Vector-Borne Tularemia

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Tularemia is a zoonosis caused by the highly invasive bacterium *Francisella tularensis*. It is transmitted to humans by direct contact with infected animals or by vectors, such as ticks, mosquitos, and flies.

Keywords: vector-borne diseases ; lymph node excision ; serology

1. Pathogenesis of Tularemia

F. tularensis is a gram-negative, aerobic, facultative intracellular bacterium. Taxonomically, it is divided into four known subspecies: *F. tularensis* subsp. *tularensis*, *F. tularensis* subsp. *holarctica*, *F. tularensis* subsp. *Mediasiatica,* and *F. tularensis* subsp. *novicida*. Earlier publications considered *F. novicida* and *F. tularensis* as a separate species. *F. novicida* differs from other subtypes in its lessened ability of tissue invasion and tissue damage in mammals [1]. It is also not a part of the select agent list of the United States and does not require as excessive laboratory safety regulations as other subtypes [2]. The re-classification of subspecies, however, remains debatable [3][4].

Subsp. *tularensis* and *holarctica*, previously called type A and B, respectively, are the most relevant subtypes for clinical practice [5][6]. Subsp. *tularensis* is almost exclusively present in Northern America and causes a more severe form of the disease. It is particularly virulent, with an infectious dose of <10 colony forming units (CFUs) [7][8]. The type A strains are further separated into subtypes A.I and A.II, with A.I being the most virulent [9]. In cases of pulmonary infections with subsp. *tularensis* without treatment, the mortality of up to 60% is described [10]. The less virulent type subsp. *holarctica* with the infectious dose of 100–1000 CFUs causes the majority of infections in Europe [11][12]. The infection results in a milder, sometimes even subclinical disease [5][13][14]. Both pathogens can persist in the environment for weeks or even months [15].

The bacteria enter the body through minor skin or mucosa wounds. The capsule of *F. tularensis* is an essential virulence factor, enabling it to dodge polymorphonuclear neutrophil destruction. As it enters the bloodstream, it is phagocyted by circulating monocytes and macrophages of the reticuloendothelial system, where it can survive as an intracellular parasite. As a result, granulomatous lesions can arise in the affected organs [8][16]. Immunity after the infection is usually life-long, although reinfections have been described in the literature [17].

2. Transmission of Tularemia

F. tularensis was isolated from more than 100 wild animal species, domestic animals, arthropods, birds, and fish. The main reservoirs are wild mammals, such as rabbits, squirrels, and beavers. People working with these animals (e.g., hunters, butchers, and furriers) are more exposed to the infection [6][18][19].

Tularemia is transmitted to humans by direct contact with an infected animal (e.g., rabbits, beavers, hares, and rodents), most commonly when working with its meat and skin, or by arthropod bites (e.g., ticks, mosquitoes, flies, and lice). These have been previously feasting on an infected animal or water source. Other possible transmission routes are ingesting contaminated water or food and inhaling aerosolised bacteria, for instance, in hay or while handling the pathogens in laboratories [13][20]. Grass mowing, hay stacking, and other activities with possible machine driving over infected animals or their carcasses are hazardous for aerosol formation [18][21]. Tularemia has not been reported to transmit directly from human to human; hence, contact isolation of infected persons is not necessary [22].

Transmission of tularemia usually occurs from May to August during hunting season. In the USA, ticks, deer flies, and rabbits are the most common sources of infection, whereas in Northern Europe, rodents, mosquitos, and the tick *Dermacentor reticulatus* are the most common disease agent carriers [23][24].

3. Tularemia as a Tick-Borne Disease

Despite the well-established transmission route by tick bites, tularemia is rarely immediately recognised as a tick-borne disease [10]. Ticks were discovered as vectors in 1924 [25]. Tick-borne tularemia cases are reported in almost all endemic areas [26]. More than 85% of all tularemia confirmed cases in the 1960s were associated with tick bites in the United States, where still around half of the tularemia infections are related to tick bite exposure. From 2004 to 2016, 2.102 tick-borne tularemia cases were reported in the USA [27][28]. In Europe, recent reports have changed the previously understated importance of tick-borne transmission of tularemia [29]. According to Maurin et al. (2011), 11% of tularemia cases are tick-borne in France, while Guycova et al. (2010) described 12.8% of tick-borne tularemia confirmed cases in Slovakia [30][31].

Epidemiological data in a study by Rojko et al. (2016) regarding tularemia cases between 2012 and 2013 in Slovenia revealed tick-borne infections in 50% of patients. Furthermore, *Ixodes ricinus* was found to be the most prevalent species of vectors in Slovenia. In contrast, *Dermacentor reticulatus* was characterised only in the northeastern part of the country, where most tularemia cases were reported before 2012 [32].

4. Epidemiology of Tularemia

Even though tularemia is a well-studied disease, with its causative bacterium isolated in many countries, its occurrence overall is rare. However, sporadic cases and outbreaks are reported around the globe, predominantly in the northern hemisphere between 30° and 70° latitude [33]. Approximately 800 cases are reported annually in Europe. The disease is thought to be endemic in Sweden and Finland, the countries with the most cases reported in Europe. Mosquito bites are this area's most common transmission route [34]. Kosovo likewise reports one of the highest incidence rates of tularemia in Europe. The highest incidence in this country was reported in 2010, with 11.26 cases per 100,000 inhabitants [35][36]. In addition to Kosovo (1999, 2000, and 2003), the most significant outbreaks have been reported in Turkey (2005–2007) and Spain (1997, 1998, and 2007) [33]. In Europe, tularemia has not been reported in Iceland, Ireland, or the United Kingdom [37].

In the past decades, the epidemiology of the disease has changed, with several outbreaks reported in areas previously considered non-endemic. Tularemia is regarded as a locally emerging or re-emerging disease in Europe [38]. It has recently expanded its geographical range and included host animals previously not linked to tularemia, such as the red fox, the wild boar, and the raccoon dog [39][40]. The European Food Safety Authority (EFSA) and the European Center for Disease and Prevention Control (ECDC) have reported increased animal reservoirs [41]. The dynamics in epidemiology seem to have been the opposite overseas. In the USA, in the 1950s, almost 1000 cases were reported annually, whereas in 2019, a little over 270 cases were reported to the CDC [27].

In Slovenia, the disease is rare, with 1–3 cases reported annually [21][22], but the numbers have risen in the past decades [36]. From 1990 to 2020, 42 cases of tularemia were reported. Before 2012, only eight sporadic cases had been reported over the past ten years. Half of the cases occurred in the northeastern part of Slovenia. Recently, cases have been described in other areas of the country. The first clinical cases outside of the northeastern region were reported in 2012. In 2012 and 2013, a cluster of six cases occurred in the central part of Slovenia [21][42]. Epidemiological data by Rojko et al. (2016) report 31 patients with clinical diagnosis of tularemia treated in Slovenia from 2004 to 2018 [32].

Additionally, in 2021, there was an outbreak of tularemia mainly in the western part of Slovenia, with more than 35 cases confirmed, but, in other parts of Slovenia, an increase of sporadic cases was also observed [38]. There is no description of cervical ulceroglandular tularemia in Slovenia yet.

5. Treatment of Tularemia

The overall mortality of an untreated tularemia infection is 5–15% [43]. The prevailing connection to a fatal outcome is in the pulmonary form of the disease. Nevertheless, other forms may lead to terminal consequences, too. Timely diagnosis with specific antibiotic treatment significantly lowers life-threatening complications, often leaving patients entirely symptom-free. In the pre-antibiotic area, around 30% of patients with tularemia died in the USA. In infection with the more pathogenic type A, nowadays, even with prompt and appropriate antibiotic treatment, the mortality of the disease caused by this subtype is 4%. In Europe, with the less virulent subtype prevailing, however, death following tularemia is much less frequently encountered [6][18].

The antibiotic of choice depends mainly on the severity of the disease and the patient's age (**Table 1**). The best minimal inhibitory concentration is streptomycin or gentamycin when taken orally for 7–14 days [19]. Ciprofloxacin, doxycycline, and chloramphenicol are also effective and should be administered for at least 14 days. Antibiotic testing of *F. tularensis* is not routinely performed in a clinical setting as antibiotic resistance of the bacterium has never been reported [44]. Thus, aminoglycosides streptomycin, gentamicin, fluoroquinolone ciprofloxacin, and tetracycline antibiotic doxycycline are most commonly used in tularemia. First-line drugs for mild to moderate tularemia cases, which predominate in Europe, are ciprofloxacin and doxycycline. Gentamicin has been reported to result in higher relapse rates, though it is often used in patients with systemic diseases and children. In younger patients, fluoroquinolones are contraindicated owing to possible damage to the muscles and skeletal system. Ciprofloxacin is a safer choice for children 1–10 years. Streptomycin or chloramphenicol are the antibiotics of choice in pregnant women with milder forms of the disease. However, gentamicin should be used in pregnant women with severe tularaemia. Possible side effects of the medication should be weighed against the severity of the disease [19][45].

Table 1. Recommended treatment for tularemia.

Disease Severity	Treatment Regimen
Severe to moderate infection	• **Streptomycin 7.5 mg–1 g IM or IV, twice daily, 7–10 days OR** • **Gentamicin or tobramycin 5 mg/kg IV, once or twice daily, 10 days** ***Children:*** • **Gentamicin 2.5 mg/kg IV, three times daily, with OR without ciprofloxacin in 10–15 mg/kg orally, twice daily** • **Ciprofloxacin 400 mg IV or 750 mg orally, twice a day, 14–21 days OR** • **Doxycycline 100 mg orally or IV, twice a day, 14–21 days**
Mild infection	***Children:*** • **above 8 years old: doxycycline 2.2 mg/kg orally, twice daily** • **1–10 years old: ciprofloxacin 10–15 mg/kg orally, twice daily**
Hematogenous meningitis	• **Aminoglycoside + chloramphenicol 50–100 mg/kg/day IV in 4 divided doses**
Pregnancy	• **Streptomycin or chloramphenicol 15 mg/kg, four times a day, 14 days**
Prophylaxis for aerosol exposure	• **Doxycycline 100 mg orally, twice daily, 14 days OR** • **Ciprofloxacin 500 mg, orally, twice daily, 14 days**

Based on WHO guidelines and reproduced with permission from Max Maurin and Miklós Gyuranecz, The Lancet Infectious Diseases; published by Elsevier, 2016 (license number: 5367520082599) [6][19] IV—intravenously, IM—intramuscularly.

In milder forms of the disease, the recommendations are to opt for treatment with ciprofloxacin or doxycycline. While fluoroquinolones such as ciprofloxacin have been reported to have a lower relapse rate (5–10%, in contrast to 10–15% in tetracyclines), several factors contribute to choosing doxycycline in cases of the disease following a tick-bite [46]. Doxycycline empirically treats other possible tick-related illnesses (e.g., Lyme disease), which is useful in the setting of a tick bite, especially before final microbiological investigations. Additionally, doxycycline is associated with fewer side effects than ciprofloxacin. In 2018, the European Medicines Agency finalised a review of severe, disabling and potentially permanent side effects of quinolone and fluoroquinolone antibiotics, endorsing new recommendations to restrict further fluoroquinolone use. Physicians are instructed to use other antimicrobials if possible. The side effects of ciprofloxacin have proven to be long-lasting, disabling, and potentially permanent, involving tendons, muscles, joints, and the nervous system [47].

Nevertheless, doxycycline is contraindicated in children and pregnancy owing to teeth discolouration and impairment of foetal bone growth [48]. The recommended duration of treatment with tetracyclines varies in the literature. According to Maurin et al. (2016), the suggested regime for doxycycline in tularemia is three weeks long to avoid disease relapses [6]. The WHO guidelines from 2007 recommend a daily dose of 200 mg of doxycycline for at least 15 days [19].

In lymphadenitis cases, surgical drainage of a colliquative lymph node is commonly indicated besides specific antibiotic treatment. However, in the experience of Atmaca et al. (2008), as reported in their study, complete surgical removal of

tularemia-affected lymph nodes is often challenging, with adherent tissue preventing the dissection from the surrounding tissues [49]. Hence, as with other inflammatory swellings in the neck, tularemia-associated-lymphadenitis should be managed by a staged therapeutic approach. Therefore, the first point of reference for physicians in planning the surgical treatment of lymphadenopathy is for the lymph nodes in the neck area to be greater than 1 cm or 1.5 cm in the jugulodigastric nodes [50]. The decision to excise or drain the affected lymph node relies on colliquation in the lymph nodes, cellulitis over the skin, or sepsis. In those cases, immediate surgical drainage is required. Thus, conservative treatment with antibiotics is sufficient in the absence of liquefaction in the lymph nodes [51]. Nevertheless, even in lymphadenopathy cases without colliquation, surgical intervention in tularemia is usually performed to acquire tissue and pus samples to confirm a diagnosis and warrant antibiotic treatment.

References

1. Kingry, L.C.; Petersen, J.M. Comparative Review of Francisella Tularensis and Francisella Novicida. Front. Cell. Infect. Microbiol. 2014, 4, 35.
2. Select Agents and Toxins List | Federal Select Agent Program. Available online: https://www.selectagents.gov/sat/list.htm (accessed on 25 July 2022).
3. Johansson, A.; Celli, J.; Conlan, W.; Elkins, K.L.; Forsman, M.; Keim, P.S.; Larsson, P.; Manoil, C.; Nano, F.E.; Petersen, J.M.; et al. Objections to the Transfer of Francisella Novicida to the Subspecies Rank of Francisella Tularensis. Int. J. Syst. Evol. Microbiol. 2010, 60, 1717–1718.
4. Busse, H.-J.; Huber, B.; Anda, P.; Escudero, R.; Scholz, H.C.; Seibold, E.; Splettstoesser, W.D.; Kämpfer, P. Objections to the Transfer of Francisella Novicida to the Subspecies Rank of Francisella Tularensis—Response to Johansson et al. Int. J. Syst. Evol. Microbiol. 2010, 60, 1718–1720.
5. Ellis, J.; Oyston, P.C.F.; Green, M.; Titball, R.W. Tularemia. Clin. Microbiol. Rev. 2002, 15, 631–646.
6. Maurin, M.; Gyuranecz, M. Tularaemia: Clinical Aspects in Europe. Lancet Infect. Dis. 2016, 16, 113–124.
7. Sjöstedt, A. Tularemia: History, Epidemiology, Pathogen Physiology, and Clinical Manifestations. Ann. N. Y. Acad. Sci. 2007, 1105, 1–29.
8. Celli, J.; Zahrt, T.C. Mechanisms of Francisella Tularensis Intracellular Pathogenesis. Cold Spring Harb. Perspect. Med. 2013, 3, a010314.
9. Molins, C.R.; Delorey, M.J.; Yockey, B.M.; Young, J.W.; Belisle, J.T.; Schriefer, M.E.; Petersen, J.M. Virulence Difference between the Prototypic Schu S4 Strain (A1a) and Francisella Tularensis A1a, A1b, A2 and Type B Strains in a Murine Model of Infection. BMC Infect. Dis. 2014, 14, 67.
10. Strehl, J.; Schoerner, C.; Hartmann, A.; Agaimy, A. Tularemia lymphadenitis. An emerging differential diagnosis of necrotizing granulomatous cervical lymphadenitis. Der Pathologe 2014, 35, 166–172.
11. Prokšová, M.; Bavlovič, J.; Klimentová, J.; Pejchal, J.; Stulík, J. Tularemia—Zoonosis Carrying a Potential Risk of Bioterrorism. Epidemiol. Mikrobiol. Imunol. Cas. Spol. Epidemiol. Mikrobiol. Ceske Lek. Spol. JE Purkyne 2019, 68, 82–89.
12. Tully, B.G.; Huntley, J.F. Mechanisms Affecting the Acquisition, Persistence and Transmission of Francisella Tularensis in Ticks. Microorganisms 2020, 8, E1639.
13. Mörner, T. The Ecology of Tularaemia. Rev. Sci. Tech. Int. Off. Epizoot. 1992, 11, 1123–1130.
14. Gurycová, D. First Isolation of Francisella Tularensis Subsp. Tularensis in Europe. Eur. J. Epidemiol. 1998, 14, 797–802.
15. Sinclair, R.; Boone, S.A.; Greenberg, D.; Keim, P.; Gerba, C.P. Persistence of Category A Select Agents in the Environment. Appl. Environ. Microbiol. 2008, 74, 555–563.
16. Bahuaud, O.; Le Brun, C.; Lemaignen, A. Host Immunity and Francisella Tularensis: A Review of Tularemia in Immunocompromised Patients. Microorganisms 2021, 9, 2539.
17. Green, T.W.; Eigelsbach, H.T. Immunity in Tularemia: Report of Two Cases of Proved Reinfection. Arch. Intern. Med. 1950, 85, 777–782. Available online: https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/554748 (accessed on 28 June 2022).
18. Foley, J.E.; Nieto, N.C. Tularemia. Vet. Microbiol. 2010, 140, 332–338.
19. World Health Organization. WHO Guidelines on Tularaemia; World Health Organization: Geneva, Switzerland, 2007; p. 115.

20. Telford, S.R.; Goethert, H.K. Ecology of Francisella Tularensis. Annu. Rev. Entomol. 2020, 65, 351–372.
21. Porast Tularemije (Zajčje Mrzlice). Available online: https://www.nijz.si/sl/porast-tularemije-zajcje-mrzlice (accessed on 28 June 2022).
22. Tularaemia. Available online: https://www.ecdc.europa.eu/en/tularaemia (accessed on 28 June 2022).
23. Kugeler, K.J.; Mead, P.S.; Janusz, A.M.; Staples, J.E.; Kubota, K.A.; Chalcraft, L.G.; Petersen, J.M. Molecular Epidemiology of Francisella Tularensis in the United States. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2009, 48, 863–870.
24. Zellner, B.; Huntley, J.F. Ticks and Tularemia: Do We Know What We Don't Know? Front. Cell. Infect. Microbiol. 2019, 9, 146.
25. Parker, R.R.; Spencer, R.R.; Francis, E. Tularæmia: XI. Tularæmia Infection in Ticks of the Species Dermacentor Andersoni Stiles in the Bitterroot Valley, Mont. Public Health Rep. 1896–1970 1924, 39, 1057–1073.
26. Yeni, D.K.; Büyük, F.; Ashraf, A.; Shah, M.S.U.D. Tularemia: A Re-Emerging Tick-Borne Infectious Disease. Folia Microbiol. 2021, 66, 1–14.
27. CDC Tularemia Home|CDC. Available online: https://www.cdc.gov/tularemia/index.html (accessed on 29 June 2022).
28. Rosenberg, R.; Lindsey, N.P.; Fischer, M.; Gregory, C.J.; Hinckley, A.F.; Mead, P.S.; Paz-Bailey, G.; Waterman, S.H.; Drexler, N.A.; Kersh, G.J.; et al. Vital Signs: Trends in Reported Vectorborne Disease Cases—United States and Territories, 2004–2016. Morb. Mortal. Wkly. Rep. 2018, 67, 496–501.
29. Petersen, J.M.; Schriefer, M.E. Tularemia: Emergence/Re-Emergence. Vet. Res. 2005, 36, 455–467.
30. Maurin, M.; Pelloux, I.; Brion, J.P.; Del Banõ, J.-N.; Picard, A. Human Tularemia in France, 2006–2010. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2011, 53, e133–e141.
31. Gurycová, D.; Tináková, K.; Výrosteková, V.; Gacíková, E. The incidence of tularemia in Slovakia in 1997–2008. Epidemiol. Mikrobiol. Imunol. Cas. Spol. Epidemiol. Mikrobiol. Ceske Lek. Spol. JE Purkyne 2010, 59, 39–44.
32. Rojko, T.; Korva, M.; Lotrič-Furlan, S.; Strle, F.; Avšič-Županc, T. Cluster of Ulceroglandular Tularemia Cases in Slovenia. Ticks Tick-Borne Dis. 2016, 7, 1193–1197.
33. Dlugaiczyk, J.; Harrer, T.; Zwerina, J.; Traxdorf, M.; Schwarz, S.; Splettstoesser, W.; Geissdörfer, W.; Schoerner, C. Oropharyngeal Tularemia--a Differential Diagnosis of Tonsillopharyngitis and Cervical Lymphadenitis. Wien. Klin. Wochenschr. 2010, 122, 110–114.
34. Dryselius, R.; Hjertqvist, M.; Mäkitalo, S.; Lindblom, A.; Lilja, T.; Eklöf, D.; Lindström, A. Large Outbreak of Tularaemia, Central Sweden, July to September 2019. Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 2019, 24, 1900603.
35. Zajmi, D.; Berisha, M.; Kalaveshi, A.; Begolli, I.; Ramadani, N.; Hoxha, R. Epidemiological Characteristics of Tularemia in Kosova in the Period 2006–2011. Mater. Socio-Med. 2013, 25, 220–222.
36. Grunow, R.; Kalaveshi, A.; Kühn, A.; Mulliqi-Osmani, G.; Ramadani, N. Surveillance of Tularaemia in Kosovo *, 2001 to 2010. Eurosurveillance 2012, 17, 20217.
37. Factsheet on Tularaemia. Available online: https://www.ecdc.europa.eu/en/tularaemia/facts (accessed on 29 June 2022).
38. Hestvik, G.; Warns-Petit, E.; Smith, L.A.; Fox, N.J.; Uhlhorn, H.; Artois, M.; Hannant, D.; Hutchings, M.R.; Mattsson, R.; Yon, L.; et al. The Status of Tularemia in Europe in a One-Health Context: A Review. Epidemiol. Infect. 2015, 143, 2137–2160.
39. Schulze, C.; Heuner, K.; Myrtennäs, K.; Karlsson, E.; Jacob, D.; Kutzer, P.; Große, K.; Forsman, M.; Grunow, R. High and Novel Genetic Diversity of Francisella Tularensis in Germany and Indication of Environmental Persistence. Epidemiol. Infect. 2016, 144, 3025–3036.
40. Appelt, S.; Faber, M.; Köppen, K.; Jacob, D.; Grunow, R.; Heuner, K. Francisella Tularensis Subspecies Holarctica and Tularemia in Germany. Microorganisms 2020, 8, 1448.
41. European Food Safety Authority; European Centre for Disease Prevention and Control. The European Union One Health 2020 Zoonoses Report. EFSA J. 2021, 19, e06971.
42. Pojav Tularemije V Severno-Primorski Regiji. Available online: https://www.nijz.si/sl/pojav-tularemije-v-severno-primorski-regiji (accessed on 29 June 2022).
43. Tomažič, J.; Tularemija, R.M. Infekcijske Bolezni; Združenje Za Infektologijo, Slovensko Zdravniško Društvo: Ljubljana, Slovenia, 2014; pp. 517–518.

44. Gestin, B.; Valade, E.; Thibault, F.; Schneider, D.; Maurin, M. Phenotypic and Genetic Characterization of Macrolide Resistance in Francisella Tularensis Subsp. Holarctica Biovar I. J. Antimicrob. Chemother. 2010, 65, 2359–2367.
45. Dennis, D.T.; Inglesby, T.V.; Henderson, D.A.; Bartlett, J.G.; Ascher, M.S.; Eitzen, E.; Fine, A.D.; Friedlander, A.M.; Hauer, J.; Layton, M.; et al. Tularemia as a Biological Weapon: Medical and Public Health Management. JAMA 2001, 285, 2763–2773.
46. Tärnvik, A.; Chu, M.C. New Approaches to Diagnosis and Therapy of Tularemia. Ann. N. Y. Acad. Sci. 2007, 1105, 378–404.
47. EMA. Disabling and Potentially Permanent Side Effects Lead to Suspension or Restrictions of Quinolone Fluoroquinolone Antibiotics. Available online: https://www.ema.europa.eu/en/news/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone (accessed on 29 June 2022).
48. Forti, G.; Benincori, C. Doxycycline and the Teeth. Lancet Lond. Engl. 1969, 1, 782.
49. Atmaca, S.; Bayraktar, C.; Cengel, S.; Koyuncu, M. Tularemia Is Becoming Increasingly Important as a Differential Diagnosis in Suspicious Neck Masses: Experience in Turkey. Eur. Arch. Oto-Rhino-Laryngol. Off. J. Eur. Fed. Oto-Rhino-Laryngol. Soc. EUFOS Affil. Ger. Soc. Oto-Rhino-Laryngol. Head Neck Surg. 2009, 266, 1595–1598.
50. Rothweiler, R.; Fuessinger, M.A.; Schmelzeisen, R.; Metzger, M.C. Lymph Node Abscess Caused by Francisella Tularensis—A Rare Differential Diagnosis for Cervical Lymph Node Swelling: A Case Report. J. Med. Case Rep. 2019, 13, 247.
51. Theissing, J.; Rudack, C. ENT-Head and Neck Surgery: Essential Procedures; Thieme Medical Publishers: New York, NY, USA, 2010; pp. 264–265.