Title

Are age-based criteria the best way to determine eligibility for prostate cancer screening?

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COMMENTS AND RESPONSES

The Unintended, Negative Consequences of the Door-to-Antibiotic Measure for Pneumonia

TO THE EDITOR: I read with interest the recent article by Wachter and colleagues (1). An additional consequence of policies from the Centers for Medicare & Medicaid Services (CMS) has been the disruption of local pneumonia guideline processes. The 2007 American Thoracic Society–Infectious Disease Society of America pneumonia guideline (2) recommended that "locally adapted guidelines should be implemented to improve process of care variables and relevant clinical outcomes." In addition, "CAP [community-acquired pneumonia] guidelines should address a comprehensive set of elements in the process of care, rather than a single element in isolation."

A guideline was implemented in the Intermountain Healthcare System (Utah and Idaho) beginning in 1995, with a demonstrated decrease in 30-day all-cause mortality and pneumonia admission rates (3, 4). As part of multiple care elements, Intermountain's guideline recommends specific antibiotics (for example, ceftriaxone plus azithromycin for admitted patients) and recommends that antibiotics be administered at the site of initial care as soon as the diagnosis of pneumonia has been confirmed. With initiation of public reporting of CMS criteria, a competing focus developed within Intermountain Healthcare to achieve antibiotic administration within a 4-hour, and now 6-hour, window instead of our previous standard. In addition, the CMS list of acceptable antibiotics is broader than our local guideline, leading physicians at Dixie Regional Medical Center (St. George, Utah) to rewrite the local guideline to include CMS-accepted antibiotics, such as ertapenem. Compliance at Dixie Regional with Intermountain's guideline as measured by initial antibiotic prescribed decreased from 90% in January 2005 to only 55% in January 2008 (Compliance rate for community-acquired pneumonia for Dixie Regional Medical Center. Intermountain.net. Internal system Web site). Although Intermountain Healthcare System has more than 90% compliance with the CMS antibiotic timing measure, the focus of internal processes has shifted to meeting these performance measures instead of reinforcing the use of the local guideline. An earlier consequence of CMS payment policies was to reduce payments to Intermountain Healthcare for patients with pneumonia by approximately $500 000 per year (5). Our guideline recommends treating more patients with pneumonia at home, which resulted in revenue loss under CMS payment policies because reimbursement for care of a hospitalized patient with pneumonia was much higher than care of a similar patient at home. Unlike CMS pneumonia performance measures, our guideline has been shown to improve patient outcomes. Unlike reporting of specific care elements, severity-adjusted measures of outcome, such as survival to discharge home, time to return to usual activities, and 30-day mortality rate, would support local guideline development and implementation. Real improvement in pneumonia outcomes would probably result instead of what we are seeing from well-intended but flawed performance measures.

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Potential Financial Conflicts of Interest: None disclosed.

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TO THE EDITOR: I work at a tertiary community geriatric and neurologic hospital specializing in acute, subacute, and rehabilitation care. I fully agree with Wachter and colleagues' critique (1) of the flawed scientific basis of defining a time window for antibiotic administration for CAP in hospitalized patients. In 2006 and 2007, there were 40 428 inpatients with CAP in Lower Saxony (Germany). Forty-four patients were treated at my hospital. Data derived from the quality measurement tool for hospitalized patients with CAP found no association between time to first antibiotic administration and death. Because our patients have had higher CURB-65 (confusion, respiratory rate, blood pressure, and age 65 years or older) scores, were older, more often came from other hospitals or rehabilitation units, were more often bedridden, and were cognitively impaired, we add more data to the growing evidence that questions the sense of shorter door-to-antibiotic time. In a time when some physicians treat guidelines as gospel truth, it seems necessary to cite the most recent U.S. guideline (2): " . . . [T]he first antibiotic dose should be administered while still in the ED [emergency department]" is judged only as a "[m]oderate recommendation; level III evidence," but "[f]or these and other reasons, the committee did not feel that a specific time window for delivery of the first antibiotic dose should be recommended. However, the committee does feel that therapy should be administered as soon as possible after the diagnosis is considered likely." We hope that randomized, controlled trials will lead us to more reasonable quality measurement tools in future.

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Potential Financial Conflicts of Interest: None disclosed.

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TO THE EDITOR: The recent article by Wachter and colleagues (1) reported that a widely used performance measure, the administration of antibiotics within 4 hours to patients with pneumonia, may have led to increased inappropriate antibiotic use and less cost-effective care without decreasing mortality. This benchmark was used by the Joint Commission, CMS, and insurance companies. The Centers for Medicare & Medicaid Services publicly reported hospital performance on this measure, and some managed care companies tied reimbursements to it. From my own experience on a hospital committee charged with ensuring at least 90% compliance with this 4-hour requirement, I know that our organization allocated substantial resources to accomplishing this goal. We surveyed hospitals that had successfully met the 4-hour benchmark by instituting a protocol whereby patients automatically received antibiotics if they met certain criteria in triage. The 4-hour benchmark changed patterns of care. The Joint Commission recently relaxed this window to 6 hours, seemingly in recognition of the metric's limitations. Yet no study has shown a benefit from a 6-hour rule. Isn't one of the main components of quality improvement a feedback loop? There has been much press recently about the report by the Commonwealth Fund (2) which concluded that U.S. health care, while expensive, does not rate accordingly high in quality when compared with other industrialized nations. The report specifically identified pneumonia as one of the few diagnoses for which treatment has improved. This conclusion was based on 3 metrics, 1 of which was administration of antibiotics within 4 hours of patient presentation. Reporting on these findings, the *New York Times* (3) quoted the president of the National Business Group on Health as saying that "it proves once again that if you have quantitative information and metrics and make people pay attention, they change." How true, and how concerning then when the metrics are wrong.

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IN RESPONSE: We appreciate the letters, which endorse our main premise while adding new data and insights. Although we agree with most of the authors' points, we worry that the experience of a flawed measure, such as door-to-antibiotics for pneumonia, will lead some to throw out the baby (quality measurement and transparency) with the bathwater (the bad measure).

For example, Dr. Dean argues that the imposition of a national standard for pneumonia care undermined his organization's homegrown pneumonia strategy. We agree that national guidelines should provide enough flexibility to allow for individual institutional choice based on local factors, such as cost, resistance, and ease of administration, as long as the choices are compatible with the best evidence. In fact, Intermountain's preferred antibiotics were on the list of recommended antibiotics.

That said, we are concerned about the generalizability of Dr. Dean's example. Intermountain Healthcare is a large, highly evolved system with a strong infrastructure, including world-class information technology (1). Most institutions around the country don't look like that. Substantial evidence supports the value of widespread adherence to evidence-based standards (2, 3). We believe it would be a mistake to eschew thoughtful, evidence-based national guidelines because some organizations with the capacity to develop and study local guidelines might need to subsume their work to these national standards. Organizations with such capacity should become learning laboratories, testing existing guidelines and standards for effectiveness and engaging in the process of developing future evidence-based national guidelines.

Dr. Gogol states that he was skeptical of the value of the door-to-antibiotic measure because antibiotic timing had no impact on outcomes in his hospital's 44 patients with pneumonia. Here, too, individual institutions may not be able to generate the statistical power to identify even significant effects of practice changes. That should not be cause to shun national measures. But it is yet another reason to be sure that national standards are based on strong evidence, have been field-tested, and are reviewed frequently for unintended consequences.

Luckily, in part because of the door-to-antibiotic experience, both the National Quality Forum and the CMS have begun to change their processes to ensure that future measures are less likely to lead to unintended negative consequences (4). This is particularly important because, as Dr. Srouji correctly observes, there is no question that the public reporting of quality measures does have the intended effect: to change clinical practice, for better or worse.

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Are Age-Based Criteria the Best Way to Determine Eligibility for Prostate Cancer Screening?

TO THE EDITOR: The U.S. Preventive Services Task Force (USPSTF) (1) again tackles a difficult subject in updating their recommendations for prostate cancer screening. The most substantial change in the new

guideline is the grade D recommendation against screening men age 75 years or older because of a perceived lack of benefit for prostate cancer treatment in these older men. We would argue, however, that rather than adopting rigid age-based stopping criteria for screening, the medical community should pursue a more nuanced approach to screening, diagnosis, and treatment across all age strata.

Screening and potential overdiagnosis of prostate cancer are concerning primarily to the extent that they lead to overtreatment. Overtreatment is certainly a substantial problem among men with low-risk prostate cancer, particularly older men (2). With cessation of screening among older patients, however, we lose the opportunity to detect aggressive prostate cancer in those men who are most likely to have it. The incidence of high-risk prostate cancer increases with age, accounting for 42% of cancer cases diagnosed in men age 75 years or older compared with 22% in men younger than 75 years (3). As much as overtreatment of low-risk disease remains a concern, we have also found evidence of growing underuse of potentially curative local therapy among the men with high-risk disease who face the highest risk for disease-specific morbidity and mortality (4). Rigid age-based criteria, moreover, ignore substantial variation in life expectancy based on overall health and comorbid illnesses.

We have previously attempted to develop multispecialty consensus recommendations aimed at encouraging a more cautious approach to screening for prostate cancer in men older than 75 years. During these discussions, primary care physicians expressed great interest in continued screening even in older men and were reluctant to stop screening at a predetermined age. After a year-long educational campaign, stated physician preferences for continued screening beyond 75 years fell 20%. However, the demographic correlates of screeners versus nonscreeners did not change: Screeners were more likely to be older men themselves (5).

All patients with mildly elevated prostate-specific antigen levels on screening tests do not necessarily require further diagnostic evaluation. Likewise, many older men—probably a substantial majority—in whom lower-risk tumors are diagnosed can be safely followed with active surveillance (6). A greater onus must be placed on physicians (and the men they counsel) to divorce diagnosis from inevitable treatment. Older men who harbor undiagnosed aggressive tumors, however, risk substantial potential morbidity and mortality from progressive disease and should not be denied the opportunity for treatment.

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TO THE EDITOR: The USPSTF (1) defines an age cut-off for prostate cancer screening, recommending against screening for men older than 75 years or those with a life expectancy less than 10 years. It may be uncertain whether screening for prostate cancer by using prostate-specific antigen is a useful tool at any age. But an age cut-off of 75 years may be wrong for some men age 75 years or older. As Walter and Covinsky (2) reported, in 1997 the life expectancy was 14.2 years for U.S. men age 75 years in the top 25th percentile of the survival tables, 10.8 years for those age 80 years, and 7.9 years for those age 85 years. For the same age groups in the top 50th percentile, life expectancy was 9.3 years, 6.7 years, and 4.7 years, respectively. In an aging world (3), clinicians, health care providers, and political decision makers must remember that aging differs in persons with different health and functional status. The "best agers" have a life expectancy of 4.3 years in men and 4.8 years in women (top 25th percentile) at age 95 years. Biological age alone is a bad adviser for decision making.

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IN RESPONSE: We appreciate the letters from Drs. Konety and colleagues and Dr. Gogol regarding the USPSTF's updated recommendation on screening for prostate cancer (1). The USPSTF recommended against screening men age 75 years or older.

First, it is important to emphasize that a systematic review conducted in collaboration with the USPSTF (2) identified no direct evidence (that is, evidence from randomized trials) that permitted the USPSTF to determine whether prostate-specific antigen screening has a net benefit on mortality for men of any age. Although some men may benefit from earlier detection of potentially fatal cases of prostate cancer, others will be harmed by the adverse effects of detection and treatment of seemingly abnormal prostate cells that would never have caused clinical symptoms. We will not know whether the uncontrolled experiment that began in the early 1990s of screening millions of men for prostate cancer has, on the whole, increased or shortened life expectancy until ongoing randomized trials are completed.

In concluding with moderate certainty that the harms of screening men age 75 years or older outweigh the benefits, the USPSTF relied on information about the natural history of clinically detected prostate cancer from a randomized trial comparing the outcomes of radical prostatectomy with watchful waiting (3). This trial suggested that the interval required to experience a mortality benefit from prostate-specific antigen screening is greater than 10 years. Even assuming that every case of prostate cancer detected by screening is potentially fatal (not true) and that treatments are never fatal (also not true), the majority of men age 75 years or older would experience no benefits from screening.

Recently published data from the trial by Bill-Axelson and colleagues (4) suggest that the USPSTF may have set the screening "cut-off" age conservatively. In the trial, men older than 65 years who underwent prostatectomy had the same mortality rate as men who did not (4).

Dr. Konety asserts that older men who are found to have "low-risk" prostate cancer could choose to enter active surveillance rather than undergo treatment, thus reducing the harms associated with prostate cancer screening. In practice, potentially lethal prostate cancer cannot be reliably identified. Because most men desire to remove all traces of cancer, attrition rates from studies of active surveillance have been high, rendering the effectiveness of the surveillance protocol uninterpretable (2). In addition, there is no evidence that active surveillance itself leads to more benefits than harms.

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Risk Prediction Versus Diagnosis: Preserving Clinical Nuance in a Binary World

TO THE EDITOR: Vickers and colleagues (1) discuss an interesting premise in their article: Physicians should consider moving away from the practice of diagnosis and toward the incorporation of risk stratification in their day-to-day practice. This raises several practical issues. The first is that the diagnoses that were discussed are all special cases in which the diagnosis had been defined by test results. Although many common diagnoses may fit into this category, many others can be suggested but not proven definitively by routine tests (pneumonia and pulmonary embolism are 2 that quickly come to mind). In these cases, diagnosis reflects a sufficiently high level of certainty that a condition exists to move forward with management. Creating a discrete categorization greatly simplifies management decisions and communication with patients and colleagues, even though the likelihood of the condition is continuous. The more important practical issue is the implementation of risk stratification tools. As Vickers and colleagues point out in their illustration of the Framingham Risk Score (2), many such tools exist (The Medical Algorithms Project [3] currently documents more than 11 000!). This is daunting in and of itself, but in addition, some of these algorithms are also quite complex. The Acute Physiology and Chronic Health Evaluation II score (4), for example, has roughly 20 variables that must be entered. Another potential problem arises when the clinician must interpret the output of a risk stratification algorithm; it has been shown that most medicine residents have deficient knowledge in biostatistics (5). It is also unclear how to effectively convey information about risk to patients. A recent article found that patients have more difficulty interpreting a "1-in-*n*" statement than a percentage or frequency term (6). Risk stratification holds great potential as medicine begins to move from a diagnostic to a prognostic framework. Substantial changes in the medical education system will be required to teach physicians when to apply these tools, how to interpret the results, and how to convey the information to colleagues and patients.

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Potential Financial Conflicts of Interest: None disclosed.

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TO THE EDITOR: I read with great interest the article by Vickers and colleagues (1), in which they note the problem of diagnosis caused by difficulties in classification of borderline cases: One individual or very small differences in the quantities of interest may completely change categorization and consequent actions. Unfortunately, the risk prediction alternative recommended by the authors is unlikely to attenuate the problem of diagnosing diseases that are defined on a continuum. The problem described by the authors is not trivial and has preoccupied philosophers since ancient times. It is commonly referred to as the sorites paradox (from the Greek word *soros,* meaning "heap"): If one removes a single grain from a heap of sand, would it be still a heap? Yes. However, as we continue removing 1 grain of sand at a time, eventually the heap of sand is not a heap any more. So where does one draw the line? How many grains of sand make a heap? The sorites paradox has its origin in vagueness, which deals with unknowability of the borderline statements (2) (such as the case that Vickers and colleagues describe of the inherent uncertainty of distinguishing clinical consequences between the effect of a blood pressure of 140 mm Hg vs. 139 mm Hg). Many solutions have been proposed in the philosophical literature for dealing with the sorites paradox. A partial list includes fuzzy logic and fuzzy set theory approach, supervaluations, intuitionistic logic, paraconsistent logic, modal logic, possibility theory, rough sets theory, and open texture concept (3, 4). The success of the proposed solutions, to some extent, depends on the context in which the sorites paradox can apply. How effective these solutions can be in the medical arena is not known; little work has been done related to the role of vagueness in medicine. Vickers and colleagues should be applauded for drawing the attention of the medical audience to this important question. With this letter, I hope to stimulate application of the philosophy of vagueness in medicine, which despite its importance has been sorely missing.

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TO THE EDITOR: Vickers and colleagues (1) neglected to mention the greatest impediment to implementing predictions: Physicians practice in a binary world driven by diagnosis. Those who pay for health care profit from risk management and care little for clinical nuance. A diagnosis of hypertension has a direct impact on the premium that a patient will pay for health or life insurance—whether the hypertension is benign (International Classification of Diseases code 401.1) or malignant (code 401.0). A diagnosis of depression can make disability insurance unobtainable. A diagnosis of asthma can disqualify a patient from employment or from serving in the military, no matter how well the asthma is controlled. Computers are binary machines. An electronic medical record demands that specific diagnoses with fixed end points be entered into the computer. Computerized algorithms are routinely used to determine "medical necessity" and "quality care." Woe betide the patient who falls outside of the algorithm.

I routinely must explain by phone or by letter why a particular patient requires additional time in the hospital or a plan of treatment to a reviewer who complains that my plans fall outside their (proprietary) guidelines for a particular diagnosis. Often I must first comply with a series of conservative (that is, cheaper) treatments (meticulously documented) before my treatment plan will be considered. Medication formularies are driven by similar guidelines and often require pharmacy records (no samples, please!) to prove that the cheaper medication was tried first. Agencies under contract to provide quality reviews mine the same data. My outpatient care of 1 elderly patient with diabetes generates multiple individual computer-generated letters several times per year that ask why the patient is not taking an angiotensin-converting enzyme inhibitor (renal failure) or a statin (myopathy), why he still needs a proton-pump inhibitor (history of gastrointestinal bleeding and documented gastroesophageal reflux disease), and whether I have considered screening for osteoporosis (his insurance policy will not cover the cost of additional medication). Prediction modeling is a useful tool for the individual physician working with his individual patient. But outside of the examination room, diagnosis rules.

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Reference

1. Vickers AJ, Basch E, Kattan MW. Against diagnosis. Ann Intern Med. 2008;149:200-3. [PMID: 18678847]

TO THE EDITOR: In their recent article, Vickers and colleagues (1) identify problems with the use of a binary approach to the diagnosis of disease. They are to be lauded for their attempt to change how we view the act of diagnosis. However, the authors need to make a distinction between having disease and having a risk factor for disease. A disease state implies existence of symptoms or functional impairment. Diagnosis in this context is useful because it not only can predict the development of further symptoms or impairment but can also help indicate appropriate treatment and predict response to therapy. Identification of asymptomatic physical or biochemical parameters that place the patient at risk for future impairment or symptoms can perhaps be better viewed not as a disease but as a risk factor. Ideally, this would push physicians and patients to ask the obvious question: How big is the risk, and how do we know?

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Reference

1. Vickers AJ, Basch E, Kattan MW. Against diagnosis. Ann Intern Med. 2008;149:200-3. [PMID: 18678847]

IN RESPONSE: Dr. Warner, Dr. Djulbegovic, and Dr. Patrick each point to practical problems with a prediction approach. Dr. Warner concurs with a point we made in our article, which is that use of discrete categories (disease vs. no disease) simplifies clinical management and communication. We also agree with him that changes in medical education are needed to help physicians understand and communicate the results of risk prediction. A point of disagreement is that physicians' and patients' poor understanding of probabilities is a problem specific to the risk-prediction approach. For example, even if we use binary diagnostic categories, we would still want to inform the patient about their risk ("Mr. Jones, you have hypertension, which means a 20% risk for having a heart attack"). Conversely, we might use prediction models without reference to numbers at all ("Mr. Jones, you are at high risk for a heart attack, so I am going to write you a prescription for some pills").

Dr. Djulbegovic argues that regardless of whether we use a binary diagnostic category or a risk prediction model, we still have to choose a threshold to treat a patient. This can cause problems when results are close to the threshold. We agree that there is room for both descriptive and normative research on decision making near decision thresholds. We also agree with Dr. Patrick's point that we currently live in a binary world and enjoyed his description of the numerous ways in which those outside the examination room force a physician to think in simple binary terms. We are not naive about the practical challenges of implementing a prediction approach. That said, we must make medical progress in the best interests of our patients and hope that outside forces and structures follow along: We would certainly hate to see, for example, the military's need for specific criteria for service disqualification affect the way we practice medicine.

Dr. Swerlick makes a distinction between having symptoms or functional impairment and having only a risk factor for a disease. Although we focused on risk factors, we believe that binary diagnostic thinking is often inappropriate for symptomatic disease. For example, many people have symptoms of depression; a choice of a particular cut-point on a spectrum of severity does not create 2 natural categories of depressed and not depressed. A prediction approach would focus on whether treatment would do more good than harm.

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CLINICAL OBSERVATIONS

Delayed Splenic Rupture: Myth or Reality?

Background: The spleen is the most commonly injured organ in blunt abdominal trauma (1). Most splenic injuries manifest immediately after trauma, but some may occur days to weeks after blunt abdominal trauma. It is not clear whether delayed splenic rupture (DSR) represents delayed diagnosis of acute rupture or a truly delayed rupture (1, 2).

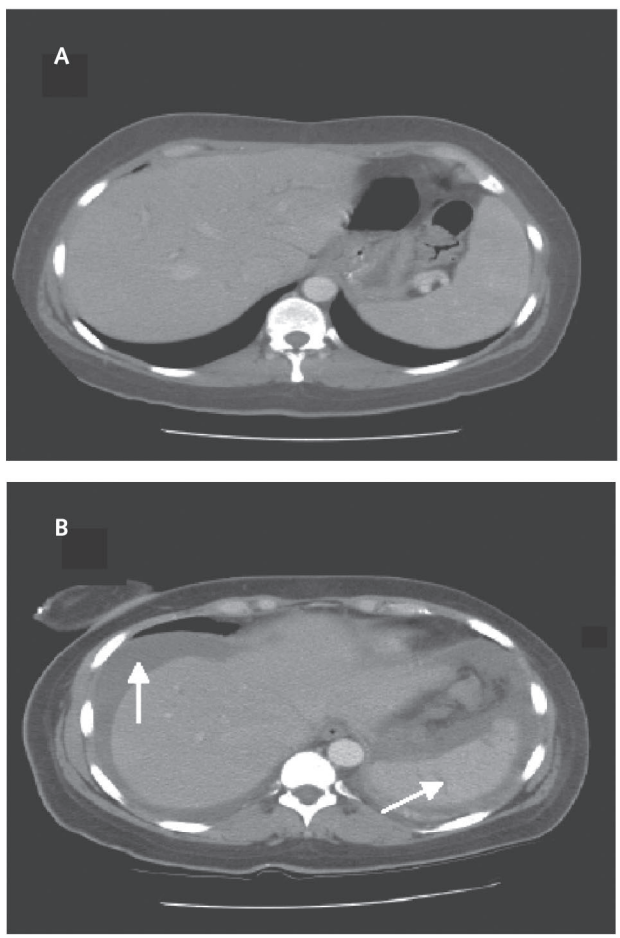
Objective: To report a case of DSR confirmed by a normal initial result on computed tomography (CT).

Case Report: A 42-year-old woman presented with 2 weeks of abdominal pain after a noncollision deceleration motor vehicle accident in which she was wearing a seatbelt. Her history included gastric bypass 4 years ago and systemic lupus erythematosus.

On initial examination, the patient was stable and in no acute distress. Abdominal examination revealed mild left upper-quadrant tenderness and a palpable spleen but no evidence of trauma.

The patient's hemoglobin level was 0.69 g/L, and results of fecal occult blood testing were positive. Computed tomography of the abdomen with intravenous contrast obtained on admission (**Figure**) was unremarkable. After 4 U of packed red blood cells was transfused, her hemoglobin level increased to 1.10 g/L. She was scheduled for esophagogastroduodenoscopy and colonoscopy. She subsequently

Figure. **Computed tomography of the abdomen.**



A. Computed tomography of the abdomen on admission. There is no evidence of splenic rupture. **B.** Repeated abdominal computed tomography 2 days later. Free intraperitoneal fluid, hypodensity in the spleen, and capsular changes consistent with splenic rupture (*arrows*) can be seen.

developed worsening nausea and emesis with retching, followed by increasing left upper-quadrant pain without evidence of hemodynamic compromise. Repeated hemoglobin testing revealed a decreased level of 0.70 g/L.

The patient did not report hematemesis, hematochezia, or melena. Emergency repeated abdominal CT with intravenous and oral contrast demonstrated intraperitoneal free fluid and capsular changes consistent with splenic rupture (**Figure**).

The patient underwent successful splenic artery embolization. Follow-up hemoglobin level remained stable. Work-up of splenomegaly, including viral serology and clotting studies, was normal. The rest of her hospital course was uneventful.

Discussion: The mechanism of DSR is either a subtle splenic lesion, undetected by conventional imagery, that progresses to rupture or an acute rupture missed by CT. Subtle splenic lesions that can progress to splenic rupture include subcapsular hematomas, pseudocysts, and pseudoaneurysms (1). False-negative CT findings may be caused by artifact or interference from surrounding tissues, which make the injury difficult to detect; by early CT done before a subcapsular hematoma has bled enough to be detected; by suboptimal technical performance of the CT machine; by diluted oral contrast; or by variability in the intravenous contrast protocol used (2).

This case demonstrates true DSR. Contributing factors include a deceleration motor vehicle accident and injury; vomiting and retching; and abdominal adhesions from previous gastric bypass surgery, which may have affected positioning and exerted traction on the spleen. In addition, underlying systemic lupus erythematosus might have also contributed to DSR through pathologic changes in the spleen.

Many cases of DSR occur in the context of an underlying disease, such as end-stage renal disease, amyloidosis (3), rheumatoid arthritis (4), and sarcoidosis (5). Although not all of these studies reported normal initial CT results, these cases support the hypothesis that certain comorbid conditions can favor the occurrence of DSR by making the spleen more fragile and by making the small splenic lesions more prone to progression to frank splenic rupture.

Conclusion: Some splenic ruptures are truly delayed. It is crucial to consider DSR in instances of acute anemia or acute abdominal pain in the presence of recent abdominal blunt trauma, even if the initial CT result is negative.

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Hypersensitivity Myocarditis Associated With Azithromycin Exposure

Background: Myocarditis is a mysterious clinical entity that poses diagnostic and therapeutic challenges. It may be caused by a viral infection or be secondary to inflammation from a bacterial, parasitic, or fungal pathogen. Rarely, it can result from a hypersensitivity allergic reaction to an inciting drug.

Objective: To report a case of fulminant myocarditis associated with azithromycin exposure.

Case Report: A 48-year-old man presented to his internist 3 months before admission with an upper respiratory tract infection and was prescribed a course of azithromycin. Within hours of the first dose of azithromycin, the patient developed fever and a diffuse maculopapular rash. He was given oral antihistamines and a 1-week prednisone taper. On completion of the steroid taper, the patient redeveloped fever and rash and, in addition, had fatigue and pruritus. Examination was documented to reveal diffuse lymphadenopathy. Laboratory work-up was clinically significant for peripheral blood eosinophilia (20% of leukocytes) and mild elevated aminotransferase levels.

Skin biopsy of the rash was performed and showed dermatitis with eosinophils consistent with drug eruption. The constellation of examination, laboratory work-up, and biopsy findings was deemed classic for the diagnosis of the DRESS (drug rash with eosinophilia and systemic symptoms) syndrome. The patient was prescribed a longer taper of corticosteroids.

Two months later, the patient presented with exertional dyspnea and pleuritic chest pain. Examination revealed bilateral basilar crackles and an S_3 gallop. Laboratory evaluation was clinically significant for an elevated troponin I level of 5.96 ng/mL, leukocyte count of 12.1×10^6 cells/L, and a mildly elevated aminotransferase level. Electrocardiography showed sinus tachycardia with a right bundle-branch block pattern. Echocardiography revealed a diffusely hypokinetic left ventricle and a small pericardial effusion. Coronary arteriography showed normal coronary arteries.

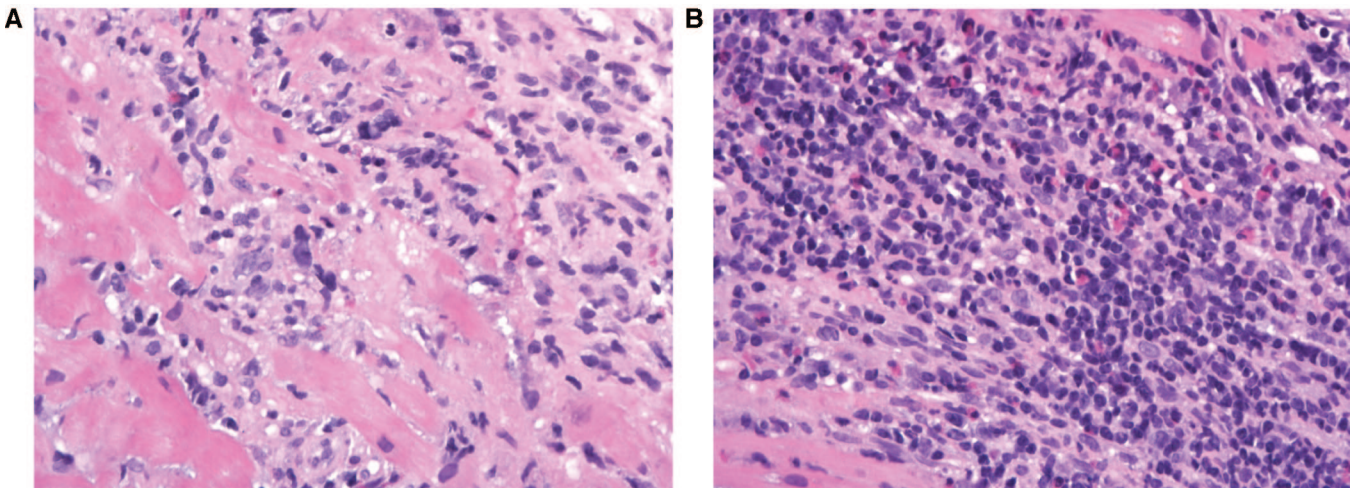
Because of the patient's history of drug reaction and peripheral eosinophilia and the development of heart failure with weaning of steroid therapy, hypersensitivity myocarditis was a concern. Endomyocardial biopsy was performed for definitive diagnosis. Histopathology revealed a combined lymphocytic and eosinophilic infiltration of the myocardium consistent with drug-associated hypersensitivity myocarditis (**Figure**). Treatment with high-dose steroids was restarted and azathioprine was added.

After 2 weeks of immunosuppressive therapy, the patient presented with hypotension and abdominal pain. Ultimately, he developed sepsis from an intra-abdominal infection. Despite broad-spectrum antibiotics, escalating pressor therapy, and aggressive resuscitation efforts, the patient died.

Discussion: Given the temporal relationship of azithromycin exposure to the development of the DRESS syndrome and heart failure, the diagnosis of hypersensitivity myocarditis seems secure. To our knowledge, this is the first reported case of the DRESS syndrome and hypersensitivity myocarditis induced by azithromycin, a commonly prescribed antibiotic.

The DRESS syndrome is a severe drug reaction characterized by rash, fever, lymphadenopathy, and single or multiple organ involve-

Figure. **Histopathologic examination of endomyocardial biopsy specimen.**



A. Myocyte necrosis with lymphocytic and eosinophilic infiltrate (hematoxylin–eosin stain, ×40). **B.** Combined eosinophilic and lymphocytic infiltration of myocardium (hematoxylin–eosin stain, ×40).

ment that occurs within 8 weeks of drug initiation. Hematologic abnormalities, including eosinophilia and atypical lymphocytosis, are the rule with this syndrome. Anticonvulsant drugs and sulfonamides account for the majority of cases of the DRESS syndrome and concomitant myocarditis, although these disorders have been associated with other drugs (1). Myocarditis has occurred in the context of the DRESS syndrome, although it is rare and typically has a fulminant course. Therefore, the development of the DRESS syndrome should warrant investigation for potential eosinophilic infiltration of myocardium.

The pathophysiologic mechanisms mediating such an allergic reaction are unclear, although a predisposition to development includes impairment in drug detoxification pathways and concomitant human herpesvirus-6 infection (2).

Hypersensitivity myocarditis itself carries a dismal prognosis, and the immunosuppressive therapy used to treat it may predispose to fatal complications. Because the majority of cases of hypersensitivity myocarditis are made at autopsy, it is clear that there is no universally accepted treatment regimen (3, 4). Our rationale for additional immunosuppressive therapy with azathioprine was based on clinical markers of deterioration and widespread myocyte necrosis on the biopsy specimen despite use of high-dose prednisone therapy.

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Acute Hepatitis E Virus Infection in an HIV-Infected Person in the United States

Background: Hepatitis E virus (HEV) is an enterically transmitted cause of viral hepatitis that is rarely noted without international travel.

Objective: To report the first case of an HIV-infected man with acute hepatitis due to HEV infection who had not traveled outside the United States.

Case Report: A 45-year-old HIV-positive man had mildly elevated aminotransferase levels that were asymptomatic. He had a CD4 cell count of 0.36×10^9 cells/L (31%) with undetectable HIV RNA (<50 copies/mL) while receiving abacavir–lamivudine, atazanavir, and ritonavir. He had visited Maine and Illinois 4 weeks previously but reported no exposure to sick persons, nonmunicipal water, or farm animals; international travel; or medication changes. He reported having had anonymous sexual partners but did not report alcohol or illicit drug use.

Over the next week, the patient developed low-grade fever, abdominal tenderness, fatigue, and diffuse myalgias. Examination revealed right upper-quadrant tenderness with a palpable liver edge. Repeated laboratory testing revealed levels of alanine aminotransferase at 1396 U/L (normal range, 0 to 45 U/L), aspartate aminotransferase at 810 U/L (normal range, 0 to 40 U/L), total bilirubin at 5.7

mg/dL (normal range, 0.4 to 2.0 mg/dL), and alkaline phosphatase at 148 (normal range, 26 to 110 U/L); prothrombin time, partial thromboplastin time, and albumin level were normal.

Medical history included HIV infection diagnosed in 1986, herpes simplex virus 2 treated with suppressive acyclovir, and gastroesophageal reflux managed with daily ranitidine. All drug treatments, including antiretroviral therapies, were discontinued because of concern about potential hepatotoxic effects. Alanine aminotransferase level peaked at 2288 IU/L and aspartate aminotransferase level peaked at 1267 IU/L during the second week of illness.

An extensive work-up for infectious causes (hepatitis A, B, and C; Epstein–Barr virus; cytomegalovirus; and syphilis) and autoimmune causes of hepatitis was negative. Acute HEV was considered; blood sent to the Centers for Disease Control and Prevention was positive for HEV IgM and IgG by enzyme-linked immunosorbent assay and HEV polymerase chain reaction. The patient promptly restarted antiretroviral therapy and has remained healthy with normalization of liver enzyme levels. Blood samples 6 months after initial presentation were negative for HEV IgM and polymerase chain reaction but remained positive for HEV IgG.

Discussion: Hepatitis E virus is a common cause of epidemic and sporadic hepatitis in the developing world, but few cases have been reported in industrialized countries. Only 4 previous nontravel cases of HEV have been reported in the United States (1); we believe this is the first case in an HIV-infected patient.

Despite the paucity of HEV cases, the rate of seropositivity for HEV IgG antibodies is approximately 20% among U.S. blood donors (2). The source is unclear, but increasing evidence suggests that HEV may be spread zoonotically from swine (2). Given the high seroprevalence of HEV, it is possible that HEV represents an important cause of previously unrecognized hepatitis. As such, serologic studies for HEV should be considered in patients presenting with acute hepatitis of unclear cause.

It is unclear whether HIV infection predisposes to HEV acquisition. Studies from endemic areas have shown higher HEV seroprevalence rates in HIV-infected persons and an association between HEV positivity and more advanced HIV disease (3). Whether this indicates an opportunistic infection or similar modes of transmission is unknown. One study suggested that oral–anal sexual contact may be associated with HEV acquisition among HIV-infected persons (4), perhaps similar to that of other enteric infections (for example, *Giardia*); however, other studies have refuted this association.

Our patient recovered uneventfully, with normalization of liver test results and disappearance of detectable HEV. Although HEV infection is usually not associated with chronic hepatitis, transplant recipients develop chronic liver disease in more than 50% of cases (5). Whether our patient's rapid reinitiation of antiretroviral therapy prevented the development of chronic hepatitis is unknown. Treatment of acute HEV infections is supportive; the impact of reversing immunosuppression in preventing chronic HEV infection requires further investigation.

Conclusion: Sporadic HEV infection may occur in patients in the United States who have no history of international travel.

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Note: The opinions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Navy, or Air Force or the Department of Defense. The authors have no commercial or other association that might pose a conflict of interest in this work. This work is original and has not been published elsewhere.

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Correction

Correction: Physician Self-disclosure During Primary Care Encounters

In the recent article by Morse and colleagues (1), the author byline contains an error. Susan McDaniel has a PhD, not an MD. The online version has been corrected.

Reference

1. Morse DS, McDaniel SH, Candib LM, Beach MC. "Enough about Me, Let's Get Back to You": Physician Self-disclosure during Primary Care Encounters. Ann Intern Med. 2008;149:835-7.