COMMENTS AND RESPONSES

Ciprofloxacin versus Tobramycin for Neutropenic Fevers

TO THE EDITOR: Peacock and colleagues (1) raise the following question: What response rate is acceptable for an antibiotic regimen used to treat presumed or proven infection in neutropenic patients? The authors reported an overall success rate of only 27% for ciprofloxacin–piperacillin and 22% for tobramycin–piperacillin. Response rates for clinically and microbiologically documented infections with each agent were 22% and 16%. The authors concluded that ciprofloxacin–piperacillin is another “clinically proven regimen” for neutropenic patients.

The first randomized trial of empirical antibiotic therapy for presumed or proven infection in neutropenic patients was conducted at our institution (2). The response rates for carbenicillin–cephalothin and carbenicillin–kanamycin, respectively, were 53% and 52% overall and 60% and 58% for documented infections. We have subsequently conducted 11 randomized trials of empirical therapy that involved at least 300 neutropenic patients. The lowest overall response rate was 50% (median, 67%; range, 50% to 81%), and the lowest response rate for documented infections was 49% (median, 67%; range, 49% to 80%). From 1985 to 1995, we were involved in five studies in which the best response rate was 74% to 81% overall and 67% to 79% for documented infections. Hence, we would not consider a response rate lower than 60% acceptable. Indeed, a 1998 study conducted by one of the authors of Peacock and colleagues’ study compared cefoperazone–sulbactam with imipenem–cilastatin and found overall “favorable response rates” of 88% and 81%, respectively (3).

Some of the definitions used in Peacock and colleagues’ study are not clear. The authors stated that patients were included if they “required antibiotic therapy for fever and presumed infection,” defined as clinically or microbiologically documented infections. However, in the Results section, they described response rates for “fevers of unknown origin.” They excluded patients with infections due to “bacteria presumed to be resistant to the study drugs.” Did they also exclude patients whose fever was due to viral or fungal infections?

The authors provided no data about response rates related to initial neutrophil count or, more important, subsequent neutrophil recovery. Why did they select piperacillin over piperacillin–tazobactam, which has activity against some β-lactamase–producing bacteria? Because their study used piperacillin, more patients could receive tobramycin as the only active antibiotic. However, aminoglycosides alone are considered suboptimal therapy for neutropenic patients (4, 5).

Patient population can affect outcome. Peacock and colleagues’ study and our recent studies included similar proportions of marrow transplant recipients, patients with leukemia, and patients with solid tumors. Also, our exclusion and response criteria were similar to theirs. We excluded patients with proven nonbacterial infections, included those with proven bacterial infections, and evaluated response to initial infection in those who developed superinfections, but these differences do not explain the discrepant response rates. Peacock and colleagues’ study was multi-institutional, but should that account for such disparate results?

We believe that physicians should select a regimen with response rates higher than 50% unless there are compelling reasons not to do so. Are the regimens examined by Peacock and colleagues really acceptable, especially since their analysis excluded antibiotic-resistant infection?

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References

TO THE EDITOR: From the introduction and discussion in Peacock and colleagues’ article on piperacillin–tobramycin versus piperacillin–ciprofloxacin (1), the reader is left with the impression that combination therapy is favorable to monotherapy for neutropenic fever. The authors noted that combination antibiotic therapy has been used for neutropenic fever since the 1970s. However, most studies have failed to show a difference in efficacy between combination therapy and monotherapy (2). Several reviews and guidelines, including those referenced by Peacock and colleagues, recommend monotherapy for uncomplicated neutropenic fever and monotherapy or combination therapy for more complicated cases (2, 3).

The authors state, “Although monotherapy has been used in this patient population . . . combination therapy remains an important therapeutic option, in part because of development of resistance . . . and toxicity” (1). It is counterintuitive that the use of a single antibiotic would result in more drug toxicity than combination therapy. In addition, it is not clear what impact the authors are suggesting combination therapy would have on resistance. While uncontrolled ecologic analyses have suggested a possible association between the use of combination therapy and the suppression of antimicrobial resistance (4), a careful investigation of the development of resistance in specific isolates failed to show a benefit of combination therapy over monotherapy (5). If Peacock and colleagues are concerned about empirical coverage of increasingly resistant organisms, the usual combination of a β-lactam and an aminoglycoside may be suboptimal if the latter antibiotic is the only active agent in the regimen.

Therapeutic studies of antimicrobial agents in the empirical treatment of neutropenic fever are important as new and challenging antimicrobial resistance patterns emerge. It should be noted, how-
ever, that combination therapy has not been shown to offer an advantage over monotherapy in this setting.

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References

IN RESPONSE: Drs. Bodey, Rolston, and Raad question the low antibiotic response rate of our study compared with those of previous series. The difference involves study design, not drug efficacy. In our study, addition of any antifungal or antiviral agent was one of the definitions of failure. Patients were not excluded if their febrile episode proved to be viral or fungal. Had addition of nonantibacterial agents been allowed as suggested by consensus panels (1), response rates of 61% to 69% would have been noted. As we mentioned in the Discussion, studies with similar design have had similar responses (2).

Drs. Bodey, Rolston, and Raad are correct that the definition of fever of unknown origin is unclear. The Methods section should have stated that patients “required antibiotic therapy for fever and/or presumed infection.” They also question the degree of neutropenia between groups. Our Table 1 showed that both the degree of neutropenia at study onset and the duration were similar between groups. Piperacillin was used rather than piperacillin–tazobactam because the latter was not yet on the market.

With regard to the questions of Drs. Linkin and Fishman, our study was not designed to assess combination versus monotherapy in the management of neutropenic fever. The experimental combination regimen was compared with the most “traditional” regimen used to treat neutropenic fever—an antipseudomonal β-lactam and an aminoglycoside (the gold standard). We, like others, feel that monotherapy has a role in the management of selected patients and may be a regimen of choice depending on local patterns of infection, antibiotic susceptibilities, and patient profiles. Although Drs. Linkin and Fishman question whether combination therapy hinders the development of antimicrobial resistance, the Infectious Diseases Society of America expert panel cites the “minimal emergence of drug-resistant strains during treatment” as one of the advantages of combination therapy (1). The investigation cited by Drs. Linkin and Fishman that failed to show a benefit of combination therapy over monotherapy in suppression of resistance involved patients with bloodstream infection due to a single genus (Enterobacter); only 6% of that study sample had neutropenia (3). It is therefore unclear if those results can be extrapolated to neutropenic patient populations. Regarding relative toxicity, it goes without saying that any antimicrobial agent or combination of agents has the potential for toxicity. We agree that the results of available randomized, controlled trials do not show a difference in efficacy between combination therapy and monotherapy. For clinicians who prefer to use a more traditional combination regimen for the management of neutropenic fever, our study provides an alternative: ciprofloxacin–piperacillin.

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References

Reversible Myopathy after Statin Therapy in Patients with Normal Creatine Kinase Levels

TO THE EDITOR: The brief communication by Phillips and colleagues (1) parallels what we have observed at the National Naval Medical Center in Bethesda, Maryland, where we recently withdrew 5 patients from statin therapy secondary to severe muscle cramps. These patients started receiving therapy for elevated levels of low-density lipoprotein cholesterol and met all National Cholesterol Education Program guidelines for initiation of pharmacologic therapy. They had normal baseline renal and hepatic function and did not take any drugs that are known to interact with statins (2). All 5 patients received dietary counseling and simvastatin in daily doses of 20 to 40 mg. All showed benefit from therapy but developed severe nocturnal cramps and proximal upper and lower muscle weakness within 3 to 4 months of therapy initiation. Physical examination demonstrated grade 4/5 weakness in 4 patients and grade 3/5 weakness in 1 patient. Laboratory evaluation revealed normal complete blood count, chemistry panel, liver-associated enzyme levels, thyroid function, and creatine kinase levels. However, although creatine kinase levels were within normal limits, they showed up to a 40% increase over baseline levels. Symptoms resolved within 3 to 4 weeks of therapy cessation. One patient tried a different agent (atorvastatin, 20 mg/d for 1 month, then 40 mg/d), which was successful for 3 months before recurrence of muscle cramps with normal results on laboratory studies. The patient’s symptoms again resolved when the drug was withdrawn.

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TO THE EDITOR: I was disappointed that Vaughn and colleagues’ review of testicular cancer treatment (1) did not mention gynaecomastia as an important clue to the presence of human chorionic gonadotropin (HCG)—secreting tumors. Although gynaecomastia occurs in fewer than 10% of patients with testicular cancer, it is one of the more specific findings on physical examination for HCG-secreting neoplasms and should bring the diagnosis to mind, particularly if the onset of gynaecomastia is recent or sudden. Gynaecomastia secondary to HCG is due to the luteinizing hormone–like activity of high levels of HCG, which stimulates a relative excess of estradiol secretion compared with testosterone production by the Leydig cells of the testes. This process alters the estradiol–testosterone ratio and stimulates ductal and stromal proliferation within the male breast. In addition, some HCG-secreting tumors have also been described with high levels of intratumor aromatase activity, which converts testosterone to estradiol and further increases estrogen levels. Survivors of germ-cell tumors several months after completion of cytotoxic chemotherapy. This is related not to disease recurrence but presumably to hormonal influences, since these patients may have elevated gonadotropin levels and an increased estradiol–testosterone ratio (1, 2). A normal serum HCG level in this setting should reassure both patient and physician.

TO THE EDITOR: Highly active antiretroviral therapy (HAART) has had a profound influence on the natural history of HIV infection but does not lead to HIV eradication (1). More conservative approaches to treatment have been suggested because of the complex nature of the regimen, the high cost of therapy, and lifestyle issues (2). Furthermore, with continued exposure to HAART, patients have begun to experience myriad unexpected adverse events, including redistribution of body fat, lipid and bone disorders, cardiovascular complications, and lactic acidosis (3). Without near-perfect adherence, patients may also incur therapy-associated mutations that may compromise long-term viral suppression.

We initiated a process by which 38 of our HIV-infected clinic patients were permitted to stop HAART after they approached a CD4+ cell count of 0.5 × 10^9 cells/L on at least two consecutive occasions in the setting of an HIV viral load consistently less than 50 copies/mL. Although our data are immature, with a median follow-up of 9.5 months (range, 3 to 47 months), we note that already 9 patients have needed to restart HAART after relatively brief treatment interruptions. These 9 patients stopped HAART with CD4+ cell counts ranging from 0.526 to 1.3 × 10^9 cells/L. Reasons for restarting HAART are outlined in the Table on page 438; in each case, there was a rapid and significant decrease in CD4+ cell count.

We echo the concern recently outlined by Kane (4) that stopping HAART may be deleterious, even for patients who have achieved significant immune reconstitution. Although we surmise that a subset of patients—perhaps those who began HAART before developing an AIDS-defining illness, had CD4+ cell counts greater than 0.3 × 10^9 cells/L, and had moderately elevated HIV viral loads—could safely interrupt treatment (5), this approach is fraught with potential complications. Prospective studies addressing this issue are in progress and should provide further guidance regarding the pros and cons of such a strategy.

**Chronic HIV Infection**

**TO THE EDITOR:**

Highly active antiretroviral therapy (HAART) has had a profound influence on the natural history of HIV infection but does not lead to HIV eradication (1). More conservative approaches to treatment have been suggested because of the complex nature of the regimen, the high cost of therapy, and lifestyle issues (2). Furthermore, with continued exposure to HAART, patients have begun to experience myriad unexpected adverse events, including redistribution of body fat, lipid and bone disorders, cardiovascular complications, and lactic acidosis (3). Without near-perfect adherence, patients may also incur therapy-associated mutations that may compromise long-term viral suppression.

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**Benjamin Jacobs**

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**References**


**IN RESPONSE:**

Breast enlargement or tenderness may be an important, albeit uncommon, sign of the presence of an HCG-secreting germ-cell tumor. However, reversible gynaecomastia may also develop in patients with germ-cell tumors several months after completion of cytotoxic chemotherapy. This is related not to disease recurrence but presumably to hormonal influences, since these patients may have elevated gonadotropin levels and an increased estradiol–testosterone ratio (1, 2). A normal serum HCG level in this setting should reassure both patient and physician.

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**References**


**Long-Term Medical Care of Testicular Cancer Survivors**

**TO THE EDITOR:** I was disappointed that Vaughn and colleagues’ review of testicular cancer treatment (1) did not mention gynaecomastia as an important clue to the presence of human chorionic gonadotropin (HCG)—secreting tumors. Although gynaecomastia occurs in fewer than 10% of patients with testicular cancer, it is one of the more specific findings on physical examination for HCG-secreting neoplasms and should bring the diagnosis to mind, particularly if the onset of gynaecomastia is recent or sudden. Gynaecomastia secondary to HCG is due to the luteinizing hormone–like activity of high levels of HCG, which stimulates a relative excess of estradiol secretion compared with testosterone production by the Leydig cells of the testes. This process alters the estradiol–testosterone ratio and stimulates ductal and stromal proliferation within the male breast. In addition, some HCG-secreting tumors have also been described with high levels of intratumor aromatase activity, which converts testosterone to estradiol and further increases estrogen levels. Survivors of testicular cancer should be counselled to see their physician immediately if breast enlargement or discomfort occurs. In addition to HCG, levels of luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol should be determined in such patients.

**Kevin T. Tong, MD**

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**Reference**

## Table. Reasons for Restarting Highly Active Antiretroviral Therapy*

<table>
<thead>
<tr>
<th>Patient</th>
<th>CDC Class</th>
<th>Time off HAART</th>
<th>CD4+ Cell Count before Treatment Interruption</th>
<th>CD4+ Cell Count at HAART Reinitiation</th>
<th>HIV Viral Load at HAART Reinitiation</th>
<th>Reasons for Restarting HAART</th>
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<tr>
<td>1</td>
<td>C3</td>
<td>10</td>
<td>0.576 ( \times 10^9 ) cells/L</td>
<td>0.174</td>
<td>28 739</td>
<td>Decrease in CD4+ cell count; herpes zoster reactivation</td>
</tr>
<tr>
<td>2</td>
<td>B1</td>
<td>3</td>
<td>1.3</td>
<td>0.605</td>
<td>63 718</td>
<td>Platelet count ( 5 \times 10^9 ) cells/L with mucosal bleeding</td>
</tr>
<tr>
<td>3</td>
<td>C3</td>
<td>5</td>
<td>0.5</td>
<td>0.157</td>
<td>27 909</td>
<td>Platelet count ( 65 \times 10^9 ) cells/L; hepatitis B virus reactivation; sinusitis</td>
</tr>
<tr>
<td>4</td>
<td>B2</td>
<td>2</td>
<td>0.431</td>
<td>0.381</td>
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</tr>
<tr>
<td>5</td>
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<td>3</td>
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<td>0.287</td>
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</tr>
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<td>6</td>
<td>C3</td>
<td>11</td>
<td>0.526</td>
<td>0.149</td>
<td>295 000</td>
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</tr>
<tr>
<td>7</td>
<td>B2</td>
<td>5</td>
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<td>0.268</td>
<td>83 600</td>
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<tr>
<td>8</td>
<td>C3</td>
<td>3</td>
<td>0.64B</td>
<td>0.51</td>
<td>17 000</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>9</td>
<td>A2</td>
<td>2</td>
<td>0.61</td>
<td>0.227</td>
<td>18 000</td>
<td>Decrease in CD4+ cell count</td>
</tr>
</tbody>
</table>

* CDC = Centers for Disease Control and Prevention; HAART = highly active antiretroviral therapy.

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### Corrections

#### Correction: Central Pontine Myelinolysis

In a letter on central pontine myelinolysis (1), the middle panel of the figure was erroneously rotated 180 degrees.

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### Reference


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### Correction: Color Duplex Ultrasonography Compared with Contrast Venography in Patients Suspected of Having Deep Venous Thrombosis of the Upper Extremities

In an article comparing color duplex ultrasonography with contrast venography in patients with suspected deep venous thrombosis of the upper extremities (1), Figure 1 contained errors. In the fourth row, the numbers of patients who received venography and no venography, respectively, should be 46 and 7 in the thrombosis group and 53 and 14 in the normal group. In the fifth row, the number of patients in the thrombosis group who had normal results on venography should be 10 and the number of patients in the normal group who had thrombosis on venography should be 8. All other numbers in the figure are correct.

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### Reference

Annual Physical Examination: Necessary or Needless?

TO THE EDITOR: I enjoyed Dr. Laine’s editorial on the annual physical examination (1), as I have long shared many of her opinions and have had many similar discussions with the internal medicine residents I have precepted. I would like to add a few points to Dr. Laine’s eloquent presentation.

I believe that the health benefits primary care physicians provide are often incremental. Studies have shown that physician advice to quit smoking increases quitting rates by a couple of percentage points per year. It seems likely that the same would hold true for other health behaviors. There are probably very few of us, at any age, who would not be candidates for at least some health advice, such as on diet, exercise, or substance use or abuse. It also seems logical to believe that at least to some degree, repetition of health advice may have cumulative value.

An area receiving increasing attention is that of patient adherence. Studies have shown that better adherence leads to better health outcomes and that one major factor promoting adherence is rapport with a physician. It is my belief that the annual physician examination is an extremely valuable building block in achieving such rapport.

Although much of the above is opinion and not evidence-based (a point I discuss with my residents), it is also true that absence of evidence is not evidence of uselessness. "Soft" research is especially difficult to conduct well. Until studies are available, I shall continue to gently recommend annual physician examinations for my patients.

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Reference