MICRODIS

MICRODIS Working Paper Series

2008-July-04

**Clinical Characteristics of
Leptospirosis in a 7-months
Retrospective Hospital-Based Study
in Jakarta, Indonesia.**

Authors:

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About MICRODIS

MICRODIS is an Integrated Project funded under the EU Sixth Framework Programme – Thematic Priority 6.3 Global Change and Ecosystems (Contract number GOCE-CT-2007-036877).

Why create MICRODIS?

Disaster losses are increasing with great consequence to the survival, dignity and livelihoods of individuals and communities, particularly of the poor in developed and less developed countries. Disaster risk arises when hazards interact with physical, social, economic and environmental vulnerabilities. In the past two decades, more than 200 million people have been affected, on average, every year by these extreme events.

Environmentally unsound practices, global environmental changes, population growth, urbanisation, social injustice, poverty, conflicts, and short-term economic visions are producing these vulnerable societies. This takes on particular urgency in the face of long-term risks brought about by climate change, and goes beyond environmental degradation or the mismanagement of natural resources.

There is now international acknowledgment that efforts to reduce disaster risks must be systematically integrated into policies, plans and programmes for sustainable development and poverty reduction. The MICRODIS project locates itself within this above framework.

What are the Objectives and Goals of MICRODIS?

MICRODIS is a project with the overall goal to strengthen preparedness, mitigation and prevention strategies in order to reduce the health, social and economic impacts of extreme events on communities.

Broad Objectives

⇨ To strengthen the scientific and empirical foundation on the relationship between extreme events and their health, social and economic impacts.
⇨ To develop and integrate concepts, method, tools and databases towards a common global approach.
⇨ To improve human resources and coping capacity in Asia and Europe though training and knowledge sharing.

For example, the MICRODIS project will, among others, specifically aim at:

- developing an integrated impact methodology,
- establishing an evidence-base of primary field research through surveys,
- increasing the coverage accuracy and resolution of global disaster data.

Where will MICRODIS operate?

The two regions which form the focus of the MICRODIS project are:

1. European Union, associated countries and new accession states: Belgium, France, Finland, Germany, the Netherlands, Norway, the United Kingdom.
2. South and Southeast Asia regions: India, Indonesia, the Philippines and Vietnam.

These regions have been selected based on their high frequency of extreme events and the impact on affected communities.

What Extreme Events will MICRODIS focus on?

There are twelve broad and twenty-three sub-groups of distinct extreme events, ranging from chronic slow onset phenomena to acute rapid onset ones. The health and socio-economic impact implications differ vastly between these twenty three types and addressing all of these would compromise the quality and applicability of the project results, risking over-generalisation.

In both Asia and the European Union, three types of extreme events, namely **foods**, **earthquakes**, and **windstorms**, account for nearly seventy-five percent of the occurrence of all extreme events. The MICRODIS project will concentrate on these three phenomena.

Partners

European Union and Associated Countries

Belgium	Université catholique de Louvain
Finland	Finnish Institute of Occupational Health
France	University of Paris – Sorbonne (FERURBAT)
Germany	EVAPLAN – University of Heidelberg
Netherlands	HealthNet International
Norway	SWECO GRONER
U.K.	University of Greenwich
U.K.	University of Northumbria
U.S.A.	United Nations Office for the Coordination of Humanitarian Affairs

South and Southeast Asian Partners

India	Jadavpur University
India	Voluntary Health Association of India
India	University of Delhi
Indonesia	University of Indonesia
Philippines	Citizens' Disaster Response Center
Philippines	Xavier University
Vietnam Hanoi	School of Public Health

ABSTRACT:

INTRODUCTION Leptospirosis is a widespread zoonosis with protean clinical presentations, ranging from a mild flu-like illness ("anicteric form") to a fulminant disease, also known as the "Weil's disease" or "icteric form", characterized by multiple organ impairment.

METHODS: We retrospectively analyzed medical records from 5 major hospitals in Jakarta over a 7 month period and obtained clinical information for 208 confirmed cases (confirmation by IgM-M rapid immunochromatography dipstick assay).

RESULTS: Mean age was 39.2 [36.7-41.1] years, with no significant age difference between men and women (p=0.21). The most frequently reported symptoms were fever (86.5%), nausea (77.9%), vomiting (62.5%) and diarrhea (41.35%).The frequency of symptoms was not significantly different across sex and age groups. Overall, our patients presented high leucocytosis (12.5 [CI95% 11.7-13.3]*10^3/mm³), thrombocytopenia (91.2 [80.6-103.2]*10^3/mm³), elevated creatinin levels (2.5 [2.2-2.8]mg/dl) and elevated bilirubin levels (2.2 [1.7-2.8] mg/dl). Acute renal failure (ARF) was defined as a creatinin level >1.5mg/dl and was observed in 68.7% of our patients. Nearly 70% of the patients had thrombocytopenia (<150*10^3/mm³). Nineteen percent of the patients with ARF had completely normal bilirubin levels (<1 mg/dl), showing that leptospirosis may lead to renal impairment without hyperbilirubinemia. More than half of these had concomitant thrombocytopenia. Our study reveals that the severity of leptospirosis is unrelated to the presence of hyperbilirubinemia, and shows a high prevalence of ARF and thrombocytopenia in severe leptospirosis. The best model for predicting fatal outcome included hyperleucocytosis (white blood cells (WBC) count >16 000/mm³) together with elevated creatinin levels (>3mg/dl) and low thrombopenia (platelet count <60 000/mm³). This model accounted for 39.1% of the variance in predicting death. Disease length was not statistically different (p=0.22) between deaths and survivors, indicating that death occurred late in the disease course. Overall case fatality rate was 6.25%.Leptospirosis was suspected in only 31.7% of our confirmed cases, at entry, and confounded with dengue in 27.1%.

1. **Introduction**

Leptospirosis is an emerging zoonotic infectious disease caused by spirochetes, *leptospira interrogans*, which has a worldwide distribution but is more common in the tropics[1, 2]. Pathogens are maintained in animal reservoirs (mainly small mammals but also domestic animals) by chronic infection of their proximal renal tubules [1, 2]. Infected animals can shed pathogens in their urine throughout their entire lifetime [1, 2].

Humans are infected through direct or indirect contact with animal urine [1]. The usual port of entry is through skin abrasion or through the conjunctiva, but infection may also occur in intact skin following prolonged immersion in infected waters[2].

Incidence rates of the disease are underestimated due to the lack of awareness of the disease [1-3], and a broad spectrum of symptoms[2], that can mimic the clinical presentations of many other diseases[4-8]. Symptoms range from a mild flu-like illness to a fulminant disease with jaundice and multiple organ impairment, also known as the "Weil's disease" [1, 2].

Leptospirosis has commonly been considered as an infectious disease associated with environmental risk factors [1, 2, 9, 10], especially occupational risk factors[11, 12] mainly related to farming. However, in the last years some examples of large urban outbreaks have been reported in Brazil[4, 13, 14] and in Argentina[15], especially in situations of urban floods[14, 15] or following heavy rainfall[4, 14].

On the 31st of January 2007, heavy rainfall led to floods in the city of Jakarta, Indonesia. In the aftermath of these floods, many cases of leptospirosis were reported from several hospitals to the Provincial Health Office (PHO).
Clinical characteristics of leptospirosis in Jakarta have seldom been described. Leptospirosis was described by Smit et al[16] in 175 patients in Sumatra, in 1970, and Light et al[17] published a case-report on 2 patients in Jakarta in 1971. Moreover, few large clinical case-series on leptospirosis[10-12, 18, 19] have been described elsewhere. Therefore, the aim of this study is to depict the clinical characteristics of leptospirosis patients treated in main general hospitals in Jakarta, and to put it in the light of our understanding from previous studies to further corroborate the knowledge on clinical aspects of leptospirosis.

2. **Methods**

2.1. Study design and data collection

Leptospirosis is a notifiable disease in Indonesia. Hence, in this case-series study, we first collected data from the PHO of Jakarta to identify the hospitals (in Jakarta) that had reported the highest number of leptospirosis cases between November 1st, 2006 and May 31st, 2007.

Based on the reported figures, we obtained clinical data from five major hospitals in Jakarta (RSU Persahabatan, RSU Sumber Waras, RSU Tarakan, RSU Budi Asih, RSU Cengkareng),that together reported 83.0% of all reported cases of leptospirosis during that period. After receiving permission from each hospital, medical records were consulted to obtain demographic information (sex, age), the first/ initial clinical data at the time of admission at the hospitals (symptoms, entry and final diagnosis, duration of illness in days, length of stay and disease course) and laboratory analysis (including diagnostic confirmation). A total number of 216 cases were retrieved. Eight cases were excluded due to missing laboratory confirmation test (4) or negative confirmation test (4). We ended up with 208 cases.

Cases were defined as suspected clinical cases with supportive serological findings (positive leptospira IgM by IgM-M rapid immunochromatography dipstick assay).

2.2. Statistical methods

All analyses were carried out using STATA/IC 10.0® and Microsoft Excel 2007® softwares.

Odds ratios (OR), and Pearson's χ^2 test were utilized to compare the frequency of symptoms across the sex and age categories, as well as for comparing survivors to deaths. Assuming the bias of under-reporting some symptoms, we decided to consider as absent the symptoms that were explicitly reported as not present, and those for which no information could be collected.

For analyzing the laboratory values, we decided to exclude the 13 pediatric patients (<18 years old) for two main reasons; first, normal values in children differ from the ones in adults and second, the number of pediatric cases was too small to

allow a separate analysis for the pediatric sample. Thus, we ended up with 195 adults for the analysis on laboratory variables.

Unpaired Student t-test (for normal distributions) or Mann-Whitney U-tests (for non normal distributions) were used to compare continuous variables in two unpaired groups (sex groups, age groups, deaths and survivors). A two-sample proportion test was used to compare the proportion of cases with anaemia and the Case Fatality Ratio (CFR) in men and women. Lack of hematocrit was defined as a hematocrit <37% in women and <40% in men, according to the Indonesian standards[20].

The cut-off values for separating pathologic values from normal values were also chosen based on the Indonesian standards[20].
Prognostic factors for death were analyzed by using the χ^2 statistic for testing differences for categorical variables between deaths and survivors. Relevant variables were introduced into a multiple logistic regression model.

All tests were carried out at a significance level of 0.05. All results were expressed as means with 95% confidence intervals (CIs) or ±Standard Deviation (±SD), as median with range (minimum-maximum) for non-normal distributions, as OR with 95% CIs and p-values.

3. Results

3.1. Demographic Results
We observed a normal distribution for age and sex in our sample. Mean age (±SD) was 39.3 (±14.2) years for the total population. Mean age in males (38.9±13.9 years) and in females (40.8±15.1 years) was not different (p=0.21).
Very few cases (6.25%) were observed <18 years old and no cases were observed <5 years old.

Overall, there were 161 men (77.4 [71-83] %) and 47 women (22.6[17-29] %). Majority of cases were middle-aged women and men, with 71.4% of men and 65.9% of the women in the 26-55 years old age group respectively.

3.2. Symptoms

The most frequently reported symptoms were fever (86.5%), nausea (77.9%), vomiting (62.5%) and diarrhea (41.3%). Jaundice at physical examination was reported in only 9.6% of the cases. Oliguria was present in 3.4%. No cases of meningitis have been reported.

Flu-like symptoms were under-represented, when compared with most of other large case series (table 1). For instance, headache was noticed in only 18.6% of the cases and myalgia in 22.6%. Conjunctival injection was present in 6.7%. Twenty-one percent of the patients complained of cough.

We analyzed the results of other large hospital-based series, either prospective or retrospective, in which patients were selected only on the basis of the diagnosis and not on any additional criteria of severity. Table 1 displays the percentages of the main symptoms observed in these studies.

We identified no difference in symptoms between men and women in the total population or across the age groups, except for oliguria that was more frequent in the elderly (oliguria in ≥55 years old, OR 4.8 [1.0-22.8]). No other symptom was significantly associated with ageing.

Table 1: Proportion (%) of reported symptoms in large hospital-based case-studies.

Studies	Number of patients	Study location	fever	headache	myalgia	vomiting	nausea	abdominal pain	diarrhea	Jaundice
Katz et al[10]	353	Hawaii, USA	99	89	91	73	77	51	53	39
Park et al[23]	93	Chonbuk Province, Korea	97	70	88	32	46	40	36	16
LaRocque et al[18]	63	Dhaka, Bangladesh	100	82	85	84	97	39	37	5
Peric et al[12]	270	Croatia	100	NR	77	79	NR	NR	44	62
Christova et al[19]	154	Bulgaria	93,5	12,3	66,9	18,2	22,7	7,1	NR	59,7
Ciceroni et al[11]	106	Italy	81,1	11,3	18,9	4,7	2,8	NR	2,8	58,5
le Polain et al	*208*	*Jakarta, Indonesia*	*86,5*	*18,3*	*22,6*	*62,5*	*77,9*	*26,5*	*41,4*	*9,7*

3.3. Lab Analysis

3.3.1. General

Table 2 displays the main characteristics of the laboratory variables that were analyzed. Overall, our patients presented high leucocytosis (12.5 (CI95% 11.7-13.3) $*10^3/mm^3$), thrombocytopenia (91.2 (80.6-103.2)$*10^3/mm^3$), elevated creatinin levels (2.5 (2.2-2.8)mg/dl) and elevated bilirubin levels (2.2 (1.7-2.8) mg/dl). Transaminases were elevated, although not importantly (sGPT 48.9 (43.5-55.1) IU/l, sGOT 44.5 (38.7-51.2) IU/l). Seventy-two percent of the males had anemia, and 80% of the females, which was not statistically different (p=0.14).

We were unable to define Acute Renal Failure (ARF) based on the calculation of the Glomerular Filtration Rate (GFR) with the Cockroft formula, since we had no information on the patients' weight, which is an essential variable for the formula. Therefore, ARF was defined based on a level of blood creatinin >1.5 mg/dl. We observed ARF in nearly 70% of the cases.

Thrombocytopenia (<150 000/mm³) was also observed in nearly 70% of our patients. Nearly 22% of the patients had a platelet count under 50 000/mm³. Hyperbilirubinemia (total bilirubin >1.0mg/dl) was seen in 78.5% of the patients. Forty-nine percent of the patients had total bilirubin levels above 10 mg/dl. Hyperbilirubinemia together with ARF and thrombocytopenia was seen in 40.5% of the cases. Noteworthy, nineteen percent of the patients with ARF (≥1.5 mg/dl) had completely normal bilirubin values (<1 mg/dl). On the other hand, hyperbilirubinemia was observed without renal impairment (<1.5mg/dl) in 22.6% of the cases. Thrombocytopenia was the only laboratory abnormality seen in 3.6% of our patients. When hyperbilirubinemia and ARF were both observed, thrombopenia was frequently observed too (in 72.7% of the cases).

Table 2: Laboratory Analysis

Name of variable (unit)	total n	% or mean(+CI95%)
White Blood Cells (WBC) count (*10³/mm³)	194	12.5 (11.7-13.3)
Platelet count (*10³/mm³)	195	91.2 (80.6-103.2)
Creatinin (mg/dl)	186	2.5 (2.2-2.8)
Bilirubin (mg/dl)	121	2.2 (1.7-2.8)
sGPT (IU/l)	176	48.9 (43.5-55.1)
sGOT(IU/l)	175	44.5 (38.7-51.2)
Hemoglobin Males	149	12.9 (12.6-13.1)
Hemoglobin Females	45	11.4 (10.9-12.0)
Anemia Males (Hematocrit male <40%)	150	72%
Anemia Females (Hematocrit female <37%)	45	80%
Leucocytosis (WBC >11 000/mm³)	195	61.50%
Thrombocytopaenia (Platelets <150 000/mm³)	195	68.70%
Hyperbilirubinemia (bilirubin >1,0 mg/dl)	195	78.50%
ARF (creatinin >1.5mg/dl)	195	68.70%
sGOT >19,0 IU/l	195	88.20%
sGPT >23,0 IU/l	195	77.90%

3.3.2. Predictors of fatal outcome

The overall CFR was 6.2% (13/208). The CFR in males was lower (5.6%) than the one in females (6.5%), but not statistically different (p=0.46).

Several prognostic factors for death were identified, among which most were biological values. The results are shown in table 3. In patients with ARF, the CFR was 9.7%. The group of patients with a creatinin level >3.0 mg/dl had a CFR of 13.4%. Creatinin >3.0mg/dl was also a strong independent predictor of death (p<0.01). Thrombocytopenia <60 000/mm³ was another independent prognostic factor for death (p<0.01), as well as hyperleucocytosis (high WBC count) >16 000/mm³ (p<0.01). The CFR rose to 17.8% in the group of patients with a platelet count <60 000/mm³ and to 20.0% in the patients with a WBC count over 16 000/mm³.

Interestingly, high bilirubin was not a prognostic factor for death, at any cut-off value. No symptoms were significantly associated with fatal outcome neither. The strongest model for predicting fatal outcome (table 4) included hyperleucocytosis (white blood cells (WBC) count >16 000/mm³) together with elevated creatinin levels (>3mg/dl) and thrombopenia (platelet count <60 000/mm³). This model accounted for 39.1% of the variance in predicting death.

Table 3: Risk Factors for Death

Factors	Survivors(n/total)	Deaths(n/total)	p-value
WBC count >16 000/mm³	44/182	11/13	<0.01
Platelet count < 60 000/mm³	46/182	10/13	<0.01
Creatinin >3mg/dl	61/182	11/13	<0.01
Bilirubin >10mg/dl	87/182	9/13	0.13
Age >55 years	26/195	4/13	0.08
Arthralgia	16/195	3/13	0.07
Dyspnea	24/195	3/13	0.27
Diarrhea	78/195	8/13	0.13
Oliguria	7/195	0/13	0.49
Female sex	43/195	4/13	0.46

Table 4: Model for Predicting Fatal Outcome

Factors	Odds Ratios	95% CI	p-value
WBC count >16 000/mm³	11.2	2.2-57.9	<0.01
Platelet count < 60 000/mm³	9.8	2.3-41.8	<0.01
Creatinin >3mg/dl	8.9	1.0-77.2	0.05

Pseudo R^2 39.09

3.4. Disease Length

Overall, mean duration of disease prior to arrival was 4.2 (±1.8) days. Mean duration prior to arrival was not statistically different in survivors (4.2 (±1.7) days) and deaths (4.8 (±2.1) days) (p=0.78).

We considered the total disease length as the sum of the duration of disease prior to arrival and the duration of hospitalization. The overall median (and range) duration was 11 (3-53) days. The median (and range) duration in men was 11(5-53) days and was 11(3-37) days in women.

Median disease duration in survivors was 11(3-53) days, while it was 9 (3-28) days in non-survivors, which was not statistically different (p=0.22), suggesting that death did not came early in the disease course.

3.5. Accuracy of Initial Diagnosis

In our study, leptospirosis was suspected in 31.4% of the cases at admission. Table 5 shows the different diagnosis first given at the admission in our 208 patients.

Since dengue is a common disease in Indonesia, and may have some similar clinical presentations, Dengue Fever (DF) or Dengue Hemorrhagic Fever (DHF) has been diagnosed in 27.05% of the leptospirosis patients at the time of admission.

Ten percent of the patients were thought to have gastro-enteritis.

Table 5: Diagnoses at entry

Entry diagnoses	Absolute Frequency	Percentages
Leptospirosis	65	31.3
DHF	56	27.0
Typhoid fever	3	1.4
Gastroenteritis	21	10.1
Others	64	30.2
Total	**208**	**100**

4. Discussion

4.1. Clinical Presentation of Leptospirosis

This article gives an overview of the clinical presentation of leptospirosis in 208 patients from the city of Jakarta. Leptospirosis has protean manifestations, with symptoms ranging from a mild flu-like illness ("anicteric form") to a fulminant disease, also known as the "Weil's disease" or the "icteric form" occurring in 5% to 10% of the cases, and characterized by multiple organ impairment[1, 2].

The exact mechanisms explaining the clinical presentations of leptospirosis remain poorly understood[1]. An important proportion of infected individuals develop mild-or asymptomatic diseases, as reported by many studies[9, 21, 22]. In patients developing the less-severe anicteric form of the disease, symptoms classically include fever, chills, myalgia, conjunctival suffusion, anorexia, nausea and vomiting[1, 2].

Surprisingly, we found an important prevalence of diarrhea, which is not classically described in leptospirosis. Some other studies, however, have reported diarrhea in almost equivalent proportions[10, 12, 18, 23].

Cough was noticed in 21.5% of our patients. This is consistent with results from some previous studies, in France (29%)[24] and in Israel (24%)[25], but higher than in another study in Italy (6.6%)[11] and one in Bulgaria (4.5%)[19].

Conjunctival suffusion has been considered as a pathognomonic sign in leptospirosis. Several case-series have reported this symptom, with a prevalence ranging from 7.1% to 28%[10, 12, 14, 19, 24]. However, conjunctival suffusion was noted in only 6.7% of the cases in our series. This can be related to an under-detection of conjunctival suffusion, as this needs to be looked at carefully. It may also reflect a particular clinical aspect of leptospirosis in Jakarta. Conjunctival suffusion is interesting as it may help practitioners to differentiate leptospirosis from other febrile illnesses, such as dengue fever, in which conjunctival suffusion is absent.

Meningitis was absent from our case-series. This is different from what has been reported by other studies in which meningitis was present in 10% to 12% of the patients[11, 19]. However, Park et al[23] identified only one case of meningitis, out of 93 patients, in a study that was carried out in South Korea. It is unclear whether our observation is a result of a lack in precision or if these results reflect a characteristic of leptospirosis in Jakarta.

Severe leptospirosis (Weil's disease or "icteric form") classically presents with jaundice, acute renal failure (ARF), hemorrhage and even pulmonary or cardiac involvement[1, 2]. Rarer symptoms consist of skin desquamation[26], bilateral facial palsy[27] or pancreatitis[28].

We did not observe any of these rarer symptoms in our case-series. Noteworthy, many patients in our case-series developed signs of severity (such as ARF or thrombocytopenia), while maintaining their bilirubin levels at normal ranges. Previous studies[29, 30] have already described that organ impairment could occur independently, and was not necessarily related to the presence of hyperbilirubinemia. Also, in our series, the liver enzymes (sGOT, SGPT) were only mildly elevated, suggesting that liver necrosis did not occur, and that liver impairment was not the major threat in our patients. In the Seychelles, Yersin et al[30]described patients developing severe clinical syndromes, such as acute renal failure and pulmonary haemorrhage, with absence of hyperbilirubinemia. Turhan et al[29], in Istanbul, described one single patient with hyperbilirubinemia out of six severe cases of leptospirosis requiring intensive care.

It is also interesting to notice that no cut-off values in bilirubin levels could be associated with fatal outcome in our study. Moreover, bilirubin was not included our model predicting death.

Similarly to our findings, elevated WBC counts, thrombocytopenia and elevated creatinin levels have been identified as independent prognostic factors for death by others[14, 31-33], although the cut-off values for these variables differ from one study to another. In the Reunion Island, Paganin et al[31] found WBC count >13 000/mm³, thrombocytopenia <50 000/mm³ and blood creatinin levels >2.25mg/dl as independent predictors of death, among others. Ko et al[14], in Brazil, found that creatinin >4 mg/dl was a strong predictor of fatal outcome. White blood cells >12 900/mm³ was identified as risk factor for death by Dupont et al[32] in the French West-Indies.

Altered mental status was the strongest predictor of fatality in the study done by Ko et al[14]. Other predictors of outcome included oliguria, hyperkaliemia, arrhythmia, elevated blood urea nitrogen and respiratory insufficiency[14]. Dupont et al[32] also found other independent factors associated with mortality, such as dyspnea, alveolar infiltration, repolarization abnormalities and oliguria. Panaphut et al[33] conducted a prospective cohort study in Thailand and found four independent risk factors associated with mortality, which were hypotension, hyperkaliemia, the presence of pulmonary rales and oliguria. Many studies found oliguria as a strong independent factor for predicting outcome[14, 32-35]. This could not be confirmed in our study.

However, results from other studies tend to confirm that the severity of leptospirosis seems not related to liver damage, but more to renal failure, as well as respiratory and also probably cardiac failure. Elevated creatinin levels, hyperkaliemia, elevated blood nitrogen and oliguria are risk factors for death that were identified in many studies, and that all illustrate the severe renal impairment in leptospirosis. In our study, we could only analyze the renal function based on levels of creatinin, as we could not analyze the level of blood nitrogen and blood potassium.

We could not investigate the exact causes of death, since we did not perform post-mortem examinations. Reported causes of death from other studies included myocarditis, septic shock, massive and multiple organ failure and acute respiratory failure [37] with pulmonary haemorrhage[31].

The case-fatality rate we observed (6.2%) is consistent with what has been reported in previous hospital based studies in Korea (5%)[23], in Brazil (5.2%)[14], in

the Seychelles (8%)[30], in New-Caledonia (5.4%)[36] and in Bulgaria (6.6%)[19]. Katz et al reported a lower CFR (1.4%) in a large hospital based study in Hawaii[10]. Other hospital based studies have reported higher case fatality rates, such as an 11% mortality in Brazil[4] a 12.9% mortality in the Reunion Island[31], a 15% in Thailand[33] and an 18% in the West Indies[32]. In a case series among 110 patients with leptospirosis and acute renal failure in Brazil, Daher et al[35] reported a 22% of mortality rate and Covic et al[34] described a 26% mortality in 58 patients with leptospirosis and ARF in Romania, illustrating the higher case fatality rates with concomitant ARF. Again, these examples emphasize the importance of renal impairment in the severity of leptospirosis.

The difference in CFR between studies can be due to the differences in health care facilities and quality, but may be likely due to different patient inclusion criteria from one study to another.

In our study we also observed higher case fatality rates when criteria for severity were considered, especially high creatinin levels, hyperleucocytosis and severe thrombocytopenia. However, when ARF was considered, the mortality rate was still lower than in other reported studies of selected cases with ARF[25, 38], which illustrates either the quality of health care in Jakarta's hospitals, a different clinical pattern of leptospirosis in Jakarta or both.

4.2. Accuracy of Diagnosis

Our findings show that without serologic evidence, the initial clinical diagnosis is often difficult, and that differential diagnosis includes a variety of infectious diseases.

In tropical settings, the clinical presentation of leptospirosis may mimic dengue, dengue hemorrhagic fever[4-6, 14, 18], malaria[7] or ricketsial infection such as scrub typhus[8] or endemic typhus[7]. Leptospirosis may also be confounded with viral hepatitis. Laras et al[3] evaluated the causes of jaundice in different areas in South- and South-East Asia, including Jakarta. They found that leptospirosis accounted for 11% of the causes of jaundice in Jakarta.

The difficulty in distinguishing between signs and symptoms of dengue and of leptospirosis in areas where both are endemic, has been reported several times[4-6, 18]. Levett et al[5] hypothesized that the high mortality observed in the Barbados

during the leptospirosis outbreak of 1995 was partly due to a misdiagnosis of the severe cases, first thought to be dengue virus infections.

A study in Bangladesh analyzed acute-phase serum specimens from 359 patients first diagnosed with dengue fever, but who had no laboratory evidence of dengue infection[18].Their study revealed that 18% of these patients were positive for leptospira IgM antibodies. In Brazil, a hospital-based survey on leptospirosis reported that 36 % (out of 81 leptospirosis cases) were initially diagnosed as dengue cases and only 27 % got leptospirosis as first diagnosis. Recently, a study evaluated the causes of febrile illnesses in 812 children in a rural area in Thailand. Sixty-one percent of the children were found to have dengue fever, and 6% leptospirosis[37].

In endemic areas, practitioners in health facilities should include leptospirosis as a differential diagnosis in patients showing signs compatible with DF/DHF. Further studies should be conducted to compare and differentiate dengue fever and leptospirosis in areas endemic for both infections, in order to improve early diagnosis of leptospirosis.

4.3. Limitation

In our sample, serological confirmation was carried only by IgM-M rapid immunochromatography dipstick assay. It could not be done with the classical Microagglutination test (MAT), and PCR or culture could not be carried out neither. Hence, we were unable to get information concerning the infecting serogroups.
We collected the initial symptoms at admission retrospectively. Therefore, we were dependent on the quality of reporting for each medical doctor, since no standardized questionnaire was utilized. Therefore, it is plausible that some symptoms were under-reported.

Conclusion

With the myriad of clinical presentation in leptospirosis, the awareness of clinicians must remain high, especially in endemic areas and in the context of floods. Leptospirosis is not easy to recognize and is often confounded with dengue fever in endemic countries. Symptoms are wide-ranging. We found that gastro-intestinal symptoms, and especially diarrhea, were often described. Interestingly, we found that the severity of the disease was not related to the level of bilirubin per se. Some

patients developed signs of severity, such as thrombocytopenia or elevated blood creatinin levels, while maintaining bilirubin levels at normal ranges.

Thrombocytopenia and acute renal failure are complications that frequently occur in leptospirosis, and can occur independently from each other. Both were identified as important predictors of death, and included in a model predicting death, together with hyperleucocytosis.

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