Hepatic Safety and Postexposure Prophylaxis

Str—In the March supplement of Clinical Infectious Diseases [1] dedicated to hepatic safety and antiretroviral agents, the issue of postexposure prophylaxis (PEP) was not considered. However, concerns about PEP safety should arise because of its wide and increasing use following occupational and nonoccupational exposures to human immunodeficiency virus (HIV). Moreover, information derived from antiretroviral use in uninfected healthy individuals can provide further insights into direct drug toxicity not confounded by underlying diseases, use of illicit substances, or other causes of liver injury.

In patients receiving PEP, indirect hyperbilirubinemia is frequent but not clinically relevant when indinavir-including regimens are used; 2 cases of nelfinavir-associated acute hepatitis with cholestatic features were also reported [2]. The Italian Registry of Antiretroviral Post-Exposure Prophylaxis, using the AIDS Clinical Trial Group toxicity grading, did not find any instances of severe transaminase elevations in 207 individuals receiving 2 nucleoside reverse-transcriptase inhibitors (NRTIs), and found grade three elevation in 2 (0.5%) of 429 individuals receiving 2 NRTI plus a protease inhibitor [3].

However, treatment with nevirapine was associated with cases of life-threatening hepatitis [4] in uninfected individuals and with a frequency of severe, mostly rash-associated, hepatotoxicity that was significantly higher than that observed among HIV-infected patients [3, 5].

Recently, Patel et al. [5] described 30 cases of hepatotoxicity—including 14 severe cases and 1 case of fulminant hepatic necrosis—associated with nevirapine—including PEP, although they concluded that attributing the cause of hepatotoxicity to nevirapine could be problematic because of the concomitant exposure to other antiretrovirals.

Similarly, Dieterich et al. [6] reviewed available cohort studies on the risk of nevirapine-associated hepatotoxicity among HIV-infected patients and concluded that the overall rate of transaminase elevations is similar for all antiretrovirals, although the frequency of symptomatic hepatic events is significantly higher in nevirapine-treated individuals. These data, already presented elsewhere [6], were criticized by US Food and Drug Administration representatives [7], who, taking into account a possible bias in selection of the study population, found that the frequency of asymptomatic transaminase elevations was significantly higher in the nevirapine group (6% of subjects) than in control group (3%).

In an updated review of the above-mentioned Italian Registry data [3], we identified 1 grade three and 2 rash-associated grade four transaminase elevations among 10 women and 8 men receiving nevirapine-including PEP, for an incidence of 25 cases per 100 person-months. All cases occurred in female health care workers, none of whom had concurrent viral hepatitis. Although a selection bias caused by reporting of “positive” cases cannot be ruled out, these findings clearly suggest a prevalent role of nevirapine in causing hepatotoxicity.

Finally, female sex and high pretreatment CD4+ cell count are independent risk factors for developing hepatotoxicity among HIV-infected patients [6–8].

PEP data support these associations, suggestive of an immune-mediated basis for nevirapine rash-associated hepatotoxicity, and suggest a yet unexplained relationship between this adverse reaction and the level of immunocompetence.

In conclusion, available data suggest that antiretroviral-induced hepatotoxicity during PEP is rare, often mild to moderate in severity, and always reversible; in fact, nevirapine is the only antiretroviral whose inclusion in a PEP regimen is discouraged [9–10].

Acknowledgment

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Conflict of interest. All authors: No conflict.

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Reply to Puro et al.

Sir—In response to Puro et al. [1], we remind readers that nevirapine should only be used for the indications found on the product label. The product label clearly states nevirapine should not be used in the context of postexposure prophylaxis. The use of nevirapine, like the use of any antiretroviral drug, should be based on a risk-benefit assessment. We believe that the risk for patients who are not infected with HIV outweighs the benefit, especially since there are other treatment options available. Empirical observation of several spontaneous cases of liver failure, which may make liver transplantation necessary or result in death, has led the manufacturer, Boehringer-Ingelheim, to conclude that nevirapine should not be used as postexposure prophylaxis in HIV-negative patients.

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Broadened Definition for Hospital-Acquired Infective Endocarditis

Sir—in their article on hospital-acquired infective endocarditis (IE), Ben-Ami et al. [1] suggest that the traditional definition of hospital-acquired IE should be modified to include cases in recently hospitalized patients (i.e., those discharged from the hospital within 6 months before the onset of symptoms). Indeed, recently hospitalized patients with IE in their cohort are similar, with respect to in-hospital mortality and distribution of bacterial isolates, to patients who have traditionally defined hospital-acquired IE. Both of these groups significantly differ from patients with community-acquired IE [1].

To test the proposed new definition, we reviewed data on IE episodes observed at National Institute for Infectious Diseases “Lazzaro Spallanzani” (Rome, Italy) during 2000–2003. Injection drug users were excluded from the analysis because of the peculiar clinical and microbiological pattern of IE in this population [2].

Thirty patients with community-acquired definite IE (on the basis of the Duke criteria [3]) were observed; 24 had native valve IE, 5 had late prosthetic valve IE, and 1 had cardiac pacemaker infection. The mean age (±SD) of patients was 56.6 ± 16.3 years, and 21 patients (70%) were male. In 17 cases, a known valvular disease preexisted; comorbid conditions were present in 5 patients, including diabetes (3 patients), arterial hypertension, and chronic renal insufficiency. The in-hospital mortality rate was 22% (2 patients). Nine episodes (30%) of IE fulfilled the broadened definition of hospital-acquired IE proposed by Ben-Ami et al. [1]; during the 6 months prior to hospital admission, 4 patients had been hospitalized, 2 had undergone surgical operations, 1 had been undergoing dialysis, 1 had undergone dental treatment, and 1 had undergone gastric endoscopy. Seven patients had native valve IE, and 2 had late prosthetic valve IE. In 3 episodes, no pathogens were isolated from blood cultures; in the remaining 6 episodes, blood cultures yielded viridans group streptococci (2 episodes), group B Streptococcus species (1 episode), methicillin-susceptible Staphylococcus aureus (2 episodes), and Enterococcus faecalis (1 episode).

No statistically significant differences were found between the remaining 21 patients with community-acquired IE with regard to age, sex, preexisting comorbidity, native or prosthetic valve localization, blood culture isolates, and in-hospital mortality (P = .08, by Fisher’s exact test).

Thus, the proportion of recently hospitalized patients with IE in our cohort was similar to that observed by Ben-Ami et al. [1]. Conversely, the distribution of bacterial isolates was different. This may be a result of different study populations or different epidemiological patterns in Italy than in Israel. Indeed, our patients were younger and had fewer comorbid conditions—findings that could also account for the lower mortality rate we observed.

Moreover, the epidemiology of pathogens traditionally considered to be associated with health care is changing. For example, the nosocomial incidence of community-acquired, methicillin-resistant S. aureus (MRSA) infection is increasing, and MRSA can no longer be considered an exclusively nosocomial pathogen [4–6]. Moreover, community-associated and health care–associated MRSA isolates have distinct resistance profiles and microbiological characteristics [6] that could be used to distinguish them.

According to Ben-Ami et al. [1], sus-
picion of a nosocomial infection among patients with IE and recent hospitalization could justify the empirical use of vancomycin as part of the initial empirical antimicrobial regimen. However, the authors do not provide data to support this conclusion. We believe that more sound evidence is needed before a broader definition of nosocomial IE should be accepted and IE management modified accordingly.

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Conflict of interest. All authors: No conflict.

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Reply to Cicalini et al.

Sir—We welcome the effort made by Cicalini et al. [1] to validate our observations [2] in a different population. However, before one concludes that their results contradict our own, several points should be considered. Cicalini et al. [1] state that 4 of the patients with cases included in the broadened definition of hospital-acquired infective endocarditis (IE) had been discharged from the hospital within the previous 6 months. However, it is unclear whether the other 5 patients—whose cases were included because the patients had undergone invasive procedures (i.e., surgery, dental work, endoscopy, and dialysis)—underwent these procedures during hospitalization or as outpatients. In our study, patients who underwent invasive procedures as outpatients were assigned to the true community-acquired IE group: 10 (20%) of 49 episodes of true community-acquired IE were associated with such procedures [2]. Therefore, it is possible that only 4 of the patients described by Cicalini and colleagues had cases that fit our broadened definition of hospital-acquired IE. Because the individual associations of bacterial isolates with specific patients are not provided, the distribution of bacterial species among these 4 patients is unknown. However, the small number of recently hospitalized patients, as well as the high proportion of culture-negative IE episodes (3 of 9 episodes), preclude a meaningful assessment of the bacteriological and clinical characteristics of this group. Finally, we hypothesized that IE in recently hospitalized patients reflects the prevalence of bacterial isolates in the discharging medical institution. Therefore, the characteristics of hospital-acquired IE (as traditionally defined) in the relevant medical institution should also be considered when assessing the significance of recent hospitalization. These data are not reported by Cicalini et al. [1].

Currently, there is no well-established definition of hospital-acquired IE. On the basis of our observations, we proposed that patients who had been discharged from the hospital ≤6 months before the onset of their symptoms should be considered to have hospital-acquired infections. However, we agree with Cicalini et al. [1] that a widely applicable definition should be based on data from diverse epidemiological settings. We hope that our observations will encourage other researchers to examine local data, so that this emerging medical problem can be better addressed.

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Conflict of interest. All authors: No conflict.

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References


Antemortem Diagnosis of Human Rabies

Sir—We previously reported the use of nucleic acid sequence-based amplification (NASBA) for the detection of rabies virus RNA in samples of saliva, CSF, and/or urine obtained during life from 8 patients infected with rabies [1, 2]. Here, we summarize the results of NASBA in correlation with the clinical onset of symptoms of the disease.

From September 1998 through March 2004, we collected and tested 58 specimens from 23 rabies patients (20 with furious
and 3 with paralytic rabies). Samples collected included: 27 saliva, 14 CSF, 15 urine, and 1 tear specimen; and extracted hairs from 1 patient. All patients had been bitten by stray dogs. Postmortem brain samples from all patients were positive for rabies virus by either fluorescence antibody testing or mouse inoculation; all samples were also positive for rabies virus by either NASBA or RT-PCR. All samples, except the first 4 specimens, which were frozen, stored, and examined retrospectively [1], were kept at 4°C for 24–48 h until examined for the presence of the rabies nucleocapsid gene. In 21 of 23 patients, we identified rabies RNA in specimens obtained on the first day of hospitalization. Specimens collected within 3 days after clinical onset yielded the highest number of positive results with saliva samples having the highest rate of positivity (7 of 8 specimens), followed by CSF (4 of 6) and urine (2 of 5). The sensitivity of all specimens types dropped after 3 days; however, saliva remained the most practical and reliable source for virus detection (11 of 15 specimens positive during days 4–6 after onset and 1 of 2 positive during days 7–9). The test sensitivity for urine (3 of 9 specimens positive for rabies virus RNA) and CSF (2 of 7) was comparable during days 4–6. Test results for 2 saliva specimens, 1 CSF specimen, and 1 urine specimen obtained during days 10–12 were all negative. Of particular interest were the test results for hairs extracted from 1 patient obtained 4 days after onset of symptoms. Fifty hair samples were extracted from this patient instead of excising skin with hair follicles from the nape of the neck [3]. We were able to demonstrate the presence of rabies RNA in the ends of the hair follicles.

Negative results were obtained exclusively from tests performed on samples collected sequentially from 2 patients with paralytic rabies. Samples tested from the first patient included saliva, CSF, and urine collected on day 11 after onset and saliva collected on day 12. Samples tested from the second patient included CSF and urine collected on day 4, saliva and urine collected on days 5 and 6, and tears collected on day 7. For a third patient with paralytic rabies, results from a CSF sample collected on day 3 were positive, but results for saliva samples collected on days 3 and 7 were both negative.

In summary, we conclude that molecular methods, although useful and extremely sensitive, may not always give positive results for patients with rabies. This may be due to the intermittency of virus shedding, the timing of sample collection, and the type of specimens collected. Moreover, the extent the clinical type of rabies (particularly paralytic rabies and cases with atypical features) [4] influences the outcome of laboratory results remains to be determined. We strongly urge that specimens be collected simultaneously from several sources and examined; they should include saliva, urine, and CSF. Sample collection should be repeated until a diagnosis is confirmed [5]. Postmortem examination should also be conducted in all suspected cases of rabies and other encephalitides, regardless of the results of antemortem examination.

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References


Infection by Drug-Resistant Streptococcus pneumoniae Is Not Linked to Increased Mortality

Sir—We congratulate Dr. Aspa and colleagues and the Pneumococcal Pneumonia in Spain Study Group [1] for their large, labor-intensive study of 638 cases of community-acquired pneumonia due to Streptococcus pneumoniae. We take issue with only one point made in an otherwise excellent study: “The impact of drug-resistant S. pneumoniae on morbidity and mortality is still controversial” [1, p. 795]. The authors underestimate the potency of their own findings when they claim that the issue is controversial. If it is controversial, the authors have provided additional support for the numerous authorities on pneumococcal infection who claim that drug resistance is an artifact of the NCCLS guidelines, with few clinical implications. Their major finding was that in vitro resistance to macrolides and β-lactam agents did not result in increased morbidity or increased mortality—a finding that has been reiterated in >20 peer-reviewed articles, including our own [2].

The authors cited the Centers for Disease Control and Prevention (CDC; Atlanta, GA) study [3] in which mortality was significantly associated with an MIC of penicillin of ≥4 µg/mL, and they suggested that high-level resistance may be associated with an adverse outcome. In fact, the CDC study did not attempt to correlate discordant therapy with out-
come, because it was merely a survey of drug-resistant *S. pneumoniae* strains that had been isolated from sterile sites. Clinical details, including the severity of illness at onset and the antibiotics administered, were not available, which is a fact that the CDC investigators themselves conceded.

In the study of Aspa et al. [1], only 3 of 638 patients were infected by pneumococci with an MIC of penicillin of 4 \( \mu \text{g/mL} \), and no pneumococci had an MIC of penicillin of \( \geq 8 \mu \text{g/mL} \). The authors say that their study was probably underpowered to establish the real impact on the outcome of these resistant pneumococci (resistance was defined as an MIC of penicillin of \( \geq 4 \mu \text{g/mL} \)). We suggest that the authors have confused clinical significance with statistical significance. What was the antibiotic therapy that was administered, the severity of the illness, and the outcome for the 3 patients who were infected with highly resistant pneumococci, compared with these factors among the patients who were infected with penicillin-susceptible pneumococci and/or nonsusceptible pneumococci?

In our study of 844 patients with pneumococcal bacteremia, a total of 13 patients were infected with drug-resistant *S. pneumoniae* that had MICs of \( \geq 8 \mu \text{g/mL} \), and only 1 patient died (a mortality rate that is notably lower than that for the entire group of patients with bacteremia) [4]. No patients were severely ill, and severe illness is the primary predictor of mortality. Of 4 patients who received discordant therapy during the first day in our study, all survived. It appears that the favorable pharmacodynamics of the macrolides and \( \beta \)-lactam agents trump the usefulness of a single MIC value. Thus, there was a trend toward decreased morbidity and mortality if patients were infected with a pneumococcus with high-level penicillin resistance; this is similar to the finding of Aspa and colleagues [1] that complications, such as disseminated intravascular coagulation, empyema, and bacteremia, were less frequent among patients who were infected with penicillin-resistant pneumococci than among patients who were infected with penicillin-susceptible pneumococci (a confirmatory observation that has been made by numerous investigators). The authors’ suggestion that a study of several thousand patients be undertaken to identify more patients with MICs of \( \geq 4 \mu \text{g/mL} \) seems to be an exercise in futility, given that there is no trend toward increased morbidity or mortality in virtually any of the patient studies that have addressed this issue.

Much of the world has shifted its choice of empirical antibiotic therapy on the basis of microbiologic surveys of drug-resistant *S. pneumoniae*. \( \beta \)-Lactam antibiotics and macrolides that are clinically effective are being shunted aside, and drugs such as quinolones are given to cover the extremely minute percentage of patients who might be infected with pneumococci that have high-level in vitro resistance. Unnecessarily prescribing broad-spectrum antibiotics has drawbacks, including provocation of the emergence of pneumococci that are resistant to these antibiotics, as is already occurring in the case of quinolone use.

We believe that the most clinically relevant conclusion that can be drawn from the data presented by the Pneumococcal Pneumonia in Spain Study Group is that these shifts in antimicrobial prescribing practices for drug-resistant *S. pneumoniae*, as defined by NCCLS breakpoints, are not supported by evidence.

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**Reply to Yu and Baddour**

Sr—We thank Dr. Yu and Dr. Baddour [1] for their interest in our article [2] and for the comments in their letter, and we apologize for having missed the article published within the past year that addresses a similar question [3].

We agree with their statement that, currently, there is no consistent relationship between penicillin MIC values and mortality, although some reports of poor outcomes among patients infected with drug-resistant *Streptococcus pneumoniae* strains do exist in the literature. Much of the controversy relates to the interpretation of the breakpoint classification for drug susceptibility and resistance in the pneumococcus. The recognition of this controversy has prompted the NCCLS to modify the in vitro breakpoints for amoxicillin and cephalosporin in nonmeningal infections, keeping the historical breakpoint for penicillin as a frame of reference. Despite this modification, the present system of reporting is still confusing, because achievable levels of resistance at the sites of infections are well above the current NCCLS breakpoints for many antibiotics, provided that the antibiotics are dosed adequately. However, some authors have reported treatment failure when a macrolide was used to treat a pneumococcal infection caused by a macrolide-resistant strain [4–8]. This is particularly important in Europe, where the predominant mecha-
nism of resistance is typically high grade, as you can see in our study. To add to the confusion, the emergence of resistance to macrolide agents during treatment has been recently reported [9]. Being involved in this debate, we conclude that prudence in prescribing practices is probably well advised.

Nor can we forget that our study reflects the way in which its participating hospitals work. There is a possibility that some bias has been introduced; for example, the timing of administration of the first dose could have varied from one hospital to another, or the criteria for admission to the intensive care unit may have been different among hospitals. This possibility of the introduction of bias was our reasoning for not being conclusive in our study.

When we say “The impact of drug-resistant S. pneumoniae on morbidity and mortality is still controversial” [2, p. 795], we are only echoing the enormous body of literature that this topic has generated. What is more, variations of this same phrase are generically used as an introduction to the theme of drug resistance in many articles, and, without going into too much detail, a variation even makes an appearance in the magnificent article that Dr. Yu coauthored recently [10].

Concerning your request for more information about factors related to the morbidity and/or mortality associated with episodes of illness in patients with elevated MICs of penicillin, we have provided a table (table 1) that shows outcome data and clinical data for patients with MICs of penicillin and amoxicillin of $\geq 4 \mu g/mL$ in our series. In addition, we have analyzed different factors related to mortality in patients with pneumococcal pneumonia. The results of our analysis are in the process of being reviewed for publication.

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#### Conflict of interest.

All authors: No conflict.

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### References


### Visceral Leishmaniasis as a Cause of Anemia in HIV-Infected Patients

Sir—In their recent article, Volberding et al. [1] offer an accurate analysis of the possible causes of anemia in HIV-positive patients and give useful information about its management. However, among the treatable causes of anemia reported in table 3, the authors did not mention several opportunistic infections, such as leishmaniasis, histoplasmosis, tuberculosis, and pneumocystosis. Among the above-mentioned infections, visceral leishmaniasis is particularly frequent in the Medi-

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### Table 1. Patients from whom high-level penicillin-resistant Streptococcus pneumoniae strains were isolated.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Comorbidity</th>
<th>Initial antibiotic therapy (dosage)</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Neurologic conditions and suspected aspiration</td>
<td>Amox-clav (2000/200 mg iv q8h)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>92</td>
<td>Heart failure, renal failure, neurologic conditions, and previous β-lactam therapy</td>
<td>Amox-clav (2000/200 mg iv q8h)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>Diabetes, renal failure, aspiration, and neoplastic and cardiologic conditions</td>
<td>Amox-clav (2000/200 mg iv q8h)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NOTE. High-level resistance was defined by an MIC of $\geq 4 \mu g/mL$. Amox-clav, amoxicillin-clavulanic acid.
terranean basin [2], but there is evidence that its occurrence will increase in areas such as Brazil and India, where overlapping of leishmaniasis and HIV infection is an emerging problem [3].

Although visceral leishmaniasis is not considered an AIDS-defining disease, it behaves like an opportunistic infection, presenting in patients with <200 CD4 lymphocytes/µL in 92% of cases. Interestingly, in geographic areas where visceral leishmaniasis is endemic, AIDS appears to increase the risk of clinical visceral leishmaniasis by 100–1000 times [4]. As far as diagnosis is concerned, it should be highlighted that serologic tests are usually unreliable because such findings are positive only in 40–50% of HIV/Leishmania co-infected patients [4]; furthermore, bone marrow microscopy and culture also have the limitations of low sensitivity, compared with the results from HIV-negative patients, and they are especially time consuming [4, 5]. In patients with HIV/Leishmania co-infection, PCR analysis of either peripheral blood or bone marrow aspirate specimens has emerged as the most sensitive and specific diagnostic method, and use of PCR should be added to the proposed diagnostic algorithm for anemia in HIV-infected patients [6, 7].

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