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THE EDITORIALIST REPLIES: In their letter, Drs. Lebowhl and Green reiterate the controversial implications of undiagnosed asymptomatic celiac disease that I raised in my editorial. A rigorous review of the evidence-based literature on this issue would confirm that the question of whether it is appropriate to identify clinically silent cases of celiac disease as a preventive form of intervention for negative clinical outcomes is far from settled. Theoretically, only prospective clinical studies (which are ethically inconceivable) could establish in a convincing fashion the possible complications of untreated celiac disease in the absence of symptoms. It is for this very reason that I strongly support the concept of a systemic process of case finding,¹ in which patients

with symptoms or conditions known to be associated with celiac disease are specifically identified.² This approach is associated with high levels of compliance with treatment,³ is a terrific vehicle for educating health care professionals, is cost effective, and will probably pave the way for more sensitive and specific algorithms for the diagnosis of celiac disease.

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Bevacizumab in Renal-Cell Cancer

TO THE EDITOR: In the report on their randomized, placebo-controlled, phase 2 trial evaluating bevacizumab, Yang et al. (July 31 issue)¹ conclude that bevacizumab significantly prolongs the time to progression of metastatic renal-cell cancer. I believe this conclusion is inappropriate. Although the patients are randomly assigned to the treatment groups in a randomized phase 2 study, it is not equivalent to a phase 3 study. The purpose of a randomized phase 2 trial is to select one of several novel regimens for the next phase of testing. One can only be reassured that the selected regimen is probably not significantly worse than the other regimens being evaluated.²

Therefore, the proper conclusion is that bevacizumab at a dose of 10 mg per kilogram of body weight appears to be promising in the treatment of metastatic renal cancer and should be studied further.

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Urinary Tract Infection

TO THE EDITOR: In the Clinical Practice article by Fihn on acute uncomplicated urinary tract infection in women (July 17 issue),¹ the recommendations for treatment appear to be somewhat out of date. First, the expected rates of clinical failure among women treated with trimethoprim-sulfamethoxazole for acute uncomplicated cystitis are now more secure and suggest that fluoroquinolones or nitrofurantoin should be considered first-line treatment in many

parts of the United States. In an Israeli study with a 29 percent rate of in vitro resistance to trimethoprim-sulfamethoxazole, the rate of clinical failure was 23 percent overall and 46 percent among patients with pathogens that were resistant to trimethoprim-sulfamethoxazole.² Second, after the Infectious Diseases Society of America issued its 1999 guidelines for the treatment of urinary tract infection in women with acute uncomplicated py-

elonephritis, it was demonstrated that 7 days of ciprofloxacin therapy was superior to 14 days of treatment with trimethoprim–sulfamethoxazole (largely because clinical failure among women treated with trimethoprim–sulfamethoxazole was associated with the 18 percent rate of in vitro resistance to trimethoprim–sulfamethoxazole in a study conducted in the United States between 1994 and 1997).³ These findings have led to the recommendation in annual antimicrobial guidebooks that the former treatment be used.⁴ Although better surveillance data regarding resistance and studies of quality-of-life and cost outcomes are needed, the days of trimethoprim–sulfamethoxazole as the treatment of choice for uncomplicated urinary tract infection in women may be numbered.

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Editor's note: Dr. Talan reports having received grant support and honorariums for lecturing from Bayer, Ortho McNeil, and Aventis.

1. Fihn SD. Acute uncomplicated urinary tract infection in women. *N Engl J Med* 2003;349:259-66.
2. Raz R, Chazan Y, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis* 2002;34:1165-9.
3. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA* 2000;283:1583-90.
4. Gilbert DN, Sande MA, Moellering RC, eds. *The Sanford guide to antimicrobial therapy* 2003. 33rd ed. Hyde Park, Vt.: Antimicrobial Therapy, 2003:23.

TO THE EDITOR: We were surprised to see that Fihn advocated the use of trimethoprim without a pregnancy test. Fihn mentions that trimethoprim is a known teratogen in animals and that coitus increases the risk of cystitis. Coitus is associated with pregnancy.

At Charing Cross Hospital, we use cephalexin, a second-generation cephalosporin, for the treatment of uncomplicated urinary tract infection in women. Although the cost of trimethoprim itself is lower, the cost of trimethoprim plus a measurement of beta human chorionic gonadotropin is higher than the cost of treatment with 500 mg of oral cephalexin twice daily three days per week. In addition, in our population, there is an 85 percent sensitiv-

ity to cephalexin and a 68 percent sensitivity to trimethoprim.

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DR. FIHN REPLIES: As advocated by Dr. Talan and discussed in my article, fluoroquinolones and nitrofurantoin are reasonable alternative treatments for acute cystitis when the local rate of resistance to trimethoprim–sulfamethoxazole is high. Dr. Talan cites a study from Israel in which the rate of resistance approached 30 percent and empirical therapy with trimethoprim–sulfamethoxazole achieved a microbiologic cure in only 77 percent of women.¹ Higher cure rates would be expected in locales where the rate of resistance is lower. The critical question remains at what level of ambient resistance trimethoprim–sulfamethoxazole should no longer be considered first-line therapy. Le and Miller concluded that prescribing fluoroquinolones became cost effective when resistance reached 22 percent, but they did not take into account the public health concern about promoting resistance to fluoroquinolones.² In the United States, approximately 10 percent of isolates of *Escherichia coli* from urine are resistant to fluoroquinolones, and the prevalence is rising.³ More liberal use of these valuable agents could accelerate the emergence of resistance. Drs. Hoey and Probst advocate treatment with cephalexin, citing low rates of resistance in London. Experience with cephalosporins in the United States, however, has been disappointing, with resistance averaging 70 percent nationally.² Trimethoprim is definitely contraindicated in pregnancy, but a measurement of beta human chorionic gonadotropin will generally be obtained, irrespective of the agent prescribed, if pregnancy is suspected because of the need for closer follow-up. However, treatment with a beta-lactam or a cephalosporin without a pregnancy test may be reasonable in some circumstances.

Dr. Talan also correctly points to the efficacy of a seven-day course of a fluoroquinolone for women with uncomplicated acute pyelonephritis. As his study showed, trimethoprim–sulfamethoxazole is highly effective in women with sensitive organisms, although information on sensitivity is typically unavailable when treatment is initiated.

I also wish to point out an error in my article in the first sentence of the last paragraph on page 261: lines 4 and 5 should have read, “can be safely treated as outpatients if they do not have complicating factors and signs of systemic toxicity,” rather than “if they do not have factors associated with an upper tract or complicated infection or signs of systemic toxicity,” as printed.

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Renal Failure with the Use of Zoledronic Acid

TO THE EDITOR: Zoledronic acid (Zometa, Novartis Pharmaceuticals) is a potent bisphosphonate that inhibits bone resorption. In trials of treatment for bone metastases, 9 to 15 percent of the patients who received 4 mg of zoledronic acid over a 15-minute period had renal deterioration, defined by elevations in the serum creatinine level.^{1,2} With marketed use of the drug, renal deterioration progressing to renal failure and dialysis has been reported. Although the causes of renal deterioration are multifactorial, acute tubular necrosis has been described as a potential mechanism associated with zoledronic acid.³

We identified 72 cases in the Food and Drug Administration (FDA) Adverse Event Reporting System from August 2001 to March 2003 in which physicians reported renal failure associated with zoledronic acid (Table 1). Our case series consisted of a heterogeneous group of patients, including 42 patients with multiple myeloma, 22 with solid tumors, 2 with benign conditions, and 6 with unknown diagnoses. The demographic characteristics and outcomes were similar for patients with and those without multiple myeloma. Treatment details, including hydration status, were not uniform-

Table 1. Demographic Characteristics of the Patients.

Characteristic	All Patients (N=72)	Patients without Multiple Myeloma* (N=24)
Country (no. of patients)		
United States	56	20
Other	16	4
Age (yr) †		
Range	42–91	47–91
Mean	71	69
Sex (no. of patients) ‡		
Female	39	14
Male	29	9
Cancer diagnosis (no. of patients)		
Multiple myeloma §	42	0
Breast	11	11
Prostate	6	6
Renal cell	1	1
Renal cell and squamous cell ¶	1	1
Adrenal	1	1
Bladder	1	1
Lung	1	1
None (benign condition)	2	2
Unknown	6	0