of deferring antimicrobial therapy in favor of a prolonged search or unassailable evidence of the source of the infection has been difficult to justify given studies in patients with septic shock that documented mortality benefits from the administration of antimicrobials to which the pathogenic organism was sensitive,[2] better outcomes with combination therapy as compared with monotherapy therapy,[3] and particularly the realization that each hour that antimicrobial therapy is deferred has been associated with a 7.6% decrease in survival for patients with septic shock.[4] The training we received to identify the source of any serious infection is as valid today as it was when it was first brought to our attention; what has changed is the amount of time allotted for performing investigations before starting antibiotic therapy.

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Since publication of his article, the author reports no further potential conflict of interest.

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
2. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237-48.
3. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 2010;38:1773-85.
4. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96.

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Case 9-2014: A Woman with Increasing Dyspnea

TO THE EDITOR: Saukkonen et al. (March 20 issue)[1] describe a 34-year-old woman with severe pulmonary hypertension and Raynaud's phenomenon due to mixed connective-tissue disease. However, the authors never identified the cause of severe systemic hypertension (which is not typically seen in mixed connective-tissue disease) in this patient. Particularly in light of her autoimmune disease, I wonder whether she was tested for the antiphospholipid syndrome. In one of his early descriptions of this syndrome in 1984, Hughes reported labile hypertension, often with associated livedo reticularis, Raynaud's phenomenon, or both.[2] Indeed, since then, hypertension — often severe — has been observed in as many as 40 to 50% of patients with primary antiphospholipid syndrome. Hypertension in this syndrome is most often renovascular in origin, including not only thrombosis or focal arterial stenosis of the renal artery, but also intrarenal thrombotic microangiopathy (antiphospholipid syndrome nephropathy), and severe hypertension may be the initial manifestation of the antiphospholipid syndrome in these patients.[3] Hypertension in this syndrome may also occur as a result of an associated autonomic disorder (e.g., hyperadrenergic postural tachycardia syndrome), and these patients also often have livedo reticularis, Raynaud's phenomenon, or both.[4]

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No potential conflict of interest relevant to this letter was reported.

1. Case Records of the Massachusetts General Hospital (Case 9-2014). N Engl J Med 2014;370:1149-57.
2. Hughes GRV. The Prosser-White oration 1983: connective tissue disease and the skin. Clin Exp Dermatol 1984;9:535-44.
3. Karim MY, Alba P, Tungekar MF, et al. Hypertension as the presenting feature of the antiphospholipid syndrome. Lupus 2002;11:253-6.
4. Schofield JR, Blitshteyn S, Shoenfeld Y, Hughes GRV. Postural tachycardia syndrome (POTS) and other autonomic disorders in antiphospholipid (Hughes) syndrome (APS). Lupus 2014;23:697-702.

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TO THE EDITOR: We would like to raise two issues with regard to the Case Record by Saukkonen et al. First, pulmonary veno-occlusive disease should be considered in the differential diagnosis of pulmonary arterial hypertension associated with connective-tissue diseases. Pulmonary arterial hypertension and pulmonary veno-occlusive disease share predisposing conditions and clinical and hemodynamic features. The exclusion of pulmonary veno-occlusive disease is crucial, since patients with pulmonary veno-occlusive disease, besides having a worse prognosis, may

have life-threatening complications when pulmonary vasodilators are administered.[1] Involvement of the pulmonary venous compartment occurs in 75% of patients who have pulmonary arterial hypertension associated with connective-tissue disease; this may contribute to their worse prognosis.[2] Definitive differentiation requires histologic analysis. Ground-glass opacities, smooth thickening of interlobular septa, and enlarged mediastinal lymph nodes detected on computed tomography (CT) are also valuable for the diagnosis of pulmonary veno-occlusive disease.[3]

Second, the patient described in the Case Record had advanced pulmonary arterial hypertension associated with mixed connective-tissue disease. Inflammation plays a crucial role in pulmonary arterial hypertension, especially with coexisting connective-tissue diseases. One study showed that 50% of patients in New York Heart Association class II or III who had pulmonary arterial hypertension associated with systemic lupus erythematosus (SLE) and mixed connective-tissue disease had a response to first-line immunosuppressive regimens (glucocorticoids and intravenous cyclophosphamide).[4] Advanced pulmonary arterial hypertension associated with SLE or mixed connective-tissue disease warrants the use of pulmonary vasodilators, but the use of aggressive immunosuppressive regimens also may be considered.[4]

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1. Huertas A, Girerd B, Dorfmuller P, O'Callaghan D, Humbert M, Montani D. Pulmonary veno-occlusive disease: advances in clinical management and treatments. Expert Rev Respir Med 2011;5:217-29.
2. Dorfmüller P, Humbert M, Perros F, et al. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. Hum Pathol 2007;38:893-902.
3. Günther S, Jaïs X, Maitre S, et al. Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. Arthritis Rheum 2012;64:2995-3005.
4. Jais X, Launay D, Yaici A, et al. Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. Arthritis Rheum 2008;58:521-31.

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THE DISCUSSANT REPLIES: Schofield raises the possibility that renovascular disease due to antiphospholipid antibody syndrome caused systemic hypertension in the patient described in the Case Record. This possibility was considered, but it was excluded from the published article because of space limitations. Although this patient's urine contained blood and protein, we cannot know whether this was the result of end-organ damage from severe systemic hypertension or was from a primary renal process.

In patients with mixed connective-tissue disease, antiphospholipid antibodies may be associated with pulmonary hypertension (as in our patient) but not with thrombosis.[1] It would not surprise me if this patient was found to have antiphospholipid antibodies. Perhaps she will meet the criteria for SLE one day, as can happen in patients with mixed connective-tissue disease.[2] I suspect that volume overload (accounting for her distended neck veins and edema to the level of the knees), as well as the adrenergic surge associated with her distress, contributed to her systemic hypertension on presentation.

Tombetti et al. suggest the consideration of pulmonary veno-occlusive disease in the differential diagnosis of pulmonary hypertension associated with mixed connective-tissue disease. This association was described in one of eight patients with connective-tissue disease and pulmonary hypertension in the study they cite[3] and in at least one other patient.[4] The importance of these rare associations is not clear. As Tombetti and colleagues point out, findings on CT can be helpful in the diagnosis of pulmonary veno-occlusive disease. The patient discussed in our case had "clear lungs" on CT, without findings associated with pulmonary veno-occlusive disease.

Tombetti et al. note that vasodilators pose a risk among patients with pulmonary veno-occlusive disease. If vasodilators are tried, short-acting agents are administered in a cardiac catheterization laboratory or in a critical care unit to allow for immediate resuscitation in the uncommon event of a catastrophic decompensation. Tombetti et al. also emphasize the importance of immunosuppression in the treatment of this patient with mixed connective-tissue disease and pulmonary hypertension. Fortunately, as Dr. Lauren D. Moore noted at the conclusion of the Case Record, "She is also being treated with hydroxy-

chloroquine and prednisone for mixed connective-tissue disease and is doing very well."

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Since publication of his article, the author reports no further potential conflict of interest.

1. Komatireddy GR, Wang GS, Sharp GC, Hoffman RWJ. Antiphospholipid antibodies among anti-U1-70 kDa autoantibody positive patients with mixed connective tissue disease. J Rheumatol 1997;24:319-22.
2. Venables PJ. Mixed connective tissue disease. Lupus 2006; 15:132-7.
3. Dorfmüller P, Humbert M, Perros F, et al. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. Hum Pathol 2007;38:893-902.
4. Zhang L, Visscher D, Rihal C, Aubry MC. Pulmonary veno-occlusive disease as a primary cause of pulmonary hypertension in a patient with mixed connective tissue disease. Rheumatol Int 2007;27:1163-5.

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A Randomized Trial of Robot-Assisted Laparoscopic Radical Cystectomy

TO THE EDITOR: Radical cystectomy is the standard management of nonmetastatic, invasive bladder cancer. However, this treatment is associated with clinically significant perioperative complications and prolonged recovery time among patients with this disease, who are typically older and often have a history of smoking and coexisting conditions.[1,2] Retrospective studies indicate that robot-assisted laparoscopic surgery is associated with a reduced risk of complications and shorter hospital stay, as compared with open surgery,[3] but data are lacking from randomized trials. We report the results of a randomized, controlled trial (ClinicalTrials.gov number, NCT01076387) designed to assess whether robot-assisted laparoscopic radical cystectomy would be associated with a lower rate of perioperative complications than open surgery (with the technique of extracorporeal urinary diversion used in both approaches); the study protocol is available with the full text of this letter at NEJM.org.

Patients with bladder cancer of clinical stage Ta–3N0–3M0 (according to the 2010 tumor–node–metastasis [TNM] classification system from the American Joint Committee on Cancer and the International Union against Cancer) who were scheduled for definitive treatment with the use of radical cystectomy were recruited at Memorial Sloan Kettering Cancer Center from March 2010 through March 2013. Four surgeons with experience in open surgery performed all open procedures, and three surgeons with extensive experience in robot-assisted pelvic surgery performed the robotic procedures. All the surgeons had completed a urologic oncology fellowship and had at least 10 years of operative experience after completion of the fellowship. The primary outcome was the rate of complications of grade 2 to 5 within 90 days after surgery, on the basis of a five-grade Clavien system (with grades ranging from 1 to 5, and higher grades indicating greater severity).[4]

Table 1. Outcomes after Radical Cystectomy in the Intention-to-Treat Analysis.*

Variable	Robot-Assisted Surgery (N=60)	Open Surgery (N=58)	Difference (95% CI)	P Value
Complication — no. of patients (%)				
Grade 2–5	37 (62)	38 (66)	–4 (–21 to 13)	0.66
Grade 3–5	13 (22)	12 (21)	1 (–14 to 16)	0.90
Operating-room time — min	456±82	329±77	127 (98 to 156)	<0.001
Length of stay in hospital — days	8±3	8±5	0 (–2 to 1)	0.53

* Plus–minus values are means ±SD. Differences between percentages are measured in percentage points. Complications were assessed according to a five-grade modified Clavien system (with grades ranging from 1 to 5 and higher grades indicating greater severity).[4] CI denotes confidence interval.