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Leptospirosis pulmonary haemorrhage syndrome

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Abstract

Sri Lanka remains a hotspot for leptospirosis and the incidence has been rising over the past few decades. Leptospirosis Pulmonary Haemorrhage Syndrome (LPHS) is a severe manifestation of leptospirosis, characterized by acute respiratory distress and significant pulmonary haemorrhage leading to devastating clinical outcomes. Recent epidemiological studies indicate a concerning rise in mortality rates attributed to LPHS, particularly in endemic regions such as Sri Lanka.

This article explores the clinical features, pathophysiology, diagnosis and management options of LPHS, emphasizing the need for heightened awareness among healthcare professionals. As a re-immerging zoonotic disease in an endemic country like Sri Lanka, severe leptospirosis such as LPHS needs prompt clinical diagnosis and management. Furthermore, we discuss the potential mechanisms underlying pulmonary haemorrhage, including immune-mediated injury due to cytokine storm and coagulopathy, which contribute to adverse outcomes in affected patients.

Among severe manifestations of leptospirosis, LPHS carries a high rate of mortality. Therefore, high degree of clinical suspicion is necessary, especially in resource poor settings where access to intensive care is limited. Thus, early diagnosis and timely intervention remain paramount in improving prognosis. Antibiotics, pulse steroid therapy, therapeutic plasma exchange and ventilatory support remains the main management options. In severe refractory hypoxemia veno-venous extra corporeal membrane oxygenation has been tried with some success.

We highlight the importance of continuous surveillance and ongoing research to further enhance the knowledge regarding LHPS and its therapeutic options to address the growing public health challenge posed by this severe complication of leptospirosis.

Introduction

Leptospirosis is increasingly recognized as a significant and emerging global public health concern, owing to its epidemic potential and rising incidence in both developing and developed countries.[1] An estimated 1.03 million cases and approximately 60,000 deaths occur annually worldwide.[1] The disease is caused by spirochetes of the genus *Leptospira*, of which 14 species are currently considered potentially pathogenic. Out of which, nine definitively pathogenic and five classified as intermediate pathogens. Although a wide range of mammals can serve as reservoirs, rodents are the primary vectors responsible for human transmission.[2]

In recent years, leptospirosis has been classified as a re-emerging infectious disease. This re-emergence is largely attributed to climatic changes such as increased frequency of extreme weather events and flooding, particularly in tropical regions. Additionally, urbanization-related factors such as the proliferation of rodents in densely populated slums, increased human contact with contaminated environments, and the popularity of recreational water activities have contributed to the rising incidence of the disease in urban settings.[3]

In Sri Lanka, epidemiological surveillance data indicate a marked rise in leptospirosis cases over the past few decades, with a sharp increase observed in the last ten-year period beginning in 2015. In that year,

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approximately 4,300 cases were reported, rising to 13,700 cases by 2024. While improved disease notification and reporting mechanisms may partly explain this increase, a parallel and concerning rise in mortality has also been observed from 71 deaths in 2015 to 320 in 2024.[4] Limited death reviews and autopsy data suggest that the primary causes of mortality are severe pulmonary hemorrhage, myocarditis, and complications related to prolonged intensive care management, often involving multiple organ dysfunction.

Clinical patterns of leptospirosis

Leptospirosis in humans can present as a mild, self-limiting illness or as a severe multi-system disease characterized by high fever, renal failure, jaundice, aseptic meningitis, and a range of other clinical manifestations. Traditionally, leptospirosis has been classified into two forms: the anicteric (mild) form, which is the predominant presentation, and the icteric (severe) form. When the classic triad of jaundice, renal impairment, and bleeding diathesis is present, the condition is termed Weil's syndrome, which involves severe renal and hepatic dysfunction along with hemorrhagic manifestations.

In 1995, during an outbreak in Nicaragua, a distinct form of severe leptospirosis with predominant pulmonary manifestations and high mortality was reported.[5] This entity was later recognized as leptospirosis pulmonary haemorrhage syndrome (LPHS), characterized by extensive pulmonary hemorrhage as the leading cause of death, often with minimal or no renal or hepatic involvement. Similar clinical patterns were subsequently reported in several countries, including Korea, China, and Brazil. In certain regions, LPHS has emerged as the primary cause of leptospirosis-related mortality, reinforcing its recognition as a distinct clinical entity over the past two decades.[3] Surveillance data from Salvador, Brazil, indicate that severe pulmonary hemorrhagic syndrome (SPHS) patients were first identified in 2003, despite active monitoring, suggesting its emergence as a newly recognized complication with geographical variations in distribution.[3,6]

The first documented cases of leptospirosis-related pulmonary hemorrhage in Sri Lanka dates back to 1977, based on an autopsy series of seven cases where subpleural and intrapulmonary hemorrhages were identified as the primary cause of mortality.[7] A subsequent autopsy series from Teaching Hospital, Karapitiya in 2008 reported that among 25 leptospirosis-related deaths, 21 had undergone post-mortem examination, revealing severe pulmonary hemorrhage as the cause of death.[8] More recently in 2019, a case series from the same institution documented 76 confirmed cases of leptospirosis pulmonary haemorrhage syndrome.[10] These findings provide compelling evidence that leptospirosis-associated pulmonary hemorrhage is a well-established complication in Sri Lanka, contributing significantly to disease-related mortality, in line with global observations.[7,9,10]

Recent studies and clinical observations from Sri Lanka suggest that severe leptospirosis exhibits diverse clinical manifestations. A study from southern Sri Lanka reported that among patients with severe leptospirosis, 94% had acute kidney injury, 60% experienced hemodynamic instability, nearly 40% developed pulmonary hemorrhage, 33% exhibited myocarditis, and 12.5% had severe liver involvement.[11] These findings challenge the conventional notion that jaundice alone is a marker of severity, emphasizing that the extent of individual organ dysfunction or multi-organ involvement is a more reliable determinant of disease severity and associated mortality.

Pathophysiology

Understanding the pathophysiology of leptospirosis is fundamental in the management of severe disease forms such as LPHS. Disease manifestations depend on both microbial and host factors.[18] Although exact pathophysiology of severe disease is not fully understood it is evident that the disarray of host immune response causing a cytokine storm is likely to be responsible.[12]

Pathogenicity is related to the presence of lipopolysaccharides (LPS), hemolysins, outer membrane proteins and adhesion molecules on the bacteria.[13,14] Host innate immune response is triggered by identification of these bacterial molecules by Toll-like receptors and nucleotide-binding oligomerization domain-like receptors on macrophages and neutrophils.[14] Although Leptospira are susceptible to phagocytosis by macrophages some escape the phagosome.[14] Furthermore, overproduction of reactive oxygen species by macrophages contribute to severe tissue damage.[12]

Leptospira can evade complement mediated destruction as the surface metalloproteinases inhibit the attachment of membrane attack complex.[12] Various molecular signaling pathways are responsible for triggering the genes encoding pro-inflammatory cytokines (TNF, IL-8, IL-6 , IL-1β) and anti-inflammatory cytokines (IL-10, TGFβ, IL-4 ,IL-13).[4,18] Hemolysin also activates the pro inflammatory cytokine production.[12] The balance between pro and anti-inflammatory

cytokine production is needed for the controlled host immune response. However, if there is an exaggerated cytokine production (cytokine storm) this would lead to severe disease[14] as a result of enhanced tissue damage. Cytokine storm seen in leptospirosis is similar to other bacterial sepsis.[14] Particularly high levels of IL-5, IL-6, IL-8, and IL-10 are seen in LPHS.[14] There is a significant correlation of cytokine concentration with the disease severity.[15]

Adaptive immune response is primarily via antibodies (IgM and IgG) produced against *Leptospira* LPS and other surface proteins.[15] Typically, after an infection, *Leptospira* antibodies would last for 6-8 years. However, there is little evidence that the antibodies would protect the host from other *Leptospira* serovars.[15]

Main mechanisms responsible for pulmonary damages are toxin mediated and immune mediated pathways.[16,17] Outer membrane proteins, haemolysin and peptidoglycans are responsible for toxin mediated vascular endothelial damage leading to pulmonary haemorrhages.[17] Toxin mediated vascular injury in the form of small vessel vasculitis leads to pulmonary haemorrhages.[18] Immune mediated pulmonary haemorrhage is mediated through cytokines. Particularly higher levels of IL-6, IL-8, and IL-10 are seen in LPHS compared to other severe forms of leptospirosis.[14] These multiple mechanisms ultimately result in severe lung damage seen in LPHS characterized by diffuse petechiae in lung parenchyma, intra-alveolar and interstitial haemorrhage and haemorrhagic infiltrates.[18]

Severe leptospirosis

Severe leptospirosis is characterized by hemodynamic instability and the presence of one or more of the following: oliguric acute kidney injury, pulmonary haemorrhage, and evidence of myocarditis. Early differentiation of severe leptospirosis from mild cases is critical, as severe cases are associated with high mortality. Clinical and biochemical parameters can aid in early identification. Oliguria and hypotension in the early stages often signal severe disease. Hypotension is a frequent finding in severe leptospirosis.[10,11] Notably, severe leptospirosis shares pathophysiological similarities with bacterial sepsis. Duarte-Neto et al. identified striking histopathological and immunological similarities in the spleens of patients who succumbed to pulmonary haemorrhage due to leptospirosis and those who died of bacterial septic shock. Their findings indicate that severe leptospirosis induces an immunosuppressive state at its terminal stage, akin to septic shock.[5]

Clinical recognition of LPHS

Clinical manifestations of LPHS include dyspnoea, lung crepitations, massive haemoptysis, radiographic evidence of alveolar haemorrhage, and rapid clinical deterioration requiring ventilatory support.[3] Observations from Sri Lankan patients indicate that haemodynamic instability frequently precedes pulmonary haemorrhage, with tachypnoea, arterial hypoxia, declining peripheral oxygen saturation, haemoptysis, and chest X-ray infiltrates heralding severe LPHS.[10] Among these, tachypnoea and arterial hypoxia are often the earliest signs. Although haemoptysis strongly suggests pulmonary haemorrhage, it is not always present, particularly in early stages. A progressive decline in haemoglobin or haematocrit levels over the course of illness is another valuable indicator of pulmonary haemorrhage. In suspected cases, early detection of worsening of hypoxia through arterial blood gas analysis is also important for timely diagnosis.

In some cases, patients deteriorate rapidly, requiring escalating oxygen support and progressing to respiratory failure within a short period. This fulminant course is characteristic of severe LPHS or SPHS.[10]

Diagnosis

Diagnosis of LPHS in a suspected patient with leptospirosis ideally requires the confirmation of leptospirosis infection and the pulmonary involvement.

Laboratory diagnosis of leptospirosis

Although laboratory diagnosis is difficult to obtain when a patient is deteriorating fast it is important to try to ascertain the diagnosis. Several diagnostic methods are available. Dark field microscopy and culture could be used to identify and isolate the organism; however, the yield is low[19] and not very useful in clinical diagnosis. Polymerase chain reaction (PCR) for Leptospira DNA identification is more useful as it enables rapid and early diagnosis.[19] Traditionally, microscopic agglutination test (MAT) has been widely used to detect Leptospira IgM antibodies. These antibodies become detectable between 6th to 10th day and a fourfold rise in the titer between the acute and convalescent samples is required for the confirmation of diagnosis.[19]

Radiographic features of LPHS

Chest X-rays in LPHS typically reveal three distinct patterns, appearing from the 3rd to 4th day of the illness:

1. Multiple, predominantly nodular opacities (1-7 mm), progressing into coalescent forms known as “cotton wool shadows” with focal consolidation.
2. Large confluent areas of airspace consolidation.
3. Diffuse, ill-defined ground-glass opacities.

These radiographic changes are initially peripheral and asymmetrical. In some cases, differentiating pulmonary haemorrhage from pulmonary oedema can be challenging, particularly when leptospirosis-associated myocarditis leads to pulmonary congestion. In such instances, expert radiological interpretation and high-resolution computed tomography (HRCT) may be required. HRCT findings in leptospirosis pulmonary hemorrhage include ground-glass opacities, airspace nodules, consolidations, and a crazy-paving pattern, with bilateral and diffuse distribution, that often predominate in the lower lung zones.[20]

Management

Early recognition of severe leptospirosis is essential for guiding the management and improving outcomes. All suspected leptospirosis patients – acute febrile illness in endemic regions accompanied by arthralgia, myalgia, headache, with a history of exposure to contaminated water- should undergo close monitoring. Simple clinical parameters such as pulse rate, blood pressure, and capillary refill time are vital for detecting early hemodynamic instability, a key indicator of severe disease. Systematic assessment for organ involvement is essential to determine disease progression.

Antibiotic therapy should be initiated promptly in all suspected cases of leptospirosis. Early antibiotic administration has been associated with reduced complications and improved outcomes.

- **Mild disease:** Oral doxycycline (100 mg twice daily for 7 days) or azithromycin (500 mg once daily for 3 days). Alternatively, amoxicillin (500mg tds for 1 week to 10 days) or ampicillin (500-750mg tds for 1 week to 10 days) may also be used.[21]
- **Severe disease:** Intravenous benzylpenicillin (1.5 million units every 6 hours) or ceftriaxone (1 g daily) for one week is recommended. Intravenous cefotaxime can also be used. It is important to note that *Leptospira* are not sensitive to chloramphenicol, metronidazole, rifampicin or vancomycin.[21]

Severe leptospirosis is frequently complicated by acute kidney injury, myocarditis LPHS and SPHS, sometimes leading to multiorgan failure. Careful monitoring to detect these complications and prompt initiation of appropriate organ support therapy is crucial in the management of severe leptospirosis.

Management of LPHS

Given the high mortality associated with LPHS, a pragmatic and timely approach is required for clinical diagnosis and treatment, especially as laboratory confirmation of leptospirosis is often delayed.

- **Hemodynamic monitoring and supportive care:** Due to the high prevalence of shock and acute kidney injury in LPHS, close hemodynamic monitoring and prompt supportive interventions are critical. Initial management should focus on judicious fluid resuscitation with careful attention to avoid fluid overload, followed by the initiation of vasopressor therapy with noradrenalin for patients with persistent hypotension. Serial assessment of lactate levels, urine output, and peripheral perfusion parameters can guide in tailoring resuscitation strategies.
- **Oxygen therapy:** Hypoxia is a frequent manifestation of respiratory involvement in leptospirosis, particularly in LPHS. Judicious administration of oxygen is critical in improving patient outcomes. As oxygen requirement increases, escalation of oxygen therapy should be conducted carefully, with close monitoring of the work of breathing.
- **Antibiotics:** In LPHS, intravenous ceftriaxone 1g daily or cefotaxime 1gm 8 hourly for one week is recommended. Early initiation is crucial for reducing morbidity and mortality.
- **Corticosteroids:** In the national guidelines, intravenous methylprednisolone is recommended for severe leptospirosis, particularly in LPHS, although this is not based on high-quality evidence.[22] Due to observed benefits in cases of early pulmonary haemorrhage, pulse-dose intravenous methylprednisolone (500 mg to1 g) is often commenced in LPHS.[22] Questions remain about the optimal dose, type and the duration of steroid therapy. However, recent evidence has questioned its efficacy in severe leptospirosis other than LPHS.[23] There is no robust evidence to support high dose corticosteroids in severe leptospirosis,[23] and their use may potentially increase the risk of nosocomial infections. Well-designed randomized controlled trials are urgently needed to define the role of corticosteroids in this context.

- **Therapeutic Plasma Exchange (TPE):** Given the suspected immune-mediated pathogenesis of alveolar hemorrhage in LPHS, the role of immunomodulatory therapies has been explored. TPE has shown promising results in case reports and studies, including a study from Teaching Hospital Karapitiya, Sri Lanka which demonstrated improved survival in LPHS patients treated with TPE.[10] Use of TPE has become standard therapy despite absence of evidence from clinical trials. Given the lack of other modalities of treatment with demonstrated benefit, it would be appropriate to use TPE in LPHS. Tachypnoea and arterial hypoxia with any of the following evidence of pulmonary hemorrhage such as suggestive chest X ray infiltrates, haemoptysis, or sudden drop in haemoglobin may be considered as an indication to initiate TPE.
- **Ventilatory support:** Early recognition of impending respiratory failure is essential, and timely endotracheal intubation is critical to avoid the onset of a vicious cycle of patient self-inflicted lung injury (p-SILI). This phenomenon, driven by excessive respiratory effort in the setting of compromised alveolar-capillary integrity, can exacerbate the already damaged lung architecture due to pulmonary hemorrhage. Prompt respiratory support not only prevents further lung injury but is also a key determinant of survival in fulminant LPHS.
- Lung-protective ventilation strategies, incorporating low tidal volumes (6 mL/kg predicted body weight) and appropriate levels of positive end-expiratory pressure (PEEP), are recommended to minimize ventilator-induced lung injury.[24] In cases of severe hypoxemia, adjunctive strategies such as prone positioning may be beneficial.

  Non-invasive ventilation (NIV) may be considered in selected, hemodynamically stable patients without altered sensorium; however, many deteriorate rapidly, warranting early endotracheal intubation and invasive mechanical ventilation.
- **Veno-venous extracorporeal membrane oxygenation (VV-ECMO):** Patients who are not responding to standard mechanical ventilation requiring high partial pressure of arterial oxygen to fraction of inspired oxygen ratio, may benefit from extracorporeal membrane oxygenation.[25] Though LHPS is associated with high mortality, some patients with refractory hypoxemia despite multiple adjunctive therapy as described above, respiratory functions could be successfully supported by V V-ECMO.[25]
- **Renal replacement therapy (RRT)** is often required in patients with oliguric or anuric renal failure, particularly when complicated by fluid overload, hyperkalemia, or severe metabolic acidosis. Both intermittent hemodialysis and continuous renal replacement therapy (CRRT) have been used effectively in this context. Early initiation of RRT has been associated with better outcomes in patients with multi-organ dysfunction.

Conclusions

Leptospirosis pulmonary hemorrhage has emerged as a significant cause of mortality in several endemic regions, including Sri Lanka. Early recognition, appropriate supportive care, and targeted therapeutic interventions, such as antibiotics, corticosteroids, ventilatory support and TPE, play crucial roles in improving patient outcomes. Further research is needed to refine management strategies which will enable us to reduce mortality associated with this life-threatening complication.

Key points

1. Leptospirosis is an endemic zoonotic disease, incidence of which has sharply risen in Sri Lanka over the past decade.
2. Severe Leptospirosis has diverse clinical manifestations and one of the serious complications is leptospirosis pulmonary haemorrhage syndrome (LPHS).
3. Immune mediated mechanisms are implicated in the pathogenesis of LPHS which has high mortality despite careful management.
4. Clinical features of LHPS are characterized by rapid deterioration of respiratory function which will present as hemodynamic instability, tachypnoea, refractory hypoxemia and massive hemoptysis. Therefore, close monitoring is necessary to identify this complication early.
5. Antibiotics, corticosteroid pulse therapy, ventilatory support, therapeutic plasma exchange and VV-ECMO in LPHS are the main therapeutic options.

Author declaration

Conflict of interests

Authors do not have any conflict of interests.

Author contribution

WHU conceptualized the design of the CME article. Both authors contributed equally to writing the manuscript and editing of the final draft.

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