

Legionnaires' Disease

What is Legionnaires' disease?

Legionnaires' disease, also known as Legionella pneumonia, is a rare but serious infectious disease caused by the bacterium *Legionella pneumophila*. It mainly affects the lungs but may also spread into other organs. The first discovery of the organism came in 1976, when an outbreak of pneumonia occurred at an American Legion convention in Philadelphia. A total of 221 people contracted the infection and 34 died. The second largest outbreak was at a hospital in England in 1985, when a total of 101 people contracted the disease and 28 died.



The pathogen is an intracellular bacterium. It infects, multiplies within and eventually kills immune-competent white blood cells known as macrophages; by various metabolic pathways, the bacteria themselves are capable of avoiding destruction by the macrophage. *L. pneumophila* can also infect free-living amoebae, and is nearly ubiquitous in warm fresh water supplies, such as air conditioning systems and cooling towers.

Infection with the organism takes place by respiratory transmission, i.e. by breathing airborne droplets, e.g. in a shower, a whirlpool or in an area with air conditioning. Most community outbreaks have been linked to cooling towers or evaporative condensers which can spread droplets of water over a wide area. Legionnaires' disease is not transmitted from person to person, thus isolation precautions are not needed, and it does not occur from drinking contaminated water.

The disease has no particular clinical features that clearly distinguish it from other types of pneumonia, and laboratory investigations must be carried out to confirm the diagnosis. The incubation period is short. The disease normally takes between two and ten days to develop. The beginning is characterised by a gradual onset of flu-like symptoms. People experience fever, chills, and a dry cough. Patients may then develop severe pneumonia which is not responsive to antibiotic treatment with penicillins or aminoglycosides. Legionnaires' disease also has the potential to spread into the gastrointestinal tract and the central nervous system. Accordingly, patients with advanced infections may experience diarrhoea, nausea, and confusion.

Who does Legionnaires' disease affect?
This particular form of pneumonia is especially seen in individuals with a deficient immune system. Legionnaires' disease more commonly affects smokers or people with other chest problems. It is uncommon in younger people and is very uncommon under the age of 20. Usually, cases occur sporadically, mostly in late summer and early autumn.

In Europe, there are no reliable epidemiological data, as the disease is seriously under-reported. Estimates vary between 10,000 and 20,000 cases every year. In 2003, the European Surveillance Scheme for Travel Associated Legionnaires' disease reported 632 cases of infection. Most cases occurred in people between 50 and 69 years of age. Men were affected three times more often than women. The death rate was around 10 per cent. The 12,000 or so cases of Legionnaires' disease per year in the USA usually involve middle-aged or immune-compromised individuals.

Present treatments

Hospital admission is indicated in almost all patients. Intensive care unit admission may be needed, depending on clinical judgment of severity, presence of concomitant disease, general health of the patient, and availability of adequate patient monitoring.

The treatment of choice is therapy with high doses of macrolide antibiotics, given via intravenous infusion every six hours. Less severely ill patients may receive lower doses of the medicine orally twice a day. Some prefer macrolides of the second generation or quinolones as antibiotic treatment. Seriously ill patients should receive a combination therapy consisting of a macrolide antibiotic plus a tuberculostatic compound. Treatment should be continued for at least three weeks to prevent relapses.

Even with appropriate care and therapy, mortality is 10-20 per cent in community-acquired cases and is higher among immune-compromised or hospitalised patients. Patients who respond convalesce slowly, and X-ray abnormalities usually persist longer than one month.

What's in the development pipeline?

Recently obtained data on the effectiveness of new types of quinolone antimicrobial agents support studies on the clinical effectiveness of such compounds for the treatment of Legionnaires' disease. A new glycylicycline antimicrobial compound has also been shown to be effective in animal models.

Another new class of antibacterials are the ketolides, which, like macrolides, exert their antibacterial activity by interacting with the bacterial ribosome and inhibiting its ability to make new proteins. Ketolides have been found to be effective *in vivo* against *L. pneumophila*.

Research groups are busy establishing cell lines as model systems to study the invasiveness and biology of *L. pneumophila*. In these models, it is hoped to distinguish invasion from adherence, as only virulent strains of the organism are both adherent and invasive. Outer membrane proteins are key molecules in the parasite-host cell interaction. Scientists are also looking into chronically infected cell cultures that are considered to be a useful tool for studying long-term interactions between virulent strains of the bacterium and mammalian cells.

Such model systems offer unique opportunities to study parasite-directed uptake into macrophages, as well as to stage specific host-parasite interactions. The investigations should make it possible to understand how the bacterium is capable of adapting to hosts as different as amoebae, which are microorganisms living in aqueous environments, and man. They should also open new avenues to create improved diagnostics, more effective therapeutic weapons and biocides for decontaminating water systems.

The longer-term future

In September 2004, several research groups jointly published the genomic sequence of *L. pneumophila*. According to the scientific report, the genome contains 3.4 million

Legionnaires' disease is a rare but serious lung infection caused by a bacterium. Antibiotics have saved many lives and research continues to develop new antibiotics. Genetic research should lead to more effective treatments.



Most outbreaks of Legionnaires' disease have come from water-distribution and airconditioning systems in large buildings.



Electron-microscopic picture of *Legionella pneumophila*

base pairs arranged in a chromosomal ring form which holds some 3,000 genes. These include selective expansions of important gene families, genes for unexpected metabolic pathways, and previously unknown candidate virulence determinants.

Specific analysis yielded some relationship of the genome of *Legionella pneumophila* with the genome of *Coxiella burnetii*, the bacterial agent which causes Q-fever in farm animals. Q-fever may also be transmitted to humans. Like *Legionella* species, the pathogen *Coxiella burnetii* is attacked and taken up by pulmonary macrophages but cannot be destroyed by the white blood cells. A comparative analysis of both genomes may lead to better insights into this phenomenon.

The report also highlights the genes that may account for *Legionella's* ability to survive in protozoa, mammalian macrophages, and inhospitable environmental niches and that may define new therapeutic targets for further medicines and vaccines.

Human immune genetics play an important role. Innate and adaptive immunity plays a critical role in the defence of the lung and other mucosal surfaces of the human body when exposed to micro-organisms. Anti-microbial peptides, fluids and cytokines are important immune weapons, as they form the protective barrier for the respiratory tract. The notion that susceptibility to infections of the lung may be genetically fixed and could result in failure to activate adaptive immunity is widely accepted. Recognition of specific gene defects affecting the immune system to overcome invading pathogens may shed light upon such mechanisms. Advances in immune-genetics may thus lead to the identification of strategies in the development of further anti-infectious and anti-inflammatory medicines.

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