A, Ikizler TA, Dwyer JP. COVID-19 and the inpatient dialysis

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Hospital-acquired and ventilator-associated pneumonia: Diagnosis, management, and prevention

ABSTRACT

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) cause significant inpatient morbidity and mortality. They are especially challenging to diagnose promptly in the intensive care unit because a plethora of other causes can contribute to clinical decline in complex, critically ill patients. The authors describe the diagnosis, management, and prevention of these diseases based on current guidelines and recent evidence.

KEY POINTS

Noninvasive testing such as blood and sputum cultures and the staphylococcal nasal swab should be conducted in a patient with suspected HAP or VAP to isolate the culprit organism and tailor antibiotic therapy.

Procalcitonin testing should not be used to decide whether to start antibiotics but can be used in conjunction with clinical judgment to decide course duration.

Patients with suspected HAP or VAP who are immunocompromised, hemodynamically unstable, or unable to produce timely lower respiratory tract samples for microbiologic testing merit empiric antibiotic treatment with a regimen based on individual risk factors and local antibiotic resistance.

Nursing care bundles addressing aspiration risk factors can reduce the incidence of HAP and VAP in the hospital.

ALTHOUGH GUIDELINES are available for managing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)[1,2] and our understanding of these diseases is growing, their incidence does not seem to be decreasing.[3]

And the toll is high. About 10% of patients put on mechanical ventilation develop VAP,[3] and the mortality rate in VAP has been estimated at 13%.[4] Together, HAP and VAP accounted for 22% of hospital-acquired infections in a 2014 survey of 183 US hospitals.[5] Patients with VAP face a longer hospital course and incur higher healthcare costs than similarly ill patients without VAP.[1]

This review discusses the diagnosis, management, and prevention of HAP and VAP using the 2016 guidelines from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS),[1] as well as recent literature regarding controversial topics such as the role for procalcitonin testing and adjunctive inhaled aminoglycosides.

■ TERMS

HAP is a new pneumonia (a lower respiratory tract infection verified by the presence of a new pulmonary infiltrate on imaging) that develops more than 48 hours after admission in nonintubated patients.

VAP, the most common and fatal nosocomial infection of critical care, is a new pneumonia that develops after 48 hours of endotracheal intubation. Importantly, by the time of VAP onset, patients may have already been extubated.

'Healthcare-associated pneumonia' is no longer recognized

Of note, the term "healthcare-associated pneumonia" (HCAP) has been removed from the 2016 guidelines.[1]

HCAP was defined in the IDSA/ATS 2005 guidelines as pneumonia developing in a person hospitalized for more than 48 hours in the last 90 days, residing in a nursing home or extended-care facility, or receiving home infusion therapy, wound care, or chronic dialysis.[6] As patients who frequently interface with the healthcare system were suspected of harboring multidrug-resistant organisms, the empiric antibiotic regimen recommended for HCAP mirrored that recommended for HAP and VAP.

But a systematic review and meta-analysis of 24 studies revealed that these criteria for HCAP did not reliably correlate with the presence of multidrug-resistant organisms.[7] Mortality in HCAP was not associated with multidrug-resistant organisms, but rather was associated with patient age and comorbidities.

The designation of HCAP was ultimately determined to have minimal practical value in decision-making about empiric antibiotic selection and overall prognostication. Patients who would have previously qualified for a diagnosis of HCAP should instead be treated as having community-acquired pneumonia unless they have specific individual risk factors that call for broad-spectrum empiric antibiotic treatment (see below).

■ ASPIRATION IS AN IMPORTANT CAUSE OF HAP AND VAP

Aspiration is an important contributor to the pathogenesis of HAP and VAP. Further, proton-pump inhibitors and histamine-2 receptor blockers, by suppressing acid production, can allow nosocomial pathogens to colonize the oropharynx and endotracheal tube and be aspirated.[2] VAP-specific risk factors such as age, recent surgery, and admission for neurologic causes or cardiovascular failure all increase the risk of aspiration.[8,9]

■ CHALLENGING TO DIAGNOSE

HAP and VAP can be challenging to diagnose promptly, owing to limited diagnostic tests and a broad differential diagnosis for patients who develop increasing oxygen requirements, leukocytosis, and secretions in the intensive care unit (ICU). Respiratory decline accompanied by fevers and a productive cough—or following a witnessed or suspected aspiration event in the hospital—can suggest developing pneumonia. While scoring systems such as the Clinical Pulmonary Infection Score are used to guide the management of community-acquired pneumonia, the IDSA/ATS guidelines suggest using clinical criteria alone for the management of HAP and VAP.[1,10]

According to the guidelines, the diagnosis of HAP and VAP requires all of the following:
- New lung infiltrates on chest imaging
- Respiratory decline
- Fever
- Productive cough.

Absence of a new infiltrate significantly lowers the probability of VAP and can guide the clinician to alternative causes of inpatient respiratory decline, including pulmonary embolism.[1]

Noninvasive tests

Once an infiltrate is observed and HAP or VAP is suspected as the cause of respiratory decline, several noninvasive tests are recommended to isolate a pathogen and promptly tailor empiric antibiotics to the culprit organism.

Blood cultures are recommended for all patients diagnosed with HAP or VAP.[1] Fifteen percent of patients with VAP are bacteremic, and up to 25% of blood cultures from this group demonstrate pathogens reflective of a secondary, nonpulmonary source of infection.[1]

Thus, blood cultures can be useful to identify the pathogen responsible for HAP or VAP, especially if respiratory cultures are unrevealing, and also to inform the clinician as to the presence of additional concomitant infections unrelated to the respiratory tract. For example, *Candida* and *Enterococcus* species are not known to cause pneumonia, and so detecting these pathogens in the bloodstream may direct the clinician to a separate and previously unsuspected site of infection such as a catheter-related bloodstream infection.

Sputum cultures should be obtained in patients with HAP and in nonintubated patients with VAP who are capable of producing

By the time of VAP onset, patients may have already been extubated

a sufficient sample, characterized by few to no squamous epithelial cells on Gram stain.

For patients who cannot produce an adequate sputum sample, semiquantitative sputum samples obtained by noninvasive methods (eg, endotracheal aspiration) are preferred over quantitative samples obtained by noninvasive or invasive methods such as bronchoscopy and blind bronchial sampling (mini-bronchoalveolar lavage) in an effort to reduce cost and patient harm associated with quantitative and invasive testing.[1] Quantitative testing may be falsely unremarkable if antibiotics have been started before sample collection and may erroneously trigger the cessation of appropriate therapy. Further, no improvement in mortality rate, length of ICU stay, or duration of mechanical ventilation has been observed in patients who underwent invasive sampling.[1]

However, invasive sampling may be merited for an immunocompromised patient or a patient experiencing continued clinical decline despite appropriate antibiotics and with a negative noninvasive evaluation, given its improved diagnostic yield.[11]

Should invasive sampling be attempted, high cellularity (> 400,000 cells/mL) and the presence of more than 50% neutrophils in bronchoalveolar lavage fluid can implicate VAP.[12,13] The IDSA/ATS guidelines suggest discontinuing antibiotics if the final bronchoalveolar lavage culture results demonstrate fewer than 10^4 colony-forming units/mL, though it should be noted that the yield of bronchoscopic cultures dramatically decreases after 72 hours of antibiotic exposure.[1] Negative bronchoscopic cultures obtained from a patient on empiric antibiotic therapy may rule out multidrug-resistant organisms but do not entirely rule out pneumonia.

Polymerase chain reaction (PCR) testing has been increasingly employed to diagnose pathogens responsible for HAP and VAP and to guide antibiotic stewardship measures.

The *Staphylococcus aureus* nasal swab, a PCR-based test, demonstrated a high negative predictive value for methicillin-resistant *S aureus* (MRSA) colonization in a patient population with a 10% prevalence of MRSA.[14] The sensitivity of this test is higher when used for HAP (sensitivity 85%, specificity 92%) than

for VAP (sensitivity 40%, specificity 94%). Given that a patient's nasal colonization pattern reliably predicts which *Staphylococcus* species could be responsible for an ongoing pneumonia, the nasal swab has been widely used as an antibiotic stewardship tool, prompting safe discontinuation of anti-MRSA agents when negative, particularly in the context of HAP.[14]

The respiratory viral panel, a PCR-based nasopharyngeal swab, should be used especially during influenza season to identify viral causes of HAP and VAP for which antibiotic therapy may not be necessary.[1]

Within the first 2 days in the hospital, pneumonia is most likely attributable to community-acquired organisms. After 48 hours, culprit organisms include pathogens to which the patient was exposed in the hospital.[1]

Antibiotic use within the 90 days preceding new pneumonia is the only known risk factor consistently correlated with MRSA and multidrug-resistant *Pseudomonas aeruginosa* HAP and VAP.[1] Patients with the following risk factors may be additionally predisposed to VAP due to multidrug-resistant organisms:
- Cystic fibrosis or bronchiectasis
- Septic shock
- Acute respiratory distress syndrome
- Renal replacement therapy before VAP
- At least 5 days of hospitalization.[1]

Viruses cause up to 20% of cases of HAP and VAP.[15] An observational study of 262 patients with HAP determined that respiratory syncytial virus, parainfluenza virus, and rhinovirus were the most common causative pathogens, and 8% of all HAP cases were caused by bacterial and viral coinfection.[15]

Procalcitonin testing can help differentiate viral from bacterial pathogens in patients with HAP or VAP and potentially identify cases of coinfection. While any infectious pneumonia can elevate this serum biomarker, typical bacteria tend to lead to higher procalcitonin levels than atypical bacteria or viruses.[16] Cytokines, associated with bacterial infections, enhance procalcitonin release, whereas interferons, associated with viral infections, inhibit procalcitonin release.

Procalcitonin testing is not perfect, however, as procalcitonin is not elevated in up to 23% of typical bacterial infections.[16] A systematic review and meta-analysis of 15

In the absence of a new infiltrate, consider other causes of inpatient respiratory decline, including pulmonary embolism

randomized controlled trials in ICU patients evaluated procalcitonin guidance in initiating antibiotics compared with clinical judgment alone and noted no difference in short-term mortality. However, procalcitonin-guided cessation of antibiotics was associated with a lower mortality rate than cessation of antibiotics based on clinical judgment alone.[17]

In keeping with these results, the IDSA/ATS guidelines state that procalcitonin should not replace clinical judgment to decide on antibiotic initiation for patients with a diagnosis of HAP or VAP, but can be monitored over the course of therapy to note a trend, and can be used in conjunction with clinical judgment to de-escalate and eventually discontinue antibiotics.[1]

Our understanding of the use of procalcitonin in HAP and VAP management is still in its infancy. There is no consensus on this subject, but we offer the following, based on our own experience and the relationship between procalcitonin levels and cytokines and interferons:

- Elevated procalcitonin in a patient with a PCR-proven viral infection such as influenza can suggest bacterial superinfection and merit continuation of antibiotic therapy.
- A low-positive or negative procalcitonin level in a patient with PCR-proven viral infection may lend confidence to the diagnosis of viral HAP or VAP and prompt safe discontinuation of antibiotics.
- A negative procalcitonin in a patient with a clinical history suggesting alternative causes of respiratory decline or marked improvement with diuresis can also support antibiotic cessation.

■ MANAGEMENT OF HAP AND VAP

Although delaying the start of antibiotic therapy is associated with a higher risk of death in the context of sepsis, recent studies argue that antibiotics may not be immediately required in every patient with suspected HAP or VAP.

Two different strategies—clinical and bacteriologic—can be used in this decision. In the clinical strategy, antibiotics are started in patients with a new pulmonary infiltrate concerning for HAP or VAP if they meet 2 of the following 3 criteria: fever, productive cough, and leukocytosis. In the bacteriologic strategy, antibiotics are held until quantitative cultures of lower respiratory tract samples confirm a diagnosis of HAP or VAP.

A single-center observational study[18] comparing these 2 strategies noted that, while patients managed with the clinical strategy were rapidly started on antibiotics, they experienced a lower chance of receiving initially appropriate therapy, a longer duration of treatment, and a significantly higher rate of in-hospital mortality, possibly due to selection of resistant organisms. However, certain patients do merit prompt and aggressive antibiotic therapy even before culture results become available: those with hemodynamic or respiratory instability, those with immunocompromised status, and those for whom timely sampling of lower respiratory tract secretions is not feasible.[1]

Initial empiric coverage of MRSA, gram-negative bacteria

Once the decision to treat a patient with suspected HAP or VAP is made, an institution-specific antibiogram should guide the selection of an empiric antibiotic regimen that best addresses local organism prevalence and antibiotic resistance patterns.[1] If such an antibiogram is not readily available, a regimen with empiric coverage of methicillin-susceptible S aureus and gram-negative bacilli such as P aeruginosa should be selected, eg, piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem.

One antipseudomonal agent or two? Patients who recently received intravenous antibiotics or are at high risk of death merit double coverage of P aeruginosa with antibiotics from 2 different classes for empiric treatment of HAP. Placement in an ICU where more than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy is an additional indication for the initiation of 2 antipseudomonal agents to treat VAP.[1] Patients with P aeruginosa pneumonia complicated by bacteremia who receive empiric antipseudomonal combination therapy have a lower mortality rate than those who receive antipseudomonal monotherapy.[19] Combination therapy ensures timely initiation of at least 1 active agent. Patients who receive

Understanding of the use of procalcitonin in HAP and VAP is still in its infancy

antipseudomonal monotherapy may experience delays to the initiation of an appropriate antipseudomonal agent if resistance to the chosen agent is present.

Is MRSA coverage needed? Not all patients with HAP or VAP need empiric MRSA coverage. Vancomycin or linezolid should be initiated only in those who received intravenous antibiotics in the last 90 days, are hospitalized in a unit where at least 20% of S aureus isolates are methicillin-resistant or where the prevalence of MRSA is unknown, or are at high mortality risk.[1]

Additionally, despite the role of aspiration in the development of HAP and VAP, empiric anaerobic coverage is not always indicated. This is because over the first 48 hours of hospitalization, bacterial colonization of the oropharynx and endotracheal tube evolves from a predominance of streptococcal and anaerobic species to a predominance of gram-negative, nosocomial flora.

Role for inhaled antibiotics. The guidelines discourage the use of intravenous aminoglycosides and polymyxins, given concerns for nephrotoxicity in critically ill patients with HAP or VAP. However, for VAP due to pathogens susceptible only to aminoglycosides or polymyxins, inhaled aminoglycosides or colistin can and should be used in conjunction with their intravenous formulations.[1]

Systemic aminoglycosides achieve low concentrations in respiratory secretions and in epithelial lining fluid of the lung, resulting in subtherapeutic levels that may encourage the development of multidrug-resistant organisms.[20] Inhaled antibiotics are not associated with the degree of nephrotoxicity seen in patients given the equivalent intravenous formulations, and their addition to systemic antibiotics may allow for higher drug concentrations at the site of infection, which in turn may help improve clinical cure rates and reduce the duration of mechanical ventilation.

Adjunctive inhaled antibiotics have not been demonstrated to affect overall mortality rates in VAP. The relationships between adjunctive inhaled antibiotics and ICU length of stay, hospital length of stay, and prevalence of multidrug-resistant organisms have yet to be elucidated.

Final tailored regimen

Regardless of the empiric regimen initiated, culture susceptibilities can allow for appropriate tailoring of antibiotics to the culprit organisms responsible for HAP and VAP.

Aspiration events that precipitate HAP and VAP are inherently polymicrobial. Thus, even if sputum cultures demonstrate only 1 pathogen, the final antibiotic regimen used to treat a patient with suspected aspiration should still include coverage of oral and enteric flora, including gram-negative and anaerobic bacteria.

Duration of treatment

The duration of the antibiotic course in uncomplicated HAP and VAP is 7 days, as longer courses have not been shown to reduce rates of recurrent pneumonia, treatment failure, duration of mechanical ventilation, hospital length of stay, or mortality.[1] If a patient is hemodynamically stable, is needing less oxygen, and is tolerating oral intake, oral antibiotics can be used to complete a course of therapy for uncomplicated HAP or VAP.

HAP and VAP associated with pulmonary or extrapulmonary complications, such as empyema or bacteremia, merit longer course durations specific to these issues. Pneumonias due to *Pseudomonas* or *Acinetobacter* species are also considered complicated and merit at least 2 weeks of antibiotic therapy due to the risk of relapse associated with shorter course durations.[21] Follow-up chest imaging during the same admission is not indicated unless the patient continues to decline. In such a case, repeat radiography or computed tomography of the chest may detect a pulmonary complication requiring procedural intervention or, alternatively, may guide the clinician to search for unrelated causes of decline if signs on imaging are improved.

Infectious disease consultation for evaluation and antibiotic management can be helpful in an immunocompromised patient or a patient experiencing continued clinical decline on appropriate antibiotic therapy. Pulmonary consultation is indicated for patients who develop complications requiring procedural intervention such as empyema and in patients who merit invasive sampling of the lower respiratory tract.

Preventing HAP and VAP is as important as diagnosing and managing them

■ PREVENTING HAP AND VAP

Preventing HAP and VAP is as important as diagnosing and managing them and depends upon multiple approaches to address individual aspiration risk factors and nosocomial transmission of disease.

Preventing colonization and aspiration

Regular oral care, assessment of the need for proton-pump inhibitor and histamine-2-receptor blocker therapy, and early identification and treatment of dysphagia—especially in the elderly and in patients with recent stroke or surgical procedures—are key features to preventing oropharyngeal colonization of pathogenic organisms, aspiration, and ensuing HAP or VAP. A systematic review and meta-analysis including 2 studies of critically ill, nonventilated patients reported significant risk reduction in HAP through the use of chlorhexidine oral cleansing, electric toothbrushing, and oral hygiene instruction.[22]

Data supporting oral care in VAP prevention are more robust, with several institutions worldwide reporting reduced VAP incidence in association with ICU "bundles" including an oral care component.

One institution implemented a protocol involving twice-daily chlorhexidine oral cleansing in addition to elevating the head of the bed to more than 30 degrees, once-daily respiratory therapy-driven weaning attempts, and conversion from a nasogastric to an orogastric tube as feasible for all ventilated trauma patients.[23] One year after this protocol was implemented, the incidence of VAP had declined, and patients without VAP accrued fewer total ventilator days, ICU days, and hospital days, although their mortality rate was no lower than in patients with VAP.

Other strategies to reduce aspiration risk include maintaining tracheal cuff pressure, eliminating nonessential tracheal suction, and avoiding gastric overdistention. A 20-bed academic medical ICU developed a task force and an educational session to raise awareness about aspiration prevention with subsequent assessments of compliance with these strategies.[24] These interventions increased compliance dramatically over a 2-year time span, during which the center noticed a 51% decrease in VAP incidence as well as decreased ventilator

days and healthcare costs. Standardized use of aspiration-prevention strategies and didactic modules, championed by an invested multidisciplinary team, can collectively reduce aspiration risk and associated pneumonia.[1]

Managing the microbiome

Probiotics and antibiotics in HAP and VAP prevention are still under evaluation. In theory, probiotics could reduce VAP by improving intestinal barrier function, increasing host cell antimicrobial peptides, and regulating the composition of intestinal flora to reduce overgrowth and colonization by pathogenic organisms.[25] However, large, randomized controlled trials should be conducted to determine the clinical efficacy of this strategy.

The French Society of Anesthesia and Intensive Care Medicine and the French Society of Intensive Care 2017 guidelines recommend selective digestive decontamination with a topical antiseptic administered enterally for up to 5 days to prevent HAP and VAP.[26]

These guidelines cite meta-analyses of randomized controlled trials demonstrating a relationship between selective digestive decontamination and decreased mortality as well as decreased acquisition of multidrug-resistant organisms, but acknowledge that the role of selective digestive decontamination may be limited in units that already face high prevalence of multidrug-resistant organisms. A theoretical risk of increased *Clostridioides difficile* incidence with routine selective digestive decontamination use has yet to be explored.

These seemingly opposing strategies of HAP and VAP prevention require further investigation.

Infection control

In addition to addressing individual patient risk factors for HAP and VAP, clinicians should address potential for nosocomial transmission of pathogens typically responsible for pneumonia.

Timely vaccinations for both patients and providers reliably reduce transmission of influenza, *Haemophilus influenzae*, and *Streptococcus pneumoniae* pneumonia.[27] While these pathogens are not commonly associated with the hospital setting, transmission from patients hospitalized with community-acquired pneumonia or from ill healthcare providers to oth-

Several institutions report decreased incidence of VAP using ICU care 'bundles'

ers on the same unit has been reported and may precipitate HAP and VAP.

Hospital-wide respiratory hygiene measures such as hand hygiene and the use of masks or tissues for patients with a cough can reduce the spread of respiratory pathogens. Observational studies suggest some benefit to routine stethoscope and procedural equipment cleaning, though single-patient stethoscopes and universal gown-glove contact isolation are primarily supported by theoretical benefit.

■ ONGOING EFFORTS

As we continue to face HAP and VAP in our hospital systems, ongoing efforts to improve their diagnosis, management, and prevention will be critical to reduce morbidity and mortality related to these nosocomial infections. ■

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All *Cleveland Clinic Journal of Medicine* CME activities are now eligible for MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select "CME & MOC" and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

October 2020 CME/MOC activity
Estimated time to complete the activity: up to 1 hour

Hospital-acquired and ventilator-associated pneumonia: Diagnosis, management, and prevention

Release date: October 1, 2020
Expiration date: September 30, 2021

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Successful completion of this activity enables the participant to earn up to 1.0 MOCA 2.0 points; points earned will be equivalent to the amount of CME credit claimed for the activity. Please note: It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOCA 2.0™ points.

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Your credit will be reported to the ABA within 60 days of claiming credit after the course.

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ABPath CC: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 Lifelong Learning (Part II) credits in the American Board of Pathology's Continuing Certification (CC) program (formerly known as MOC). Participants will earn CC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABPath CC credit.

Your credit will be reported to the ABPath within 60 days of claiming credit after the course.

ABP MOC: Successful completion of this CME activity, which includes participation in the activity and individual assessment of and feedback to the learner, enables the learner to earn up to 1.0 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABP MOC credit.

Your credit will be reported to the ABP within 60 days of claiming credit after the course.

ABS MOC: This activity qualifies for 1.0 self-assessment credit toward Part 2 of the American Board of Surgery (ABS) Maintenance of Certification (MOC) Program.

Please note: It is the participant's responsibility to self-report their participation to the American Board of Surgery, per board policy.