

## Correspondence



## Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen

*To the Editor:* In 1998, the American College of Gastroenterology recommended that patients at high risk for hemorrhage and perforation from ulcers induced by aspirin and other nonselective nonsteroidal antiinflammatory drugs (NSAIDs) should be considered for prophylaxis with misoprostol. In this sense, proton-pump inhibitors are an acceptable alternative for the prevention of NSAID-related complications.<sup>1</sup> Double doses of histamine H<sub>2</sub>-receptor antagonists and standard doses of proton-pump inhibitors are also effective in preventing endoscopically detectable duodenal and gastric ulcers.<sup>2</sup> Risk factors for NSAID-related complications include a history of gastrointestinal events (ulcer or hemorrhage), age over 60 years, use of a high dose of NSAIDs, concurrent use of glucocorticoids, and concurrent use of anticoagulants.

Thus, the design of the study by Bombardier et al. (Nov. 23 issue)<sup>3</sup> surprised us. Assuming a lower risk of adverse gastrointestinal events in the rofecoxib group than in the naproxen group,<sup>4</sup> we could understand the absence of prophylaxis in the rofecoxib group. However, in the naproxen group, in which about half the patients were over the age of 60 (mean [ $\pm$ SD] age, 58 $\pm$ 10 years), 56.2 percent were receiving glucocorticoids, and 7.8 percent had a history of clinical gastrointestinal events, the lack of prophylaxis does not seem ethical. Indeed, H<sub>2</sub>-receptor antagonists were used in just 8.3 percent of the patients in this group, and at low doses. Prophylaxis for patients in the naproxen group — as recommended — would not have lessened the potential value of the study results.

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1. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. *Am J Gastroenterol* 1998;93:2037-46.
2. Rostom A, Wells G, Tugwell P, Welch V, Dube C, McGowan J. Prevention of NSAID-induced gastroduodenal ulcers (Cochrane Review). In: *The Cochrane Library*. Issue 4. Oxford, England: Update Software, 2000.
3. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
4. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282:1929-33.

*To the Editor:* Bombardier and colleagues do not elaborate on the adverse renal events observed with rofecoxib in their study (rate of renal events, 1.2 percent in the rofecoxib group and 0.9 percent in the naproxen group). In studies involving young volunteers, selective cyclooxygenase-2 inhibitors have been shown to decrease renal prostacyclin levels and cause transient retention of sodium without depression of the glomerular filtration rate.<sup>1,2</sup> Similar observations have been made in clinical studies of rofecoxib in elderly patients.<sup>3</sup> Can the authors provide some additional information on these adverse events?

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1. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci U S A* 1999;96:272-7. [Erratum, *Proc Natl Acad Sci U S A* 1999;96:5890.]
2. Catella-Lawson F, McAdam B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther* 1999;289:735-41.
3. Swan SK, Rudy DW, Lassetter KC, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet: a randomized, controlled trial. *Ann Intern Med* 2000;133:1-9.

The authors reply:

*To the Editor:* Delgado Fernández et al. suggest that the lack of prophylaxis in some of the patients in our trial does not seem ethical. The ethical aspects of including patients with risk factors, such as a history of gastrointestinal events, without the use of a proton-pump inhibitor or misoprostol

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were carefully considered by the steering committee during the development of the protocol. We clearly and strongly indicated in the protocol that no patient who needed to receive protective gastrointestinal therapy because of a history of gastrointestinal events should be enrolled in the study. Furthermore, in no patient could these drugs be discontinued for the purpose of enrollment in the study. Patients who were enrolled in the study were not believed by their treating physicians to require use of these agents and would not have received prophylactic therapy even if they had not participated in the trial. Patients in the study were, however, allowed to take low-dose H<sub>2</sub>-receptor antagonists. The mean time between the prior gastrointestinal event and enrollment in the study was 12 years, indicating that the history was remote in most of the patients.

Misoprostol has been shown to reduce the incidence of clinically important gastrointestinal events in patients taking NSAIDs,<sup>1</sup> and proton-pump inhibitors have been shown to reduce the incidence of gastroduodenal ulcers on endoscopy.<sup>2</sup> The use of these agents could potentially have confounded our results and would not have allowed us to address our primary hypothesis: that the highly selective cyclooxygenase-2 inhibitor rofecoxib would cause fewer clinical upper gastrointestinal events than a nonselective NSAID. An even larger outcome study would be required to evaluate properly the incidence of gastrointestinal events with a cyclooxygenase inhibitor as compared with a nonselective NSAID plus a protective agent.

Gupta asks us to elaborate on the adverse renal events reported in our article. The events described were related to decreases in renal function — primarily increases in creatinine (in 1.0 percent of the rofecoxib group and 0.7 percent of the naproxen group). Most were transient increases that resolved with therapy. Only 0.2 percent of the patients in each group withdrew from the study because of decreased renal function.

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1. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;123:241-9.

2. Yeomans ND, Tulassay Z, Juhász L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1998;338:719-26.

### Nasal Carriage of *Staphylococcus aureus*

*To the Editor:* The study conducted by von Eiff and colleagues (Jan. 4 issue)<sup>1</sup> might give readers the impression that a bacterial nose swab was merely a blind sample from the

vestibulum nasi. The authors do not provide a precise description of the method used to obtain bacterial swabs from the nose. A colleague and I found that the bacterial spectrum differs considerably between the vestibulum nasi and the cavitas nasi; for example, *Staphylococcus aureus* was present in the cavitas nasi but not in the vestibulum nasi in 22 percent of 412 patients ( $P=0.001$ ).<sup>2</sup> This finding indicates that disinfection of the vestibule alone may not prevent colonization of the nasal cavity by *S. aureus*. The fact that the bacterial populations differ is not surprising, because the linings of the vestibule and cavity differ and constitute dissimilar microenvironments. There is also evidence of a genetically determined affinity between the nasal mucosa cells and certain bacteria such as *S. aureus*.<sup>3</sup> From our experience, nasal swabs should always be obtained through a nasal speculum with the help of a head mirror so as to obtain representative microbial samples from both the vestibule and the cavity.

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1. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. *N Engl J Med* 2001;344:11-6.

2. Glück U, Gebbers J-O. The nose as bacterial reservoir: important differences between the vestibule and cavity. *Laryngoscope* 2000;110:426-8.

3. Kinsman OS, McKenna R, Noble WC. Association between histocompatibility antigens (HLA) and nasal carriage of *Staphylococcus aureus*. *J Med Microbiol* 1983;16:215-20.

*To the Editor:* Von Eiff et al. reported that the origin of a substantial proportion of cases of *S. aureus* bacteremia is endogenous — from the nares. We suggest that in some cases nasal colonization with *S. aureus* may be secondary to chronic ischemic skin lesions.

In response to a marked increase in the frequency of methicillin-resistant *S. aureus*, we increased hygienic measures and studied patients with arterial or venous leg ulcers or diabetic foot lesions. We monitored patients prospectively and determined the incidence of methicillin-resistant *S. aureus* infections in skin lesions and in the usual sites of colonization, such as the nose and armpits. From January 1997 to March 1998, all inpatients with ischemic skin lesions were enrolled. Bacteriologic swabs for methicillin-resistant *S. aureus* were obtained from skin lesions, the anterior nares, and the armpits of patients at admission and at discharge. A total of 160 consecutive patients were enrolled, including 18 with diabetic foot infections, 45 with venous leg ulcers, 65 with arterial leg ulcers, and 32 with other causes of skin necrosis. Methicillin-resistant *S. aureus* was isolated from skin lesions in the case of 64 patients (40 percent) and from swabs of the nose or armpits in the case of only 18 patients (11 percent), including 11 patients with methicillin-resistant *S. aureus* isolated from skin lesions; 55 percent of the patients with infections had no evidence of colonization. At discharge, nine new infections with methicillin-resistant *S. aureus* and two instances of colonization were observed.

Our data show that the prevalence of methicillin-resistant *S. aureus* was very high in these high-risk patients. However, when preventive measures were undertaken, the rate of acquisition was low during hospitalization. The swabs of skin lesions provided the best indicator of the presence of

methicillin-resistant *S. aureus*. The rate of colonization with methicillin-resistant *S. aureus* in patients with ischemic lesions was different from that reported by von Eiff et al. or the rate among patients in the intensive care unit.<sup>1</sup> Although screening of these high-risk patients is essential, attempts to eliminate nasal carriage of *S. aureus* should be considered only after skin lesions have completely healed.

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1. Revised guidelines for the control of methicillin-resistant *Staphylococcus aureus* infection in hospitals. *J Hosp Infect* 1998;39:253-90. [Erratum, *J Hosp Infect* 1999;42:83.]

*To the Editor:* The report by von Eiff et al. of the relation of nasal colonization with *S. aureus* to bacteremia does not reveal the proportion of patients with *S. aureus* bacteremia who had negative nasal cultures for *S. aureus*. Consequently, the proportion of episodes of *S. aureus* bacteremia that were caused by the patient's own nasal *S. aureus* strain cannot be determined from the data presented, in contrast to the assertion of von Eiff et al. and the authors of the accompanying editorial<sup>1</sup> that the results show this proportion to be greater than 50 percent. Yet, these data are needed to clarify the true proportion of episodes of *S. aureus* bacteremia that could be prevented by an effective program to eliminate nasal colonization.

The report also does not reveal the total number of patients who were prospectively screened to identify the 1278 patients who had nasal colonization with *S. aureus*. This denominator is needed to clarify the cost-benefit ratio for the comprehensive screening of all patients admitted to the hospital that the editorialists propose. The cost per colonized patient identified should vary inversely with the prevalence of colonization in the screened population.

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1. Archer GL, Climo MW. *Staphylococcus aureus* bacteremia — consider the source. *N Engl J Med* 2001;344:55-6.

*To the Editor:* It was in treating victims of the devastating Cocoanut Grove fire in Boston in November 1942 that penicillin made its first large and highly acclaimed clinical appearance in the United States.<sup>1</sup> The success of penicillin bred its overuse. An increasing prevalence of penicillin resistance among gram-positive cocci has led to a progressive narrowing of the spectrum of indications for this remarkable, but narrow-spectrum agent. To add insult to injury, a severe shortage of penicillin G in the United States, which began in 1999, has made it very difficult for physicians to obtain this drug to treat susceptible microorganisms for which penicillin G is still the treatment of choice.<sup>2</sup> This drug shortage has led to a paradoxical scenario. Half a century after its introduction as a "priceless miracle drug," penicillin

G now must be imported from Austria, and the costs of a 10-day treatment course have increased to almost \$200. These costs are even higher than those for an equivalent course of broad-spectrum antibiotics such as levofloxacin or ampicillin-sulbactam.

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1. Cope O. Care of the victims of the Cocoanut Grove fire at the Massachusetts General Hospital. *N Engl J Med* 1943;229:138-47.  
2. Harbath S. Antibiotic policy and penicillin-G shortage. *Lancet* 2000; 355:1650.

The authors reply:

*To the Editor:* The nasal swabs were obtained from the anterior nares according to what was considered the state-of-the-art method to identify patients as carriers of *S. aureus*.<sup>1-3</sup> Although other sites may be involved, carriage of *S. aureus* is most common in the anterior nares. The swab cultures in the single-center part of our study were obtained as part of routine surveillance cultures. Although the study by Glück and Gebbers is interesting<sup>4</sup> and we agree that nasal swabs obtained through a nose speculum with the help of a head mirror may yield additional information regarding colonization, this approach has not been a routine technique for surveillance cultures.

We agree with Lecomte et al. that in some cases nasal colonization with *S. aureus* may be secondary to chronic ischemic skin lesions. Skin damage caused by minor lesions, eczema, psoriasis, or the insertion of foreign bodies increases the risk of nasal carriage.<sup>5</sup> Also, *S. aureus* adheres better to nasal epithelial cells obtained from carriers or from patients with eczema than to nasal epithelial cells obtained from other persons. However, the reservoir for chronic staphylococcal carriage has been shown to be the anterior nares. In our study, we found that for most of the strains, the isolates from the blood were identical to those from the anterior nares of a patient as well as from areas other than the nares.

Previous studies were not large and did not use modern molecular methods to determine the clonal relation of the organisms. Therefore, the purpose of our study was to correlate strains colonizing the anterior nares with strains derived from the blood in patients with *S. aureus* bacteremia, using an established molecular-typing method. Analyzing the results of both approaches (the rates of clonal identity between *S. aureus* strains isolated from blood and those isolated from the anterior nares before and after the detection of bacteremia were 85.7 percent and 82.2 percent, respectively), we concluded that a substantial proportion of cases of *S. aureus* bacteremia appear to be of endogenous origin. We agree with Johnson that additional data, such as the proportion of patients with *S. aureus* bacteremia who had negative nasal cultures for *S. aureus*, would be helpful to define the risk of bacteremia in carriers of *S. aureus*. In future

clinical trials, an assessment of the relative risk may permit an evaluation of screening and preventive strategies.

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2. VandenBergh MF, Yzerman EP, van Belkum A, Boelens HA, Sijmons M, Verbrugh HA. Follow-up of *Staphylococcus aureus* nasal carriage after 8 years: redefining the persistent carrier state. *J Clin Microbiol* 1999;37:3133-40.
3. Pujol M, Pena C, Pallares R, et al. Nosocomial *Staphylococcus aureus* bacteremia among nasal carriers of methicillin-resistant and methicillin-susceptible strains. *Am J Med* 1996;100:509-16.
4. Glück U, Gebbers J-O. The nose as bacterial reservoir: important differences between the vestibule and cavity. *Laryngoscope* 2000;110:426-8.
5. Casewell MW. The nose: an underestimated source of *Staphylococcus aureus* causing wound infection. *J Hosp Infect* 1998;40:Suppl B:S3-S11.

## Diastolic Dysfunction and Hypertension

*To the Editor:* Gandhi et al. (Jan. 4 issue)<sup>1</sup> may well be correct in their conclusion that diastolic dysfunction is the primary cause of pulmonary edema in hypertensive heart failure, but the left ventricular ejection fraction is probably inadequate as the sole measure of global systolic function on the basis of which to exclude the possible role of systolic dysfunction. The ejection fraction is recognized to be a relatively crude measure of left ventricular systolic function. Assessment of the ventricular long-axis excursion or velocity by Doppler imaging of the tissue may be a more sensitive index of ventricular function.<sup>2</sup> The longitudinal fibers in the myocardium lie in the subendocardium and are therefore especially prone to ischemia, which may be insufficient to produce an obvious regional wall-motion abnormality or an obvious change in the ejection fraction.

Recently, in a group of patients with diastolic heart failure, it was found that both systolic excursion and systolic velocity were significantly reduced in patients with diastolic heart failure, as compared with those in an age-matched group of normal subjects, although the left ventricular ejection fraction was within the normal range.<sup>3</sup> It appeared that the patients with diastolic heart failure were an intermediate group between subjects with normal cardiac function and those with obviously depressed systolic function and heart failure. Thus, systolic function may not be truly normal in this group of patients; rather, there may be more subtle changes in ventricular systolic function that affect diastole and that cannot be detected by the measurement of the ejection fraction.

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1. Gandhi SK, Powers JC, Nomeir A-M, et al. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001;344:17-22.
2. Hencin MY, Gibson DG. Long axis function in disease. *Heart* 1999;81:229-31.

3. Yip GWK, Wang M, Ho PY, Sanderson JE. Left ventricular long axis in diastolic heart failure: is left ventricular function truly normal? *Eur J Echocardiogr* 2000;2:Suppl 2:S60.

*To the Editor:* Gandhi et al. showed that the occurrence of acute pulmonary edema in patients with marked hypertension was due to the isolated, transient exacerbation of diastolic dysfunction. In their discussion, the authors rule out the occurrence of systolic dysfunction or mitral regurgitation as a cause of the pulmonary edema, but they do not explicitly identify the mechanism underlying diastolic dysfunction. Hypertension results in an increase in afterload on the left ventricle. It is well known that, in contrast to a limited elevation of afterload,<sup>1</sup> a substantial increase in afterload slows myocardial relaxation to such an extent that it induces an upward shift in the end-diastolic pressure–volume relation even in healthy hearts.<sup>2</sup> The resulting diastolic dysfunction is due to the lack of sufficient time for the ventricle to relax completely.<sup>3</sup> This mechanism might help to explain the results of Gandhi et al.: the delay in relaxation of the ventricle might exacerbate the diastolic dysfunction and congestion caused by severe hypertension. Such a mechanism is even more likely to be present in patients who have alterations in diastolic function when their blood pressure is normal, as evidenced by the pseudo-normal, if not still restrictive, mitral-inflow signals after treatment. We suggest that there is an alternative meaning for the title of the editorial that accompanied the report of Gandhi et al.: “Diastolic Heart Failure — No Time to Relax.”<sup>4</sup>

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1. Leite-Moreira AF, Gillebert TC. Nonuniform course of left ventricular pressure fall and its regulation by load and contractile state. *Circulation* 1994;90:2481-91.
2. Leite-Moreira AF, Correia-Pinto J, Gillebert TC. Afterload induced changes in myocardial relaxation: a mechanism for diastolic dysfunction. *Cardiovasc Res* 1999;43:344-53.
3. Leite-Moreira AF, Correia-Pinto J. Load as an acute determinant of end-diastolic pressure-volume relation. *Am J Physiol Heart Circ Physiol* 2001;280:H51-H59.
4. Vasan RS, Benjamin EJ. Diastolic heart failure — no time to relax. *N Engl J Med* 2001;344:56-9.

*To the Editor:* Gandhi et al. studied hypertensive patients who presented with acute pulmonary edema and noted that there was preserved left ventricular systolic function, which did not change substantially after the resolution of the symptoms. The authors infer that diastolic dysfunction was the cause of pulmonary edema. The only other possibilities they entertain are pulmonary disease and transient severe mitral regurgitation. An important underlying cause of transient pulmonary edema in hypertensive patients is renal-artery stenosis, especially in patients with bilateral disease or severe stenosis in a solitary functioning kidney.<sup>1</sup> Pulmonary edema usually resolves after diuresis, as was the case with patients included in the study by Gandhi et al. In pa-

tients who have recurrent pulmonary edema with renal-artery disease, resolution after successful percutaneous renal-artery revascularization has been reported.<sup>2</sup> This treatable cause of acute pulmonary edema should be considered in hypertensive patients with normal or nearly normal left ventricular systolic function.

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1. Missouriis CG, Buckenham T, Vallance PJ, MacGregor GA. Renal artery stenosis masquerading as congestive heart failure. *Lancet* 1993;341:1521-2.
2. Rajachandran M, Schainfeld R, Chaudhry GM, Pieczek A, Haley L, Rosenfield K. Episodic pulmonary edema in association with renal artery stenosis: successful treatment by percutaneous renal artery revascularization. *J Am Coll Cardiol* 1997;29:486A.

The authors reply:

*To the Editor:* We agree with Drs. Yip and Sanderson that patients with a normal ejection fraction and diastolic dysfunction may have subtle abnormalities of left ventricular contraction. The ejection fraction (the stroke volume divided by the end-diastolic volume) is an integrated measure of left ventricular systolic performance. Thus, it can remain in the normal range despite a mild depression of myocardial contraction.<sup>1</sup> Our finding that there was no decrease in the ejection fraction during acute hypertensive pulmonary edema indicates that any transient myocardial dysfunction that was present was not sufficient to depress left ventricular ejection. Although many of the patients in our study who had normal ejection fractions may have had subtle abnormalities of myocardial contraction, a transient decrease in systolic function was not the cause of the hypertensive pulmonary edema.

Elegant studies by Leite-Moreira et al. have demonstrated that marked increases in the systolic load increase the left ventricular diastolic pressure and slow left ventricular relaxation.<sup>2</sup> This mechanism contributes to the diastolic dysfunction in patients with hypertensive pulmonary edema. The left ventricle compensates for an acute increase in afterload by using preload reserve. If the left ventricular distensibility is reduced because of preexisting diastolic dysfunction or the effects of markedly elevated systolic pressure, there will also be a marked increase in left atrial pressure. Although slowed relaxation has a role, we doubt that it is the only mechanism contributing to the development of pulmonary edema.<sup>3</sup>

Drs. Chaudhry and Schainfeld emphasize the important point that hypertensive pulmonary edema can occur in patients with bilateral renal-artery stenosis. Although renal-artery stenting is a potentially attractive therapy, its role in preventing recurrent pulmonary edema has not been defined.

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2. Leite-Moreira AF, Correia-Pinto J, Gillebert TC. Afterload induced changes in myocardial relaxation: a mechanism for diastolic dysfunction. *Cardiovasc Res* 1999;43:344-53.
3. Little WC. Enhanced load dependence of relaxation in heart failure: clinical implications. *Circulation* 1992;85:2326-8.

vascular medicine. Vol. 1. 6th ed. Philadelphia: W.B. Saunders, 2001:479-502.

2. Leite-Moreira AF, Correia-Pinto J, Gillebert TC. Afterload induced changes in myocardial relaxation: a mechanism for diastolic dysfunction. *Cardiovasc Res* 1999;43:344-53.

3. Little WC. Enhanced load dependence of relaxation in heart failure: clinical implications. *Circulation* 1992;85:2326-8.

The editorialists reply:

*To the Editor:* We thank Leite-Moreira et al. for drawing attention to the intended double meaning of the title of our editorial, "Diastolic Heart Failure — No Time to Relax." Diastolic heart failure is characterized by the inability of the left ventricle to relax effectively during the time of diastole. The clinical and scientific communities' approach to diastolic heart failure has been characterized by an incomplete implementation of the primary preventive therapy that is known to be efficacious (treating hypertension), the lack of a gold standard for the diagnosis of the condition, and a paucity of evidence-based strategies to guide therapy. Hence, our message, reflected in the title, was that it is not time for the clinical and research communities to relax in seeking a solution to the fundamental problem of impaired left ventricular relaxation.

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### Long-Term Outcomes after Treatment for Refractory Immune Thrombocytopenic Purpura

*To the Editor:* In April 1993, my colleagues and I reported in the *Journal* our experience with combination chemotherapy as a treatment for patients with severe refractory immune thrombocytopenic purpura.<sup>1</sup> We now provide long-term follow-up data on the initial eight patients with immune thrombocytopenic purpura and on four additional patients (Table 1). All patients had severe disease with periodic mucosal bleeding, and in all splenectomy had failed, as had an average of five other therapies. Of the 12 patients treated, 5 had a complete remission (a normal platelet count) and 1 had a partial remission (a platelet count of more than 50,000 per microliter); these remissions persisted without further therapy until the last follow-up visit or until their death from another cause (a cerebrovascular accident in Patient 5 and fulminant hepatitis C acquired from a transfusion in Patient 6). Remissions in the four surviving patients have lasted from more than 60 to more than 150 months.

Of the remaining six patients, two had a complete remission but relapsed 4 months and 35 months after treatment; Patient 7 is alive and in complete remission after high-dose therapy with cyclophosphamide (50 mg per kilogram of body weight per day for 4 days), and in Patient 8 normal platelet counts were maintained with prednisone (10 to 30 mg per day) and danazol (200 mg per day) until fungal abscesses developed and she died from a generalized fungal infection. Patient 9 had no response to combination che-

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**TABLE 1.** RESPONSES TO COMBINATION CHEMOTHERAPY OF PATIENTS WITH REFRACTORY IMMUNE THROMBOCYTOPENIC PURPURA.\*

PATIENT NO.	TYPE OF COMBINATION CHEMOTHERAPY†	NO. OF COURSES	RESPONSE TO COMBINATION CHEMOTHERAPY	DURATION OF RESPONSE mo	ADDITIONAL THERAPY AFTER COMBINATION CHEMOTHERAPY	OUTCOME	CAUSE OF DEATH
1	CMOPP	4	Complete remission	>150		Complete remission, alive	
2	CMOPP	4	Complete remission	>129		Complete remission, alive	
3	CEP	6	Complete remission	>65		Complete remission, alive	
4	CEP	4	Complete remission	>60		Complete remission, alive	
5	CVP	5	Complete remission	48		Complete remission, died	Cerebrovascular accident
6	CEP	5	Partial remission	13		Partial remission, died	Hepatitis C
7	CEP	6	Complete remission, relapse	35	Cyclophosphamide (50 mg/kg/day for 4 days)	Complete remission, alive	
8	CEP	4	Complete remission, relapse	4	Prednisone and danazol	Partial remission, died	Fungal infection
9	CEP	2	No response		Prednisone, danazol, and colchicine	Complete remission, alive	
10	CEP	2‡	Partial remission, relapse	1		No response, died	Central nervous system bleeding
11	CMOPP	4	No response			No response, died	Central nervous system bleeding
12	CEP	3	No response			No response, died	Central nervous system bleeding

\*Complete remission is defined as a normal platelet count (more than 140,000 per cubic millimeter), partial remission as a platelet count of more than 50,000 per cubic millimeter, and no response as a platelet count of less than 30,000 per cubic millimeter.

†CMOPP denotes 750 mg of intravenous cyclophosphamide per square meter of body-surface area and 2 mg of intravenous vincristine per square meter on days 1 and 8; 40 mg of prednisone per square meter on days 1 through 14; and 100 mg of procarbazine per square meter on days 1 through 10. CEP denotes 750 mg of intravenous cyclophosphamide per square meter and 2 mg of intravenous vincristine per square meter on days 1 and 8, plus 100 mg of etoposide per square meter on days 15, 16, and 17. CVP denotes 750 mg of intravenous cyclophosphamide per square meter and 2 mg of intravenous vincristine per square meter on days 1 and 8, plus 40 mg of prednisone per square meter on days 1 through 14.

‡The patient refused further therapy after the second course of combination chemotherapy.

motherapy but subsequently had a response to danazol (200 to 400 mg per day), colchicine (0.6 mg per day), and prednisone (10 to 15 mg per day), and she has had normal platelet counts for more than five years; her condition had previously been resistant to these drugs. The remaining three patients had no persistent response to combination chemotherapy or any other therapy and died within a few months as a result of central nervous system bleeding due to unremitting thrombocytopenia.

In summary, one half of this small group of patients with severe, life-threatening immune thrombocytopenic purpura remained in remission without further therapy after combination chemotherapy of the type used for lymphomas. Some of the other patients appeared to have responses to

treatments that had previously failed. Combination chemotherapy should be considered for the select group of patients with severe refractory immune thrombocytopenic purpura in whom other forms of therapy have failed and who are at risk for death from their disease.

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1. Figueroa M, Gehlsen J, Hammond D, et al. Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med* 1993; 328:1226-9.

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