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Legionella pneumophila as an important public health problem – epidemiology and clinical management of Legionnaires' disease

Legionella pneumophila jako ważny problem zdrowia publicznego – epidemiologia i postępowanie kliniczne w chorobie legionistów

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Abstract

Introduction and Objective. *Legionella pneumophila* (*L.pneumophila*) is a Gram-negative aerobic bacteria with rod-shaped cells. It occurs in humid environments, in moist soil and compost material. *L.pneumophila* in humans can cause a respiratory disease called Legionnaires' disease and Pontiac fever. Human infection is most commonly caused by inhalation of Legionella-containing aerosols produced by contaminated water sources. The bacterium has the ability to multiply inside alveolar macrophages and blood monocytes.

Brief description of the state of knowledge. Following exposure to Legionella-containing aerosol, individuals may become asymptomatic or symptomatic depending on their current health status. The onset of LD is acute, with high fever, myalgia and cough. On the other hand, approximately 50% of patients additionally have neurological and gastrointestinal disturbance, relative bradycardia, hypophosphataemia or elevated ferritin levels. In addition to clinical signs, laboratory confirmation is necessary to make a diagnosis; tests are performed on the basis of sputum, secretions from the respiratory tract; tissue, blood, serum and urine samples.

Summary. *L. pneumophila* is increasingly being identified as the leading cause of community-acquired pneumonia and is an important public health problem. Air conditioning is increasingly documented as a source of infection in community-acquired *L. pneumophila* outbreaks. In order to prevent the occurrence of *Legionella* infection, it is primarily necessary to reduce the number of outbreaks and their size. There is currently no vaccine available against *Legionella* infection.

Key words

Legionella, Legionnaires' disease, Legionella pneumophila, Legionellosis

Streszczenie

Wprowadzenie i cel pracy. *Legionella pneumophila* (*L. pneumophila*) to Gram-ujemna bakteria tlenowa o komórkach w kształcie pałeczek. Występuje w wilgotnym środowisku, a także w wilgotnej glebie i materiale kompostowym. *L. pneumophila* u ludzi może powodować chorobę układu oddechowego zwaną chorobą legionistów i gorączką Pontiac. Zakażenie człowieka najczęściej spowodowane jest wdychaniem aerozoli zawierających Legionellę, wytwarzanych przez zanieczyszczone źródła wody. Bakteria ma zdolność namnażania się wewnątrz makrofagów pęcherzykowych i monocytów krwi.

Opis stanu wiedzy. W wyniku narażenia na aerozol zawierający Legionellę u poszczególnych osób może wystąpić zakażenie bezobjawowe lub objawy, w zależności od ich aktualnego stanu zdrowia. Początek LD jest ostry, z wysoką gorączką, bólami mięśni i kaszlem. U ok. 50% pacjentów występują dodatkowo zaburzenia neurologiczne i żołądkowo-jelitowe, względna bradykardia, hipofosfatemia lub podwyższony poziom ferrytyny. Oprócz objawów klinicznych do postawienia diagnozy konieczne jest potwierdzenie laboratoryjne; badania wykonuje się na podstawie plwociny, wydzieliny z dróg oddechowych, próbki tkanek, krwi, surowicy i moczu.

Podsumowanie. *L. pneumophila* coraz częściej uznawana jest za główną przyczynę pozaszpitalnego zapalenia płuc i stanowi ważny problem zdrowia publicznego. Coraz częściej dokumentuje się, że źródłem infekcji w przypadku pozaszpitalnych ognisk *L. pneumophila* jest klimatyzacja. Aby zapobiec wystąpieniu zakażenia Legionellą, należy przede wszystkim ograniczyć liczbę ognisk tej bakterii i ich wielkość. Obecnie nie jest dostępna szczepionka przeciwko zakażeniu Legionellą.

Słowa kluczowe

Legionella, *Legionella pneumophilla*, legioneloza, choroba legionistów

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INTRODUCTION

Legionella pneumophila (*L.pneumophila*) is a Gram-negative aerobic bacteria with rod-shaped cells. It occurs in humid environments, in moist soil and compost material [1]. *L.pneumophila* in humans can cause a respiratory disease called Legionnaires' disease. Legionellosis is any disease caused by Legionella, including the above and others such as Pontiac fever and Pittsburgh pneumonia. Pontiac fever is self-limiting illness [2] which was discovered in the summer of 1976 during a massive pneumonia outbreak in Philadelphia in the USA. This hitherto unknown respiratory disease affected 221 participants at the 58th annual convention of the American Legion. 34 fatal cases were reported at that time [3]. This disease was discovered in the summer of 1976 during a massive pneumonia outbreak in Philadelphia in the United States of America. This hitherto unknown respiratory disease affected 221 of participants at the 58th annual convention of American Legion. 34 fatal cases were reported at that time [3].

The Center for Disease Control and Prevention (CDC), given the scale of the epidemic and the occurrence of unknown causative factor, organised the biggest team in its history to identify the source of infection. In December 1976, scientists Joseph E. McDade and Charles C. Shepard identified the bacteria that was the causative factor of Legionnaires' disease. The bacteria was rod-shaped and Gram-negative. It was named Legionella pneumophila in honor of the American Legion [4].

There are 65 species in the genus Legionella, but not all of them cause Legionnaires' disease equally often. The species are divided into more than 70 serogroups. The serogroup (Sg) 1 strain causes approximately 90% of cases of *L. pneumophila* Legionnaires' disease, which accounts for 80–90% of cases in Europe and the USA [5]. L. longbeachae is the leading cause of LD in Australia and New Zealand and is the only specie s naturally found in soil [2].

OBJECTIVE

The review is based on an extensive literature review using the PubMed database without time limits to present Legionella as a disease entity, and a detailed discussion of the current diagnostic approach and available therapeutic methods. The main assumption of the review is to summarise previous scientific reports based on databases such as: PubMed, Google Scholar.

MATERIALS AND METHOD

Transmission and risk factors. Human infection is most commonly caused by inhalation of Legionella-containing aerosols produced by contaminated water sources. The bacterium is found in water reservoirs, both natural and artificial, in systems such as air conditioning and air humidifiers. The pathogen is sensitive to desiccation, while in a humid environment it can survive for over a year. Although human-to-human transmission may exist, it is rare [6]. The bacterium has the ability to multiply inside alveolar macrophages and blood monocytes. Infection occurs after the microorganism enters the respiratory tract via droplets and encounters alveolar macrophages in the lower respiratory tract [7]. After being engulfed by a macrophage, L. pneumophila remodels its phagosome into a Legionella-containing vacuole (LCV) [8]LCV is surrounded by a double membrane [7]. *L. pneumophila* secretes over 300 bacterial effectors from the LCV into the cytosol using the type 4 secretion system (T4SS), encoded by the Dot/Icm gene [8, 9]. Dot/Icm deficient strains do not form LCVs and cannot prevent acidification phagosome. Such strains do not replicate intracellularly [10]. The incubation period of LD is thought to be 2–10 days [11].

The majority of healthy people who are exposed to Legionella do not fall ill. It is more common for the disease to manifest in individuals with an increased risk of infection. These are people over 50, men, current or former smokers, people with pulmonary diseases, such as chronic obstructive airway disease or pulmonary emphysema, people with comorbidities such as diabetes mellitus, neoplasms, renal failure or taking medications to suppress the immune system [12]. Legionella infection is the most common during the summer and early autumn seasons.

Clinical presentation. Following exposure to Legionella containing aerosol, individuals may become asymptomatic or symptomatic depending on their current health status. The onset of LD is acute, with high fever, myalgia and cough. On the other hand, approximately 50% of patients additionally have neurological and gastro-intestinal disturbances, relative bradycardia, hypophosphataemia, or elevated ferritin levels. This disease is often complicated by extrapulmonary spread, causing mortality on 8–12% level [13]. Furthermore, in rare cases, Legionella may be presented as 'extrapulmonary Legionella pneumophila infection', with absence of pneumonia, affecting soft tissues, synovial fluid or heart [14].

Mild, self-limited, non-pneumonia-related Pontiac fever has also been linked to exposure to aerosols containing Legionella. The disease has a short incubation period, usually 24–48 hours, and lasts for about 2–5 days. The disease is more common in younger individuals. Pontiac fever is usually diagnosed only when cases occur in the form of an epidemiological outbreak, possibly due to the mild nature of the symptoms, but also because of the lack of established diagnostic criteria [11]. The disease is not fatal.

Pneumonia caused by *L. pneumophila* can be suspected when beta-lactam or aminoglycoside antibiotics are ineffective, the patient is in a serious condition or immunosuppressed, has liver or kidney failure, diabetes mellitus, stayed in the place of exposure, or worked with plumbing/water installations directly prior to infection.

Diagnosis. In addition to clinical signs, laboratory confirmation is necessary to make a diagnosis; tests are performed on the basis of sputum, secretions from the respiratory tract; tissue, blood, serum and urine samples [13]. The range of diagnostic possibilities includes serological and antibody based tests: bacterial cultures, urine antigen tests and nucleic acid amplification tests [15].

In laboratory tests, an increase in the activity of ALT, AST and CK, as well as hyphonatraemia can be observed in the blood serum. On the other hand, protein and haematuria may be present in the urinalysis. A chest X-ray shows an infiltration in the lungs located near the pleura, unilateral or bilateral. The described lesion may have features of disintegration.

Antigen tests on urine and PCR test are the gold standard in the diagnostic of *L.pneumophila* infection. The urine sample test, which detects a component of the bacterial cell wall, is now widely used as a first-line screening method because it is easy to perform, cheap, and the results are quickly available. Unfortunately, this test is diagnostically limited as it detects only *L. pneumophila* Sg1.

The usefulness of PCR-based tests as a complement to other diagnostic methods has been demonstrated by the development of a rapid and reliable multiplex PCR test that allows the detection of 4 clinically-relevant non-pneumophila species from human sputum samples [16]

In the case of retrospective epidemiological studies and when the infectious agent cannot be isolated, the serological method is then used. Nevertheless, culture on a specific medium remains the standard reference method for the diagnosis and identification of Legionella, as it allows the identification of different species and serogroups, followed by epidemiological studies of their distribution.

Treatment. Patients with confirmed disease (by PCR test, urine antigen test or sputum culture) are commonly treated with the antibiotics levofloxacin or azithromycin, which are currently preferred for their bactericidal properties, good tissue penetration and efficacy targeting multiple serogroups. For extrapulmonary Legionella infection, patients are commonly treated with a fluoroquinolone (e.g. levofloxacin) in combination with various procedures, such as incision and drainage [17].

Resistance to the above-mentioned antibiotics is relatively rare [18]. Given the rare reported cases of resistance, recommended antimicrobial therapy includes fluoroquinolones (ciprofloxacin, levofloxacin or moxifloxacin) or macrolides (azithromycin).

Fluoroquinolones are used in the first line of treatment:

- Levofloxacin administered intravenously or intramuscularly at a dose of 500 mg one to two times a day;
- Ciprofloxacin 400 mg intravenously twice daily or orally 500 mg twice daily;
- Ofloxacin orally 400 mg twice a day;
- Moxifloxacin orally at a dose of 400 mg once a day.

Second line treatment:

- Macrolide: azithromycin 500 mg once a day, clarithromycin 500 mg twice a day, or erythromycin 500 mg 4 times a day;
- doxycycline orally or intravenously at an initial dose of 200 mg, followed by 100 mg once a day (twice a day in more severe cases).

Recovery is most likely if the right antibiotics are given early enough. Patients with LD should receive treatment for at least 5–14 days, with azithromycin cycles being shorter due to its long half-life. Treatment should not be discontinued until the patient has been fever-free for 48–72 hours. The duration of antibiotic use should always be adjusted according to clinical response, with appropriate extensions up to 21 days, or 10 days for azithromycin in immunocompromised patients [19].

Prevention. In the case of a suspected epidemiological outbreak, it is very important to report it to the responsible authorities for implementing health policy in order to take epidemiological and environmental measures. Legionella is one of the opportunistic pathogens which is the most commonly reported water-borne pathogen in industrialised countries. Several environmental sources have been linked to Legionella outbreaks, including hot tubs, decorative fountains and water distribution systems. Colonisation of air conditioning and air humidifiers by Legionella spp. is increasingly recognised as one of the main sources of outbreaks of Legionella infection in society [20].

The methods to prevent infection are: avoiding and monitoring critical places, avoiding water stagnation and maintaining extreme temperatures above 60°C or below 25°C [21]. To remove bacteria from air conditioners or humidifiers, they must be emptied, washed to remove organic contaminants and sediment, and disinfected with monochloramine or chlorine. However, monochloramine is more effective than chlorine in killing Legionella in biofilms [20].

SUMMARY

L. pneumophila is increasingly being identified as the leading cause of community-acquired pneumonia and is an important problem for public health. Air conditioning is increasingly documented as a source of infection in community-acquired *L. pneumophila* outbreaks. In order to prevent the occurrence of Legionella infection, it is primarily necessary to reduce the number of outbreaks and their size. There is currently no vaccine available against Legionella infection.

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