Leptospirosis and acute renal failure – clinical experiences and a review of the literature

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Summary
About 50 cases of leptospirosis are diagnosed each year in the United Kingdom, with an overall mortality of 5%. Renal failure, in association with jaundice, is commonly held responsible for this figure. Over a period of 18 years, 6 cases of leptospirosis complicated by renal failure were treated at the Royal Air Force Renal Unit; there were 4 survivors. The 2 deaths occurred before the unit policy of daily haemodialysis and total parenteral nutrition, and were both from haemorrhagic complications.

The authors believe that patients with leptospirosis and progressive renal impairment should be managed in renal units experienced in the management of the hypercatabolic patient, and that this should improve their prognosis.

Introduction
The incidence of leptospirosis in the U.K. is low, about 50 cases being diagnosed each year. It is now well recognized that Weil’s disease and leptospirosis are not synonymous and that serogroups other than Leptospira icterohaemorrhagiae may cause a similar clinical syndrome.

Acute renal failure (ARF) occurs in about 10% of cases and the case histories below demonstrate the presentation, course and management of those admitted to the R.A.F. Renal Unit.

Case histories
Case 1
A 26-year-old serviceman, a keen water skier, presented in October 1959 with a one-week history of headache, backache, malaise and anorexia. His temperature was 102°F (39°C) and a diagnosis of influenza was made. Four days later he developed myalgia and became jaundiced and oliguric. On admission to hospital his blood urea was 50 mmol/l (300 mg/100 ml). Platelet count was $160 \times 10^9$/l and the prothrombin time was normal. Haemodialysis was started but, despite 5 dialyses, he died of a cerebral haemorrhage, confirmed at post-mortem. The kidneys showed tubular necrosis and areas of interstitial infiltration with mononuclear cells. Scattered haemorrhages were also present. Special stains demonstrated the presence of leptospires in the kidneys.

Case 2
A 43-year-old slaughterman presented in October 1959 with a 6-day history of fever, headache and vomiting. He developed a petechial skin rash on the trunk, conjunctival suffusion, jaundice and oliguria. On admission to hospital his blood urea was 93.3 mmol/l (560 mg/100 ml). Routine coagulation studies were normal. He was transferred to Halton where he required one haemodialysis before a spontaneous diuresis ensued and renal function returned to normal.

Case 3
A 49-year-old schoolmaster presented in August 1966 with a 10-day history of fever, diarrhoea and vomiting. Before this, he had been wading barefoot in local marshland. Two days after presentation he became jaundiced and developed petechial haemorrhages on the trunk. Oliguria ensued and on admission to hospital the blood urea was 78.3 mmol/l (470 mg/100 ml). He was haemodialysed once but developed severe gastro-intestinal bleeding, which eventually necessitated partial gastrectomy. He died postoperatively. The gastrectomy specimen showed numerous acute gastric erosions with fresh
bleeding. At post-mortem the kidneys showed diffuse tubular necrosis with a severe interstitial inflammatory infiltrate. Leptospires were not identified.

Case 4
A 34-year-old coalman presented in October 1973 with a history of malaise, abdominal pain and fever. Two days later he developed a frontal headache with signs of meningism, a maculopapular rash on the trunk and arthralgia of the right wrist. On admission to hospital his blood urea was 64 mmol/l (384 mg/100 ml) and he was found to be jaundiced and oliguric. Peritoneal dialysis was initially started but because of his hypercatabolic state he was transferred to Halton for haemodialysis. On arrival, conjunctival suffusion, severe oral ulceration and gastro-intestinal bleeding were noted. Platelet count was 300 x 10^9/l and routine coagulation studies normal. He received 5 haemodialyses at daily intervals and total parenteral nutrition. A spontaneous diuresis ensued. Renal function was normal on review.

Case 5
A 23-year-old service man, who had recently been pot-holing, was admitted in July 1977 with a 3-day history of headache, backache and malaise. He was febrile and oliguric. Two days later he became jaundiced and developed gastro-intestinal bleeding and haemoptysis. Platelet count was 200 x 10^9/l and the British Comparative Ratio (BCR) 1·6. Vitamin K supplements were given to correct this. The blood urea was 100 mmol/l (600 mg/100 ml) and he required 10 haemodialyses at daily intervals before a diuresis ensued. Catabolism was controlled by the use of total parenteral nutrition. Renal function was normal on review.

Case 6
A 46-year-old pig farmer presented in November 1977 with a one-week history of fever, headache and myalgia. Seven days later he became jaundiced, oliguric and developed a maculopapular rash on the trunk. On admission to hospital his blood urea was 40 mmol/l (240 mg/100 ml). Platelet count was 300 x 10^9/l and the BCR 1·3. Vitamin K supplements were given to correct this. After 7 haemodialyses at daily intervals, and catabolic control by total parenteral nutrition, there was a diuresis and renal function returned to normal.

Laboratory diagnosis
The diagnosis of leptospirosis can be confirmed by microscopy, culture or serology. Microscopic diagnosis is made by dark ground or phase contrast techniques, but neither method is entirely reliable. In experienced hands, it may nevertheless be useful with counts of more than 200 000 leptospires/ml of blood or urine (Tops and Wehrle, 1972).

Culture of leptospires from blood, CSF and urine is the only absolute proof of leptospirosis and no other method will firmly identify the agglutinogenic serogroup (Turner, 1967). Isolation was not attempted in the present cases because of the unavailability of suitable media at the time.

Most laboratories use serological methods for the diagnosis of leptospirosis. This relies upon the CFT, and the Leptospirosis Reference Laboratory with more specific agglutination reactions using pools of killed antigens each representing one serogroup (Turner, 1968). The correlation between the CFT and agglutination reactions is so good that the CFT is quite adequate for the diagnosis of leptospirosis, the actual serotype of the infecting leptospire being clinically unimportant (Turner, 1968). Since the CFT antibodies often rise earlier than the agglutinins they are clinically more useful.

As the rise in CFT is usually early and rapid, high plateau results are common, with the demonstration of rising titres somewhat uncommon, as the paired sera that are usually supplied rarely include sera taken early enough in the illness. As CFT antibodies tend to fall early, residual titres are not a problem. Agglutination titres are rarely of clinical importance but provide useful confirmation and have epidemiological significance.

Discussion
There are about 50 cases of human leptospirosis diagnosed each year in the U.K. with a mortality of 5% (Turner, 1975). Heath, Alexander and Galton, (1965) reported a mortality of 7% in a series of 322 recorded cases of leptospirosis in the U.S.A.

Renal involvement in leptospirosis occurs in about 50% of cases. In the series of Heath et al. (1965) features included pyuria (35%), haematuria (27%), raised blood urea (26%), proteinuria (19%), and dysuria (5%); oliguria and anuria occurred in 10%. The fatalities occurred in those patients where renal failure was associated with jaundice. Two other factors associated with an increased mortality were age over 60 years and co-existent unrelated disease.

The presence of proteinuria, haematuria, pyuria and casts, tends to occur towards the end of the leptospiraemic phase of the illness between 4 and 7 days. Azotaemia, not necessarily associated with oliguria, occurs in approximately 25% of patients and is usually associated with the presence of jaundice. In 75% of this group the blood urea does
not exceed 16.6 mmol/l (100 mg/100 ml) (Beeson and McDermott, 1975).

Histological features of human leptospirosis have been obtained from both renal biopsy (Sitprija and Evans, 1970; Barratt-Connor, Child and Carter, 1970) and experimental studies. The characteristic lesion is in the tubule. Proximal and distal convoluted tubules are dilated and their lining cells flattened or necrotic. In severe cases, tubulorrhexis is seen, together with interstitial oedema and lymphocytic infiltration. Electron microscopy (De Brito et al., 1965, 1967; Marshall, 1974) shows the organisms concentrated around the tubules and in the tubular lumen. A striking feature is damage to the brush border. Glomeruli show focal thickening of the basement membrane without the presence of electron dense deposits. A glomerulitis is rare. The pathogenesis of acute renal failure in leptospirosis is not fully understood. De Brito (1968) considered the changes to be secondary to a toxin, but a vascular disturbance is a possibility. Sitprija (1968) considered acute renal failure in leptospirosis to be a result of ECF depletion, but in a subsequent paper with Evans (Sitprija and Evans, 1970), interstitial damage was cited as the most important factor.

**TABLE 1. Summary of laboratory findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum specimen day of illness</th>
<th>Leptospirobl complement fixation test</th>
<th>Leptospiral agglutinations</th>
<th>Leptospires demonstrated by darkground microscopy</th>
<th>Post-mortem tissue</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6th</td>
<td>Negative</td>
<td>L. icterohaemorrhagiae 1 : 3000</td>
<td>No</td>
<td>Yes, in kidneys</td>
<td>Died of cerebro-vascular accident</td>
</tr>
<tr>
<td></td>
<td>14th</td>
<td>—</td>
<td>L. canicola 1 : 3000</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7th</td>
<td>Nil obtained</td>
<td>L. icterohaemorrhagiae 1 : 3000</td>
<td>No</td>
<td>—</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>—</td>
<td>L. canicola negative</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7th</td>
<td>Multiple cross reactions 1 : 100–1 : 300</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Not found</td>
</tr>
<tr>
<td></td>
<td>11th</td>
<td>—</td>
<td>Multiple cross reactions 1 : 100–1 : 300</td>
<td>—</td>
<td>—</td>
<td>Died of cardiac arrest post-op. for gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>4</td>
<td>12th</td>
<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>Yes</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td>17th</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4th 1 : 1280</td>
<td>Multiple strong cross reactions 1 : 300</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td>9th 1 : 1280</td>
<td>Fewer at 1 : 1000</td>
<td>—</td>
<td>No</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple strong cross reactions 1 : 300</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7th 1 : 1280</td>
<td>Multiple strong cross reactions 1 : 300</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td>13th 1 : 1280</td>
<td>Fewer at 1 : 1000</td>
<td>—</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**ARF occurs in approximately 10% of diagnosed cases and in the U.K. this amounts to about 5 cases per year. In this paper are described 6 cases referred to the Royal Air Force Renal Unit over an 18-year period, 3 since 1974. Overall mortality in this series was 33%. However, both deaths occurred in the early days of dialysis and the last 3 cases have all survived.**

Recent reviews of leptospirosis stress the importance of early treatment of renal failure by dialysis, particularly as the disease is usually self-limiting. Renal function returns to normal in survivors (Simpson et al., 1967).

Once renal failure has developed, treatment should preferably be performed in a specialized renal unit. The complications of renal failure in leptospirosis are similar to those well described from other causes. In particular, they include secondary infection and haemorrhage. The risk of bleeding in uraemia is increased by the bleeding tendency of the underlying illness. Haemolysins have been demonstrated in cultures of pathogenic leptospires and intra-vascular haemolysis is associated with severe cases. Thrombocytopenia may itself be sufficient to cause bleeding. Hypophosphatemia and capillary damage are also contributing factors (Beeson and MacDermott, 1975). The 2 deaths in this series
occurred from haemorrhagic complications, the first from a cerebral haemorrhage and the second from gastro-intestinal bleeding.

The bleeding diathesis in leptospirosis should not, however, be considered a contraindication to haemodialysis (Rainford, 1977). Indeed, haemodialysis is mandatory for the hypercatabolic state (Flynn, 1967) so commonly associated with the jaundiced patient. Daily haemodialysis with maintenance of the blood urea below 33 mmol/l (200 mg/100 ml) has been shown significantly to reduce the incidence of uraemic complications in acute renal failure and improve survival (Rainford, 1977; Parsons et al., 1961; Teschan et al., 1960). The last 3 patients in the present series were treated by daily haemodialysis combined with total parenteral nutrition and all survived. Provision of intravenous volume for sufficient parenteral feeding to control catabolism is the most cogent reason for daily haemodialysis.

The use of the H₂ histamine receptor antagonist, cimetidine, appeared to reduce the severity of gastro-intestinal bleeding in the last 2 cases. Since cimetidine has been used routinely in catabolic patients, the authors have had no deaths from severe gastro-intestinal haemorrhage, whatever the aetiology of the acute renal failure (these findings will be published elsewhere).

Penicillin still remains the antibiotic of choice and should be continued for at least 10 days (Manson-Bahr, 1966). However, its use does not appear to affect the overall mortality and, in the authors' experience, a dramatic response is not to be expected. All patients in this series were treated with penicillin.

The duration of ARF in this series was 1–2 weeks, renal function returning to normal in survivors by 3–4 weeks.

The case histories described contrast the outcome in 2 groups of patients. Those treated by daily dialysis and total parenteral nutrition (cases 4–6) all survived. In the earlier group (cases 1–3) uraemic complications resulted in 2 deaths despite intermittent haemodialysis. These patients did not receive sufficient nutrition to control catabolism.

Prompt recognition of renal failure in leptospirosis, and early referral to specialist renal units experienced in the management of the hypercatabolic patient should reduce the incidence of complications and lower mortality.

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References
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