Clinical Practice: Second Opinion

nephron
Clinical
Practice

Nephron 2018;138:129–136
DOI: 10.1159/000480691

Received: August 2, 2017
Accepted after revision: August 19, 2017
Published online: September 20, 2017

Leptospirosis Renal Disease: Emerging Culprit of Chronic Kidney Disease Unknown Etiology

Chih-Wei Yang

Kidney Research Center, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

Keywords
Leptospirosis · Chronic kidney disease unknown etiology (CKDu) · Chronic kidney disease

Abstract
Leptospirosis is the most prevalent zoonosis affecting more than 1 million populations worldwide. Interestingly, leptospirosis endemic regions coincide with chronic kidney disease (CKD) hotspots largely due to flooding and agricultural overlaps. Acute leptospirosis induces multiple organ dysfunction including acute kidney injury and may predispose to CKD and end-stage renal disease, if not treated timely. Asymptomatic infection may carry the bacteria in the kidney and CKD progresses insidiously. Histologic finding of leptospirosis renal disease includes tubulointerstitial nephritis, interstitial fibrosis, and tubular atrophy. Proximal tubule dysfunction and hypokalemia are observed in adult male workers with leptospirosis, a characteristic similarity to CKD unknown etiology (CKDu). CKDu is a form of CKD that is not attributable to traditional risk factors clustering in agricultural communities affecting young male farmers. Kidney pathology shows a chronic tubulointerstitial disease. CKDu is being reported as an endemic nephropathy across the globe. Recent surveys suggest that asymptomatic leptospira renal colonization is an overlooked risk for renal fibrosis and CKDu. Population with anti-leptospira seropositivity is associated with lower estimated glomerular filtration rate in endemic regions and carrier may progress to CKD. Leptospirosis has been considered as a risk factor for CKDu in Sri Lanka and in Mesoamerican area. Sugarcane workers in Nicaragua showed increased anti-leptospira seropositivity and higher urinary biomarkers for kidney injury. Emerging evidence with signs of infection were reported in these endemic population, indicating that leptospira exposure could play a role in CKDu as a cause of primary kidney disease or a susceptible factor when secondary injury such as heat stress or dehydration aggravates kidney disease. Therefore, leptospirosis as an emerging culprit of CKDu deserves further in-depth investigation.

Leptospirosis is a re-emerging infectious disease and a leading zoonotic cause of morbidity and mortality affecting both animals and humans worldwide. This spirochetal zoonosis affects vulnerable populations via occupational animal contact, recreational exposure, and the consequence of flooding. Leptospirosis has become an emerging global public health threat affecting approximately 1.03 million population annually estimated to

E-Mail karger@karger.com
www.karger.com/nef

Dr. Chih-Wei Yang
Kidney Research Center, Chang Gung Memorial Hospital
Chang Gung University College of Medicine
No. 5, Fu-Hsing Street, Taoyuan 33333 (Taiwan)
E-Mail cwyang@ms1.hinet.net

account for 2.90 million years of life with disability global lost and is expected to become more prevalent due to global warming and extreme climatic events [1]. More than 300 serovars have been identified among leptospires, one century after discovery of the pathogen. Men are predominantly affected in 80% of the total burden. The high prevalence of this disease is contributed by the large number of animals that carry leptospira in renal tubules excreting into the environment via urine. Human infection results from accidental contact with carrier animals or contaminated environment. Majority of leptospiral infections are mild or sub-clinical illness and may recover without complications. However, a small proportion develops various complications ranging from multiple organ dysfunctions to death. Most cases of leptospirosis are detected by Microscopic Agglutination Test (MAT) for serology identification and PCR amplification of bacterial DNA from blood and urine. Urine DNA can be detected in animals that have asymptomatic kidney infection. Because of nonspecific symptoms, inadequate surveillance system, and lack of point-of-care rapid diagnostic tests, leptospirosis has been underdiagnosed.

Leptospirosis tends to develop in certain occupational groups with exposure risk of infected animal and contaminated environment and is prevalent as a disease of poverty [2]. It is also considered an occupational disease affecting paddy workers, animal handlers, sewer workers, gold mining workers, and sugarcane workers [3]. Sugarcane workers have the highest prevalence of anti-leptospiral antibodies among the occupational groups. For example, 45% of the sugarcane workers were infected in Trinidad and 59% in Chinandega, Nicaragua [4, 5]. Likewise, sugarcane workers were 5 times more likely to contract leptospirosis than were nonmanual indoor workers in Barbados [6, 7]. Highly infested rodents in the sugarcane field are the suspected vectors for the high transmission rate.

Leptospirosis Epidemiology

Leptospirosis is prevalent in warm climates particularly in tropical and sub-tropical areas. A number of leptospirosis outbreaks have occurred after cyclone and flooding in the past years in various places such as Nicaragua, Brazil, Thailand, Sri Lanka, and India etc. Between 2007 and 2013, global alerts of the leptospirosis surveillance by HealthMap database revealed that more than half of the 787 global alerts occurred in the Americas Region (63%) [8]. These alerts developed particularly in Brazil (18%), Nicaragua (6%), and Argentina (5%). The region with the second highest percentage of alerts is in Western Pacific (15%), followed by South-East Asia (14%) and Europe (8%) [8]. However, not all countries have yet recognized leptospirosis as an important public health threat to establish leptospirosis case surveillance [8]. Therefore, leptospirosis is assumed to be underdiagnosed and underreported worldwide by WHO [9].

CKD Hotspots versus Leptospirosis Global Map

Chronic kidney disease (CKD) is not homogeneously distributed worldwide. CKD hotspots are observed with higher incidence of CKD and are distributed in different countries, regions, communities, or ethnicities [10, 11]. Some have been explained of the cause of CKD, such as cadmium in Itai-Itai disease in Japan and aristolochic acid in Balkan nephropathy, whereas the etiology of many others remained unclear, therefore termed CKD of unknown etiology (CKDu) [12]. CKDu is a form of CKD that is not attributable to any traditional risk factor, such as diabetes, hypertension, or HIV. A common feature of CKDu is the occurrence among young male farmers in agricultural communities. Clinically, they usually present with normal or mildly elevated blood pressure, progressive reduction in renal function, low-grade proteinuria, and often hyperuricemia, and or hypokalemia. Kidney pathology shows a chronic tubulointerstitial disease with fibrosis [13]. Examples of global epidemic of CKDu include Mesoamerica, Sri Lanka, African Americans, Aboriginals in Australia, and India. CKDu is a major public health threat causing significant morbidity and mortality affecting middle-aged men with more than 20,000 casualties in Mesoamerica areas and elsewhere with high mortality due to end-stage renal disease. However, despite their geographical separation, there are striking similarities between these endemic nephropathies [12]. On the other hand, leptospirosis affects a large proportion of population and is estimated to occur in adult men with age of 20–50 years, similar to regions of CKDu where agricultural workers were largely encountered. Highest estimates of leptospirosis were observed in South and Southeast Asia, Oceania, Caribbean, Andean, Central, Tropical Latin America, and East Sub-Saharan Africa [2]. Important to note, among the CKD hotspots where CKDu developed, endemic areas of leptospirosis tend to coincide with the high incidence of CKDu. This geographic overlap strongly suggests leptospirosis could play a possible role in CKDu which deserves in-depth investi-

gation. For example, in Sri Lanka, where CKDu is highly prevalent in the central dry zone with paddy field, leptospirosis outbreaks were found notably in historic record, with the most recent ones in 2008 and 2011 [14, 15]. Another example is the sugarcane fields in Chichigalpa, Chinandega in Nicaragua, a focus of CKDu development, where leptospirosis is prevalent, with a major outbreak occurring in 1995 after flooding [16, 17]. In these CKDu patients, some have experienced clinical manifestations of acute infection, similar to having episodes of acute leptospirosis [18]. Thus, it is speculated that infectious pathogens particularly leptospira, shedding through urine and feces from highly infested rodents, may infect workers during the process of cultivating and harvesting sugarcane or after exposure to major flooding containing leptospira [18]. Once infected, this difficult-to-diagnose neglected tropical disease, particularly in the resource-poor setting, may hinder proper clinical identification and timely treatment. Therefore, the bacteria may not have been thoroughly eradicated and kept multiplying within the kidney. Despite increasing mechanization and the use of more protective clothing, agricultural workers are still at high environment risk of leptospirosis in which kidney injury may insidiously develop and progress.

Leptospirosis Renal Disease

Leptospirosis has been increasingly recognized as an important infectious disease in Taiwan since 1997 and Leptospira santarosai serovar Shermani is the main serovar encountered [19]. Leptospirosis appears to be underestimated in Taiwan and affects at least 10% of patients with multiple organ dysfunctions [20]. Acute severe infection may present with multiple organ dysfunctions, and the most common triad is fever, jaundice, and acute renal failure [19]. Acute renal failure characterized by proximal tubule dysfunction, hypokalemia, and non-oliguria is manifested with histological findings of mainly acute tubulointerstitial nephritis and acute tubular necrosis [21]. Timely treatment with penicillin and tetracycline are effective and may dramatically rescue patients from multiple organ failure. On the other hand, chronic leptospirosis may develop if leptospira persists in the tubular lumen and interstitium as a continuum of acute kidney injury or asymptomatic renal colonization with insidious clinical symptoms that occur in 2.3–52.7% of population at risk [4, 22]. Chronic leptospira kidney infection may present with characteristic chronic tubulointerstitial nephritis and interstitial fibrosis, a well-known characteristic in animals. Leptospira outer membrane proteins elicit tubular injury and inflammation through toll-like receptors-dependent pathway followed by activation of nuclear transcription factor kappa B and mitogen-activated protein kinases and a differential induction of chemokines and cytokines relevant to tubular inflammation [23]. Leptospira outer membrane protein may also induce activation of the transforming growth factor-beta/Smad-associated fibrosis pathway leading to accumulation of extracellular matrix [24]. Leptospirosis renal disease, therefore, is a model for understanding the result of pathogen-induced tubulointerstitial nephritis and fibrosis [25–27]. In particular, toll-like receptors may be important mediators.

Diagnosis of leptospirosis is based on clinical and epidemiologic data and is confirmed through serology tests. The most widely used serology method MAT is performed using 2 blood samples collected 2 weeks apart. The MAT results are considered positive when the antibody titers are 4 times higher than the reference value for diagnosis of acute leptospirosis. Leptospirosis renal disease is characterized by tubulointerstitial nephritis. In animals, kidney disease, either acute or chronic carrier leptospirosis, can be confirmed by detecting leptospira DNA from kidney tissue or urine [28]. Appropriate antibiotics such as penicillin or tetracycline are effective for leptospiral nephropathy [28].

Leptospirosis Chronic Carrier and CKD

Leptospira infection may induce renal fibrosis as is evidenced in in vitro and animal study indicating the propensity that infection may lead to renal fibrosis [24, 29]. In Sri Lanka, in a long-term follow up of leptospirosis patients with overt AKI, 9% of patients developed an early stage of CKD [30]. As leptospira may colonize in the proximal tubule resulting in chronic tubulointerstitial nephritis and fibrosis, asymptomatic exposure to leptospira infection carries the risk for CKD. In the southern part of Taiwan, flooding was frequent as a result of typhoons. Of 3,045 survey participants, 33.2% of the individuals have had previous leptospira exposure harboring positive anti-leptospiral antibody. These seropositive populations disclosed a 2.5% lower level of estimated glomerular filtration rate (eGFR) and a higher percentage of CKD at stage 3a-5 (14.4 vs. 8.5%), than those without leptospira exposure [22]. In a leptospiral endemic town, subjects with a higher anti-leptospiral antibody by MAT titer of more than 400 showed a decreased eGFR and higher

urinary kidney injury molecule-1 creatinine ratio level as compared with those having lower titers of MAT in a 2-year cohort. Furthermore, 2 residents with persistently high MAT titers had detectable urine leptospira DNA and deteriorating renal function in a 2-year cohort indicating that asymptomatic kidney infection may lead to CKD [22].

Pathogenic leptospira may persist in asymptomatic domestic animals, humans, and environmental water sources [31]. Humans are known to excrete leptospires in their urine after recovery from illness and there are reports showing development of asymptomatic leptospiuria in settings of high disease transmission. In the Amazon area, 4.1% of Peruvian residents carry leptospira asymptomatically [32]. In Tamil Nadu, India, positive urine leptospira DNA was identified from 52.7% (129 of 245) asymptomatic participants. Serological results showed that 20.4% (50 of 245) of persons with urine DNA positivity were even negative for MAT indicating that deficient immunity may allow the persistence of carrier status [33]. In Nicaragua, after a major outbreak of leptospirosis in 1995, 85 out of 566 (15.0%) persons were found to be seropositive by immunoglobulin M enzyme-linked immunosorbent assay, in which only 25 (29.4%) reported having a febrile illness during the preceding 2 months; the remaining 60 (70.6%) had asymptomatic infection [34]. Multivariable analysis revealed that having an indoor water source remained independently protective against leptospirosis [34]. These data indicate that leptospira may remain in the renal tubule for a certain period after infection, however, clinically remains asymptomatic. In the carrier status, large mammals including humans are estimated to excrete much more urine and shed significantly more leptospira per day than rats from a meta-analysis [35].Thus, in leptospirosis endemic regions a greater possibility exists in humans as maintenance host rather than incidental hosts. The carrier status of chronic leptospirosis within the kidney, in individuals with asymptomatic clinical settings, represents an overlooked focus in the need for intensive public health attention. Finally, identification of the kidney-prone pathogens and the mechanism of pathogen-host interaction serve as a new global strategy for CKD prevention and eradication.

Nicaragua

In Nicaragua, heat stress and dehydration are suggested to play role in Mesoamerican nephropathy. Interestingly, the area of high CKD prevalence superimposed on the leptospira endemic area; thus, leptospirosis is also postulated as a possible cause in Central American workers but direct evidence is pending [36]. Riefkohl et al. [4] took further steps to study the role of leptospira infection in CKDu. Job-specific Leptospira anti-leptospiral antibody seroprevalence and its association with kidney disease biomarkers were studied in 282 sugarcane workers, 47 sugarcane applicants, and 160 workers in other industries. Consistent to previous studies, leptospira antibody seroprevalence differed among job categories and was highest among sugarcane cutters (59%). In addition, seropositive sugarcane workers had higher levels of biomarker of kidney injury (IL-18, NGAL, and NAG) compared to those who were seronegative [4]. This indicates that leptospiral exposure may undergo subclinical kidney injury.

Leptospira seropositivity was not associated with reduction of eGFR in sugarcane workers. However, leptospira seropositivity was associated with eGFR decline in sugarcane applicants, who was excluded by initial employee physical check due to elevated creatinine at the time of testing [4]. These data indicate that leptospira infection is associated with kidney dysfunction, a consistent finding to previous population study where leptospira seropositivity is associated with declined eGFR [22]. On the other hand, urine albumin/creatinine ratio is not associated with leptospira exposure consistent to the nonproteinuric renal disease of CKDu. This study showed that leptospirosis, in most of cases that do not develop overt AKI, can cause some degree of subclinical kidney injury. Individuals who are seropositive to leptospira could be more susceptible to additional kidney insults such as heat stress and dehydration. Urine leptospira DNA was not detected in this group and what is yet to be done in this study is the detection of leptospira DNA within the kidney. Future clinical study needs to aim for detecting leptospira pathogen within the kidney of individuals exposed to leptospira infection that develop CKD at extreme heat environment as second hit.

Sri Lanka

Sri Lanka, located near the equator, has experienced a rising incidence of CKDu for the past 2 decades particularly in central dry zonal areas, concentrated with paddy fields. Researchers have established hypotheses to identify potential risk factors for causative agents. However, the precise risk factors and the pathogenesis of CKDu has yet to be proven. Histology of renal biopsy done at sus-

Table 1. Similarities between leptospirosis renal disease and CKDu

	Leptospirosis renal disease	CKDu
Risk factors	Hot climate, flooding	Hot climate
Field worker	Paddy, sugarcane	Paddy, sugarcane
Animal contact	+	?
Gender preference	Middle age male	Middle age male
Tubulointerstitial nephritis	+	+
Interstitial fibrosis	+	+
Nonproteinuria	+	+
Proximal tubule dysfunction	+	+
Hypokalemia	+	+

pected CKDu patients was compatible with an interstitial nephritis mixed with acute and chronic tubulointerstitial lesions and glomerular scarring [37]. Therefore, CKDu in Sri Lanka is suspected to be preceded by an acute episode of tubulointerstitial nephritis indicating infection of a particular cause [38]. For the past decades in Sri Lanka, reduction of malaria was associated with concurrent increase of several tropical diseases including dengue, leptospirosis, and rickettsioses [39]. In 2008, a leptospirosis outbreak occurred near the dry zone, and in 2011, another outbreak of leptospirosis came to attention in the relatively dry district of Anuradhapura [14]. For the causative agents, both leptospirosis and hantavirus infections are important zoonotic diseases naturally maintained and transmitted via infected rodent and are known to be causes of acute kidney damage that can proceed into chronic renal failure. Several studies have reported presence of both infections in Sri Lanka. The proposed infectious hypothesis is under evaluation by means of observational study design to disclose the relationship between leptospirosis and CKDu in Sri Lanka [40].

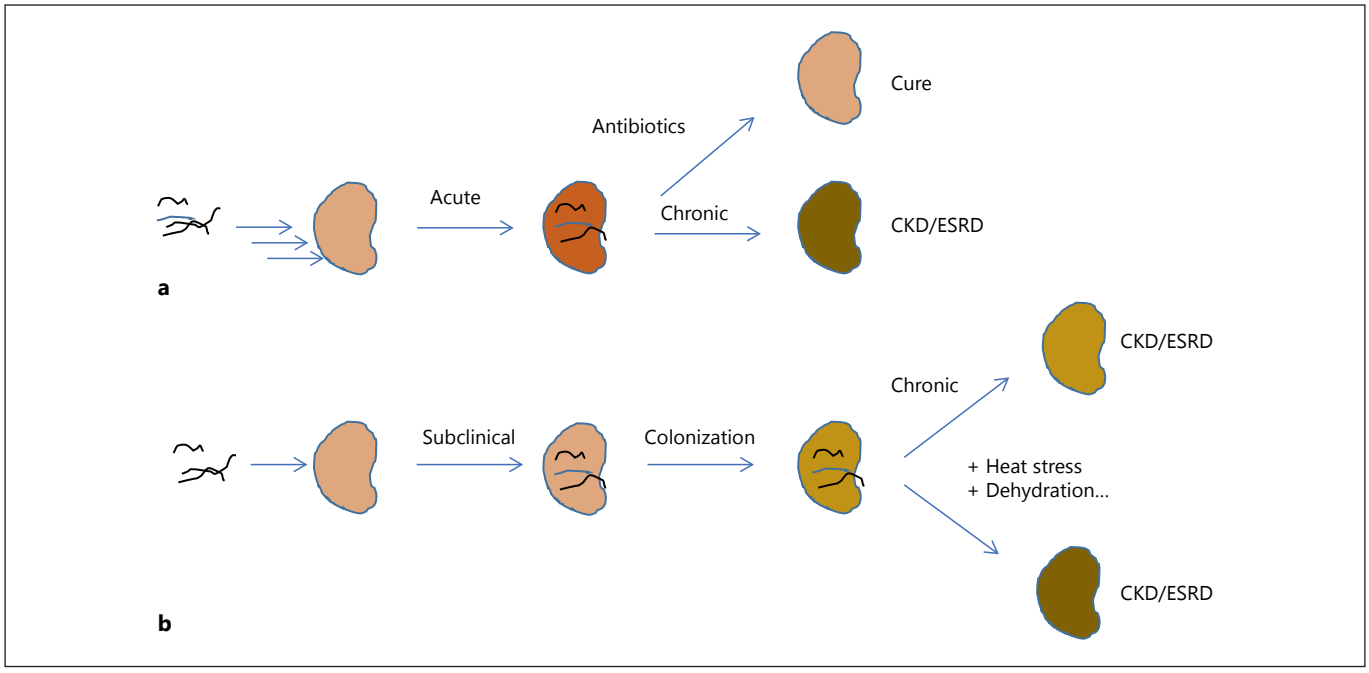
From Current Hypothesis to Second Opinion

Heat stress, dehydration, and kidney dysfunction were commonly observed among sugarcane cutters. High serum uric acid was associated with reduced kidney function [41]. These events when repeated on a daily basis may cause permanently reduced GFR [42]. The heat stress and dehydration hypothesis, however, cannot explain why the incidence of CKDu went up in Sri Lanka along with modernized mechanization of paddy farming in the 1990s and the nonexistence of CKDu in hotter northern Sri Lanka, Cuba, and Myanmar. Similarly, in Nicaragua, these events cannot explain why CKDu was heavily observed only in sugarcane fields where leptospirosis was prevalent. Existing evidence supports occupational and environmental toxins are the primary triggers and the similarity of CKDu between Mesoamerican nephropathy and Sri Lanka narrow down to a common single caustic agent that ubiquitously persists in these 2 regions, that is, leptospirosis (Table 1). This indicates that heat stress and dehydration may be a contributory or a necessary risk factor, but which may not cause CKDu by itself [43].

CKDu: A Neglected Tropical Disease with an Infectious Etiology?

Considering the similarities between CKDu and leptospirosis renal disease, the geographical overlap with the similar population affected and the epidemiological evidence of CKD with leptospira exposure, leptospirosis has become a priority candidate cause of CKDu deserves to be confirmed. Leptospira infection induces acute kidney injury. If not treated properly, an AKI to CKD continuum may develop. On the other hand, CKD may develop in asymptomatic population where carrier status of leptospira persists in the kidney contributing to the progression of kidney disease. Secondary injury including heat stress and dehydration may further aggravate the kidney injury. Thus, leptospira infection may be a cause of primary kidney disease or a CKD susceptibility factor, when kidney injury persists insidiously. In the field workers exposed to extreme heat and dehydration, CKD may be aggravated as second hit superimposed on preexisting kidney injury by insidious leptospira infection (Fig. 1).

Both leptospirosis and hantaviral infections are important zoonotic diseases, transmitted via rodents, known to be causes of acute kidney injury and may proceed to CKD



Color version available online

Fig. 1. Natural history of leptospirosis renal disease. **a** Leptospira infection induces acute kidney injury. If not treated properly, an AKI to CKD continuum may develop. **b** On the other hand, CKD may develop in asymptomatic population where carrier status of leptospira persists in the kidney contributing to the progression of kidney disease. Thus, leptospira infection may be a cause of primary kidney disease or a CKD susceptibility factor, when kidney injury persists insidiously.

[44]. Both infections have similar clinical presentations and epidemiological features likely to be clinically misdiagnosed and indistinguishable due to non-specific presentation [28, 45]. Recent report indicates higher hantavirus seropositivity among CKDu patients in Sri Lanka [46]. Therefore, both diseases await extensive study.

We propose in this Second Opinion that leptospira infection deserves to be studied in-depth to understand the hidden cause of CKDu. Detection of pathogen should be done in the available tissue by kidney biopsy and in urine. The correlation of leptospira serology and CKD is worthwhile to confirm in different geographical CKD hotspots. Intervention with clean water would help to improve sanitation environment particularly in poor-resource settings to avoid water-borne transmission. The final gain of this approach will be warranted when early treatment with appropriate antibiotics to intervene CKD progression and to rescue the population from the vicious cycle of infection-initiated CKDu have become realistic.

Disclosure Statement

The author has no conflict of interest to declare.

References

1 Torgerson PR, Hagan JE, Costa F, Calcagno J, Kane M, Martinez-Silveira MS, Goris MG, Stein C, Ko AI, Abela-Ridder B: Global burden of leptospirosis: estimated in terms of disability adjusted life years. PLoS Negl Trop Dis 2015;9:e0004122.

2 Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-Silveira MS, Stein C, Abela-Ridder B, Ko AI: Global morbidity and mortality of leptospirosis: a systematic review. PLoS Negl Trop Dis 2015;9:e0003898.

3 World Health Organization: Human Leptospirosis: Guidance for Diagnosis, Surveillance and Contro, 2003.

4 Riefkohl A, Ramirez-Rubio O, Laws RL, McClean MD, Weiner DE, Kaufman JS, Galloway RL, Shadomy SV, Guerra M, Amador JJ, Sanchez JM, Lopez-Pilarte D, Parikh CR, Leibler JH, Brooks DR: Leptospira seropositivity as a risk factor for Mesoamerican Nephropathy. Int J Occup Environ Health 2017:1–10.

5 Everard CO, Hayes RJ, Fraser-Chanpong GM: A serosurvey for leptospirosis in Trinidad among urban and rural dwellers and persons occupationally at risk. Trans R Soc Trop Med Hyg 1985;79:96–105.

6 Everard CO, Bennett S, Edwards CN, Nicholson GD, Hassell TA, Carrington DG, Everard JD: An investigation of some risk factors for severe leptospirosis on Barbados. J Trop Med Hyg 1992;95:13–22.

7 Damude DF, Jones CJ, White HS, Myers DM: The problem of human leptospirosis in Barbados. Trans R Soc Trop Med Hyg 1979;73:169–177.
8 Schneider MC, Jancloes M, Buss DF, Aldighieri S, Bertherat E, Najera P, Galan DI, Durski K, Espinal MA: Leptospirosis: a silent epidemic disease. Int J Environ Res Public Health 2013;10:7229–7234.
9 World Health Organization: Report of the First Meeting of the Leptospirosis Burden Epidemiology Reference Group. Geneva, Switzerland, 2010.
10 Abraham G, Varughese S, Thandavan T, Iyengar A, Fernando E, Naqvi SA, Sheriff R, Ur-Rashid H, Gopalakrishnan N, Kafle RK: Chronic kidney disease hotspots in developing countries in South Asia. Clin Kidney J 2016;9:135–141.
11 Martin-Cleary C, Ortiz A: CKD hotspots around the world: where, why and what the lessons are. A CKJ review series. Clin Kidney J 2014;7:519–523.
12 Gifford FJ, Gifford RM, Eddleston M, Dhaun N: Endemic nephropathy around the world. Kidney Int Rep 2017;2:282–292.
13 Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW: CKD of uncertain etiology: a systematic review. Clin J Am Soc Nephrol 2016;11:379–385.
14 Agampodi SB, Dahanayaka NJ, Bandaranayaka AK, Perera M, Priyankara S, Weerawansa P, Matthias MA, Vinetz JM: Regional differences of leptospirosis in Sri Lanka: observations from a flood-associated outbreak in 2011. PLoS Negl Trop Dis 2014;8:e2626.
15 Agampodi SB, Peacock SJ, Thevanesam V, Nugegoda DB, Smythe L, Thaipadungpanit J, Craig SB, Burns MA, Dohnt M, Boonsilp S, Senaratne T, Kumara A, Palihawadana P, Perera S, Vinetz JM: Leptospirosis outbreak in Sri Lanka in 2008: lessons for assessing the global burden of disease. Am J Trop Med Hyg 2011;85:471–478.
16 Trevejo RT, Rigau-Perez JG, Ashford DA, McClure EM, Jarquin-Gonzalez C, Amador JJ, de los Reyes JO, Gonzalez A, Zaki SR, Shieh WJ, McLean RG, Nasci RS, Weyant RS, Bolin CA, Bragg SL, Perkins BA, Spiegel RA: Epidemic leptospirosis associated with pulmonary hemorrhage-Nicaragua, 1995. J Infect Dis 1998;178:1457–1463.
17 Schneider MC, Najera P, Aldighieri S, Bacallao J, Soto A, Marquino W, Altamirano L, Saenz C, Marin J, Jimenez E, Moynihan M, Espinal M: Leptospirosis outbreaks in Nicaragua: identifying critical areas and exploring drivers for evidence-based planning. Int J Environ Res Public Health 2012;9:3883–3910.
18 Murray KO, Fischer RS, Chavarria D, Duttmann C, Garcia MN, Gorchakov R, Hotez PJ, Jiron W, Leibler JH, Lopez JE, Mandayam S, Marin A, Sheleby J: Mesoamerican nephropathy: a neglected tropical disease with an infectious etiology? Microbes Infect 2015;17:671–675.
19 Yang CW: Leptospirosis in Taiwan – an underestimated infectious disease. Chang Gung Med J 2007;30:109–115.
20 Yang HY, Yen TH, Lin CY, Chen YC, Pan MJ, Lee CH, Yu CC, Wu MS, Wu SS, Weng CH, Chen KH, Hung CC, Yang CW: Early identification of leptospirosis as an ignored cause of multiple organ dysfunction syndrome. Shock 2012;38:24–29.
21 Yang CW, Wu MS, Pan MJ: Leptospirosis renal disease. Nephrol Dial Transplant 2001;16(suppl 5):73–77.
22 Yang HY, Hung CC, Liu SH, Guo YG, Chen YC, Ko YC, Huang CT, Chou LF, Tian YC, Chang MY, Hsu HH, Lin MY, Hwang SJ, Yang CW: Overlooked risk for chronic kidney disease after leptospiral infection: a population-based survey and epidemiological cohort evidence. PLoS Negl Trop Dis 2015;9:e0004105.
23 Tian YC, Hung CC, Li YJ, Chen YC, Chang MY, Yen TH, Hsu HH, Wu MS, Phillips A, Yang CW: Leptospira santorosai Serovar Shermani detergent extract induces an increase in fibronectin production through a Toll-like receptor 2-mediated pathway. Infect Immun 2011;79:1134–1142.
24 Tian YC, Chen YC, Hung CC, Chang CT, Wu MS, Phillips AO, Yang CW: Leptospiral outer membrane protein induces extracellular matrix accumulation through a TGF-beta1/Smad-dependent pathway. J Am Soc Nephrol 2006;17:2792–2798.
25 Chang MY, Cheng YC, Hsu SH, Ma TL, Chou LF, Hsu HH, Tian YC, Chen YC, Sun YJ, Hung CC, Pan RL, Yang CW: Leptospiral outer membrane protein LipL32 induces inflammation and kidney injury in zebrafish larvae. Sci Rep 2016;6:27838.
26 Hsu SH, Lo YY, Tung JY, Ko YC, Sun YJ, Hung CC, Yang CW, Tseng FG, Fu CC, Pan RL: Leptospiral outer membrane lipoprotein LipL32 binding on toll-like receptor 2 of renal cells as determined with an atomic force microscope. Biochemistry 2010;49:5408–5417.
27 Yang CW: Leptospirosis renal disease: understanding the initiation by Toll-like receptors. Kidney Int 2007;72:918–925.
28 Andrade L, de Francesco Daher E, Seguro AC: Leptospiral nephropathy. Semin Nephrol 2008;28:383–394.
29 Fanton dM, Quellard N, Fernandez B, Ratet G, Lacroix-Lamande S, Vandewalle A, Boneca IG, Goujon JM, Werts C: Leptospira Interrogans induces fibrosis in the mouse kidney through Inos-dependent, TLR- and NLR-independent signaling pathways. PLoS Negl Trop Dis 2014;8:e2664.
30 Herath NJ, Kularatne SA, Weerakoon KG, Wazil A, Subasinghe N, Ratnatunga NV: Long term outcome of acute kidney injury due to leptospirosis? A longitudinal study in Sri Lanka. BMC Res Notes 2014;7:398.
31 Kurilung A, Chanchaithong P, Lugsomya K, Niyomtham W, Wuthiekanun V, Prapasarakul N: Molecular detection and isolation of pathogenic Leptospira from asymptomatic humans, domestic animals and water sources in Nan province, a rural area of Thailand. Res Vet Sci 2017;115:146–154.
32 Ganoza CA, Matthias MA, Saito M, Cespedes M, Gotuzzo E, Vinetz JM: Asymptomatic renal colonization of humans in the peruvian Amazon by Leptospira. PLoS Negl Trop Dis 2010;4:e612.
33 Sivasankari K, Shanmughapriya S, Natarajaseenivasan K: Leptospiral renal colonization status in asymptomatic rural population of Tiruchirapalli district, Tamilnadu, India. Pathog Glob Health 2016;110:209–215.
34 Ashford DA, Kaiser RM, Spiegel RA, Perkins BA, Weyant RS, Bragg SL, Plikaytis B, Jarquin C, De Lose Reyes JO, Amador JJ: Asymptomatic infection and risk factors for leptospirosis in Nicaragua. Am J Trop Med Hyg 2000;63:249–254.
35 Barragan V, Nieto N, Keim P, Pearson T: Meta-analysis to estimate the load of Leptospira excreted in urine: beyond rats as important sources of transmission in low-income rural communities. BMC Res Notes 2017;10:71.
36 Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH: Resolving the enigma of the mesoamerican nephropathy: a research workshop summary. Am J Kidney Dis 2014;63:396–404.
37 Badurdeen Z, Nanayakkara N, Ratnatunga NV, Wazil AW, Abeysekera TD, Rajakrishna PN, Thinnarachchi JP, Kumarasiri R, Welagedera DD, Rajapaksha N, Alwis AP: Chronic kidney disease of uncertain etiology in Sri Lanka is a possible sequel of interstitial nephritis! Clin Nephrol 2016;86(suppl 1):106–109.
38 Nanayakkara S, Komiya T, Ratnatunga N, Senevirathna ST, Harada KH, Hitomi T, Gobe G, Muso E, Abeysekera T, Koizumi A: Tubulointerstitial damage as the major pathological lesion in endemic chronic kidney disease among farmers in North Central Province of Sri Lanka. Environ Health Prev Med 2012;17:213–221.
39 Agampodi S, Wijerathne B, Weerakoon K: Situation of Sri Lanka, where autochthonous malaria is no longer a problem, and other infections dominate, such as dengue, leptospirosis and rickettsioses. Curr Opin Infect Dis 2016;29:446–452.
40 Gamage CD, Sarathkumara YD: Chronic kidney disease of uncertain etiology in Sri Lanka: are leptospirosis and Hantaviral infection likely causes? Med Hypotheses 2016;91:16–19.
41 Wesseling C, Aragon A, Gonzalez M, Weiss I, Glaser J, Rivard CJ, Roncal-Jimenez C, Correa-Rotter R, Johnson RJ: Heat stress, hydration and uric acid: a cross-sectional study in workers of three occupations in a hotspot of Mesoamerican nephropathy in Nicaragua. BMJ Open 2016;6:e011034.

42 Wesseling C, Aragon A, Gonzalez M, Weiss I, Glaser J, Bobadilla NA, Roncal-Jimenez C, Correa-Rotter R, Johnson RJ, Barregard L: Kidney function in sugarcane cutters in Nicaragua – a longitudinal study of workers at risk of Mesoamerican nephropathy. Environ Res 2016;147:125–132.
43 Jayasumana C, Orantes C, Herrera R, Almaguer M, Lopez L, Silva LC, Ordunez P, Siribaddana S, Gunatilake S, De Broe ME: Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. Nephrol Dial Transplant 2017;32:234–241.
44 Sion ML, Hatzitolios AI, Armenaka MC, Toulis EN, Kalampalika D, Mikoudi KD: Acute renal failure caused by leptospirosis and Hantavirus infection in an urban hospital. Eur J Intern Med 2002;13:264–268.
45 Bi Z, Formenty PB, Roth CE: Hantavirus infection: a review and global update. J Infect Dev Ctries 2008;2:3–23.
46 Gamage CD, Yoshimatsu K, Sarathkumara YD, Kulendiran T, Nanayakkara N, Arikawa J: Serological evidence of hantavirus infection in Girandurukotte, an area endemic for chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka. Int J Infect Dis 2017;57:77–78.