CORRESPONDENCE

Treatment of Acute Lung Injury Attributed to Leptospirosis

SIR—We read with interest the report of Marotto et al. [1] on the features and outcome of acute lung injury in leptospirosis. The severity of illness attributed to pulmonary hemorrhage due to Leptospira interrogans infection and the resulting mortality rate of 55% presented in their report are impressive. A significant portion of these patients also suffered from acute renal failure and shock, which were also independent risk factors for patient mortality.

It is worth knowing whether the authors had used adjunctive supportive measures while caring for their patients, such as nitric oxide inhalation (iNO) or hemofiltration. We have recently published a report of leptospirosis complicated by massive pulmonary hemorrhage and acute renal failure that was unresponsive to conventional medical treatment [2]. The institution of iNO and hemofiltration resulted in prompt clinical improvement of both the acute lung injury and renal failure, and a favorable outcome of this patient.

Continuous hemofiltration has been employed for the removal of circulating cytokines in patients with sepsis and multiple organ dysfunction [3], as well as in patients with severe leptospirosis [4]. In addition, the effectiveness of iNO in sepsis, established acute respiratory distress syndrome [5, 6], and Hantavirus pulmonary syndrome [7] have been reported. These data could support the experimental use of such measures in critically ill patients with life-threatening leptospirosis and may offer a possible survival benefit. However, both their safety and efficacy have yet to be evaluated in controlled studies. In this regard, the risks and benefits of hemofiltration and iNO use during pulmonary hemorrhage should be taken into account because of the antiplatelet effect of NO, the use of anticoagulants during hemofiltration, and the thrombocytopenia commonly associated with leptospirosis.

Finally, more than two-thirds of patients in the study by Marotto et al. [1] had septic shock. It would have been valuable if the authors had stated whether hemodynamic compromise in various patients occurred before or after the administration of antibiotics, since a cytokine-mediated septic shock–like phenomenon (namely, the Jarisch-Herxheimer reaction) during the treatment of leptospirosis is well documented [8].

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References

Intradermal Postexposure Rabies Vaccine Regimens

SIR—Economical intradermal (id) postexposure rabies vaccine regimens were devised 10–15 years ago to make the excellent modern vaccines available to more people in areas where nerve tissue vaccines were used. Plotkin [1] discusses the treatment regimens and states that the id dose is 0.1 or 0.2 mL per site, depending on the brand of vaccine used. The data in table 4 of Plotkin’s article apparently confirmed that this applied to the 8-site regimen, but the statement applies only to the 2-site regimen.

Four rabies vaccines are recommended by the World Health Organization (WHO) for id use [2]. The 8-site id regimen (see table 1 here) was initially tested when human diploid-cell vaccine (Imovax rabies; Aventis Pasteur, Lyon, France) was the only tissue-culture vaccine available [3], but it can also be used with purified chick embryo cell vaccine (Rabipur/RabAvert; Chiron Behring, Marburg, Germany) [4] and purified duck embryo vaccine (Lyssavac-N; Berna, Bern, Switzerland), because the volume of vaccine in 1 ampoule is 1.0 mL. The other recommended vaccine, purified Vero cell vaccine (PVVR; Verorab; Aventis Pasteur), has only 0.5 mL per ampoule and it has not been tested with the 8-site regimen. If it were, the logical dose would be 0.05 mL per site.

The 2-site id regimen (see table 1 here) was designed for use
Table 1. Economical intradermal (id) postexposure rabies treatment regimens, compared with the standard im schedule.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>No. of sites injected on treatment day</th>
<th>Total no. ampoules used</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-Site id, 0.1 mL per site</td>
<td>0 3 7 14 28 91</td>
<td>&lt;2</td>
</tr>
<tr>
<td>2-Site id, 0.1 or 0.2 mL per site</td>
<td>2&lt;sup&gt;a&lt;/sup&gt; 2 2 1 1</td>
<td>&lt;2</td>
</tr>
<tr>
<td>1-Site im, 1.0 or 0.5 mL</td>
<td>1 1 1 1 1 5</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> No. of sites injected over the deltoid, thigh, suprascapular, and lower anterior abdominal wall.

<sup>b</sup> No. of sites injected over the deltoid and thigh.

<sup>c</sup> One or 2 sites injected over deltoid.

with PVRV [5]. It requires a dose of 0.1 mL per site for PVRV and a dose of 0.2 mL per site for the other 3 vaccines. Both of these regimens use a similar total amount (<2 ampoules) of vaccine per course of treatment.

There are several advantages to using the 8-site method. First, rapid induction of neutralizing antibody makes the 8-site method the treatment of choice when no rabies immunoglobulin is used (which is the case for >90% of postexposure treatments in Third World countries). Second, there is a wide margin of safety, because (a) if up to half of the 8 id injections on day 0 are not truly id injections, then the immune response will still be adequate [4], and (b) use of a whole ampoule on day 0 avoids the need to share ampoules of vaccine between patients during emergency treatment and also eliminates any risk of contaminating or wasting vaccine. Third, administration of a large antigenic stimulus on day 0 gives the best chance of survival to those patients who are “low responders” [6] to the vaccine and to those who fail to return on time for subsequent doses (a common problem in areas in the rural tropics).

The complexity of these treatments demonstrates the urgent need for an improved, simplified single regimen that is suitable for use with all WHO-recommended vaccines. Efforts are being made to establish such a regimen. Meanwhile, there is reluctance to use these vaccines economically. This deprives many patients of excellent treatment and perpetuates double standards of treatment in the Third World. The use of rabies vaccines of nerve tissue origin (Semple and suckling mouse brain vaccines) would be considered unethical in the United States today, but these obsolete vaccines are still given to millions of individuals in other parts of the world each year.

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Infection May Not Have Been Caused by Exophiala jeanselmei

SIR—In a recent Photo Quiz [1] in Clinical Infectious Diseases, a nodular lesion at the base of the third finger of a 74-year-old retired farmer’s right hand was identified as being caused by Exophiala jeanselmei, on the basis of the presence of hyphal elements in the excised tissue and the micromorphology of the fungus as described in the text and the micromorphology of the fungus (see figure 3 in the Photo Quiz), which does not show any of the characteristics of E. jeanselmei, we believe that E. jeanselmei is not the causative agent in this case.

E. jeanselmei [2] is a melanoid hyphomycete that is known to cause eumycotic black-grain mycetoma, phaeohyphomycosis, and, rarely, chromoblastomycosis. When E. jeanselmei causes mycetoma in tissue, it produces black, vermiform granules [3]. As a causative agent of phaeohyphomycosis, the fungus is seen in tissue as phaeoid, yeastlike cells and branched or unbranched septate hyphae [4]. In rare cases, when the fungus causes chromoblastomycosis, it produces pigmented, thick-walled, mureiform cells (sclerotic bodies) [5]. With regard to the case featured in the Photo Quiz, the authors did not mention whether the hyphal and yeastlike cells shown in figure 2 were pigmented (phaeoid).

In culture, E. jeanselmei is polymorphic. Its early growth is yeastlike and mucoid, and because of its distinct morphologic form, it is classified, under the form-genus Phaeoannellomyces, as P. elegans [6]. It consists of spherical, subspherical cells, each of which forms a reduced anellidic butt that produces conidia.
On further incubation, the yeastlike colonies develop velvety, olivaceous-green aerial mycelium. This mycelial form is known by the binomial “E. jeanselmei.” Vegetative septate, phaeoid-branching hyphae produce lateral and terminal tapering (lageniform) conidiophores. At their tips, these conidiophores bear conidiogenous cells that are annellidic with inconspicuous annellated zones. The conidiogenous cells produce one-celled, smooth, ellipsoidal conidia [2, 7]. Figure 3 in the Photo Quiz does not show any of these characteristics of E. jeanselmei. In our opinion, the identity of the causative agent in this case still remains unknown.

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Detection of Selected Fastidious Bacteria

Str—My experience with the laboratory diagnosis of legionnaires disease (LD) differs in some ways from that described by Doern [1]. I consider expectorated sputum and, especially, endotracheal suction specimens to be equivalent or superior to bronchoscopically obtained specimens (BOS) for the culture diagnosis of LD. The yield of non-BOS has been equivalent or superior to the yield of BOS in every instance in which I have been able to compare specimens collected from the same patient. In fact, the number of colonies of Legionella species isolated from sputum or endotracheal aspirate specimens can be up to 10-fold greater than the number isolated from BOS. I suspect that this difference can be attributed to dilution of the BOS by lavage fluid, to the use of lidocaine, saline, or both, and perhaps to sampling error. Culture diagnosis of LD severe enough to cause respiratory failure is usually relatively easy. It is true that patients with less severe LD may produce little sputum; my experience is that a specimen suitable for culture can be obtained from these patients by a determined and patient physician or nurse. Less than 0.1 mL of high-quality sputum is required for culture diagnosis of LD.

On the other hand, in my laboratory, pleural fluid specimens from patients with LD have had a relatively low culture yield. Immunosuppressed patients are most likely to have a positive pleural fluid culture, sometimes before the pneumonia becomes apparent by radiography and sometimes when only an empyema is present. Since culture and analysis of pleural fluid are often indicated in pneumonia of unknown etiology, this fluid, as well as sputum, should be cultured in patients suspected of having LD.

Doern [1] is correct in saying that use of selective buffered charcoal yeast extract (BCYE) media is important for the optimal culture yield of Legionella species. I would add that it is also important to use a selective medium that does not contain a β-lactam, because several different Legionella species and subtypes are susceptible to β-lactams. Our laboratory uses 2 different selective BCYE media and a non-selective medium, and also pretreats part of the specimen with an acidic solution, for a total of 6 plates per specimen. I find it rare for colonies of Legionella species to grow on plates after 2 days of incubation, and I generally find that the most growth occurs on the third and fourth day of incubation. Very rarely, some Legionella species isolates require 10–14 days of incubation before growth is apparent.

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Silver/Copper Ionization Is Effective for Control of Legionella

Sir—As the manufacturer of the Tarn Pure ionization system used in the hospital discussed by Rohr et al. [1], I feel obliged to respond. The system was correctly installed by our own engineers and initially set to give the correct levels of silver and copper ions within the hot water circulating loops. The recommended levels for effective disinfection are 40 µg/L of silver and 400 µg/L of copper. Initially the effect was to kill the high levels of Legionella bacteria and to disrupt established biofilm in the water system.

It appears that the output of our systems was reduced to comply with the maximum level normally allowed in Germany of 10 µg/L of silver. No doubt due to absorption by debris, silver levels dropped to 5 µg/L for some time, and the copper levels only registered the same as the background level of copper before the system was activated. It should be noted that the initial, correct levels of treatment had a medium- to long-term effect even when the systems were running at a very low output.

Therefore, we must conclude that the evaluation of Rohr et al. had no significant findings; it cannot be concluded that there was any build-up of resistance to the ionic treatment. The results obtained from our many installations in the United States, Europe and in the United Kingdom clearly indicate that Tarn-Pure systems are effective when they are set to produce correct levels of silver and copper. The Health and Safety Executive (the regulatory body responsible for controlling all forms of hazards regarding the public at large in the United Kingdom) states that ionization is effective when silver levels are 20-40 µg/L and copper levels are 400 µg/L, as we recommend [2; pg. 2]. We have installations that have been in continuous use for many years, and there is no evidence that resistance to the treatment has developed.

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References

Hepatitis A Virus Vaccination among Injecting Drug Users: Do We Have to Change the Vaccination Schedule?

Sir—Injection drugs users (IDUs) are considered at risk for hepatitis A virus (HAV) infection [1]. The observation of ful-
minant hepatitis associated with HAV superinfection in patients with chronic hepatitis C drew further attention to the problem because of the very high rates of hepatitis C virus (HCV) seropositivity among IDUs [2].

For some years the plasma-derived vaccine Havrix (Smith-Kline Beecham Biologicals, Rixensart, Belgium) has been available. Initially it was administered at a dose of 720 IU at months 0, 1, and 6; more recently it was proposed that the dose for adults be 1440 IU, administered either at months 0 and 6 or at months 0 and 12. In northeastern Italy, where HAV seroprevalence among young adults is low (3.7%) [3], HAV vaccination is free for IDUs and is performed at Public Centers for Drug Users. Because the responsiveness of IDUs to hepatitis B virus vaccination has been demonstrated to be low [4], we undertook to evaluate the antibody response to HAV vaccination in IDUs attending 3 Public Centers for Drug Users, using Havrix at a dose of 1440 IU and administered according to the new schedule of 0 and 6 months. More than 95% of healthy adults develop HAV antibodies within 1 month after receiving a single dose of Havrix, and up to 80% have antibodies within 2 weeks [5].

All subjects in our study were heroin addicts who were HCV positive and HIV negative and who had not received immunosuppressant or steroid therapy. Antibody response has been measured 2 months after the first or the second dose of vaccine.

Ninety-three subjects received the first dose. After 2 months antibody response was measured in 65 subjects of whom only 39 (60%) showed a protective titer (≥20 mIU/mL). Of the remaining 26 subjects, antibody response was measured in 11, all of whom showed a protective titer.

This study strongly suggests that only the HAV vaccination schedule of administration at months 0 and 6 is suitable for the population of IDUs. We would recommend that for IDUs, the schedule of administration at months 0 and 12 be abandoned in favor of administration at months 0 and 6, to abbreviate the unprotected period. Further studies are needed to improve the HAV vaccination schedule for IDUs.

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Possibility of the Use of Oral Long-Acting Tetracyclines in the Treatment of Lyme Neuroborreliosis

SIR—We have read with interest and would like to praise both the well-done study of Dotevall and Hagberg [1] and the ensuing discussion regarding the use of doxycycline versus minocycline for treatment of CNS spirochetal infections [2, 3]. We believe that an additional comment on this discussion may be warranted.

We previously performed an open study on the treatment of neurosyphilis in patients who were allergic to penicillin, using oral minocycline, 100 mg b.i.d. for 14 consecutive days per month for 9 months [4]. We were surprised that no clinically detectable CNS or gastrointestinal side effects were registered over a total of 294 person-days of administration of minocycline, although they were actively sought by means of a follow-up questionnaire and clinical examination. Our selection of a long-acting tetracycline for treatment of our patients was made on the basis of tetracycline activity against Treponema pallidum, the satisfactory pharmacokinetics of doxycycline across the blood-brain barrier [5], and the excellent lipid solubility of minocycline [6]. However, we chose minocycline because it was the only tetracycline available in our hospital pharmacy.

Therefore, our experience supports the use of oral minocycline for CNS infections by spirochetes, including not only Borrelia burgdorferi, as suggested by Cunha [2], but also T. pallidum. In this regard, some of the disadvantages of the use of minocycline—namely, discoloration of the teeth, skin, and nails—are likely to be either irrelevant or not applicable to the majority of patients, because tertiary CNS manifestations of T. pallidum and infection most frequently appear in adults and not in teens and children. In general, this also applies to most patients with neuroborreliosis. A recent epidemiological study of Lyme disease in Europe [7] showed that the incidence of neuroborreliosis in children aged <15 years (28%) was higher than that in adults (14%). However, given the higher incidence...
of Lyme disease among adults (≥75%), a semisynthetic tetracycline could have been administered to ≥70% of the patients with neuroborreliosis.

However, we believe that the real point at issue in the previous discussion [2, 3] is represented by the possibility of safe and effective use of oral long-acting tetracyclines for tertiary manifestations of spirochetal diseases. This point is not clearly indicated in widely distributed guides for the treatment of infectious diseases [8, 9], in particular with respect to neurosyphilis and the loading dose of doxycycline for neuroborreliosis.

On the basis of clinical experience, it would seem that both doxycycline and minocycline can be used for these conditions. Until a controlled trial is performed (with, possibly, control of plasma, CSF, and tissue pharmacokinetic parameters) in patients with neurosyphilis or neuroborreliosis, only personal experience and preferences, in addition to adequate clinical monitoring, should be used to instruct the choice of drug.

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