Deferred Care for Emergency Department Users with Nonacute Conditions

TO THE EDITOR: In describing a randomized trial on deferring care for emergency department users with nonacute conditions, Washington and colleagues concluded, “Clinically detailed standardized screening criteria can safely identify patients at public hospital emergency departments for referral to next-day care. However, larger studies are needed to assess the possibility of adverse effects” (1).

This study suffers from selection bias. Of the patients screened, 421 met deferred care criteria but only 156 (37%) were studied. When faced with the possibility of being denied emergency department care, sicker patients are more likely to decline to participate in studies like this one; 147 (35%) patients approached for Washington and colleagues’ study declined. The study excluded other patients who may have been sicker, such as “patients who were taken immediately to the treatment area” and “any patient who . . . required a more detailed evaluation.”

Another inaccuracy is confusing negative results with insufficient power to demonstrate an effect. The point estimates from the data suggest that patients in the deferred care group had less improvement in health status, worse health at follow-up, and more days in bed and disability days. None of these differences were statistically significant, but, as the authors pointed out, the confidence intervals were so wide that it cannot be determined whether delaying care caused harm.

Finally, the abstract summarizes the results inaccurately. Although the Discussion section points out the limitations of the study, the Conclusions section of the abstract (reproduced in the first paragraph of this letter) overstates the results. It would be more accurate to say, “The screening criteria, combined with nurses’ subjective judgments and patients’ self-assessment, identified patients whose care could be delayed. Although the sample size in the study was insufficient to obtain precise estimates of the clinical impact, the point estimates suggest worse health status, greater duration of illness, and greater pain in the patients denied emergency department care.” This description of Washington and colleagues’ findings is more consistent with previous research on “nonurgent” emergency department use (2, 3).

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References

TO THE EDITOR: The prominence with which Annals featured the trial by Washington and colleagues (1) is welcome. However, I would like to emphasize the authors’ observation that even though this study randomly assigned and evaluated patients carefully, it should be viewed as a pilot study. I disagree with the proposal that the rule is now ready for validation in other settings.

The development of useful triage criteria should adhere to the standards proposed for other clinical decision rules (2). There should be an orderly sequence of studies, as follows: 1) explicit definition of adverse events using data and consensus when necessary, 2) reproducibility of candidate predictors, 3) derivation of a decision rule using a sample large enough to include hundreds of adverse events, 4) validation of the rule in many new settings, and 5) a group-randomized trial of the rule itself.

Such a progression of studies has been successful in evaluating radiographic criteria for blunt ankle–foot injury (3) and safe discharge from the emergency department of patients with community-acquired pneumonia (4). The proposed next-day rules should be derived at least as rigorously as the rules for predicting ankle fracture, an adverse outcome much less serious than the types of triage errors that any practicing physician has encountered in regular practice (for example, epiglottitis or myocardial infarction presenting as sore throat). Studies of this size will require high levels of funding. The next-day rules proposed by Washington and colleagues might be viewed as an emergency measure to relieve emergency department overcrowding but should not be viewed as a standard until much larger studies with defined adverse events have been performed.

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References
ing is driven by an entirely different set of factors, most notably a nationwide decline in the number of staffed inpatient beds and a widespread shortage of nurses. This forces emergency departments to hold admitted patients in examination rooms and hallways for hours or even days until a vacant inpatient bed is available (2).

The authors claimed that “patients with nonemergency conditions often use emergency departments as portals of entry into the health care system, not because they think they require immediate care.” In fact, the vast majority of patients with nonurgent conditions who seek treatment in emergency departments do so because they are experiencing pain or worrisome symptoms and have nowhere else to go (3, 4).

Several years ago, researchers interviewed more than 6000 walk-in patients who sought care in 56 U.S. emergency departments during a single 24-hour period (3). Nearly all of the eligible patients (96%) agreed to be interviewed. Eighty-six percent cited one or more clinical reasons for seeking care in an emergency department. Nearly half thought they had an emergent or urgent condition or were too sick to go elsewhere. Nineteen percent reported that they had initially contacted another health care provider but were told to seek care in an emergency department.

The Medicaid Access Study Group trained research assistants in 9 U.S. cities to pose as Medicaid patients with 1 of 3 uncomfortable but patently minor problems (sore throat, low back pain, or dysuria) (5). When the research assistants subsequently telephoned a random sample of primary care practices, public health clinics, hospital clinics, and urgent care centers in search of a timely appointment, few were willing to see them. When providers were pressed to identify an alternative, the most common advice was “no advice.” The next most common recommendation was “Go to an emergency department.”

Rather than randomly sample emergency department patients around the clock, Washington and colleagues recruited a convenience sample between 7:00 a.m. and 3:00 p.m., Monday through Thursday. This represents fewer than 20% of the hours in which patients seek care in emergency departments. To rationalize this approach, Washington and colleagues made the unsubstantiated claim that “more after-hours users may use emergency departments out of convenience for nonacute conditions” than daytime weekday users. In the experience of many clinicians, patients who come to the emergency department “after hours” tend to be sicker, on average, than daytime users. To allay concerns about sampling bias, the authors could have compared the clinical characteristics of emergency department patients seen during weekday business hours to those seen on nights, weekends, and holidays. This was not done.

Only 1176 patients were screened during the 226 weekday shifts available for recruitment—an average of 5 patients per day. After identifying 421 patients who met deferred care criteria, the authors immediately excluded 29% of them, including “patients who were taken immediately to the treatment area” (conditions not specified), “women in active labor” (otherwise, abdominal pain qualified for deferred care), “patients who did not speak English or Spanish” (common in many parts of the United States), and most important, “any patient who, in the nurse’s judgment, required a more detailed evaluation to exclude the presence of an emergent condition” (a loophole big enough to drive a truck through). This raises serious concerns about selection bias.

Nearly half of the remaining 299 patients declined to participate, despite being told that they would have to wait an average of 3.5 hours to be seen in the emergency department. This left the team with 156 patients, two-tenths of one percent of the total seen in the Harbor–UCLA (University of California, Los Angeles) emergency department during the 13-month study interval. To detect nonparticipant bias, the clinical, social, and demographic characteristics of those who declined to participate could have been compared with those who agreed. This was not done.

To avoid harm, any scheme to defer emergency department care should be sensitive enough to ensure that seriously ill patients are not turned away. Although such mistakes are rare, they can be catastrophic. Examples include sudden airway compromise from missed epiglottitis, the development of septic shock from missed pyelonephritis, and the rapid development of spinal cord compression from a missed epidural abscess. This is more than a hypothetical concern. Studies have consistently found that between 4% and 5.5% of patients initially classified as “nonurgent” at the triage desk are found, after further evaluation in the emergency department, to require hospitalization (3).

Washington and colleagues’ study was too underpowered to exclude an unacceptable rate of serious adverse events in the deferred care group. The 95% CI for adverse events in a study this size ranges from a low of 0% to a high of 4%. Even so, the authors conceded that patients allocated to deferred care may have experienced up to 1 additional day of symptoms and up to 1 additional day of disability compared with those who received immediate treatment. For the working poor, this is a high price to pay for agreeing to leave the emergency department without being seen.

Policymakers tempted to implement this strategy should ask themselves 3 questions.

1. Is it wise? After conducting a detailed history and directed examination, and even obtaining selected laboratory tests, wouldn’t it be more prudent to simply treat the patient and arrange follow-up rather than start the process all over again the following day? The time burden imposed on patients was not reported in Washington and colleagues’ study but was probably substantial. Forty-three percent of participants allocated to deferred care stated that they would not choose it again.

2. Is it safe? If and when criteria for deferred care fail, as they will from time to time, patients will be harmed. With the skyrocketing cost of liability insurance, hospitals and emergency physicians can ill afford more lawsuits. Furthermore, in light of differing interpretations of Emergency Medical Treatment and Active Labor Act obligations by different regional offices of the Centers for Medicare & Medicaid Services (formerly Health Care Financing Administration), it is conceivable that widespread implementation of deferred care could trigger a wave of investigations and sanctions (6).

3. Is it fair? The authors reported that participants in this study were “of all adult age groups, ethnically diverse, poor, and uninsured.” Recent reports by the Institute of Medicine cite overwhelming evidence that the uninsured and members of ethnic and racial minority groups face formidable barriers to care and suffer worse health outcomes as a result (7–9). Deferred care is designed to benefit hospitals and third-party payers, not the patients they serve.

None of these flaws deterred Washington and colleagues from claiming that deferred care criteria can be safely used to deny emergency department treatment to up to 12 million patients per year. This claim was echoed in an accompanying editorial in the same
issue (10), the journal’s press materials, and consequently by the news media.

Denial of emergency department care is fraught with clinical, legal, and moral hazards. It should not be done without ample justification and compelling evidence of safety. The study by Washington and colleagues provides neither. Primum non nocere.

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References

IN RESPONSE: The correspondents raise concerns that our study suffers from selection bias; lacks sufficient statistical power to prove the safety of the deferred care criteria; fails to follow standard methods for decision rule development; fails to address the root cause of emergency department overcrowding; and proposes an unsafe, unfair solution to the current access crisis in emergency care. This letter addresses each of these concerns.

Our study’s goal was to test the hypothesis that a population of ambulatory patients exists who seek emergency department care for non–life-threatening conditions and can safely await primary care evaluation on the following day. Had we set out to estimate the prevalence of such patients in the general population of emergency department patients, our sampling method would have represented a serious threat to the study’s external validity. In fact, the study’s design and purpose render the issue of external validity moot but preserve internal validity. Our findings apply to exactly the group of patients we chose to study and support safe next-day care in this group. Our discussion challenges others to replicate this finding in other settings as a prerequisite to wider implementation.

Our study had adequate power to exclude clinically important differences in our primary outcome, change in health status. The 95% CI for change in health status excluded a clinically important difference between groups. For our secondary outcomes, much was made of the fact that the 95% CI included the possibility that the deferred care group may have had 1 extra bed day because of illness. We note that the 95% CI also included the possibility that the deferred care group had 0.8 less bed day because of illness.

The excellent work of McGinn and colleagues in developing decision rules, which Dr. Pitts cited, represents one but not the only approach. A large body of literature supports the RAND–UCLA Appropriateness Method we chose (1). Both methods require large validation studies in diverse populations, as emphasized in our Discussion.

We thank Dr. Kellermann for citing previous work confirming that a minority of patients presenting to emergency departments consider their conditions emergent or urgent (2). Many studies show that emergency department overcrowding has many causes, including internal patient flow issues and patient volume (3). We have addressed a single facet of the problem.

Dr. Kellermann’s contention that our intervention was designed to benefit hospitals and third-party payers rather than the study participants reflects a narrow view of emergency department overcrowding. Previous work has amply shown that prolonged waiting times in the emergency department are also unsafe (4). Readers concerned about possible legal consequences of deferring care should consider that long waiting times can also violate the patient antidumping statute (5). Finally, we dispute the claim that deferring primary care to a clinic setting is less fair than a “treat and refer every patient” approach. The differences in quality, outcomes, and costs between the two approaches are worth additional study.

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References

Pneumonitis with Antiandrogens

TO THE EDITOR: Bennett and colleagues (1) rightly reminded prescribers about the association of pneumonitis with antiandrogens.
The authors calculated the incidence of pneumonitis on the basis of the number of cases reported to the U.S. Food and Drug Administration (FDA)’s Adverse Event Reporting System and the number of persons using antiandrogens. However, the calculation of incidence rates from spontaneously reported data is fundamentally flawed because of extensive underreporting; fewer than 10% of serious reactions are reported to the FDA (2). Moreover, reporting can be influenced by several factors, including the length of time a product has been on the market, reporting practices of pharmaceutical companies, physicians’ awareness of the event, and publicity effects. For these reasons, reporting rates are not incidence rates and should be interpreted with caution.

We presented a poster at an international pharmacovigilance conference comparing risk for interstitial pneumonitis and pulmonary fibrosis in persons taking antiandrogens (3). Adjusting for years of marketing and calendar time, we found that the relative risks for pulmonary toxicity associated with nilutamide, bicalutamide, and flutamide were 303, 5, and 1, respectively, compared with the background rate (4). If one were to adjust for underreporting, these relative risk estimates would be higher, suggesting that all 3 products are associated with pulmonary toxicity. However, the risk for interstitial pneumonitis and pulmonary fibrosis associated with nilutamide appears to be far greater than that associated with the other antiandrogens. As a result, a black box warning regarding pulmonary toxicity was added to the labeling for nilutamide, while the labels for bicalutamide and flutamide include pulmonary toxicity in the adverse reactions section.

Health care professionals are encouraged to report adverse events to manufacturers and directly to the FDA through the MedWatch program at 800-332-1088 (or www.fda.gov/medwatch).

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Disclaimer: The views in this letter are those of the authors and not necessarily those of the U.S. Food and Drug Administration.

References

Management of Acute Renal Failure

TO THE EDITOR: Esson and Schrier (1) provided a valuable review of acute tubular necrosis (ATN). However, several of their assertions merit further discussion. First, use of the term pseudo acute respiratory distress syndrome (ARDS) should be discouraged. Patients with “leaky pulmonary vasculature” and resultant noncardiogenic pulmonary edema who meet criteria for ARDS according to the most recent consensus definition (2) have ARDS, not pseudo ARDS. A reduction in lung compliance (“initially normal” in pseudo ARDS, according to the authors) is not a diagnostic criterion for ARDS. Moreover, there is evidence that lung compliance in ARDS may vary considerably depending on the etiologic insult that precipitates acute lung injury, independent of fluid balance (3). While the consensus definition has acknowledged limitations, it serves an important, clinically relevant purpose by allowing comparison with trial results, encouraging clarity among practitioners, and standardizing management, which includes judicious fluid administration and avoidance of...
ventilator-induced lung injury regardless of precipitant. Use of the term pseudo ARDS threatens to obscure this purpose.

Second, while the authors correctly caution against overzealous fluid administration, I am concerned that their comments may be erroneously interpreted as advocacy of volume restriction as a preventive measure in sepsis. Hypoperfusion not only may lead to recurrent ischemic renal injury, it may also initiate ischemic injury in other organs (particularly in splanchic and coronary blood distributions) and result in multisystem organ failure. Appropriate management of sepsis and other distributive shock states often requires impressive amounts of fluid resuscitation, and 1 recent study has suggested that such volume repletion is best accomplished early (4).

Third, ongoing controversy notwithstanding, pulmonary artery catheterization often provides useful information about fluid management in patients with acute lung injury. Indeed, this was one of the conclusions of the seminal study that found fluid restriction in ARDS to be beneficial (5).

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Disclaimer: The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the U.S. Department of the Army or the U.S. Department of Defense.

References

TO THE EDITOR: In their review on ATN, Drs. Esson and Schrier use the term pseudo ARDS to describe a scenario in which overzealous fluid administration in septic patients with "leaky pulmonary vasculature" precipitates noncardiogenic pulmonary edema, leads to mechanical ventilation and its associated complications, and causes patients to be classified as having multiorgan failure (1). This is a very idiosyncratic view of events leading to multiorgan failure in sepsis. The Editor and interested readers should check any recent textbook on critical care medicine published in the past 10 years to inform themselves about the correct sequence of events.

The term pseudo ARDS is unknown in the pulmonary and critical care literature. A search for this term ("pseudo ARDS" OR "pseudo-ARDS") in PubMed on 4 December 2002 revealed only an editorial in an obscure journal that was coauthored by Dr. Schrier (2); this is also the reference Drs. Esson and Schrier cited in their review to support their description of events.

The authors argued against aggressive hemodynamic management while citing a narrow selection of publications, some of which actually do not support their statements. Gattinoni and colleagues (3), reference 74 in Esson and Schrier’s review, saw no difference between treatment groups, and in the meta-analysis by Heyland and associates (4), Esson and Schrier’s reference 75, the data suggested a possible benefit when aggressive hemodynamic management was started perioperatively in high-risk surgical patients. More recent data, ignored by Esson and Schrier, also show them to be wrong (5).

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References

TO THE EDITOR: The article by Esson and Schrier on ATN (1) might be clearer with 1 additional comment. In the paragraph after they mention oliguric and nonoliguric ATN, they present a table showing laboratory values that distinguish prerenal azotemia from ATN. I think it is important to say that the urine chemistry values are useful only if the patient is oliguric. If the patient is nonoliguric, sodium excretion, for example, may be affected by sodium intake.

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Reference

IN RESPONSE: We coined the term pseudo ARDS to focus on a very common, clinically important situation in intensive care units. A parallel could be made between prolonged prerenal azotemia eventually leading to ischemic ATN. Prolonged pseudo or preadult ARDS may lead to ARDS in association with evidence of pulmonary capillary damage and stiff lungs, as diagnosed clinically by a decrease in pulmonary compliance. We use the term pseudo ARDS or pre-ARDS to describe a clinical syndrome of noncardiogenic pulmonary edema in the absence of evidence of decreased pulmonary compliance. We realize that many clinicians group these clinical entities together, independent of pulmonary compliance, as ARDS; we believe, however, that from a pathophysiologic, prognostic, and therapeutic viewpoint, these clinical entities may be substantially different.
Both pseudo ARDS and ARDS are frequently associated with sepsis. Studies in animals have shown that vasodilation with an arterial vasodilator, such as minoxidil, is associated with increases in albumin distribution space and a failure of interstitial hydrostatic pressure to rise during saline administration (1). These changes in interstitial Starling forces thus favor an increase in interstitial fluid volume during saline infusion. We frequently consult on ventilated patients with acute renal failure in the intensive care unit who have a 20-L positive fluid balance that has not been quantitatively recognized because the pulmonary capillary wedge pressures are not considered elevated (<18 mm Hg). Excess saline fluid has been administered to resuscitate the patient and has led to pulmonary edema, hypoxia, and ventilatory support. In the early stage, most of these patients do not have decreased pulmonary compliance, that is, stiff lungs. However, the mortality rate among them will ultimately be as high as 80%. It has been reported that patient mortality rates begin increasing after the patient has spent 48 hours on a respirator. The potential barotrauma, oxygen toxicity, and pulmonary infections that may occur with prolonged ventilatory support frequently lead to stiff lungs and what virtually all authorities would consider bona fide ARDS.

We believe that not distinguishing clinically between pseudo ARDS and ARDS may be detrimental to patients in the intensive care unit. Marked improvement in the pulmonary edema of pseudo ARDS after diuresis or ultrafiltration may allow much earlier extubation and removal of ventilatory support before ARDS develops. With ARDS and prolonged ventilatory support, mortality rates are very high, particularly in the presence of renal and multiorgan failure.

Randomized studies should be performed in septic patients to determine whether early resuscitation with limited volume expansion (for example, 2 to 3 L of saline), albumin, and vasopressin (which constricts vasodilated areas associated with sepsis, including skin, muscle, and splanchnic circulation), compared with large volumes of saline, can reduce the need for ventilatory support and the development of ARDS with decreased pulmonary compliance, and thereby improve survival.

Regarding Dr. Finucane’s comments, it is important to emphasize that the urinary chemistry values in our table are generally applicable to both oliguric and nonoliguric ATN. Large daily volumes of glucose and water administered to burn patients with nonoliguric ATN were originally reported with low urinary sodium concentration of less than 10 mmol/L. However, in other settings, urinary sodium levels in nonoliguric patients with ATN generally exceed 30 mmol/L. Urinary sodium level and fractional excretion of sodium are usually somewhat lower in patients with nonoliguric ATN than in those with oliguric ATN but are generally well above those seen with prerenal azotemia (2).

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References


Screening for Prostate Cancer

TO THE EDITOR: It seems to me that the U.S. Preventive Services Task Force (USPSTF) embedded some inappropriate and dangerous values under the guise of research in its recommendation and rational statement on prostate cancer screening (1). The USPSTF claimed that “screening is associated with important harms” and recommended that “clinicians discuss with patients the potential benefits and possible harms of PSA [prostate-specific antigen] screening.” Well, crossing the street is associated with potential harms, as is the human quest for scientific and medical knowledge. Perhaps we should close our medical schools and all return to caves. Alternatively, we can strive to learn as much as we can about ourselves and our health and make the most informed decisions possible based on the most thorough knowledge biomedical science can reasonably provide.

The USPSTF offered no evidence that screening is harmful, that is, that any patient was directly harmed as the result of a PSA test. Rather, it seemed to confound things with an improper goal of trying to shield us from the appropriate anxiety that ought to accompany a diagnosis of a potentially life-threatening disease. It would seem that the USPSTF also felt the need to shield the physician from the responsibility of educating the patient about the numerous approaches to treatment of prostate cancer, and the risks associated with any treatment, by simply avoiding the diagnosis. Whom is the USPSTF protecting by replacing the legitimate approach of “watchful waiting” with its recommendation of what I would term “blissful ignorance”? The important discussion of the risks of various approaches to prostate cancer treatment makes sense only after a diagnosis has been made, not before screening. By suggesting that it is not even necessary to find out whether one has prostate cancer by utilizing simple and harmless testing procedures, the USPSTF is depriving us, the male population, of the important ability to attempt to guide and control our own lives to the greatest extent possible.

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Reference

TO THE EDITOR: I distributed the summary of the USPSTF prostate cancer screening guideline to an advocacy group of professionals and businessmen who are prostate cancer survivors. The conclusion that “evidence is insufficient to determine whether the benefits outweigh the harms for a screened population” (1) triggered an almost palpable feeling of dismay. Every one of us has frequently and most sincerely wished that he had been diagnosed earlier by routine screening. We want to emphasize the following points to Annals readers.

1. Prostate cancer is the most common cause of cancer death in nonsmoking men.

2. Screening with digital rectal examination and PSA tests is
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remarkably sensitive in detecting the higher-grade prostate tumors that merit consideration for treatment, although it is less sensitive for lower-grade tumors.

3. Prostate cancer usually progresses slowly but will inevitably kill an otherwise healthy host, given sufficient time. The rate of progression can be predicted by Gleason scores determined on biopsy.

4. Therapeutic interventions that offer cure are well established, even though the literature comparing long-term outcomes and the efficacy of different treatments is woefully inadequate.

The accompanying review by Harris and Lohr (2) comprehensively documented the side effects of the available treatments for prostate cancer but did not describe the consequences of metastatic prostate cancer. How can any discussion of risks and benefits exclude discussion of pain, anxiety, depression, and death from advancing cancer? Eschewing routine PSA screening for healthy middle-aged men is paternalistic, potentially excluding patients from important choices about their lives. A positive result on a screening PSA test confronts a patient and his doctor with difficult choices in the face of dysfunctional treatment literature, but it also emphasizes why a patient needs a doctor far more than he needs a guideline. My advocacy group believes that prostate cancer screening should be routine for all men who have a reasonable life expectancy. Physicians who adopt the “know-nothing” screening position outlined in the USPSTF guidelines must recognize that they thereby assign a higher value to avoiding side effects of treatment than avoiding premature death from cancer. Please remember that from the perspective of our prostate cancer advocacy group, dead is worse than alive with side effects.

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References

In Response: Drs. Smith and Robertson share the common view that all prostate cancer, if left alone, will grow, spread, and kill. This is fortunately not the case. Some cancerous prostate tumors clearly grow and spread with devastating consequences, as both correspondents remind us, but most do not. The core of the difficulty is that clinicians cannot tell which is which at the time of diagnosis following a positive result on a screening test.

Autopsy studies show that approximately 30% of men at age 50 years, 50% of men at age 70 years, and almost all men by age 100 years have histologic cancer in the prostate. Thus, the tendency to recommend treatment for all men with a diagnosis of prostate cancer undoubtedly appropriately treats some but also harms those whose cancer could safely have been left alone. Even men who choose watchful waiting live with the awareness of having prostate cancer. In either case—treatment or watchful waiting—some men may suffer more harm than good from screening.

As with all screening tests, the USPSTF believes that individuals who are unwilling to undergo further diagnostic testing, treatment, and follow-up for positive test results should think carefully before having a prostate cancer screening test. Reasonable men may decide not to pursue such knowledge. Forcing men to learn they have prostate cancer through routine screening is, we believe, more paternalistic than offering them the opportunity to participate in an informed choice about whether to be screened in the first place.

Men now face a very difficult decision in balancing the potential benefit of screening, which may be enormous—avoidance of death from prostate cancer—against the potential harms, which are also significant and well documented. The USPSTF believes that the decision should be firmly in the hands of the patient. Unfortunately, we found the scientific evidence insufficient to recommend for or against routine screening. We hope that trials of screening now under way will provide better-quality evidence on which to base the decision.

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Clinical Observation

Iron Overload Related to Excessive Vitamin C Intake

To the Editor: A 61-year-old woman was referred to the University of Washington iron overload clinic after presenting with fatigue. She reported a 27-year history of oral iron supplementation with 325 mg of ferrous sulfate twice per day, along with 15 000 mg of oral vitamin C per day as self-initiated prophylaxis against recurrent upper respiratory tract infections. Her medical, medication, family, and social history were otherwise unremarkable. She did not report alcohol use.

Physical examination demonstrated a normal-sized liver, no bronzing of the skin, and no signs of chronic liver disease. On laboratory evaluation, her hematocrit was 0.44, serum ferritin level was 4470 μg/L, serum iron level was 37 μmol/L, and total iron-binding capacity was 37 μmol/L (transferrin saturation, 100%). Serum aminotransferase, bilirubin, and albumin levels were normal. Contrast-enhanced magnetic resonance imaging showed abnormally low signal intensity in the liver, spleen, and bone marrow that was consistent with iron overload. Liver biopsy demonstrated markedly increased stainable iron in both hepatocytes and Kupffer cells, without evidence of a periportal-to-pericentral gradient of iron staining as typically seen in hereditary hemochromatosis (Figure). Hepatic iron concentration was 557 μmol/g dry weight, and the hepatic index (hepatic iron concentration in μmol/g divided by age in years) was 9.1. Genotyping for the C282Y and H63D mutations in the HFE gene demonstrated a wild-type profile.

The patient was advised to discontinue using all vitamin C, and weekly phlebotomy, 500 mL, was initiated. After 6 months of treatment, the patient’s serum ferritin level was less than 2000 μg/L and her generalized fatigue abated. We planned to continue weekly phlebotomy until the ferritin level was less than 50 μg/L.

Iron stores are regulated by iron absorption in the proximal small intestine. Iron overload may occur through increased duodenal iron absorption, parenteral iron administration, or blood transfusion. Increased iron absorption may be appropriate (for example, hemolysis, increased erythrocyte turnover, blood loss) or inappropriate (he-
Figure. Perls Prussian blue iron stain demonstrating 4+ mixed (hepatocellular and Kupffer cell) iron deposition.

No zonation pattern is present. (Original magnification, ×400.)

redimentary hemochromatosis, African iron overload, or other rare disorders) (1). Excessive dietary intake of iron-rich foods or medicinal preparations has not been reported to lead to iron overload in the absence of predisposing conditions. Vitamin C, administered at doses of up to 1 g, has been correlated with iron absorption in single meals containing non-heme iron (2). However, overall iron stores were not increased in the setting of supplementation with moderate doses of vitamin C (3). Vitamin C reduces iron from the ferric to ferrous state, facilitating duodenal absorption. In addition, vitamin C inhibits lysosomal degradation of ferritin, promotes iron release from the ferritin shell, and enhances ferritin synthesis in the presence of iron (4, 5). These properties can lead to dramatic increases in duodenal iron absorption in both iron-deficient and iron-replete persons.

To our knowledge, clinically significant iron overload from a combination of iron and large doses of vitamin C has not previously been reported. Although it is theoretically possible that iron overload in our patient could have resulted from an as-yet-unknown defect in one or more of the other iron-regulatory proteins, we believe that this is unlikely. Recent reports have shown that novel mutations in HFE, transferrin receptor 2, and ferroportin are associated with increased iron accumulation in isolated cases (6–8). However, other than the C282Y and H63D mutations in HFE, these mutations are extremely rare causes of iron overload, and our patient had no family history of iron overload to suggest a genetic cause. Therefore, we feel that hepatic iron accumulation in our patient was due solely to the combination of vitamin C and iron intake. This case serves as a reminder that excessive vitamin intake may have deleterious clinical consequences.

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References

Correction

Correction: Next-Day Care for Emergency Department Users with Nonacute Conditions

An article on deferred care for emergency department users with nonacute conditions (1) contained an error. In Table 2 on page 711, the unadjusted between-group difference in the percentage of patients reporting moderate or greater pain while awaiting care should be −0.5 percentage point rather than 0.5 percentage point. The associated confidence interval is reported correctly.

Reference

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