ABSTRACT:
The case-fatality rate of severe leptospirosis is above 50% at delayed intensive treatment. Our purpose was to assess the prognostic value of the early clinical diagnosis of leptospirosis.

Material and Methods: One hundred consecutive patients with leptospirosis were treated in the Clinic of Infectious Diseases at University Hospital “Dr Georgi Stranski” - Pleven (1976 - 2018). They were distributed retrospectively in groups with mild, moderate, and severe course (27, 39, and 34, respectively). The once interesting for prognosis was the risk for severe course. Data were analyzed with statistical software (IBM SPSS Statistics 19.0).

Results: The mild cases were hospitalized meanly three days after clinical onset (range 1-7 days). The early clinical diagnosis was leptospirosis, acute viral hepatitis, and “flu-like” (23/27, 85.19%; 3/27, 11.11%; 1/27, 3.70%, respectively).

The moderate cases were hospitalized meanly four days after clinical onset (range 1-10 days). Nineteen moderate cases (48.72%) were misdiagnosed as aseptic meningitis, acute viral hepatitis, viral infection, obstructive jaundice, and nephrolithiasis. Comorbidity was registered in 33.33%.

The severe cases were hospitalized meanly five days after clinical onset (range 2-12 days). Misdiagnoses (in 35.29%) were obstructive jaundice, acute pancreatitis, cholecystitis, pneumonia, and sepsis. Comorbidity was registered in 44.12%.

The comparative analysis revealed that the patients hospitalized after the fourth day since clinical onset had a significantly more severe course (p<0.05).

Conclusion: The time between clinical onset and hospital admission has significant prognostic value and could be assessed with other clinical predictors of leptospirosis. The early clinical diagnosis is of great importance for initiating intensive treatment (including hemodialysis).

Keywords: leptospirosis, diagnosis, prognosis,
The analysis of mild cases of leptospirosis found that the clinical onset was within meanly three days before the hospital admission (range 1-7 days; sd 1.49). The incubation period was clear at eight patients (8/27; 29.63%) (mean 6.9 days; range 2-12 days; sd 4.09). All mild cases were hospitalized in the Clinic of Infectious Diagnosis, and the early clinical diagnosis was leptospirosis in 23 cases (23/27; 85.19%), three acute viral hepatitis (3/27; 11.11%), and one was misdiagnosed as “flu-like” (1/27; 3.70%). All mild cases were without comorbidity. Risk exposures were registered in 25 mild cases (92.59%).

The analysis of moderate cases of leptospirosis found that the clinical onset was within meanly four days before the hospital admission (range 1-10 days; sd 1.99). The incubation period was clear at nine patients (9/39; 23.08%) (mean 8.6 days; range 2-15 days; sd 4.66). Nine moderate cases (23.08%) were hospitalized in different clinical wards (three in surgical clinics and six in clinics of Internal Medicine). Nineteen moderate cases (48.72%) were misdiagnosed – the first clinical diagnosis was aseptic meningitis in nine cases (23/39; 23.08%) (eight of them with abnormal results of the parameters of cerebrospinal fluid). Other misdiagnoses were acute viral hepatitis, viral infection, obstructive jaundice, nephrolithiasis (each of these at two of the moderate cases – 5.13%, respectively). Comorbidity was registered at thirteen moderate cases (33.33%) – hypertonic disease and chronic alcoholism at two, respectively (7.69%, respectively), chronic obstructive pulmonary disease, ischemic heart disease, pyelonephritis, cholelithiasis, diabetes mellitus, past tuberculosis, and blindness (2.56%, respectively). Risk exposures were registered in 34 moderate cases (87.18%).

The severe cases with leptospirosis were hospitalized within a meanly five days after the clinical onset (range 2-12 days; sd 2.11). The incubation period was clear in eight severe patients (8/27; 23.53%) (mean 6.25 days; range 3-10 days; sd 2.87). Twelve severe cases (35.29%) were hospitalized in inappropriate for the diagnosis “leptospirosis” clinical wards (six in surgical clinics and the remainder in internal wards of non-tertiary hospitals). The same twelve patients were misdiagnosed (35.29%), and the first diagnosis on admission was obstructive jaundice (3/34; 8.82%, respectively), acute pancreatitis, acute cholecystitis, pneumonia, and sepsis (each at 2/34; 5.88%, respectively), and pulmonary edema at one (2.94%). Comorbidity was registered in fifteen severe cases (44.12%)
as follows: hypertonic disease (5/34; 14.71%, respectively), ischemic heart disease, chronic alcoholism, tuberculosis (each at 3/34; 8.82%, respectively), diabetes mellitus, stomach ulcer, and cholelithiasis (each at 2/34; 5.88%, respectively). Risk exposures were registered in 23 severe cases (67.65%).

The general distribution of the patients according to the days after the clinical onset and hospital admission is shown in Figure 3.

**Fig. 3.** General distribution of the patients according to the day of hospital admission after the clinical onset

The distribution of the patients with different severity according to the days from the clinical onset and hospital admission is shown in Figure 4. It is obvious that more patients were hospitalized to the fourth day (including) after the clinical onset, and the treatment was initiated without delay.

**Fig. 4.** Distribution of the patients with different severity according to the day of hospital admission after the clinical onset

The mentioned above data about the distribution of the severity according to the day of hospital admission correlate with the exposed information about the early clinical diagnosis. At the same time, this correlation coincides with the knowledge about the pathogenesis of leptospirosis and concretely that the first (leptospiremic) phase of the disease is four to seven days and after then appear systemic involvements. Based on this fact, we performed comparative distribution of the cases with different severity of leptospirosis according to the time of hos-
hospital admission (to the fourth day since the clinical onset and later), as shown in Figure 5. The comparative analysis revealed that the patients hospitalized after the fourth day since clinical onset had a significantly more severe course of the disease (p<0.05). This confirms our proposed above hypothesis. The trends of the course in different severity of leptospirosis are shown in Figure 6.

**Fig. 5.** Comparative distribution of the cases with different severity of leptospirosis according to the time of hospital admission (to the fourth day since the clinical onset and later)

**Fig. 6.** Trends, of course, in different severity of leptospirosis

**DISCUSSION**

Leptospirosis is an infectious disease caused by the *Leptospira interrogans*. The disease is characterized by a broad spectrum of clinical manifestations, including fever, chills, conjunctivitis, and muscular pains. In mild cases, the disease may be subclinical. Jaundice and renal failure occur in the severe form known as Weil’s disease. Leptospires enter the host through abrasions in the skin or through intact mucous membranes. Infection through the intestinal mucosa can occur when a contaminated with *Leptospira* food is ingested. After the entry, leptospires spread through the bloodstream to all organs mul-
tiplying in the blood and tissues. Within 24 hours, the organisms can be isolated in most tissues except the brain, skeletal muscles, and aqueous humor. After 48 hours, they are recoverable from nearly all tissues. Multisystem involvement is a result of bacterial invasion and toxic reactions. The clearance of the leptospires is by phagocytosis and humoral mechanisms. The organisms rapidly disappear from the blood when agglutinins appear. After the leptospiremic phase, which lasts from 4 to 7 days, the leptospires can be recovered only from renal and ocular tissues. Leptospiruria continues for 1 to 4 weeks [11, 12, 13].

The mean incubation period is 10 days, ranging from 5 to 14 days. Precise determination of exposures may be difficult, leading to significant imprecision in estimated incubation times. It is valid for our study. The incubation period was clear only at nine patients. The acute, septicemic phase of illness begins abruptly with high fever, headache, chills, and myalgias; conjunctival suffusion; abdominal pain; anorexia, nausea, and vomiting; diarrhea; cough. Conjunctival suffusion and muscle tenderness in the calf and lumbar areas are the most characteristic physical findings. Other common signs include hepatomegaly, and splenomegaly [13, 15, 16]. All these signs and symptoms are presented in our cases. The acute phase lasts from 4 to 7 days. Routine laboratory tests are indicative of a bacterial infection. Meningeal signs are not prominent in this phase [13]. This correlates with our study – eight of our patients were with abnormal results of the parameters of cerebrospinal fluid. Death is rare in the acute phase of illness [13]. We confirm this statement – only in one of our deceased cases the lethal outcome was during this period.

The immune phase of the illness generally lasts from 4 to 30 days. The disappearance of leptospires from the blood and cerebrospinal fluid coincides with the appearance of specific IgM antibodies. The organisms can be detected in almost all tissues, organs and in urine for several weeks, depending on the severity of the disease. In addition to the acute phase symptoms, the immune phase is characterized by variable combinations of symptoms as jaundice, renal failure, conjunctival suffusion with or without hemorrhages, pulmonary symptoms, cardiac arrhythmias, aseptic meningitis, muscle tenderness, and hepatosplenomegaly [16, 17, 18, 19]. These symptoms were found in our patients with the different frequency depending on severity.

The intimate mechanisms by which leptospires cause a disease are not clearly understood. Potential virulence factors include surface proteins, production of toxins, and immune mechanisms. Human susceptibility to leptospirosis may be related to poor recognition of leptospiral LPS by the innate immune system. Human Toll-like receptor (TLR) 4, which response to extremely low concentrations of gram-negative LPS (endotoxin), appears to be unable to bind leptospiral LPS, perhaps because of the unique methylated phosphate residue of its lipid A. Direct tissue damage may be due to production of hemolytic toxins, which act as phospholipases, sphingomyelinas, or pore-forming proteins [13, 20]. Recent work is focused on the important role of surface lipoproteins in leptospirotic pathogenesis. LipL32 is the major outer membrane lipoprotein. It is highly conserved among pathogenic serovars [13, 20]. Also, LipL32 is a major target of the human immune response and appears to be involved in the pathogenesis of tubulo-interstitial nephritis [13, 16, 20]. The response of virulent leptospires to the increased osmolarity of host tissues is by inducing expression of the multifunctional Lig surface proteins. These proteins mediate interactions with fibronectin, fibrinogen, and other extracellular matrix factors. Except of this, Lig proteins are early antigens. IgM antibodies to their immunoglobulin-like repeats appear early in infection, and facilitate the detection of acute infection. The endostatin-like LenA protein binds the complement regulatory protein, factor H, thus suggesting an important role in serum resistance. All these mechanisms are at the base of the variable severity of leptospirosis.

In conclusion, the time between the clinical onset and the hospital admission has a significant prognostic value and could be assessed with other clinical predictors of leptospirosis. The early clinical diagnosis is of great importance for the initiation of prompt intensive treatment (including hemodialysis).

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