A Review of Four Cases of Leptospirosis Presenting for Acute Care to a Tertiary Paediatric Hospital in Singapore

Dear Editor,

Leptospirosis is a widespread and potentially fatal zoonosis that is endemic in many tropical regions.[1] Small mammals are the most important reservoirs. Humans commonly become infected through direct contact with an infected animal or through contact via soil or water contaminated with urine from an infected animal. Leptospirosis ranges in severity from a mild, influenza-like illness to a severe infection characterised by multiorgan dysfunction. The combination of jaundice and renal failure is known as Weil's disease. The incubation period is 2 to 30 days and illness usually occurs 5 to14 days after exposure.[2] Based on the World Health Organization's laboratory criteria of leptospirosis, a probable diagnosis can be made when a positive result is obtained from a rapid screening test such as IgM enzyme-linked immunosorbent assay (ELISA), latex agglutination test, lateral flow or dipstick. A confirmatory diagnosis can be made based on any of the following: isolation from blood or other clinical materials through culture of pathogenic Leptospira, a positive polymerase chain reaction (PCR) result using a validated method (primarily for blood and serum in the early stages of infection) or a fourfold or greater rise in titre or seroconversion in microscopic agglutination test (MAT) on paired samples obtained at least 2 weeks apart.[3]

On 28 September 2016, leptospirosis was added to the list of notifiable infectious diseases in Singapore. A total of 53 human leptospirosis cases were notified in 2017.[4] In the first 48 weeks of 2018, 39 cases of leptospirosis were notified compared to 48 cases over the same period in 2017.[5]

In Singapore, a lower incidence of leptospirosis was observed in children compared to adults. According to data published by the Ministry of Health, the risk factors associated with leptospirosis included being male and aged between 15 and 34 years.[6] The annual incidence of leptospirosis cases reported in Singapore for the age group 5 to14 years were 0.8, 0.4 and 0.8 per 100,000 residents in 2013, 2014 and 2015, respectively. No case of leptospirosis was reported in the age group 0 to 4 years. Comparatively, the annual incidence of leptospirosis cases reported in the age group 15 to 24 years were 1.5, 1.6 and 0.8 per 100,000 residents in 2013, 2014 and 2015, respectively. In 2016, the incidence of reported leptospirosis cases in the age groups 0 to 14 years, 15 to 24 years and 25 to 34 years were 0, 0.9 and 0.2 per 100,000 residents, respectively.[7]

Under the requirements of Singapore's Communicable Diseases Live and Enhanced Surveillance (CDLENS) system, leptospirosis is notifiable within 24 hours when there is clinical suspicion or positive laboratory results have been obtained from any of the following tests: isolation of *Leptospira* from blood or cerebral spinal fluid or urine, PCR, serology (4 times or greater increase in *Leptospira* agglutination titre between acute-phase and convalescent-phase serum specimens) or immunoglobulin M (IgM).[8]

This study is a retrospective review of patients diagnosed with probable leptospirosis in a tertiary paediatric hospital in Singapore. They were identified from an electronic database of all patients referred to its Infectious Diseases Service. The diagnosis of leptospirosis was made by antibody detection (*Leptospira* IgM). The aim of this case series is to better characterise the clinical profiles of paediatric patients with probable leptospirosis and to provide a detailed description of severe leptospirosis in children. The study was approved by the Institutional Review Board and approval was also obtained for waiver of consent.

Case 1

A 15-year-old Pakistani girl presented on 17 November 2011 for fever, vomitting and abdominal pain. She had travelled to Malaysia from 30 October 2011 to 4 November 2011 where she did white water rafting and drank unboiled river water. She was hypotensive at 90/50 mmHg and tachycardic. Her physical examination was unremarkable. Her laboratory tests revealed leukocytosis, hyperbilirubinaemia, elevated creatine kinase-muscle/brain (CK-MB) and troponin I. She was admitted to the intensive care unit for septic shock and required fluid boluses and dopamine infusion. She did not require ventilatory support. There were concerns of intra-abdominal sepsis in view of vomitting and abdominal pain. She was treated with intravenous ceftriaxone and metronidazole. Her electrocardiogram was normal and echocardiogram showed good contractility. Tests for influenza, dengue, typhoid, group A streptococcus, melioidosis and blood cultures were negative. Her chest radiograph revealed bilateral pneumonia with pleural effusions. Her *Leptospira* IgM returned positive on 25 November and *Mycoplasma pneumoniae* total antibody titre was 160. She was discharged well and completed a 10-day course of ceftriaxone and clarithromycin (for presumptive mycoplasma infection).

Case 2

A 3-year-old girl who resides in Indonesia presented on 30 December 2013 for fever, diarrhoea, vomitting and abdominal pain. She had been admitted to a hospital in Indonesia 12 days earlier. Initial physical examination was normal other than a maculopapular rash on her trunk and limbs. She was initially treated for enteric fever with intravenous ceftriaxone. Laboratory tests revealed elevated C-reactive protein and erythrocyte sedimentation rate. On 2 January 2014, she developed right lower limb swelling. Tests for respiratory viruses, dengue, chikungunya, typhoid, melioidosis, rickettsia, bartonella, group A streptococcus, malaria and blood cultures were negative. Tuberculin skin test was negative. Magnetic resonance imaging of her right thigh showed right tibial shaft osteomyelitis. In view of sightings of rats at her home in Indonesia, *Leptospira* IgM was sent. She completed a week of intravenous ceftriaxone and was discharged with oral cephalexin for a total of 6 weeks for treatment of osteomyelitis. Her *Leptospira* IgM returned positive after she was discharged.

Case 3

A 10-year-old girl travelled to Australia, Indonesia and Malaysia in August 2015 and presented on 16 September 2015 for fever, chest pain and vomitting. There was report of sightings of rats during her travels. She was hypotensive and tachycardic with cool peripheries. Her laboratory tests revealed elevated transaminases, elevated serum creatinine, raised cardiac enzymes (CK-MB/troponin I), raised C-reactive protein and raised erythrocyte sedimentation rate. Her echocardiogram showed poor contractility. She was admitted to the intensive care unit and treated for acute myocarditis. She developed ventricular tachycardia and subsequently bradycardia with complete heart block. She was started on extracorporeal membrane oxygenation from 17 to 28 September 2015. She also developed acute kidney injury that required renal replacement therapy, ventilator-associated pneumonia and left lower limb deep vein thrombosis. Tests for adenovirus, enterovirus, rickettsia, legionella, toxoplasma were negative. Galactomannan antigen testing for bronchoalveolar lavage (BAL) fluid was positive and *Candida parapsilosis* complex was detected in the BAL fluid. *Leptospira* IgM was done on 25 September 2015 and came back positive on 30 September 2015. She was empirically treated with intravenous piperacillin-tazobactam, vancomycin, meropenem, voriconazole and 2 doses of intravenous immunoglobulin (on 19 and 20 September 2015). She received 9 days of meropenem in view of her critically ill state and subsequently switched to ceftriaxone for 5 days after she improved. Prior to discharge, her echocardiogram showed normal biventricular function. She was discharged well on 15 October 2015.

Case 4

A 14-year-old boy attended an outdoor school camp from 1 to 3 July 2017 and presented on 26 July with fever, abdominal pain, nausea and jaundice after he had contact with murky water. He had scleral icterus and hepatosplenomegaly. His laboratory results revealed conjugated hyperbilirubinaemia with elevated transaminases, pyuria and haematuria. He was treated for acute infective hepatitis. Tests for hepatitis A, B and C, Epstein-Barr virus, cytomegalovirus, adenovirus, influenza, enterovirus, melioidosis, dengue and rickettsia were negative. On his second day of admission, he developed sudden onset of chest pain with no haemodynamic instability. Electrocardiogram showed ST elevation in leads V4-6 and ST depression in V1. Cardiac enzymes were raised and echocardiogram showed mildly decreased left ventricular systolic function indicating myocardial injury. He was transferred to the intensive care unit and commenced on milrinone. He was treated empirically with intravenous piperacillin-tazobactam. His fever persisted and he developed bilateral conjunctivitis. There were concerns of a possible diagnosis of atypical Kawasaki disease. *Leptospira* IgM done on 27 July 2017 was negative, but when repeated on 3 August, it returned positive. His cardiac enzymes improved, fever resolved and he completed a week of oral doxycycline upon discharge.

Discussion

To our knowledge, this is the first paediatric case series of leptospirosis in Singapore and the first to provide a detailed description of severe leptospirosis in children in Singapore. Table 1 summarises the clinical and laboratory data of the patients in our series. There were 2 prior publications on leptospirosis from Singapore but they were not relevant to our study.[9,10]

In our series, the diagnosis of probable leptospirosis was made by IgM ELISA (SERION ELISA classic *Leptospira* IgM, catalogue No. ESR125M; SERION RF-Absorbent, catalogue No. Z200) performed according to manufacturer's instructions. Results were reported as negative, indeterminate or positive. The serological gold standard test is microscopic agglutination test (MAT) which is difficult to perform. As such, *Leptospira* IgM ELISA is commonly performed in clinical laboratories for early diagnosis.[11]

Leptospirosis is one of the most important differential diagnoses associated with febrile illness in returned travellers. In our series, 3 of 4 cases had recent travel to Southeast Asian countries. This is consistent with reports from Japan that all imported cases of travel-related leptospirosis contracted the infection in Southeast Asian countries.[12] All our cases reported recreational activities in fresh water or contact with rats within the expected incubation period (2-30 days) for leptospirosis.

Table 1. Summary of Patients' Clinical Information and Treatment

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Date of admission	17 November 2011	30 December 2013	16 September 2015	26 July 2017
Age (years)	15	3	10	14
Gender	Female	Female	Female	Male
Ethnicity	Pakistani	Chinese	Arab-Indian	Chinese
Travel location	Malaysia	Indonesia	Australia, Indonesia, Malaysia	None
Exposure	White water rafting	Rats	Rats	Outdoor camp, swam in ponds
Interval between travel/exposure and presentation (days)	13	12	16	23
Fever duration (days)	2	14	2	6
Abdominal pain duration (days)	12	3	0	5
Vomitting (days)	2	14	1	0
Chest pain (days)	0	0	1	1
Rash	No	Maculopapular	No	No
Jaundice	No	No	No	Yes
Other signs	Hypotension	Right lower limb swelling	Hypotension	Conjunctival injection, hepatosplenomegaly
WBC on admission/peak, 10^9/L	11.93/17.8	12.84/12.84	12.61/22.94	9.43/11.27
Platelets on admission/nadir, 10^9/L	375	200	260	235
	295	200	71	235
CRP peak, mg/L	60.5	52.8	321.3	157.8
Pro-calcitonin peak, µg/L	-	-	5	0.55
ESR peak*	25 mm/50 min	110 mm/hr	18 mm/hr	68 mm/hr
Bilirubin peak (total/direct), µmol/L	25/4	6/4	132/92	197/144
AST/ALT peak, U/L	31/27	21/12	305/147	109/212
Kidney dysfunction (serum creatinine peak), µmol	No	No	Yes (367)	No
Creatine kinase peak, U/L	168	68	20,634	359
Cardiac dysfunction (peak troponin-I, range)†	Yes (0.31 ng/mL, ≤0.1 ng/mL)	No	Yes (44,274 ng/L, ≤10 ng/L)	Yes (12,642 ng/L, ≤10 ng/L)
Other investigations	CXR pulmonary infiltrates, pleural effusion	MRI: Osteomyelitis of right tibial shaft	Microscopic haematuria, ECG: ventricular tachycardia, heart block	US: hepatomegaly
Interventions				
Inotropes	Yes	No	Yes	Yes
Ventilation	No	No	Yes	No
Dialysis	No	No	Yes	No
ECMO	No	No	Yes	No
Length of hospital stay (days)	11	9	29	12
Antibiotic therapy and duration	Ceftriaxone 10 days, clarithromycin 10 days	Ceftriaxone 7 days, cephalexin 42 days	Piperacillin-tazobactam 5 days, meropenem 9 days, ceftriaxone 5 days	Piperacillin-tazobactam 5 days, doxycycline 7 days

ALT: Alanine transaminase; AST: Aspartate transaminase; CRP: C-reactive protein; CXR: Chest radiograph; ECG: Electrocardiogram; ECMO: Extracorporeal membrane oxygenation; ESR: Erythrocyte sedimentation; MRI: Magnetic resonance imaging; US: Ultrasound; WBC: White blood count
*ESR was reported in mm/50 min (range 0-20 mm/50 min) before it switched to mm/hr (range 3-15 mm/hr) from August 2013.
†Troponin-I was reported in ng/mL (range ≤0.1 ng/mL) before it switched to high-sensitive troponin-I in ng/L (range ≤10 ng/L) from December 2014.

The clinical features of leptospirosis are non-specific and its signs and symptoms are similar to many other infectious diseases including influenza, malaria, dengue fever and typhoid fever. Conjunctival injection is a characteristic and relatively specific manifestation that can distinguish leptospirosis from other infectious diseases.[13,14] Though rare, leptospirosis has been reported to present as acute acalculous cholecystitis and pancreatitis.[15] In our series, only 1 case was reported to have conjunctival injection. The most common symptoms in our series were fever, abdominal pain and vomitting.

In our series, 3 of 4 patients had myocardial injury or myocarditis. Myocarditis and myocardial failure have been reported in severe cases of leptospirosis. However, its frequency of occurrence, exact pathophysiological basis and contribution to morbidity and mortality are not well understood. Cardiac involvement—demonstrated electrocardiographically or clinically—tends to predict poor outcome.[16]

In view of the varied presentation of leptospirosis, particularly fever with conjunctival suffusion, Kawasaki disease is an important differential. Kawasaki disease has been reported in patients with leptospirosis.[17] Leptospirosis is believed to produce milder symptoms in children with lower rates of classic signs and symptoms of Weil's disease.[18] Among children, adolescents and adults with severe leptospirosis, there is a higher need of dialysis in adults suggesting severe acute kidney injury and milder renal disease in children.[19] In our series, 3 cases required admission to the intensive care unit and inotropic support with one needing extracorporeal membrane oxygenation and dialysis. This highlights the severity of the cases in our series. There were no fatalities in our patients.

Severe cases of leptospirosis should be treated with high doses of intravenous penicillin. Third-generation cephalosporins, such as ceftriaxone and cefotaxime, and quinolone antibiotics are also effective. Oral antibiotics such as amoxycillin, ampicillin, doxycycline or erythromycin can be considered in less severe cases.[20] Antibiotic treatment for leptospirosis is shown to decrease the duration of clinical illness by 2 to 4 days. The selection of penicillin, doxycycline or cephalosporin does not seem to impact mortality or duration of fever.[21] In all 4 cases, there was initial clinical suspicion of leptospirosis. However, as the presentations were non-specific and in view of the clinical severity, empirical antibiotics (ceftriaxone and piperacillin-tazobactam) were started while awaiting confirmatory laboratory results.

In conclusion, a diagnosis of leptospirosis must be considered in children who present with a febrile illness, especially in returned travellers, and where there is a history of recreational activity in fresh water or contact with rats. The presentations are varied and non-specific and can overlap with many infections as well as Kawasaki disease. This series also highlights the severity of paediatric leptospirosis as 3 of 4 cases required admission to the intensive care unit with cardiac involvement. A high index of suspicion is therefore needed to institute early treatment and to reduce morbidity and mortality.

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