ISSN: 1220-3173; E-ISSN: 2457-7618

ACUTE RENAL FAILURE BY LEPTOSPIROSIS

INSUFICIENȚA RENALĂ ACUTĂ PRIN LEPTOSPIROZĂ

C. LIBRIMIR[1)*], M. NICOLICIOIU[1)], L. NEGRUȚIU[1)], L. GEORGESCU[1)], R.D. PALICICA[2)], I. ROMOȘAN[1)]

ABSTRACT | REZUMAT

The present paper presents 40 cases of patients with acute renal failure (ARF) by leptospirosis, hospitalised between 1970 and 1981 in the Hemodialysis Centre of the Medical Clinic No. II in Timisoara, representing 4.2% of the total ARF patients hospitalised during the mentioned period and 25% of the infectious cases (with the exception of septic abortion). The ARF was characterised by severe nitrogen retention with a marked increase rate. The hepatic impairment was moderate. Conservative treatment was applied in 14 patients, while hemodialysis - associated treatment was administered in other 15 cases. Unfavourable evolutions (45% of cases) were mainly caused by major haemorrhages (digestive), regarded as a severity prognosis element. Further experience of one of the authors of the original study confirms previous studies on 11 additional cases during the period 1982-2017.

Keywords: ARF, *Leptospira*, zoonosis

Sunt comunicate 40 de cazuri de bolnavi cu insuficiență renală acută (IRA) prin leptospiroză, internați între anii 1970 și 1981 în Serviciul de Hemodializă al Clinicii a II-a Medicale din Timișoara, reprezentând 4,2% din totalul bolnavilor de IRA internați în aceeași perioadă și 25% din cazurile de natură infecțioasă (exceptând avortul septic). IRA s-a caracterizat printr-o retenție azotată severă cu marcată rată de creștere. Afectarea hepatică a fost moderată. S-a aplicat tratament conservator la 14 pacienți și tratament asociat cu hemodializă în 15 cazuri. Evoluția nefavorabilă (45% din cazuri) a fost determinată mai ales de sindromul hemoragipar major (hemoragie digestivă), considerat ca element de prognostic sever. Experiența ulterioară a unuia din autorii studiului original confirmă studiile anterioare pe încă 11 cazuri în perioada 1982-2017.

Cuvinte cheie: IRA, *Leptospira*, zoonoza

Leptospirosis is a pantropic disease, most frequently causing renal, hepatic and meningocerebral lesions, completed by less frequent but more severe cardiac lesions (6, 17, 28). The paper aims to present anatomic-clinical characteristics of acute renal failure (ARF) cases produced by leptospirosis and to establish a diagnostic and therapeutic approach to be used for future cases.

MATERIALS AND METHODS

Between 1970 and 1981, of a total of 690 patients with ARF of various aetiologies, the diagnosis of ARF by leptospirosis was set in 29 cases (4.2%) which were included in group A (17). Regarding ARF caused by infections, excluding post-abortion sepsis (18), in 110 patients leptospirosis was diagnosed in 26% of cases.

Between 1982 and 2017 patients were examined at the Clinic for Infectious Diseases (group B).

Cases included 19 men and 10 women, aged between 16-65 years, with a mean age of 40 years for group A and 6 men and 5 women with a mean age of 36 years for group B.

All patients were transferred from other hospitals for the syndrome of acute renal failure and admitted in the haemodialysis department (group A) and in the Clinic for Infectious Diseases Timisoara (group B), respectively.

The diagnosis of leptospirosis was set based on clinical data (fever, shivers, headache, myalgia, conjunctival congestion,meningo-encephalitic syndrome, jaundice, dyspeptic disorders, and haemorrhagic syndrome), laboratory findings (ESR, haemogram, fibrinogen, serological test for leptospirosis – agglutination-lysis test, complement fixation) and histological data obtained by necropsy.

The ARF was diagnosed by clinical data (oligo-anuria corroborated to relevant cytology), laboratory results (serum urea, uric acid, creatinine, clearance tests, serum ionogram, osmolarity), urinary tests (uri-

1) University of Medicine and Pharmacy "Victor Babeş" Timișoara, Romania
2) Banat`s University of Agricultural Science and Veterinary Medicine "King Michael I of Romania", Faculty of Veterinary Medicine Timișoara, Romania
*) *Corresponding author: librimir.cosmin@umft.ro*

nalysis, Addis sediment, proteinuria, ionogram, osmolarity) and renal histology (bioptic puncture with optic microscopic examination and/or electron microscopy, necropsy) and histopathologic tests.

Liver impairment was diagnosed by clinical symptoms (hepatomegaly, splenomegaly, jaundice), laboratory findings (serum transaminase levels–GOT, GPT, bilirubin, alkaline phosphatase, cholinesterase, prothrombin time by the Quick method, proteinogram, thymol reaction) and histopathologic data obtained by necropsy.

In order to exclude other infectious aetiologies, blood cultures, urine cultures and other serologic examinations were performed.

RESULTS AND DISCUSSIONS

Clinical signs of leptospirosis were present in all the 40 cases (Table 1). Of all meningo-encephalic signs, coma was present in 10 cases, obnubilation in 3, delirium in 4, meningeal signs in 21, photophobia in 3 and facial paresis in one case. The haemorrhagic syndrome was present in 80% of cases and it was manifested by severe digestive haemorrhage (hematemesis, melena) in 21 cases, ecchymosis and petechiae in 11, purpura in 11, gingival bleeding in 5 and epistaxis in 5 cases.

The serological diagnosis was performed in 30 of the 40 cases with positive results in 25 patients in whom the following serotypes were detected: *L.* Canicola 11, *L.* Pomona 6, *L.* Icteohemoragiae 6, *L.* Wolffi 4, *L.* Grippotyphosa 4, *L.* Hyos 7, and untyped 6.

The diagnosis of acute renal failure relied on the following criteria: oligo-anuria, high uremia levels in all cases (125-600 mg/dL), creatinine levels between 3.5-16 mg/dL, electrolyte and acid-basic disbalance.

In 5 of the 40 cases diuresis was maintained, while 35 patients had oligo-anuria: anuria up to 3 days in 11 patients, between 4-9 days in 12 cases and over 10 days in 4 cases. The mean duration of anuria was 4 days.

The renal bioptic puncture was performed in 5 cases, with the following lesions revealed by optic microscopic examination:

a) Discrete glomerular changes characterised by quasi-normal aspect, mesangial hyperplasia and serous infiltration in the filtration space;

b) Various degrees of tubular lesions, characterised by degenerative lesions, atrophy and necrosis of epithelial cells, sometimes with ruptures of the tubular basal membrane. Additionally, epithelial regenerative aspects were observed;

c) Interstitial mononuclear infiltrate, rare eosinophils and oedema foci (Fig. 1 and 2).

The same lesions were observed on necroptic pieces. In one case even *Leptospirae* were detected. Electron microscopy revealed contorted tubules epithelium with alterations of the cytoplasmic organelles with disorganisation of the nuclear chromatin and spherical intranuclear inclusions, vacuolar mitochondrial dystrophia and lysed cristae, with gigantic vacuole and degenerative granulovacuolar lesions (Fig. 3 and 4).

Liver impairment was revealed by the following findings: moderate, ecographically visible hepatomegaly in 35 cases, elevated transaminases with levels 5 times higher than normal values, increased values for bilirubin, alkaline phosphatase, decreased cholinesterase, altered proteinogram, Quick index under 80%. The histopathology test performed in 11 of the deceased patients revealed marked, predominantly centrilobular cholestasis, in all cases, dystrophic lesions in various degrees, focal necrosis and haemorrhage.

Conservative treatment was applied in 25 cases and hemodialysis in 15 cases. As the etiological diagnosis was not established, after collection of biological specimens for blood culture and serology, two antibiotics were introduced: a semisynthetic penicillin and gentamycin, with dosage adjusted to the degree of re-

Table 1

Clinical signs of leptospirosis

Clinical data	Fever	Shiver	Headache	Myalgia	Conjunctival congestion	Pharyngeal pain	Meningeal syndrome	Dyspeptic syndrome	Haemorrhagic syndrome
No. cases	40	40	40	40	30	32	24	40	35

Table 2

Laboratory results

Laboratory findings	Increased ESR	Leucocytosis	Fibrinogen over 4g%	Positive serology for leptospirosis
No of cases	**38**	**35**	**35**	**35**

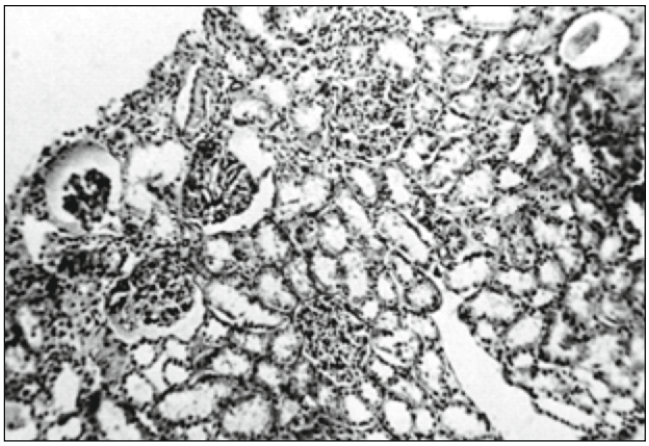

Fig. 1. Discrete mesangial cell proliferation, H&E stain

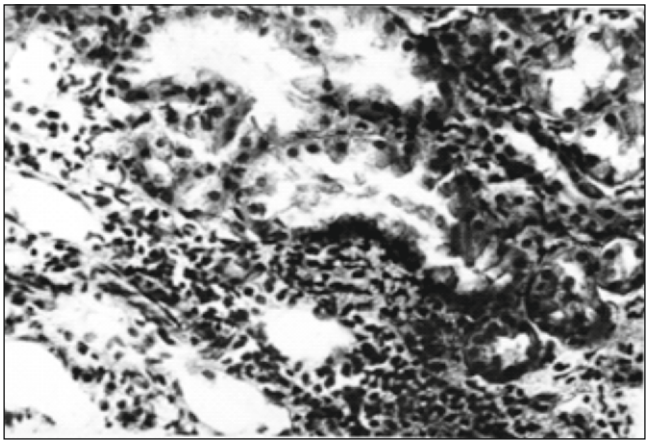

Fig. 2. Tubular dilatation with regenerative aspects of the tubular epithelium, H&E stain

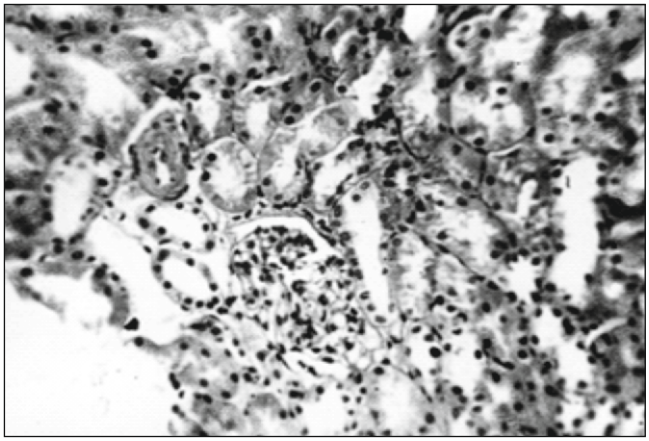

Fig. 3. Focal tubular necrosis with tubular dilatation, H&E stain

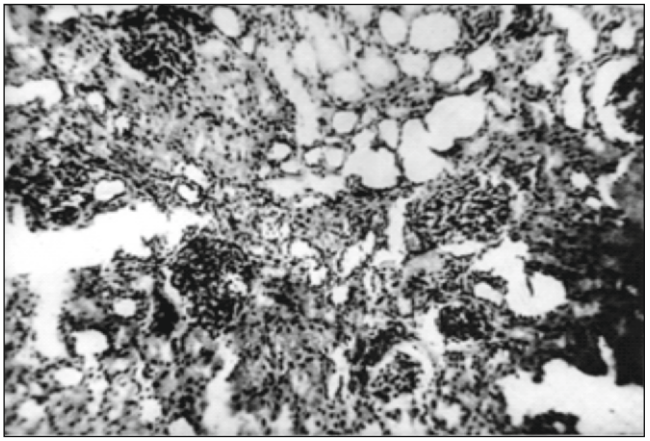

Fig. 4. Tubule-interstitial nephritis, discrete tubule-interstitial inflammatory infiltrate with tubular oedema and unicellular necrosis, H&E stain

nal failure, given the fact that another sepsis could not be excluded from the start.

Hydro-electrolyte and acid-basic rebalance was performed depending on the degree of hydration and the results of the serum ionogram, followed by attempts to reinitiate diuresis with furosemide 100 mg IV, every 4 hours. Positive results from the first day (over 4-500 ml urine in 24 hours) suggested a continuation of the treatment with furosemide, gradually decreasing the dose in parallel with the increase of the diuresis.

Ensuring a minimum of calories and anti-catabolic mea-sures were initially achieved by intravenous infusion with 10% glucose, saline solution and aminoacids, and later with oral feeding after improvement of the digestive tolerance.

Liver protection was also administered: aspatofort, vitamins of group B and K, arginine, sorbitol, rocmalin. Therapy was supplemented with antiemetics, cholagogues and choleretic drugs, and digestive ferments. In cases of massive haemorrhage, isogroup isoRh blood, fresh-frozen plasma and cryoprecipitate were administered.

In 15 cases hemodialysis was introduced, 1-6 sessions, with an average of 2.6 sessions per case. The frequency of hemodialysis sessions was imposed by the evolution, the objectives being to achieve a good clinical status, increased digestive tolerance, hydroelectrolyte and acid-base balance and reduction of nitrogen retention.

Evolution. The evolution was satisfactory in 27 of 49 cases (67.5%) and unfavourable in 13 (32.5%). Of these, 12 died and one was discharged from the hospital in an aggravated state. In all deceased cases, severe digestive haemorrhage was present, with additional acute pulmonary oedema by toxic myocarditis in 4 cases, cerebral haemorrhage in 2 cases, haemorrhage in the ventricular septum in 4 cases, haemorrhagic pancreatitis in one patient and haemorrhage in the adrenal glands in 2 cases.

In cases with favourable evolution, periodic monitoring revealed normalisation of liver tests, rehabilitation of the renal function after 3 months in 5 cases and after 12 months in one case, respectively.

Discussions.

The frequency of leptospirosis is statistically considered to be low. Mortality in leptospirosis depends on various criteria, like geographic areas, serotypes and age, between 15-55% (11, 20, 28). Our cases selected over several decades (1970 – 2017) reveal a frequency of 4% out of ARF of infectious causes.

Leptospirosis occurs most frequently in tropical regions, being endemic, with clusters during the rainy seasons located in the flooded areas. The incidence of leptospirosis in some endemic countries is increasing. In Thailand, for example, the incidence increased 30 times from 1995 to 2000 (19). In Brazil, data of the Ministry of Health showed that between 1996 and 2005 (33),174 cases of leptospirosis were signalled, and in 2007, 1547 new cases were detected, most of them in the Southern region (45.7%). In the USA, 40-120 cases are reported yearly to the Center for Disease Control and Prevention. These cases probably represent a significant underestimation of the total number of „possible" cases. Certain professional groups are at a particular risk to become infected, such as agriculture workers, sewage workers, slaughterhouse staff as well as workers in the fishing industry. These may become infected by direct exposure or by contact with contaminated water and soil.

In countries with developed tourism, exposure or contact with domestic animals also represents an important source of leptospirosis. The contact with water during water sports such as rowing, surfing, swimming and water skiing increases the risk for leptospirosis. Sometimes *Leptospira* infections are acquired during travels abroad.

In a recent study conducted in Belgium and The Netherlands, 14% of the confirmed leptospirosis patients acquired the infection while travelling in tropical areas, especially in South-Eastern Asia. Laboratory acquired infections are rare. Occasionally, leptospirosis occurs after immersion in contaminated water (after fishing or automobile accidents).

Leptospirosis is more frequently associated to certain professions (17, 28) and also to activating in poor hygiene conditions. This is also confirmed by our cases: contact with polluted waters in 15 cases (plumbers, fishermen), animal farm workers in 2 cases, very poor hygiene conditions in 5 cases.

In our study, the number of cases of ARF by leptospirosis is higher than in other statistics (3, 22), with some studies (8, 17, 21) rarely citing leptospirosis among the possible causes for infection induced ARF. This is most likely due to water contamination and pond fishing.

Even though the clinical signs suggesting the diagnosis were present in most cases (fever, shiver, headache, myalgia in all cases and haemorrhagic syndrome in 70% of cases, oligo-anuria in 90% of cases, the meningocerebral syndrome in 65% of cases), hospital admission is usually very delayed (in one case this occurred on the 5th day after onset, in 26 cases after the 10th day from onset, respectively), with altered general status (8 comatose cases) and severe nitrogen retention (11 cases) with the uraemia level over 300 mg% (1, 2).

The onset of nonspecific signs of "viral infection" or jaundice suggesting acute hepatitis are causes for delayed etiologic treatment. Sometimes the symptoms mimic other diseases leading to both delayed treatment and delayed hospital admission in specialised departments (16).

Acute renal failure was characterised by a severe nitrogen retention, with a high increase rate especially as a result of muscular catabolism, the hydro-electrolyte and acid-base disturbances being moderate, with a short oligo-anuric period (with an average duration of 5 days), ARF was apparently severe by the increased degree of nitrogen retention and the hypercatabolic form, and the unfavourable evolution was determined by haemorrhagic complications. Hepatic impairment was moderate (17, 18).

Regarding the deaths, we mention the constant presence of the severe haemorrhagic syndrome with hematemesis and melena, as well as haemorrhages in other organs (cerebral, cardiac, adrenal gland, pancreas) which represented the most frequent cause of death. As for the causes of the haemorrhagic syndrome, the capillary-toxic effect of Leptospira was incriminated, completed by a moderate degree of liver impairment and sometimes the disseminated intravascular coagulation syndrome (4, 5, 14, 29, 37).

The pathogenic mechanism of ARF in leptospirosis is most probably due to renal hemodynamic and ischemic disturbances, similar to those encountered in the shock kidney, usually followed by secondary tubular necrosis. The action of bacterial toxins on the interstitial and tubular structures might add up triggering a secondary inflammatory reaction (8, 25). Recently, an immune mechanism by immune circulating complexes has also been incriminated (3, 6, 8, 17, 25).

CONCLUSIONS

Acute renal failure by leptospirosis represents 40% of ARF of infectious causes. The hepatic impairment is present in most cases but has a moderate intensity and does not represent an essential prognosis element, but it may delay diagnosis. Any organ can be affected because leptospirosis is an infectious vasculitis. The haemorrhagic syndrome is frequent and often intense, influencing the evolution and prognosis. The etiologic diagnosis by serology is not rapid enough so an early clinical diagnosis is imperatively required based upon the multivisceral association (renal, meningoencephalitis, hepatic and haemorrhagic syndrome). Antibiotic treatment against leptospirosis is required even if this an aetiology of ARF is only suspected. There are over 210 serovariants of the 23 serotypes presently described, and the same serovariant may induce different clinical symptoms.

REFERENCES

1. *Ahmad S.N., Shah S., Ahmad F.M.H.,* (2005), Laboratory diagnosis of leptospirosis. Journal Postgrad Med, 51:195-200
2. *Bărăităreanu S., Stanca L.E., Gurău M.R., Daneș D.,* (2019), Research on the *Leptospira* infection prevalence in stray dogs in a Romanian shelter. Revista Romana de Medicina Veterinara, 29(1):37-41
3. *Bușilă V.T., Pop C., Vasilescu I., Topciu V.I., Popian R., Cucuruz L., Alexandrescu R., Isacson I., Son C., Cravcevsshi V., Zilberman L., Fitarau A., Jicman M.*, (1957), The Clinical Aspects of Leptospirosis. Stud Cercet Inframicrobiol Microbiol Parazitol, 8(2):259-280
4. *Celigny-Solac P., Vilde L.J.,* (1979), Leptospiroses. Conc.Medical, 101(4):991
5. *Cerqueira T.B., Athanazio D.A., Spichler A.S., Seguro A.C.,* (2008), Renal involvement in leptospirosis - new insights into pathophysiology and treatment. Braz J Infect Dis, 12(3):248-252
6. *Cetin B.D., Harmankaya O., Hasman H., Gunduz A., Oktar M., Seber E.*, (2004), Acute renal failure: A common manifestation of leptospirosis, Ren Fail, 26:655-661
7. *Costica I.I.*, (1972), Acute renal failure (in Romanian), In: Boli renale bilaterale, (Ed.) Medicală, Bucharest, Romania, 15
8. *Daher E.F., Silva Jr. G.B., Karbage N.N.N., Carvalho Jr. P.C., Kataoka R.S., Silva E.C., Magalhaes M.M., Mota R.M., Araujo S.M., Gutierrez-Adrianzen O.A., Liborio A.B.*, (2009), Predictors of oliguric acute kidney injury in leptospirosis: a retrospective study on 196 consecutive patients. Nephron Clin Pract, 112(1):25-30
9. *Daoual P., Mathieu P., Bloch P., Barale F.*, (1978), Leptospirose avec Immunisation anti-membrane basale glomérulaire. Nouv Presse Méd, 7(3):535
10. *Doudier B., Garcia S., Quennee V., Jamo P., Broqui P.*, (2006), Prognostic factors associated with severe leptospirosis. Clin Microbiol Infect, 12(4): 299-300
11. *Estevoyer M.J., Marquelet D., Baufle H.G., Beque O., Michel-Briand Y., Pageaut G.,* (1980), Leptospirose grave avec localisation cardiaque, Nouv Presse Méd, 9(2):597
12. *Ganeval D.,* (1978), Les insuffisances rénal interstitielles aigués, Rev Prat, 28(3):827
13. *Gluhovschi N., Topciu V., Levin S., Glavan B., Stan N., Nistor T.*, (1964), Treatment and chemoprevention with anticid in leptospirosis (in Romanian), Rev Zooteh Med Vet, 14:52-59
14. *Herrmann-Storck C., Saint-Louis M., Foucand T., Lamaury I., Deloumeaux J., Baranton G., Simonetti M., Sertour N., Nicolas M., Salin J., Cornet M.,* (2010), Severe leptospirosis in hospitalized patients, Guadeloupe. Emerg Infect Dis, 16 (2):331-334
15. *Lai K.N., Aarons K., Woodroffe A.J., Clarkson A.R.*, (1982), Renal lesion in leptospirosis. Aust N Z J Med, 12(4):276-279
16. *Lecour H., Miranda M., Magro C., Rocha A., Gonçalves V.,* (1989), Human leptospirosis - a review of 50 cases. Infection, 17(1):8-12
17. *Mendoza M.T., Tan S., Torres D., Tupasi T.E.*, (1979), Human leptospirosis: Clinical and laboratory diagnosis. J Phil Med Assn 55:219-224
18. *Nicolicioiu M., Romoșan I., Mănescu N., Golea O., Georgescu L., Zosin C.,* (1982), Acute insufficiency due to leptospirosis (In Romanian). Medicina Interna, 34:545-552
19. *Nicolicioiu M., Manescu N., Romosan I., Golea O., Georgescu L., Zosin C.,* (1982), Acute insufficiency post-abordum (in Romanian). Medicina Interna, 34:553-560
20. *Nicolicioiu M., Gavrilescu M., Mănescu N., Golea O., Sabo H., Zosin C.*, (1977), Nephropathy in leptospirosis (in Romanian). Zilele medicale timisene, Timisoara, Romania
21. *Podea D.,* (1978), Acute renal failure in leptospirosis (in Romanian). Lucrare de diplomă, I.M. Timi-

soara, Romania
22. *Proca E.,* (1968), Acute renal failure (in Romanian). (Ed.) Medicala, Bucharest, Romania
23. *Podrom I.,* (1970), Kidney in leptospirosis (in Romanian). Viata Medicala, 17:55
24. *Romosan I.,* (1986), Kidney in Infectious Diseases / Secondary Nephropathy (in Romanian). (Ed.) Academiei, Bucharest, Romania
25. *Romosan I.,* (1995), Kidney in liver disease (in Romanian), (Ed.) Helicon, Timisoara, Romania
26. *Russu G.,* (1978), Acute renal failure (in Romanian), In: Nefrologie practică, (Ed.) Junimea, Iasi, Romania, 108
27. *Sanchez F.M., Durieux P., Galanaud P., Brivet F., Labayle D., Buffet C.,* (1977), Relation entre canicule et leptospirose. Nouv Presse Med, 6:469
28. *Seguro A.C., Lomar A.V., Rocha A.S.,* (1990), Acute renal failure of leptospirosis: Nonoliguric and hypokalemic forms. Nephron, 55(2):146-151
29. *Sitprija V., Evans H.,* (1970), The kidney in human leptospirosis. American Journal Med, 49(6):780-788
30. *Smits H.L., Anayina Y.V., Chereshsky A., Dancel L., Lai-A-Fat R.F.M., Chee H.D., Levett P.N., Masuzawa T., Yanagihara Y., Muthusethupathi M.A., Sanders E.J., Sasaki D.M., Domen H., Yersin C., Aye T., Bragg S.L., Gussenhoven G.C., Goris M.G., Terpstra W.J., Hartskeerl R.A.*, (1999), International multicenter evaluation of the clinical utility of a dipstick assay for detection of *Leptospira*-specific immunoglobulin M antibodies in human serum specimens. Journal Clin Microbiol, 37(9): 2904-2909
31. *Topciu V.L.*, (1979), Immunological reactions in the protection of the macro-organism against microorganisms (in Romanian). Timişoara Medicală, 14(1):42-48
32. *Topciu V.L.*, (1957), The role of the *Citellus citetlus* as a reservoir of virus in leptospirosis (in Romanian). Acad RPR, Baza Timisoara St si Cercet St, 4(3-4):51-54
33. *Topciu V.L., Gluhovschi N.*, (1957), Isolation of a pathogenic leptospira strain from a horse with an acute form of leptospirosis (in Romanian). Acad RPR, Baza Timisoara, St si Cercet St, 4(3-4):61-64
34. *Topciu V.L., Marin I., Cucuruz L., Elias I.M., Reichrath S., Porsche T., Frasinel N.*, (1957), Isolation of Strains of Pathogenic Leptospira from Rodents and Humans. Studii Cerc Inframicrobiol, 8(1):115-120
35. *Topciu V.L., Lazar Z., Dragan I.A., Danetiu I., Nicolicioiu M.,* (1977), Cases of acute leptospirosis that occurred during 1976. Zilele medicale timişene, Timisoara, Romania
36. *Ungureanu A., Baraitareanu S, Gurau M.R., Daneş D.,* (2014), Studies concerning the non-invasive sampling for canine leptospirosis DNA search: routine diagnostic and surveillance screening. Lucrari Stiintifice - Universitatea de Stiinte Agricole a Banatului Timisoara, Medicina Veterinara, 47(3): 126-131
37. *Voiculescu M.,* (1968), Leptospirosis (in Romanian), In: Boli infecţioase, (Ed.) Medicala, Bucharest, Romania, 730
38. *World Health Organization,* (2003), Human leptospirosis: guidance for diagnosis, surveillance and control. Available at: https://apps.who.int/iris/handle/10665/42667 (Accesed: 15.05.2019)
39. *Wagenaar J.F.P., Goris M.G.A., Partiningrum M.L., Isbandrio B., Hartskeerl R.A., Brandjes D.P.M., Meijers J.C., Gasem M.H., van Gorp E.C.,* (2010), Coagulation disorders in patients with severe leptospirosis are associated with severe bleeding and coagulopathy. Tropical Medicine and International Health, 15(2):152-159
40. *Yang C.W., Wu M.S., Pan M.J.,* (2001), Leptospiral renal disease. Nephrol Dial Transplant, 16(Suppl 5):73-77
41. Zosin C., (1979), Acute renal failure (in Romanian), In: Nefrologia clinica, (Ed.) Medicala, Bucharest, Romania.