RESPIRATORY MANIFESTATIONS OF LEPTOSPIROSIS

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ABSTRACT
Purpose: Respiratory manifestations in leptospirosis can vary from subtle symptoms to deadly pulmonary hemorrhage and ARDS. Our objective was to analyze respiratory symptoms and to assess their prognostic value in leptospirosis.

Material and methods: We performed analysis of clinical data and X-ray findings in 100 consecutive cases of leptospirosis, treated in Clinic of Infectious Diseases at University Hospital – Pleven (1976-2018) (mean age 37±18 years, 90 male, 13% lethal outcome). Statistical methods – t-test and χ² test (for parametric and non-parametric distributions, respectively; p<0.05 was considered as significant); Pirson’s test (φ-coefficient: weak correlation in φ<0.3, moderate – 0.3< φ <0.7 and strong in φ>0.7); odds ratio (OR).

Results: The characteristic manifestations were fever (100%), hepatomegaly (92%), myalgia (86%), vomiting (84%), splenomegaly (74%), oliguria (69%), jaundice (63%), hypotension (49%), abdominal pain (41%), and hemorrhagic diathesis (37%). The most frequent respiratory symptoms (especially in icteric cases) were decreased breath (37%), rales (17%), tachypnea (15%), and dyspnea (13%). Comparative study of respiratory symptoms in different according to severity forms revealed higher prevalence in severe cases (p<0.001). X-rays (in 34 severe cases) revealed infiltrative changes in nine cases and interstitial and alveolar congestion (suggesting lung edema) in thirteen. Comparative analysis of survived and deceased severe cases revealed that mentioned above respiratory symptoms occur more often in deceased patients (p<0.001). The lethal outcome strongly correlated with lung edema (OR 25.00; p=0.66).

Conclusions: Respiratory dysfunctions in our study were nonspecific and correlated with severity. The lung edema is important factor for death, and its prevention requires prompt intensive interdisciplinary treatment.

Key words: leptospirosis, respiratory symptoms, X-ray,

INTRODUCTION
Leptospirosis is a globally distributed zoonosis, caused by pathogenic spirochetes of the genus Leptospira. The clinical spectrum of leptospirosis ranges from asymptomatic or flu-like episodes to severe forms. Severe cases occur in 5-15% of all human infections, typically presenting as Weil’s disease – a triad of jaundice, acute renal failure (ARF), and hemorrhages [1]. According to many reports, the emergence of severe pulmonary hemorrhage syndrome (SPHS) in leptospirosis has recently become of crucial importance, which may present as acute respiratory distress syndrome (ARDS) or massive pulmonary hemorrhage with case fatality higher than 50% [2-5]. Vijayachari P et al. (2015) mentioned that the case series in Andaman Islands in 1929 was probably the first report of pulmonary hemorrhage as a manifestation of leptospirosis [6]. The clinical presentation of leptospirosis varies in different geographic areas. In Nicaragua and Peru, SPHS is uncommon and presents without classic syndromes of jaundice and renal failure [2]. Similar observations had reported in Thailand [7, 8, 9], India [9], and Argentina [10]. In the city of Salvador, Brazil, ARF without SPHS is the major cause of death [2]. There are 1.03 (95% CI 0.43 –1.75) million cases of leptospirosis worldwide each year and 58,900 deaths (95% CI 23,800 – 95,900) [11, 12]. These facts correspond to an estimated 2.9 million disability-adjusted life years (DALY) annually, including 2.8 million years of life lost due to premature death [13].

The older age, oliguria, hyperkalemia, increased serum creatinine, ARDS, pulmonary hemorrhage, elevated bilirubin, hypotension, arrhythmia, and altered mental status have been found as independent prognostic factors for death in leptospirosis [7, 8, 9, 14]. However, these studies have typically been hospital-based, not population-based. Intrinsic virulence variations among serovars explain disease severity partially but mild and severe forms may be caused by a broad range of pathogenic serovars [2]. Delay between onset and hospitalization has also been highlighted as determinant of poor outcome.

Our objectives were to evaluate the prevalence of the clinical characteristics associated with fatal outcome in severe hospitalized patients with leptospirosis in the region of Pleven, Bulgaria, and to assess the respiratory manifestations as prognostic criterion for severity and mortality in leptospirosis.

MATERIAL AND METHODS
We performed retrospective study of hundred consecutive leptospirosis cases treated after written informed consent in Clinic of Infectious Diseases at University Hospital – Pleven (1976-2018) (lethal outcome in 13%). A re-
Prospective database for patients with leptospirosis (1976-1984) was initiated and continued prospectively to the December 31st 2018. Microscopic agglutination test (MAT) (performed in the National Reference Laboratory at National Center of Infectious and Parasitic Diseases – Sofia) had been used and positive diagnosis was confirmed if an initial titer of $e^{100}$ for MAT was observed.

The data were obtained through the medical documentation of cases. The protocol included review of medical records, with description of demographic, epidemiologic, clinical, and laboratory data from lethal and survived cases. The cases were divided in two groups – group A (with respiratory manifestations) and group B (without respiratory manifestations). Comparative analysis of clinical manifestations, laboratory parameters and outcome in both groups was performed. The data were analyzed by Statgraphics Plus Version 2.1. package. T-test and $\chi^2$ test had been used for parametric and non-parametric distributions, respectively; $p<0.05$ was considered to be significant.

According to the following definitions [15], severity of cases was complexly assessed as mild, moderate and severe:

- Mild leptospirosis had been defined at mild to moderate intoxication, anicteric or mild icteric, without hemorrhagic diathesis, involvement of respiratory, cardiac and central nervous system (CNS), with mild renal dysfunction without ARF.
- Moderate form of leptospirosis had been defined at markedly demonstrated intoxication, moderate jaundice, skin hemorrhages, transitory cardiovascular abnormalities without myocardial dysfunction, ARF improving without dialysis.
- Severe leptospirosis had been defined at severe intoxication, intensive jaundice with severe hepatic dysfunction, skin hemorrhages and visceral bleeding, toxic myocarditis, severe ARF requiring dialysis, common respiratory and CNS-involvement.

We used $\varphi$-coefficient by modified Pearson’s test about correlation of severity with age (interpreted by three-grade score as follows: weak correlation at $\varphi<0.3$, moderate $0.31<\varphi<0.7$ and strong – $\varphi\geq0.7$). Odds ratios (ORs) were calculated.

**RESULTS**

One hundred consecutive patients with leptospirosis were treated in Clinic of Infectious Diseases at University Hospital – Pleven, Bulgaria since January 1st 1976 to December 31st 2018. The mean age of the patients was $37\pm18$ (8–78) years, 90 of them were males, and 61% – urban residents. The mean annual incidence of leptospirosis for 42-year period in Pleven’ region was 0.37 per 100 000 population.

Risk exposures to animal excrements after water and animal contacts (57% and 34%, respectively) were certified in 88% of the cases and 78% were admitted during the summer months.

The prevalence of symptoms in whole series and separately in groups with and without respiratory manifestations respectively is shown on Table 1. Fever (100%), hepatomegaly (92%), conjunctival injections (87%), myalgia (86%), vomiting (84%), shivering (78%), splenomegaly (74%), headache (67%), oliguria (63%), jaundice (63%), hypotension (49%), abdominal pain (41%), and hemorrhagic diathesis (37%) were the characteristic manifestations. The most frequent respiratory symptoms were decreased breath (39%), rales (18%), tachypnea (14%), and dyspnea (11%). The comparative analysis of prevalence of symptoms in group A and group B revealed significantly higher prevalence of conjunctival injections, hemorrhagic syndrome, oliguria, tachycardia, hypotension, and arrhythmia in the group with respiratory manifestations ($p<0.05$). Moreover, respiratory symptoms were observed more often in icteric cases ($p<0.05$).

**Table 1.** Leptospirosis in Pleven region (1976–2018) – prevalence of the symptoms

<table>
<thead>
<tr>
<th>Symptoms and syndromes</th>
<th>Whole series (N=100) %</th>
<th>Group A (n=20) %</th>
<th>Group B (n=80) %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Shivering</td>
<td>78</td>
<td>74</td>
<td>79</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Myalgia</td>
<td>86</td>
<td>74</td>
<td>90</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10</td>
<td>4</td>
<td>12</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Conjunctival injections</td>
<td>87</td>
<td>100</td>
<td>83</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Jaundice</td>
<td>63</td>
<td>78</td>
<td>58</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Hemorrhagic syndrome</td>
<td>37</td>
<td>70</td>
<td>27</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Skin hemorrhages</td>
<td>27</td>
<td>48</td>
<td>21</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Conjunctival suffusions</td>
<td>8</td>
<td>13</td>
<td>6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>10</td>
<td>13</td>
<td>9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2</td>
<td>9</td>
<td>0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>11</td>
<td>30</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Melena</td>
<td>4</td>
<td>13</td>
<td>1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hematuria</td>
<td>21</td>
<td>43</td>
<td>14</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
The comparative analysis of laboratory findings in groups with and without respiratory manifestations (group A, group B, respectively) revealed significantly higher mean serum levels of urea, creatinine, total/direct bilirubin, transaminases, lactate dehydrogenase, creatine kinase, total protein and albumins in the group with respiratory manifestations (p<0.05). These results demonstrate that renal and hepatic functions are affected manifestly in patients with respiratory manifestations (Table 2).

Table 2. Leptospirosis in Pleven region (1976-2018) – laboratory parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference value</th>
<th>Whole series mean ± SD (min-max)</th>
<th>Group A mean ± SD (min-max)</th>
<th>Group B mean ± SD (min-max)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L)</td>
<td>120-188</td>
<td>132 ± 20 (65-168)</td>
<td>129 ± 24 (65-162)</td>
<td>133 ± 17 (91-168)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>WBC (cells x 10^9/L)</td>
<td>4.0-11.0</td>
<td>13.5 ± 6.5 (2.9-32.0)</td>
<td>16.7 ± 7.0 (6-27.6)</td>
<td>12.5 ± 6.1 (2.9-32.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>50-80</td>
<td>81 ± 16 (60-96)</td>
<td>85 ± 14 (60-80)</td>
<td>71 ± 15 (60-96)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Platelets (cells x 10^9/L)</td>
<td>150-400</td>
<td>146 ± 104 (8-445)</td>
<td>111 ± 89 (8-437)</td>
<td>165 ± 109 (17-445)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>1.7-8.3</td>
<td>22.5 ± 16.9 (2.8-98.6)</td>
<td>34.4 ± 18.4 (7.6-98.6)</td>
<td>17.8 ± 13.8 (2.8-65.2)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>44.2-134</td>
<td>279.7 ± 197 (56-818)</td>
<td>141 ± 67 (162-695)</td>
<td>240 ± 194 (56-818)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
X-ray investigations (performed in 34 severe cases) revealed infiltrative changes in nine cases and interstitial and alveolar congestion (suggesting lung edema) in thirteen.

According to the definitions for mild, moderate and severe leptospirosis mentioned above and after assessment of clinical and laboratory findings showed above, we established the following distribution of cases in the whole series: mild, moderate and severe cases were 27, 39 and 34, respectively. The same distribution in both compared groups was in group A – zero, 3 and 20, respectively; in group B – 27, 36 and 14, respectively. It is visible that more of cases with respiratory manifestations had severe course of leptospirosis.

We used \( \phi \)-coefficient by modified Pearson’s test (interpreted by three-grade score as follows: weak correlation at \( \phi < 0.3 \), moderate 0.31\(<\phi<0.7 \) and strong – \( \phi \geq 0.7 \) about correlation of severity with presence of respiratory manifestations. Strong correlation of severity was established in group A (\( \phi = 0.85 \)).

Eighty seven percent of cases survived and were discharged after mean hospital treatment 14.9±7.3 days (from 1 to 46 days) and 13% were fatal after mean hospital treatment 4.2±2.6 days (from 1 to 10 days) (OR 32.4; \( p<0.0005 \)).

The clinical onset of leptospirosis in deceased patients was mainly five days before admission in hospital. All of them had fever, muscular pains, oligo/anuria, two had epistaxis and hemorrhagic rash before admission. Ten deceased patients had co-morbidity including hypertonic disease and chronic alcohol abuse (respectively three cases), past myocardial infarction, stomach ulcer, past tuberculosis (respectively two), podagra and calculous cholecystitis (respectively one). Six deceased patients before referral to our clinic were admitted in internal or surgery wards with different clinical diagnosis – acute pancreatitis, obstructive jaundice and sepsis. All of patients with lethal outcome had, besides ARF, at least two other major organ failures. Nine of fatal cases had affected consciousness and multi-site hemorrhagic diathesis. The major tanatogenic factors were pulmonary and brain edema (OR 25.00; \( \phi = 0.659082 \) and 17.29; \( \phi = 0.527778 \), respectively) due to severe ARF. Moderate correlation of lethal outcome with ARF (OR 2,200; \( \phi = 0.420096 \)), visceral
bleeding (OR 1.428571; ϕ=0.375), age above 40 years (OR 11.000; ϕ= 0.433013) and mild correlation with jaundice (OR 1.53846; ϕ=0.30773) had been found.

Seven deceased cases were investigated pathomorphologically. Macroscopically, severe pulmonary edema, brain edema followed by cerebellar inclination, multisite bleeding, and enlarged congestive liver were established in all of autopsied. Pancreatitis was found in five of cases, peritonitis – in one. The histological investigations had revealed gastrointestinal and myocardial hemorrhages, focal myocardial necrosis, destructured liver architectonic, and severe tubular necrosis of kidneys in all investigated.

**DISCUSSION**

Leptospirosis is a re-emerging zoonosis with broad clinical spectrum from anicteric and usually self-limiting acute febrile illness to icteric and occasionally fatal form. Icteric leptospirosis is a much more severe disease in which the clinical course is often very rapidly progressive [1]. It was well demonstrated in our study, that mild to moderately elevated transaminases levels were seen in whole series and both compared groups contrasting to high serum bilirubin levels. Totally, 63% of cases were icteric (78% of cases in group A and 41% in group B; p<0.05), but hepatic dysfunction was observed in 71%. We had observed severe course in 34% of all cases.

The complications of severe leptospirosis emphasize the multisystemic nature of the disease. Leptospirosis is a common cause of ARF, which occurs in 16 to 40% of cases. In patients with ARF, oliguria was a significant predictor of death. Some factors seem to be related to death in Weil’s disease such as age, gender, presence of oliguria, jaundice, and pulmonary involvement [2]. In our study, 63% of cases had oliguria (87% of cases from group A and 52% from group B; p<0.0005). All thirteen deceased patients (13%) had severe ARF, leading to lung edema and brain edema, which were causes for the death. This conclusion was confirmed by patomorphological investigations and correlated with other studies [16].

The occurrence of pulmonary symptoms in leptospirosis was first noted by Silverstein [quoted to 1]. Later reports had shown that pulmonary involvement may be a major manifestation of leptospirosis in some serial and sporadic cases [17]. Lung involvement occurs in 20 to 70% of cases, and the clinical severity ranges from mild dyspnea to SPHS [2]. The severity of respiratory involvement is not depending on the presence of jaundice. Patients may present with a wide spectrum of symptoms, ranging from cough, dyspnea, and hemoptysis (mild or severe) to ARDS. Intra-alveolar hemorrhage was detected in the majority of patients, even in the absence of manifested pulmonary symptoms. Pulmonary hemorrhage may be severe and life-threatening [1]. Capillary injury in the lungs leads to leakage and extravasation of blood cells. The inflammatory reaction by infiltration of monocytes and neutrophils, is mild when compared with vascular damage. Lung edema, fibrin depositions and proliferation of fibroblasts are frequent and further hamper respiratory function [16, 18, 19]. These changes can lead to intra-alveolar hemorrhage and ARDS, which is often fatal. Mortality of severe leptospirosis caused by cardiac and renal failure is 5 to 15%, while SPHS and respiratory failure causes fatalities in >50% [7, 14]. During the past decade, there has been a global increase in recognition of the severe pulmonary form of leptospirosis and Weil’s disease with pulmonary involvement. Spichler A. et al. (2008) had conducted the largest and most comprehensive population-based study hitherto reported. That analysis does present a reliable understanding of features that predict lethal outcome in severe leptospirosis [2]. In our study, we had not observed severe pulmonary form of leptospirosis without ARF. Acute respiratory failure had observed in 14% of all cases as a part of multiorgan failure (61% of cases from group A and no one in group B; p<0.0005).

The initial symptoms of dyspnea and hemoptysis, combined with auscultation anomalies, indicate severe lung involvement [16]. Imaging typically reveals patchy alveolar infiltrates bilaterally, like large snowflakes, and areas of consolidation, as reported in the presented cases [20]. Symptoms usually begin between the fourth and sixth day of disease and may be fatal in less than 72 hours [2, 16]. In addition to adequate antibiotic therapy, admission to the ICU and mechanical ventilation may be necessary to secure adequate blood oxygenation.

**In conclusion**, leptospirosis in Pleven region is not common but had presented severe course in one third of cases. Respiratory dysfunctions in the present study were nonspecific (being a part of multiorgan disorders) and correlated with severity. We had not observed cases with primary pulmonary hemorrhages. The lung edema is important factor for death in leptospirosis, and its prevention requires prompt intensive treatment with an interdisciplinary approach.

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