Reply

Sir,

In our study [1], nine patients completed the 6-month pulse cyclophosphamide therapy, a number that approaches that of the study by Bircan and Kara [2]. However, only one (11.1%) of them has maintained remission 2 years after stopping cyclophosphamide. Additionally, in the earlier study concerning oral cyclophosphamide in steroid-dependent nephrotic patients [3], despite the fact that steroids were continued throughout the 12-week cyclophosphamide course, the authors concluded that it is unlikely that this could be responsible for better results according to their earlier study in 1981. On the other hand, cumulative steroid dose was higher in the study by Bircan and Kara [2]. Also, the protocol of steroid withdrawal after stopping cyclophosphamide and the percentage of patients that became steroid independent were not mentioned. Moreover, the claim that ‘long-term side effects were absent’ cannot be completely accepted if there was no testing for gonadal toxicity.

Actually, we are sceptical about the conclusion in Bircan and Kara’s study [2] that intravenous cyclophosphamide is the drug of choice for steroid-dependent nephrotic syndrome. Nevertheless, it remains possible that previous adjunctive therapy, renal pathology (neither of which were indicated in the study by Bircan and Kara), racial and genetic factors and selection criteria have an effect on the results obtained.

Conflict of interest statement. None declared.

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Table 1. Serum lipid parameters in patients with severe leptospirosis on admission and 1 month after their recovery in comparison with patients with acute bacterial infections and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients with severe leptospirosis on admission (n = 5)</th>
<th>Patients with severe leptospirosis 1 month after recovery (n = 5)</th>
<th>Patients with acute bacterial infections on admission (n = 45)</th>
<th>Control population (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Chol (mg/dl)</td>
<td>89 ± 20a</td>
<td>178 ± 35b</td>
<td>98 ± 19</td>
<td>204 ± 42</td>
</tr>
<tr>
<td>TRG (mg/dl)</td>
<td>292 ± 51a,c</td>
<td>143 ± 48b</td>
<td>127 ± 61</td>
<td>120 ± 98</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>19 ± 7a</td>
<td>29 ± 8b</td>
<td>20 ± 8</td>
<td>42 ± 8</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>17 ± 10a,c</td>
<td>120 ± 27b</td>
<td>59 ± 19</td>
<td>120 ± 36</td>
</tr>
<tr>
<td>ApoAI (mg/dl)</td>
<td>56 ± 19a</td>
<td>97 ± 20b</td>
<td>64 ± 22</td>
<td>146 ± 24</td>
</tr>
<tr>
<td>ApoB (mg/dl)</td>
<td>158 ± 18a,c</td>
<td>146 ± 23</td>
<td>66 ± 20</td>
<td>102 ± 26</td>
</tr>
<tr>
<td>ApoE (mg/l)</td>
<td>99 ± 25a,c</td>
<td>40 ± 18b</td>
<td>47 ± 23</td>
<td>39 ± 11</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>1.0 (0.8–3.2)a,c</td>
<td>2.8 (0.8–13.2)b</td>
<td>3.85 (0.8–33.2)</td>
<td>7.9 (0.8–56.0)</td>
</tr>
</tbody>
</table>

All values are expressed as means ± SD, except for Lp(a), which is expressed as median (range). *P < 0.05 for comparison between leptospirosis patients on admission and control subjects and *P < 0.05 between leptospirosis patients on admission vs patients with acute bacterial infections, by unpaired t-test for all parameters, except for Lp(a), where the Kruskal–Wallis test was used. **P < 0.05 for comparison between leptospirosis patients on admission vs leptospirosis patients 1 month after recovery, by paired t-test for all comparisons, except for Lp(a) where the Wilcoxon matched pairs test was used. T-Chol, total cholesterol; TRG, triglycerides; HDL-C, high-density lipoprotein cholesterol.
those with acute bacterial infections were found (Table 1). Finally, the abnormalities of the serum lipid profile tended to return to normal 1 month after recovery from the acute disease (Table 1).

Alterations of the serum lipid profile in the course of acute bacterial and parasitic infections have been described [2,3]. These alterations are mainly cytokine-mediated: interleukin-6 stimulates the LDL receptor gene expression, resulting in decreased levels of total and LDL cholesterol [4]; tumour necrosis factor-α (TNF-α) decreases the activity of lipoprotein lipase and stimulates hepatic triglyceride synthesis, thus resulting in hypertriglyceridaemia [5]; and transforming growth factor-β1 and TNF-α, which predominate in severe inflammation, inhibit the expression of the Apo(a) gene [6], resulting in a negative acute-phase behaviour of Lp(a) [3]. Excess of these cytokines in severe leptospirosis might be responsible for the more pronounced increase in the levels of triglycerides and decrease in the levels of LDL-C and Lp(a) compared to patients with common bacterial infections, thus reflecting the severity of the underlying inflammatory reaction. Furthermore, markedly elevated levels of ApoE during the acute phase of the disease, possibly due to increased ApoE synthesis by the activated macrophages and/or the liver, might contribute to the observed hypertriglyceridaemia, since excess ApoE has been shown to accelerate the secretion rate and decrease the efficiency of lipolysis of the triglyceride-rich lipoproteins [7]. This finding is in agreement with our previous observations that ApoE behaves as a positive acute-phase protein in patients with infection [2,3]. Finally, we have observed a similar pattern of pronounced abnormalities in lipoprotein metabolism in patients with hantavirus-related haemorrhagic fever (data not shown).

We conclude that not only hypertriglyceridaemia, but also markedly decreased levels of LDL-C and Lp(a) as well as increased levels of ApoE, albeit not specific, are useful markers in suspected cases of severe leptospirosis, possibly related to the severity of the underlying inflammatory process. Measurement of serum lipids, therefore, could be useful in assessing the severity of the underlying infection in acute febrile patients.

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6. Ramharack R, Barkalow D, Spahr MA. Dominant negative effect of TGF-β1 and TNF-α on basal and IL-6-induced lipoprotein (a) and apolipoprotein (a) mRNA expression in primary monkey hepatocyte cultures. Arterioscler Thromb Vasc Biol 1998; 18: 984–990

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Reply

Sir,

We thank Liberopoulos et al. for their interest in our article on acute renal failure in severe leptospirosis [1]. We are pleased to reply to their comments and to provide complementary results. In addition to hypertriglyceridaemia, we found in our study that total cholesterol levels were 157 ± 49 mg/dl (mean ± SD) and that there was a significant inverse correlation between total cholesterol and bilirubin levels ($r = -0.50, P < 0.05$). We confirm, therefore, that not only hypertriglyceridaemia, but also relative hypocholesterolaemia were associated with severe leptospirosis. Changes in the serum lipid profile could be explained by the existence of hepatic dysfunction and/or by the direct action of inflammatory cytokines. Thus, when the hepatic function falls, the activity of a key enzyme in lipic hepatic metabolism, lecithin cholesterol acyltransferase (LCAT), is reduced and there exists an inverse relation between LCAT and plasma bilirubin levels [2,3]. On the other hand, cytokines may affect plasma levels of triglyceride, cholesterol and lipoproteins by modulating the synthesis and secretion of apolipoproteins, lipolytic enzyme activities or the expression of lipoprotein receptors [4]. A number of cytokines, including tumour necrosis factor-α and the interferons, increase serum triglyceride levels due to an increase in hepatic very low-density lipoprotein (VLDL) secretion and production or delayed clearance secondary to a decrease in lipoprotein lipase activity and/or apolipoprotein (Apo) E levels on VLDL. Moreover, cytokines decrease the concentration of cellular ApoAI mRNA and the hepatic synthesis and/or secretion of apolipoproteins in a dose-related fashion, which may explain, in part, the hypocholesterolaemia seen during acute inflammation [5]. We agree with Liberopoulos et al. that measurement of the serum lipid profile in suspected cases of leptospirosis might be useful in assessing the severity of the underlying infection in these patients [6,7].

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