CLINICAL PROFILE OF PATIENTS DIAGNOSED WITH LEPTOSPIROSIS AFTER A TYPHOON: A MULTICENTER STUDY

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Abstract. This study described the clinical features and complications of leptospirosis among patients seen at nine tertiary hospitals from September 28 to November 30, 2009 after a heavy rainfall typhoon. The clinical findings of the confirmed cases were compared with the previous clinical studies on seasonal leptospirosis in the Philippines. Risk factors for complicated disease were also identified. Confirmed cases were based on any of the following: positive leptospiral cultures of blood or urine, single high leptospira microscopic agglutination test (MAT) titer of 1:1,600, a fourfold rise in MAT, and/or seroconversion. Of 670 patients with possible leptospirosis, 591 were probable by the WHO criteria, 259 (44%) were confirmed. Diagnosis was confirmed by MAT 176 (68%), by culture 57 (22%), and by MAT and culture 26 (10%). The mean age of the confirmed cases was 38.9 years (SD 14.3). The majority were males (82%) and had a history of wading in floodwaters (98%). The majority of the patients presented with nonspecific signs, with fever as the most common (98.5%). Other findings were myalgia (78.1%), malaise (74.9%), conjunctival suffusion (59.3%), oliguria (56.6%), diarrhea (39%), and jaundice (38%). Most of the patients presented with a moderate-to-severe form of leptospirosis (83%). Complications identified were renal failure (82%), pulmonary hemorrhage (8%), meningitis (5%), and myocarditis (4%). Mortality rate was 5%, mostly due to pulmonary hemorrhage. This study emphasizes the importance of public awareness and high index of suspicion among clinicians of leptospirosis during the monsoon months when flooding is common. Early recognition and detection of the disease should decrease morbidity and mortality.

Keywords: leptospirosis, clinical profile, typhoon, community outbreak, Philippines

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INTRODUCTION

Leptospirosis is a re-emerging zoonosis of global importance because of its ability to cause disease in epidemic proportions (Pappas *et al*, 2008). Leptospirosis is highly prevalent in Asia Pacific Region,

and outbreaks in developing countries are most frequently related to normal daily activities, overcrowding, poor sanitation, and climatic conditions (Victoriano *et al*, 2009). It is an acute bacterial infection caused by spirochetes, with different pathogenic species of the genus *Leptospira.* Large numbers of animals (both wild and domestic) act as carriers or vectors that contaminate the human environment. Leptospirosis has been recognized as an endemic zoonosis and has re-emerged in areas with rapid urbanization, poor environmental sanitation, poor garbage disposal system, deforestation, and increased incidence of typhoons.

Recent outbreaks after flooding in several areas raised new awareness concerning the risk of leptospirosis in densely populated urban communities, such as Metro Manila in the Philippines (population of ≈10M). In urban areas of developing countries, a contaminated environment due to various factors–such as inadequate drainage and poor sanitation facilities for both man and animals, presence of animal carriers such as stray dogs and household rats, poor condition of slaughterhouses and people walking barefoot–all contribute to the spread of this disease.

In a case-control study in Surat City, India, after a flood, 62 laboratory confirmed leptospirosis cases out of 129 suspected cases were studied (Bhardwaj *et al*, 2008). The risk factors for acquisition of leptospirosis identified were contact of injured part with floodwater, walking barefoot, constant presence of rats in household, and spending more than four days in cleaning.

A cross sectional seroprevalence study in flood-prone rural areas in Lao People's Democratic Republic reported an overall prevalence of leptospiral infection of 23.9% (Kawaguchi *et al*, 2008). Identified risk factors for having leptospirosis were male sex, recent flooding on one's own property, and collecting wood in the forest.

In a leptospirosis outbreak in Mumbai, India, 323 suspected leptospirosis cases after a monsoon deluge in 2005 were studied (Meenakshi *et al*, 2009). Although no report on risk factors of acquisition, this study focused on describing clinical features of leptospirosis patients after the typhoon. The majority were males presenting with only fever and other nonspecific symptoms.

The Philippines has an approximate rainfall varying from 965 to 4,064 millimeters per year. On September 26, 2009, typhoon Ketsana (local name Ondoy) inundated Metro Manila with a heavy rainfall of 455 mm in just 24 hours that affected several cities and municipalities. Four-to-seven days later, Metro Manila and some other surrounding provinces were still underwater. Some of the houses that were flooded took more than 24 hours before they were completely cleaned. Cleaning up of flooded areas took days to weeks due to the mounds of garbage and mud that were left behind when the floodwaters subsided. Within a week after the typhoon, cases of leptospirosis were seen in different Metro Manila hospitals. This study was therefore developed to answer the research question: What are the clinical features of patients diagnosed with confirmed leptospirosis after the heavy rainfall Typhoon Ondoy?

The research objectives are to: 1) describe the common presenting symptoms and signs of patients during the leptospirosis outbreak; 2) identify the differences in the clinical presentation/spectrum of

the disease of patients with leptospirosis after the heavy rainfall (Ondoy) compared to previous studies published in Philippine journals and outbreak reports in other countries; and 3) describe the complications of patients with confirmed leptospirosis and the risk factors associated with renal failure, pulmonary hemorrhage and mortality.

MATERIALS AND METHODS

This was a cross sectional analytical study that described the clinical features and complications of leptospirosis among patients seen at nine tertiary hospitals from September 28 to November 30, 2009 after the heavy rainfall typhoon. The clinical findings of the confirmed cases were compared with the previous clinical studies on seasonal leptospirosis published in Philippine journals. These publications were mostly case series. Risk factors for complicated disease were also identified.

Ethical consideration

The Ethics Review Board of the Philippine General Hospital, University of Philippines Manila approved this study (Ref Nº MED 2009-11-10-119; 2009 Dec 21).

Patient population

Inclusion criteria. Patients suspected of leptospirosis after the heavy flooding of Metro Manila by Typhoon Ondoy, who consulted and/or were admitted in the following hospitals: University of the Philippines-Philippine General Hospital(UP-PGH), National Kidney and Transplant Institute (NKTI), The Medical City (TMC), University of Santo Tomas Hospital (USTH), Manila Doctors Hospital (MDH), Ospital ng Maynila Medical Center (OMMC), Cardinal Santos Medical Center (CSMC), East Avenue Medical Center (EAMC), and Makati Medical Center (MMC) from September 28, 2009 to November 30, 2009 were included in this study. These hospitals cater to the major cities and peri-urban areas flooded by Ondoy.

Criteria for suspected leptospirosis. Patients with history of exposure to floodwaters with any of the following signs and symptoms: fever, headache, myalgia, conjunctival suffusion, diarrhea and abdominal pain, jaundice, decreased urine output and changes in sensorium/ meningism were considered possible or suspected leptospirosis.

A standardized questionnaire was used and filled up by participating health care workers in their respective medical centers. The demographic profile and clinical course of the patients were obtained through patient interview and chart review. These included name, age, sex, occupation, and presence of co-morbidities. A history of wading and swimming in floodwaters was asked. Presence of leg wounds, ingestion of floodwater, and flood related injuries were also asked. The signs and symptoms of fever, headache, myalgia, conjunctival suffusion, abdominal pain, vomiting, diarrhea, and complications of organ dysfunction were noted. Analysis of data was done only for confirmed cases.

Exclusion criteria. Patients with criteria for suspected leptospirosis but later with definitive diagnosis other than leptospirosis were excluded.

Confirmed cases

Using the WHO criteria of definitive leptospirosis, laboratory confirmation of the diagnosis was based on any of the following (WHO, 2003): a) a positive leptospiral culture of the blood and/or urine; b) a high positive single micro-agglutination test (MAT) titer of 1:1,600. Blood extracted from the patient any time during his ad-

mission with single leptospirosis MAT titer of ≥1:1,600 was considered confirmed leptospirosis case; c) seroconversion from an initial negative to a positive antibody titer by MAT. An initial negative MAT titer that became positive on second sample is referred to as seroconversion and is considered confirmed leptospirosis case; d) fourfold rise in antibody titers by MAT from acute to convalescent.

Initial MAT titer representing acute phase was determined by extracting blood upon patients' consult or admission. A repeat blood extraction was done 7-10 days after the first extraction or just prior to patients' discharge to represent MAT titer of the convalescent phase. A fourfold rise of MAT titers from acute to convalescent phase was considered a confirmed leptospirosis case.

Other laboratory tests obtained were CBC with platelet count, urinalysis, serum creatinine, BUN, serum potassium, serum transaminases, chest x-ray, and electrocardiogram.

Culture isolation procedures

Blood was collected aseptically from suspected cases and inoculated into a tube of EMJH liquid media. Two drops of whole blood was inoculated in one EMJH culture tube and incubated at 28ºC for 5-6 weeks. Dark-field examination of the inoculated tubes for leptospires was done weekly for 6 consecutive weeks for detection of live leptospires.

Leptospiral urine culture was done for patients who were seen during the later phase of illness. Urine specimens were centrifuged, diluted with buffered saline, and then filtered before inoculation to EMJH culture media. Cultures were incubated at 28º to 30ºC and examined weekly by dark-field microscopy for up to 6 weeks before being discarded as negative.

Micro-agglutination test (MAT) procedures

For this study, the genus specific micro-agglutination titer method was used. *Leptospira biflexa* Patoc 1 strain of leptospira, a saprophytic strain was used since it can be agglutinated by antileptospiral antibodies present in the patients' serum regardless of the serovar of the causative pathogenic strain.

Antileptospiral antibody present in the patients' serum was tested against live Patoc leptospira antigen. Blood was collected aseptically from suspected cases. An initial 1:50 dilution of the serum was made. A 0.1 ml of liquid medium culture of the living leptospires, containing approximately 10 organisms per ml was then added and mixed to this initial dilution. A 4-fold serial dilution from the initial dilution (1:100, 1:400, 1:1,600, 1:6,400 and 1:25,600) in a microtiter plate was done. These were then read under dark field microscope after three hours of incubation at room temperature. The endpoint titer was 50%, or half of the leptospires compared with the negative control suspension had disappeared or agglutinated.

All culture and serologic examination for leptospirosis were done in a single laboratory, the Infectious Disease Section (IDS) laboratory, Medical Research Laboratory of the University of the Philippines Philippine General Hospital.

Data analysis

Data were entered using Microsoft Excel and analyses were carried out using the Statistical Package for the Social Sciences software (SPSS®; version 17; IBM, Armonk, NY). Descriptive data were summarized using frequencies and percentages for categorical data. For continuous data, means and standard deviations were computed. Bivariate and multivariable logistic regression analyses

were utilized to determine the significant poor prognostic factors. Odds ratios with 95% CI were determined.

Definition of terms

Acute renal failure: progressive azotemia (creatinine >176 mol/l or >2 mg/dl) or oliguria that may or may not require dialysis (peritoneal/hemodialysis) (Edmilao *et al*, 1995; Cordero and Valdez, 2000; Villela *et al*, 2000). Conjunctival suffusion: eye redness without exudates (Levett and Haake, 2010). Exposure to animal carcass: presence of dead rats or other animals in the nearby flooded area. Fever: axillary temperature of ≥38ºC (Speelman, 2005). Hypotension: BP<90 systolic or 40 mmHG less than patients normal blood pressure (Speelman, 2005). Meningitis: presence of any of the following: intense, bitemporal and frontal throbbing headache, with or without delirium (Levett and Haake, 2010). Mild leptospirosis: clinically compatible leptospirosis with stable vital signs, anicteric sclera, with good urine output, and no evidence of meningitis, sepsis/septic shock, difficulty of breathing nor jaundice (Levett and Haake, 2010). Moderate-severe leptospirosis: presence of any of the following without any severe indicators: beginning renal failure (azotemia, decreased urine output), dyspnea with or without need for oxygen support, basal infiltrates on chest x-ray, conjunctival suffusion, abdominal pain, and meningismus (Levett and Haake, 2010). Myocarditis: chest pain, arrhythmia on ECG, with or without cardiomegaly on chest x-ray or pericardial effusion on echocardiogram (Levett and Haake, 2010). Oliguria: urine output <400 ml/day (Speelman, 2005). Possible leptospirosis: patients with history of wading in floodwaters plus any of the following: fever, headache, myalgia, conjunctival suffusion, jaundice, meningismus and decreased urine output. Probable leptospirosis: patients with history of wading in floodwaters plus any of the following: fever, headache, myalgia, conjunctival suffusion, jaundice, meningismus and decreased urine output with negative serology or culture results. Pulmonary hemorrhage: presence of respiratory distress (RR >30 cpm) with progressing pulmonary infiltrates with or without hemoptysis (Levett and Haake, 2010). Thrombocytopenia: platelet count <100,000/mm^3. Severe leptospirosis: presence of any of the following: jaundice, renal failure, pulmonary hemorrhage, new-onset cardiac arrhythmias, hypotension even after adequate fluid resuscitation, active bleeding, sensorial changes (Levett and Haake, 2010). Weil's syndrome: most distinctive form of severe leptospirosis characterized by impaired hepatic and renal function with signs of hemorrhage (Levett and Haake, 2010).

RESULTS

Six hundred seventy possible leptospirosis patients were screened from the nine tertiary hospitals in Metro Manila who consulted and/or were admitted from September 28, 2009 to November 30, 2009 after the typhoon Ondoy. Of these, only 591 probable leptospirosis cases were included in the study, as clinical data were not extracted and/or no specimens were sent from these patients.

Out of the 591 probable leptospirosis cases, 259 were confirmed. The mean age was 38.9 (SD 14.3) and the majority were males (82%). Most (81%) had no significant comorbidities and were unemployed (38%). Patients (71%) came from Metro Manila and the remainder (29%) came from the surrounding provinces of Metro Manila. A significant proportion of confirmed cases (98%) of leptospirosis had a

Table 1
Demographic profile and distribution of confirmed leptospirosis patients (*N*=259).

Characteristic	Confirmed
Age (yrs), Mean (±SD)	38.9 (SD 14.3)
Sex, *n* (%)	
Male	213 (82.0)
Female	46 (18.0)
Occupation, *n* (%)	
Unemployed	161 (62.0)
Employed	92 (36.0)
Student	6 (2.0)
Comorbidities, *n* (%)	49 (18.9)
Waded/Swam in flood waters, *n* (%)	253 (98.0)
Swallowed flood water, *n* (%)	58 (22.4)
Presence of wound, *n* (%)	95 (37.3)
Exposure to animal carcass, *n* (%)	39 (15.0)
Duration of illness before admission, *n* (%)	
<7 dys	196 (75.7)
≥7 dys	57 (22.0)
Hospital admission, *n* (%)	
Ward	231 (89.2)
ICU	27 (10.5)
OPD	1 (0.4)
Hospital stay (days)	3 (SD 3.26)

Table 2
Laboratory confirmed leptospirosis cases (*N*=259).

Laboratory diagnosis	*n* (%)
Positive culture	57 (22.0)
Blood cultures	55 (21.2)
Urine cultures	2 (0.8)
Serology (MAT)	176 (68.0)
Single high titer	127 (49.0)
Fourfold rise	33 (13.0)
Seroconversion	16 (6.1)
Positive serology and culture	26 (10.0)

history of exposure to flood waters. Only 22.5% had an open wound and 37.3% swallowed floodwaters. Fifteen percent of the cases were exposed to animal carcass present in the flooded area (Table 1).

Most of the patients (75.7%) consulted during their first week of illness. UP-Philippine General Hospital received the most cases (34.8%). Other patients were seen in the following hospitals: National Kidney and Transplant Institute, Quezon City (29.7%); The Medical City, Pasig City (20.9%); other Manila hospitals, including UST Hospital (4.3%); Manila Doctors Hospital (2.7%); Ospital ng Maynila Medical Center (2.3%); Cardinal Santos Medical Center, San Juan (2%); East Avenue Medical Center, Quezon City (2%); and Makati Medical Center, Makati City (1.54%). The majority of patients (89.2%) were subsequently admitted. Most stayed in hospital for less than 10 days.

Table 3
Clinical and laboratory features of confirmed leptospirosis cases (*N*=259).

Characteristic	Confirmed *n* (%)
Non-specific	
Fever	255 (98.5)
Myalgia/calf tenderness	200 (78.1)
Malaise	194 (74.9)
Headache	144 (55.6)
Chills	116 (44.8)
Conjunctival suffusion	153 (59.3)
Hypotension	61 (23.6)
Gastrointestinal	
Nausea/Vomiting	136 (52.7)
Abdominal pain	133 (52.0)
Diarrhea	101 (39.0)
Jaundice	98 (38.0)
GI bleeding	41 (16.1)
Renal	
Oliguria	145 (56.6)
Hematuria	57 (22.3)
Pulmonary	
Cough	78 (30.5)
Dyspnea	56 (21.6)
Crackles/rales	60 (23.3)
Hemoptysis	38 (14.9)
Hematologic	
Hemorrhagic signs (epistaxis, petechiae) laboratory	36 (14.6)
Thrombocytopenia (<100,000/mm^3)	44 (17.0)
Leukocytosis (wbc>12,000)	117 (45.2)
Elevated creatinine (>176 mol/l)	164 (63.8)
Elevated AST (> 37 SI Units)	86 (33.3)
Elevated serum K (>4)	40 (15.4)
Elevated blood urea nitrogen (>10-20 mg/dl)	139 (57.0)

Table 4
Severe complications and mortality among confirmed cases of leptospirosis.

Complications	Total *n*=259 (%)	Mortality *n*=14 (%)	*p*-value
Renal failure	213 (82.0)	12 (86.0)	
Upon admission	190 (73.6)	11 (78.6)	0.810
Progression	23 (8.9)	1 (7.0)	0.870
Pulmonary hemorrhage	22 (8.5)	10 (71.4)	<0.001

Table 5
Risk factors for pulmonary hemorrhage (univariate analysis).

Risk factor	OR	95% CI	*p*-value
Age	1.70	0.64-4.47	0.291
Sex	0.67	0.13-3.41	0.634
Oliguria	4.00	1.30-11.60	0.035
Hemoptysis	2.35	0.76-7.27	0.137
Hypotension	6.05	2.10-17.37	0.001
Jaundice	4.00	1.50-10.00	0.010
Thrombocytopenia	3.00	1.20-8.00	0.030
Elevated creatinine	6.00	1.50-28.00	0.020

Table 6
Risk factors for pulmonary hemorrhage (multivariate analysis).

Risk factor	OR	95% CI	*p*-value
Age	1.70	0.64-4.47	0.291
Sex	0.67	0.13-3.41	0.634
Oliguria	1.82	0.51-6.51	0.358
Hemoptysis	2.35	0.76-7.27	0.137
Hypotension	6.05	2.10-17.37	0.001
Jaundice	2.33	0.79-6.88	0.125
Thrombocytopenia	1.11	0.35-3.48	0.864
Elevated creatinine	2.66	0.52-13.55	0.240

Of the confirmed leptospirosis patients, 55 (21.2%) had a positive blood culture, while two patients (0.8%) had positive urine culture. Serologic diagnoses by MAT were initial high titer in 127 (49%) cases, a four-fold rise in 33 (13%) and seroconversion in 16 (6.1%). Twenty-six patients (10%) tested positive to both serology and culture (Table 2).

Clinical and laboratory features

Among the confirmed patients studied, the average incubation period was 11.6±4.4 days. Fever was the most common presenting sign (255, 98.5%). Other signs and symptoms were myalgia (200, 78.1%), malaise (194, 79%), headache (144, 55.6%), and chills (116, 44.8%). Presence of conjunctival suffusion was seen in 153 patients (59.3%). Gastrointestinal symptoms reported were nausea and vomiting (136, 52.7%), diarrhea (10, 39%), and jaundice 98 (38%). Pulmonary signs and symptoms included cough (78, 30.5%), dyspnea (56, 21.6%), crackles (60, 23.3%), and hemoptysis (38, 14.9%). Oliguria was present in (145, 56.6%). Hemorrhage was seen in (36, 14.6%) patients. Bleeding manifestations were hematuria, gastrointestinal bleeding, and epistaxis or petechiae (Table 3).

Thrombocytopenia was present in only 44 patients (17%). Leukocytosis, or WBC >12,000, was seen in 117 (45.2%).

Table 7
Risk factors associated with renal failure in leptospirosis (univariate analysis).

Factor	OR	95% CI	*p*-value
Age	0.251	1.22-2.22	0.616
Sex	0.566	1.4-5.6	0.452
Duration of illness before admission	15.000	8.76-16.42	0.001
Creatinine at baseline	4.700	2.2-5.78	0.031
Thrombocytpenia	3.380	1.33-6.78	0.026
ICU admission	5.400	2.39-8.10	0.020
Difficulty of breathing	10.100	5.53-12.32	0.001
Oliguria	3.420	1.45-5.66	0.007
Crackles	10.100	5.53-12.32	0.001
Jaundice	6.320	1.34-8.19	0.012

Table 8
Risk factors associated with renal failure in leptospirosis (multivariate analysis).

Factor	OR	95% CI	*p*-value
Age	0.251	1.22-2.22	0.616
Sex	0.566	1.40-5.60	0.452
Duration of illness before admission (≥7 days)	15.000	8.76-16.42	0.001
Baseline creatinine (>176 mol/l)	4.700	2.20-5.78	0.031
Thrombocytopenia (<100,000/mm^3)	3.380	1.33-6.78	0.026

More than half (63.8%) of the study population had azotemia or an elevated creatinine level of >176mmol/l or >2mg/dl. Only 86 (33%) had an elevated serum AST level, and 40 (15.4%) had an elevated serum K level (Table 3).

The more severe complications of leptospirosis identified were renal failure (82%) and pulmonary hemorrhage (8.5%) as shown in Table 4. Nevertheless, 245 (95%) patients were discharged after they improved. The mortality rate was 5%, the majority due to pulmonary hemorrhage in 10 patients (71%). The other cause of death was shock in 4 patients (29%).

Pulmonary hemorrhage

Pulmonary hemorrhage occurred in 22 patients (8.5%). On univariate analysis, identified predictors for pulmonary hemorrhage were elevated creatinine (>176 mmol/l) (OR=6; 95% CI: 1.5-28), thrombocytopenia (OR=3; 95% CI: 1.2-8), jaundice (OR=4; 95% CI: 1.5-10.0), oliguria (OR=4; 95% CI: 1.3-11.6), and hypotension (OR=6; 95% CI: 2.3-14). However on multivariate analysis, only hypotension was found to be an independent predictor for pulmonary hemorrhage (OR=6; 95% CI: 2.10-17.37) (Tables 5 and 6).

Acute renal failure

Several risk factors associated with renal failure were identified. On univariate analysis, identified significant risk factors were delayed consultation and admission,

Table 9
Comparison of different published local dtudies on leptospirosis.

Reference	Sulit, 1963	Alora *et al*, 1973	Mendoza *et al*, 1979	Basaca-Sevilla *et al*, 1981	Manoloto *et al*, 1980	Villanueva *et al*, 1989	Edmilao *et al*, 1995	Casiple *et al*, 1998	Reyes and Peña 2001	Orpilla-Bautista and Panaligan 2002	This study, 2009
Number of patients	22	17	34	29	104	191	59	53	147	83	259
Signs and symptoms (%)											
Fever	100.0	100.0	92.0	100.0	97.1	100.0	100.0	100.0	95.2	99.0	98.0
Myalgia	71.0	71.0	92.0	40.0	82.9	95.3	68.0	91.0	92.5	87.0	78.1
Headache	62.0	58.8	NR	65.5	64.4	88.5	81.3	74.1	50.0	NR	55.6
Conjunctival suffusion	62.0	41.0	62.0	60.0	79.8	95.8	76.0	83.0	85.0	99.0	59.3
Abdominal pain	86.0	71.0	91.0	70.0	69.2	NR	61.0	NR	NR	26.5	52.0
Diarrhea	33.0	6.0	NR	20.0	33.6	NR	61.0	NR	NR	NR	39.0
Jaundice	100.0	29.0	74.0	60.0	70.2	77.0	68.0	60.0	56.5	1.0	38.0
Oliguria	33.0	29.0	NR	60.0	19.2	68.0	83.0	NR	37.9	66.0	56.6
Renal failure	100.0	17.6	80.0	NR	74.0	100.0	93.0	NR	89.8	89.1	82.0
Pulmonary hemorrhage	NR	6.0	NR	3.0	5	1.0	19.0	NR	NR	13.3	8.5
Thrombocytopenia	NR	NR	NR	NR	NR	50.0	61.0	NR	NR	30.0	17.0
CNS manifestations	43.0	35.0	24.0	18.0	12.5	20.9	17.0	8.0	2.7	NR	5.0
Mortality rate	43.0	24.0	6.0	NR	17.0	9.0	25.0	7.0	11.0	18.0	5.0

NR, not reported.

azotemia, thrombocytopenia, ICU admission and signs and symptoms of dyspnea, oliguria, crackles, and jaundice (Table 7).

On multivariate analysis, however the significant risk factors associated with the development of acute renal failure were duration of illness prior to admission of more than 7 days, baseline creatinine level of >176 mol/l and thrombocytopenia of <100,000/mm^3 (Table 8). Renal failure in this study was defined as progressive azotemia from a creatinine of >176/mmol/l, or oliguria.

DISCUSSION

Ecologic studies of urban epidemics of leptospirosis identified that cases geographically cluster in areas of poor sanitation and flooding during periods of heavy rainfall (Ko *et al*, 1999). In a population-based, cross sectional seroepidemiologic study in Peru, risk factors for leptospiral seropositivity include living in areas near a river and with poor sanitation (Johnson *et al*, 2004). Natural disasters (*eg*, floods and hurricanes) are recognized as increasing the risk for exposure to leptospira through contact with contaminated water or mud (Gaynor *et al*, 2007).

Table 9 shows the results of the 2009 leptospirosis outbreak in comparison with other published local hospital-based studies on leptospirosis. Previous studies were all seasonal cases of leptospirosis collected over a four-to-ten year period (retrospective studies). Diagnoses were all based on clinical criteria except for three studies. Two studies, UST 1967-1971 (Alora *et al*, 1973) and PGH 1995-1996 (Casiple, 1998), had serologic diagnosis. Only the study in 1978 in PGH (Mendoza *et al*, 1979) did leptospiral cultures to confirm the diagnosis.

The present study has the biggest study population and analyses were based on confirmed cases in an outbreak situation. Similar to the previous local studies, the majority of the patients in this outbreak study had nonspecific signs and symptoms. In the UST review of 17 cases of leptospirosis patients, prominent features described were fever, myalgia, headache, pharyngitis, abdominal pain, nuchal rigidity, conjunctival suffusion, and gastrocnemius tenderness (Alora *et al*, 1973).

In the report on human leptospirosis in 1979, clinical manifestations of leptospirosis were nonspecific such that clinicians gave different initial diagnoses before suspecting leptospirosis (Mendoza *et al*, 1979). Leptospirosis was suspected initially in only 61-65% of the patients in the above-mentioned study. The study included hospitalized and clinic patients with fever as the initial presentation. Fifty percent of those hospitalized had hepatorenal manifestations.

Another report from UST of 104 cases of leptospirosis, fever, calf tenderness and conjunctival suffusion were the most prominent features (Manaloto *et al*, 1980). The clinical findings of this study compare well with Philippine retrospective studies (Table 9) involving patients with seasonal leptospirosis. What is noteworthy is the decreasing number of patients presenting with conjunctival suffusion and more patients with diarrhea. Jaundice used to be prominent in the earlier studies; in our study, it was observed in only 38%. In the earlier studies, more CNS manifestations were observed.

More cases with pulmonary hemorrhage were observed from studies in 1996 and in 2001 compared with the present study. Renal failure remains a consistent finding in most of the studies. Previously,

pulmonary manifestations in leptospirosis were infrequently reported. However, in later reports on leptospirosis, more pulmonary manifestations were described in the study population. In this study, 253 (98%) of the total 259 confirmed leptospirosis had significant exposure to flood waters after the typhoon Ondoy.

In its pathogenesis, the leptospira enter through a skin break, mucous membrane or even the genital tract. Having open wounds increased risk for infection in a leptospirosis outbreak associated with flooding at a university campus in Oahu, Hawaii (Gaynor *et al*, 2007). Although open wounds were not that commonly observed in this study, the study patients reported other means of exposure to flood waters, such as prolonged and repeated wading, swimming and even ingestion of floodwaters.

Clinical manifestations of leptospirosis may be nonspecific to fatal. Consistent with previous reports of leptospirosis after a flood, the disease usually occurs among males exposed to floodwater with fever as the most common presenting symptom (Casiple, 1998; Cordero and Valdez, 2000). Fever was a consistent finding; therefore, a diagnosis of leptospirosis in an afebrile patient may make the diagnosis doubtful. Moreover, all clinical studies on leptospirosis outbreak after a flood indicated that nonspecific symptoms, such as headache, myalgia, abdominal pain, and diarrhea were common, and CNS manifestations were rare. Unlike other outbreak studies in Korea, Brazil, and India, renal failure was more frequently seen in the Philippines. This was the most common complication of human leptospirosis in this study. Outbreak rates ranged 5-15%. Similar to this study, there was no serovar identification of the outbreak strains. There are, however, no syndromes associated with specific serovars (Levett and Haake, 2010). Therefore, variations in the leptospiral infecting strains cannot explain the differences in the manifestations. The majority (83%) of the patients studied had moderate to severe form of leptospirosis; 39% with Weil's syndrome. The comparison of various clinical studies on leptospirosis outbreaks after a typhoon is shown in Table 10.

When compared with previous Philippine published reports (Table 9), more complications of acute renal failure and pulmonary hemorrhage were observed among the patients in this study. Based on these findings, it seems that the study population were sicker than the ones seen during times of seasonal leptospirosis. The majority of patients needed hospitalization for moderate to severe leptospirosis. They also had heavy exposure to floods. Based on the epidemiologic findings of swimming in floods and ingestion of floodwaters, although not statistically significant, these patients had more exposure to the organisms and therefore more inoculum or heavy leptospiral burden of the disease. This possibly may explain why more severe cases were observed.

Hypotension was identified as a predictor of pulmonary hemorrhage in this study. Hypotension indicates microcirculation impairment, increased capillary permeability from vasculitis, and even unrecognized bleeding. Vasculitis is the same pathogenesis for pulmonary hemorrhage in leptospirosis. Therefore, presence of hypotension may indicate severe vasculitis and can predict impending pulmonary hemorrhage.

Acute renal failure is one of the most common complications of leptospirosis. Its presence is a marker of severity and is an indication for hospitalization. The incidence varies from 10% to 60 % (Divate

Table 10
Clinical features of leptospirosis outbreak after typhoon Ondoy in comparison with outbreaks in other countries.

Reference	Park *et al*, 1990 Korea	Ko *et al*, 1999 Brazil	Pappachan *et al*, 2004 India	This study, 2009 Philippines
Number of patients	93	193	237	259
Signs and symptoms				
Fever	97.0	93.8	100.0	98.0
Myalgia	88.0	93.8	39.7	78.1
Headache	70.0	74.6	NR	55.6
Conjunctival suffusion	58.0	28.5	24.5	59.3
Abdominal pain	40.0	NR	4.2	52.0
Diarrhea	36.0	NR	7.6	39.0
Jaundice	16.0	92.7	81.4	38.0
Oliguria	NR	33.2	37.6	56.6
Renal failure	15.0	23.9	NR	82.0
Pulmonary hemorrhage	40.0	15.0	7.6	8.5
Thrombocytopenia	18.0	NR	14.3	17.0
CNS manifestations	6.0	24.9	2.1	5.0
Mortality rate	5.0	15.0	NR	5.0

NR, not reported.

et al, 2002). In this study, renal failure occurred in 82% of cases. Delayed consultation, azotemia, and thrombocytopenia were risk factors identified for developing acute kidney injury. Understandably with delayed consultation, medical intervention to prevent complications is also delayed. Therefore, patients who consulted late were found to have renal failure already present. Both azotemia and thrombocytopenia are laboratory reflections of renal abnormality in leptospirosis, which can be acute tubular necrosis and interstitial nephritis (Edmilao *et al*, 1995; Villela *et al*, 2000).

Despite the outbreak that involved many patients, mortality was only 5% in this study. This probably can be attributed to better medical intervention and care of the patients in tertiary hospitals where the patients were admitted and the timely recognition of the disease and the early declaration of an outbreak by the Department of Health. However, most of the mortality was due to pulmonary hemorrhage (71%), similar to the study done in Salvador, Brazil, where the case fatality rate due to leptospirosis associated severe pulmonary hemorrhagic syndrome (SPHS) was 74% (Gouveia *et al*, 2008).

This is the first report on a leptospirosis community outbreak in the Philippines after a heavy rainfall typhoon. Some variations in the clinical manifestations were observed compared to other local seasonal clinical studies. This study emphasizes the importance of awareness of the disease by the public during monsoon months to seek early consultation to decrease morbidity and mortality. The

clinical manifestations described will guide clinicians to have a high index of suspicion for leptospirosis after typhoons and floods.

Based on the clinical features described in this study population, leptospirosis should be part of the differential diagnosis for a patient consulting with nonspecific symptoms following a typhoon, with history of exposure to floodwaters. Chemoprophylaxis may play a role in those exposed, especially in an outbreak situation.

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