

LYMPHOCYTIC CHORIOMENINGITIS VIRUS INFECTION- WHAT IS DONE AND PROSPECTS FOR FUTURE STUDIES

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ABSTRACT

Background:

Lymphocytic choriomeningitis virus (LCMV) infection is a neglected rodent-borne zoonotic infection but it is found all over the world because of the cosmopolitan distribution of its reservoirs. The diagnostic of this disease is not widely applied that is why it has been underreported. The aim of this study is to investigate infection with LCMV in hospitalized patients in 2015-2022 in Bulgaria and to analyse the data compared to the worldwide data available in this field of research.

Materials/methods: A total of 66 serum samples and 25 cerebrospinal fluid (CSF) samples from 73 patients with suspected LCMV infection from different hospitals in Bulgaria were collected. All samples were tested with a commercial enzyme-linked immunosorbent assay (Human LCMV-Ab ELISA, SSBT, China), based on the principle of double-antibody sandwich technique to detect Human LCMV-Antibody.

Results: A total of 11/91 (12.09%) positive samples were found in 5 males and 6 females throughout the study period. The positive samples were from patients from the cities: Sofia, Stara Zagora, Montana. A total of 3/25 (12%) positive samples were from CSF samples and 8/66 positive samples (12.12%) were from serum samples.

Conclusions: It's found that this infection occurs in

our country and should not be underestimated, due to the possible severe neurological course and the danger of fetal damage in pregnant women. The diagnosis of LCMV infection is based on previous experience, placed in the light of the continuous introduction of new more sensitive and specific approaches.

Key words: *Lymphocytic choriomeningitis virus*, diagnosis, serology

INTRODUCTION

Lymphocytic choriomeningitis virus (LCMV) infection is an acute viral disease, zoonanthroponosis, occurring in various forms in humans, and causing intrauterine infection with fetal damage in pregnant women. In the recent decades, LCMV has been prevalent among mice in the Americas, Africa, Asia, Europe, Australia; it circulates practically worldwide. It can cause aseptic meningitis, especially in patients who report contact with rodents, although clinical cases are rarely recorded. The diagnosis of this disease, mainly serological, is limited to a small number of laboratories and it is difficult to determine the incidence and seroprevalence rates [1, 2]. LCMV was the first isolated arenavirus, detected accidentally in 1933 by Armstrong and Lillie during an encephalitis outbreak (St. Louis, Missouri, USA). In Bulgaria, LCMV was isolated for the first time in 1956 [3]. LCMV infection is detected in 20% of the cases of aseptic meningitis [3]. There are about 30 strains of LCMV that have been isolated from rodents and humans in the USA, Europe, Japan that show distinct patterns of tissue tropism. [4, 5]. Traub identified the common house mouse (*Mus musculus*) as the natural reservoir host of the virus in 1935 [6]. Mice infected in the intrauterine period cannot mount an immune response and develop asymptomatic life-long infection with large quantities of virus in nasal secretions, saliva, milk, semen, urine, and feces [7]. Hamsters and pet mice have been identified as sources of infection [8, 9]. In animals, horizontal and vertical transmission is possible and bites also play a role. Human infections occur after mucosal exposure to aerosols contaminated with rodent excreta, direct contact with rodents or through rodent bites [10]. Transmission from human to human has not been documented, except through organ transplantation

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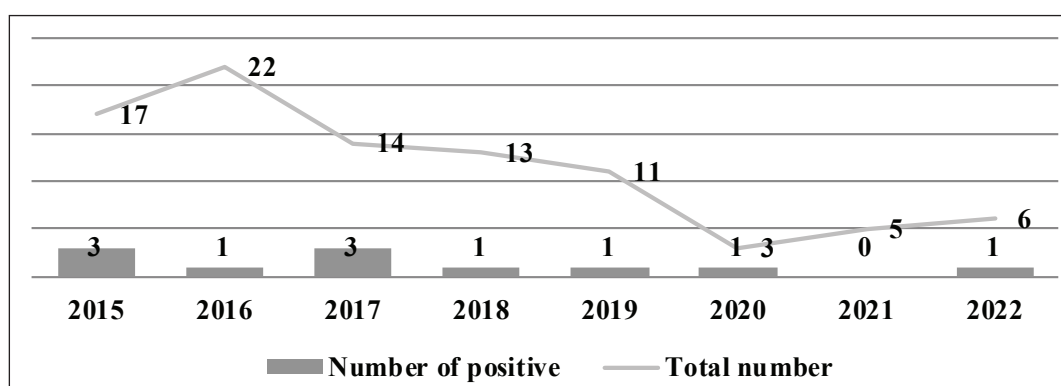


Figure 1. Distribution of number of positive samples over all samples tested.

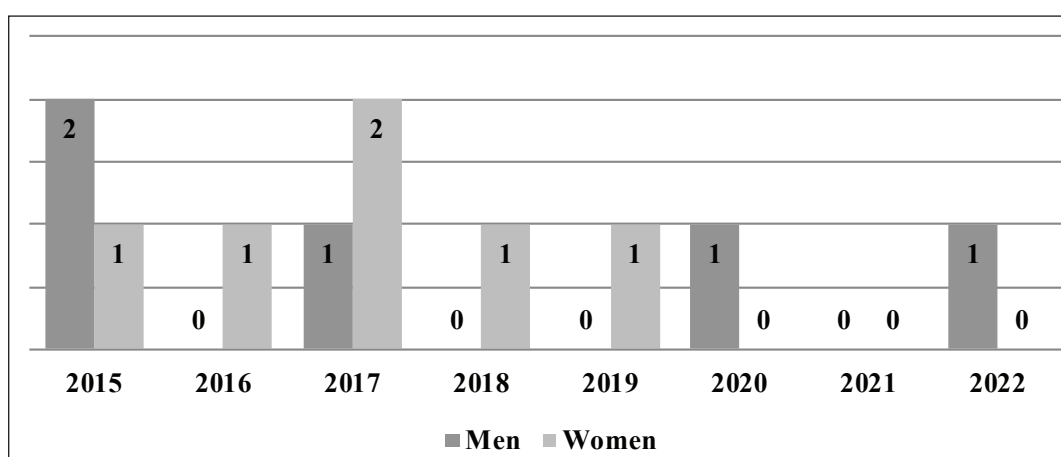


Figure 2. Distribution of positive samples of the patients by sex.

[11, 12] and vertical transmission from infected pregnant women to fetus [13]. The portal of entry is the mucosal lining of the digestive system or the respiratory tract. The viruses attach to cell surface receptors during the infection and are internalized by endocytosis. The incubation period is 3-13 days. The clinical forms of LCMV infection are: inapparent, flu-like, meningitis, meningoencephalitis, hemorrhagic, fetal infections. LCMV infection may be asymptomatic in immunocompetent persons (one third of infected or present as a non-specific, self-limiting febrile disease. However, the illness can progress to meningitis or meningoencephalitis. Most cases recover fully within one to three weeks [14]. In immunocompromised patients, such as organ transplant recipients, infection can resemble the Lassa hemorrhagic fever with a very high fatality rate [11,12]. Many reports from Germany, Lithuania, and France in the 1970s have shown the association of intrauterine LCMV infection with spontaneous

abortion and a congenital LCMV infection that occurs with hydrocephalus, chorioretinitis and periventricular calcifications in 87.5% of the cases [15-17]. Mortality among newborns with congenital infection is about 35% and 70% of them show long-term neurologic consequences [18]. There are also asymptomatic forms of the infection, as evidenced by the presence of antibodies in non-diseased individuals. The prevalence of LCMV in patients with fever and neurologic manifestations and healthy persons was analyzed in southern Iraq (2012-2016). The seroprevalence was 12.2% in the healthy control group and 7% in the acute febrile patients [19]. The most typical classic form is meningitis. Fever lasts 7-14 days and often has a two-wave pattern. During the second phase, which develops after 8-10 days, neurological manifestations also appear. The disease has a long undulating course with periods of improvement and deterioration but the prognosis is favorable. The meningoencephalitis form is less

common but more severe, with more neurological symptoms and mental disorders. The CSF is often not clear, with elevated protein levels and pleocytosis, mainly lymphocytes (98-100%).

The aim of this study is to investigate infection with LCMV in hospitalized patients in 2015-2022 in Bulgaria and to analyse the data compared to the worldwide data available in this field of research.

MATERIALS AND METHODS

A total of 66 serum and 25 cerebrospinal fluid (CSF) samples from 73 patients with suspected LCMV infection from different hospitals in Bulgaria were collected as follows: 13 serum samples and 4 CSF samples in 2015, 16 serum samples and 6 CSF samples in 2016, 11 serum samples and 3 CSF samples in 2017, 8 serum samples and 5 CSF samples in 2018, 8 serum samples and 3 CSF samples in 2019, 3 serum samples in 2020, 3 serum samples and 2 CSF samples in 2021, 4 serum samples and 2 CSF samples in 2022. The samples were taken from 35 men and 38 women. The patients had the following diagnoses: encephalitis - 12, meningitis - 26, meningoencephalitis - 28, cerebral edema - 3. There were only 4 patients with flu-like symptoms and with epidemiological data of contact with rodents. Human LCMV-Ab ELISA kit (Shanghai Sunred Biological Technology Co., Ltd., China), based on the principle of double-antibody sandwich technique to detect Human LCMV-Antibody was used according to the manufacturer's instructions.

RESULTS AND DISCUSSION

A total of 11/91 (12.09%) positive samples were found in the patients throughout the study period in 5 males and 6 females (Fig.1, Fig.2). In 2015 three cases of LCMV infection (3/17, 17.65%) were detected in patient samples (two males and one female) using the ELISA method (Fig.1, Fig.2). The men had meningoencephalitis and cerebral edema, and the woman had meningitis (Fig.5). One of the men also had reported contact with rodents. In 2016 one positive sample (1/22, 4.55%) was found from a woman with meningoencephalitis (Fig.1, Fig.2, Fig.5). The number of laboratory positive samples in 2017 was three (3/14, 21.43%), from two women with meningitis and one man with encephalitis

(Fig.1, Fig.2, Fig.5). In the period 2018-2020 infection was proven in three patients altogether – one in each year (1/13, 7.69%; 1/11, 9.09%; 1/3, 33.33%, respectively). Of the three, two were women with meningoencephalitis and the third was a man with meningitis (Fig.1, Fig.2, Fig.5). The small number of samples examined in 2020 is explained by the COVID-19 pandemic that started in 2020, when all other infections were neglected for a certain period of time. In 2021 only five samples from suspected patients were tested, but no positive samples were found among them. Of the six examined samples in 2022 one positive sample (1/6, 16.67%) was found from a man with meningitis (Fig.1, Fig.2, Fig.5). The four samples from patients with flu-like illnesses were tested but the results were negative.

High rates of positive samples were found in the years 2015, 2017, 2022, 17.65%, 21.43% and 16.67%, respectively. The highest percentage of positive samples was found in 2020, but too few samples were tested (1/3, 33.33%). The distribution of positive cases by age was as follows - two in each of the age groups 0 to 9 years, 40 to 49, 50 to 59 and 60 to 69 and one in the age groups: 10 to 19, 20 to 29, 30 to 39 years (Fig.3). The positive samples for LCMV infection were from patients from the cities: Sofia - 6, Stara Zagora - 4, Montana - 1.

A total of three (3/25, 12%) positive CSF samples and eight (8/66, 12.12%) positive serum samples were found (Fig.4). They were from patients with the following diagnoses: meningitis (5 cases), meningoencephalitis (4 cases), encephalitis (1 case), cerebral edema (1 case) (Fig.5). According to literature data, the most common form of infection is meningitis, which was also confirmed by us. A recent publication from 2021 for a study conducted in our country on the etiological structure of neuroinfections showed the presence of LCMV in 3% of the cases of viral and bacterial neuroinfections in the University hospital of Stara Zagora [20]. Several studies showed higher LCMV seropositivity in individuals exposed to rodents. LCMV was detected in 8% of hospitalized patients with neuroinvasive disease in 1950s in the United States, especially during winter when mice move indoors [21]. In the 1990s, the seroprevalence rates were found to be 2.3% in Argentina [22], 2.4% in Texas (USA) [23], 4%

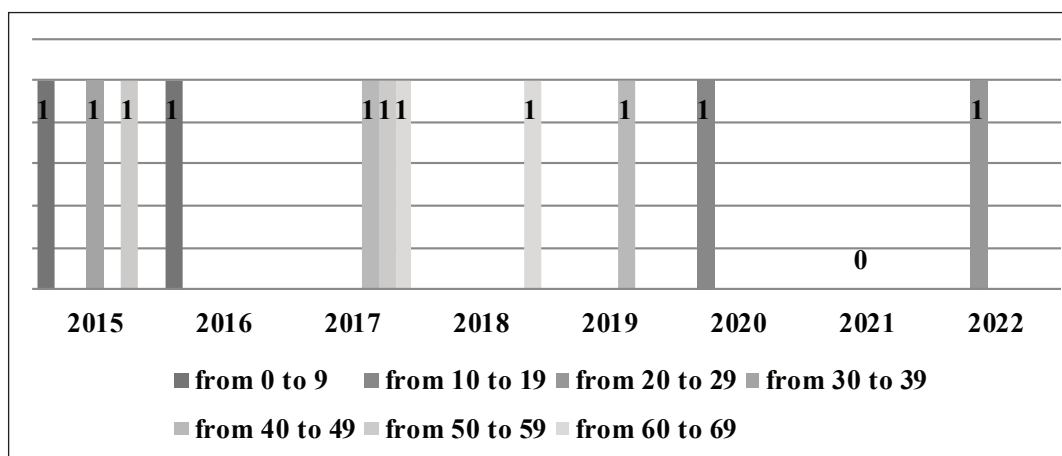


Figure 3. Distribution of positive samples of the patients by age.

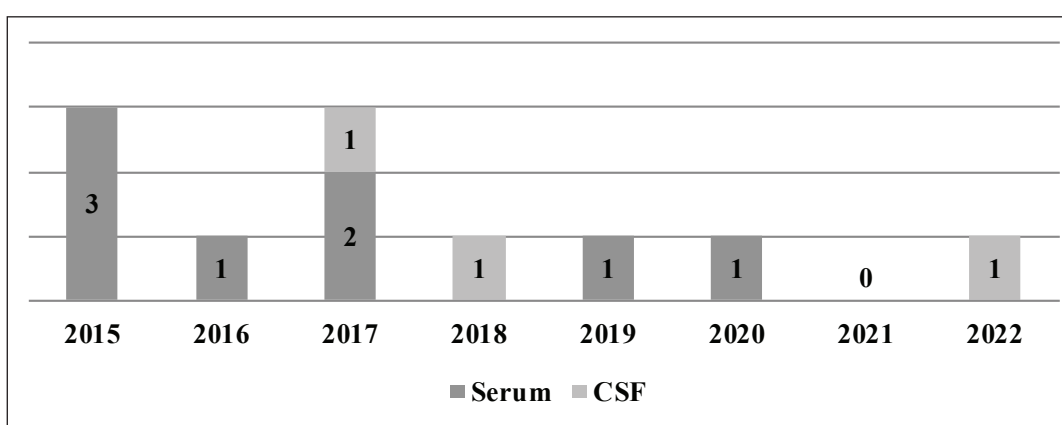


Figure 4. Distribution of positive samples of the patients by type of the sample.

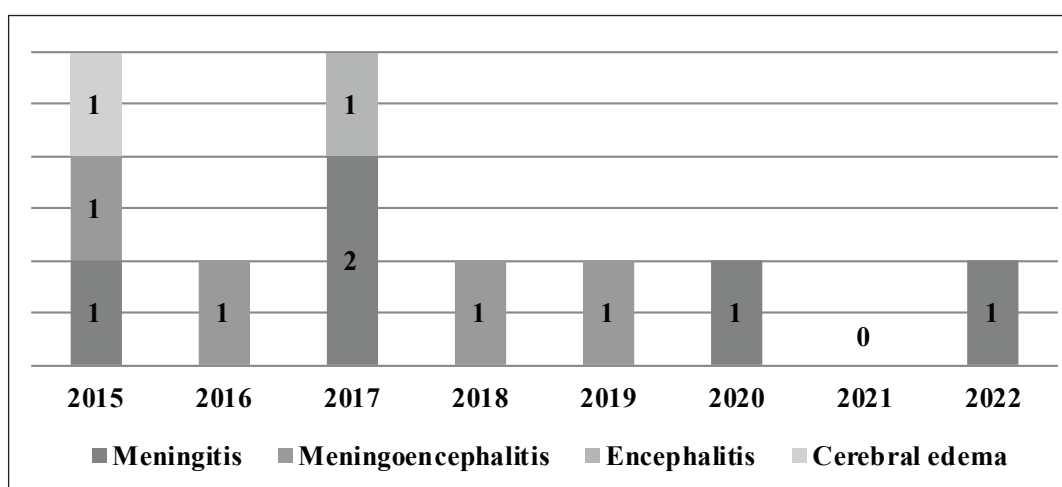


Figure 5. Distribution of positive samples of the patients by clinical manifestations.

in Canada [24], and 4.3-5.1% in Alabama (USA) [23]. Two studies from 2000s showed a seropositivity of 1.7% in Spain [25] and 3.3% in Argentina [26]. A study from Finland (2013-14) found that 5.0% of patients with neuroinvasive disease tested positive for LCMV IgG antibodies. Seropositivity was equally distributed between female and male patients [27], as our results also showed. A study in Gabon (2015-17) showed a high LCMV seropositivity of 21.5% [28]. Another study conducted in the continental Croatian regions (2017-18) showed an overall seroprevalence of 6.8%, ranging from 3.9% in non-exposed populations to 9.8% in professionally exposed individuals (forest workers, hunters, persons in frequent contacts with rodents) [29, 30]. Seroprevalence studies conducted among the general population have revealed that up to 15% seropositivity [31, 27, 25, 26, 32, 33]. This data correlates well with our results. An Austrian study found that 13% of employees of the Vienna zoo were LCMV seropositive [34]. A study from Italy conducted among forest workers showed an increase in the LCMV seroprevalence from 2.5% in 2002 [32] to 7% in 2015. Additionally, seroprevalence was high among hunters (12.9%) [35]. In 2012, 8 to 47% of the employees of rodent breeding facilities in the USA tested LCMV seropositive [36]. In our country, seroepidemiological studies conducted by Katsarov in the 80s showed the presence of antibodies among livestock breeders and forest workers between 6.8% and 24.6% [3].

Antiviral therapeutic options in human LCMV infection are currently exceptionally limited and the majority of research and future prospects are focused on repurposing antiviral drugs approved for the treatment of other infectious diseases. The first antiviral drug repurposed for the treatment of transplantation-associated LCMV infection in humans was ribavirin, a guanosine analogue with complex mechanisms of action including direct inhibition of RNA-dependent RNA polymerase [37]. The antiviral drug favipravir (pyrazinecarboxamide derivative) inhibits the activity of RdRp of various RNA viruses. It is currently used and evaluated in clinical trials for the therapy of COVID-19 [38]. Umifenovir (arbidol) is an indolycarboxylic acid that inhibits various stages of viral replication [39]. It is used for the prevention and treatment of influenza virus infection and is currently

being evaluated in clinical trials as a COVID-19 antiviral drug. Kim et al. (2019) identified 10 anti-LCMV compounds inhibiting different steps in the replication cycle that represent promising candidates for further pre-clinical evaluation [40]. Bösch et al. (2020) showed that landornamide A inhibits LCMV infection in mouse cells in vitro. [41]. Encouraging data comes from a related field, the treatment of Lassa virus infection. Mire et al. (2017) reported that combinations of human monoclonal antibodies (huMAbs) specific for glycoproteins of Lassa virus provided a 100% rescue, even when treatment was initiated at advanced stages of the disease [42]. Several of these huMAbs cross-react with LCMV glycoprotein complex in vitro, suggesting that further studies specifically focusing on monoclonal-antibody based treatment of LCMV are warranted [43, 44]. The treatment of LCMV infection is pathogenetic and symptomatic. Immunity is humoral and cellular, and remains lifelong after recovery. There is no vaccine prophylaxis available. General epidemiological measures (control of rodents, protection of water sources and food, etc.) are carried out in the cases of infectious outbreak. Reverse genetically engineered recombinant LCMV (rLCMV) is an important candidate for the development of vector-based vaccines [45]. Schmidt et al. (2020) constructed a new vaccine TT1-E7E6 based on replicating attenuated LCMV [46]. An assay based on RT-PCR has been developed for the detection of LCMV RNA in blood and CSF. The highly sensitive assays target the envelope precursor glycoprotein (GPC) and nucleoprotein (NP) genes [47, 48]. Testing of serum and CSF by both serology and RT-PCR is recommended to improve diagnostic yield [49]. Additionally, next-generation sequencing has been used retrospectively for donor-derived LCMV infection [50]. The application of these new methods of diagnosis of LCMV infection and new drugs for its treatment, based on modern achievements in science are good future prospects for our country. Many epidemiological studies showed that wild mice are infected with LCMV in some regions of the world. LCMV antibodies were detected in 25% of Norway rats (*Rattus norvegicus*) from the UK [51], in 5.6% of wild rodents (6.1% *Apodemus flavicollis*, 3.3% *Clethrionomys glareolus* and 14.3% *Microtus arvalis*) in Trentino, Italy [32], in 2.9% of wild mice

(*Mus musculus*) in China [52], in 6.9- 20.1% of *M. musculus* in urban areas of Argentina [22]. Another data showed LCMV antibodies in 2.4% of rodents trapped in Turkey [53], in 9% of mice (*M. musculus*, *M. spretus*) caught in Spain [25], in 10% among mice in Sincelejo, Colombia, [54]. The prevalence was highest in locations with high anthropogenic influence (53.33%), while it was significantly lower in rodents from natural habitats [55]. The seropositivity of trapped rodents from breeding facilities in the USA varied from 20.8% to 66% [36]. Only 0.4% of rats trapped in the Mekong Delta or purchased in wet markets in Vietnam (2012 - 2013) were LCMV seropositive [33]. There are currently no studies available on the presence of specific antibodies against LCMV in rodents in Bulgaria and this is a perspective field for future research.

CONCLUSIONS

Although the general clinical interest for the disease is low and LCMV is rarely considered, our study found 12.09% positive samples from hospitalized patients suspected for LCMV infection. Fatal LCMV infection in several cases of transplant recipients highlight the pathogenic potential and clinical significance of this neglected human pathogen. Even though we have not conducted studies among pregnant women, other studies show that LCMV should be considered as a fetal teratogen [56, 57, 58] and obstetricians should be aware of an emerging role of LCMV in addition to TORCH panel. Timely diagnosis of LCMV infection using the most common serological methods, as well as the introduction of modern molecular genetic methods will clarify the importance of this pathogen in our country and prevent possible complications in pregnant women.

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REFERENCES

- Centers for Diseases Control and Prevention. Lymphocytic Choriomeningitis Virus (LCMV). Available online: <https://www.cdc.gov/vhf/lcm/index.html> (accessed on 10 April 2021).
- Vilibic-Cavlek, T.; Savic, V.; Ferenc, T.; Mrzljak, A.; Barbic, L.; Bogdanic, M.; Stevanovic, V.; Tabain, I.; Ferencak, I.; Zidovec-Lepej, S. Lymphocytic Choriomeningitis-Emerging Trends of a Neglected Virus: A Narrative Review. *Trop. Med. Infect. Dis.* 2021, 6, 88, 1-19. <https://doi.org/10.3390/tropicalmed6020088>
- Arbovirus infections. Viral hemorrhagic fevers and bioterrorism. Kamarinchev B., Monev V., Voinova V., Serbezov V., Novkirishki V., Katsarov G., Kalvachev Z., Dikov I., Arabadzhiev K., Mekushinov K., Tiholova M., Nenova M., Gacheva N., Hristova T. Edited by Prof. V. Serbezov and Associate Professor Z. Kalvachev. Chapter: Serbezov V., Nenova M., Voinova V., Katsarov G., Kalvachev Z. Lymphocytic choriomeningitis, HMI, Sofia, 2005, 162-170.
- Takagi, T.; Ohsawa, M.; Morita, C.; Sato, H.; Ohsawa, K. Genomic analysis and pathogenic characteristics of lymphocytic choriomeningitis virus strains isolated in Japan. *Comp. Med.* 2012, 62, 185-192. PMID: 22776051 PMCID: PMC3364700
- Takagi, T.; Ohsawa, M.; Yamanaka, H.; Matsuda, N.; Sato, H.; Ohsawa, K. Difference of two new LCMV strains in lethality and viral genome load in tissues. *Exp. Anim.* 2017, 66, 199-208. <https://doi.org/10.1538/expanim.16-0097>
- Traub, E. A filterable virus recovered from white mice. *Science* 1935, 81, 298-299. <https://doi.org/10.1126/science.81.2099.298>
- Lapošová, K.; Pastoreková, S.; Tomášková, J. Lymphocytic choriomeningitis virus: Invisible but not innocent. *Acta Virol.* 2013, 57, 160-170. https://doi.org/10.4149/av_2013_02_160
- Hotchin, J.; Sikora, E.; Kinch, W.; Hinman, A.; Woodall, J. Lymphocytic choriomeningitis in a hamster colony causes infection of hospital personnel. *Science* 1974, 185, 1173-1174. *Trop. Med. Infect. Dis.* 2021, 6, 88 16 of 19. <https://doi.org/10.1126/SCIENCE.185.4157.1173>
- Ackermann, R.; Stille, W.; Blumenthal, K. Syrische Goldhamster als unbertrager von lymphozytärer choriomeningitis. *Deutsche Medizinische Wochenschrift* 1972, 97, 1725-1731. <https://doi.org/10.1055/s-0028-1107638>
- Rollin, P.E.; Nichol, S.T.; Zaki, S.; Ksiazek, T.G. Arenaviruses and Filoviruses. *Manual of Clinical Microbiology*, 11th ed.; Jorgensen, J.H., Phaller, M.A., Carroll, K.C., Landry, M.L., Funke, G., Richter, S.S., Warnock, D.W., Eds.; ASM Press: Washington, DC, USA, 2015; pp. 1669-1686.
- Centers for Disease Control and Prevention (CDC). Lymphocytic choriomeningitis virus infection in organ transplant recipients in Massachusetts, Rhode Island, 2005. *Morb. Mortal. Wkly. Rep.* 2005, 54, 537-539.
- MacNeil, A.; Ströher, U.; Farnon, E.; Campbell, S.; Cannon, D.; Paddock, C.D.; Drew, C.P.; Kuehnert, M.; Knust, B.; Gruenen-Felder, R.; et al. Solid organ transplant-associated lymphocytic choriomeningitis, United States, 2011. *Emerg. Infect. Dis.* 2012, 18, 1256-1262. <https://doi.org/10.3201/eid1808.120212>
- Komrower, G.M.; Williams, B.L.; Stones, P.B. Lymphocytic choriomeningitis in the newborn; Probable transplacental infection. *Lancet* 1955, 268, 697-698. [https://doi.org/10.1016/s0140-6736\(55\)91066-7](https://doi.org/10.1016/s0140-6736(55)91066-7)
- Bonthius, D.J. The arenaviruses. *Neurotropic Viral Infections*; Reiss, C.S., Ed.; Springer: Berlin/Heidelberg, Germany, 2016; pp. 149-174. https://doi.org/10.1007/978-3-319-33133-1_6
- Ackermann, R.; Körver, G.; Turss, R.; Wönne, R.; Hochgesand, P. Pränatale infektion mit dem virus der lymphozytären choriomeningitis: Bericht über zwei fälle. *Deutsche*

- Medizinische Wochenschrift 1974, 99, 629-632. <https://doi.org/10.1055/s-0028-1107814>
16. Sheinbergas, M. Hydrocephalus due to prenatal infection with the lymphocytic choriomeningitis virus. *Infection* 1976, 4, 185-191. <https://doi.org/10.1007/bf01638922>.
17. Chastel, C.; Bosshard, S.; Le Goff, F.; Quillien, M.C.; Gilly, R.; Aymard, M. Infection transplacentaire par le virus de la chorioméningite lymphocytaire. Résultats d'une enquête sérologique rétrospective en France. *Nouvelle Presse Medicale* 1978, 7, 1089-1092. PMID: 662624
18. Wright, R.; Johnson, D.; Neumann, M.; Ksiazek, T.G.; Rollin, P.; Keech, R.V.; Bonthius, D.J.; Hitchon, P.; Grose, C.F.; Bell, W.E.; et al. Congenital lymphocytic choriomeningitis virus syndrome: A disease that mimics congenital toxoplasmosis or cytomegalovirus infection. *Pediatrics* 1997, 100, e9. <https://doi.org/10.1542/peds.100.1.e9>
19. Alburkat, H.; Jääskeläinen, A.J.; Barakat, A.M.; Hasony, H.J.; Sironen, T.; Al-Hello, H.; Smura, T.; Vapalahti, O. Lymphocytic choriomeningitis virus infections and seroprevalence, Southern Iraq. *Emerg. Infect. Dis.* 2020, 26, 3002-3006. <https://doi.org/10.3201/eid2612.201792>
20. Pekova L, Halacheva K, Dochev I. Comparative analysis of clinical and laboratory parameters between viral and bacterial neuroinfections. *Probl. Inf. Parasit. Dis. Vol.* 49, 2021,1, 26-31. <https://doi.org/10.58395/pipd.v49i1.53>
21. Adair, C.V.; Gauld, R.L.; Smadel, J.E. Aseptic meningitis, a disease of diverse etiology: Clinical and etiologic studies on 854 cases. *Ann. Intern. Med.* 1953, 39, 675-704. <https://doi.org/10.7326/0003-4819-39-4-675>
22. Ambrosio, A., Saavedra M., Gamboa G., Maiza A., Mariani M. Ecological and epidemiological features of lymphocytic choriomeningitis virus activity in Argentina. Book chapter: *Curr. Top. Virol. Vol.* 12, 2014, 53-63.
23. Stephensen, C.B.; Blount, S.R.; Lanford, R.E.; Holmes, K.V.; Montali, R.J.; Fleenor, M.E.; Shaw, J.F. Prevalence of serum antibodies against lymphocytic choriomeningitis virus in selected populations from two, U.S. cities. *J. Med. Virol.* 1992, 38, 27-31. DOI 10.1002/jmv.1890380107
24. Marrie, T.J.; Saron, M.F. Seroprevalence of lymphocytic choriomeningitis virus in Nova Scotia. *Am. J. Trop. Med. Hyg.* 1998, 58, 47-49. <https://doi.org/10.4269/ajtmh.1998.58.47>
25. Lledó, L.; Gegúndez, M.I.; Saz, J.V.; Bahamontes, N.; Beltrán, M. Lymphocytic choriomeningitis virus infection in a province of Spain: Analysis of sera from the general population and wild rodents. *J. Med. Virol.* 2003, 70, 273-275. <https://doi.org/10.1002/jmv.10389>
26. Riera, L.; Castillo, E.; del Carmen, M.S.; Priotto, J.; Sottosanti, J.; Polop, J.; Ambrosio, A.M. Serological study of the lymphochoriomeningitis virus (LCMV) in an inner city of Argentina. *J. Med. Virol.* 2005, 76, 285-289. <https://doi.org/10.1002/jmv.20357>
27. Fevola, C.; Kuivanen, S.; Smura, T.; Vaheri, A.; Kallio-Kokko, H.; Hauffe, H.C.; Vapalahti, O.; Jääskeläinen, A.J. Seroprevalence of lymphocytic choriomeningitis virus and Ljungan virus in Finnish patients with suspected neurological infections. *J. Med. Virol.* 2018, 90, 429-435. <https://doi.org/10.1002/jmv.24966>
28. Ushijima, Y.; Abe, H.; Ozeki, T.; Ondo, G.N.; Mbadinga, M.J.V.M.; Bikangui, R.; Nze-Nkogue, C.; Akomo-Okoue, E.F.; Ella, G.W.E.; Koumba, L.B.M.; et al. Identification of potential novel hosts and the risk of infection with lymphocytic choriomeningitis virus in humans in Gabon, Central Africa. *Int. J. Infect. Dis.* 2021, 105, 452-459. <https://doi.org/10.1016/j.ijid.2021.02.105>
29. Vilbic-Cavlek, T.; Oreski, T.; Korva, M.; Kolaric, B.; Stevanovic, V.; Zidovec-Lepej, S.; Tabain, I.; Jelcic, P.; Miklausic-Pavic, B.; Savic, V. et al. Prevalence and risk factors for lymphocytic choriomeningitis virus infection in continental Croatian regions. *Trop. Med. Infect. Dis.* 2021, 6, 67. <https://doi.org/10.3390/tropicalmed6020067>
30. Vilbic-Cavlek, T.; Barbic, L.; Mrzljak, A.; Brnic, D.; Klobucar, A.; Ilic, M.; Janev-Holcer, N.; Bogdanic, M.; Jemersic, L.; Stevanovic, V.; et al. Emerging and neglected viruses of zoonotic importance in Croatia. *Pathogens* 2021, 10, 73. <https://doi.org/10.3390/pathogens10010073>
31. Barakat, A.M.; Lapahat, O.; Hasoni, H.J. Lymphocytic choriomeningitis virus (LCMV) in Southern Iraq. *Int. J. Sci. Eng. Res.* 2015, 6, 1523-1535.
32. Kallio-Kokko, H.; Laakkonen, J.; Rizzoli, A.; Tagliapietra, V.; Cattadori, I.; Perkins, S.E.; Hudson, P.J.; Cristofolini, A.; Versini, W.; Vapalahti, O.; et al. Hantavirus and arenavirus antibody prevalence in rodents and humans in Trentino, Northern Italy. *Epidemiol. Infect.* 2006, 134, 830-836. <https://doi.org/10.1017/s0950268805005431>
33. Van Cuong, N.; Carrique-Mas, J.; Be, H.V.; An, N.N.; Tue, N.T.; Anh, N.L.; Anh, P.H.; Phuc, N.T.; Baker, S.; Voutilainen, L.; et al. Rodents and risk in the Mekong delta of Vietnam: Seroprevalence of selected zoonotic viruses in rodents and humans. *Vector Borne Zoonotic Dis.* 2015, 15, 65-72. <https://doi.org/10.1089/vbz.2014.1603>
34. Juncker-Voss, M.; Prosl, H.; Lussy, H.; Enzenberg, U.; Auer, H.; Lassnig, H.; Müller, M.; Nowotny, N. Screening for antibodies against zoonotic agents among employees of the Zoological garden of Vienna, Schönbrunn, Austria. *Berliner und Münchener Tierärztliche Wochenschrift* 2004, 117, 404-409. PMID: 15495931
35. Tagliapietra, V.; Rosà, R.; Rossi, C.; Rosso, F.; Hauffe, H.C.; Tommasini, M.; Versini, W.; Cristallo, A.F.; Rizzoli, A. Emerging rodent-borne viral zoonoses in Trento, Italy. *Ecohealth* 2018, 15, 695-704. <https://doi.org/10.1007/s10393-018-1335-4>
36. Knust, B.; Ströher, U.; Edison, L.; Albariño, C.G.; Lovejoy, J.; Armeanu, E.; House, J.; Cory, D.; Horton, C.; Fowler, K.L.; et al. Lymphocytic choriomeningitis virus in employees and mice at multipremises feeder-rodent operation, United States, 2012. *Emerg. Infect. Dis.* 2014, 20, 240-247. <https://doi.org/10.3201/eid2002.130860>
37. Ramírez-Olivencia, G.; Estébanez, M.; Membrillo, F.J.; Ybarra, M.D.C. Use of ribavirin in viruses other than hepatitis C. A review of the evidence. *Enferm. Infecc. Microbiol. Clin.* 2019, 37, 602-608. <https://doi.org/10.1016/j.eimc.2018.05.008>
38. Tian, D.; Liu, Y.; Liang, C.; Xin, L.; Xie, X.; Zhang, D.; Wan, M.; Li, H.; Fu, X.; Liu, H.; et al. review An update of emerging small-molecule therapeutic options for COVID-19. *Biomed. Pharmacother.* 2021, 137, 111313. <https://doi.org/10.1016/j.biopha.2021.111313>
39. Indari, O.; Jakhmola, S.; Manivannan, E.; Jha, H.C. An update on antiviral therapy against SARS-CoV-2: How far have we come? *Front. Pharmacol.* 2021, 12, 632677. <https://doi.org/10.3389/fphar.2021.632677>
40. Kim, Y.J.; Cubitt, B.; Chen, E.; Hull, M.V.; Chatterjee, A.K.; Cai, Y.; Kuhn, J.H.; de la Torre, J.C. The ReFRAME library as a comprehensive drug repurposing library to identify mammarenavirus inhibitors. *Antivir. Res.* 2019, 169, 104558. <https://doi.org/10.1016/j.antiviral.2019.104558>
41. Bösch, N.M.; Borsa, M.; Greczmiel, U.; Morinaka, B.I.; Gugger, M.; Oxenius, A.; Vagstad, A.L.; Piel, J. Landornamides: Antiviral ornithine-containing ribosomal peptides discovered through genome mining. *Angewandte Chemie* 2020, 59, 11763-11768. *Trop. Med. Infect. Dis.* 2021, 6, 88 19 of 19 <https://doi.org/10.1002/anie.201916321>
42. Mire, C.E.; Cross, R.W.; Geisbert, J.B.; Borisevich, V.; Agans, K.N.; Deer, D.J.; Heinrich, M.L.; Rowland, M.M.; Goba, A.; Momoh, M.; et al. Human-monoclonal-antibody therapy protects nonhuman primates against advanced Lassa fever.

- Nat. Med. 2017, 23, 1146-1149. <https://doi.org/10.1038/nm.4396>
43. Robinson, J.E.; Hastie, K.M.; Cross, R.W.; Yenni, R.; Elliott, D.H.; Rouelle, J.A.; Kannadka, C.B.; Smira, A.A.; Garry, C.E.; Bradley, B.T.; et al. Most neutralizing human monoclonal antibodies target novel epitopes requiring both Lassa virus glycoprotein subunits. *Nat. Commun.* 2016, 7, 11544. <https://doi.org/10.1038/ncomms11544>
44. Cross, R.W.; Hastie, K.M.; Mire, C.E.; Robinson, J.E.; Geisbert, T.W.; Branco, L.M.; Saphire, E.O.; Garry, R.F. Antibody therapy for Lassa fever. *Curr. Opin. Virol.* 2019, 37, 97-104. <https://doi.org/10.1016/j.coviro.2019.07.003>
45. Krolik, M.; Csepreghi, L.; Hartmann, F.; Engetschwiler, C.; Flatz, L. Recombinant lymphocytic choriomeningitis virus-based vaccine vector protects type I interferon receptor deficient mice from viral challenge. *Vaccine* 2021, 39, 1257-1264. <https://doi.org/10.1016/j.vaccine.2021.01.047>
46. Schmidt, S.; Bonilla, W.V.; Reiter, A.; Stemeseder, F.; Kleissner, T.; Oeler, D.; Berka, U.; El-Gazzar, A.; Kiefmann, B.; Schulha, S.C.; et al. Live-attenuated lymphocytic choriomeningitis virus-based vaccines for active immunotherapy of HPV16-positive cancer. *Oncoimmunology* 2020, 9, 1809960. <https://doi.org/10.1080/2162402x.2020.1809960>
47. Wilson, M.R.; Peters, C.J. Diseases of the central nervous system caused by lymphocytic choriomeningitis virus and other arenaviruses. In *Handbook of Clinical Neurology*, 3rd ed.; Tselis, A.C., Booss, J., Eds.; Elsevier: Amsterdam, The Netherlands, 2014; Volume 123, pp. 671-681. <https://doi.org/10.1016/b978-0-444-53488-0.00033-x>
48. Cordey, S.; Sahli, R.; Moraz, M.L.; Estrade, C.; Morandi, L.; Cherpillod, P.; Charrel, R.N.; Kunz, S.; Kaiser, L. Analytical validation of a lymphocytic choriomeningitis virus real-time RT-PCR assay. *J. Virol. Methods* 2011, 177, 118-122. <https://doi.org/10.1016/j.jviromet.2011.06.018>
49. Anesi, J.A.; Silveira, F.P.; AST infectious diseases community of practice. Arenaviruses and west Nile virus in solid organ transplant recipients: Guidelines from the American society of transplantation infectious diseases community of practice. *Clin. Transplant.* 2019, 33, e13576. <https://doi.org/10.1111/ctr.13576>
50. Palacios, G.; Druce, J.; Du, L.; Tran, T.; Birch, C.; Briesse, T.; Conlan, S.; Quan, P.L.; Hui, J.; Marshall, J.; et al. A new arenavirus in a cluster of fatal transplant-associated diseases. *N. Engl. J. Med.* 2008, 358, 991-998. <https://doi.org/10.1056/nejmoa073785>
51. Stuart, A.M.; Prescott, C.V.; MacIntyre, S.; Sethar, A.; Neuman, B.W.; McCarthy, N.D.; Wimalarathna, H.; Maiden, M.C.J. The role of rodents as carriers of disease on UK farms: A preliminary investigation. In *Proceedings of the 8th European Vertebrate Pest Management Conference*, Berlin, Germany, 26-30 September 2011; Julius-Kühn-Archiv: Quedlinburg, Germany, 2011; Volume 432, pp. 198-199. *Trop. Med. Infect. Dis.* 2021, 6, 88 17 of 19. <https://doi.org/10.5073/jka.2011.432.110>
52. Morita, C.; Tsuchiya, K.; Ueno, H.; Muramatsu, Y.; Kojimahara, A.; Suzuki, H.; Miyashita, N.; Moriwaki, K.; Jin, M.L.; Wu, X.L.; et al. Seroepidemiological survey of lymphocytic choriomeningitis virus in wild house mice in China with particular reference to their subspecies. *Microbiol. Immunol.* 1996, 40, 313-315. <https://doi.org/10.1111/j.1348-0421.1996.tb03342.x>
53. Laakkonen, J.; Kallio-Kokko, H.; Oktem, M.A.; Blasdel, K.; Plyusnina, A.; Niemimaa, J.; Karata, S.; Plyusnin, A.; Vaheri, A.; Henttonen, H. Serological survey for viral pathogens in Turkish rodents. *J. Wildl. Dis.* 2006, 42, 672-676. <https://doi.org/10.7589/0090-3558-42.3.672>
54. Castellar, A.; Guevara, M.; Rodas, J.D.; Londoño, A.F.; Arroyave, E.; Díaz, F.J.; Levis, S.; Blanco, P.J. First evidence of lymphocytic choriomeningitis virus (Arenavirus) infection in *Mus musculus* rodents captured in the urban area of the municipality of Sincelejo, Sucre, Colombia. *Biomedica* 2017, 37, 75-85. <https://doi.org/10.7705/biomedica.v37i2.3226>
55. Duh, D.; Hasic, S.; Buzan, E. The impact of illegal waste sites on a transmission of zoonotic viruses. *Virol. J.* 2017, 14, 134. <https://doi.org/10.1186/s12985-017-0798-1>
56. Barton, L.L.; Peters, C.J.; Ksiazek, T.G. Lymphocytic choriomeningitis virus: An unrecognized teratogenic pathogen. *Emerg. Infect. Dis.* 1995, 1, 152-153. <https://doi.org/10.3201/eid0104.950410>
57. Barton, L.L.; Mets, M.B.; Beauchamp, C.L. Lymphocytic choriomeningitis virus: Emerging fetal teratogen. *Am. J. Obstet. Gynecol.* 2002, 187, 1715-1716. <https://doi.org/10.1067/mob.2002.126297>
58. Kinori, M.; Schwartzstein, H.; Zeid, J.L.; Kurup, S.P.; Mets, M.B. Congenital lymphocytic choriomeningitis virus-An underdiagnosed fetal teratogen. *J. AAPOS* 2018, 22, 79.e1-81.e1. <https://doi.org/10.1016/j.jaapos.2017.08.011>