Correspondence

Oral Pentoxifylline and Pentavalent Antimony for Treatment of Leishmaniasis: Promising but Inconclusive Evidence of Superiority, Compared with Antimony Monotherapy

To the Editor—Machado et al. [1] recently reported the results of a double-blind, placebo-controlled, randomized clinical trial that compared the effectiveness of pentoxifylline and antimony dual therapy with that of antimony monotherapy in patients with mucosal leishmaniasis. The authors concluded that dual therapy reduced healing time and was superior to antimony monotherapy for leishmaniasis eradication. However, the results should be interpreted cautiously. Critical methodologic limitations warrant attention to foster appropriate clinical interpretation.

The study by Machado et al. [1] illustrates the inability of small-sample randomization to allocate groups with comparable baseline risks for the outcome. Participation was limited to 23 participants overall—11 participants in the intervention group and 12 participants in the control group. Randomization of small study populations may introduce accidental bias from failure to maintain equal distribution of confounders between comparison groups, regardless of statistical significance [2]. Machado et al. [1] reported a lack of statistically significant differences between the 2 groups. However, the study was insufficiently powered to observe statistically significant differences, and the observed clinically relevant differences between groups suggest the introduction of bias. Previous studies have reported that older age, male sex, longer duration of symptoms, and previous cutaneous leishmaniasis may be related to risk of mucosal leishmaniasis, disease severity, and time to cure [3, 4]. The antimony plus placebo group was older and had a greater proportion of male participants, longer duration of symptoms, and greater frequency of cutaneous leishmaniasis, compared with the antimony plus pentoxifylline group; these findings indicate that the pentoxifylline group had a greater probability for eradication at baseline than did the placebo group. Consequently, a greater probability of cure in the group who received dual therapy, compared with the group who received monotherapy, may have created a positive bias away from the null (i.e., overestimated the effectiveness of dual therapy). Accidental bias offers a plausible alternative explanation for the authors’ findings, emphasizes the inadequacy of hypothesis testing to evaluate the comparability of small groups [5, 6], and underscores the necessity for a larger randomized trial.

It is unclear why Machado et al. [1] did not provide an effect estimate, such as risk difference or hazard ratio, using robust statistical techniques for small trials [7]. The failure to report an effect estimate undermines comparison. Furthermore, effect estimates facilitate cost-effectiveness evaluations, which are particularly important for resource-limited regions where leishmaniasis commonly occurs. Effect estimates with corresponding confidence intervals for the outcome would have more appropriately elucidated the potential clinical use of dual therapy.

The small sample size used by Machado et al. [1] greatly limited potential inferences because of the failure to produce comparable groups after randomization and compromised statistical testing. Therefore, the study may not constitute decisive evidence for the superiority of pentoxifylline and antimony dual therapy for mucosal leishmaniasis. Future studies should recognize the limitations of hypothesis testing and P values to evaluate whether small groups are comparable after randomization [5, 6]. Ultimately, small sample sizes may lead to inconclusive inferences and warrant conservative interpretations from a clinical perspective until further evidence is available.

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Reply to Ojha et al.

To the Editor—Our article in Clinical Infectious Diseases [1] has generated a critical commentary from Ojha et al. [2]. The basis of these criticisms centers around perceived bias in the assignment of patients to the 2 treatment groups in the context of the small sample size in our study; the authors claim that the antimony group was older, included more men, and had longer duration of symptoms. Then, Ojha and colleagues link this potential unequal distribution to the statement, “Previous studies have reported that older age, male sex, longer duration of symptoms, and previous cutaneous leishmaniasis may be related to risk of mucosal leishmaniasis [ML], disease severity, and time to cure [3, 4]” [2, p. 1104].

We disagree with these claims by Ojha et al. [2]. First, neither age, sex, nor longer duration of disease in the group who received antimony plus pentoxifylline, compared with the group who received antimony plus placebo, was statistically significantly different. In our trial [1], we could not identify major issues that make us believe that our randomization failed. This was partially supported by our randomization process and the reasonable balance observed in patients’ characteristics between the 2 treatment arms.

Second, the studies cited by Ojha et al. [2–4] did not examine or report differences in severity of mucosal disease or response to therapy as variables that were influenced by age, sex, or prolonged disease. Specifically, the study by Castellucci et al. [3] (L. Castellucci is from our group) was a retrospective cohort study that evaluated genetic influences in the development of ML. This study showed a familial aggregation of ML, with no data regarding the severity of ML in these patients. In the study by Machado-Coelho et al. [4], older age, male sex, and longer duration of cutaneous leishmaniasis were found to be risk factors for development of ML. This study did not report any information about the severity of ML or treatment outcome, and it certainly did not link these with age, sex, and duration of cutaneous leishmaniasis. Therefore, neither study cited by Ojha et al. [2] provide support for their claims that these risk factors may impact therapeutic outcome, which suggests that the claims lack scientific merit and are erroneous.

In addition to the absence of differences in these variables between the 2 groups, there was also no difference between groups in terms of the severity of mucosal disease (assessed by an otorhinological examination). Although the severity of ML lesions may vary widely [5], only patients with deep ulcers and nasal septum involvement were enrolled in our study [1]. It is important to note that the randomization of severe forms of ML did not differ between the 2 treatment groups.

We agree that large trials are important and achieve higher statistical power and more quantitative documentation regarding the effects of treatment than do small trials. However, ML is a rare disease predominantly associated with Leishmania braziliensis infection, which only occurs in 3% of the patients who develop cutaneous leishmaniasis [6]. Despite the high incidence of disease in our study region in Corte de Pedra, Brazil, we see only ~20 new cases of ML per year, and the majority of the patients have an early stage of disease. Therefore, a larger randomized clinical trial of severe ML would require a multicenter study. Ojha et al. [2] should acknowledge that, despite the issues and problems associated with small studies, they are sometimes the only feasible initial approach to the study of diseases that occur with low frequency in difficult-to-access populations. Thus, the tremendous value of small studies should not be minimized.

Lastly, we agree that more robust statistical tests are necessary for analyzing small studies in which large sample theory is violated, and parametric assumptions are not tenable in general. Therefore, in our original article [1], we used nonparametric methods, recognizing that we were working with a small sample size. There are several methods that can be used as robust statistical techniques for small trials [7]. However, we do not believe that these alternatives would be helpful for statistical estimation and inference in studies involving small sample sizes, although different methods may handle different aspects of the problem better than others.

In our article [1], we were cautious in our recommendations. Given our current comments in response to Ojha et al. [2], our interpretation of the observations and conclusions remain unchanged: “pentoxifylline combined with Sb” [antimony] is, therefore, a therapeutic choice for patients with mucosal leishmaniasis who have advanced forms of the disease” [1, p. 792]. We do not claim that a larger study is not needed; indeed, it is our hope to inspire a larger study through our novel and intriguing findings.

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References


CORRESPONDENCE • CID 2007:45 (15 October) • 1105
Comparison of 2 Studies of Treatment of Invasive Aspergillosis

To the Editor—Congratulations to Cornely et al. [1] for completing another important randomized study of invasive aspergillosis (IA). This is the second largest completed such study, and enrollment occurred remarkably fast, being completed in 18 months. At face value, it would be easy to make 2 conclusions from this study with respect to the treatment of IA: (1) the efficacy of 3 mg/kg of liposomal amphotericin B is essentially equivalent to that of 10 mg/kg liposomal amphotericin B (although the latter is slightly more toxic), and (2) liposomal amphotericin B has the same efficacy as voriconazole. Although the first conclusion is probably valid, the second needs further analysis and should be questioned.

I, as well as others, have demonstrated very different response rates among different patient groups with IA [2, 3], and these response rates depended on how early the diagnosis was achieved [4, 5]. Other factors that are important for a successful outcome include the dose of corticosteroids once the diagnosis has been made [6]. For example, it has been known for many years that patients with IA after allogeneic hematopoietic stem cell transplantation (HSCT) generally experience a poor outcome, with an associated mortality rate that is typically >75%, whereas patients with acute leukemia whose neutropenia resolves have a mortality rate that is generally <50% and, in some series, <30%. These differing outcomes are critically important in interpreting therapeutic trials of IA, because different trials enroll different proportions of at-risk patients. This is particularly germane to a comparison of the study by Cornely et al. [1] with the randomized study by Herbrecht et al. [7], in which voriconazole is compared with standard amphotericin B.

Many clinicians would argue that patients with acute leukemia are “at high risk” and, therefore, should be considered to be in the same risk group as those who have received an allogeneic HSCT, but a critical distinction needs to be made between the high risk of acquisition of IA and a high risk of dying of IA. These risks differ markedly between patients with acute leukemia (who have a moderate to low risk of death if treated) and patients with allogeneic HSCT (who, even if treated, have high risk of death), as they do between patients with HIV infection and patients with AIDS, in whom the risk of acquisition of IA is low (2%–4%), but the risk of dying of IA exceeds 80% [8, 9]. A similar contrast applies between risks of IA acquisition and IA-related death in liver transplant recipients [9].

In table 1, the different underlying conditions, enrollment characteristics, and outcomes from the 2 trials [1, 7] are summarized. For both trials, modified intent-to-treat populations are shown. This table shows considerable differences between the studies. For example, in the study by Cornely et al. [1], >90% of the patients had hematological malignancy (including autologous HSCT), whereas <60% of the patients in the study by Herbrecht et al. [7] had hematological malignancy, with a higher proportion of allogeneic HSCT recipients and patients with AIDS, (P < .001). However, the biggest contrast between the studies was with respect to the confirmation of disease. Two-thirds of the patients in the study by Herbrecht et al. [7] had microbiologically confirmed disease, whereas <40% of the patients in the study by Cornely et al. [1] had microbiologically confirmed disease (P < .001). Antigen testing was not performed as a direct part of the study by Herbrecht et al. [7]; therefore, all microbiological confirmation related to histological examination, culture, and microscopic examination findings. Furthermore, >20% of the cases in the study by Cornely et al. [1] were confirmed by antigen testing only (usually an early diagnostic feature), and ~15% of cases were otherwise microbiologically confirmed by other methods. This major difference is accounted for by the use of halo signs (an early sign of infection [5, 10]), which were used at enrollment for approximately one-third of the patients in the study by Herbrecht et al. [7], compared with nearly 60% of the patients in the study by Cornely et al. [1] (P < .001). In accordance with this, the proportion of patients with proven IA, usually achieved later during the course of disease, was much lower in the study by Cornely et al. [1] (9% vs. 39%; P < .001). Thus, the study by Cornely et al. [1] enrolled many more patients with early disease and a higher proportion of patients with a “good prognosis,” compared with the study by Herbrecht et al. [7].

In the study by Herbrecht et al. [7], all evaluations were performed at 12 weeks, regardless of how long the patients had received the initially assigned therapy, although a secondary analysis examined responses at the completion of assigned therapy. In the study by Cornely et al. [1], responses were evaluated at the end of treatment, which had a median duration of 14–15 days but ranged from 1 day to 60 days. Eighty-four–day (12-week) responses were not reported in the study by Cornely et al. [1], although survival was reported. In the study by Herbrecht et al. [7], major efforts were made by the Data Review Committee to distinguish patients who experienced partial responses, who had to have at least 50% improvement in their radiologic abnormalities, from those who experienced less improvement, who were categorized as having a stable response. Such efforts included clearly defined a priori criteria, duplicate assessments, and clinician input into the final
Table 1. Comparison of patient characteristics at enrollment and outcomes of the voriconazole versus amphotericin B study by Herbrecht et al. [7] and the dose comparison study of liposomal amphotericin B by Cornely et al. [1].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Modified intent-to-treat subgroup</th>
<th>Herbrecht et al. [7]</th>
<th>Cornely et al. [1]</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Voriconazole group, % of patients</td>
<td>AmB group, % of patients</td>
<td>Total no. of patients</td>
<td>3 mg/kg of L-AmB group, % of patients</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>52.1</td>
<td>58.6</td>
<td>153</td>
<td>93</td>
</tr>
<tr>
<td>Autologous HSCT</td>
<td>4.2</td>
<td>4.5</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>25.7</td>
<td>22.6</td>
<td>67</td>
<td>16</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>6.2</td>
<td>3.8</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>4.2</td>
<td>5.3</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>7.6</td>
<td>5.3</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Diagnostic modalities</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Microbiologically confirmed</td>
<td>68.1</td>
<td>63.2</td>
<td>182</td>
<td>38</td>
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<tr>
<td>Antigen testing only</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Culture and histologic and microscopic examinations</td>
<td>68.1</td>
<td>63.1</td>
<td>182</td>
<td>13</td>
</tr>
<tr>
<td>Halo sign only</td>
<td>31.9</td>
<td>36.8</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td>Certainty of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven IA</td>
<td>46.5</td>
<td>30.8</td>
<td>108</td>
<td>7</td>
</tr>
<tr>
<td>Probable IA</td>
<td>53.5</td>
<td>69.2</td>
<td>169</td>
<td>93</td>
</tr>
<tr>
<td>Outcome of IA only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success at 12 weeks</td>
<td>52.8</td>
<td>31.6</td>
<td>118</td>
<td>NA</td>
</tr>
<tr>
<td>Success at end of therapy</td>
<td>53.5</td>
<td>21.8</td>
<td>106</td>
<td>50</td>
</tr>
<tr>
<td>Favorable response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>20.8</td>
<td>16.5</td>
<td>52</td>
<td>1^c</td>
</tr>
<tr>
<td>Partial response</td>
<td>31.9</td>
<td>15.0</td>
<td>66</td>
<td>49^c</td>
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<tr>
<td>Unfavorable response</td>
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<td></td>
<td></td>
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<tr>
<td>Stable</td>
<td>5.6</td>
<td>6.0</td>
<td>18</td>
<td>7^c</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>38.2</td>
<td>58.6</td>
<td>153</td>
<td>34^c</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>3.5</td>
<td>3.8</td>
<td>10</td>
<td>6^c</td>
</tr>
<tr>
<td>Survival at 12 weeks</td>
<td>70.8</td>
<td>57.9</td>
<td>179</td>
<td>72</td>
</tr>
<tr>
<td>Success in various subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 weeks in Europe^g</td>
<td>57.0</td>
<td>36.9</td>
<td>170</td>
<td>50</td>
</tr>
<tr>
<td>At 12 weeks in the United States^g</td>
<td>46.6</td>
<td>22.5</td>
<td>107</td>
<td>...</td>
</tr>
<tr>
<td>In the context of hematological malignancy</td>
<td>63.0</td>
<td>38.1</td>
<td>83</td>
<td>53</td>
</tr>
<tr>
<td>In the context of allogeneic HSCT</td>
<td>32.4</td>
<td>13.3</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>In patients with neutropenia at baseline</td>
<td>50.8</td>
<td>31.7</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>In patients with pulmonary IA</td>
<td>54.5</td>
<td>34.2</td>
<td>107</td>
<td>51</td>
</tr>
<tr>
<td>In patients with extrapulmonary IA</td>
<td>42.9</td>
<td>12.5</td>
<td>11</td>
<td>33</td>
</tr>
</tbody>
</table>

NOTE. AmB, conventional amphotericin B; HSCT, hematopoietic stem cell transplantation; IA, invasive aspergillosis; L-AmB, liposomal AmB; NA, not applicable.

a Determined by χ² test.
b P value refers to “culture and histologic and microscopic examinations” and “halo sign only.”
c O. Cornely, personal communication.
d The vast majority of patients enrolled in substudy 150–307 [7] were from Europe, and the largest enrolling countries were Germany and France.
e Most of the patients in the 150–602 substudy (reported by Herbrecht et al. [7] as part of the whole study) were from the United States, but substantial proportions of these patients were enrolled from all over the world.

...
with a good outcome overall, such cases would clearly be classified as treatment failure under current conventional criteria. Given that the majority of patients in the study by Cornely et al. [1] were very similar to those in the study by Caillot et al. [13], these divergent findings require an explanation. The precise details of the radiologic measurements and the algorithm for assigning response in the study by Cornely et al. [1] need to be elaborated.

A remarkable difference between the studies by Herbrecht et al. [7] and Cornely et al. [1] involved the rate of complete responses, which was >20% and 1%–2%, respectively. This, in part, probably reflects the 2-week assessment time in the study by Cornely et al. [1] and/or inferior efficacy. Are 12-week responses available? Complete response is the best outcome for patients, and a rate of only 1%–2% is clearly unsatisfactory.

It has been clearly demonstrated that early treatment results in better outcome, and the study by Cornely et al. [1] gives data on early treatment in patients derived almost entirely from hematologic units. This is laudable, and all of the investigators are to be congratulated for achieving such good results with relatively low mortality. The results of the study by Cornely et al. [1] provide indirect support for earlier diagnosis contributing to a good outcome. These data are in accord with decreasing mortality rates associated with IA in patients in hematologic units in other centers [13, 15].

In summary, Cornely et al. [1] have clearly demonstrated that 3 mg/kg of liposomal amphotericin B is the appropriate dose for the treatment for IA and that larger doses are not of value. The authors have not shown that this drug is as good as voriconazole, because their study enrolled broadly a better prognostic group (more patients with hematologic malignancy), achieved the diagnosis earlier, and probably used less stringent criteria for determining partial responses radiologically. There remains a very significant question mark over the criteria used for assessing a partial response, compared with a stable response. Voriconazole should remain the drug of first choice for all patients with IA if it can be administered and if drug interactions do not prevent its use.

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Reply to Denning

To the Editor—We appreciate Dr. Denning's [1] comparison of the 2 clinical trials of antifungal agents [2, 3]. However, there are pitfalls in drawing conclusions from historical comparisons between randomized trials.

Both trials had similar designs, but diagnostic tools and strategies have evolved since the earlier trial. Multislice-CT and galactomannan screening enhanced detection of invasive aspergillosis (IA) in our trial.

Patients with acute leukemia and other malignancies cannot be lumped into a “good prognostic” group. Instead, patients
with acute leukemia are associated with a substantial mortality attributable to IA [4]. Multivariate logistic regression analyses of factors associated with higher mortality are cited in our article [3] and have been presented in greater detail elsewhere [5]. Significant survival differences were found for allogeneic stem cell transplantation versus no transplantation (40% vs. 71%; \( P < .001 \)), uncontrolled versus controlled underlying malignancy at baseline (54% vs. 81%; \( P < .001 \)), and persistent versus resolved neutropenia at the end of study drug treatment (46% vs. 79%; \( P < .001 \)).

Our trial [3] included a high proportion of patients with the poor prognostic factor of uncontrolled malignancy. This factor was not reported in the voriconazole study [2]. Our trial also included a higher proportion of neutropenic patients (73% of the patients had neutropenia at baseline). In the voriconazole trial, 45% of the patients were reported to have neutropenia, defined as neutropenia being present within 2 weeks before baseline, and thus, neutropenia could have resolved in many patients by the time of study entry.

Both trials used similar diagnostic criteria for IA, including the diagnosis of probable disease in stem cell transplant recipients and neutropenic patients on the basis of presence of a halo sign. This has recently been supported by other researchers [6]. There was a higher percentage of probable IA on the basis of a “halo sign only” in stem cell transplant recipients and neutropenic patients in the trial of liposomal amphotericin B (AmBiLoad trial) [3], compared with the voriconazole trial [2]. However, the number of “proven” cases that Dr. Denning [1] cites for the voriconazole trial is incorrect. That trial used a definition of “definite” IA based on the presence of various criteria, including Aspergillus species isolated from bronchoalveolar lavage specimens. According to the subsequently published European Organization for Research and Treatment of Cancer/Mycoses Study Group definitions [7], cases involving positive bronchoalveolar lavage culture results are classified as “probable.” The “halo sign only” subgroups in both studies had better response rates, compared with the patients with microbiologically documented infection, highlighting the importance of early treatment [2, 3, 8, 9].

Data review board evaluations in our study were based on those of the voriconazole study. The AmBiLoad trial was conducted according to the highest standards, using appropriate independent, blinded review boards. The rigorous methodology was highlighted by an external expert [10]. The criterion for partial radiologic response, as stated in the protocol, was major improvement in radiographic abnormalities on relevant scans performed at end of treatment, as compared to baseline. Factors considered for major improvements include (1) disappearance of halo sign and/or appearance of air crescent sign and/or (2) decreased estimated size of lesions. Development of new lesions was assessed as treatment failure. An increase in the size of lesions associated with recovery of neutrophils, as described by Caillot et al. [11], was classified as treatment failure if this was an end-of-treatment finding.

The 1%-2% complete response rate is indicative of substantial but incomplete clearing of CT abnormalities, as expected after a median duration of treatment of 14–15 days.

Also, because of the availability of more-sensitive multislice-CT scanners during the time our trial was conducted, there was a greater ability to detect minimal residual pulmonary disease at the end of treatment, which was assessed as a partial, rather than a complete, response by our data review board.

Because of its rigorous trial design, the AmBiLoad trial [3] established the effectiveness of liposomal amphotericin B for treatment of IA. Because no direct comparative trial has been performed for voriconazole versus liposomal amphotericin B, we did not claim equivalence of the 2 drugs for the treatment of IA. Voriconazole and liposomal amphotericin B are the only antifungal agents for which randomized trials using the current diagnostic and response evaluation criteria for IA have been performed. Both demonstrate response rates of ~50% and 12-week survival of >70%. For clinicians making evidence-based treatment decisions for their patients with IA, both drugs can be considered to be good therapeutic options.

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Leptospirosis in Egypt: Is It the Tip of an Iceberg?

To the Editor—The description by D. J. Larrey, in 1812, of the jaundice that affected Napoleon’s troops during the French campaign in Egypt prompted subsequent writers to postulate that it was probably Weil disease [1].

To date, all studies of leptospirosis in Egypt have been conducted by the US Naval Medical Research Unit, Number 3 (NAMRU-3), because the microscopic agglutination test (MAT; the gold-standard serologic test) had never been available in Egyptian governmental laboratories. For example, in 1972, a multicenter serological survey revealed Leptospira antibodies in 5.6% of abattoir workers and patients with different diseases and in 4%–44% of live-
variable results. Cross-reaction of IgM antibodies was the lack of MAT data to confirm definitively cases in which the tests gave highly variable results. Cross-reaction of IgM antibodies with those associated with other acute infections was described in the manufacturer’s leaflet. However, this study increased physicians’ awareness of leptospirosis, particularly when associated with acute renal failure.

Although these studies document a highly endemic state of leptospirosis in Egypt, they did not assess risk factors and morbidity and mortality rates among the confirmed cases in which L. icterohemorrhagiae was predominant (the major serotype associated with fatal human leptospirosis). Thus, we are left wondering whether these data constitute the tip of an iceberg.

Certainly, physicians in fever hospitals are the only health care workers in close contact with patients who have infectious diseases. Therefore, the Ministry of Health and Population has to support research units in some fever hospitals in Egypt. For leptospirosis, nationwide community-based and case-control studies should be conducted through these units, in conjunction with epidemiologists and veterinarians.

A successful example of such collaboration was established for brucellosis through personal efforts in our community [5]. There is a need to set up reference laboratories for leptospirosis in fever hospitals provided with high-quality MAT and PCR amplification, which has proved to be sensitive for early diagnosis of leptospirosis [4].

In conclusion, an integrated, multidisciplinary system for zoonoses should be supported in Egypt. Leptospirosis is the best area to start, because it is an officially nonreported infection, even though it has been found to be endemic. Attempts to clarify its epidemiology could be made by research units in fever hospitals and thereby lead to implementation of a national control program.

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