Is it Time to Rethink the Use of Steroids for Pulmonary Leptospirosis?

Raajeev V Hingorani1, Rishi Kumar2, Ashit V Hegde3, Rajeev N Soman4, Rasika A Sirsat5, Camilla Rodrigues6, Anjali Shetty6

Abstract
Pulmonary involvement is a fairly common complication of leptospirosis. A high dose of steroids is often used in the treatment of pulmonary leptospirosis. Here we report two cases who developed severe invasive fungal infections following the use of steroids for pulmonary leptospirosis. Routine use of steroids for pulmonary leptospirosis may do more harm than good as the evidence for this practice is sparse.

Introduction
In leptospirosis, pulmonary involvement is a known complication. The use of various treatment measures have been tried in such cases, including the early use of pulse steroid therapy.

In the following two cases, we used steroids and both patients contracted severe invasive fungal infection.

Case Report

Case 1
A 45 year old lady, was admitted to an ICU of another hospital with fever, vomiting, abdominal pain and breathlessness. She had hypotension and acute renal failure requiring vasopressors and renal replacement therapy. She was treated with intravenous meropenem, colistin, piperacillin-tazobactam and moxifloxacin. Leptospira IgM was positive and the chest X-ray showed infiltrates in bilateral upper and lower zones. She was given six days of pulse methylprednisolone therapy. Her condition did not improve and she was shifted to another hospital. Intravenous methylprednisolone 125 mg 8 hourly was continued for a further three days, and the initial antibiotics were changed to colistin and cefepime. Blood culture grew Candida tropicalis for which fluconazole was added. She was then shifted to our hospital in a comatose state, on a ventilator with hypotension, severe lactic acidosis, digital infarcts in all limbs and multiorgan dysfunction. Colistin with meropenem and vancomycin were going on. Imaging of the brain suggested hemorrhage in the right parietal, left frontal and left cerebellar region. Repeat blood culture grew Enterococcus spp. and a growth of Candida tropicalis. In view of ongoing candidemia, fluconazole was changed to anidulafungin.

After receiving a further two days of methylprednisolone, her tracheal culture subsequently grew Lichtheimia corymbifera (previously Absidia corymbifera) suggestive of invasive mold (Mucormycotina) infection. Methylprednisolone was changed to dexamethasone for cerebral edema and later to hydrocortisone for septic shock, despite which she succumbed on the same day, after a total of sixteen days of hospitalisation.

Case 2
A 52 year male, vegetable vendor by occupation was admitted to our hospital with fever, loose motions and vomiting, along with severe myalgia and headache. He had no underlying comorbidities. On examination, he had conjunctival suffusion with forearm petechial rashes, tachycardia, respiratory failure requiring noninvasive ventilation (NIV) with FiO2 of 50%.

Chest x-ray showed bilateral pulmonary infiltrates requiring noninvasive ventilation (NIV). Leptospira IgM was positive. He received two bolus doses of methylprednisolone 250 mg each. He improved temporarily and was off NIV for a day. He was started on intravenous amoxycillin-clavulanic acid and tigecycline for three days before his sputum culture grew Aspergillus flavus, Syncephalastrum racemosum (Mucormycotina) and Scedosporium prolificans. Three days after admission, he developed worsening dyspnoea requiring intubation and hypotension needing vasopressors. His X-ray revealed fresh infiltrates and cavity. He also had acute kidney injury, requiring renal replacement therapy. Four days later, he developed an episode of gastric bleed. Upper gastrointestinal scopy revealed a large ulcer in the anterior wall of the greater curvature of stomach with black necrotic base. Gastric ulcer biopsy revealed Aspergillus flavus and Candida spp. He was treated with liposomal amphotericin B. Nasogastric amphotericin B was given in view of gastric fungal disease. He later developed left eye corneal ulcer with endophthalmitis thought to be fungal, for which he was given intravitreal amphotericin B. The vitreous culture came negative. Four days later, he developed right-sided hemiplegia. MRI showed a large left high frontoparietal bleed with edema around it, with a midline shift and early uncal herniation suspected to be due to angioinvasive fungal disease. Liposomal Amphotericin was continued...
for 42 days followed by posaconazole for 4 weeks. After a six month stay in the hospital, he was discharged with improvement in his general condition.

Discussion

These two patients presented with pulmonary leptospirosis and were given steroids which we suspect to be the risk factor for life-threatening invasive mold infection.

Both the patients had received broad-spectrum antibiotics prior to the onset of mold infection, as mentioned above. The first patient had an internal jugular venous catheter in situ and a femoral hemodialysis catheter as well before mold was isolated, however the second patient did not have any form of central venous access before mold was isolated.

Both the patients did not receive total parenteral nutrition.

Though classically the use of broad spectrum antibiotics and central venous access are predisposing factors for invasive candidial infection, they have not been reported to predispose an individual to invasive mold infection.

Neither of these two patients were found to be having risk factors for invasive mold infection such as diabetes mellitus or any immunocompromised state on investigation.

There have been few small-scale studies on the use of methylprednisolone in pulmonary leptospirosis.

It has been observed that corticosteroids reduce mortality and change outcome significantly when used early in the management of pulmonary leptospirosis. Corticosteroids affected outcome only if given within the first 12 hours after the onset of pulmonary manifestations.

Methylprednisolone with noninvasive ventilation was found to be life-saving in pulmonary leptospirosis. The above combination was cost-effective and a suitable therapeutic measure, for the management of leptospirosis.

Early glucocorticoid pulse therapy has been found to be beneficial if given soon after the onset of dyspnea to all the patients with pulmonary leptospirosis. Steroids are thought to have an effect on the mediators of inflammatory process.

But guidelines do not promote the use of steroids.

As per the Clinical Practice Guidelines for Leptospirosis 2010 (CPG 2010) prepared by the ‘Leptospirosis Task Force’ comprising the Philippine Society for Microbiology and Infectious Diseases, Philippine Society of Nephrology, and Philippine College of Chest Physicians, it is quoted that although benefits of corticosteroids in acute lung injury and adult respiratory distress syndrome has been extensively studied and accepted, the evidence for use of corticosteroids within the first 12 hours of onset of pulmonary leptospirosis is confined to occasional case reports or brief studies.

The WHO guidelines for leptospirosis, also state that there is no recommendation for the use of steroids in the management of pulmonary complications of leptospirosis.

There is an ongoing randomised controlled trial of pulse methylprednisolone vs. placebo in treatment of pulmonary involvement associated with severe leptospirosis. The results to conclusively establish the role of corticosteroids in pulmonary leptospirosis are awaited.

As per an article in The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group, it was stated that prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day for prednisone equivalent for more than 3 weeks predisposes to invasive fungal disease.

High dose short-term steroids predisposed our two patients to develop invasive fungal infection leading to intracerebral bleed, and extensive morbidity and mortality.

It is also interesting to note that though several other patients in our ICU received high dose steroids for a variety of other reasons, only these two patients with leptospirosis developed such severe infections with fungi other than candida. Whether leptospirosis is an independent risk factor for invasive fungal disease needs to be studied.

Hence, we advise caution to the physicians to use steroids very judiciously in pulmonary leptospirosis, until its role is conclusively established by way of more extensive studies in the future.

References