

# Respiratory infections caused by *Legionella pneumophila*

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## SUMMARY

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*The number of cases of legionellosis has significantly increased in recent years as a travel-associated disease. The European Surveillance Scheme for Travel-Associated Legionnaire's Disease was established in 1987 year and now all confirmed cases are notified and analyzed.*

*However, legionellosis still is a diagnostic and therapeutic problem, because of its multi-organ clinical symptoms. In the treatment macrolides are recommended as a first line therapy, and fluoroquinolones when no improvement after macrolide application or intolerance are observed. Several official guidelines were written about prevention of Legionnaires' disease. Primary prevention is essentially based on control and maintaining of water-distribution system. Secondary prevention should be a prompt response to identification of a case in order to find the source of Legionella. Above mentioned guidelines are also helpful to obtain recovery of disease and decrease the mortality and serious complications.*

**Key words:** diagnosis, therapy

Every year in the United States the doctors report more than 10 million patients with symptoms from the respiratory system. 500 thousands of them require hospitalization due to pneumonia, and 45 thousands is dying. For these reasons, in *Str. pneumoniae* is considered the sixth cause responsible for mortality [8]. In a growing number of cases caused by atypical bacteria including *Legionella pneumophila* is responsible for severe respiratory inflammations.

## STRESZCZENIE

*Zakażenia układu oddechowego wywołane przez Legionella pneumophila*

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*Liczba przypadków legionellozy ulega w ostatnich latach znaczącemu zwiększeniu jako choroby związanej z podróżami. Utworzony w 1987 r. Europejski Nadzór nad Chorobą Legionistów jako związaną z podróżami zobowiązuje do informowania o potwierdzonych przypadkach zachorowań w celu dalszych analiz.*

*Legioneloza stanowi nadal problem diagnostyczny i terapeutyczny, ponieważ jest chorobą obciążającą wiele narządów. Zalecane jest stosowanie makrolidów, a w przypadku braku poprawy lub nietolerancji leku – fluorochinolonów. Kilka oficjalnych zaleceń zostało opracowanych, aby zapobiegać występowaniu choroby legionistów. Jako pierwszy i podstawowy punkt w tych działaniach podkreśla się kontrolowanie i nadzór nad systemami dostarczania wody. Wtórny działaniem prewencyjnym powinno być właściwe postępowanie w przypadku stwierdzenia zachorowania, aby ustalić jego źródło. Powyższe zasady postępowania są także pomocne w uzyskiwaniu poprawy klinicznej, zmniejszeniu umieralności i liczby ciężkich powikłań.*

**Słowa kluczowe:** legioneloza, diagnostyka, leczenie

## EPIDEMIOLOGY OF INFECTIONS

The spectacular emergence of the problem of infections caused by *Legionella pneumophila* occurred in 1976 at the Hotel BellaVista Stanford in Philadelphia during the annual congress of the American Legion, when 221 people fell ill and 36 (16%) died [10]. It is now known that the natural environment for the bacteria are water tanks, and air conditioning systems,

swimming pools, showers, and nebulizers and respirators [20].

Significantly more likely to recognize the symptoms of *Legionella* infection in summertime, which is facilitated by heat and humidity. In Italy, in a hospital in Apulia in the years 2001–2003 in 37 patients severe pneumonia was caused by *Legionella pneumophila*, confirmed by diagnostic tests (antigen detection in urine). Thanks to a supervision system in the years 1996–2000 only 9 infections caused by this pathogen were observed [13].

Legionellosis is under the constant supervision of the European Group for infections caused by the species of *Legionella pneumophila* (EWGLI – European Working Group on Legionella Infections). In the years 1993–2000 based on reported data from 28 countries the diagnosis of *Legionella pneumophila* infection was confirmed in more than 12 000 patients. In more than 70% of cases in the years 1999–2001 diagnosis of infection was determined by detection of antigen in the urine, and 18.1% in serological tests. In 2000 in Europe determined the incidence rate was calculated as 5.4 cases per 1 million inhabitants [22]. In this group, in most cases were pneumonia, often severe, and in connection with travel, known as “foreign travel pneumonia” or “travel-associated disease” [10]. For this reason, established in 1987, the European Surveillance (European Surveillance Scheme for Travel Associated Legionnaires) is able to identify cases and detect sources of infection. The composition of this team consists of 29 laboratories in 25 countries [10].

According to data provided by EWGLI in the years 1993–2006 legionella-induced pneumonia was reported in 41 627 cases. It should be mentioned that in 1993, 1.242 cases were reported from 19 countries, with the calculation of average morbidity of 0.41/100 thousands residents, and in 2006 there were 6.280 cases in 35 countries and the incidence rate was 1.12/100 thousands of population [acc.15].

In 1954 yr. a first case of inflammation caused by a “pathogen-like amoeba” (today called on legionella) was described in Poland [21]. In the years 1987–2006 according to data obtained from the European Union 17 patients were probably infected legionella in Poland [23]. In 1997 at the National Institute of Hygiene in Warsaw started diagnostic tests in the direction of the legionella-infected material and confirmed the presence of the pathogen in 5 clinical cases, and 16 achieved a positive result without clinical symptoms [22]. Based on it about 220 cases of legionella infection were estimated in Poland every year. Current data do not confirm the validity of this calculation. Since 2002, because of threat of legionellosis, a systematic study of water in hotels, banks, homes and

health care institutions are performed two times a year. It has been shown that strains of *Legionella pneumophila* sg-2-14 are found in approximately 30% of cases suspected of being infected [21]. This requires special care and systematically control the epidemic situation. In 2005, the infection was diagnosed in 21 patients, and in 2006 – in 89, indicating the incidence of disease in the rate of 0.055 and 0.23 [23]. Recently the occurrence of epidemic outbreaks caused by *Legionella pneumophila* was reported in the department of ophthalmology in Jastrzębie Zdrój [1, 11]. Pneumonia, which occurred in 4 patients, was failed. The immediate cause was a faulty hot water distribution structure that favored the release of circulation and reproduction of bacteria.

In Poland, in 2001–2008 a total of 169 cases of legionellosis, including most cases of pneumonia, were reported in the province of Mazovia, Silesia and Lublin. It should be noted that in 2006 among 89 cases was up 46 children [15].

## CHARACTERISTICS OF THE PATHOGEN

The most (80-90%) of cases of legionellosis is caused by Gram-negative rods belonging to the family *Legionellaceae*, genus *Legionella*. The new division based taxonomic genetic differentiation within the genus *Legionella* that two new types – *Tatlockia* and *Fluoribacter*. Responsible for serious illness is the species of *Legionella pneumophila*, including 50–75% of *L. pneumophila* sg 1, and 5–20% of cases – the species *L. micdadei*, *L. Longbeach*, *L. dumofii*, *L. bozemanii* and others [5]. It should be emphasized that the number of newly included species of the genus *Legionella* is steadily increasing and is now isolated more than 50 species and 70 serogroups [7].

Genus *Legionella* bacteria have the ability to actively penetrate into the cells of amoeba (*Acanthamoeba*, *Hertmannella*, *Naegleria*, *Platyamoeba*) in the aquatic environment, as well as inside macrophages in the human body. It is a protective mechanism of bacteria against adverse effects of the environment and represents a kind of hide the natural immune responses [24, 25].

## PATHOGENESIS OF INFECTION

Infection occurs through inhalation. Bacteria contaminated water aerosol with 2–5 µm droplet size is inhaled into the respiratory tract, where it develops intracellularly and guides to the inflammatory process. Transmission has not been shown of *Legionella* infection from person to person [5]. Bacteria could enter the respiratory tract and goes primarily to the cytoplasm of macrophages due to the presence on

their surface immunoglobulin receptors [4]. The results suggest that they are also occupied respiratory epithelial cells, especially by some strains of *Legionella*, which have from 100 to 1000 times greater invasiveness, which directs their further action. This effect is dependent on the bacterial heat shock proteins (Hsp60), which means that in macrophages, there is no complete killing of bacteria, because the connection is blocked between phagosomes and lysosomes [9]. Phagolysosomes when combined with the endoplasmic reticular network condition are able for further replication of the bacteria. Mature forms of bacteria found in phagosomes are 10–100 times more active than the other and lead to cell death. Some of them takes the form of “vegetative” and the next part replicates inside cells [9]. The role of neutrophils in this infection has not been established, emphasizing the defensive activity of lymphocytes that Hsp60 release stimulated by interferon and interleukin-inflammatory action [18]. Damage of other organs (kidney, liver, digestive system, brain or muscle) occurs rarely. The reason for these changes is released from the destructive bacteria resulting from bacterial endotoxin lipopolysaccharides [28], and the action of proteases released in the body [26].

The dose causing infection was not yet determined. When *Legionella* contamination of water is 103–105 cfu/l – sporadic cases can be expected, and if exceeded 105 cfu/l – the outbreak of the epidemic may be determined, especially in conditions of elevated water temperature in the range 25–45°C. Multiplication of bacteria in such an environment conducive to access to nutrients (rock, sediment, biofilm). The slow flow of hot water in a hospital outside installations may be responsible for bacteria replication. For this reason a hot water tanks should be very carefully considered for storage, similarly as showers, humidifiers, hydrotherapy pools, respirators and dialyzers. In studies conducted in Poland showed that in 132 (78.7%) water samples were collected for 169 bacteria of the genus *Legionella*. The most dangerous *Legionella pneumophila* was isolated from 16 samples, which indicated a significant failure in supervision and the possibility of severe illness [12].

*Legionella pneumophila* to survive in eukaryotic host cells, requires a special way of eating, so called Type IV secretion system, referred to as the Dot/Icm, which causes bacterial effector proteins pass into the host cell cytoplasm [14]. Studies in recent years have revealed the existence of numerous proteins, the above mentioned Dot/Icm secretion system, but their function is not fully been determined. Known, however, that these are proteins that allow “live” bacteria in the new conditions.

## CLINICAL FORMS OF INFECTION

Due to place the source of infection three types of legionellosis are distinguishes [15]:

- associated with travel – TAP (travel-associated pneumonia);
- acquired at home – CAP (community acquired pneumonia);
- acquired during hospitalization – HAP (hospital acquired pneumonia).

Due to the course of infection with *Legionella pneumophila* the different clinical pictures are induced.

“Pontiac fever” is a form of mild, flu-like inflammation in the respiratory tract [5]. About 2–10 days after infection the most of non-specific symptoms is observed as headaches and muscle pain, lack of appetite and fever states. The physical examination can be normal in the bronchial tree and lung parenchyma. Chest X-ray examinations do not indicate the presence of inflammatory changes.

“Legionnaires disease” is an atypical pneumonia caused by *Legionella pneumophila* and is characterized by a severe course with a significant mortality – up to 30% [5]. The disease begins as Pontiac fever, which is the non-specific symptoms, among which is dominated by severe headache and fever (up to 40°C) with chills. Usually accompanied by severe muscle pains and cough, initially dry, and after 2–3 days – damp. Dyspnea is reported in half of patients, depending on comorbidities and the dynamics of the disease. Changes in the pleural cavity are responsible for chest pain occurring during breathing. The hemoptysis is seen in 1/3 of patients, pointing to the accompanying changes in thromboembolic events. In the half of the patients some disorders of the digestive system in the form of nausea, vomiting and abdominal pain are observed. Depending on the degree hypoxemia the growing states of confusion, hallucinations, and even fainting are determined in patients. Physical examination of the lung fields reveals rales and crackles indicating extensive occupation.

## CHANGES IN CHEST X-RAY EXAMINATION

Changes in chest x-ray examination observed in the most of patients during an epidemic in Philadelphia in 1005 subsequent cases showed a typical picture of pneumonia with rapid progression of inflammatory infiltrate. Bilateral changes were also observed, mainly in the lower lobes [19], and in 25% of patients a form of lung abscesses was diagnosed [27]. In the most of patients an enlargement of lymph nodes and presence of fluid in the pleural cavities were documented [19]. Moreover, the quick resolution of

the above changes was underlined during an effective treatment [16].

## DIAGNOSTIC METHODS

Applied diagnostic methods are dependent on the type of infection. In the case of travel-related infections the rapid tests are recommended to detect infections caused by *L. pneumophila*. Antigen detection test is dominated by bacteria in the urine (80% of tests).

Microbiological testing of material derived from the airways during bronchoscopy combined with bronchoalveolar lavage is possible to reliably identify, together with an indication of other strains of *Legionella* [17]. In Polish conditions the main serological diagnostic method are preferred to diagnosis of legionellosis. The presence of IgM antibodies indicates fresh infection. In the period 1998–2005 serum was a testing material in over 60% and in 81% samples the results were positive. The urine was tested at that time in 33% of cases and in 9% the positive results were determined [15].

## TREATMENT OF LEGIONELLOSIS

During epidemic disease in 1976 in Philadelphia erythromycin was considered as the drug of first choice, especially in severe cases of the disease, with the addition of rifampicin for 3 weeks [2]. The new macrolides (clarithromycin and azithromycin) show significant activity *in vitro* and high intracellular concentrations in macrophages in relation to this pathogen [3, 6].

Azithromycin and clarithromycin may be administered over a period not much shorter than 10–14 days because of their pharmacodynamic characteristics. If no improvement or contraindications to macrolides are detected the use of fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), should be considered. The duration of treatment should not be less than 10–14 days [3,6]. Results of treatment of 458 patients in Spain given by *Pedro-Botet* [16] indicate that the administration of fluoroquinolones (mainly levofloxacin) gave a better clinical effect than the use of macrolides (clarithromycin or erythromycin), reducing the number of complications and significantly less time in hospital. Comparative studies of azithromycin and fluoroquinolones in *Legionella pneumophila* infection are also undertaken and suggest the usefulness of the two formulations (tab.).

Combining antibiotics during a severe treatment of the syndrome is by all means advisable and recommended by generally accepted accounting principles. This is confirmed by the analysis on conducted trials [Bartlet].

**Table.** Recommended doses of antibiotics in patients with *Legionella pneumophila* infection [acc.16]

Antibiotic	Doses	Application
Azithromycin	500 mg	p.o. or iv. one time a day
Clarithromycin	500 mg	p.o. two times a day
Erythromycin	1 g	iv. in every 6 hour
Ciprofloxacin	500 mg	p.o. or iv. one time a day
Levofloxacin	500 mg 500 mg	iv. two times a day p.o. two times a day
Doxycyclin	100 mg	p.o. or iv. two times a day
Rifampicyna	300 mg	p.o. or iv. two times a day

## REFERENCES

- Antończyk M.: *Rozpoznanie, opracowanie, wygaszanie i postępowanie po wygaszeniu ogniska epidemicznego legionelli w oddziale okulistyki w Wojewódzkim Szpitalu Specjalistycznym nr 2 w Jastrzębiu Zdroju w okresie 11.12.2006 r. – 31.03.2007 r.* Nowa Med., 2009; 1,66-67.
- Baltch A.I., Smith R.P., Ritz W.: *Inhibitory and bactericidal activities of levofloxacin, ofloxacin, erythromycin, and rifampin used singly and in combination against Legionella pneumophila.* Antimicrob. Agents Chemother., 1995,39; 1661-6.
- Bartlett J.G.: *Is activity against "atypical" pathogens necessary in the treatment protocols for community-acquired pneumonia? Issues with combination therapy.* Clin. Infect. Dis.. 2008;47 Suppl 3: S232-6 .
- Bellinger-Kawahara C.G., Horwitz M.A.: *Complement component C3 fixes selectively to the major outer membrane protein (MOMP) of Legionella pneumophila and mediates phagocytosis of liposome-MOMP complexes by human monocytes.* J. Exp. Med., 1990; 172,1201-8.
- Bocca S., Laurenti P., Borella P. et al.: *Prospective 3-year surveillance for nosocomial and environmental Legionella pneumophila: implications for infection control.* Infect. Control Hosp. Epidemiol., 2006; 27(5): 459-65.
- Chinn R.: *Antimicrobial therapy of nosocomial pneumonia.* – in – Jarvis W.R. (edt.) Nosocomial pneumonia. Marcel Dekker, Inc., New York, Basel, 2000, 93-124.
- Fields B.S., Benson F., Besser R.E.: *Legionella and Legionnaires Disease: 25 years of investigation.* Clin. Microb. Rev., 2002; 15/3, 506-526.
- Goetz M.B.: *Pyogenic bacterial pneumonia, lung abscess, and empyema.* – in – Murray J.F., Nadel J.A., Mason R.J., Boushey H.A. (edts.): Textbook of respiratory medicine. W.B. Saunders Company, Philadelphia, London, New York, St. Louis, Sydney, Toronto, 2000, 985-1041.
- Hoffman P.S.: *Invasion of eukaryotic cells by Legionella pneumophila: A common strategy for all hosts?* Can. J. Infect. Dis., 1997; 8, 139-44.
- Jarraud S., Reyrolle M., Riffard S., Lo Presti F., Etienne J.: *Legionnaires' disease in travelers.* Bull. Soc. Pathol. Exot., 1998; 91(5 Pt 1-2): 486-9.
- Juda T.: *Legionella – doświadczenia Wojewódzkiego Szpitala Specjalistycznego w Jastrzębiu Zdroju – przypadki kliniczne.* Nowa Med., 2009; 1, 68.
- Matuszewska R., Krogulska B.: *Problem występowania pałeczek Legionella w instalacjach i urządzeniach wytwarzających aerozol wodno-powietrzny w obiektach służby zdrowia w Polsce.* Nowa Med.,2009; 1, 56-60.
- Montagna M.T, Napoli C., Tato D., Spilotros G., Como D., Barbuti S.: *Legionellosis in Apulia (Italy): an underevaluated disease.* Ann. Ig., 2005; 17(1): 3-9.
- Ninio S, Celli J, Roy CR.: *A Legionella pneumophila effector protein encoded in a region of genomic plasticity binds to Dot/Icm-modified vacuoles.* PLoS Pathog. 2009; 5(1): e1000278.
- Pancer K., Stypułkowska-Misiurewicz H.: *Epidemiologia zachorowań wywołanych przez Legionella sp.* Nowa Med., 2009; 1, 61-65.

16. Pedro-Botet L, Yu VL. *Legionella: macrolides or quinolones?* Clin Microbiol Infect. 2006 May;12 Suppl 3: 25-30.
  17. Ricketts K.D., Joseph C.A.: *Legionnaires' disease in Europe: 2005-2006*. Eur. Surveill., 2007; 12, 12-17.
  18. Roig J., Domínguez C., Morea J.: *Legionnaires' disease*. Chest, 1994; 105, 1817-20.
  19. Storch G.A., Sagel S.S., Baine W.B.: *The chest rentgenogram in sporadic cases of legionnaires' disease*. JAMA, 1981; 245, 587-91.
  20. Stout J.E., Yu V.L.: *Legionellosis*. N. Engl. J. Med., 1997, 337; 682-987.
  21. Stypułkowska-Misiurewicz H., Pancer K.: *Legionellosis – a new infection in Poland*. Przegl. Epidemiol., 2002; 56(4): 567-76.
  22. Stypułkowska-Misiurewicz H., Pancer K.: *Legionellosis in Poland in 2001-2002 and epidemiological situation in Europe*. Przegl. Epidemiol., 2003; 57(4): 599-606.
  23. Stypułkowska-Misiurewicz H, Pancer K.: *Legionellosis in Poland in 2006*. Przegl Epidemiol. 2008; 62(2): 261-5.
  24. Wery N.: *Dynamics of Legionella spp. and bacterial population during the proliferation of L. pneumophila in coolin tower facility*. Apply Environ. Microbiol., 2008; 74,3030-37.
  25. Wery N., Bru-Adan V., Minervini C. et al.: *Dynamics of Legionella spp. and bacterial population during the proliferation of L. pneumophila in coolin tower facility*. Appl. Environ. Microbiol., 2008; 74(10), 3030-37.
  26. Williams A., Baskerville A., Dowsett A.B. et al.: *Immunocytochemical demonstration of the association between Legionella pneumophila, its tissue-destructive protease, and pulmonary lesions in experimental legionnaires' disease*. J. Pathol., 1987;153,257-61.
  27. Venkatachalam K.K., Saravolatz L.D., Christopher K.L.: *Legionnaires' disease: A cause of lung abscess*. JAMA, 1979; 241, 597-601.
  28. Zahringer U., Knirel Y.A., Lindner B. et al.: *The lipopolysaccharide of Legionella pneumophila serogroup 1 (strain Philadelphia 1): Chemical structure and biological significance*. Prog. Clin. Biol. Res., 1995; 392, 113-6.
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