

HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ASSOCIATED WITH LEPTOSPIROSIS IN A CRITICAL CARE SETTING: A CASE SERIES OF FIVE PATIENTS

Dr Sana Tariq ^{*1}, Dr Shafqat Ali², Dr Zainab Ahsan³

^{1,3}Intern Medicine, CMH Lahore, ²Resident Medicine, CMH Lahore

DOI: <https://doi.org/10.5281/zenodo.22076934>

Keywords

leptospirosis; haemophagocytic lymphohistiocytosis; HScore; critical care; therapeutic plasma exchange; secondary HLH; case series

Article History

Received: 26 January 2026

Accepted: 11 March 2026

Published: 25 March 2026

Copyright @Author

Corresponding Author: *

Sana

Abstract

Background: Leptospirosis is a zoonotic spirochaetal infection endemic across tropical low- and middle-income countries. In its severe form it generates an IL-1/IL-6/TNF-driven hyperinflammatory state that can, on rare occasions, tip over into secondary haemophagocytic lymphohistiocytosis (HLH). The two share a clinical picture – fever, cytopenias, organomegaly and multi-organ dysfunction – which means HLH is easily overlooked in this population.

Methods: We retrospectively describe five patients – four adults and one child – with serologically confirmed leptospirosis and HLH who were managed in the intensive care unit of a tertiary hospital. Each was scored against both the HLH-2004 criteria and the HScore.

Results: The patients were aged 12–39 years and all were male. Ferritin ranged from 2,065 to 8,219 ng/mL, triglycerides from 275 to 390 mg/dL and fibrinogen from 110 to 140 mg/dL; every patient had splenomegaly and cytopenias. Bone marrow haemophagocytosis was found in four of the five (marrow was not examined in Case 5, where consent was declined). The presentations varied widely: meningoencephalitis with herpes simplex virus type 1 (HSV-1) co-infection (Case 1); fever of unknown origin with cardiogenic shock and an ejection fraction of 20% (Case 2); a petechial rash with a platelet count of $5 \times 10^3/\mu\text{L}$ and hepatorenal dysfunction (Case 3); meningoencephalitis with right thalamic and left cerebellar infarcts (Case 4); and extensively drug-resistant (XDR) *Salmonella* Typhi co-infection in a 12-year-old boy (Case 5). Every patient was screened on admission for dengue (NS1 antigen and IgM) and for malaria under the institutional protocol for acute undifferentiated febrile illness, and both were negative throughout. Four patients met at least five of the eight HLH-2004 criteria, and Case 5 met five of eight even without bone marrow confirmation. All five cleared the HScore diagnostic threshold of 169, with totals of 187–244. Soluble CD25 and natural killer (NK) cell activity assays were not available. Every patient received five sessions of therapeutic plasma exchange and pulsed methylprednisolone (1–2 g/day for five days) alongside pathogen-directed antimicrobial therapy; none received etoposide. All five survived to intensive care discharge after stays of 6–14 days.

Conclusions: HLH should be actively ruled out before multi-organ failure in leptospirosis is put down to the infection alone. In resource-limited units where sCD25 and NK-cell assays are unavailable, the HScore can still be calculated in full, and it was diagnostic in all five patients – including the one in whom bone marrow was not examined. Dengue and malaria, the two leading competing febrile illnesses here and both recognised triggers of secondary HLH, were excluded

in every case; dengue is, in addition, a known cause of false-positive anti-*Leptospira* antibody. Even so, *Leptospira* infection rested on a single positive IgM, without microscopic agglutination testing or PCR, and two patients carried a competing infectious trigger, so the relationship we report is best read as association rather than proven causation.

Introduction

Leptospirosis is caused by pathogenic spirochaetes of the genus *Leptospira* and is acquired through direct or indirect contact with the urine of infected rodents and other reservoir animals. It is endemic throughout tropical and subtropical low- and middle-income countries. The diagnosis rests on a history of epidemiological or occupational exposure together with serology – the microscopic agglutination test (MAT) being the WHO-endorsed reference standard – or on molecular detection by polymerase chain reaction (PCR). Around 10% of infections progress to severe disease, with renal, hepatic, cardiac, pulmonary and neurological involvement.^{1,2}

The burden is considerable. In 2019 the global productivity cost of leptospirosis, measured in disability-adjusted life years and adjusted for gross domestic product, was put at USD 29.3 billion (range USD 11.6–52.3 billion). Southeast Asia bears the heaviest load, accounting for as much as 38.9% of cases, and 47.1% of the burden falls on 53 lower-income countries.³

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome sustained by persistently activated cytotoxic lymphocytes and macrophages. The primary form arises from inherited defects in cytotoxic granule function; the secondary form (sHLH) is set off by infection, malignancy, autoimmune disease or drugs and carries a mortality of roughly 41% in adults.⁴ In the critically ill it is being recognised more often, though it is still frequently taken for sepsis and diagnosed late, or missed altogether.⁵ Infection-associated sHLH has been catalogued in detail for dengue,⁶ tick-borne pathogens⁷ and malaria, yet the leptospirosis association has surfaced only as isolated case reports.^{8,9}

The difficulty is that severe leptospirosis and HLH are phenotypic mimics of one another. Fever, thrombocytopenia, anaemia, splenomegaly, hepatic and renal dysfunction and coagulopathy

all occur in both. Faced with Weil's syndrome and multi-organ failure, a clinician sees a picture that leptospirosis appears to explain on its own, and nothing prompts a search for anything further. Here we present five patients who developed HLH during confirmed leptospirosis in a critical care setting, score each against current diagnostic instruments, and set out the investigations we consider discriminating in a resource-limited intensive care unit.

Cases

All five patients were investigated under the institutional protocol for acute undifferentiated febrile illness, which mandates testing on admission for dengue (NS1 antigen and IgM serology) and for malaria. Dengue and malaria were negative in every patient. Blood cultures were obtained in all patients and were sterile except in Case 5, in whom extensively drug-resistant *Salmonella* Typhi was isolated.

Case 1

A 24-year-old man came to the Emergency Department with memory loss, cold sweating and a one-day history of fever. He was assessed by psychiatry, and contrast-enhanced brain magnetic resonance imaging (MRI) was requested; he denied any substance misuse. Neurology advised intensive care admission. Cerebrospinal fluid (CSF) showed normal glucose with raised protein and a lymphocytic pleocytosis, in keeping with a viral cause, and samples were sent to exclude tuberculous meningitis and herpes simplex encephalitis.

In the unit his Glasgow Coma Scale (GCS) dropped abruptly, and he was intubated and placed on mechanical ventilation. *Leptospira* serology returned positive with elevated IgM titres. He had several seizures during his stay that required sedation. Investigations showed the platelet count falling to $70 \times 10^3/\mu\text{L}$ and

haemoglobin of 8.5 g/dL, with ferritin markedly elevated at 3,400 ng/mL, triglycerides of 365 mg/dL and a low fibrinogen of 120 mg/dL. Soluble CD25 testing was not available locally. Bone marrow biopsy demonstrated haemophagocytosis; brain imaging was normal, but abdominal ultrasonography showed splenomegaly.

He also tested positive for herpes simplex virus type 1, indicating co-infection with *Leptospira*, and was started on doxycycline, ceftriaxone and aciclovir. For the HLH he received five sessions of therapeutic plasma exchange and methylprednisolone 1 g once daily for five days. He improved steadily, was weaned from the ventilator, and left the intensive care unit after a total stay of 14 days.

Case 2

A 39-year-old man presented with three weeks of fever and chills. The spleen tip was palpable on examination and confirmed on ultrasonography. The fever was intermittent and nocturnal with nothing else to accompany it, and he was admitted to the ward as a pyrexia of unknown origin. Haemoglobin was 7.0 g/dL and the platelet count $84 \times 10^3/\mu\text{L}$, a bicytopenia. Haematology arranged a bone marrow biopsy, which showed moderate haemophagocytosis.

He came to depend on noradrenaline to maintain his blood pressure and was moved to intensive care. Hypoxaemia developed and he was started on continuous positive airway pressure (CPAP). A multidisciplinary team elected to proceed with intubation and mechanical ventilation, five sessions of therapeutic plasma exchange, and methylprednisolone 1 g daily for five days. Renal and hepatic function held steady, but cardiac function fell away to an ejection fraction of 20%. *Leptospira* IgM serology returned positive while plasma exchange was under way. Ferritin was 4,480 ng/mL, schistocytes 0.5%, triglycerides 290 mg/dL and fibrinogen 140 mg/dL, and he was transfused red cells for anaemia.

A further crisis came with hypotension to 70/36 mmHg, which needed more noradrenaline. He stayed sedated and ventilated for five days and was extubated on the sixth. His GCS improved and he

moved to high-flow nasal oxygen alternating with CPAP. He left intensive care after a cumulative stay of 10 days. Ceftriaxone was his only antimicrobial.

Case 3

A 22-year-old man attended the Dermatology outpatient clinic with a petechial rash after occupational water immersion during military training. He was afebrile at presentation, and no fever was documented at any point during the admission. Baseline tests showed a platelet count of $5 \times 10^3/\mu\text{L}$ and haemoglobin of 9.3 g/dL, which prompted urgent medical review, and he was admitted to intensive care for close monitoring. The rest of the systemic examination was unremarkable. He was given a mega-unit platelet transfusion, and haematology recommended a bone marrow biopsy.

He then dropped his blood pressure to 70/30 mmHg and needed vasopressor support. On the strength of a raised ferritin (3,005 ng/mL), hypertriglyceridaemia (390 mg/dL) and hypofibrinogenaemia (110 mg/dL), all pointing strongly to HLH, a multidisciplinary meeting opted for therapeutic plasma exchange. Bone marrow biopsy confirmed moderate haemophagocytosis and *Leptospira* serology was positive. Hepatic and renal function were deranged (alanine aminotransferase 605 IU/L, serum creatinine 1.67 mg/dL), in keeping with multi-organ involvement, and ultrasonography showed mild splenomegaly.

He was treated with intravenous ceftriaxone and underwent five sessions of therapeutic plasma exchange with methylprednisolone 1 g once daily for five days, after which the ferritin began to fall. He was discharged from the medical intensive care unit after 11 days.

Case 4

A 32-year-old man presented with persistent vomiting, fever and headache, drowsy and with a neurological status that had been declining over the preceding five days. He was jaundiced, with a GCS of 7/15 and bilaterally equal, reactive pupils, and was admitted to the Medical Intensive Care Unit to exclude viral encephalitis. He reported

swimming in a public pool before the symptoms began.

He was intubated and ventilated in pressure-control assist-control mode. Leptospira serology returned positive, consistent with leptospiral meningoencephalitis, and MRI showed a right thalamic infarct and a left cerebellar infarct. A multidisciplinary team treated him with intravenous ceftriaxone alongside empirical intravenous aciclovir while herpes simplex encephalitis was being excluded; herpes simplex virus testing was negative and aciclovir was stopped. Serum ferritin was 8,219 ng/mL, triglycerides 275 mg/dL and fibrinogen 124 mg/dL, and the full blood count showed haemoglobin 7.6 g/dL and platelets $46 \times 10^3/\mu\text{L}$. Liver and renal function and cardiac function were all normal, ultrasonography showed moderate splenomegaly, and bone marrow biopsy demonstrated severe haemophagocytosis.

He received five sessions of therapeutic plasma exchange and methylprednisolone 2 g intravenously once daily for five days. He stayed ventilated for five days, was then weaned, and was transferred out of intensive care after roughly 13 days.

Case 5

A 12-year-old boy presented with a temperature of 103°F (39.4°C) that had come and gone over a

week, together with abdominal pain and a poor appetite. Examination revealed splenomegaly. He was admitted to the ward as presumed enteric fever and started on empirical antibiotics, and the fever spikes persisted, though less intense, while blood cultures were awaited.

At 72 hours the blood cultures grew extensively drug-resistant (XDR) *Salmonella* Typhi, and meropenem was begun. Persistent epigastric pain and nausea prompted measurement of serum amylase and lipase, both of which were elevated. When the fever failed to settle after five days of meropenem, *Leptospira* serology was sent in view of rodent exposure at home, and the *Leptospira* IgM returned positive at 48 hours. Investigations showed ferritin 2,065 ng/mL, fibrinogen 123 mg/dL, triglycerides 345 mg/dL, a total leucocyte count of $2.3 \times 10^3/\mu\text{L}$, platelets $56 \times 10^3/\mu\text{L}$ and haemoglobin 9.2 g/dL.

Bone marrow examination was not performed, as consent for the procedure was declined. Doxycycline was added, along with five sessions of therapeutic plasma exchange and methylprednisolone 1 g daily. He improved over the following days as the ferritin fell. He completed 14 days of intravenous meropenem, seven days of doxycycline and five sessions of plasma exchange before discharge from the ward, having spent a total of six days in intensive care beforehand.

Table 1. Clinical and laboratory summary

Parameter	Case 1 (24/M)	Case 2 (39/M)	Case 3 (22/M)	Case 4 (32/M)	Case 5 (12/M)
Presenting features	Fever, memory loss, seizures	Fever/chills, 3 weeks	Petechial rash (afebrile)	Vomiting, headache, jaundice	Fever, abdominal pain
Exposure history	Not reported	Not reported	Occupational water immersion	Swimming, public pool	Rodent exposure at home
Neurological	Meningoencephalitis, GCS fall	Not reported	Unremarkable	GCS 7/15; thalamic cerebellar infarcts +	Not reported
Cardiac	Normal	EF 20%, shock	Shock (70/30 mmHg)	Normal	Not reported

Parameter	Case 1 (24/M)	Case 2 (39/M)	Case 3 (22/M)	Case 4 (32/M)	Case 5 (12/M)
Fever documented	Yes (1 day)	Yes (3 weeks)	No	Yes	Yes (103°F, 1 week)
Haemoglobin (g/dL)	8.5	7.0	9.3	7.6	9.2
Platelets ($\times 10^3/\mu\text{L}$)	70	84	5	46	56
TLC ($\times 10^3/\mu\text{L}$)	Not reported	Not reported	Not reported	Not reported	2.3
Ferritin (ng/mL)	3,400	4,480	3,005	8,219	2,065
Triglycerides (mg/dL)	365	290	390	275	345
Fibrinogen (mg/dL)	120	140	110	124	123
AST	Not reported	Not reported	Not reported (ALT 605)	Normal	Not reported
Splenomegaly	Yes (USG)	Yes (USG)	Mild (USG)	Moderate (USG)	Yes (exam)
Bone marrow	Haemophagocytosis	Moderate haemophagocytosis	Moderate haemophagocytosis	Severe haemophagocytosis	Not performed (consent declined)
Dengue NS1 + IgM	Negative	Negative	Negative	Negative	Negative
Malaria screen	Negative	Negative	Negative	Negative	Negative
Co-infection	HSV-1 (confirmed)	None identified	None identified	None (HSV tested, negative)	XDR S. Typhi (blood culture)
Leptospira test	IgM positive	IgM positive	Serology positive	Serology positive	IgM positive
HLH therapy	TPE $\times 5$; MP 1 g $\times 5$ d	TPE $\times 5$; MP 1 g $\times 5$ d	TPE $\times 5$; MP 1 g $\times 5$ d	TPE $\times 5$; MP 2 g $\times 5$ d	TPE $\times 5$; MP 1 g
Antimicrobials	Doxycycline, ceftriaxone, aciclovir	Ceftriaxone	Ceftriaxone	Ceftriaxone; aciclovir stopped after negative HSV test	Meropenem, doxycycline
ICU stay (days)	14	10	11	~ 13	6
Outcome	Survived	Survived	Survived	Survived	Survived

AST, aspartate aminotransferase; EF, ejection fraction; GCS, Glasgow Coma Scale; HSV-1, herpes simplex virus type 1; MP, methylprednisolone; TLC, total leucocyte count; TPE, therapeutic plasma exchange; USG, ultrasonography; XDR, extensively drug-resistant.

Table 2. HLH-2004 criteria mapping

HLH-2004 criterion	Case 1	Case 2	Case 3	Case 4	Case 5
1. Fever $\geq 38.5^{\circ}\text{C}$	Yes	Yes	Not documented	Yes	Yes
2. Splenomegaly	Yes	Yes	Yes (mild)	Yes (moderate)	Yes
3. Cytopenias (≥ 2 lineages)	Yes (Hb 8.5; Plt 70)	Yes (Hb 7.0; Plt 84)	Yes (Hb 9.3; Plt 5)	Yes (Hb 7.6; Plt 46)	Yes (Hb 9.2; Plt 56; TLC 2.3)
4. TG ≥ 265 mg/dL and/or fibrinogen ≤ 150 mg/dL	Yes (TG 365; Fib 120)	Yes (TG 290; Fib 140)	Yes (TG 390; Fib 110)	Yes (TG 275; Fib 124)	Yes (TG 345; Fib 123)
5. Haemophagocytosis on bone marrow	Yes	Yes	Yes	Yes	Not performed
6. Low/absent NK-cell activity	Not available	Not available	Not available	Not available	Not available
7. Ferritin ≥ 500 ng/mL	Yes (3,400)	Yes (4,480)	Yes (3,005)	Yes (8,219)	Yes (2,065)
8. sCD25 $\geq 2,400$ U/mL	Not available	Not available	Not available	Not available	Not available
Criteria met / 8	6	6	5	6	5
Meets HLH-2004 threshold ($\geq 5/8$)	Yes	Yes	Yes	Yes	Yes

A diagnosis of HLH by the HLH-2004 criteria requires ≥ 5 of 8 criteria, or a consistent molecular diagnosis. The 2024 revision of these criteria (HLH-2024) removed NK-cell activity, leaving seven variables; NK-cell activity and sCD25 assays were not available at our institution. Case 3 was afebrile at presentation and no fever was documented during admission, so criterion 1 is scored as not met. Bone marrow examination was not performed in Case 5 (consent declined) and is scored as not met rather than as a missing value. NK, natural killer; sCD25, soluble CD25; TG, triglycerides; Fib, fibrinogen.

Table 3. HScore components and totals

HScore component (points)	Case 1	Case 2	Case 3	Case 4	Case 5
Known immunosuppression (0/18)	0	0	0	0	0
Temperature (0/33/49)	33 ^a	33 ^a	0 ^b	33 ^a	49 ^c
Organomegaly (0/23/38)	23	23	23	23	23
No. of cytopenias (0/24/34)	24 (2)	24 (2)	0 (1) ^d	24 (2)	34 (3)
Ferritin (0/35/50)	35	35	35	50	35
Triglycerides (0/44/64)	64	44	64	44	44
Fibrinogen (0/30)	30	30	30	30	30
AST (0/19)	0 ^e	0 ^e	0 ^e	0	0 ^e
Haemophagocytosis (0/35)	35	35	35	35	0

HScore component	Case 1	Case 2	Case 3	Case 4	Case 5
Total HScore	244	224	187	239	215
Exceeds threshold of 169	Yes	Yes	Yes	Yes	Yes

HScore computed per Fardet et al. Cut-off 169 (sensitivity 93.0%, specificity 86.0%). Unavailable variables were scored 0, so all totals are conservative minima. ^aFever documented but the maximum recorded temperature was not retrievable; scored in the 38.4–39.4°C band. ^bAfebrile; no fever documented. ^c103°F = 39.4°C, scored in the >39.4°C band; scoring in the 38.4–39.4°C band instead would give a total of 199, still above threshold. ^dHScore defines cytopenia as haemoglobin ≤9.2 g/dL, leucocytes ≤5,000/mm³ or platelets ≤110,000/mm³; Case 3 had a haemoglobin of 9.3 g/dL and therefore scores only one lineage. ^eAST not recorded; scored 0. Case 3 had an ALT of 605 IU/L, so a score of 19 is likely and would give a total of 206.

Discussion

This series describes five critically ill patients with serologically confirmed leptospirosis who developed HLH and recovered on combined antimicrobial therapy, pulsed corticosteroids and therapeutic plasma exchange. Leptospirosis is not a novel trigger; isolated reports have already described the association^{8,9}; the point our cases make is that, in an endemic setting, the two conditions are clinically superimposable, so HLH will be missed unless it is deliberately looked for.

Biological plausibility

A coherent mechanistic path runs from Leptospira infection to macrophage activation. Leptospiral lipopolysaccharide is structurally atypical and, in human cells, is sensed through Toll-like receptor 2 (TLR2) rather than TLR4, driving NF-κB-dependent transcription of IL-1β, IL-6 and TNF-α.¹⁰ In experimental models the difference between hosts is one of timing: resistant animals mount an early, self-limiting cytokine response, whereas susceptible ones show a delayed and then overwhelming surge of pro-inflammatory mediators with too little counter-regulatory IL-10 – the signature of an uncompensated cytokine storm.¹⁰ Severe leptospirosis is thus already an IL-1/IL-6/TNF-driven hyperinflammatory state², and those are exactly the axes that keep the macrophage activation loop running in sHLH. Leptospirosis needs no special mechanism to trigger HLH; it plausibly sits at the extreme end of a shared inflammatory continuum.

The mimicry problem

This overlap is the source of the diagnostic problem our series illustrates. Severe leptospirosis by itself produces fever, thrombocytopenia, anaemia, splenomegaly, hepatic and renal dysfunction, and coagulopathy.² Every one of those features is also an HLH criterion. What set the two apart in our patients was hyperferritinaemia out of proportion to sepsis (2,065–8,219 ng/mL), the pairing of hypertriglyceridaemia with hypofibrinogenaemia, and haemophagocytosis on marrow. In Cases 2 and 4, tellingly, renal and hepatic function were preserved or near-normal despite profound cytopenias and extreme ferritin elevation – a dissociation that fits classical Weil's syndrome poorly and should raise the suspicion of a superimposed hyperinflammatory process, though it remains hypothesis-generating and needs confirmation in larger cohorts. The practical rule can be reduced to three Fs: in leptospirosis that is not improving as expected, persistent fever, falling blood counts and a rising ferritin should prompt a formal assessment for HLH.¹⁵

Applying diagnostic criteria in a resource-limited critical care setting

Classifying HLH in our setting was limited by what we could test: soluble CD25 (sIL-2R) and NK-cell functional assays were not performed, since neither is available at our institution. That limitation is typical of most intensive care units in South Asia, and it bears directly on how well existing criteria travel to such settings. The 2024 revision of the HLH-2004 criteria¹² removed NK-cell activity from the diagnostic set, leaving seven

variables – a change that makes the criteria far more usable in centres such as ours. In the first multicentre validation of sHLH diagnostic criteria, the revised (NK-free) set performed comparably to the original, the HScore retained good discrimination at a cut-off of 169, and ferritin ≥ 500 $\mu\text{g/L}$ gave a mean sensitivity of 94.0% as a screening threshold.¹⁴

Because the HScore¹³ requires only temperature, organomegaly, cytopenias, ferritin, triglycerides, fibrinogen, aspartate aminotransferase, immunosuppression status and marrow haemophagocytosis, it can be computed in full in our environment. We scored all five patients (Table 3); every total cleared the threshold of 169, ranging from 187 to 244 even with unavailable variables set to zero. It was most instructive in Case 5, where marrow was not examined: forfeiting the 35 points for haemophagocytosis, the patient still scored 215, comfortably above threshold. The HScore has, moreover, been validated specifically in the critically ill, in whom marrow haemophagocytosis is an insensitive marker.¹⁹ We would therefore make the HScore the pragmatic first-line test for suspected sHLH in leptospirosis-endemic, resource-limited intensive care units, and reserve bone marrow examination for cases in which an occult haematological malignancy has to be excluded.

Clinical spectrum and organ-specific manifestations

Our patients show how varied the presentation of leptospirosis-associated HLH can be. Cases 1 and 4 were neuroinvasive: meningoencephalitis with a reduced GCS and seizures in Case 1, and a GCS of 7/15 with right thalamic and left cerebellar infarcts in Case 4. Leptospirosis is an established cause of aseptic meningitis and meningoencephalitis, and cerebrovascular complications, while uncommon, are recognised.² On the data available, direct leptospiral invasion of the central nervous system cannot be separated from central nervous system involvement by HLH itself, and the two may coexist. Case 2 showed profound myocardial depression, with an ejection fraction of 20% alongside bicytopenia, splenomegaly and marrow haemophagocytosis – a

reminder that cardiac failure can dominate the picture even when the underlying process is systemic. Case 3 reached a dermatology clinic with a petechial rash and isolated severe thrombocytopenia ($5 \times 10^3/\mu\text{L}$) and no documented fever at all, which underscores that HLH deserves consideration even when the presentation looks organ-specific and even when fever, its cardinal feature, is absent.

Co-infection and the limits of causal attribution

Two patients carried a documented second trigger. Case 1 was co-positive for HSV-1, itself an established cause of sHLH; a narrative review of 34 reported cases attributed 64.7% to HSV-1, with a mortality of 41.2%.¹⁸ Case 5 had culture-confirmed XDR *Salmonella* Typhi bacteraemia together with a positive *Leptospira* IgM. In neither patient can we pin the hyperinflammatory state on *Leptospira* alone, and we do not try to. Far from being a flaw in the series, this reflects the local epidemiology: in South Asia, patients with acute undifferentiated febrile illness often carry more than one pathogen, and it is biologically plausible that concurrent triggers add up to breach the threshold for uncontrolled macrophage activation. Reports of infection-associated HLH from endemic regions are therefore best read as showing association rather than proven causation, unless one pathogen has been rigorously confirmed and the competing triggers excluded.

Case 4 is the instructive one here. His encephalitic syndrome closely resembled Case 1 and he too received empirical aciclovir, but HSV testing was negative and the antiviral was withdrawn. He had the highest ferritin in the series (8,219 ng/mL), severe marrow haemophagocytosis and an HScore of 239, yet – crucially – normal liver and renal function, so his hyperferritinaemia cannot be blamed on hepatic injury. With no competing pathogen found, Case 4 is the cleanest attribution to *Leptospira* in the series and, to our mind, the strongest single argument that *Leptospira* alone can precipitate HLH.

Exclusion of competing endemic triggers

Dengue warrants separate discussion, because it is the single most important competing diagnosis

here and its exclusion is what lets the present series be interpreted at all. Three things make it dangerous. First, it is co-endemic with leptospirosis across South and Southeast Asia and produces a clinically indistinguishable syndrome of fever, thrombocytopenia, petechiae, hepatic dysfunction and shock. Second, it is an established trigger of secondary HLH, with 133 published cases and a reported mortality of 19.3%.⁶ Third, and most important for any series resting on serology, dengue is a documented source of false-positive anti-*Leptospira* antibody – including on the microscopic agglutination test – through cross-reactivity with leptospiral outer-surface membrane antigens.² A “leptospirosis-associated HLH” series assembled without dengue testing could, in part, be misclassified dengue-associated HLH.

In our cohort, dengue NS1 antigen and dengue IgM were both done on admission in all five patients under the febrile-illness protocol, and both were negative every time. The pairing matters: NS1 antigenaemia is detectable from the first day of fever, whereas IgM appears only around day four or five, so together the two assays cover the whole illness window and close the gap IgM alone would leave in a patient like Case 1, who presented after a single day of fever. Case 3 shows most sharply why this exclusion is load-bearing: a young man with a petechial rash and a platelet count of $5 \times 10^3/\mu\text{L}$ is, on clinical grounds alone, a textbook dengue case, and his leptospirosis hangs on a single IgM. It is the negative NS1 and IgM that separate him from that alternative.

Malaria was excluded in all five patients by the same admission protocol, and this is no trivial exclusion. Malaria is a recognised trigger of secondary HLH, arising in roughly 0.34% of malaria admissions in one multicentre series – most of the roughly 80 cases reported to date coming from Asia – and it shares with both leptospirosis and HLH the core phenotype of fever, anaemia, thrombocytopenia and splenomegaly.²⁰ Routinely excluding the two most prevalent competing febrile illnesses in our population, in every patient, is thus a methodological strength of the series rather than an incidental laboratory detail.

We stress, even so, that the work-up went no further than dengue, malaria and blood culture. HSV was confirmed in Case 1 and actively excluded in Case 4, but was not sought in Cases 2, 3 and 5. Epstein-Barr virus – the most frequently reported infectious trigger of secondary HLH worldwide – was not excluded in any patient, nor were cytomegalovirus, brucellosis or rickettsial disease. So the absence of a co-pathogen in Cases 2 and 3 reflects how far the investigation went rather than a systematic exclusion of every plausible alternative, and EBV in particular remains an unexcluded confounder throughout the series.

Management

Our approach rested on two principles. The first was to treat the trigger, so every patient received directed antimicrobial therapy. Ceftriaxone was the backbone in four of the five (Cases 1–4), in line with its established first-line role in severe leptospirosis; doxycycline was added in Case 1 and used in Case 5. Both encephalitis patients received aciclovir – as directed therapy in Case 1, where HSV-1 was confirmed, and empirically in Case 4, where it was stopped once HSV testing came back negative. Meropenem covered the XDR *Salmonella* Typhi bacteraemia in Case 5. Where the trigger of infection-associated sHLH is treatable, prompt pathogen-directed therapy has the clearest rationale of any intervention, and current expert opinion warns against reaching reflexively for etoposide-based cytotoxic therapy in this group.¹⁶ All of ours presented in severe sepsis or septic shock, where the myelosuppressive and immunosuppressive effects of etoposide are especially hazardous. The second principle was to interrupt the cytokine loop: every patient received pulsed intravenous methylprednisolone (1 g daily for five days; 2 g daily in Case 4) with five sessions of therapeutic plasma exchange (TPE). None received etoposide, all five survived to discharge, and a falling ferritin served as the principal marker of biochemical response.

TPE calls for an explicit caveat. Under the American Society for Apheresis guidelines it is a Category III indication (Grade 2C) for HLH and macrophage activation syndrome, which means its

optimal role is unsettled and each decision should be individualised.¹⁷ In each case our reasoning was non-selective cytokine removal in a vasopressor-dependent patient with progressive multi-organ dysfunction, as an adjunct to – never a substitute for – corticosteroids and antimicrobial therapy; local protocol and what was available also tipped the balance towards TPE over cytotoxic regimens. Uncontrolled improvement in five patients cannot establish efficacy, and we cannot exclude the possibility that antimicrobial therapy and corticosteroids alone accounted for recovery. Emerging cytokine-directed agents – anakinra, ruxolitinib and emapalumab – offer a more mechanistically targeted option and may be preferable where they can be obtained.¹⁶

Paediatric considerations

Case 5 stands out as the only child and one of two patients with a confirmed second pathogen. At 12 years of age, primary HLH from a germline defect in cytotoxic granule function stays on the differential and would ideally be excluded by genetic testing, which our institution could not perform. His ferritin of 2,065 ng/mL, though clearly raised, was the lowest in the series, and the missing bone marrow examination lowers diagnostic certainty. Even so, pancytopenia, splenomegaly, hypertriglyceridaemia, hypofibrinogenaemia and confirmed leptospirosis together gave an HScore of 215, above threshold, and he met five of eight HLH-2004 criteria without any marrow contribution. Where feasible, we recommend that children with suspected infection-triggered HLH be tested for the recognised primary HLH loci (PRF1, UNC13D, STX11, STXBP2), particularly when there is a relevant family history or recurrent episodes.

Limitations

Several limitations constrain what can be concluded. First, *Leptospira* infection rested on a single positive IgM in every patient; neither MAT – the WHO-endorsed reference standard, which requires a fourfold rise in paired sera – nor PCR was performed. A one-off IgM cannot reliably separate acute infection from residual antibody in an endemic population, and cross-reactivity with

other tropical pathogens is well described.² Second, sCD25 and NK-cell function were unavailable, so patients could not be scored against the full historical HLH-2004 criterion set. Third, marrow was not examined in Case 5 (consent declined), and haemophagocytosis is in any event neither sensitive nor specific for HLH in the critically ill.¹⁹ Fourth, although dengue (NS1 and IgM) and malaria were excluded in all five patients, the broader microbiological work-up was not exhaustive: HSV was sought only in Cases 1 and 4, and Epstein-Barr virus, cytomegalovirus, brucellosis and rickettsial disease were not excluded in anyone. EBV is the most commonly reported infectious trigger of secondary HLH, and its exclusion should be treated as mandatory in future series of this kind. Fifth, genetic testing for primary HLH was not done in our paediatric patient. Sixth, several variables – maximum temperature and AST in most patients – were not recorded at the time, so every HScore reported here is a conservative minimum. Seventh, this is a small, retrospective, single-centre series with no control group: we cannot estimate the incidence of HLH among our leptospirosis patients, nor say whether any intervention changed outcome, and the preference for TPE over an etoposide-based regimen was not randomised and may reflect local practice rather than evidence of superiority. Finally, follow-up ran only to the index admission, so neurological recovery, HLH relapse and longer-term mortality remain unknown.

Conclusion

HLH is a recognised but almost certainly under-diagnosed complication of severe leptospirosis: the two conditions share a phenotype, and the discriminating investigations are not ordered as a matter of routine. Whereas dengue-associated⁶, tick-borne⁷ and malaria-associated HLH have been catalogued systematically, the leptospirosis association is still confined to isolated case reports, and no pooled synthesis exists. For leptospirosis-endemic, resource-limited intensive care units we recommend measuring ferritin in any patient with leptospirosis whose fever persists as the blood counts fall, calculating an HScore once ferritin exceeds 500 ng/mL, and actively excluding HLH

before multi-organ failure is attributed to leptospirosis alone. In all five of our patients the HScore was diagnostic, including the one in whom bone marrow could not be examined. Recognition, prompt pathogen-directed therapy and timely immunomodulation appear compatible with survival even in the critically ill; the added value of therapeutic plasma exchange remains unproven and warrants prospective evaluation.

Conflict of interest

The authors declare no conflicts of interest related to this work.

Funding

No external funding was received for this study.

Data availability

The data supporting this case series are available from the corresponding author upon reasonable request, subject to institutional data-sharing policies and patient confidentiality protections.

References

- Rajapakse S. Leptospirosis: clinical aspects. *Clin Med (Lond)*. 2022;22(1):14-17. doi:10.7861/clinmed.2021-0784
- Rajapakse S, Fernando N, Dreyfus A, et al. Leptospirosis. *Nat Rev Dis Primers*. 2025;11(1):32. doi:10.1038/s41572-025-00614-5
- Almazar CA, Montala YB, Rivera WL. Leptospirosis in Southeast Asia: investigating seroprevalence, transmission patterns, and diagnostic challenges. *Trop Med Infect Dis*. 2026;11(1):18. doi:10.3390/tropicalmed11010018
- Hsu JI, Nikiforow S, Berliner N. Hemophagocytic lymphohistiocytosis in adults. *Blood*. 2026;147(10):1037-1047. doi:10.1182/blood.2025031100
- Montrucchio G, Traversi R, Arrigo G, et al. Hemophagocytic lymphohistiocytosis in the adult critically ill: a narrative review of case reports and case series. *Front Med (Lausanne)*. 2025;12:1622770. doi:10.3389/fmed.2025.1622770
- Sourris A, Vorria A, Kypraiou D, Tsantes AG, Ioannou P. Hemophagocytic lymphohistiocytosis triggered by dengue: a narrative review and individual patient data meta-analysis. *Viruses*. 2025;17(8):1047. doi:10.3390/v17081047
- Jevtic D, Dagnon da Silva M, Haylock AB, et al. Hemophagocytic lymphohistiocytosis (HLH) in patients with tick-borne illness: a scoping review of 98 cases. *Infect Dis Rep*. 2024;16(2):154-171. doi:10.3390/idr16020012
- Jevtic D, Djokic D, Redzic D, Aleksic D, Parezanovic M, Pasic S. Secondary hemophagocytic lymphohistiocytosis in a child with *Leptospira* infection: a case report. *Turk J Pediatr*. 2018;60(6):735-738.
- Basurto-Hurtado MR, Becerra-Sepúlveda LO, García-Pérez AP, Granados-Molina EA. Secondary hemophagocytic lymphohistiocytosis in a patient with severe leptospirosis: a case report. *J Med Case Rep*. 2026;20(1):46. doi:10.1186/s13256-025-05561-z
- Cagliero J, Villanueva SYAM, Matsui M. Leptospirosis pathophysiology: into the storm of cytokines. *Front Cell Infect Microbiol*. 2018;8:204. doi:10.3389/fcimb.2018.00204
- Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131. doi:10.1002/pbc.21039
- Henter JI, Sieni E, Eriksson J, et al. Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. *Blood*. 2024;144(22):2308-2318. doi:10.1182/blood.2024025077
- Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome.

- Arthritis Rheumatol.* 2014;66(9):2613-2620. doi:10.1002/art.38690
- Lachmann G, Knaak C, Vorderwülbecke G, et al. Multicenter validation of secondary hemophagocytic lymphohistiocytosis diagnostic criteria. *J Intern Med.* 2025. doi:10.1111/joim.20065
- Cox MF, Mackenzie S, Low R, et al. Diagnosis and investigation of suspected haemophagocytic lymphohistiocytosis in adults: 2023 Hyperinflammation and HLH Across Speciality Collaboration (HiHASC) consensus guideline. *Lancet Rheumatol.* 2024;6(1):e51-e62. doi:10.1016/S2665-9913(23)00273-4
- La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood.* 2019;133(23):2465-2477. doi:10.1182/blood.2018894618
- Connelly-Smith L, Alquist CR, Aqui NA, et al. Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the Writing Committee of the American Society for Apheresis: the ninth special issue. *J Clin Apher.* 2023;38(2):77-278. doi:10.1002/jca.22043
- Papazachariou A, Ioannou P. Hemophagocytic lymphohistiocytosis triggered by herpes simplex virus 1 and 2: a narrative review. *Hematol Rep.* 2024;16(3):487-503. doi:10.3390/hematolrep16030047
- Knaak C, Nyvlt P, Schuster FS, et al. Hemophagocytic lymphohistiocytosis in critically ill patients: diagnostic reliability of HLH-2004 criteria and HScore. *Crit Care.* 2020;24(1):244. doi:10.1186/s13054-020-02941-3
- Orth HM, Wiemer D, Schneitler S, et al. Hemophagocytic lymphohistiocytosis – how common and how severe is it as a complication of malaria? Retrospective case series and review of the literature. *Infection.* 2024;52(2):471-482. doi:10.1007/s15010-023-02104-w

